

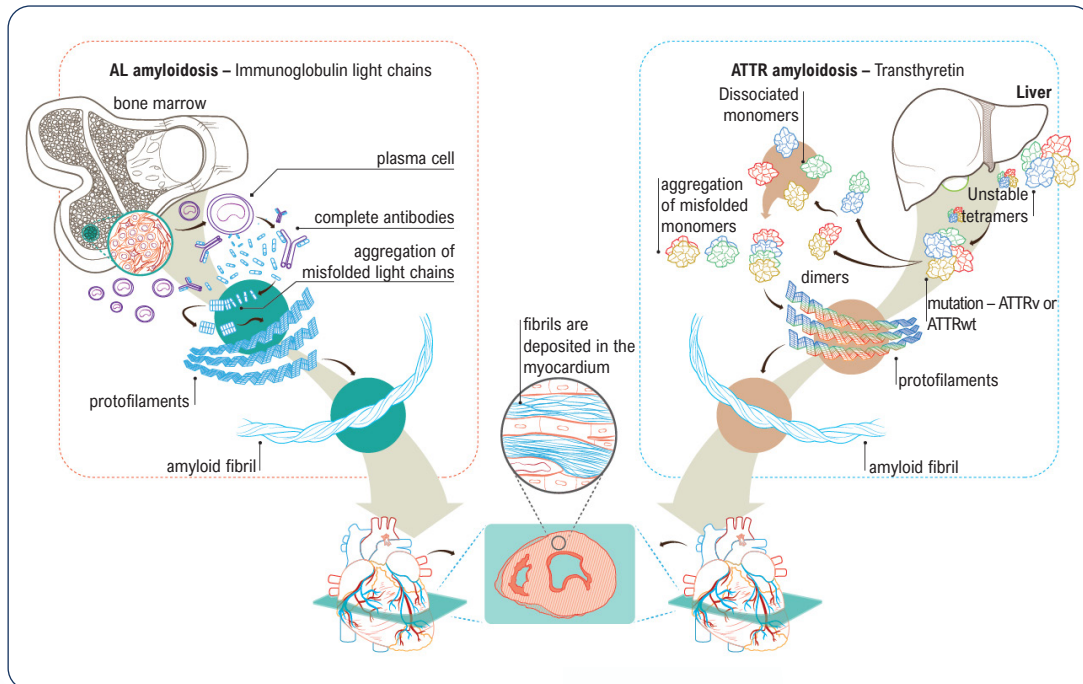


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**Atrial fibrillation in ELSA-Brasil baseline**

**Thiol Levels in Rheumatic Mitral Valve Disease**

**Risk of Death in the Elderly with Dyssomnias and Depressi**

**Arterial Stiffness and Body Composition**

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## Arquivos Brasileiros de Cardiologia

**Volume 117, Nº 3, September 2021**

Indexing: ISI (Thomson Scientific), Cumulated Index Medicus (NLM),  
SCOPUS, MEDLINE, EMBASE, LILACS, SciELO, PubMed



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## The Double-Orifice Technique in Mitral Valve Repair: 35 Years of History

Pablo Maria Alberto Pomerantzeff,<sup>1</sup>  Carlos Manuel de Almeida Brandão,<sup>1</sup> Arlindo Riso,<sup>1</sup> Fabio Biscegli Jatene<sup>1</sup>

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The advantages of mitral valve repair are lower morbidity and mortality, reduced risk of thromboembolism and endocarditis, improved survival, and better preservation of left ventricular function. The most common cause of degenerative mitral regurgitation is a myxomatous valve with segmental prolapse of the posterior leaflet, a lesion that can be corrected by classical techniques such as quadrangular resection, but other lesions may require more complex surgical techniques, for instance, correction of anterior leaflet prolapse or Barlow disease. Mitral valve repair in rheumatic patients is still a challenge.

In December 1984, Adib Domingos Jatene MD, PhD performed the first “duplication of the mitral orifice”, in a female patient with mitral insufficiency due to rupture of anterior leaflet chordae (Figure 1). The technique restored mitral competence by anchoring the free edge of the prolapsing leaflets to the corresponding free edge of the opposing leaflet with a 5-0 polypropylene stitch reinforced with pledgets. The patient presented good immediate and long-term evolution.

In 1998, Maisano et al.,<sup>1</sup> published the technique of “duplication of the mitral orifice”, known as the “edge-to-edge” technique, which had been performed since 1991

according to the authors. Subsequently, Alfieri et al. published the midterm results of this single technique,<sup>2</sup> showing effectiveness and durability, and the same group recently published the long-term (18 years) results.<sup>3</sup>

Since 1980, we have been performing mitral valve repair with different techniques, including the “duplication of the mitral orifice”, as published in 1994 by our group,<sup>4</sup> with good long-term (17 years) results.<sup>5</sup> We perform this type of mitral valve repair in patients who have a large valve ring so that there is no risk of causing stenosis. Evidently, cusp tissue degeneration must be evaluated in the operative act, as well as the tendinous cords and the papillary muscles, but we must remember that once mitral insufficiency has been corrected, cusp stress is greatly reduced. Another important detail in any mitral valve repair is the analysis of coaptation between the anterior and posterior cusps, using the saline test, injected through the mitral into the left ventricle. When we use the mitral duplication of the mitral orifice, we must verify not only the coaptation in the duplication site, which is obviously good, given that there is a suture between the cusps, but also coaptation throughout the extent of the edge between the anterior and posterior cusps.

### Keywords

Mitral Valve/surgery; Heart Valve Diseases/surgery; Morbidity and Mortality; Thromboembolism/prevention and control; Endocarditis/prevention and control.

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Manuscript received February 01, 2021, revised manuscript March 03, 2021, accepted March 03, 2021

DOI: <https://doi.org/10.36660/abc.20210067>

| HOSPITAL DAS CLÍNICAS<br>DA<br>Faculdade de Medicina da Universidade de São Paulo                                                                                   |                              | ETIQUETA DE IDENTIFICAÇÃO             |                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|---------------------------------------|------------------------------|
| <b>RELATÓRIO DE CIRURGIA<br/>PRONTUÁRIO</b>                                                                                                                         |                              |                                       |                              |
| Nº DE REGISTRO<br>5032334                                                                                                                                           | DATA CIRURGIA<br>04/12/84    | NOME DO PACIENTE<br>Prof. Adib Jatene | CLÍNICA<br>EVAL              |
| 1º ASSISTENTE<br>Dr. Antônio                                                                                                                                        | 2º ASSISTENTE<br>Dr. Glaucio | 3º ASSISTENTE<br>Dr. Maina            | Nº MATRÍCULA<br>586.124      |
| TIPO DE ANESTESIA<br>geral                                                                                                                                          | AGENTE ANESTÉSICO            | HORA DE INÍCIO DA ANESTESIA<br>16:270 | HORA DE TÉRMINO DA ANESTESIA |
| DIAGNÓSTICO PRÉ-OPERATÓRIO<br>DURA LESÃO MITRAL — 394.2                                                                                                             |                              |                                       |                              |
| DIAGNÓSTICO (S) PÓS-OPERATÓRIO                                                                                                                                      |                              |                                       |                              |
| - INSUFICIÊNCIA MITRAL POR ROTURA DE CORDA NO<br>POLÍGONO DE SPAIN — 424.0                                                                                          |                              |                                       |                              |
| PROCEDIMENTO (S) CIRÚRGICO (S)<br>- PLÁSTICA DE VALVA MITRAL: DUPLICAÇÃO DE ORELHÃO MITRAL — 32.034.01.0                                                            |                              |                                       |                              |
| ACIDENTE DURANTE ATO CIRÚRGICO<br>1. SIM 2. NÃO                                                                                                                     |                              |                                       |                              |
| BÓPIA DE CONSULTA<br>ENCAMINHAMENTO IMEDIATO AO PACIENTE APÓS TÉRMINO DO ATO CIRÚRGICO<br>1. INTERNA 2. TERAPIA INTENSIVA 3. RESERVA 4. OUTRO DURANTE ATO CIRÚRGICO |                              |                                       |                              |

| DESCRIÇÃO DA CIRURGIA                                                    |
|--------------------------------------------------------------------------|
| 1. Incisão lateral direita no 4º EICE da linha hialda e linha            |
| 2. Abertura hialda no meio inframamário                                  |
| 3. Abertura longitudinal do Pleuródico                                   |
| 4. Suturas de OEC mediante camadas de Biot Ant-Hemoral D e               |
| antes as OEC                                                             |
| 5. Espalhamento a 32° de afastamento de OEC com perfuração de cordão     |
| por fúlio 16, trado da linha Atrial                                      |
| 6. Abertura do AE. Valva testada com corações sintéticos                 |
| Valva mitral: não completa na sua porção média por pulso                 |
| no folheto septal devido a rotura de corda. Anel mitral                  |
| de 1º 6cm. folheto sem lesão                                             |
| 7. Fato física de valva mitral, aproximando-se                           |
| o folheto septal do mural, na sua porção                                 |
| prolapsoada através de 1 ponto de sutura                                 |
| 1.0 ancorado em Teflon                                                   |
| 8. Com isso a valva ficou com 2 orifícios                                |
| sendo o anterior de 1.2cm de diâmetro                                    |
| 9. Teste de Valva com lavagem batendo nos horns                          |
| 10. Teste de Or pelo AE e Atrial. Desaparecimento de OEC. Apertamento    |
| 11. Fechamento do AE com hêmico de OEC                                   |
| 12. Sutura de OEC com monitorização do AE (± 10mmHg) sem intercorrências |
| 13. Hemostase e lavagem de Hemostase                                     |
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| 100. Sutura de OEC                                                       |

Figure 1 – Surgical report of mitral valve repair with the double-orifice technique.

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# Atrial Fibrillation Diagnosis using ECG Records and Self-Report in the Community: Cross-Sectional Analysis from ELSA-Brasil

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University of Birmingham College of Medical and Dental Sciences - Institute of Applied Health Research,<sup>7</sup> Birmingham - Reino Unido da Grã-Bretanha

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## Abstract

**Background:** Atrial fibrillation or flutter (AFF) is the most common sustained cardiac arrhythmia. Limited data can be found on AFF epidemiology in South America.

**Objective:** The present study sought to describe the clinical epidemiology of AFF and the use of stroke prevention medication in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) baseline assessment.

**Methods:** This study analyzed data from 13,260 ELSA-Brasil participants. AFF was defined according to ECG recording or by self-report. Logistic regression models were built to analyze factors associated with AFF. This study also analyzed if age and sex were associated with anticoagulant use for stroke prevention. Significance level was set at 5%.

**Results:** Median age was 51 years and 7,213 (54.4%) participants were women. AFF was present in 333 (2.5%) participants. Increasing age (odds ratio [OR]:1.05; 95% confidence interval [95%CI]: 1.04–1.07), hypertension (OR:1.44; 95%CI: 1.14–1.81), coronary heart disease (OR: 5.11; 95%CI: 3.85–6.79), heart failure (OR:7.37; 95%CI: 5.00–10.87), and rheumatic fever (OR:3.38; 95%CI: 2.28–5.02) were associated with AFF. From 185 participants with AFF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ , only 20 (10.8%) used anticoagulants (50.0% among those with AFF in the baseline ECG). Stroke prevention in this group was associated with a higher age (1.8% vs 17.7% in those aged  $\leq 54$  and  $\geq 65$  years, respectively;  $p=0.013$ ). A trend towards a reduced anticoagulant use was observed in women (7.1% vs. 16.4% in women and men, respectively;  $p=0.055$ ).

**Conclusions:** At the ELSA-Brasil baseline, 2.5% of the participants had AFF. The lack of stroke prevention was common, which is an especially challenging point for healthcare in this setting.

**Keywords:** Atrial Fibrillation; Epidemiology; Electrocardiography/methods; Anticoagulants; Longitudinal Study; Aged; Stroke; Embolism.

## Introduction

Atrial fibrillation is the most prevalent sustained cardiac arrhythmia, with an approximate lifetime risk of 25%<sup>1</sup> and an estimated 33.3 million prevalent cases globally.<sup>2</sup> In São Paulo, Brazil, a population-based study<sup>3</sup> found that

3.2% of men and 2.0% of women aged 65 years or older had atrial fibrillation. Another large database of primary care patients aged 5 years or older (71% aged  $\geq 40$  years) in Minas Gerais, Brazil,<sup>4</sup> found that 2.4% of men and 1.3% of women had atrial fibrillation. Risk factors for atrial fibrillation or flutter include age, hypertension, diabetes, smoking, obesity, heart failure, valve disease, and myocardial infarction.<sup>5–7</sup>

Risk-based thromboembolic (including stroke) prevention therapy is recommended for patients with atrial fibrillation or flutter (AFF).<sup>8,9</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASc scores<sup>10</sup> are currently the main strategy to evaluate thromboembolic risk in these individuals.<sup>11</sup> Oral antithrombotic therapy is recommended for those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ .<sup>9</sup>

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Manuscript received December 02, 2019, revised manuscript July 15, 2020, accepted August 16, 2020

**DOI:** <https://doi.org/10.36660/abc.20190873>

Oral anticoagulation therapy, however, still represents a challenge in clinical practice,<sup>12,13</sup> and a significant proportion of AFF disease burden is still associated with incident stroke,<sup>14</sup> especially in women.<sup>15,16</sup> This is even more important in Brazil, where although age-adjusted incident rates of stroke in the country have been falling in recent years,<sup>17</sup> stroke mortality is still high when compared to other South American countries, with a higher impact on the less developed states of the nation.<sup>17,18</sup>

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a large multicenter cohort of individuals of 35 to 74 years of age in six Brazilian cities, whose aim is to study the incidence and associated factors for cardiovascular diseases and diabetes. The objectives of the present study are to describe the frequency of AFF at the ELSA-Brasil baseline and the use of stroke prevention medication in participants with AFF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ .

## Methods

### Study setting and design

The ELSA-Brasil design<sup>19</sup> and cohort profile<sup>20</sup> are detailed elsewhere. Briefly, ELSA-Brasil is a cohort study of 15,105 civil servants from six Brazilian cities (São Paulo, Belo Horizonte, Porto Alegre, Salvador, Rio de Janeiro, and Vitória). Baseline assessments took place from August 2008 to December 2010 and included in-person interviews conducted by trained personnel, using clinical, laboratory, and imaging exams. Since baseline, all participants receive a yearly telephone follow-up contact. Four years after enrollment (2012-2014), all participants were invited to undergo onsite reassessment, which included new questionnaires, and clinical and laboratory evaluations. This reassessment was attended by 14,014 (92.8%) participants. Informed consent was obtained from all participants. Study protocol is in accordance to the Brazilian National Health Council 466/2012 resolution and was approved by the Institutional Review Board in each participating center.

### Atrial fibrillation or flutter diagnosis

Methods to record electrocardiographic (ECG) tracings in ELSA-Brasil are detailed elsewhere.<sup>21</sup> ECG at the baseline was performed in each center, using a Burdick Atria 6100 device, calibrated at 10 mm/mV and a speed of 25 mm/second. The recordings were transmitted to the reading center in Minas Gerais Investigation Center. Analyses followed the Glasgow system,<sup>22</sup> and were coded according to the Minnesota Coding System. Selected codes (including AFF) were manually reviewed by trained staff. In addition, in the onsite reassessment conducted in 2012-2014, participants were asked the following question: "Did a physician ever say that you have/had atrial fibrillation?" Participants who answered "yes" to that question were asked "How old were you the first time a physician told you that you have/had atrial fibrillation?"

The present study defined AFF diagnosis at the baseline if the participant (a) had an ECG recording with AFF in the ELSA-Brasil baseline assessment (n=48) or (b) indicated that they have had an atrial fibrillation diagnosis at an age lower

than his/her age upon ELSA-Brasil enrollment (n=285). Most analyses are presented for all AFF cases and according to each definition criterion.

### Study sample

This study included ELSA-Brasil participants for whom AFF diagnosis at the baseline could be assessed. From the 15,105 ELSA-Brasil participants, 663 (4.4%) participants were excluded because they did not have a valid ECG reading at the baseline nor a valid answer for the AFF in the 2012-2014 onsite reassessment, and 1,182 (7.8%) were excluded because they had a valid ECG reading at the baseline without AFF, but without a valid answer for the AFF in the 2012-2014 onsite reassessment (impairing the assessment of paroxysmal AFF). Therefore, our main sample consisted of 13,260 (87.8%) participants.

### Other variables

Age, sex, race, level of education, monthly family income, and smoking status were self-reported and stratified accordingly. Monthly income was transformed into US dollars (using a conversion rate of BRL 2.00=USD 1.00, based on the exchange rate at the baseline). Race was defined, as adopted by the Brazilian National Census, as Black, Mixed, White, Asian, and Native (Indigenous). The anthropometric measurements in the ELSA-Brasil were assessed using standard techniques,<sup>23</sup> and body mass index (BMI) was calculated by dividing weight by height squared. BMI was categorized as normal ( $< 25 \text{ kg/m}^2$ ), overweight ( $\geq 25 \text{ kg/m}^2$  and  $< 30 \text{ kg/m}^2$ ), and obese ( $\geq 30 \text{ kg/m}^2$ ). Hypertension was defined as the report of the use of medications to treat hypertension, a systolic blood pressure  $\geq 140 \text{ mmHg}$ , or a diastolic blood pressure  $\geq 90 \text{ mmHg}$  upon ELSA-Brasil baseline assessment. Diabetes was defined as a medical history of diabetes mellitus, the report of the use of medications to treat diabetes mellitus, a fasting serum glucose  $\geq 126 \text{ mg/dl}$ , HbA1c levels  $\geq 6.5\%$ , or a 2-h oral glucose tolerance test  $\geq 200 \text{ mg/dl}$ . Dyslipidemia was defined as the report of the use of lipid lowering treatment or an LDL cholesterol level  $\geq 130 \text{ mg/dl}$ . Abdominal obesity was defined as a waist circumference  $> 88 \text{ cm}$  in women and  $> 102 \text{ cm}$  in men. Previous medical diagnosis of heart failure, stroke, rheumatic fever, and thromboembolic event were assessed by self-report. Coronary artery disease was defined by a previous medical diagnosis of myocardial infarction or angina pectoris or by previous coronary revascularization. Ankle and brachial pressure measurements for ankle-brachial index (ABI) calculation is described in detail in Miname et al.<sup>24</sup> According to the findings of that study, ABI was calculated as the ratio between the minimum leg systolic pressure and the maximum arm systolic pressure for higher sensitivity. Peripheral artery disease was defined as an ABI  $< 1.0$ .<sup>24,25</sup> For medication use data, other than questionnaires, patients were asked to bring to the baseline assessment of all medications and prescription drugs they were currently taking.<sup>26</sup> Use of anticoagulants was defined by using a medication under Anatomical Therapeutic Chemical (ATC) codes B01AA or B01AB. Use of antiplatelet agents was defined by using a medication under ATC code B01AC. For participants without previous coronary artery disease or stroke, 10-year atherosclerotic cardiovascular

disease (ASCVD) risk was calculated according to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.<sup>27</sup> CHA<sub>2</sub>DS<sub>2</sub>-VASC scores were calculated according to Lip et al.<sup>11</sup> and categorized as 0 or 1 point, 2 or 3 points, and  $\geq 4$  points.

### Statistical analysis

Categorical variables are presented as counts and proportions, and were compared using Chi-squared or Fisher's exact tests. Continuous variables (age, body-mass index, ankle-brachial index and 10-year ASCVD risk) have non-normal distribution ( $p < 0.001$  for all, using the Anderson-Darling test), and are presented as medians and interquartile ranges and compared among groups using Mann-Whitney U tests. Crude and age- and sex-adjusted logistic regression models were built to analyze if AFF diagnosis at the ELSA-Brasil baseline was associated with age, sex, race, level of education, monthly income, smoking status, hypertension, diabetes and dyslipidemia diagnoses, BMI, abdominal obesity, peripheral artery disease, coronary heart disease, heart failure, stroke, rheumatic fever, and a 10-year CHD risk  $> 10\%$ . Binary logistic regression was used to analyze the association with all AFF cases, while multinomial logistic regression was used to analyze the association with AFF cases according to each definition criterion (by ECG recording or self-report) in separate. The significance level was set at 5%, and R software, version 3.5.1, was used in all analyses.

### Results

Among the 13,260 participants included in the analyses, 333 (2.5%) had AFF at the ELSA-Brasil baseline, 176/7,213 (2.4%) women and 157/6,047 (2.6%) men. According to age strata, the frequency of AFF diagnosis was 1.2%, 2.2%, 2.9%, and 5.4% for ages  $< 45$ , 45-54, 55-64, and  $> 64$  years, respectively. Table 1 shows the study's sample characteristics, according to the presence of AFF diagnosis at the ELSA-Brasil baseline. Individuals of non-white races represented 47.9% of the sample, and most participants had a college degree or higher education.

Table 2 shows crude and age- and sex-adjusted odds ratios for the association with the presence of AFF diagnosis at the ELSA-Brasil baseline. Considering all AFF cases, higher age ( $p < 0.001$ ), higher income ( $p = 0.044$ ), hypertension ( $p = 0.002$ ), coronary heart disease ( $p < 0.001$ ), heart failure ( $p < 0.001$ ), and rheumatic fever diagnoses ( $p < 0.001$ ) were positively associated with AFF in the adjusted models. Restricting the cases to the 48 participants who presented AFF in the baseline ECG, higher age ( $p < 0.001$ ), male sex ( $p = 0.037$ ), peripheral artery disease ( $p = 0.026$ ), heart failure ( $p < 0.001$ ), and rheumatic fever diagnoses ( $p < 0.001$ ) were positively associated with AFF in the adjusted models. Supplemental Table 1 shows crude model results for these associations.

CHA<sub>2</sub>DS<sub>2</sub>-VASC scores could be calculated for 331 (99.4%) of the 333 participants with AFF diagnosis at the baseline (Table 3). As expected, individuals with higher CHA<sub>2</sub>DS<sub>2</sub>-VASC scores were older ( $p < 0.001$ ), were more likely to be women ( $p = 0.002$ ), and presented a higher cardiovascular risk

( $p < 0.001$ ). Among 185 participants with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 2$ , only 20 (10.8%) received anticoagulant therapy (16/32; 50.0% when restricting cases to the 48 participants who presented AFF in the baseline ECG).

Table 4 shows the prevalence of oral anticoagulant use in participants with AFF and a CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 2$ , according to age and sex. Considering all AFF cases, anticoagulant use was more frequent in those with a higher age ( $p = 0.013$ ), and a trend towards lower anticoagulant use in women ( $p = 0.055$ ). Supplemental table 2 shows that the frequency of anticoagulant use in men was numerically higher than in women for all age strata, but no significant differences were discovered when analyzing all AFF cases nor when restricting them to those participants who presented with AFF in the baseline ECG.

### Discussion

#### Contextualization and discussion of main findings

In our cohort sample, 2.5% of the included participants presented AFF at the baseline. Age, male sex, income, hypertension, coronary heart disease, peripheral artery disease, heart failure, and rheumatic fever diagnoses were positively associated with AFF. Second, most participants with AFF and a CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 2$  did not receive anticoagulants and/or antiplatelet agents. Third, oral anticoagulant use was more common in those with a higher age, while women were less commonly treated.

Comparing AFF prevalence across samples is challenging because of differences in study design, study setting, and age and sex distribution upon recruitment. A review of the global epidemiology of atrial fibrillation<sup>28</sup> found a reported worldwide prevalence ranging from 0.1% to 6.0%, depending on the age strata and sex analyzed. Although this study reports a similar frequency of AFF diagnosis in the sample when compared to the cited Brazilian studies,<sup>3,4</sup> these studies have marked differences and are complementary. For example, Kawabata-Yoshihara et al.<sup>3</sup> performed a systematic door knock of individuals 65 years of age or older, while Marcolino et al.<sup>4</sup> used a large ECG database from the Telehealth Network of Minas Gerais consisting of individuals 5 years of age or older who received medical care in primary care units. Both studies considered AFF diagnosis according to ECG recordings upon assessment. When comparing the findings from those studies to the findings from the present study, a higher frequency of AFF was found when similar age strata are compared. This is most likely influenced by case definitions, as the present study also included a self-reported medical diagnosis as a diagnostic criterion. However, considering only the ECG tracings during assessment and excluding medical history from case definitions may yield the highest specificity and reduce self-reported information error, but it can also underestimate prevalence rates due to the under-recognition of paroxysmal atrial fibrillation.

The association between heart failure and atrial fibrillation has clinical importance. Healey et al.<sup>12</sup> analyzed data from 15,400 individuals with AFF in 47 countries. After one year of follow-up, death occurred in 11% of the cohort, and heart

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**Table 1 – Study sample characteristics according to the presence of atrial fibrillation or flutter in the ELSA-Brasil baseline**

|                                                            | No atrial<br>fibrillation or<br>flutter<br>(N=12,927) | Atrial fibrillation or flutter |                                |                          | Total<br>(N=13,260) | p-value  |
|------------------------------------------------------------|-------------------------------------------------------|--------------------------------|--------------------------------|--------------------------|---------------------|----------|
|                                                            |                                                       | By ECG recording<br>(N=48)     | By self-report<br>only (N=285) | All AFF cases<br>(N=333) |                     |          |
| Age (years; median [P25 - P75])                            | 51.0 [45.0 – 58.0]                                    | 61.5 [56.0 – 71.0]             | 54.0 [49.0 – 62.0]             | 56.0 [49.0 – 63.0]       | 51.0 [45.0 – 58.0]  | <0.001 ‡ |
| Female sex (N (%))                                         | 7.037 (54.4%)                                         | 18 (37.5%)                     | 158 (55.4%)                    | 176 (52.9%)              | 7.213 (54.4%)       | 0.61 †   |
| Race (N (%))                                               |                                                       |                                |                                |                          |                     |          |
| White                                                      | 6.652 (52.1%)                                         | 29 (61.7%)                     | 154 (54.6%)                    | 183 (55.6%)              | 6.835 (52.1%)       | 0.039 †  |
| Mixed                                                      | 3.608 (28.2%)                                         | 11 (23.4%)                     | 74 (26.2%)                     | 85 (25.8%)               | 3.693 (28.2%)       |          |
| Black                                                      | 2.069 (16.2%)                                         | 7 (14.9%)                      | 35 (12.4%)                     | 42 (12.8%)               | 2.111 (16.1%)       |          |
| Other                                                      | 449 (3.5%)                                            | 0 (0.0%)                       | 19 (6.7%)                      | 19 (5.8%)                | 468 (3.6%)          |          |
| Level of education (N (%))                                 |                                                       |                                |                                |                          |                     |          |
| Up to incomplete high school                               | 1.529 (11.8%)                                         | 13 (27.1%)                     | 34 (11.9%)                     | 47 (14.1%)               | 1.576 (11.9%)       | 0.10 †   |
| High school                                                | 4.443 (34.4%)                                         | 12 (25.0%)                     | 85 (29.8%)                     | 97 (29.1%)               | 4.540 (34.2%)       |          |
| College or above                                           | 6.955 (53.8%)                                         | 23 (47.9%)                     | 166 (58.2%)                    | 189 (56.8%)              | 7.144 (53.9%)       |          |
| Monthly income (N (%))                                     |                                                       |                                |                                |                          |                     |          |
| <USD1245                                                   | 3.357 (26.1%)                                         | 15 (31.2%)                     | 58 (20.4%)                     | 73 (22.0%)               | 3.430 (26.0%)       | 0.001 †  |
| USD1245-3319                                               | 5.679 (44.1%)                                         | 12 (25.0%)                     | 115 (40.5%)                    | 127 (38.3%)              | 5.806 (43.9%)       |          |
| ≥ USD3320                                                  | 3.845 (29.9%)                                         | 21 (43.8%)                     | 111 (39.1%)                    | 132 (39.8%)              | 3.977 (30.1%)       |          |
| Smoking status (N (%))                                     |                                                       |                                |                                |                          |                     |          |
| Never smoked                                               | 7.467 (57.8%)                                         | 29 (60.4%)                     | 161 (56.5%)                    | 190 (57.1%)              | 7.657 (57.7%)       | 0.75 †   |
| Past smoker                                                | 3.822 (29.6%)                                         | 13 (27.1%)                     | 91 (31.9%)                     | 104 (31.2%)              | 3.926 (29.6%)       |          |
| Current smoker                                             | 1.637 (12.7%)                                         | 6 (12.5%)                      | 33 (11.6%)                     | 39 (11.7%)               | 1.676 (12.6%)       |          |
| Hypertension (N (%))                                       | 4.463 (34.5%)                                         | 30 (62.5%)                     | 136 (47.7%)                    | 166 (49.8%)              | 4.629 (34.9%)       | <0.001 † |
| Diabetes (N (%))                                           | 2.438 (18.9%)                                         | 15 (31.2%)                     | 66 (23.2%)                     | 81 (24.3%)               | 2.519 (19.0%)       | 0.015 †  |
| Dyslipidemia (N (%))                                       | 7.489 (58.0%)                                         | 27 (56.2%)                     | 188 (66.0%)                    | 215 (64.6%)              | 7.704 (58.1%)       | 0.019 †  |
| Body-mass index (kg/m2; median [P25 - P75])                | 26.3 [23.7 – 29.5]                                    | 27.4 [25.4 – 30.4]             | 26.2 [23.9 – 30.2]             | 26.5 [24.1 – 30.3]       | 26.3 [23.7 – 29.6]  | 0.35 ‡   |
| Body-mass index classification<br>(N (%))                  |                                                       |                                |                                |                          |                     |          |
| Normal                                                     | 4.791 (37.1%)                                         | 10 (20.8%)                     | 104 (36.5%)                    | 114 (34.2%)              | 4.905 (37.0%)       | 0.057 †  |
| Overweight                                                 | 5.238 (40.5%)                                         | 24 (50.0%)                     | 102 (35.8%)                    | 126 (37.8%)              | 5.364 (40.5%)       |          |
| Obese                                                      | 2.892 (22.4%)                                         | 14 (29.2%)                     | 79 (27.7%)                     | 93 (27.9%)               | 2.985 (22.5%)       |          |
| Abdominal obesity (N (%))                                  | 4.656 (36.0%)                                         | 20 (41.7%)                     | 113 (39.6%)                    | 133 (39.9%)              | 4.789 (36.1%)       | 0.16 †   |
| Ankle-brachial index (median [P25 - P75])                  | 1.18 [1.12 – 1.23]                                    | 1.13 [1.04 – 1.20]             | 1.17 [1.11 – 1.24]             | 1.16 [1.10 – 1.23]       | 1.18 [1.12 – 1.23]  | 0.008 ‡  |
| Peripheral artery disease (N (%))                          | 403 (3.1%)                                            | 6 (12.5%)                      | 12 (4.2%)                      | 18 (5.4%)                | 421 (3.2%)          | 0.025 †  |
| Use of anticoagulants (N (%))                              | 37 (0.3%)                                             | 19 (39.6%)                     | 5 (1.8%)                       | 24 (7.2%)                | 61 (0.5%)           | <0.001 † |
| Use of antiplatelet agents (N (%))                         | 706 (5.5%)                                            | 7 (14.6%)                      | 45 (15.8%)                     | 52 (15.6%)               | 758 (5.7%)          | <0.001 † |
| Use of anticoagulant and/or antiplatelet<br>agents (N (%)) | 741 (5.7%)                                            | 26 (54.2%)                     | 50 (17.5%)                     | 76 (22.8%)               | 817 (6.2%)          | <0.001 † |
| Coronary artery disease (N (%))                            | 536 (4.2%)                                            | 7 (14.6%)                      | 67 (23.5%)                     | 74 (22.2%)               | 610 (4.6%)          | <0.001 † |
| Heart failure (N (%))                                      | 160 (1.2%)                                            | 10 (20.8%)                     | 26 (9.2%)                      | 36 (10.8%)               | 196 (1.5%)          | <0.001 † |
| Stroke (N (%))                                             | 153 (1.2%)                                            | 1 (2.1%)                       | 7 (2.5%)                       | 8 (2.4%)                 | 161 (1.2%)          | 0.067 †  |
| Rheumatic fever (N (%))                                    | 352 (2.7%)                                            | 7 (14.6%)                      | 23 (8.1%)                      | 30 (9.0%)                | 382 (2.9%)          | <0.001 † |
| Thromboembolic event (N (%))                               | 198 (1.5%)                                            | 4 (8.3%)                       | 5 (1.8%)                       | 9 (2.7%)                 | 207 (1.6%)          | 0.11 †   |
| 10-year ASCVD risk (median [P25 - P75])                    | 2.8% [1.1% - 7.1%]                                    | 11.8% [4.2% –<br>18.5%]        | 2.7% [1.4% – 7.9%]             | 3.4% [1.5% - 10.4%]      | 2.8% [1.1% – 7.2%]  | 0.001 ‡  |
| 10-year ASCVD risk > 10% (N (%))                           | 2075 (16.9%)                                          | 23 (57.5%)                     | 41 (19.2%)                     | 64 (25.2%)               | 2139 (17.1%)        | 0.001 †  |

The 10-year ASCVD risk is defined only in participants without prior coronary artery disease or stroke. AFF: Atrial fibrillation or flutter. ASCVD: Atherosclerotic cardiovascular disease. P-values are presented for the comparison between the no atrial fibrillation or flutter (N=12,927) and all AFF case (N=333) groups, using † Chi-squared or ‡ Mann-Whitney U tests

**Table 2 – Age- and sex-adjusted odds ratios (95% CIs) for the association with atrial fibrillation or flutter in the ELSA-Brasil baseline**

| Variable                              | Atrial fibrillation or flutter |                             |                       |
|---------------------------------------|--------------------------------|-----------------------------|-----------------------|
|                                       | By ECG recording (N=48)        | By self-report only (N=285) | All AFF cases (N=333) |
| Age (one-year increase)               | 1.12 [1.09 – 1.16]             | 1.04 (1.03 – 1.06) †        | 1.05 (1.04 – 1.07) †  |
| Female sex                            | 0.53 (0.30 – 0.96) †           | 1.05 (0.83 – 1.33)          | 0.95 (0.76 – 1.18)    |
| <b>Race*</b>                          |                                |                             |                       |
| White                                 | 1.0 (Reference)                | 1.0 (Reference)             | 1.0 (Reference)       |
| Mixed                                 | 0.92 (0.45 – 1.85)             | 0.95 (0.72 – 1.26)          | 0.94 (0.72 – 1.22)    |
| Black                                 | (0.43 – 2.27)                  | 0.76 (0.52 – 1.10)          | 0.79 (0.56 – 1.10)    |
| <b>Level of education</b>             |                                |                             |                       |
| Up to incomplete high school          | 1.73 (0.87 – 3.43)             | 0.79 (0.54 – 1.15)          | 0.92 (0.66 – 1.27)    |
| High school                           | 1.12 (0.55 – 2.28)             | 0.86 (0.66 – 1.12)          | 0.88 (0.69 – 1.13)    |
| College or above                      | 1.0 (Reference)                | 1.0 (Reference)             | 1.0 (Reference)       |
| <b>Monthly income</b>                 |                                |                             |                       |
| <USD1245                              | 1.27 (0.64 – 2.51)             | 0.67 (0.48 – 0.93) †        | 0.74 (0.55 – 0.99) †  |
| USD1245-3319                          | 0.61 (0.29 – 1.25)             | 0.80 (0.61 – 1.04)          | 0.77 (0.60 – 0.99) †  |
| ≥ USD3320 (N (%))                     | 1.0 (Reference)                | 1.0 (Reference)             | 1.0 (Reference)       |
| <b>Smoking status</b>                 |                                |                             |                       |
| Never smoked                          | (Reference)                    | (Reference)                 | 1.0 (Reference)       |
| Past smoker                           | 0.57 (0.29 – 1.12)             | 0.98 (0.75 – 1.27)          | 0.90 (0.70 – 1.16)    |
| Current smoker                        | 1.00 (0.42 – 2.40)             | 0.93 (0.64 – 1.36)          | 0.93 (0.65 – 1.32)    |
| Hypertension                          | 1.65 (0.89 – 3.03)             | 1.41 (1.10 – 1.81) †        | 1.44 (1.14 – 1.81) †  |
| Diabetes                              | 1.11 (0.60 – 2.08)             | 1.06 (0.80 – 1.41)          | 1.07 (0.82 – 1.39)    |
| Dyslipidemia                          | 0.66 (0.37 – 1.18)             | 1.22 (0.95 – 1.57)          | 1.10 (0.87 – 1.39)    |
| <b>Body-mass index classification</b> |                                |                             |                       |
| Normal                                | 1.0 (Reference)                | 1.0 (Reference)             | 1.0 (Reference)       |
| Overweight                            | 1.88 (0.90 – 3.95)             | 0.85 (0.64 – 1.12)          | 0.94 (0.72 – 1.21)    |
| Obese                                 | 2.21 (0.97 – 5.00)             | 1.19 (0.88 – 1.60)          | 1.27 (0.96 – 1.68)    |
| Abdominal obesity                     | 1.15 (0.63 – 2.08)             | 1.04 (0.81 – 1.33)          | 1.05 (0.83 – 1.32)    |
| Peripheral artery disease             | 2.72 (1.13 – 6.54) †           | 1.16 (0.64 – 2.10)          | 1.44 (0.88 – 2.35)    |
| Coronary artery disease               | 1.87 (0.81 – 4.28)             | 5.99 (4.44 – 8.09) †        | 5.11 (3.85 – 6.79) †  |
| Heart failure                         | 11.67 (5.58 – 24.40) †         | 6.51 (4.19 – 10.11) †       | 7.37 (5.00 – 10.87) † |
| Stroke                                | 0.90 (0.12 – 6.67)             | 1.65 (0.76 – 3.57)          | 1.51 (0.73 – 3.13)    |
| Rheumatic fever                       | 5.75 (2.55 – 12.98) †          | 3.02 (1.94 – 4.70) †        | 3.38 (2.28 – 5.02) †  |
| 10-year ASCVD risk > 10%              | 1.56 (0.63 – 3.85)             | 0.78 (0.50 – 1.21)          | 0.95 (0.65 – 1.40)    |

\*The small proportion of individuals of other races in the sample precluded estimation. AFF: Atrial fibrillation or flutter. ASCVD: Atherosclerotic cardiovascular disease. Odds ratios and p-values were obtained from logistic regression models adjusted for age and sex. †p<0.05.

failure was the most common cause of death (30%). Similarly, individuals with peripheral artery disease and AFF have a higher risk of stroke when compared to those with only AFF.<sup>29</sup> It is important to note that, in recent decades, rheumatic heart disease has decreased as a cause of mortality in Brazil,<sup>30</sup> and although new cases in the country are less common, current middle-aged and older adults may have had rheumatic fever during childhood. Therefore, the prevalence and mortality due to rheumatic heart disease in Brazil is not negligible,<sup>31</sup>

which is reinforced by our finding that 9.0% of the individuals with AFF in this study's sample (and 2.9% overall) presented a medical history of rheumatic fever.

A striking finding of the present study was that 89.2% of all participants with AFF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 2 did not receive anticoagulants. This is more important considering that ELSA-Brasil participants have a higher mean level of education and income when compared to the general Brazilian population.<sup>20</sup> Although self-reported diagnoses may

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**Table 3 – Characteristics of participants with atrial fibrillation or flutter in the ELSA-Brasil baseline according to CHA<sub>2</sub>DS<sub>2</sub>-VASc scores**

|                                         | Atrial fibrillation or flutter                                |                                                               |                                                                |                                                                |                                                                |                                                                | p-value  |
|-----------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------|----------|
|                                         | By ECG recording                                              |                                                               | By self-report only                                            |                                                                | All AFF cases                                                  |                                                                |          |
|                                         | CHA <sub>2</sub> DS <sub>2</sub> -VASc<br>score < 2<br>(N=16) | CHA <sub>2</sub> DS <sub>2</sub> -VASc<br>score ≥ 2<br>(N=32) | CHA <sub>2</sub> DS <sub>2</sub> -VASc<br>score < 2<br>(N=130) | CHA <sub>2</sub> DS <sub>2</sub> -VASc<br>score ≥ 2<br>(N=153) | CHA <sub>2</sub> DS <sub>2</sub> -VASc<br>score < 2<br>(N=146) | CHA <sub>2</sub> DS <sub>2</sub> -VASc<br>score ≥ 2<br>(N=185) |          |
| Age (years; median [P25 - P75])         | 56.0 [49.5 – 61.2]                                            | 67.5 [58.0 – 71.2]                                            | 49.5 [45.0 – 56.0]                                             | 59.0 [53.0 – 66.0]                                             | 50.0 [45.0 – 57.0]                                             | 60.0 [53.0 – 68.0]                                             | <0.001 ‡ |
| Female sex (N (%))                      | 3 (18.8%)                                                     | 15 (46.9%)                                                    | 60 (46.2%)                                                     | 97 (63.4%)                                                     | 63 (43.2%)                                                     | 112 (60.5%)                                                    | 0.002 †  |
| Coronary artery disease (N (%))         | 0 (0.0%)                                                      | 7 (21.9%)                                                     | 2 (1.5%)                                                       | 64 (41.8%)                                                     | 2 (1.4%)                                                       | 71 (38.4%)                                                     | <0.001 † |
| Stroke (N (%))                          | 0 (0.0%)                                                      | 1 (3.1%)                                                      | 0 (0.0%)                                                       | 7 (4.6%)                                                       | 0 (0.0%)                                                       | 8 (4.3%)                                                       | 0.010 ¥  |
| 10-year ASCVD risk > 10% (N (%))        | 7 (43.8%)                                                     | 16 (66.7%)                                                    | 15 (11.7%)                                                     | 26 (30.6%)                                                     | 22 (15.3%)                                                     | 42 (38.5%)                                                     | <0.001 † |
| Prior ASCVD or 10-year ASCVD risk > 10% | 7 (43.8%)                                                     | 24 (75.0%)                                                    | 17 (13.1%)                                                     | 94 (61.4%)                                                     | 24 (16.4%)                                                     | 118 (63.8%)                                                    | <0.001 † |
| Use of anticoagulants (N (%))           | 3 (18.8%)                                                     | 16 (50.0%)                                                    | 1 (0.8%)                                                       | 4 (2.6%)                                                       | 4 (2.7%)                                                       | 20 (10.8%)                                                     | 0.005 ¥  |
| Use of antiplatelet agents (N (%))      | 2 (12.5%)                                                     | 5 (15.6%)                                                     | 2 (1.5%)                                                       | 43 (28.1%)                                                     | 4 (2.7%)                                                       | 48 (25.9%)                                                     | <0.001 † |

The 10-year ASCVD risk is defined only in participants without prior coronary artery disease or stroke. AFF: Atrial fibrillation or flutter. ASCVD: Atherosclerotic cardiovascular disease. P-values are presented for the comparison between the CHA<sub>2</sub>DS<sub>2</sub>-VASc score < 2 (N=146) and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 2 (N=185) groups among all AFF cases using † Chi-squared, ‡ Mann-Whitney U or ¥ Fisher's exact tests

**Table 4 – Frequency of anticoagulant use according to age and sex in participants with atrial fibrillation or flutter and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 2 in the ELSA-Brasil baseline**

| Atrial fibrillation or flutter and a CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥ 2 |                            |                                |                          |         |
|---------------------------------------------------------------------------------------|----------------------------|--------------------------------|--------------------------|---------|
| Variable                                                                              | By ECG recording<br>(N=32) | By self-report only<br>(N=153) | All AFF cases<br>(N=185) | p-value |
| Age (years)                                                                           |                            |                                |                          |         |
| ≤ 54                                                                                  | 1 / 3 (33.3%)              | 0 / 52 (0.0%)                  | 1 / 55 (1.8%)            | 0.013   |
| 55 – 64                                                                               | 6 / 11 (54.5%)             | 2 / 57 (3.5%)                  | 8 / 68 (11.8%)           |         |
| ≥ 65                                                                                  | 9 / 18 (50.0%)             | 2 / 44 (4.5%)                  | 11 / 62 (17.7%)          |         |
| Sex                                                                                   |                            |                                |                          |         |
| Male                                                                                  | 9 / 17 (52.9%)             | 3 / 56 (5.4%)                  | 12 / 73 (16.4%)          | 0.055   |
| Female                                                                                | 7 / 15 (46.7%)             | 1 / 97 (1.0%)                  | 8 / 112 (7.1%)           |         |

The frequency of anticoagulant use according to age and sex, considering all AFF cases with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 2 was compared using Fisher's exact tests.

have influenced our finding of low rates of stroke prevention, when we limited analyses to participants with a documented AFF in the baseline ECG recording, half of them still had not received anticoagulants.

Although concerning, these low stroke prevention prescription rates are not exclusive to our sample. A similar study conducted by Healey et al.<sup>12</sup> described that, by geographic region, 32% (North America, Western Europe, Australia, and the Middle East) to 70% (China) guideline-indicated patients did not receive oral anticoagulant therapy. In South America, where ELSA-Brasil is located, the frequency of non-prescription was 55%. Ogilvie et al.<sup>32</sup>

reported a systematic review of studies reporting the use of oral anticoagulants in atrial fibrillation outside of clinical trials. They found that 21/29 (72.4%) studies in patients with prior stroke or transient ischemic attack, as well as 5/9 (55.6%) studies in patients with high thromboembolic risk according to risk scores, reported prescriptions levels of below 60%.

The under-prescription of stroke prevention medication seems to be a more severe problem in women,<sup>33</sup> which is in accordance with our data. Khurshid et al.<sup>34</sup> analyzed electronic medical data from 4,388 patients with atrial fibrillation and found that women, when compared to men, received less anticoagulant therapy at 1, 3, and 6 months after atrial

fibrillation diagnosis. In addition, Emdin et al.<sup>35</sup> performed a systematic review and meta-analysis of 30 cohort studies and found that women, as compared to men, with atrial fibrillation had a higher risk of all-cause mortality, cardiovascular mortality, and stroke. These authors highlight that, besides the underuse of stroke prevention medication, other explanations for worse outcomes, such as the higher rates of adverse effects from anticoagulant<sup>36</sup> and antiarrhythmic<sup>37</sup> therapies in women are equally plausible. In addition, some authors have highlighted worse anticoagulation control in women receiving warfarin. For example, Sullivan et al.<sup>38</sup> analyzed data from 4,060 participants of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, and found that women, as compared to men, on warfarin spent significantly more time below the international normalized ratio (INR) therapeutic range (29% vs 26%). It is also important to note that, the ELSA-Brasil baseline assessment occurred from 2008 to 2010. At that time, the use of direct-acting oral anticoagulants for stroke prevention in AFF was very rare.

### Strengths and limitations

This study does have some strengths. We analyzed data from a large, multicenter sample of individuals who were not recruited from clinical settings. This reduces potential biases in the study of factors associated with atrial fibrillation and diagnosis and the prescription of stroke prevention medications, approximating our external validity to the general population. The comprehensive ELSA-Brasil protocol allowed for the analysis of medication use according to CHA<sub>2</sub>DS<sub>2</sub>-VASc thromboembolic risk scores. This study must also be interpreted within its context. As stated earlier, this study's case definition may be prone to self-reported information misclassifications. Although this strategy minimizes the under-recognition of paroxysmal atrial fibrillation, it is important to acknowledge that self-reported cases were an important proportion of all AFF cases, and this may have influenced some of our results. Data on the frequency of individuals within the INR therapeutic range or on bleeding risk scores was not available. However, we believe that the risk of high bleeding is unable to explain a substantial part of the lack of stroke prevention in this sample.

### Conclusions

In conclusion, a 2.5% frequency of AFF diagnosis was found at the ELSA-Brasil baseline assessment. Age, male

sex, peripheral artery disease, heart failure, or rheumatic fever diagnoses were associated with AFF. Almost 90% of the subsample of participants with AFF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  (50% considering only those diagnosed by ECG records) did not receive anticoagulants.

### Author Contributions

Conception and design of the research: Santos I S, Lotufo P A, Barreto SM, Ribeiro AL, Bensenor I M; Acquisition of data: Lotufo P A, Brant L, Pinto-Filho MM, Barreto SM, Ribeiro AL, Bensenor I M; Analysis and interpretation of the data: Santos I S, Lotufo P A, Brant L, Pinto-Filho MM, Pereira AC, Barreto SM, Ribeiro AL, Thomas GN, Lip GYH, Bensenor I M; Statistical analysis: Santos I S; Obtaining financing: Lotufo P A, Barreto SM, Ribeiro AL, Bensenor I M; Writing of the manuscript: Santos I S, Bensenor I M; Critical revision of the manuscript for intellectual content: Lotufo P A, Brant L, Pinto-Filho MM, Pereira AC, Barreto SM, Ribeiro AL, Thomas GN, Lip GYH.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

This study was partially funded by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology (Financiadora de Estudos e Projetos and CNPq National Research Council) (grants 01 06 0010.00 RS, 01 06 0212.00 BA, 01 06 0300.00 ES, 01 06 0278.00 MG, 01 06 0115.00 SP, 01 06 0071.00 RJ).

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário da USP under the protocol number 659/06. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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## \*Supplemental Materials

For additional information, please [click here](#).



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## Brazilian Population Presents Prevalence of Atrial Fibrillation Similar to Higher Income Countries, and a Low Use of Anticoagulation Therapy

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Short Editorial related to the article: Atrial Fibrillation Diagnosis using ECG Records and Self-Report in the Community: Cross-Sectional Analysis from ELSA-Brasil

Atrial fibrillation (AF) is the most incident arrhythmia and its frequency is increasing as a greater proportion of people over 60 years of age have been become a worldwide tendency.

There is an exponential increase of AF with the advancing of age from 50-59 years, of 5 fold in 60 – 69 years, of 7 fold in 70 – 79 years, and of 9 fold over 80 years.<sup>1</sup>

Men present a higher incidence of AF.<sup>1-3</sup>

A large survey in male veterans also showed ethnic differences in age-adjusted prevalence of AF: 3% in Hispanics, 3.4% in blacks, 3.6% in Asians, 5.2% in Pacific Islanders, 5.4% in Native Americans, and 5.7% in whites.<sup>4</sup>

Other risk factors for AF include a sedentary lifestyle, smoking, obesity, Diabetes Mellitus, obstructive sleep apnea, hypertension, alcohol consumption, coronary heart disease, and heart failure.<sup>5</sup>

A systematic review of studies published since 2015 showed that 30% of strokes were caused by AF.<sup>6</sup>

### Keywords

Atrial Fibrillation; Epidemiology; Prevalence; Risk Factors; Rate, Survival; Young Adult; Middle-Aged; Arrhythmias, Cardiac.

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**DOI:** <https://doi.org/10.36660/abc.20210562>

As observed from these initial considerations, AF is a potentially dangerous condition with a great impact on disability, death, and health costs.<sup>7</sup> The latter has been studied extensively by Barros & Silva et al.<sup>8</sup>

Brazilian age-adjusted mortality rate by ischemic stroke and its complications in 2019 was 28.62/100,000 inhabitants between 35 to 74 years of age (37.10 in men and 21.39 in women) (calculated from DATASUS and IBGE data with Joinpoint software)

On this issue, Santos et al.<sup>9</sup> presents the results of AF prevalence in an extensive Brazilian cohort – ELSA-Brasil: 15,105 civil servants from six Brazilian state capitals (São Paulo, Belo Horizonte, Porto Alegre, Salvador, Rio de Janeiro, and Vitória).<sup>10</sup>

AF frequency of 2.5% was similar to other international studies<sup>1,11</sup> as well as to a retrospective Brazilian study from the state of Minas Gerais.<sup>3</sup>

The main associated conditions with AF were heart failure (OR 7.35), coronary disease (OR 5.11), rheumatic fever (3.38), age increment (OR 1.05 per year), and hypertension (OR 1.44). The rate of anticoagulation therapy was very low, 7.25% in the basal condition. Although low, this anticoagulation frequency was higher than that found in the initial condition of KP-RHTYTHM (0.7%) but less than after diagnosis in that study (38%).<sup>12</sup>

In conclusion, the AF burden in the Brazilian population is similar to the global population and the poor anticoagulation rate in the self-reporting subjects, 85% of all cases, a bad consortium for public health.

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## Serum Thiol Levels and Thiol/Disulfide Homeostasis in Patients with Rheumatic Mitral Valve Disease and Healthy Subjects

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### Abstract

**Background:** Rheumatic mitral valve disease (RMVD) is the most common presentation of rheumatic heart disease (RHD). Inflammation and fibrosis processes also play significant roles in its pathogenesis. Recent studies showed that thiols and thiol-disulfide are promising novel oxidative stress markers.

**Objectives:** The present study aimed to evaluate differences in the serum thiol and thiol-disulfide levels in patients with RMVD and the control group.

**Methods:** Ninety-two patients with RMVD were enrolled in the study. Fifty-four healthy subjects, age, and gender-matched with the study group, were also included in the study as a control group. This study investigated thiol levels in patients with RMVD and the control group. P-values lower than 0.05 were considered statistically significant.

**Results:** The patients with RMVD presented higher systolic pulmonary artery pressure (SPAP) and left atrial (LA) diameter levels than the control group. Native thiol ( $407 \pm 83 \mu\text{mol/L}$  vs.  $297 \pm 65 \mu\text{mol/L}$ ,  $p < 0.001$ ) and total thiol ( $442 \pm 82 \mu\text{mol/L}$  vs.  $329 \pm 65 \mu\text{mol/L}$ ,  $p < 0.001$ ) levels were higher in the control group. Disulfide ( $16.7 \pm 4.9 \mu\text{mol/L}$  vs.  $14.8 \pm 3.7 \mu\text{mol/L}$ ,  $p = 0.011$ ) levels were higher in the group of patients with RMVD. A positive correlation was found between disulfide/native and disulfide/total thiols ratio with SPAP, LA diameter, and MS severity. Disulfide/total thiols ratio was significantly higher in patients with severe MS than with mild to moderate MS patients.

**Conclusions:** To the best of our knowledge, this is the only study of its kind that has evaluated thiol/disulfide homeostasis as a novel predictor, which was more closely related to RMVD and the severity of MS.

**Keywords:** Rheumatic Diseases; Mitral Valve Stenosis; Homeostasis; Thiol/Disulfide; Echocardiography/methods; Oxidative Stress.

### Introduction

Rheumatic heart disease (RHD) is a widely observed cardiovascular disease in children and adolescents.<sup>1</sup> Rheumatic mitral valve disease (RMVD) is the most common presentation of RHD.<sup>2</sup> A study in 2015 reported that the estimated number of RHD patients was 33.4 million worldwide.<sup>3</sup> In the PROVAR study, the authors screened 5,996 students, whose median age was 11.9 (range 9.0 to 15.0), with echocardiography. The authors reported that RHD prevalence was 42/1,000 in Brazilian children.<sup>4</sup>

Rheumatic heart disease occurs after an autoimmune reaction, which is triggered by an untreated streptococcal upper

respiratory tract infection. This process causes severe valvular injury in genetically susceptible subjects.<sup>5</sup> Despite the unknown pathophysiology of RHD, there are hypotheses that several autoimmune and inflammatory reactions, oxidative stress, immune system genes, and polymorphisms are related to RHD.<sup>5-9</sup>

Thiols are crucial antioxidant agents in human physiology. Thiol concentrations are lower in plasma. This occurs because thiols mostly consist of human plasma albumin with low-molecular-weight thiols, including cysteine (Cys), homocysteine, glutathione, cysteinyl glycine, and  $\gamma$ -glutamyl-cysteine.<sup>10</sup> The oxidative processes can transform thiols into many different molecules. The thiol-disulfide is one of the products of the oxidative reactions in which thiols are involved.<sup>11</sup> The oxidation of Cys residues may produce a reversible production of various disulfides, such as low-molecular-mass thiols and protein thiol molecules. Furthermore, disulfide residues can be converted into thiol groups to keep the thiol/disulfide homeostasis stable.<sup>12</sup> Therefore, thiols consist of a crucial part of the total amount of antioxidants and play a significant role in the antioxidant mechanism for radical oxygen species (ROS).<sup>13</sup>

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Manuscript received March 10, 2020, accepted July 13, 2020, accepted August 16, 2020

**DOI:** <https://doi.org/10.36660/abc.20200161>

The current studies demonstrated that the thiol-disulfide ratio had significant value as a promising oxidative stress marker.<sup>14,15</sup> Although the importance of thiol metabolism was evaluated in different cardiovascular diseases and procedures, such as myocardial infarction or coronary artery bypass surgery, its expression in RHD is unknown.<sup>14,16</sup> This study, due to the pathophysiological component of RVD, aimed to evaluate the thiol levels in RMVD patients and healthy subjects.

## Methods

Ninety-two patients with RMVD who were admitted to our cardiology clinic between April 2018 and December 2019 were enrolled in the study. Fifty-four healthy subjects, matched to patients, were also included in the study as a control group. Gender, age, body mass index (BMI), comorbidities, left ventricle ejection fraction, and smoking status were considered for the pairing of the groups.

Written informed consent was obtained for all participants. The exclusion criteria were patients with Marfan syndrome, bicuspid aortic valve, non-rheumatic mitral valve pathologies, or prior open-heart surgery. Furthermore, patients with liver, thyroid, and kidney diseases, blood disorders, connective tissue or inflammatory disease, any history of cancer, and acute or chronic infection were also excluded from the study.

The relevant demographic, anthropometric, and medical history data were recorded. Clinical information, such as Framingham's coronary risk factors (hypertension (HT), diabetes mellitus (DM), smoking, hyperlipidemia, and family history of coronary disease history), were also collected.

Transthoracic two-dimensional and color flow Doppler echocardiography was used in all patients using ultrasound with 2.5-MHz transducers (Toshiba SSH160A). The M-mode echocardiography was used to measure the left atrial diameter, and the planimetric and pressure half time methods to assess the mitral valve area. The transmitral gradient was defined with a continuous wave Doppler in an apical four-chamber view. Colour-flow Doppler was performed to observe the presence and severity of mitral regurgitation (MR). Pulmonary artery systolic pressure was measured by continuous-wave Doppler studies using the Bernoulli equation. The criteria for the diagnosis of RMVD included the mitral valve area  $\leq 2.5$  cm<sup>2</sup>, the presence of leaflet thickening, commissural fusion, and changing in the subvalvular area, detected by an echocardiogram.<sup>17</sup>

Blood samples were drawn from the antecubital vein during hospital admission. The blood samples of the patients and control groups were taken in the morning after a 12-hour fasting period. All blood samples were collected into tubes containing no additives. Serum was obtained after centrifugation at 1,500 g for 10 minutes and stored at -80°C until analysis.

Thiol/disulfide homeostasis was conducted by the procedure determined by Erel et al.<sup>18</sup> Subsequently, free functional thiol groups were obtained with the reduction of disulfide bonds. Sodium borohydride was applied as a reductant, and unused reductant was removed by formaldehyde. After 5, 5'-dithiobis-(2-nitrobenzoic) acid reaction, all thiol groups, both native and

reduced, were defined. Dynamic disulfide quantity ( $-S-S-$ ) was confirmed by half of the difference between the native and total thiols. After evaluating the magnitude of native thiol ( $-SH$ ) and disulfide ( $-S-S-$ ), the disulfide/native thiol ( $-S-S-/-SH$ ) ratio was calculated.<sup>18</sup>

## Statistical Analysis

The normality of data was analyzed using the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were presented as mean and standard deviation. The variables with non-normal distribution were presented as median (interquartile range), and categorical data as number and percentage. Independent samples t-test was used to compare groups for continuous data with normal distribution, whereas the Mann-Whitney U test was performed for variables with non-normal distribution. Categorical data were analyzed using the Chi-square or Fisher's Exact tests. The relations among the numerical and categorical variables were analyzed with Spearman correlation analysis. Differences were accepted as significant at the two-sided  $p < 0.05$  level. All statistical analysis was carried out using the Statistical Package for Social Sciences program (SPSS) for Windows version 22 (IBM SPSS Inc., Chicago, IL).

## Results

A total of 146 subjects, of which 92 had RMVD and 54 did not, were included in the study. The demographic, clinical, and laboratory data of the study groups are displayed in Table 1. In patients with RMVD, a total of 22 (24%) were male and 70 (76%) were female, whereas 15 (28%) patients were male and 39 (72%) were female in the control group. The mean age was  $48 \pm 10$  years and  $46.7 \pm 11.2$  years in the patients with RMVD and control groups, respectively. No differences were found between the groups in terms of age, gender, BMI, HT, DM, smoking, and other laboratory parameters. As expected, the patients with RMVD had higher systolic pulmonary artery pressure (SPAP) and left atrial (LA) diameter levels than in the control group.

Native thiol ( $407 \pm 83$   $\mu\text{mol/L}$  vs.  $297 \pm 65$   $\mu\text{mol/L}$ ,  $p < 0.001$ ) and total thiol ( $442 \pm 82$   $\mu\text{mol/L}$  vs.  $329 \pm 65$   $\mu\text{mol/L}$ ,  $p < 0.001$ ) levels were higher in the control group. Disulfide ( $16.7 \pm 4.9$   $\mu\text{mol/L}$  vs.  $14.8 \pm 3.7$   $\mu\text{mol/L}$ ,  $p = 0.011$ ) levels were elevated in patients with RMVD group. The mean disulfide/total thiol ratios and disulfide/native thiol ratios were higher in patients with RMVD group, while native thiol/disulfide ratios, and total thiol/disulfide ratios were higher in the control group. The levels of native thiol, total thiol, disulfide, disulfide/thiols, and thiols/disulfide ratio between the patients with and without RMVD are shown in Table 2.

Correlation analysis showed that there were positive correlations between disulfide levels and mitral stenosis severity (mitral valve area  $< 1.5$  cm<sup>2</sup>); between the disulfide/total and the native/thiol ratio with SPAP, LA diameter, and mitral stenosis severity. Furthermore, there were negative correlations between native thiol and total thiol with SPAP, LA diameter, and mitral stenosis severity. Correlation analysis of thiol and disulfide parameters with echocardiographic findings is listed in Table 3.

## Original Article

**Table 1 – Baseline Clinical, Demographic, and Laboratory Characteristics of The Patients with and without Rheumatic Mitral Valve Disease**

|                                                  |         | Control (n:54)      | RMVD (n:92)      | p                   |
|--------------------------------------------------|---------|---------------------|------------------|---------------------|
| Age<br>(Median,IQR1-IQR3)                        |         | 45 (39.3 - 54.5)    | 48 (42 - 55.8)   | 0.304 <sup>m</sup>  |
| Sex (n,%)                                        | Male    | 15 (28%)            | 22 (24%)         | 0.604 <sup>x²</sup> |
|                                                  | Female  | 39 (72%)            | 70 (76%)         |                     |
| DM (n,%)                                         | No      | 48 (89%)            | 88 (96%)         | 0.133 <sup>x²</sup> |
|                                                  | Yes     | 6 (11%)             | 4 (4%)           |                     |
| HT (n,%)                                         | No      | 46 (85%)            | 79 (86%)         | 0.492 <sup>x²</sup> |
|                                                  | Yes     | 8 (15%)             | 13 (14%)         |                     |
| Smoking (n,%)                                    | No      | 40 (74%)            | 58 (63%)         | 0.134 <sup>x²</sup> |
|                                                  | Yes     | 14 (26%)            | 34 (37%)         |                     |
| BMI<br>(Median,IQR1-IQR3)                        |         | 24 (22 - 25.8)      | 24 (21.9 - 25)   | 0.139 <sup>m</sup>  |
| Glucose (mg/dL)<br>(Median,IQR1-IQR3)            |         | 94 (88.5 - 102)     | 90 (21.9 - 25)   | 0.054 <sup>m</sup>  |
| Serum creatinine (mg/dL)<br>(Median,IQR1-IQR3)   |         | 0.8 (0.6 - 0.8)     | 0.7 (0.6 - 0.8)  | 0.128 <sup>m</sup>  |
| Hemoglobin(g/L)<br>(Median,IQR1-IQR3)            |         | 14 (13 - 14)        | 13.8 (12 - 14)   | 0.509 <sup>m</sup>  |
| WBC count (x1000/mm3)<br>(Median,IQR1-IQR3)      |         | 6.4 (5.9 - 7.3)     | 6.2 (6 - 7)      | 0.423 <sup>m</sup>  |
| Platelet count (x1000/mm3)<br>(Median,IQR1-IQR3) |         | 300 (254.5 - 348.8) | 301 (277 - 313)  | 0.766 <sup>m</sup>  |
| Total cholesterol (mg/dL)<br>(Median,IQR1-IQR3)  |         | 215 (195.3 - 235)   | 197 (195 - 225)  | 0.075 <sup>m</sup>  |
| LDL, (mg/dL)<br>(Median,IQR1-IQR3)               |         | 120 (103.3 - 125)   | 114 (100 - 121)  | 0.086 <sup>m</sup>  |
| HDL, (mg/dL)<br>(Median,IQR1-IQR3)               |         | 49 (45 - 55.8)      | 51 (45.8 - 72)   | 0.113 <sup>m</sup>  |
| Triglycerides (mg/dL)<br>(Median,IQR1-IQR3)      |         | 150 (90.8 - 185)    | 148 (64 - 150)   | 0.282 <sup>m</sup>  |
| LVEF,(%)<br>(Median,IQR1-IQR3)                   |         | 61 (60 - 66)        | 60 (62.8 - 66)   | 0.155 <sup>m</sup>  |
| LA, (mm)<br>(Median,IQR1-IQR3)                   |         | 36 (35 - 37)        | 43 (38 - 47)     | <0.001 <sup>m</sup> |
| SPAP, (mmHg)<br>(Median,IQR1-IQR3)               |         | 20 (18 - 20)        | 31 (27.8 - 39.3) | <0.001 <sup>m</sup> |
| Mo/S MR                                          | Absent  | 54 (100%)           | 60 (65%)         |                     |
|                                                  | Present | 0 (0%)              | 32 (35%)         |                     |
| Severe MS                                        | Absent  | 54 (100%)           | 77 (84%)         |                     |
|                                                  | Present | 0 (0%)              | 15 (16%)         |                     |
| P-MBVP History                                   |         | 0 (0%)              | 15 (16%)         |                     |
| Surgical VR                                      |         | 0 (0%)              | 0 (0%)           |                     |
| MVA                                              |         | -                   | 2.2 ± 1.3        |                     |
| RAVD                                             |         | 0 (0%)              | 47 (51%)         |                     |

BMI: body mass index; DM: diabetes mellitus; HDL: high-density lipoprotein; HT: hypertension; LA: left atrium; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; RMVD: rheumatic mitral valve disease; SPAP: systolic pulmonary artery pressure; WBC: white blood cell; Mo/S MR: moderate or severe mitral regurgitation; P-MBVP: percutaneous mitral balloon valvuloplasty; VR: valve replacement; MVA: mitral valve area; RAVD: rheumatic aortic valve disease (Stenosis or Regurgitation).

<sup>m</sup> Mann-Whitney U Test, <sup>x²</sup> Chi Square (χ²) Test

**Table 2 – The Level of Native Thiol, Total Thiol, Disulfide, Disulfide/Thiols, and Thiols/Disulfide Ratio Between the Patients with and without Rheumatic Mitral Valve Disease**

|                                                     | Control (n:54)     | RMVD (n:92)      | p                   |
|-----------------------------------------------------|--------------------|------------------|---------------------|
| Total Thiol, (mmol/L)<br>(Mean ± SD)                | 442±82             | 329±65           | <0.001 <sup>t</sup> |
| Native Thiol, (mmol/L)<br>(Mean ± SD)               | 407±83             | 298± 65          | <0.001 <sup>t</sup> |
| Disulfide, (mmol/L)<br>(Median,IQR1-IQR3)           | 15.1 (13.4 - 17.6) | 17 (14.8 - 19.9) | 0.011 <sup>m</sup>  |
| Disulfide/Total Thiol, %x100<br>(Median,IQR1-IQR3)  | 3.4 (2.8 - 4)      | 5.4 (4.3 - 6.6)  | <0.001 <sup>m</sup> |
| Disulfide/Native Thiol, %x100<br>(Median,IQR1-IQR3) | 3.7 (3 - 4.4)      | 5.8 (4.7 - 7.4)  | <0.001 <sup>m</sup> |

RMVD: Rheumatic mitral valve disease; <sup>m</sup> Mann-Whitney U Test; <sup>t</sup> t -test

**Table 3 – Correlation Analysis of Thiol and Disulfide Parameters with Echocardiographic Findings**

|                          |                | SPAB   | Severe MS | LA     |
|--------------------------|----------------|--------|-----------|--------|
| Native thiol             | Spearman's Rho | -.598  | -.319     | -.532  |
|                          | P              | <0.001 | <0.001    | <0.001 |
| Total thiol              | Spearman's Rho | -.596  | -.300     | -.549  |
|                          | P              | <0.001 | <0.001    | <0.001 |
| Disulfide                | Spearman's Rho | .135   | .188      | .107   |
|                          | P              | 0.106  | 0.023     | 0.201  |
| Disulfide / Native thiol | Spearman's Rho | .469   | .331      | .403   |
|                          | P              | <0.001 | <0.001    | <0.001 |
| Disulfide / Total thiol  | Spearman's Rho | .473   | .333      | .405   |
|                          | P              | <0.001 | <0.001    | <0.001 |

LA: Left atrium; MS: mitral valve stenosis; SPAB: Systolic pulmonary artery pressure

The level of native thiol, total thiol, disulfide, disulfide/thiols, and thiols/disulfide ratio between the patients with and without severe rheumatic mitral valve stenosis (RMVS) is listed in Table 4. No significant difference was observed in native thiol, total thiol, and disulfide between the patients who had mild to moderate MS and severe MS or percutaneous mitral valvuloplasty history. However, disulfide/total and disulfide/native thiols ratios were significantly higher in patients with severe MS or percutaneous mitral valvuloplasty history. On the other hand, any significant difference in native thiol, total thiol, disulfide levels, and disulfide/total and disulfide/native thiols ratios was not observed according to the patients' severity of mitral regurgitation.

## Discussion

Plasma thiol levels were significantly lower in patients with RMVD, when compared to the control group. Disulfide levels and the disulfide/thiols ratio were higher in patients with RMVD. To the best of our knowledge, this is the only study that has evaluated thiol/disulfide homeostasis as a new predictor, which was more closely related to RMVD and the severity of MS.

RHD and RMVD are the severe complications of acute rheumatic fever and lead to chronic valvular lesions causing the morbidity and mortality.<sup>2</sup> RHD holds a crucial part of the health burden in many developing countries.<sup>19</sup> RMVD has a complex mechanism, the main ones of which are chronic inflammation and autoimmune reactions.

The previous studies have reported convincing evidence that there has been a progressive inflammation in RHD, and this persistent inflammation has led to damage to the valvular tissue.<sup>7</sup> Several studies assessed chronic inflammation markers in RHD patients. Some of these studies showed that elevated serum levels of hsCRP and Pentraxin-3 could be considered as markers of inflammation in RMVD patients than in healthy subjects.<sup>20,21</sup> In a recent survey, the neutrophil-to-lymphocyte ratio (NLR) was significantly higher in patients with severe RMVD than in patients with mild to moderate RMVD.<sup>22</sup>

Recent studies have shown that there were possible interactions between interleukins and chronic inflammation, including RHD development. Davutoglu et al. and Bilik et al. demonstrated that patients with RMVD had elevated plasma levels of tumor necrosis factor-alpha (TNFα), IL-2, IL-6, IL-8, and IL-17, IL-23 as predictors of progressive inflammation

**Table 4 – The Level of Native Thiol, Total Thiol, Disulfide, Disulfide/Thiols and Thiols/Disulfide Ratio Between the Patients with and without Severe Rheumatic Mitral Valve Stenosis**

|                                              | Mild-Moderate MS (n:62) | Severe MS or P-MBVP History (n:30) | p                  |
|----------------------------------------------|-------------------------|------------------------------------|--------------------|
| Total Thiol, (mmol/L)<br>(Mean ± SD)         | 335±66                  | 317±62                             | 0.125 <sup>†</sup> |
| Native Thiol, (mmol/L)<br>(Mean ± SD)        | 304±67                  | 282±59                             | 0.215 <sup>†</sup> |
| Disulfide, (mmol/L)<br>(Mean ± SD)           | 17±5                    | 19±7                               | 0.093 <sup>†</sup> |
| Disulfide/Total Thiol, %x100<br>(Mean ± SD)  | 5.2±1.7                 | 6.1±2.1                            | 0.045 <sup>†</sup> |
| Disulfide/Native Thiol, %x100<br>(Mean ± SD) | 5.8±2.1                 | 7.1±3.7                            | 0.048 <sup>†</sup> |

MS: Mitral Stenosis; P-MBVP: Percutaneous Mitral Balloon Valvuloplasty; <sup>m</sup> Mann-Whitney U Test; <sup>†</sup> t -test

and autoimmune response than in healthy subjects.<sup>23,24</sup> In previous studies, plasma and tissue oxidative stress markers were investigated in patients with RHD. They determined that levels of advanced oxidation protein products were higher in RHD patients than in controls.<sup>25,26</sup> Furthermore, our study was the first to assess novel oxidative stress markers thiol-disulfide ratio role in patients with RHD.

Oxidative stress (OS) is the imbalance between reactive oxygen species (ROS) and antioxidant substances; it may be toxic to cells by leading to membrane lipid peroxidation and membrane injury.<sup>27,28</sup> Thiols are significant antioxidants and play a substantial role in the non-enzymatic elimination of ROS.<sup>10,13</sup> Although protein thiol oxidations have been considered undesirable side reactions of oxidative stress, the identification of redox-regulated proteins showed that reversible thiol modifications were important to adjust their activity to the prevailing redox conditions of the environment.<sup>29</sup> Defining the functional importance of thiol modifications remains a significant challenge in the field, and still requires biochemical studies in different cases and diseases.

Recently, the significance of disulfide/thiol homeostasis has been demonstrated by various studies. One of these studies, by Kundi et al.,<sup>14</sup> showed that the disulfide/thiol ratio elevated in AMI, and the authors concluded that this value could be used as a predictor for the detection of acute myocardial injury.<sup>14</sup> In another study, Topuz et al. demonstrated that thiol/disulfide homeostasis might change during acute pulmonary thromboembolism. Moreover, this might be related to impaired hemodynamic measurements.<sup>30</sup> Several studies reported that decreased thiol concentrations and thiol/disulfide ratio might be a crucial factor in the development of atherosclerosis, coronary artery ectasia (CAE), and chemotherapy-induced cardiac toxicity.<sup>15,31,32</sup> Briefly, the authors concluded that oxidative stress may well involve the main factor of pathogenesis. In our study, thiol levels and the thiol/disulfide ratio are related to RMVD and the severity of rheumatic mitral valve involvement, confirming the hypothesis that the rheumatic valve is the cause of oxidative stress in addition to chronic inflammation.

To the best of our knowledge, this is the first study to evaluate the relationship between thiol/disulfide homeostasis and its impacts on RHD, as well as the intensity of valve damage in patients with RMVD. Our findings showed that thiol/disulfide homeostasis could play an essential role in the pathophysiology of rheumatic valve damage. Definitive information about the topic could be provided with in-vivo and in-vitro tissue studies.

### Limitations

The present study has several limitations. First, a relatively small sample size restricted the generalizability of the findings of our research. The lack of follow-up data and serial changes in thiols, and the absence of simultaneous measurement of another novel autoimmune and inflammatory mediators are other limitations. Thiol/disulfide values did not compare with other enzymatic and non-enzymatic oxidative stress markers. Finally, the study could be enhanced by adding genetic polymorphisms in patients with RMVD.

### Conclusions

The present study is the first to show the association between thiol levels and thiol/disulfide homeostasis in patients with RMVD. Our findings demonstrated its possible role in the severity of valve damage and in the pathophysiology of RMVD.

### Author Contributions

Conception and design of the research: Korkmaz A, Gursay T; Acquisition of data: Doğanay B, Yildiz A; Analysis and interpretation of the data: Doğanay B; Statistical analysis: Korkmaz A, Yildiz A; Writing of the manuscript: Çöteli C; Critical revision of the manuscript for intellectual content: Basyigit F, Çöteli C, Guray U, Elalmis OU.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

There were no external funding sources for this study.

## Study Association

This study is not associated with any thesis or dissertation work.

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Ankara Numune TRH Clinical Research Ethic Committee under the protocol number E-16-1096. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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## Thiol Homeostasis in Rheumatic Heart Disease: Biomarker or Risk Factor?

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Short Editorial related to the article: Serum Thiol Levels and Thiol/Disulfide Homeostasis in Patients with Rheumatic Mitral Valve Disease and Healthy Subjects

Rheumatic fever and rheumatic heart disease (RHD) lesions result from a complex network of several genes and proteins that control innate and adaptive immune responses following a *Streptococcus pyogenes* pharyngo-tonsillitis. The succeeding inflammatory process leads to the development of cardiac lesions with high production of inflammatory cytokines leading to calcification and valvular fibrosis.<sup>1</sup> However, the cellular pathways beyond these immunoregulated phenomena have not been fully elucidated.

Oxidative stress is a biological condition marked by an imbalance between reactive oxygen species production and its reduction.<sup>2</sup> Disturbances in this redox balance can cause the overproduction of peroxides and free radicals that damage all cellular components, including proteins, lipids and DNA.<sup>3</sup>

Excessive oxidative stress also plays an important role in autoimmune diseases pathogenesis, increasing inflammation and modifying the immune tolerance.<sup>4</sup> There is a complex reciprocal relationship between oxidative stress, apoptosis and autophagy. This is especially relevant in the context of autoimmune disorders.<sup>5</sup> The role of oxidative stress in RHD is still unknown.

Thiol or sulphhydryl (–SH) is a highly active and versatile form of reduced sulfur in biomolecules. It is present in amino acids such as cysteine (Cys) in peptides and proteins and is particularly sensitive to redox reactions.<sup>6</sup> They may act as a crucial redox sensor as well as a switch able to modify protein function and interactivity post-translationally. The thiol proteome and thiol-oxidoreductases are emerging areas of investigation. Changes in thiol-disulfide redox state have been studied in different diseases such as cancer, neurodegenerative and cardiovascular.<sup>7</sup>

Oxidative processes can convert thiols into many different molecules. Thiol-disulfide is one of the products of oxidative reactions in which thiols are involved. Current studies demonstrated that the thiol-disulfide ratio might be of significant value as a promising oxidative stress marker.<sup>8</sup>

The study of serum thiols level and thiol-disulfide homeostasis accessed thiol levels in patients with RHD and healthy subjects. The authors showed a positive correlation between disulfide levels and the severity of mitral stenosis as well as between total and native disulfide/thiol ratio with pulmonary artery pressure, left atrium diameter, and mitral stenosis severity. The authors conclude that plasma thiol levels were significantly lower in patients with mitral valve disease (MVD) compared to the control group. Disulfide levels and the disulfide/thiol ratio were higher in patients with MVD.<sup>9</sup>

Given the complexity and multiple compartments of whole body organization, the term “organismal oxidative stress” can be inappropriate. Furthermore, the association between thiol redox shifts is likely associated with systemic factors, such as endothelial dysfunction, due to lipid-related inflammation, diabetes, systemic thrombotic tendency, and other unknown factors. In this regard, the question is if plasma oxidative shifts reflect a biomarker of the localized disease process itself rather than a risk factor for vascular and heart disease.<sup>10</sup>

In any case, the study highlighted a new investigation area of plasma thiols pools in RHD, bringing relevant information in the pathophysiology, disease stage and even prognosis. Further studies in valvular heart disease are needed to elucidate the pathophysiological mechanism in this target organ. Subsequently, it may be possible to correlate them with findings in plasma to obtain specific biomarkers finally.

### Keywords

Rheumatic Fever; Cardiovascular Diseases; Homeostasis; Sulphydril; Risk Factors; Biomarkers.

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**DOI:** <https://doi.org/10.36660/abc.20210693>

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# Risk of Death in the Elderly with Excessive Daytime Sleepiness, Insomnia and Depression: Prospective Cohort Study in an Urban Population in Northeast Brazil

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## Abstract

**Background:** The close relationship between sleep regulation and cardiovascular events is one of the main focuses of research in contemporary medicine. Sleep habits and characteristics interfere with the cardiac rhythm and also with life expectancy, especially in the elderly.

**Objective:** To estimate the risk of death and cardiovascular events in community-dwelling elderly individuals complaining of insomnia and excessive daytime sleepiness over eight years of follow-up.

**Method:** A prospective cohort was designed with 160 elderly, with the first wave occurring in 2009 and the second in 2017. Follow-up groups were determined by exposure or not to complaints of primary insomnia and excessive daytime sleepiness with or without snoring. The covariates gender, marital status, depression, hypertension and diabetes were controlled. The primary outcome was death and the secondary outcome was cardio-cerebrovascular events (CCV). Outcome risks were estimated by relative risk (RR) through Poisson regression, adopting  $\alpha \leq 0.05$ .

**Results:** There were 40 (25.97%; 19.04-32.89) deaths over the period and 48 (30.76%; 23.52-38.01) CCV. Men had a higher risk (RR = 1.88; 1.01-3.50) of death. Depression (RR = 2.04; 1.06-3.89), insomnia severity (RR = 2.39; 1.52-4.56) and sleep latency between 16-30 minutes (RR = 3, 54; 1.26-9.94) and 31-60 minutes (RR = 2.23; 1.12-4.47) increased the risk of death independently in community-dwelling elderly. CCV were predicted only in the hypertensive and / or diabetic elderly (RR = 8.30; 1.98-34.82).

**Conclusion:** Mortality in the elderly is influenced by the emotional state and difficulty in falling asleep, unlike CCVs, which are conditioned only by arterial and metabolic blood pressure conditions.

**Keywords:** Sleep Wake Disorders/complications; Aged; Psychological Dysfunction; Mortality; Depression.

## Introduction

Sleep disorders seem to be independently related to serious health outcomes, such as cardiovascular events<sup>1,2</sup> and death.<sup>3-5</sup> Insomnia and symptoms of excessive daytime sleepiness (EDS) stand out, which are sleep conditions possibly associated with neurophysiological<sup>6</sup> and psychogenic<sup>7</sup> changes.

There is consistent evidence pointing to the relationship between dysregulation of the sleep-wake cycle and cognitive functions with brain inflammatory processes,<sup>8</sup> as well as a deficit in circulatory automatism,<sup>9</sup> resulting in cardiac overload.

Complaints related to sleep are very common in patients with cardiac, neurological and psychological morbidities. The main ones, insomnia and EDS, are milder clinical manifestations and may appear previously or in the initial stages of more debilitating sleep disorders, such as obstructive sleep apnea.<sup>10</sup>

Recent studies in Brazil revealed an association between cardiovascular risk, insomnia and EDS.<sup>11</sup> In other contexts, Lee et al.<sup>12</sup> showed, in a cohort of coronary patients, that the presence of EDS was a predictive factor for future cardiovascular events when other intervening factors were controlled.<sup>12</sup> However, it is difficult to know whether EDS appeared before or after coronary disease.

Insomnia is also related to cardiovascular events. Like EDS, it has shown to be a potential risk factor for cerebrovascular events.<sup>2</sup> Findings indicate that insomnia is associated with general mortality in men only, although it differs according to the contexts.<sup>13</sup>

In addition to these clinical conditions, either in an associated or independent manner, several parameters related to sleep may influence the occurrence of death and cardiovascular events, such as sleep efficiency, sleep

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Manuscript received February 04, 2020, revised manuscript July 06, 2020, accepted August 16, 2020

**DOI:** <https://doi.org/10.36660/abc.20200059>

duration, use of sleeping medications and involuntary body movements.<sup>13</sup> There is also the interaction with non-modifiable factors, such as gender and modifiable factors such as behavioral, lifestyle and emotional characteristics. Moreover, there are also social factors, such as level of schooling and social strata, which suggest a relationship with changes in the biological sleep rhythm.<sup>14</sup>

However, the evidence of these relationships in the Brazilian population is incipient, mainly in biologically and socially vulnerable subgroups, such as the elderly, whose proportion in the population has grown steadily even in regions with greater underdevelopment characteristics, as in the northeast region.

Thus, this article aims to investigate how the presence of insomnia and / or EDS complaints, as well as the parameters of sleep quality and depressive symptoms influence mortality and cardiovascular events in elderly community members in the long-term. We hypothesize that the presence of these dyssomnias, alone or in conjunction with depressive symptoms, modulate the likelihood of death and cardiovascular events in the elderly.

## Method

### Design

A prospective cohort study was performed. The base population for the research consists of elderly individuals living in the urban area of the city of Campina Grande, state of Paraíba, Brazil. The sample consisted of elderly participants from a cross-sectional survey carried out in 2009, developed by Lopes, Dantas and Medeiros,<sup>11</sup> in the same city and which was considered the first wave of data collection with 160 participants, designed for a study on the prevalence of EDS and insomnia. The second wave of data collection took place in 2017 to estimate the occurrence of death outcomes and cardiovascular events.

The sample size to estimate the risk of death in the exposure group (with EDS and/or insomnia), in relation to the group without exposure, considered an estimated outcome of 10% in the group without exposure and 30% in the group under exposure,<sup>10</sup> together with a 95% confidence interval to minimize type I error and 80% test power to minimize the occurrence of type II error. Thus, a minimum of 48 participants in each group was necessary for the follow-up to be able to adequately estimate the outcomes. In any case, 114 elderly people were identified in the first wave as belonging to the exposed group.

It is justified to consider EDS and insomnia exposure together due to the frequent concomitant occurrence of both in the investigated sample, in addition to being symbiotic events in the elderly.

The sample included individuals of both genders over the age of 60, screened in the first wave in 2009 and available to participate in the study. Individuals unable to answer questions and to be physically assessed were excluded from the sample.

The choice of participants in the first wave was randomly carried out in the 49 neighborhoods of the urban perimeter

established by the city of Campina Grande-PB. The streets, selected by drawing lots, were crossed from one end to the other, on both sides, skipping nine households from the corner chosen as the starting point, according to the method used by the Brazilian Institute of Geography and Statistics (IBGE, *Instituto Brasileiro de Geografia e Estatística*) for randomization in this municipality. This alternation was given by the ratio between the total number of households in the neighborhood and the number of elderly people to be visited in that neighborhood. If there were no elderly persons in the selected household, the nearest one was enrolled. When there was more than one elderly person in the household, data collection was carried out with all of them.

### Variables and Data Collection Instruments

The participants completed, in the first wave, the socio-demographic form containing data on gender (male or female), age (in years), level of schooling (illiterate, elementary school, high school, higher education), marital status (with or without a partner). In addition, some information about the presence of chronic health conditions, such as hypertension and diabetes, was investigated for the purpose of confounder control, as they are the most prevalent chronic diseases in the elderly. The diagnosis of hypertension and / or diabetes was dichotomously identified in the medical records of the health units, as well as the inclusion in the Hiperdia program. All variables of the first wave were independent variables in the cohort.

To assess the presence of excessive daytime sleepiness, the Epworth Sleepiness Scale (ESS) or Fatigue Scale<sup>15</sup> was used. Those with a score > 10 on the ESS scale were identified with EDS; scores between 11 and 16 were considered mild cases, and above the last score were considered severe cases. Complaints of insomnia were subjectively assessed based on the answers to the questions regarding the difficulty of initiating sleep, staying asleep and difficulty returning to sleep for no apparent reason.<sup>15</sup> Thus, a composite indicator was created that assessed the presence of EDS and/or insomnia called sleep disorder indicator.

Sleep latency was determined based on the Pittsburgh Sleep Quality Index (PSQI) domains. The PSQI assesses sleep quality in seven domains: subjective quality, sleep latency, sleep duration, sleep efficiency, sleep disorders, use of sleeping medication and dysfunction during the day. The score ranges from 0 to 20, with individuals with a score greater than 5 being considered having poor sleep quality. Snoring was estimated by the Stanford Snoring Scale.<sup>15</sup>

The body mass index (BMI) was measured in all participants, based on the individual's height and mass. Weight was obtained using a GEOM™ scale, model B8030, with a capacity of 150 kg and sensitivity of 100 g. Height was measured using a Wiso® adult compact measure tape stadiometer graded in centimeters. If the participant was unable to walk to the scale or adopt the orthostatic posture to have the height measured, they were excluded from the study. In addition, abdominal circumference (AC) data were collected using an inelastic measuring tape, divided into low and high cardiovascular risk participants, with the following references as the cutoff point: <84 cm for women and <104 cm for men.<sup>16</sup> A dichotomous

nutritional index was constructed as adequate (BMI <27 kg/m<sup>2</sup> and/or low cardiovascular risk) and inadequate (BMI ≥27 kg/m<sup>2</sup> and/or high cardiovascular risk).

To assess the existence of depressive symptoms in the elderly, the Sheikh and Yesavage<sup>17</sup> Geriatric Depression Scale was used, where scores from 0 to 10 are equivalent to normal status, 11 to 20 refer to mild depressive conditions and 21 to 30 points indicate possible moderate/severe depression.

The researchers were adequately trained to use the data collection instruments reliably before applying the socioeconomic questionnaire, collecting anthropometry data, applying the Geriatric Depression Scale, Epworth Sleepiness Scale and the PSQI.

The second wave of the survey was carried out in 2017. The researchers used the telephone contact strategy initially, followed by home visits, visits to the Basic Health Unit and contact with key informants, such as neighbors and relatives to locate participants and outcomes. After the participants were located, in order to estimate the outcomes, the participant's vital state (alive or dead) and the occurrence of cardiovascular and cerebrovascular disorders were verified. The events of acute myocardial infarction, arrhythmias, valvulopathies, transient ischemic attack, ischemic or hemorrhagic stroke, among others, were self-reported by the participants or their family members and confirmed from/added to the medical records in the health units and or death certificates. for those already deceased.

#### Data analysis

The inferential analysis was performed with death as the primary outcome and cardio-cerebrovascular events as the secondary one, controlling the effect of covariates such as hypertension and diabetes. The relative risk for the independent variables of the EDS/insomnia group was estimated, as well as depressive symptoms, sleep quality parameters and obesity using the Generalized Linear Modeling with a model based on Poisson distribution and the linear logarithmic function. In this inferential situation, a 5% significance level was adopted to minimize type I error. The free software R was used to carry out the analysis of descriptive and inferential data.

The research was submitted to the Research Ethics Committee of Hospital Universitário Onofre Lopes, in compliance with Resolution 466/2012 of the National Health Council, obtaining the approval number 2,048,708.

#### Results

The 160 elderly participants were aged between 60-98 years, with a mean age of 72.16 ± 7.84 years; 112 (71.2%) were women and 135 (84.4%) had complete elementary school as their highest level of schooling. The average follow-up time was 5.3 years. There were only four follow-up losses.

In this sample, 118 individuals (73.75%: 66.93-80.56) had normal results regarding EDS; 30 (18.75%: 12.70-24.79) had a mild degree of EDS and 12 (7.50 %: 3.41-11.58) had the severe form of EDS. Insomnia was present in 98 (54.9%) of the elderly, 65 (43.0%) of which at the moderate / severe

stage. The outcome death was recorded for 40 elderly people (25.97%: 19.04-32.89) and the outcome cardiovascular events occurred in 48 of them (30.76%: 23.52-38.01). Table 1 describes the distribution of the other independent variables as well as the predictive modeling.

The Poisson modeling revealed, after adjustment, that among the studied independent variables, only the presence of depressive symptoms is considered a risk factor for death in elderly community members. Elderly people with depression were 2.39 times (95%CI: 1.52-4.56) more likely to die than those without depressive symptoms. On the other hand, the composite indicators of nutritional status, sleep disorders, sleep quality and even the presence of hypertension/diabetes were not able to demonstrate any influence on mortality during the eight-year follow-up of the study (Table 2).

When analyzing the variables that make up the composite indicators included in the previous model, a new distribution for the death outcome was identified (Table 3). Having depressive symptoms remained a risk factor for death. However, it is clear that the prediction of death is higher in males, 88% more than in women (RR = 1.88; 1.01-3.50), and also in the elderly with a partner (RR=2.10; 1.20-3.68). Similarly, sleep latency indicators between 16-30 minutes (RR=2.23; 1.12-4.47) and between 31-60 minutes (RR=3.54; 1.26-9.94) predict more deaths than those who fall asleep in up to 15 minutes. Having mild insomnia was also considered a predictor of death in this sample, and those with a mild degree have 2.30 (95%CI: 1.08-4.89) more chances of dying.

For the outcome of a cardio-cerebrovascular event in the eight-year follow-up, the only independent variable that showed a predictive capacity for this outcome was the hypertension / diabetes indicator. Hypertensive and / or diabetic elderly people were almost six times more likely (RR=5.72; 95%CI: 1.87-17.46) to have cerebral cardiovascular disorders than normotensive elderly individuals and those with normal glycemic metabolism. The composite and segregated indicators of nutritional status, sleep disturbance and sleep quality did not reveal any effect in the analyzed period (Table 4).

#### Discussion

It is evident in the present study that the assessed outcomes of death and cardiovascular events are predicted by different exposures. The death of elderly community members is strongly influenced by the occurrence of depressive symptoms, with death being more common in men and in individuals living with a partner. Among the sleep characteristics, the high latency to initiate sleep and the severity of insomnia stand out as risk factors for death in the elderly. On the other hand, only hypertensive and/or diabetic elderly people showed a higher risk of developing cardiovascular outcomes.

Several studies have clarified the higher risk of death among men, mainly due to chronic conditions such as cardiovascular diseases in the elderly.<sup>18</sup> Marital status is also identified as a condition related to health vulnerability, since individuals without partners usually have less social support

## Original Article

**Table 1 – Descriptive analysis, unadjusted and adjusted model for the risk of death in the elderly in the municipality of Campina Grande, Paraíba, Brazil, 2009-2017**

| Variables                       | Risk of death    |      |           |                |           |
|---------------------------------|------------------|------|-----------|----------------|-----------|
|                                 | Unadjusted Model |      |           | Adjusted Model |           |
|                                 | n (%)            | RR   | 95%IC     | RR             | 95% IC    |
| <b>Gender</b>                   |                  |      |           |                |           |
| Male                            | 44 (28.2)        | 1.69 | 1.01-2.87 | 1.73           | 0.92-3.28 |
| Female                          | 112 (71.8)       | 1    |           | 1              |           |
| <b>Marital Status</b>           |                  |      |           |                |           |
| With partner                    | 37 (23.7)        | 1.59 | 0.91-2.77 | 1.50           | 0.86-2.62 |
| Without partner                 | 119 (76.3)       | 1    |           | 1              |           |
| <b>Depression</b>               |                  |      |           |                |           |
| Yes                             | 66 (42.3)        | 1.66 | 0.97-2.84 | 2.39           | 1.52-4.56 |
| No                              | 90 (57.7)        | 1    |           | 1              |           |
| <b>Nutritional Index</b>        |                  |      |           |                |           |
| Inappropriate                   | 36 (23.1)        | 0.76 | 0.42-1.38 | 1.12           | 0.58-2.18 |
| Adequate                        | 120 (76.9)       | 1    |           | 1              |           |
| <b>Hypertension/Diabetes</b>    |                  |      |           |                |           |
| Yes                             | 114 (73.1)       | 0.86 | 0.48-1.53 | 0.84           | 0.46-1.51 |
| No                              | 42 (26.9)        | 1    |           | 1              |           |
| <b>Sleep Disorder Indicator</b> |                  |      |           |                |           |
| Insomnia /EDS                   | 114 (81.3)       | 0.91 | 0.40-2.07 | 0.62           | 0.33-1.16 |
| Normal                          | 46 (28.7)        | 1    |           | 1              |           |
| <b>PSQI</b>                     |                  |      |           |                |           |
| Good                            | 62 (45.9)        | 0.78 | 0.43-1.41 | 0.62           | 0.33-1.16 |
| Bad                             | 73 (54.1)        | 1    |           | 1              |           |

95%CI: 95% confidence interval; RR: relative risk; EDS: excessive daytime sleepiness; PSQI: Pittsburg Sleep Quality Index.

and greater predisposition to harmful health events, such as death.<sup>19</sup> However, our findings suggest that elderly people with a partner are more vulnerable to death. The suggested explanatory hypothesis is based on the characteristics of the studied population, where the possibility of interaction between low socioeconomic conditions and low social support overburdening the spouses with reciprocal or vulnerable care. Data from the National Health Survey also point to a greater occurrence of a decline in sleep repair in individuals with a partner in Brazil.

It was shown that depressive symptoms in the elderly are risk factors for death. Depressive symptoms predicted death events for all causes, showing an interaction with the male gender.<sup>20</sup> It was also identified that depressive symptoms are predictive of mortality from cardiac ischemia in a cohort of the general population in England,<sup>21</sup> which corroborates evidence that indicates depression as the main chronic morbidity that currently affects the elderly<sup>22</sup> and that may have a direct effect or interaction with other pathological mechanisms.

Depressive conditions are usually related to sleep disorders. Lima et al.<sup>23</sup> reported that elderly women with fewer hours of sleep had worse mental health indicators

regarding the emotional aspects in a population study in Brazil.<sup>23</sup> Symptoms of insomnia and drowsiness are predictive of depression. It is possible that these conditions establish a feedback cycle that culminates in the death outcome.<sup>3</sup>

Depression as a predictor of death in the elderly is related to the worsening of chronic comorbidities.<sup>24</sup> Depression in the elderly, when associated with chronic morbidities, makes it difficult to manage other conditions, such as diabetes and hypertension, for example, especially regarding adherence to treatment and self-care.<sup>25</sup> Additionally, it also changes both pain<sup>26</sup> and general health status<sup>4</sup> perception, creating clinical manifestations that are oversized in relation to the real pathophysiological problem.

Our findings point to an exposure to the risk of death produced by increased sleep latency and the severity of insomnia in the elderly. Similarly, Lallukka et al.<sup>3</sup> revealed that in Norway and Finland, insomnia increases the likelihood of death in men,<sup>3</sup> as well as observed in the United States,<sup>27</sup> mainly due to their difficulty in initiating sleep. Insomnia is strongly associated with other factors that predict death, such as reduced or elevated sleep duration<sup>28</sup> and depression in the elderly. On the other hand, Chen et al.<sup>29</sup> identified independence between insomnia and death events in elderly

**Table 2 – Adjusted model segregated in specific sleep morbidities for the risk of death in the elderly in the city of Campina Grande, Paraíba, Brazil, 2009-2017**

| Variables                    | n (%)      | Risk of death  |           |
|------------------------------|------------|----------------|-----------|
|                              |            | Adjusted Model |           |
|                              |            | RR             | 95% CI    |
| <b>Gender</b>                |            |                |           |
| Male                         | 44 (28.2)  | 1.88           | 1.01-3.50 |
| Female                       | 112 (71.8) | 1              |           |
| <b>Marital Status</b>        |            |                |           |
| With partner                 | 37 (23.7)  | 2.10           | 1.20-3.68 |
| Without partner              | 119 (76.3) | 1              |           |
| <b>Depression</b>            |            |                |           |
| Yes                          | 66 (42.3)  | 2.04           | 1.06-389  |
| No                           | 90 (57.7)  | 1              |           |
| <b>Hypertension/Diabetes</b> |            |                |           |
| Yes                          | 114 (73.1) | 1.19           | 0.54-2.60 |
| No                           | 42 (26.9)  | 1              |           |
| <b>Nutritional Index</b>     |            |                |           |
| Inappropriate                | 36 (23.1)  | 1.27           | 0.59-2.71 |
| Adequate                     | 120 (76.9) | 1              |           |
| <b>Sleep Latency</b>         |            |                |           |
| 60 min or more               | 22 (16.2)  | 1.68           | 0.74-3.81 |
| 31-60 min                    | 19 (14.0)  | 3.54           | 1.26-9.94 |
| 16-30 min                    | 31 (22.8)  | 2.23           | 1.12-4.47 |
| Less than 15 min             | 64 (47.1)  | 1              |           |
| <b>Severity of Insomnia</b>  |            |                |           |
| Moderate/Severe              | 65 (43.0)  | 0.94           | 0.29-2.96 |
| Mild                         | 33 (21.9)  | 2.30           | 1.08-4.89 |
| Without insomnia             | 53 (35.1)  | 1              |           |
| <b>Snoring severity</b>      |            |                |           |
| Excessive                    | 38 (26.2)  | 0.69           | 0.31-1.53 |
| Mild                         | 54 (37.2)  | 1.24           | 0.58-2.65 |
| Without Snoring              | 53 (36.6)  | 1              |           |
| <b>EDS</b>                   |            |                |           |
| Moderate/Severe              | 12 (7.7)   | 1.08           | 0.43-2.68 |
| Mild                         | 29 (18.6)  | 0.60           | 0.24-1.53 |
| Without EDS                  | 115 (73.7) | 1              |           |

95%CI: 95% confidence interval; RR: relative risk; EDS: excessive daytime sleepiness.

Asian people in nine years of follow-up.<sup>29</sup> Such discrepancies may be due to contextual differences or insufficient time of follow-up for the outcome to occur.

Unlike other studies, the composite indicator of excessive daytime sleepiness and insomnia complaints, as well as its single indicators, are not predictive factors for cardiovascular events. However, Wu et al.<sup>2</sup> showed in a cohort from Taiwan that insomnia increases the risk of

cerebrovascular event, especially in young adults compared to the elderly. Cardiac events were also predicted by the presence of insomnia symptoms in other epidemiological findings.<sup>10,30</sup>

As for the outcome of cardiovascular events, our data do not indicate sleep or emotional conditions as risk factors. The only identified health conditions that were risk predictors were hypertension and / or diabetes in the

**Table 3 – Predictive model for the risk of cardio-cerebrovascular event in the elderly in the city of Campina Grande, Paraíba, Brazil, 2009-2017**

| Variables                       | Risk of CC       |            |                |            |
|---------------------------------|------------------|------------|----------------|------------|
|                                 | Unadjusted Model |            | Adjusted Model |            |
|                                 | RR               | 95% CI     | RR             | 95% CI     |
| <b>Gender</b>                   |                  |            |                |            |
| Male                            | 1.19             | 0.72-1.98  | 1.23           | 0.69-2.21  |
| Female                          | 1                |            | 1              |            |
| <b>Marital Status</b>           |                  |            |                |            |
| With partner                    | 0.98             | 0.55-1.72  | 1,03           | 0.58-1.82  |
| Without partner                 | 1                |            | 1              |            |
| <b>Depression</b>               |                  |            |                |            |
| Yes                             | 1.14             | 0.71-1.83  | 1,29           | 0.78-2.15  |
| No                              | 1                |            | 1              |            |
| <b>Nutritional Index</b>        |                  |            |                |            |
| Inappropriate                   | 0.64             | 0.33-1.25  | 0,94           | 0.55-1.62  |
| Adequate                        | 1                |            | 1              |            |
| <b>Hypertension /Diabetes</b>   |                  |            |                |            |
| Yes                             | 4.43             | 1.69-11.64 | 5,72           | 1.87-17.46 |
| No                              | 1                |            | 1              |            |
| <b>Sleep Disorder Indicator</b> |                  |            |                |            |
| Yes                             | 0.72             | 0.32-1.63  | 0,66           | 0.31-1.38  |
| No                              | 1                |            | 1              |            |
| <b>PSQI</b>                     |                  |            |                |            |
| Good                            | 1.27             | 0.76-2.10  | 1,36           | 0.82-2.27  |
| Bad                             | 1                |            | 1              |            |

CC: Cardio-Cerebrovascular Events; 95%CI: 95% confidence interval; RR: relative risk; EDS: excessive daytime sleepiness; PSQI: Pittsburg Sleep Quality Index.

elderly in the analyzed period. The scientific literature had already shown, with enough support, the deleterious effects that systemic arterial hypertension and diabetes have on the contemporary society, being a robust risk factor or component for ischemic<sup>31</sup> and hemorrhagic cerebrovascular events, cardiac ischemia and metabolic syndrome.<sup>32</sup>

Some points deserve to be highlighted when interpreting our findings. Despite the methodological rigor in the follow-up planning, important social variables such as income, social support network or social status were not controlled, which would well reflect the contextual aspects involved in exposures and outcomes. The low level of schooling in the studied population did not allow the observation of good variability regarding this characteristic and, therefore, greater inferences about its effects. The lack of good health knowledge and/or access to health services in the sample prevented a more accurate identification of possible subclinical cardiovascular events, which were identified by self-report. The lack of a diagnostic test for sleep apnea made it impossible to control the effect of this health condition on its likely interaction with sleep characteristics. Finally, the adjustment of covariates was limited by the sample size.

However, important information was obtained for the assessed elderly population, located on the peripheries of large urban centers in Brazil, in a region with peculiar sociodemographic and economic characteristics, and with few follow-up studies for vulnerable subpopulations. Thus, the identification of the independent effects that sleep and depressive symptoms have on mortality in the elderly are of considerable importance for health policies aimed at the elderly, especially for public and clinical planning. This information will be useful to support decision-making regarding the organization of care for the elderly, mainly to mitigate the predisposing vulnerabilities related to their functional capacity and survival.

## Conclusion

We identified in the assessed sample independent effects that depressive symptoms, sleep latency and insomnia severity have on the mortality of elderly people. Such conditions are characterized by their modifiable capacity and, therefore, the possibility of minimizing the probability of death if they are counteracted by appropriate management and at the adequate level of care. There are also the effects

**Table 4 – Predictive model segregated in specific sleep morbidities for the risk of cardio-cerebrovascular events in the elderly in the city of Campina Grande, Paraíba, Brazil, 2009-2017**

| Variables                    | Risk of CC     |            |
|------------------------------|----------------|------------|
|                              | Adjusted Model |            |
|                              | RR             | 95%CI      |
| <b>Gender</b>                |                |            |
| Male                         | 1.38           | 0.59-3.21  |
| Female                       | 1              |            |
| <b>Marital Status</b>        |                |            |
| With partner                 | 1.32           | 0.62-2.82  |
| Without partner              | 1              |            |
| <b>Depression</b>            |                |            |
| Yes                          | 1.32           | 0.67-2.59  |
| No                           | 1              |            |
| <b>Hypertension/Diabetes</b> |                |            |
| Yes                          | 8.30           | 1.98-34.82 |
| No                           | 1              |            |
| <b>Nutritional Index</b>     |                |            |
| Inappropriate                | 1.18           | 0.58-2.41  |
| Adequate                     | 1              |            |
| <b>Sleep Latency</b>         |                |            |
| 60 min or more               | 1.03           | 0.40-2.62  |
| 31-60 min                    | 1.34           | 0.50-3.55  |
| 16-30 min                    | 1.09           | 0.45-2.59  |
| Less than 15 min             | 1              |            |
| <b>Severity of Insomnia</b>  |                |            |
| Moderate/Severe              | 1.35           | 0.55-3.33  |
| Mild                         | 2.14           | 0.84-5.42  |
| Without insomnia             | 1              |            |
| <b>Snoring severity</b>      |                |            |
| Excessive                    | 0.99           | 0.41-2.41  |
| Mild                         | 0.96           | 0.44-2.07  |
| Without Snoring              | 1              |            |
| <b>EDS</b>                   |                |            |
| Moderate/Severe              | 0.79           | 0.26-2.43  |
| Mild                         | 0.74           | 0.28-1.97  |
| Without EDS                  | 1              |            |

CC: Cardio-Cerebrovascular Events; 95%CI: 95% confidence interval; RR: relative risk; EDS: excessive daytime sleepiness.

related to the issue of the male gender being more prone to death. This refers to the need of sectoral strategies related to both health services access and work conditions, as well as social assistance to resolve inequities.

As for the cardio-cerebrovascular events, only the presence of hypertension and/or diabetes increased their risk in elderly community members. Although they are well-known risk factors, there are gaps in the appropriate management of

these conditions when it comes to adherence to treatment and access to health services and goods, which are influenced by social issues related to income, level of schooling and gender, aiming to achieve better results in public health.

### Author Contributions

Conception and design of the research: Lopes JM, Oliveira AGRC; Acquisition of data: Lopes JM, Galvão FD; Analysis and

interpretation of the data; Statistical analysis; Writing of the manuscript; Critical revision of the manuscript for intellectual content: Lopes JM, Oliveira AGRC, Galvão FD.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Sources of Funding

There were no external funding sources for this study.

### Study Association

This article is part of the thesis of master submitted by Johnnatas Mikael Lopes, from Programa de Pós-Graduação em Saúde Coletiva da Universidade Federal do Rio Grande do Norte.

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## Active Assessment of Sleep and Depression for elderly Patients in the Outpatient Cardiology Setting: What Are We Waiting for?

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Short Editorial related to the article: *Risk of Death in the Elderly with Excessive Daytime Sleepiness, Insomnia and Depression: Prospective Cohort Study in an Urban Population in Northeast Brazil*

The relationships between sleep disturbances, depression and cardiovascular disease have gained growing interest in the last decades. Most evidence available suggests that several sleep disturbances (including sleep deprivation, insomnia and obstructive sleep apnea) are not only innocent bystanders, but may contribute to increase the cardiovascular risk.<sup>1-3</sup> The prevalence and impact of sleep disorders may vary depending on some clinical characteristics (for instance: age, gender and comorbidities). Aging is clearly a risk factor for developing sleep disturbances; consistent evidence have shown greater number of complaints associated with sleep with aging,<sup>4</sup> including insomnia<sup>5</sup> and obstructive sleep apnea.<sup>2,3</sup> The reduction in the number of hours of sleep and poor sleep quality may impair multiple domains related to the quality of life in the elderly.<sup>4-6</sup> Similarly, depression is associated with several cognitive and cardiovascular consequences.<sup>7</sup> Based on the biological plausibility linking sleep disorders and depression with cardiovascular risk,<sup>7,8</sup> and the high prevalence of cardiovascular diseases among elderly, it is reasonable to assume that sleep disorders add to the high cardiovascular burden observed in this subset of patients.

In this issue of the *Arquivos de Brasileiro de Cardiologia*, Lopes et al.<sup>9</sup> reported a prospective cohort study of 160 elderly patients (between 60 and 98 years old) aiming to estimate the risk of death and cardiovascular events after eight years of follow-up (from 2009 to 2017) in those who presented insomnia and excessive daytime sleepiness detected at baseline. Excessive daytime sleepiness, sleep quality and presence of depressive symptoms were evaluated by the Epworth Sleepiness scale, the Pittsburgh Sleep Quality Index and the Sheikh and Yesavage Geriatric Depression Scale, respectively.

The proposed cardiovascular endpoints evaluated eight years later (myocardial infarction, arrhythmias, valvulopathies, transient ischemic attack and ischemic or

hemorrhagic stroke) were self-reported by the participants or their families, and confirmed by reviewing the medical records in the respective health centers. Deaths were adjudicated using death certificates. In the follow-up, 40 deaths and 48 cardiovascular events (including cerebrovascular events) occurred in the period. The authors found that men had an 88% increased risk of death as compared to women. In addition, depression (RR=2.04; 95% CI: 1.06-3.89), the severity of insomnia (RR=2.39; 95% CI: 1.52-4.56), and sleep latency of 16-30 minutes (RR=3.54; 95% CI: 1.26-9.94) and 31-60 minutes (RR=2.23; 95% CI: 1.12-4.47) were independently associated with increased risk of death in community-dwelling elderly. Non-fatal cardiovascular and cerebrovascular events were predicted by hypertension and diabetes only. The authors argued that the association of higher mortality in men is associated with the fact that they have a higher rate of chronic diseases, such as cardiovascular diseases. Consistently, data from the Brazilian population demonstrate the difference in the prevalence of cardiovascular disease and mortality between genders, with a higher rate in men.<sup>10</sup>

Additionally, the current study reinforces the negative role of several sleep disturbances<sup>2,3</sup> and depression<sup>11,12</sup> in elderly patients. The potential mechanisms connecting sleep disturbances and depression with mortality are multiple including changes in autonomic nervous system modulation, increased sympathetic activity, systemic inflammation and atherogenesis. Moreover, disruption of some brain regulatory systems, for example hypothalamic–pituitary–adrenal axis and circadian variation of cortisol and melatonin, may contribute to this association.<sup>1</sup> Depression is frequently associated with poverty and low education level, which impose significant limitations in the access to health services.<sup>12</sup> These patients may be predisposed to lower adherence to chronic treatments, and changes in sleep patterns and lifestyle.<sup>11,12</sup>

The major contributions of the current investigation are related to the prospective study design and the location of the study population. The sleep patterns and depression status of the Northeast Brazilian population are poorly explored. The high percentage of poverty, low education and social vulnerability in comparison to other regions in Brazil may have affected the results, but underscored the need of dedicated health policies. Despite the strengths, it is important to discuss limitations of the current study. First, this is a relative small sample of patients to evaluate hard endpoints such as death and cardiovascular disease. Second, the observational design may not capture potential

### Keywords

Sleep; Depression; Elderly.

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**DOI:** <https://doi.org/10.36660/abc.20210624>

residual factors that might help to contribute to the proposed endpoints; third, the sleep complaints were based on subjective reports. It is reasonable to expect some recall bias and sleep misperceptions in a significant proportion of patients. Ideally, the availability of objective analysis of sleep duration and obstructive sleep apnea would be helpful in determining the real impact of sleep disturbances in the elderly.

In conclusion, the current study reinforces the potential role of sleep disturbances and depression in modulating mortality in the elderly. These results also underscore the need for more collaboration among sleep specialists and psychiatrists for managing these patients. Future investigations addressing appropriate interventions on these important factors will be helpful for significant advances in this important research area.

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## Association of Body Composition with Arterial Stiffness in Long-lived People

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### Abstract

**Background:** Arterial stiffness, obesity and sarcopenia correlate with each other and with cardiac outcomes in younger adults. However, there is little evidence of the association between body composition and markers of central arteries stiffness in long-lived people.

**Objective:** To evaluate the relationship between arterial stiffness and body composition in functionally independent long-lived individuals.

**Methods:** This is a cross-sectional analysis of the association between markers of arterial stiffness and body composition among participants in a longitudinal cohort of elderly individuals aged 80 years or older who were functionally independent and lived in the community. Body composition measurements were performed using dual energy X-ray absorptiometry (DEXA) and central circulation parameters (CCP) obtained by a non-invasive oscillometric method through the Mobil-O-Graph 24h PWA Monitor® device. The central parameters evaluated were: pulse wave velocity (PWV), augmentation Index (AIx), pulse pressure amplification index (PPAi) and central pulse pressure (cPP). These were correlated to total lean mass (LM) and appendicular lean mass (aLM), body fat percentage, and Baumgartner's Index (BI). The level of significance was set at 5% for all tests.

**Results:** Data from 124 elderly people with a mean age of 87.1 years (SD  $\pm$  4.3 years) were analyzed, with 74.2% of women and 57.3% of white. There was a statistically significant inverse correlation of AIx with LM ( $r = -0.391$ ,  $p < 0.001$ ), aLM ( $r = -0.378$ ,  $p < 0.001$ ), and BI ( $r = -0.258$ ,  $p = 0.004$ ). Also, cPP had an inversely proportional association with LM ( $r = -0.268$ ,  $p = 0.003$ ), aLM ( $r = -0.288$ ,  $p = 0.001$ ), and BI ( $r = -0.265$ ,  $p = 0.003$ ). When assessing the relationship between fat mass and CCP, a statistically significant direct relationship was observed only between AIx and body fat percentage ( $r = 0.197$ ,  $p = 0.029$ ).

**Conclusion:** In long-lived people, body fat percentage is directly associated with arterial stiffness and inversely associated with the amount of LM. These findings may be associated with increased cardiovascular risk.

**Keywords:** Aged; Fats; Vascular Stiffness; Body Composition; DEXA.

### Introduction

Aging is a worldwide phenomenon, and the population aged 80 years or older (long-lived people) will experience a threefold increase from 2015 to 2050, with a more accelerated increase in developing countries.<sup>1</sup>

The prevalence of chronic diseases is higher at older ages. Thus, in addition to age itself, several risk factors increase

the rate of cardiovascular (CV) events, which is still the main cause of morbidity and mortality in this age group.<sup>2-4</sup> Arterial stiffness also contributes to increase the risk of major CV events, such as acute myocardial infarction (AMI) and stroke, regardless of the presence of arterial hypertension (AH), in adults and younger elderly people.<sup>5-7</sup> There are few studies correlating arterial stiffness with CV risk among long-lived people.<sup>6,7</sup>

Another factor correlated with CV risk is the distribution and amount of fat and body lean mass. Abdominal visceral fat is associated with increased metabolic syndrome and with CV risk, even in those with adequate weight for their height.<sup>8,9</sup> This type of fat has a better association with CV risk than body mass index (BMI) in the elderly population.<sup>10-12</sup> Furthermore, reduction in lean mass is associated with greater overall and CV mortality.<sup>13,14</sup>

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Manuscript received December 20, 2019, revised manuscript July 03, 2020, accepted August 16, 2020

**DOI:** <https://doi.org/10.36660/abc.20190774>

Some studies suggest that arterial stiffness contributes to the relationship between body composition and increased CV risk.<sup>15-17</sup> However, this relationship is not clear, especially with regard to long-lived people, because, although this population has been experiencing exponential growth, they have been little studied.

Therefore, even though the mechanism linking obesity and sarcopenia with vascular damage is not well known, it is believed that there may be an association with arterial stiffness.<sup>18,19</sup>

The aim of this study was to assess the relationship between arterial stiffness and body composition in long-lived people from the community.

## Methods

A cross-sectional analysis was conducted with a prospective cohort of older adults aged 80 years or older and with functional and cognitive independence (Estudo Longevos). This study consisted of both clinical, cognitive, functional, and nutritional assessments and routine tests of scientific interest. All participants signed a free informed consent to being included in the program.

The study excluded individuals with renal failure undergoing dialysis; with hemodynamic instability requiring vasoactive drug therapy; with functional class III or IV heart failure; with psychiatric diseases that could compromise the execution of the assessments proposed in the protocol; and with severe diseases and/or cancer with life prognosis of less than a year.

This analysis comprised all individuals who underwent body composition assessment and non-invasive measurement of central circulation parameters (CCP), with an interval of no more than a year between them. The study project was approved by the Research Ethics Committee of Universidade Federal de São Paulo (CEP-UNIFESP) under CEP no. 0190/2017 and opinion no. 2.381.489.

CCP were non-invasively obtained using the Mobil-O-Graph 24h PWA Monitor® device (I.E.M. GmbH, Stolberg, Germany) validated to this end, which simultaneously measures brachial arterial pressure and pulsewave form.<sup>20-22</sup>

Blood pressure was taken in all patients on the day of protocol implementation, based on the recommendations of the VII Brazilian Guidelines on Arterial Hypertension.<sup>23</sup> Mean for the valid measurements of the following central parameters were used: pulse wave velocity (PWV), augmentation index (AIx), pulse pressure amplification index (PPAi), central pulse pressure (cPP), and correlated them with data on body composition.

Body composition was assessed by DEXA (Dual Energy X-Ray Absorptiometry) using a Hologic bone densitometry machine (Model Discovery A, Waltham, USA), which allowed to quantify total lean mass (LM), appendicular lean mass (aLM), and body fat percentage.<sup>24,25</sup> aLM was calculated by the ratio between the amount of lean mass in arms and legs, expressed in grams, and the squared height in meters (aLM in g/m<sup>2</sup>). Moreover, DEXA allows calculating the Baumgartner index (BI), which uses aLM in the numerator of the BMI formula instead of total body mass.

## Statistical analysis

Since the study used a prospective cohort of very old adults, sample size was chosen by convenience. Initially, data were descriptively analyzed.

Categorical variables were expressed as absolute and relative frequencies. Numerical continuous variables with normal distribution were described as mean and standard deviation.

The linear association between two numerical variables was assessed using the Pearson's correlation test. Partial correlations adjusted for age were also presented.

The level of significance for all statistical tests was set at 5%.

Statistical analyses were performed using the SPSS 20.0 statistical software.

## Results

A total of 124 long-lived people were assessed, of which 74.2% were women and 57.3% were white, with a mean age of  $87.1 \pm 4.3$  years, minimum of 80 years and maximum of 100 years.

Mean time elapsed from blood pressure measurements and DEXA assessments was 43.4 days. Of the total participants, 41.9% had normal weight, according to the Lipschitz classification (BMI from 22 to 27 kg/m<sup>2</sup>) and 41.1% were obese (BMI > 27 kg/m<sup>2</sup>). With regard to the distribution of body fat percentage as assessed by DEXA and divided into tertiles, 1/3 of the sample was shown to have more than 42.9% fat mass in their body composition, whereas 1/3 had from 36.4 to 42.9% of fat mass and 1/3 had less than 36.4% of fat mass.

There was an inverse association between lean mass, either appendicular or total, and arterial stiffness (Figure 1). A statistically significant association was observed between two CCPs (cPP and AI) and lean mass (Table 1).

An inversely proportion association was found between AI and the variables LM ( $r = -0.391$ ,  $p < 0.001$ ), aLM ( $r = -0.378$ ,  $p < 0.001$ ) and BI ( $r = -0.258$ ,  $p = 0.004$ ). There was also a statistically significant inverse relationship between cPP and LM ( $r = -0.268$ ,  $p = 0.030$ ), aLM ( $r = -0.288$ ,  $p = 0.001$ ), and BI ( $r = -0.265$ ,  $p = 0.003$ ). PWV did not show any statistical significant association in this analysis.

A direct relationship, but with no statistical significance, was found between PPAi and LM (Table 1).

These correlations between variables of arterial stiffness and body composition were adjusted for age, yielding similar results (Table 1 and Figure 1). Thus, AI still had an inverse relationship with LM and IB. This also occurred in the age-adjusted comparison between cPP and LM. (Table 1)

An assessment of relationship between body fat and parameters of arterial stiffness showed a statistically significant direct relationship between AI and body fat percentage, but not between AI and total body fat ( $r = -0.029$ ,  $p = 0.746$ ). This association remained after adjustment for age, as shown in Table 2. The other analyzed parameters (PWV, PPAi and cPP) did not have a statistical relationship with body fat. None of the analyzed parameters of arterial stiffness (cPP, AI, PWV, PPAi) exhibited a relationship with BMI (Table 2).

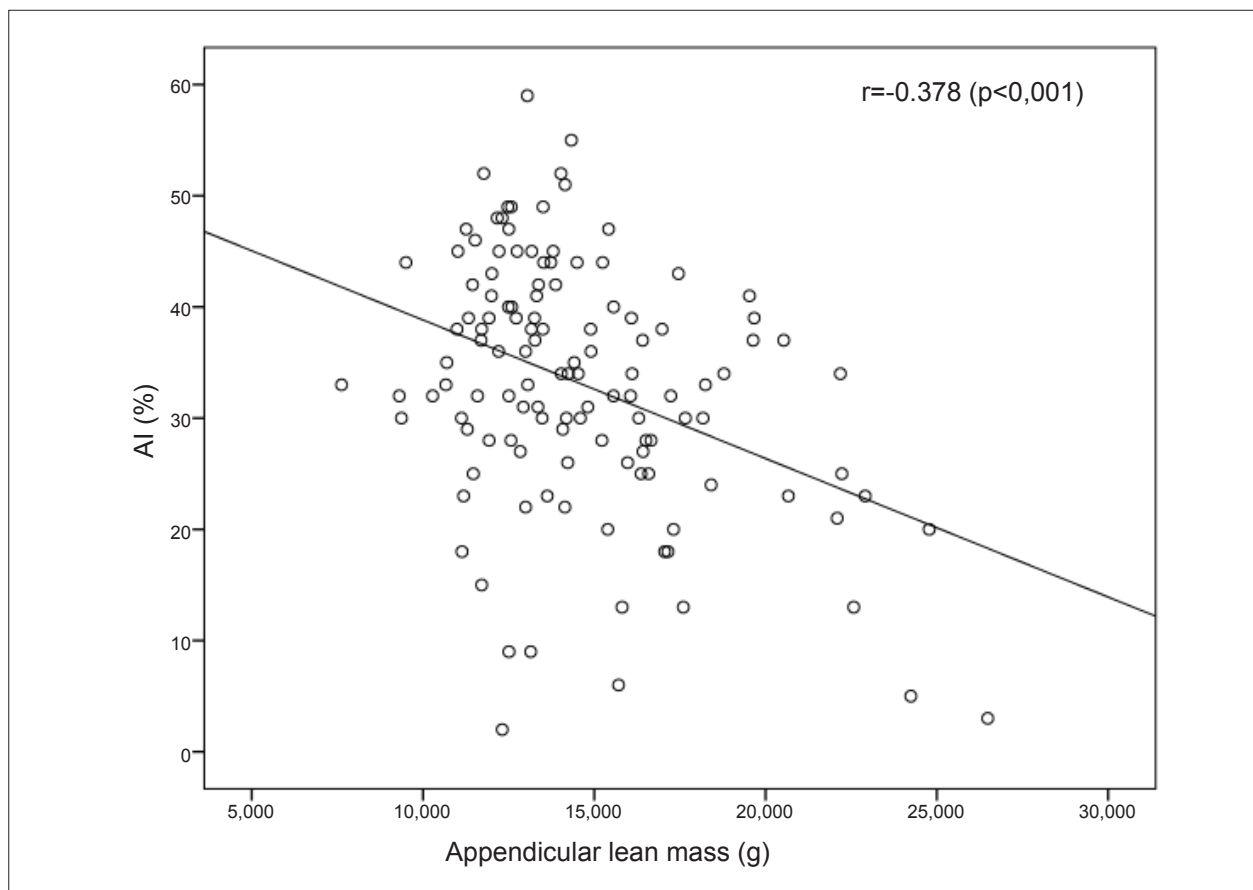


**Figure 1** – Dispersion graph showing the inverse relationship ( $r = -0.378$ ;  $p < 0.001$ ) between AI (%) and appendicular lean mass (g).

**Table 1** – Pearson's correlation between variables of arterial stiffness and body lean mass after adjustment for age

|            | LM (g)   |        | Appendicular lean mass (g) |        | Baumgartner index (kg/m <sup>2</sup> ) |        |
|------------|----------|--------|----------------------------|--------|----------------------------------------|--------|
|            | r        | p      | r                          | p      | r                                      | p      |
| cPP (mmHg) | -0.267*  | 0.003  | -0.283*                    | 0.002  | -0.263*                                | 0.003  |
| AI (%)     | -0.393** | <0.001 | -0.382**                   | <0.001 | -0.260**                               | <0.004 |
| PWV (m/s)  | -0.052   | 0.571  | -0.082                     | 0.369  | -0.102                                 | 0.263  |
| PPAi (%)   | 0.168    | 0.063  | 0.147                      | 0.106  | 0.128                                  | 0.159  |

\*  $p < 0.01$ ; \*\*  $p < 0.001$ . N=124 LM (total lean mass); cPP (central pulse pressure); AI (augmentation index); PWV (pulse wave velocity); PPAi (pulse pressure amplification index)

**Table 2** – Pearson's correlation between variables of arterial stiffness and body fat after adjustment for age

|            | FM (g) |       | Body fat percentage |       |
|------------|--------|-------|---------------------|-------|
|            | r      | p     | r                   | p     |
| cPP (mmHg) | -0.004 | 0.962 | 0.174               | 0.054 |
| AI (%)     | -0.042 | 0.642 | 0.197*              | 0.029 |
| PWV (m/s)  | 0.005  | 0.952 | 0.048               | 0.601 |
| PPAi (%)   | 0.064  | 0.479 | -0.042              | 0.647 |

\*  $p < 0.05$ ; N=124; FM (fat mass); cPP (central pulse pressure); AI (augmentation index); PWV (pulse wave velocity); PPAi (pulse pressure amplification index)

## Discussion

This is the first study to assess the association between arterial stiffness and body composition in long-lived people. This assessment found a relationship between body composition and arterial stiffness, showing that the greater the amount of muscle mass, the lower the wall stiffness of central arteries. This result may be explained by the association of AI and cPP with total and aLM, with statistical significance ( $p < 0.001$ ), even after correction for age.

A direct relationship was observed between body fat percentage and arterial stiffness as assessed by AI ( $p = 0.029$ ).

These results were consistent with those found in some studies with middle-aged adults. Wohlfahrt et al. assessed 136 volunteers with mean age of 45 years, non-obese, and without CV diseases.<sup>19</sup> They concluded that individuals with greater LM and lower fat percentage had more elastic arteries and also observed a stronger association between aortic stiffness and LM compared with fat mass. Schouten et al.<sup>26</sup> followed healthy adults and found that increased abdominal fat or loss of aLM was related to greater arterial stiffness.<sup>26</sup>

Conversely, Benetos et al.,<sup>27</sup> when analyzing 169 older adults, found that LM associated with body fat, but not with PWV. However, the sample of this study only included men of a younger age (60 to 85 years), of which 90% were aged below 75. Furthermore, other markers of arterial stiffness, such as cPP and AI, were not assessed.

Tanaka et al.,<sup>28</sup> in turn, evaluated a population consisting exclusively of diabetic women with mean age of 65 years and showed the association of arterial stiffness, as measured by PWV, both with body fat percentage and with LM.<sup>28</sup>

In the present study, there was no statistical relationship between PWV and body composition, contrary to above mentioned articles. However, the PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study, conducted with 1,126 elderly individuals aged 80 years or older, i.e., with similar age than that of participants of the present study, did not observe a correlation between PWV and CV outcomes and overall mortality.<sup>7</sup> In the PARTAGE study, PPAi showed to be the best risk marker for these events, which may suggest that other parameters should be analyzed to measure arterial stiffness among long-lived people, in addition to PWV. It is necessary to highlight that the study presented here assessed older adults from the community, whereas the PARTAGE study assessed older adults who were institutionalized, although also independent for basic activities of daily living.

Central arterial parameters were measured using Mobil-O-Graph 24h PWA Monitor®, a non-invasive equipment that uses a validated oscillometric method. A recently published systemic review with meta-analysis compared the commercially available equipment for indirect measurement of CCP.<sup>29</sup> It concluded that there is no sufficient evidence to recommend a non-invasive technique to estimate a central blood pressure as a gold-standard. Although the technology of SphygmoCor® has been more studied and validated so far, it shows a greater number of errors in blood pressure estimation on the aortic root with regard to the invasive method, more than devices that use an automatic oscillometric

method. These devices have greater accuracy and seem more promising.

The present study used the tool of choice for bone mineral density as recommended by the European Consensus on Sarcopenia for the assessment of appendicular muscle mass in clinical practice, but there was no consensus on its use to define obesity.<sup>30,31</sup>

The weak association between arterial stiffness and body fat found in this study corroborates the theory of the obesity in the elderly.<sup>32</sup> The lower association between CV diseases and obesity may be explained by a survival bias, in which individuals who reach old age are not susceptible to the metabolic hazards of excess fat. However, it is important to emphasize that, although there was excess body fat is not correlated with mortality after the age of 75, it increases the likelihood of frailty and loss of functionality, leading to dependency for activities of daily living.<sup>33</sup>

One of the remarkable limitations of the present study is the fact that it was conducted in a single center, with a population of many older adults from the community, which does not allow for the generalization of its results to diverse populations. Moreover, the relatively small sample size may be an important limiting factor for its findings. However, this was the first study to specifically assess the population aged 80 years or older living in the community and not institutionalized, whose access to clinical research is more limited, due to difficulties inherent to aging.

The design of this study does not allow suggesting a mechanism or a cause and effect relationship between the found associations. Other variables that may interfere with vascular hardening were not considered, such as: hypertension, diabetes, metabolic syndrome, and dyslipidemia. Furthermore, the present study did not assess medications currently used, such as anti-hypertensive, which could have a direct influence on CCP.<sup>34</sup>

Cohort longitudinal studies and clinical trials are needed to confirm the relationships presented with CV outcomes.

## Conclusion

In long-lived people, body fat percentage is directly associated with arterial stiffness and inversely associated with the amount of LM.

Considering that arterial stiffness may have a directly relationship with increased CV risk may lead to the hypothesis that muscle mass is inversely associated with risk of CV outcomes in long-lived people.

## Author Contributions

Conception and design of the research: Melo e Silva FV, Almonfrey FB, Freitas CMN, Almada-Filho CM, Cendoroglo MS, Miranda RD; Acquisition of data: Melo e Silva FV, Almonfrey FB, Freitas CMN, Fonte FK, Sepulveda MBC, Quadrado EB; Analysis and interpretation of the data: Melo e Silva FV, Sepulveda MBC, Almada-Filho CM, Cendoroglo MS, Miranda RD; Writing of the manuscript: Amodeo C, Póvoa R, Miranda RD; Critical revision of the manuscript for intellectual content: Melo e Silva FV, Amodeo C, Miranda RD.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This article is part of the thesis of master submitted by Flávia Veríssimo Melo e Silva, from Universidade Federal de São Paulo.

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## Chronological Age or Biological Age, Mainly a Matter of Lifestyle

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Short Editorial related to the article: Association of Body Composition with Arterial Stiffness in Long-lived People

Despite the significant global socioeconomic disparities, the world's population has grown exponentially, and the average life continues to increase significantly.<sup>1-4</sup>

If at the beginning of the 19th century, life expectancy in Europe was around 35 years, at present, only the African continent has populations with an average life expectancy of fewer than 60 years.<sup>1-3</sup>

We have, at one extreme, Japan, where the average life reaches 84 years and the other, Sierra Leone, Africa, where the expectation is 46 years. In 2019, life expectancy in Brazil increased to 76.6 years, being 73.1 for men and 80.1 years for women.<sup>1-4</sup>

A set of factors determined this overwhelming change and, among them, the best hygiene conditions, the offer of a greater quantity of food, advances in medicine and technology and, within this aspect, the fantastic development of immunization stand out.

With these transformations, the concept of age begins to be revised, with the progressive abandonment of simple chronological age, to aggregate the modern conception of biological age.<sup>4-6</sup>

Social coexistence itself and customs are already anticipated in this reality, reclassifying age groups. In Brazil, along with those considered elderly by law ( $> = 60$  years), Law no. 10,048, some have priority over the other elderly ( $> 80$  years), Law no. 13,466.

With this new perspective, the study of vascular aging is gaining increasing importance to identify individuals in the general population who present different stages of vascular aging and, consequently, different risks of the onset of cardiovascular diseases, which are the main cause of death, modifying the individual's natural history and shortening its useful life.<sup>4,7,8</sup>

The classic risk factors continue to "command" the list of possibilities of circulatory outcomes. However, the progressive recognition of their association and correlation with vascular aging, measured more accurately, begins to allow a more vigorous action to modify the natural course of these diseases.<sup>4,9,10,11</sup>

### Keywords

Aged; Healthy Aging; Life Style; Vascular Stiffness; Body Mass Index; Obesity; Stress; Sedentarism; Genetics; Spirituality.

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**DOI:** <https://doi.org/10.36660/abc.20210732>

Inadequate body composition is included in the list of factors that interfere with cardiovascular risk and, in this regard, the article by Melo e Silva et al.,<sup>12</sup> brings interesting insights, is thought-provoking and indicates a new path that is being explored worldwide.

This is a cross-sectional study of a prospective cohort of older people aged 80 years or older living in a functional and cognitive independence community.

124 long-lived with a mean age of 87.1 years (74.5% women and 57.3% white) were studied. The investigation methodology used precise and validated instruments, both of body composition and arterial stiffness, giving reliability to the measurements.

Data on arterial stiffness represented by pulse wave velocity (PWV), augmentation index (Aix), pulse pressure amplification index (PPAi), central pulse pressure (cPP), with body composition data represented by total lean mass (LM), appendicular mass (AM), body fat percentage and Baumgartner index (BI), calculated by the equipment that replaces total body mass, were correlated.

The interesting and provocative findings showed a significant inverse correlation between Aix and LM ( $r = -0.391$ ,  $p < 0.001$ ), AM ( $r = -0.378$ ,  $p < 0.001$ ) and BI ( $r = -0.258$ ,  $p = 0.004$ ). In addition, CPP presented an inverse association with LM ( $r = -0.268$ ,  $p = 0.003$ ), AM ( $r = -0.288$ ,  $p = 0.001$ ) and BI ( $r = -0.265$ ,  $p = 0.003$ ). There was a direct relationship only between Aix and body fat percentage ( $r = 0.197$ ,  $p = 0.029$ ). Statistical significance was not found for PWV.

The work has the merit of being the first to assess the association between arterial stiffness and body composition in long-lived older adults in the community. The results show that the greater the amount of muscle mass, the lower the central arterial stiffness and, on the contrary, the higher the percentage of body fat, the greater the arterial stiffness. Regarding PWV, the findings were similar to those found in the Partage (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Population Aged) study, which evaluated individuals of similar ages, more numerous, with the difference of being institutionalized.<sup>13</sup>

The encounter of the weak association between arterial stiffness and body fat is in line with the theory of the obesity paradox,<sup>14</sup> the so-called survival bias, that is, those who reached a very advanced age would be free of the metabolic harms of excess fat. This fact, however, does not mitigate the decrease in quality of life caused by body fat, loss of functionality and increased frailty.<sup>15</sup>

The limitations of a cross-sectional, single-center study with a small number of individuals do not invalidate its importance and show interesting future possibilities for longitudinal

studies, with representative samples that will indicate ways to prevent and early treat of injuries.

As proposed by Sanderson and Scherbov, this modern concept of aging describes that “chronological age is the retrospective age and measures how many years the person has lived. Every one of the same age lived the same number of years. In contrast, prospective age concerns the future.

It talks about the years of life to be lived. Those who have the same prospective age, these yes, will have the same years of future life.”<sup>5,6</sup>

This future is directly linked to genetics, but, in no less significant way, to life habits, social relationships, the ability to deal with stress and the broader concept of spirituality. A new path that unfolds.

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# Association between Plasma Thiol Parameters and Troponin Levels in Patients with Acute Coronary Syndrome and Prediction of In-Hospital Ventricular Arrhythmia

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## Abstract

**Background:** Ventricular arrhythmias (VAs) are the main cause of in-hospital mortality and morbidity in acute coronary syndrome (ACS) patients and its relationship with thiol is not known.

**Objective:** To investigate the relationship between plasma thiol levels and troponin levels in patients with ACS and to estimate in-hospital VA development during hospital stay.

**Method:** The study included 231 consecutive ST-segment elevation ACS (STE-ACS) and non-ST-segment elevation ACS (NSTEMI-ACS) patients. After application of exclusion criteria, 191 patients were included in the statistical analysis. Patients were classified into two groups: STE-ACS group (n=94) and NSTEMI-ACS group (n=97). Plasma thiol, disulphide and troponin levels were measured and troponin-to-native thiol ratio (TNTR) was calculated. A two-sided p value of less than 0.05 was considered to be statistically significant.

**Results:** Plasma native thiol, total thiol, disulphide and their ratios were similar between the groups. TNTR was significantly higher in the STE-ACS group compared to the NSTEMI-ACS group. Troponin and thiol levels correlated negatively and significantly. Native thiol was found to be an independent predictor of VA development in STE-ACS patients and in all ACS patients. TNTR was found to be an independent predictor of VA development in NSTEMI-ACS patients and in all ACS patients.

**Conclusion:** Plasma thiol levels can be used to identify ACS patients at high risk for in-hospital VA development. Correlation between troponin and thiol levels may suggest that thiols may be an important marker for diagnosis and prognosis of ACS with the help of future studies.

**Keywords:** Atherosclerosis; Coronary Artery Disease; Coronary Acute, Syndrome; Oxidative Stress; Arrhythmias, Cardiac; Acetyl-CoA-Acyltransferase.

## Introduction

Atherosclerosis is a multifactorial disease caused by endothelial damage in people with risk factors such as dyslipidemia, diabetes, smoking and genetic predisposition. Acute coronary syndrome (ACS), which is a result of this condition, includes patients with persistent ST-segment elevation (STE-ACS) and patients without persistent ST-segment elevation (NSTEMI-ACS) detected

by electrocardiography (ECG).<sup>1</sup> STE is mostly associated with total acute coronary occlusion, whereas NSTEMI-ACS is mostly related with sensitive atherosclerotic plaque and subtotal thrombosis.

Over the last ten years, many studies have demonstrated the role of overproduction of reactive oxygen species (ROS) and resulting oxidative stress in the pathogenesis of atherosclerosis.<sup>2</sup> Indeed, the metabolic process of ROS plays significant roles in the physiological functions of cells and this process is counterbalanced by the antioxidative system of the body. Oxidation of low-density lipoprotein (LDL) particles consist in the preliminary and principal phase of atherosclerosis. In addition, ROS formation contributes to apoptosis, inflammation and cell proliferation processes.<sup>3</sup>

Thiol and disulphide homeostasis status has a critical role in antioxidant protection, detoxification, apoptosis and regulation of enzymatic activity.<sup>4</sup> Recent studies have shown

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Manuscript October 01, 2019, revised manuscript August 13, 2020, accepted August 19, 2020

**DOI:** <https://doi.org/10.36660/abc.20190672>

that abnormal plasma thiol level and disulphide balance are associated with various cardiovascular diseases such as stable angina pectoris,<sup>5</sup> acute myocardial infarction (MI),<sup>6</sup> cardiac syndrome X,<sup>7</sup> coronary slow flow,<sup>8</sup> primary hypertension<sup>9</sup> and diabetes mellitus (DM).<sup>10</sup> It is known that ventricular arrhythmias (VAs), which may be due to myocardial necrosis, autonomic and electrolyte imbalance, acidosis and reperfusion injury, are the main causes of in-hospital mortality and morbidity in ACS patients.<sup>11</sup> However, there is no study in the literature regarding the relationship between oxidative process, myocardial necrosis, and in-hospital VA development in ACS patients. In this context, we aimed to investigate the relationship between plasma thiol and troponin levels in patients with ACS and its association with VA development during in-hospital follow-up.

## Methods

This observational cross-sectional study was conducted from February to May 2018 and included 231 consecutive patients from our cardiology clinic. Patients hospitalized in the coronary intensive care unit diagnosed with ACS and who underwent coronary angiography were included in the study in a prospective manner. Patients with active infectious or inflammatory diseases, malignancy, hematological disorders, severe kidney disease, severe liver disease, rheumatic disease, severe valvular disease, patients taking antioxidants and/or under vitamin replacement therapy and patients in cardiogenic shock were excluded from the study. In addition, patients with insufficient clinical data were also excluded. The study protocol was approved by the local ethics committee (No: 39/Date: 21.02.2018) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was obtained from each patient.

After the application of exclusion criteria, 191 patients were included in the statistical analysis. Patients were classified into two groups: STE-ACS group (n=94) and NSTEMI-ACS group (n=97). Diagnosis of ACS was made according to the current guidelines using history taking, ECG, imaging methods and troponin levels. Baseline clinical parameters of patients were evaluated. In-hospital mortality, VA occurrence and length of hospital stay were also evaluated and recorded. Diagnosis of STE-ACS included patients with acute onset chest pain and persistent ST-segment elevation on ECG.<sup>12</sup> Diagnosis of NSTEMI-ACS included patients with acute onset chest pain, no persistent ST-segment elevation on ECG and/or cardiac troponin levels greater than the upper limit of the normal range.<sup>13</sup> Arterial hypertension was defined as patients with repeated blood pressure measurements  $\geq 140/90$  mmHg or previous diagnosis of hypertension with antihypertensive medications. DM was defined as fasting plasma glucose levels higher than 126 mg/dL in multiple measurements or glucose level over 200 mg/dL at any measurement or active use of antidiabetic drugs and/or insulin therapy. Smoking was defined as current smoking in the previous six months. Hypercholesterolemia was defined as baseline cholesterol level of  $>200$  mg/dL and/or LDL cholesterol level of  $>130$  mg/dL or previously diagnosed and treated hypercholesterolemia.

In-hospital VA was defined as sustained or non-sustained ventricular tachycardia (VT) and ventricular fibrillation (VF). Diagnosis was determined from baseline ECG and/or telemetry recordings according to the clinical status of patients during hospital stay. In addition, telemetry recordings were retrospectively reviewed on the computer for other VA attacks before discharge. Ventricular premature beats with more than three consecutive beats were defined as VT. VTs lasting longer than thirty seconds were defined as sustained, and shorter duration was defined as non-sustained VT.

The Thrombolysis in Myocardial Infarction (TIMI) risk score consisting of 8 items, which predicts all-cause mortality at 30 days, was calculated for patients with STE-ACS and TIMI risk score consisting of 7 items, which predicts all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization at 14 days, was calculated for NSTEMI-ACS patients.<sup>14</sup> Calculation of Global Registry of Acute Coronary Events (GRACE) risk score was performed in all patients to estimate the probability of in-hospital death.<sup>15</sup>

Transthoracic echocardiography was performed using 3S-RS 1.5-3.6 MHz phased array transducer with General Electric Vivid 7 (GEMS Ultrasound, Israel) ultrasound device in the first 48 hours of hospitalization. Left ventricular ejection fraction (LVEF) was calculated from the apical 2 and 4 chamber images using the Modified Simpson's method. Coronary angiography was performed using the Siemens Axiom Sensis XP device by cannulization of the femoral artery applying the standard Judkins technique. In addition to acetylsalicylic acid, all patients received dual antiplatelet therapy with clopidogrel, prasugrel or ticagrelor according to their clinical status.

Venous blood sample measurements of patients were taken upon admission. Routine biochemistry studies were performed on Hitachi 747 autoanalyzer. High-density lipoprotein (HDL) cholesterol was measured after dextran sulphate magnesium precipitation. LDL-cholesterol was calculated using the Friedewald method. Cholesterol, fasting triglycerides, HDL-cholesterol plasma concentrations were measured using the enzymatic chemical cleaning method using Cobas 6000 (Roche Diagnostics GmbH, Mannheim, Germany). Serum troponin I levels were quantitatively measured on the Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland). Serum levels of cardiac enzymes (CK, CK-MB and troponin I) were measured on admission and repeated every day. Plasma thiol and disulphide levels were measured according to the method developed by Erel et al. immediately upon admission. Blood samples were taken into tubes containing ethylenediamine tetraacetic acid (EDTA) to determine thiol and disulphide levels. Briefly, the degradable disulphide bonds were reduced to form free functional thiol groups. Subsequently, unused reductive sodium borohydride was used and extracted with formaldehyde and then all of the native and reduced thiol groups were determined after reaction with 5,5-dithiobis-(2-nitrobenzoic) acid. Dynamic disulphide levels were calculated by half of the difference between total and native thiol. After determination of native thiol and disulphide levels, native thiol-to-disulphide ratio was calculated. Using this method, dynamic thiol-to-disulphide ratio homeostasis was determined more easily and inexpensively in approximately ten minutes.<sup>16</sup>

### Statistical analysis

All analyses were carried out using IBM SPSS Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, New York, USA). One-sample Kolmogorov-Smirnov test was used to evaluate the distribution of numerical variables. According to the results of this test, independent two samples T-test was applied to the numerical data which conforms to the normal distribution and the results were entered as mean and standard deviation. On the other hand, Mann-Whitney U test was used for skewed distributed variables. Considering the results of this test, the median and interquartile range values were used. Chi-square test was used for categorical variables. Fisher's exact test was applied in cases where the chi-square test could not be applied. For correlation analyses, Pearson's correlation analysis was preferred for data with normal distribution. Otherwise, Spearman's correlation analysis was preferred. Independent predictors of in-hospital VA were determined using logistic regression analysis. Variables that might have a clinical relationship with in-hospital VA such as LDL, age, LVEF, serum potassium and magnesium levels, neutrophil-lymphocyte ratio (NLR), admission time, troponin-to-native thiol ratio (TNTR), and troponin and native thiol were included in the logistic regression analysis. To avoid multicollinearity, we conducted multivariate analysis using three models separately. Each multivariate model included only one marker (TNTR, troponin, native thiol). Logistic regression analysis was performed separately for all groups with STE-ACS, NSTEMI-ACS and all ACS patients. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values (Youden index<sup>17</sup>) for TNTR sensitivity and specificity in predicting VA. A two-sided *p* value of less than 0.05 was considered to be statistically significant.

### Results

Demographic characteristics, laboratory parameters and clinical features of the patient groups are shown in Table 1. There was no difference between the groups in terms of age, gender, body mass index and atrial fibrillation. Percentage of hypertension, DM and admission time was higher in the NSTEMI-ACS group, whereas percentage of smokers was higher in the STE-ACS group. Neutrophil counts, platelet counts and NLR were significantly higher in the STE-ACS group compared to the NSTEMI-ACS group. Lymphocyte counts, hemoglobin, albumin, serum electrolytes including potassium, calcium, and magnesium, renal and liver function tests, and lipid parameters, except triglycerides, were comparable between the groups. Peak cardiac enzyme values including CK-MB and troponin were significantly higher in the STE-ACS group than in the NSTEMI-ACS group, whereas LVEF was lower in the STE-ACS group. Plasma native thiol, total thiol, disulphide, disulphide-to-native thiol ratio, disulphide-to-total thiol ratio, and native thiol-to-total thiol ratio was similar between the groups. However, TNTR was significantly higher in the STE-ACS group compared to the NSTEMI-ACS group. In addition, the GRACE score was significantly higher in the STE-ACS group compared to the NSTEMI-ACS group. A total of 23 patients developed in-hospital VA. Of the patients who developed in-hospital VA, 14 patients had sustained VA while 9

patients had non-sustained VA. There was no difference between the groups in terms of VA occurrence, length of hospital stay, and in-hospital mortality.

Correlation analysis of multiple variables with native thiol, total thiol and TNTR in the whole study population are presented in Table 2. Native thiol levels were significantly and negatively correlated with age, GRACE score, NLR, hospital stay and troponin (Figure 1A), whereas significantly and positively correlated with GFR, LVEF and albumin. Total thiol levels were significantly and negatively correlated with age, GRACE score, hospital stay and troponin (Figure 1B), whereas significantly and positively correlated with GFR, LVEF and albumin. TNTR levels were inversely and significantly correlated with LVEF, and positively and significantly correlated with GRACE score, NLR, CKMB and hospital stay. Correlation coefficient was weak or moderate for all significant variables included in the analysis.

Logistic regression analysis of in-hospital VA predictors for STE-ACS patients, NSTEMI-ACS patients and all ACS patients are shown in Table 3. Native thiol was found to be an independent predictor of VA development in STE patients, whereas TNTR was found to be an independent predictor of VA development in NSTEMI-ACS patients. When it comes to the whole ACS patient population, TNTR and native thiol were found to be independent predictors of VA development. In all ACS patients, the area under the curve for TNTR was 0.783 and the TNTR cut-off value (6.13) was associated with 78% sensitivity and 72% specificity to predict in-hospital VA as shown in Figure 2.

### Discussion

The findings of this study demonstrated that there was a negative correlation between troponin and plasma thiol levels in ACS patients. Furthermore, especially in NSTEMI-ACS patients and in the whole ACS patient population, TNTR was shown to be a strong and independent marker for the prediction of in-hospital VA. To the best of our knowledge, this is the first study in the literature demonstrating the relationship between thiol and in-hospital VA development in patients with ACS.

One of the main pathophysiological mechanisms in atherosclerosis is increased oxidative stress with inflammation.<sup>18</sup> Serum thiol level, which is an indicator of oxidative stress, can be manually detected by fluorescent capillary electrophoresis and/or luminescent systems. However, these systems are expensive, time consuming and difficult to apply. A colorimetric method developed by Erel et al. in 2014 has led to the automatic determination of thiol levels. Additionally, this new method is more accurate, faster and cheaper compared to previous methods.<sup>16</sup> On the other hand, NLR, which is an easily accessible and inexpensive inflammatory marker, is a parameter that demonstrates systemic inflammatory response in various cardiovascular and non-cardiovascular conditions.<sup>1</sup> In a study performed by Altiparmak et al.,<sup>7</sup> total serum and native thiol levels were found to be lower in patients with cardiac syndrome X and total serum and native thiol levels were negatively correlated with NLR.<sup>7</sup> In our study, NLR levels were significantly higher in the STE-ACS patient group compared to the NSTEMI-ACS patient group and there was a negative correlation between NLR and thiol levels in the whole ACS population. In the light of these findings, it is reasonable to speculate that plasma thiol, a marker of

**Table 1 - Demographic characteristics and laboratory findings of the study population**

| Variables                     | STE-ACS<br>(n=94) | NSTE-ACS<br>(n=97) | p value |
|-------------------------------|-------------------|--------------------|---------|
| Age, years                    | 58.7±11.1         | 62.1±13.7          | 0.06    |
| Gender (male), n (%)          | 80 (85)           | 71 (73)            | 0.05    |
| BMI (kg/m <sup>2</sup> )      | 26.9±6.9          | 28.5±5.6           | 0.14    |
| Hypertension, n (%)           | 39 (41)           | 61 (62)            | 0.003*  |
| Diabetes mellitus, n (%)      | 22 (23)           | 43 (44)            | 0.02*   |
| Smoking, n (%)                | 65 (69)           | 44 (45)            | 0.001*  |
| Atrial fibrillation, n (%)    | 0 (0)             | 8 (8)              | 0.07    |
| Admission time, hours         | 2 (1–5)           | 28 (7–72)          | <0.001* |
| Neutrophil count (K/uL)       | 7650 (5500–11525) | 6100 (4600–8150)   | <0.001* |
| Lymphocyte count (K/uL)       | 1900 (1222–3025)  | 1900 (1525–2500)   | 0.81    |
| NLR                           | 5.0 (2.0–7.9)     | 2.7 (2.1–4.5)      | 0.02*   |
| Platelet count (K/uL)         | 252±79            | 231±63             | 0.04*   |
| Hemoglobin (g/dl)             | 14.4±1.7          | 13.7±1.8           | 0.08    |
| Albumin (g/dl)                | 4.1±0.4           | 4.2±0.3            | 0.21    |
| Total cholesterol (mg/dl)     | 182±42            | 194±53             | 0.07    |
| HDL (mg/dl)                   | 37 (31–45)        | 39 (33–47)         | 0.06    |
| LDL (mg/dl)                   | 119±33.5          | 116±36.5           | 0.57    |
| Triglycerides (mg/dl)         | 97.5 (60–154)     | 130 (91–189)       | <0.001* |
| Potassium (mmol/L)            | 4.3±0.4           | 4.4±0.5            | 0.14    |
| Creatinine (mg/dl)            | 0.9 (0.7–1.0)     | 0.9 (0.7–1.1)      | 0.31    |
| GFR (mL/min/m <sup>2</sup> )  | 90 (72–144)       | 86 (60–96)         | 0.07    |
| Calcium (mg/dl)               | 9.2±0.6           | 9.3±0.5            | 0.17    |
| Magnesium (mg/dl)             | 2.0 (1.9–2.2)     | 2.0 (1.9–2.2)      | 0.79    |
| AST (U/L)                     | 30.5 (20–52)      | 30 (21–39)         | 0.34    |
| ALT (U/L)                     | 24 (16–34)        | 21 (14–30)         | 0.13    |
| CK-MB Mass (ng/mL)            | 100 (26–209)      | 13 (3–66)          | <0.001* |
| Troponin I (µg/L)             | 2571 (736–4810)   | 365 (43–1394)      | <0.001* |
| LVEF (%)                      | 43.9±8.5          | 49±11.2            | <0.001* |
| Troponin/native thiol         | 6.7 (1.9–15.8)    | 1.0 (0.1–3.8)      | <0.001* |
| Plasma native thiol (µmol/l)  | 359.8±78.4        | 366.6±68.5         | 0.52    |
| Plasma total thiol (µmol/l)   | 401.3±81.7        | 407.6±74.4         | 0.57    |
| Disulphide (µmol/l)           | 20.1±10.8         | 19.0±11.9          | 0.53    |
| Disulphide/native thiol       | 0.04 (0.03–0.08)  | 0.05 (0.03–0.07)   | 0.49    |
| Disulphide/total thiol        | 0.04 (0.03–0.07)  | 0.04 (0.02–0.06)   | 0.53    |
| Native thiol/total thiol      | 0.90 (0.86–0.94)  | 0.91 (0.87–0.95)   | 0.16    |
| TIMI risk score               | 2 (1–4)           | 4 (3–5)            | -       |
| GRACE score                   | 151.7±26.6        | 133.7±35.1         | <0.001* |
| Ventricular arrhythmia, n (%) | 13 (13.8)         | 10 (10.3)          | 0.45    |
| Length of hospital stay, days | 4 (3–5)           | 4 (3–5)            | 0.26    |
| Mortality, n (%)              | 3 (3)             | 1 (1)              | 0.36    |

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; CK-MB: creatine kinase-MB; GFR: glomerular filtration rate; HDL: high-density lipoprotein; IQR: interquartile range; LDL: low-density lipoprotein; LVEF: left ventricle ejection fraction; NLR: neutrophil/lymphocyte ratio; NSTE-ACS: Non-ST-segment elevation acute coronary syndrome; SD: standard deviation; STE: ST-segment elevation. Parameters were expressed as mean±SD and median [IQR]. \* p<0.05 was considered significant for statistical analyses.

**Table 2 – Plasma native thiol, total thiol and troponin/native thiol index parameters of acute coronary syndrome patients and their correlation with variables**

| Variables     | Native Thiol |         | Total Thiol |         | Troponin-to-Native Thiol Ratio |         |
|---------------|--------------|---------|-------------|---------|--------------------------------|---------|
|               | r            | p       | r           | p       | r                              | p       |
| Age           | -0.25        | <0.001* | -0.26       | <0.001* | +0.06                          | 0.34    |
| GFR           | +0.33        | <0.001* | +0.33       | <0.001* | -0.13                          | 0.06    |
| Grace score   | -0.36        | <0.001* | -0.35       | <0.001* | +0.40                          | <0.001* |
| LVEF (%)      | +0.19        | 0.009*  | +0.18       | 0.01*   | -0.42                          | <0.001* |
| NLR           | -0.14        | 0.04*   | -0.14       | 0.054   | +0.34                          | <0.001* |
| Albumin       | +0.39        | <0.001* | +0.41       | <0.001* | -0.12                          | 0.07    |
| Troponin      | -0.27        | <0.001* | -0.28       | <0.001* | -                              | -       |
| CK-MB Mass    | -0.11        | 0.12    | -0.10       | 0.15    | +0.63                          | <0.001* |
| Hospital stay | -0.22        | 0.002*  | -0.16       | 0.02*   | +0.23                          | 0.001*  |
| LDL           | +0.10        | 0.14    | +0.13       | 0.06    | +0.04                          | 0.57    |

CK-MB: creatine kinase-MB; GFR: glomerular filtration rate; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; NLR: neutrophil-lymphocyte ratio.

\*p<0.05 was considered significant for statistical analyses.

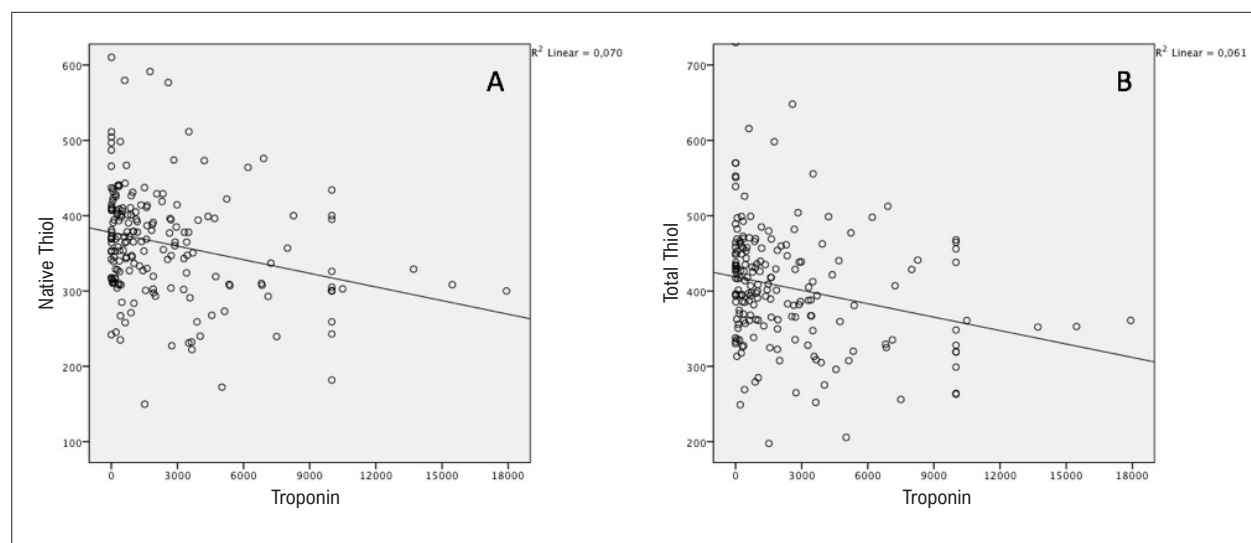


**Figure 1 – Relationship between troponin and native and total thiol levels.**

antioxidant protection in the human body, is negatively associated with increased inflammation in ACS patients.

Oxidative stress initiates the development of atherosclerosis through lipid peroxidation and formation of free radicals at first stages, and through vascular inflammation at advanced stages.<sup>19</sup> Instability of atherosclerotic plaque is triggered by increased oxidative stress and reactive oxygen radicals while antioxidant capacity decreases during this process. Subsequently, the balance of oxidative and antioxidant system, which is an important regulator of cellular protection, detoxification, apoptosis and enzymatic activities, begins to deteriorate.<sup>20</sup> A previous study showed that levels of oxidative stress markers increase after MI and reperfusion.<sup>21</sup> In our study, there was a negative and statistically significant

correlation between plasma thiol levels and age and troponin, whereas there was a positive and statistically significant correlation between thiol levels and LVEF. These results were consistent with a previous study published by Kundi et al..<sup>6</sup> Sivri et al. demonstrated lower plasma total thiol and native thiol levels in NSTEMI-ACS patients compared to the control group patients. In addition, they demonstrated an inverse relationship between the GRACE score and total plasma thiol and native thiol levels.<sup>22</sup> According to our study, which included STE-ACS and NSTEMI-ACS patients, a significant negative correlation was observed between the GRACE score and thiol parameters. Correlation of thiol with these strong diagnostic and prognostic markers such as troponin and the GRACE score might underline that it may be an important

**Table 3 – Independent predictors of ventricular arrhythmia by logistic regression analysis**

| Variables                           | OR    | 95%CI |       | p value |
|-------------------------------------|-------|-------|-------|---------|
|                                     |       | Lower | Upper |         |
| Ventricular arrhythmia/STE          |       |       |       |         |
| LDL                                 | 1.021 | 0.997 | 1.045 | 0.08    |
| Age                                 | 1.026 | 0.965 | 1.091 | 0.40    |
| LVEF (%)                            | 1.044 | 0.943 | 1.155 | 0.40    |
| Potassium                           | 0.849 | 0.214 | 3.366 | 0.81    |
| Magnesium                           | 1.072 | 0.121 | 9.518 | 0.95    |
| NLR                                 | 1.142 | 0.997 | 1.308 | 0.05    |
| Admission time                      | 1.016 | 0.994 | 1.038 | 0.15    |
| Troponin/native thiol               | 1.030 | 0.981 | 1.081 | 0.23    |
| Troponin                            | 1.000 | 1.000 | 1.000 | 0.64    |
| Native thiol                        | 0.962 | 0.937 | 0.986 | 0.03*   |
| Nagelkerke R² = 0.257, p: 0.07      |       |       |       |         |
| Ventricular arrhythmia/NSTE-ACS     |       |       |       |         |
| LDL                                 | 0.970 | 0.940 | 1.001 | 0.05    |
| Age                                 | 1.086 | 0.985 | 1.196 | 0.09    |
| LVEF (%)                            | 1.034 | 0.917 | 1.165 | 0.58    |
| Potassium                           | 1.278 | 0.218 | 7.488 | 0.78    |
| Magnesium                           | 0.105 | 0.001 | 11.00 | 0.34    |
| NLR                                 | 1.102 | 0.919 | 1.321 | 0.29    |
| Admission time                      | 1.003 | 0.988 | 1.019 | 0.68    |
| Troponin/native thiol               | 1.263 | 1.061 | 1.504 | 0.009*  |
| Troponin                            | 1.001 | 1.000 | 1.001 | 0.05    |
| Native thiol                        | 0.969 | 0.947 | 0.992 | 0.08    |
| Nagelkerke R² = 0.592, p<0.001      |       |       |       |         |
| Ventricular arrhythmia/All patients |       |       |       |         |
| LDL                                 | 1.001 | 0.987 | 1.015 | 0.90    |
| Age                                 | 1.040 | 0.998 | 1.084 | 0.06    |
| LVEF (%)                            | 0.994 | 0.940 | 1.051 | 0.82    |
| Potassium                           | 0.867 | 0.346 | 2.169 | 0.76    |
| Magnesium                           | 0.681 | 0.096 | 4.845 | 0.70    |
| NLR                                 | 1.087 | 1.000 | 1.182 | 0.05    |
| Admission time                      | 1.002 | 0.995 | 1.008 | 0.57    |
| Troponin/native thiol               | 1.059 | 1.022 | 1.098 | 0.002*  |
| Troponin                            | 1.000 | 1.000 | 1.000 | 0.10    |
| Native thiol                        | 0.976 | 0.966 | 0.986 | <0.001* |
| Nagelkerke R2 =0.240, p: 0.001      |       |       |       |         |

Multivariate logistic regression analysis. The regression model included age, low-density lipoprotein (LDL), left ventricular ejection fraction (LVEF, %), serum potassium, serum magnesium, neutrophil-lymphocyte ratio (NLR) and hospital admission time as possible independent variables. 95% CI: 95% confidence interval; OR: odds ratio. \* p<0.05 was considered significant for statistical analyses.

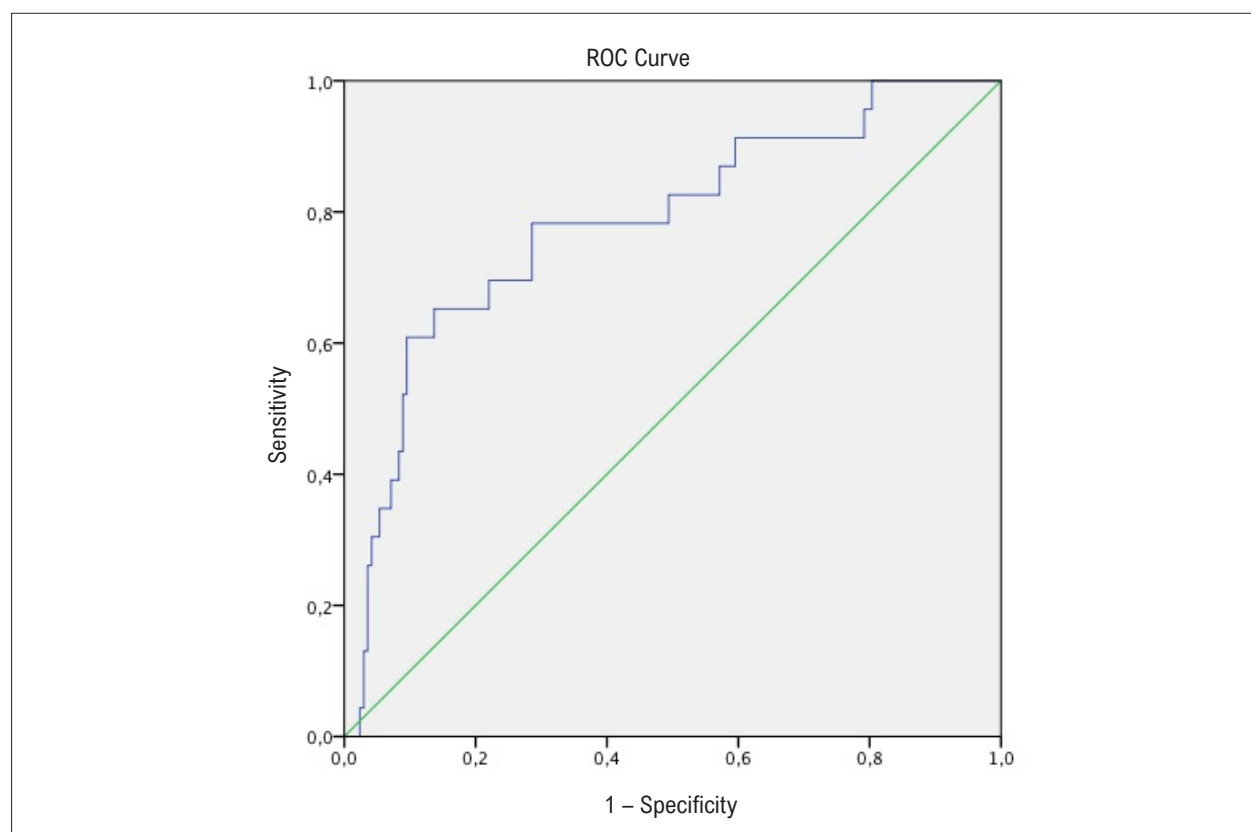


**Figure 2** – Receiver operating characteristic (ROC) curve analyses for prediction of ventricular arrhythmia development in all patients.

marker for diagnosis and prognosis of ACS with the help of future studies.

More than 80% of sudden cardiac deaths are due to atherosclerotic coronary artery disease (CAD), and the most common cause is VAs due to ischemia resulting from CAD and ACS.<sup>23</sup> Therefore, early prediction, diagnosis and effective treatment of VAs is very important. During oxidative stress, sensitivity of elderly hearts to VF increases. In one study, oxidative stress induced by hydrogen peroxide was shown to be associated with increased early afterdepolarizations and triggered activity in ventricular myocytes.<sup>24</sup> Although the myocardium has a strong defense mechanism, it is susceptible to oxidative stress because of its high workload and oxygen need. As a result of ischemia, there is a decrease in antioxidant levels such as mitochondrial superoxide dismutase and intracellular glutathione against free oxygen radicals. In addition, the production of free oxygen radicals increases in mitochondria and leukocytes, and production of oxygen metabolites increases during the reperfusion period, which can be more toxic by re-introduction of oxygen. Oxidative stress firstly causes oxidation of thiol groups and this leads to a reversible damage at the initial stage. At later stages, this process leads to accelerated necrosis and predisposition to arrhythmias. In the early period, it may induce myocardial membrane electrical imbalance, alterations in the permeability of ion channels

and cause induction of arrhythmogenic changes in the potential pattern of ventricular action.<sup>21</sup> An increase in the duration of action potential was observed after exposure to free oxygen radicals followed by the appearance of early and after depolarizations.<sup>25,26</sup> In the light of the previously published reports, we have hypothesized that thiol levels may predict VA development in ACS patients and found that TNTR can be used to predict VA development in NSTEMI-ACS patients but not in STEMI-ACS patients. This disagreement may originate in the pathophysiological and clinical diversities between STEMI-ACS and NSTEMI-ACS. STEMI-ACS is a result of total occlusion of the vessel with fibrin-rich clot, whereas NSTEMI-ACS is a result of subtotal occlusion of the vessel with platelet-rich clot. Additionally, hospital admission time is shorter in STEMI-ACS patients and, consequently, revascularization time is faster compared to NSTEMI-ACS patients. Therefore, it is reasonable to speculate that there is not sufficient time for oxidative process to progress to plasma at the cellular level in STEMI-ACS patients. However, due to the fact that revascularization time is longer in NSTEMI-ACS patients, progression of oxidative stress from cardiomyocytes to plasma can be more pronounced. In addition, NSTEMI-ACS patients are older than STEMI-ACS patients and suffer from comorbidities such as DM and/or hypertension more often compared to STEMI-ACS patients as shown in our study group. These comorbidities might have affected the oxidative status in NSTEMI-ACS patients.

Our study has several limitations. Firstly, the number of samples is relatively small and this is a single-center study. Secondly, this is an observational study and it should be supported by further clinical follow-up and experimental studies aiming to explain prognosis and pathophysiological relationships between thiol and VAs in ACS patients. Thirdly, other oxidative parameters such as total antioxidant status, total oxidant status, paraoxonase and other inflammation parameters such as CRP and fibrinogen were not evaluated in our study due to the study design. Lastly, the effect of revascularization on oxidative parameters has not been evaluated due to the study design. Further studies involving more patients with more homogenous clinical characteristics may produce more generalizing and consistent results.

## Conclusion

In conclusion, plasma thiol parameters, which are inexpensive oxidative status markers detected rapidly in blood, can be used to identify high risk for in-hospital VA development in ACS patients. Correlation between troponin and thiol levels may suggest that thiol may be an important marker for diagnosis and prognosis of ACS with the help of future studies.

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Conception and design of the research, Analysis and interpretation of the data and Writing of the manuscript: Erdoğan M, Ozturk S, Tutar EO, Arslan E, Çelik MC, Baştuğ S, Neşelioğlu S; Acquisition of data: Erdoğan M, Tutar EO, Arslan E, Çelik MC, Neşelioğlu S; Statistical analysis: Erdoğan M, Ozturk S, Çelik MC, Baştuğ S; Critical revision of the manuscript for intellectual content: Erdoğan M, Ozturk S, Tutar EO, Arslan E, Çelik MC, Baştuğ S, Neşelioğlu S.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

There were no external funding sources for this study.

## Study Association

This study is not associated with any thesis or dissertation work.

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## Elevated Thiol Levels: A New Marker of Ventricular Arrhythmias in Acute Coronary Syndrome?

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Short Editorial related to the article: Association between Plasma Thiol Parameters and Troponin Levels in Patients with Acute Coronary Syndrome and Prediction of In-Hospital Ventricular Arrhythmia

Ventricular arrhythmias in patients with acute coronary syndrome are not frequent, but they lead to a greater occurrence of complications and death.<sup>1,2</sup> Its prevalence is higher in infarction with ST-segment elevation (STEMI) and has a worse prognosis when it occurs 48 hours after admission.<sup>3</sup> Thus, a marker capable of predicting the occurrence of these events is welcome.

Three mechanisms justify the occurrence of arrhythmias in the acute phase of the infarction:

- Injured myocardium can be a substrate for the development of reentry circuits or a focus of increased automaticity;
- Triggering of arrhythmias secondary to heart rate variation;
- Modulating factors, such as electrolyte disturbances, autonomic dysfunction, persistent ischemia, or reduced left ventricular function.

Thus, the identification of markers that influence these mechanisms can be the key to a new predictor. Thiols have antioxidant activity and, during oxidative processes, they can be transformed into different molecules, such as thiol-disulfide.<sup>4</sup> Studies have already shown that the thiol-disulfide ratio is a promising marker of oxidative stress.<sup>5,6</sup>

Erdoğan et al. studied the association between plasma thiol parameters and troponin levels in patients with acute coronary syndrome (ACS) and the prediction of in-hospital ventricular arrhythmia.<sup>7</sup>

A total of 191 patients diagnosed with ACS were studied, subdivided into ACS without ST-segment elevation (SCA-SSDST) and with ST-segment elevation (SCA-SDST). In addition to the dosage of native thiol, disulfide, and the thiol-disulfide ratio, other parameters were evaluated, both in a univariate model and in the logistic regression model, such as LDL, age, LVEF, serum potassium, and magnesium levels, neutrophil-lymphocyte ratio (RNL), time to hospitalization, troponin/native thiol ratio (RTTN), and troponin.

There was no difference in plasma thiol levels (native or total), disulfide, native disulfide-thiol ratio, total disulfide-thiol ratio,

and native thiol-total thiol ratio when comparing SCA-SSDST and SCA-SDST, demonstrating that both diagnoses are similar in terms of the degree of oxidative stress. Likewise, no difference was found regarding the occurrence of ventricular arrhythmias.

In the analysis of correlation of multiple variables with oxidative stress parameters, many showed significant results, but with weak or moderate correlation. The best correlation was observed with the CK-MB mass dosage with the troponin-native thiol ratio ( $r=0.63$ ;  $p<0.001$ ), probably due to the correlation of this biomarker with troponin.

Finally, logistic regression to predict ventricular arrhythmias was performed in three scenarios: SCA-SSDST, SCA-SDST, and the entire population. In SCA-SDST, native thiol was an independent predictor, while RTTN was a predictor in SCA-SSDST. In the entire ACS population, both markers (native thiol and RTTN) were the predictor variables. A greater emphasis was given to the RTTN, which presented a good area under the curve ( $AUC=0.783$ ), with good specificity and sensitivity for predicting ventricular arrhythmias.

This is the first study to demonstrate the correlation of oxidative stress markers with ventricular arrhythmias, highlighting RTTN. The main marker currently known is the area of myocardial damage, documented through the ejection fraction.<sup>8</sup> Patients with reduced ejection fraction deserve special attention regarding the need for implantable defibrillators, due to the risk of ventricular arrhythmias.

Troponin levels directly influence RTTN and may demonstrate greater myocardial damage and, therefore, greater risk of ventricular arrhythmias. The present study does not present the ROC curve for native thiol, although it was also considered a marker in logistic regression, limiting the evaluation of this marker. We know that troponin is an important prognostic marker in patients with SCA<sup>9</sup> and has a correlation with the area of myocardial damage.

On the other hand, this and other studies have shown a correlation between thiol levels and severity (GRACE score), including the occurrence of adverse events.<sup>10</sup> Furthermore, Rajic D et al. demonstrated that the serum thiol level was an independent predictor of infarction-related complications, especially ventricular dysfunction.<sup>11</sup> Thus, the question arises whether thiol is an independent predictor of ventricular arrhythmia or another marker of ventricular damage and dysfunction.

Serum thiol dosage is not part of the routine evaluation of a patient with ACS. Therefore, broader studies are needed to assess the real impact of incorporating this technology in the management of these patients.

### Keywords

Sulfhydryl Compounds; Arrhythmias, Cardiac; Acute Coronary Syndrome.

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**DOI:** <https://doi.org/10.36660/abc.20210602>

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# VEGF121 Mediates Post-Hypoxia Cardioprotective Effects Via CaSR and Mitochondria-Dependent Protease Pathway

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## Abstract

**Background:** Cardiovascular disease is the major cause of death worldwide. Hypoxia-mediated apoptosis in cardiomyocytes is a major cause of cardiovascular disorders. Treatment with vascular endothelial growth factor (VEGF) protein has been tested but operational difficulties have limited its use. However, with the advancements of gene therapy, interest has risen in VEGF-based gene therapy in cardiovascular disorders. However, the precise mechanism by which VEGF replenishment rescues post-hypoxia damage in cardiomyocytes is not known.

**Objectives:** To investigate the effect of post-hypoxia VEGF121 expression using neonatal rat cardiomyocytes.

**Methods:** Cardiomyocytes isolated from neonatal rats were used to establish an in vitro model of hypoxia-induced cardiac injury. The effect of VEGF overexpression, alone or in combination with small-molecule inhibitors targeting calcium channel, calcium sensitive receptors (CaSR), and calpain on cell growth and proliferation on hypoxia-induced cardiomyocyte injury were determined using an MTT assay, TUNEL staining, Annexin V/PI staining, lactate dehydrogenase and caspase activity. For statistical analysis, a value of  $P < 0.05$  was considered to be significant.

**Results:** The effect of VEGF121 was found to be mediated by CaSR and calpain but was not dependent on calcium channels.

**Conclusions:** Our findings, even though using an in vitro setting, lay the foundation for future validation and pre-clinical testing of VEGF-based gene therapy in cardiovascular diseases.

**Keywords:** Vascular Endothelial Growth Factor A; Calcium Sensing Receptors; Cardiovascular Disease.

## Introduction

Cardiovascular disease is the major cause of death worldwide. The main mechanism of cardiovascular disease caused by hypoxia-ischemia is cardiomyocyte apoptosis, fibroblast proliferation and vascular endothelial cell damage, leading to vascular remodeling and cardiac dysfunction.<sup>1,2</sup> Although current treatments such as coronary angioplasty and coronary artery bypass grafting have significantly improved the prognosis in patients with cardiovascular disease and prolonged life, the mortality rate remains high.<sup>3</sup> In recent years, with the rapid development of genetic recombination technology, potential gene therapy for ischemic cardiomyopathy has become an area of major focus.<sup>4-8</sup>

Apoptosis is an important mechanism for the deterioration of heart disease after hypoxia.<sup>9</sup> The exogenous apoptosis activation

pathway stimulates the Fas receptor through external factors such as hypoxia, and the death complex in the cell membrane is activated, causing apoptosis. In the endogenous activation pathway or the mitochondria-mediated apoptosis pathway, the apoptosis-inducing factor (AIF) and cytochrome c (Cyt-c) are released after the activation of mitochondrial permeability transition pore (PTP) signal, the pro-apoptotic protein Bid is cleaved into a truncated form called tBid, which together activate caspase-induced apoptosis.<sup>10</sup>

Myocardial apoptosis is closely related to calcium overload, and it is believed that calcium overload is closely related to the mitochondria-mediated apoptosis pathway.<sup>10</sup> The calcium-sensing receptor (CaSR), as a member of the G-protein coupled receptor C-family, maintains  $Ca^{2+}$  and other metal ion homeostasis, regulates extracellular  $Ca^{2+}$ , and acts as an inhibitor and agonist in the myocardium.<sup>11</sup> Calpain is an apoptotic protein that is dependent on the activation of the mitochondrial pathway of  $Ca^{2+}$  influx. Upon activation, it can induce the final activation of caspase-3, leading to cardiomyocyte apoptosis.<sup>12</sup>

It has been shown that cardiomyocytes express VEGF receptors;<sup>13</sup> the binding of VEGF to these receptors activate mitogen-activated protein kinases<sup>14</sup> VEGF has also been shown to promote the re-entrance of cardiomyocytes into the cell cycle, leading to an increase in cell division in the heart. The latter

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Manuscript received April 05, 2020, revised manuscript June 24, 2020, accepted September 09, 2020

**DOI:** <https://doi.org/10.36660/abc.20190902>

process, if not controlled, can end up in cardiac hypertrophy.<sup>15</sup> Using a pig model of chronic myocardial ischemia, it has been shown that VEGF can also induce cardiomyocyte karyokinesis.<sup>16</sup> This establishes an important and often neglected role of VEGF in cardiomyocyte homeostasis.

Vascular endothelial growth factor (VEGF) protein therapy has been used to treat cardiovascular disease. However, it has been limited due to the high cost of VEGF protein therapy and the need for repeated drug administration.<sup>17</sup> However, with the advances made in gene therapy, VEGF gene therapy research is being actively considered. However, the mechanism through which replenishment of VEGF works remains to be determined. Here, we used liposome-mediated transfection of VEGF121 into primary cultured cardiomyocytes submitted to hypoxia to investigate the downstream effects of VEGF replenishment in cardiomyocytes.

## Methods

### Isolation of rat primary cardiomyocyte

This study was approved by the Institutional Animal Care and Use Committee of The Affiliated Hospital of Guizhou Medical University (Approval Certificate No. SCXK (Qian) 2002-0001). Cardiomyocytes were isolated from 0-3-day-old neonatal Sprague Dawley rats, as previously described.<sup>14</sup>

### Primary cell culture and grouping

The cardiomyocytes were counted and cultured in gelatin-coated 6-cm culture dishes ( $1 \times 10^7$  cells/dish) in high-glucose DMEM, without calf serum. There were 6 experimental groups - Group 1 (negative control group); Group 2 (hypoxia model group); Group 3 (hypoxia model group transfected with VEGF121); Group 4 (same as Group 3, but with calcium-channel inhibitor CdCl<sub>2</sub>); Group 5 (same as Group 3 but with CaSR receptor inhibitor NPS2390); Group 6 (same as Group 3 but with calpain inhibitor Calpeptin).

For Groups 2-6, the cells were treated with ischemia buffer (137 mM NaCl, 15.8 mM KCl, 0.49 mM MgCl<sub>2</sub>, 0.9 mM CaCl<sub>2</sub>, 4 mM HEPES, 10 mM 2-deoxyglucose, 20 mM sodium lactate and 1 mM sodium dithionite, pH 6.5)<sup>18,19</sup> for 2 h. For Groups 3-6, cells were then transfected with pcDNA3.1(+)/VEGF121 using Lipofectamine 2000 (Thermo Fisher Scientific) according to the manufacturer's guidelines and then incubated in DMEM containing 8% fetal bovine serum alone (Group 3) or with the respective inhibitors (Groups 4-6). The 24-h post-transfection supernatant of the cardiomyocytes was removed for use.

### MTT assay

The MTT assay (Sigma Millipore, USA) was used to detect cardiomyocyte growth in the different experimental groups, as previously described.<sup>20</sup> Absorbance was measured at 570 nm.

### Intracellular lactate dehydrogenase (LDH) activity and LDH leakage rate

The LDH activity was measured using the Lactate Dehydrogenase Activity Assay Kit (Sigma Millipore, USA) following the manufacturer's instructions. External leakage rate

was calculated as  $\text{LDH} = [\text{culture medium LDH} / (\text{culture medium LDH} + \text{cell LDH})] \times 100\%$ .

### TUNEL assay

For the TUNEL assay, the cardiomyocytes were cultured in 24-well plates ( $1 \times 10^4$  cells/well) for 24h and fixed in 4% paraformaldehyde for 15min. After two washes with PBS, the cardiomyocytes were incubated with Terminal deoxynucleotidyl transferase (TdT) reaction solution for 2h at 37°C. Stained cells were counted using a fluorescent microscope. The apoptosis rate was calculated according to the formula: apoptosis rate (%) =  $[\text{number of apoptotic cells} / \text{total number of cells}] \times 100\%$ .

### Annexin V/PI staining

The transfected cells were dislodged by treatment with Accutase (BD Biosciences, USA) for 2 minutes at room temperature, quickly washed in PBS and then stained with Annexin V-FITC and propidium iodide (PI; BD Biosciences, San Jose, CA, USA). Flow cytometry analysis (Cytomics FC500; Beckman Coulter, Miami, FL, USA) was used to measure the apoptotic cells. Acquisition events were standardized by using control cells. Annexin V<sup>+</sup>PI<sup>-</sup> and Annexin V<sup>+</sup>PI<sup>+</sup> were considered as the early and late apoptotic cells, respectively.

### Analysis of caspase-3 activity

Caspase-3 activity was measured using a commercial kit, according to the manufacturer's protocols (APOPCYTO Caspase-3 Colorimetric Assay Kit; Medical and Biological Laboratories, Japan) as described in a previous study.<sup>21</sup>

### Western blot analysis

At the end of the experimental time points, the cells were washed with ice-cold PBS and then lysed using RIPA buffer. The lysate was centrifuged at 12,000 g for 3 minutes and the protein concentration in the supernatant was quantified using a BSA kit (Thermo Fisher, USA). Twenty micrograms of protein of each sample was resolved by SDS-PAGE and then processed for immunoblotting, using routine methodologies.<sup>14</sup> The blot was probed with antibodies against VEGF, CaSR, calpain, AIF, the pro-apoptotic protein truncated Bid (tBid), and  $\beta$ -actin (all antibodies obtained from Abcam, USA). The same blot was stripped and probed for different antibodies.  $\beta$ -actin was used as a loading control. The densitometry analysis was performed using the NIH Image J software.

### Statistical analysis

The statistical analysis was performed using SPSS 20.0 (IBM Corporation, NY, USA). All data are shown as mean  $\pm$  standard deviation (SD). Given the small sample size, the normality test was performed using the Kolmogorov-Smirnov test. The unpaired Student's t-test was used to compare the means of two groups, while the differences between multiple groups were analyzed using one-way ANOVA. The sample size was not determined by a set methodology but was largely dictated by convenience; however, every experiment had at least three independent biological and technical replicates. A value of  $p < 0.05$  was considered as statistically significant.

## Results

### VEGF overexpression can rescue cell growth of cardiomyocytes submitted to hypoxia

Cell count and morphological characteristics (Figure 1A) of primary cultured cardiomyocytes from Group 1 on day 3 confirmed that the isolated cardiomyocytes were proliferating and growing robustly *in vitro*. Trypan blue staining was used to determine relative cell death after 3 days in culture and more than 95% of the cardiomyocytes were viable. Then, the effect of hypoxia (ischemia buffer) on VEGF protein expression in cardiomyocytes (Group B) was determined. The culture in the ischemia buffer decreased VEGF protein expression (Figure 1B), indicating successful establishment of the *in vitro* model system. Immunoblotting in Group C (hypoxia model group transfected with VEGF121) confirmed the successful overexpression of VEGF (Figure 1B).

Subsequently, the MTT assay was used to determine relative cell growth in the different experimental groups when compared to Group 1 (negative control). Hypoxia significantly inhibited cell growth in Group 2 (model group) compared to Group 1 (Figure 1C;  $p < 0.001$ ). Next, the effect of VEGF121 overexpression was tested alone or in combination with Ca<sup>2+</sup> channel inhibitor CdCl<sub>2</sub>, CaSR inhibitor NPS2390, and calpain inhibitor calpeptin. VEGF121 overexpression significantly

increased cell growth in the cardiomyocytes exposed to hypoxia. Further addition of NPS2390 and calpeptin, but not CdCl<sub>2</sub>, resulted in a synergistic effect, further increasing cardiomyocyte growth (Figure 1C).

### Detection of cardiomyocyte apoptosis

Given that VEGF overexpression showed to be increasing cardiomyocyte cell proliferation, it was decided to investigate whether VEGF overexpression was also attenuating hypoxia-induced apoptotic death in the cardiomyocytes. Apoptosis was detected by TUNEL and Annexin V/PI staining. Compared to the negative control Group 1, hypoxia induced significant apoptotic cell death (Figure 2A, B). VEGF121 overexpression significantly attenuated hypoxia-induced cell death (Figure 2A, B). As with cell proliferation, both NPS2390 and calpeptin had a synergistic effect with VEGF121 overexpression in attenuating hypoxia-induced cell death, whereas the addition of CdCl<sub>2</sub> did not have any additional effect (Figure 2A, B). Taken together, these results indicated that VEGF expression mitigates hypoxia-induced cell death via CaSR receptor activation and calpain.

### Effects of VEGF on the LDH release and caspase-3 activity

Next, it was investigated whether the effect of VEGF on cell death inhibition in cardiomyocytes was being mediated by

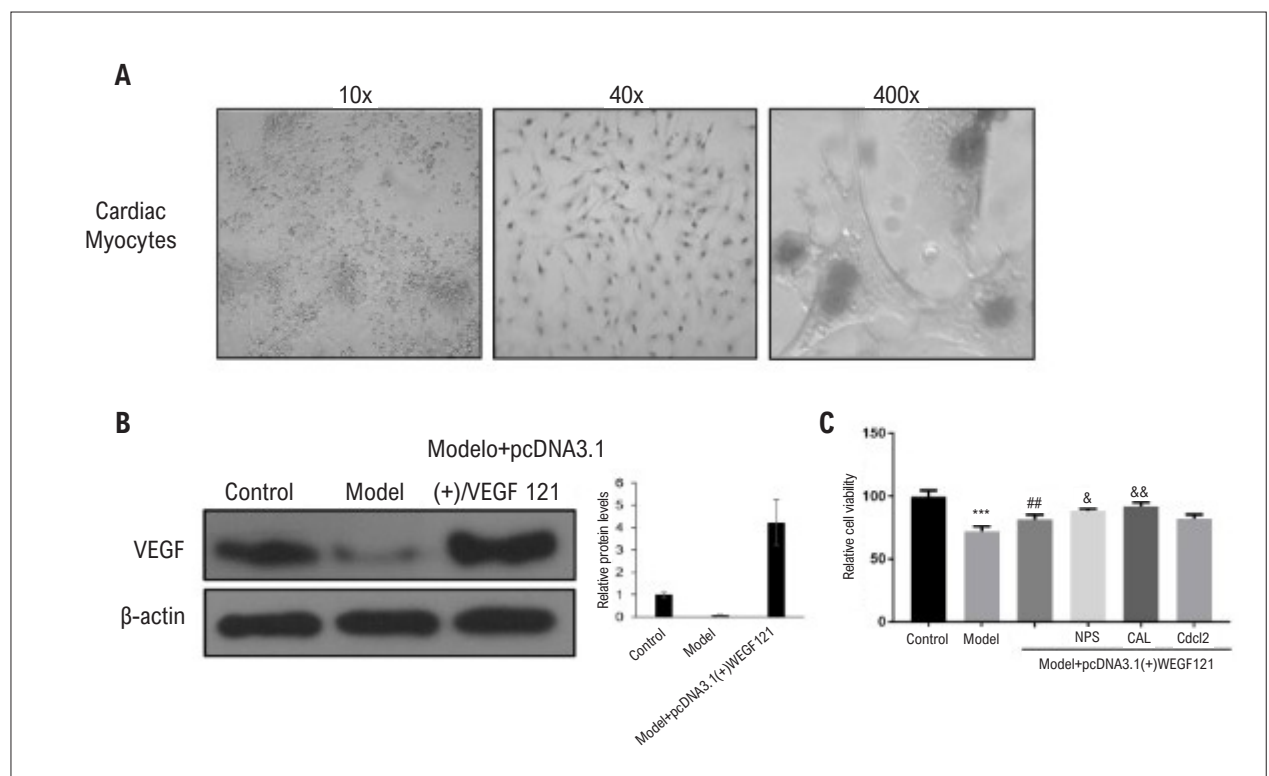


**Figure 1** – Rat cardiomyocyte hypoxia model and determination of cardiomyocyte cell growth under different experimental conditions. (A) Morphology of normal neonatal rat cardiac myocytes after 3 days (different magnifications of 10x, 40x, and 400x are shown). (B) Western blot analysis of VEGF in neonatal rat cardiac myocytes. The graph shows the relative expression normalized to  $\beta$ -actin. \* $p < 0.05$ ;  $n = 6$ . (C) the MTT proliferation assay after the indicated treatments (for 5h) in neonatal rat cardiac myocytes. Data is representative of 6 different experimental replicates. \*\*\* $p < 0.001$  vs. control group; ## $p < 0.01$  vs. Model group; & $p < 0.05$ , && $p < 0.01$  vs. Model + pcDNA3.1(+)/VEGF121 group.

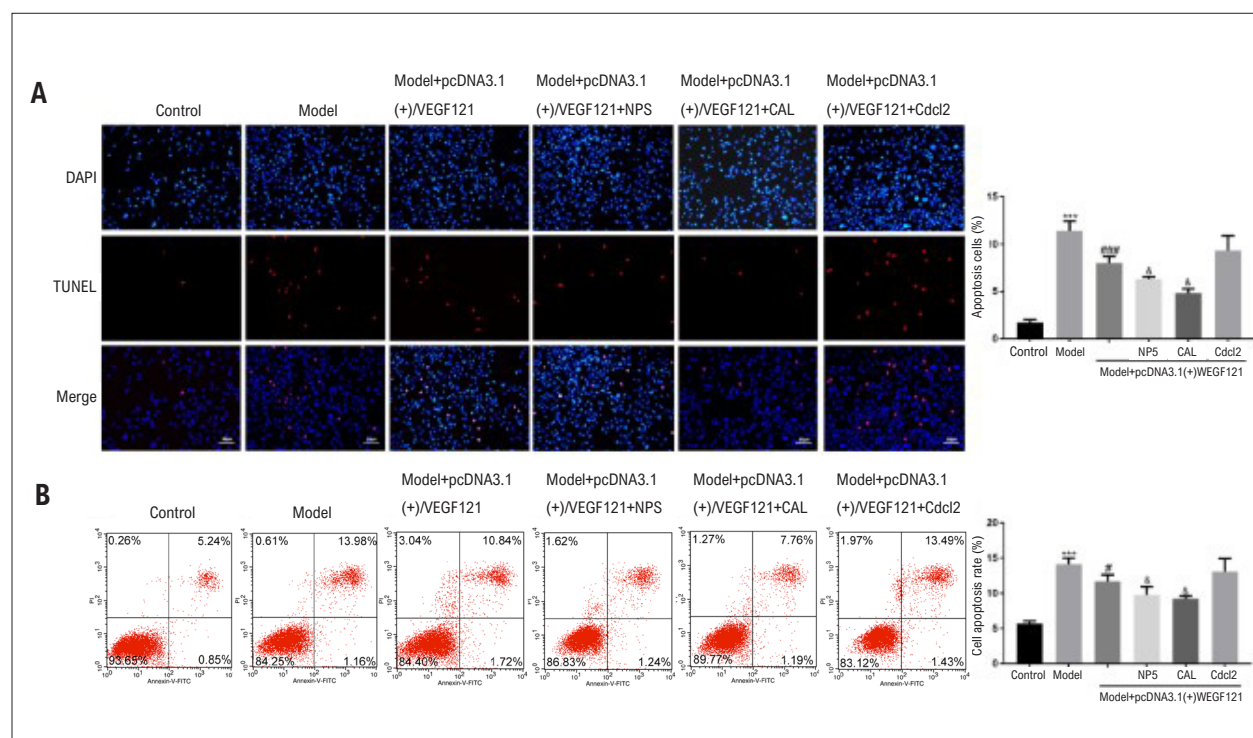


**Figure 2 – VEGF can rescue hypoxia-induced cell death in cardiomyocytes.** Experimental groups were - Group 1 (negative control group); Group 2 (hypoxia model group); Group 3 (hypoxia model group transfected with VEGF121); Group 4 (same as Group 3 but with calcium channel inhibitor CdCl<sub>2</sub>); Group 5 (same as Group 3 but with CaSR receptor inhibitor NPS2390); Group 6 (same as Group 3 but with calpain inhibitor Calpeptin). (A) TUNEL staining of cardiac myocytes following different treatments. Graph shows quantification of images. (B) Annexin V/PI staining of cardiac myocytes following different treatments. Graph shows quantification of flow cytometry data. \*\*\**p* < 0.001 vs. control group; \*\**p* < 0.01 vs. Model group; \**p* < 0.05 vs. Model + pcDNA3.1(+)/VEGF121 group; *n* = 10 in A and *n* = 3 in B.

decreasing LDH release and/or decreasing caspase-3 activity. LDH-activity in cardiomyocytes was measured, and the results showed that the LDH leakage rate in cardiomyocytes was increased after hypoxia induction ( $P < 0.001$ ). VEGF121 overexpression significantly decreased LDH leakage rate (Figure 3A). Both NPS2390 and calpeptin had a synergistic effect with VEGF121 overexpression in decreasing LDH leakage rate, whereas the addition of CdCl<sub>2</sub> did not have any additional effect (Figure 3A). A similar observation was made with caspase-3 activity (Figure 3B).

#### Impact of hypoxia and VEGF on CaSR, Calpain, AIF, and tBid expression

Hypoxia significantly induced the expression of CaSR, calpain, AIF and tBid proteins (Figure 4;  $p < 0.001$ ). The expression levels of CaSR, calpain, AIF and tBid protein decreased after transfection of cardiomyocytes with pcDNA 3.1(+)/VEGF121, which was statistically significant when compared with the hypoxia model group ( $P < 0.001$ ). After cardiomyocyte treatment with NPS2390 and Calpeptin, the expression of tBid and AIF decreased, when compared to the Model + pcDNA 3.1(+)/VEGF121 group ( $P < 0.05$ ). After pcDNA3.1(+)/VEGF121 intervention in the cardiomyocytes, the expression of CaSR decreased, which was statistically significant when compared with the model group ( $p < 0.001$ ). Again, a synergistic effect was observed with NPS2390 and calpeptin, but not with CdCl<sub>2</sub>.

#### Discussion

The main mechanisms of cardiovascular disease caused by hypoxia-ischemia are myocardial apoptosis, fibroblast proliferation and vascular endothelial cell injury.<sup>22-24</sup> VEGF, a specific mitogen of vascular endothelial cells, constitutes a family of secreted proteins, including VEGF121, VEGF165, VEGF189 and VEGF206, of which VEGF121 and VEGF165 are the main treatments for ischemic cardiomyopathy. It has been reported that VEGF121 can only bind to the VEGFR-2 receptor, and its VEGF-specific binding may attenuate angiogenesis, but other studies have also found that its ability to bind to heparin is weakened, which is more conducive to an anoxic environment. The direct injection of the VEGF121 plasmid into the pig myocardial infarction model has shown to improve blood supply and increase the number of collateral vessels at the same time, highlighting the potential of VEGF-based gene therapy. However, there are some limitations of instability, high price, and lack of high-dose application in clinical practice. At the same time, studies have also found that the gene product encoding secreted protein has a paracrine effect, compared with the cell's own protein.<sup>25</sup>

Cardiomyocytes are terminally differentiated cells, whose apoptosis is closely related to myocardial disease. Caspase-3 is the common mediator of apoptosis in cardiomyocytes.<sup>26,27</sup> Heart failure shows different apoptotic rates of cardiomyocytes. In animal experiments of heart failure caused by hypoxia-reperfusion, the apoptotic rate of cardiomyocytes can reach 14%, and heart failure

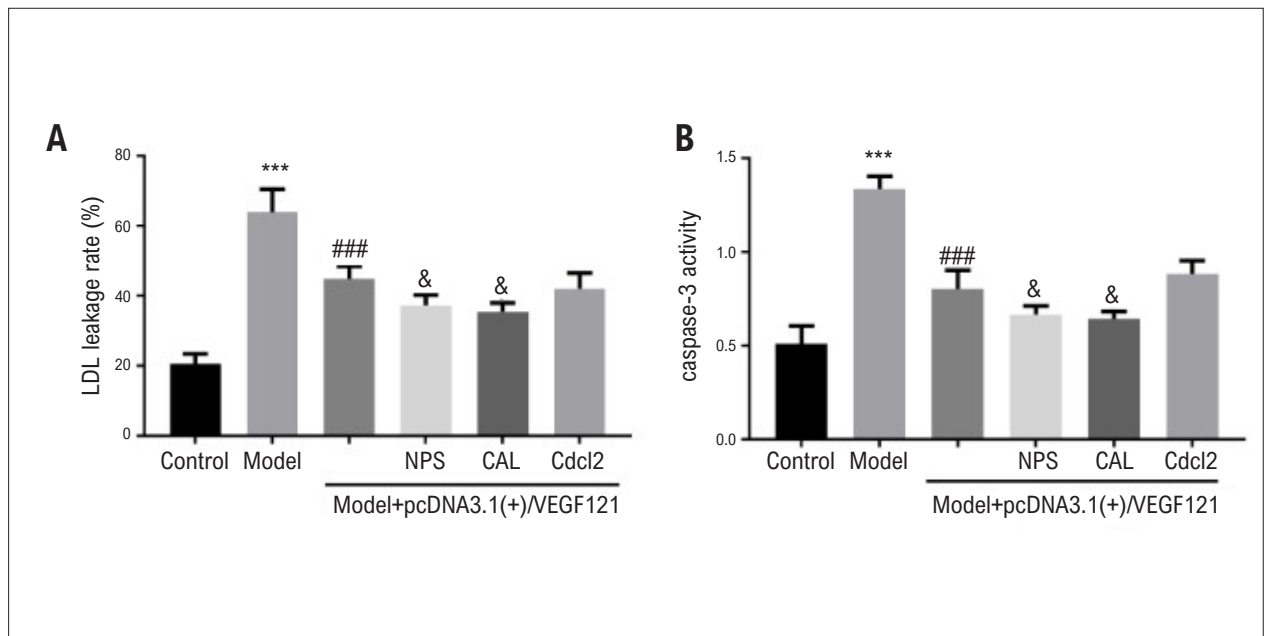


**Figure 3** – VEGF can inhibit LDH leakage and Caspase-3 activity in hypoxia-treated cardiomyocytes. Experimental groups were - Group 1 (negative control group); Group 2 (hypoxia model group); Group 3 (hypoxia model group transfected with VEGF121); Group 4 (same as Group 3 but with calcium channel inhibitor CdCl<sub>2</sub>); Group 5 (same as Group 3 but with CaSR receptor inhibitor NPS2390); Group 6 (same as Group 3 but with calpain inhibitor Calpeptin). Shown are data for LDH leakage (A) and caspase-3 activity (B) from five independent replicates. \*\*\**p* < 0.001 vs. control group; ###*p* < 0.05 vs. Model group; &*p* < 0.05 vs. Model + pcDNA3.1(+)/VEGF121 group.

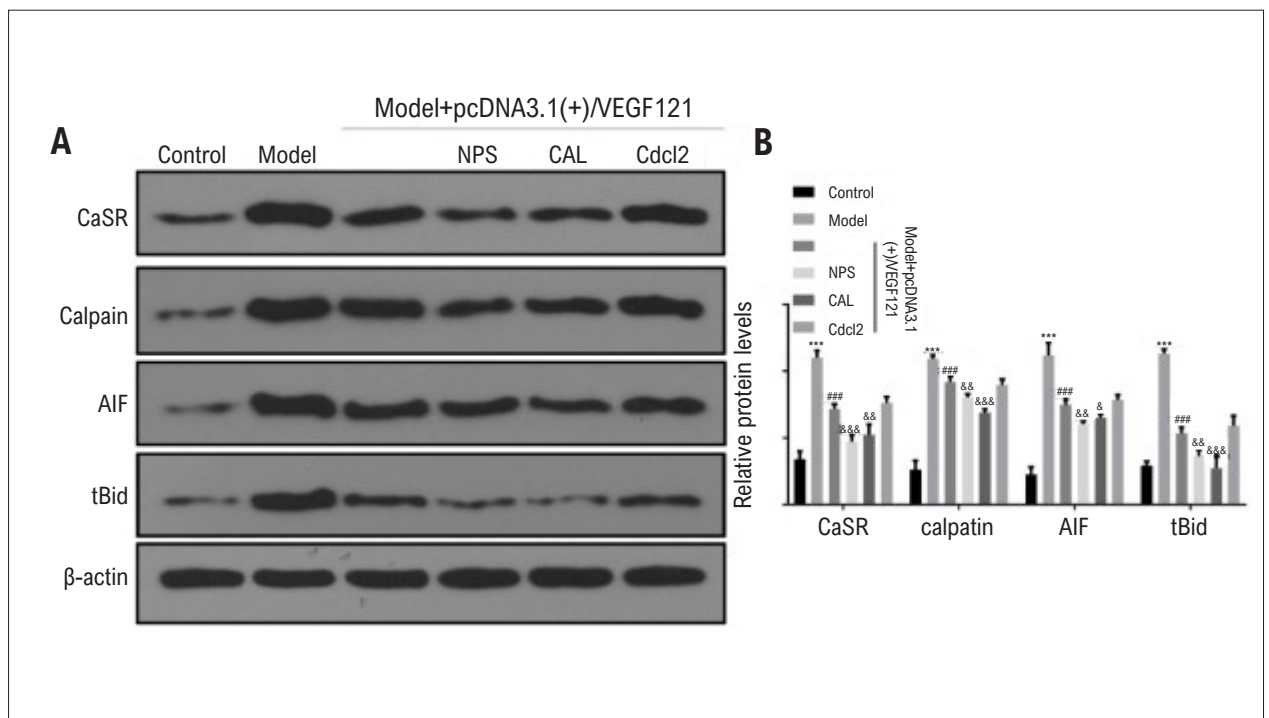


**Figure 4** – Impact of hypoxia, VEGF and indicated inhibitors on CaSR, Calpain, AIF, and tBid protein expression. Experimental groups were - Group 1 (negative control group); Group 2 (hypoxia model group); Group 3 (hypoxia model group transfected with VEGF121); Group 4 (same as Group 3 but with calcium channel inhibitor CdCl<sub>2</sub>); Group 5 (same as Group 3 but with CaSR receptor inhibitor NPS2390); Group 6 (same as Group 3 but with calpain inhibitor Calpeptin). (A, B) CaSR, Calpain, AIF and tBid were detected by Western blot. The Figure shows blots from 4 independent experiments. The graphs show densitometric analysis of blots from the four experimental replicates. \*\*\**p* < 0.001 vs. control group; ###*p* < 0.001 vs. Model group; &*p* < 0.05, &&*p* < 0.01, &&&*p* < 0.001 vs. Model + pcDNA3.1(+)/VEGF121 group.

is caused by excessive pressure overload. The apoptotic rate of cardiomyocytes in the model is only 1%,<sup>24</sup> which suggests that the study of apoptosis in a myocardial hypoxia model is of great value.

The immunoblot analysis confirmed a successful post-transfection VEGF121 expression in cardiomyocytes in the current study. Some studies have also confirmed that<sup>9</sup> the quantitation of VEGF121 in the cell supernatant can confirm the secretion and expression of cardiomyocytes of an eukaryotic expression vector and has a strong proliferative effect on endothelial cells. LDH acts as an extra-leakage rate for intracellular enzymes, and its increase is a marker of cell damage. The LDH leak rate in the hypoxic model group was high and was rescued by VEGF121. Caspase-3 activation in hypoxia was inhibited by VEGF121 and the CaSR inhibitor NPS2390, suggesting that the calpain receptor and calpain are closely related to the mechanism of cardiomyocyte apoptosis.<sup>10</sup> Given that our findings suggested that VEGF121 reverses apoptosis in cardiomyocytes post-hypoxia and CaSR inhibitor had a similar effect, it is suggested that VEGF121 is mediating its activity by inhibiting CaSR activation.

Because the dynamic changes in intracellular calcium levels are one of the important mechanisms of apoptosis,<sup>28,29</sup> the intracellular pathways that affect calcium levels, mainly through  $\text{Ca}^{2+}$  channels and  $\text{Na}^{+}/\text{Ca}^{2+}$  exchange, activate  $\text{Ca}^{2+}$  receptor pathways, such as CaSR. In other pathways,<sup>30</sup> when hypoxia is stimulated, intracellular  $\text{Ca}^{2+}$  influx increases, CaN (Calcineurin) and Bid (Bcl-2 family protein) are activated, and the mitochondrial membrane permeability is significantly increased, thereby releasing Cyt-c to cytoplasmic activation of Caspase-3, thus promoting the damage of cardiomyocyte. Since Calpain is dependent on  $\text{Ca}^{2+}$  influx activation, activated Calpain can cleave and activate Bid. Due to its special BH3 domain, tBid can induce Bax/Bak translocation, resulting in increased mitochondrial membrane permeability, and tBid can also pass through it. The non-BH3 domain induces mitochondrial membrane structural changes, opens PTP, and activates calpain to degrade CaN inhibitory proteins, thereby activating CaN, which promotes phosphorylation of Bad, leading to apoptosis.<sup>31-33</sup>

Bid is the only Bcl-2 family that can be cleaved into small molecule Bids. After activation, it promotes the polymerization of Bak and Bax, or homopolymerizes itself, promotes the remodeling of mitochondrial inner membrane and the opening of mPTP pores, resulting in the release of Cyt-c.<sup>34,35</sup> Our results showed that the expression of tBid protein in hypoxic cardiomyocytes was significantly increased. The level of tBid protein decreased with VEGF overexpression and further synergistically decreased with the addition of NPS2390 and calpeptin, but not with  $\text{CdCl}_2$  addition. It indicated that calcium ion and calpain caused a decrease in the activity of Bid after myocardial apoptosis caused by hypoxia. AIF is located in the mitochondrial inner membrane. When cardiomyocyte apoptosis occurs, the flavin protease containing NADH oxidase activity is released from the mitochondria into the cytoplasm and then translocated into the nucleus, involved in chromatin condensation and DNA fragmentation.<sup>36</sup> In this experiment, CaSR receptor inhibitor (NPS2390) and calpain inhibitor (calpeptin) were added to induce a decrease in AIF protein levels, which was statistically significant. Our results suggested that VEGF121 is involved in cardiomyocyte apoptosis after AIF. Release was associated with CaSR activation, whereas the calpain antagonist calpeptin group and the pcDNA 3.1(+)/VEGF121 intervention

group were not statistically significant, suggesting that it is not solely reliant on downstream calcium-dependent protease-induced apoptosis pathways. One potential limitation of our study is that the experiments were performed using neonatal cardiomyocytes; its relevance needs to be investigated in cardiomyocytes isolated from older rats and in *in vivo* pre-clinical models.

## Conclusion

It has been previously shown that VEGF can treat myocardial ischemia, increase vascular endothelial cell proliferation, increase myocardial collateral circulation and capillary density, thereby improving myocardial blood supply in the ischemic area and improving cardiac function.<sup>37-39</sup> However, damage to vascular endothelial cells, cardiomyocyte hypertrophy, cardiomyocyte apoptosis and fibroblast proliferation are also key pathophysiological changes in ischemic cardiomyopathy. In this study, based on the intervention groups, VEGF121 affected cardiomyocyte proliferation, confirming the biological activity of eukaryotic plasmids on cardiomyocytes. In conclusion, our findings provided a framework for future VEGF-based gene therapy approaches in cardiovascular disorders.

## Acknowledgements

We appreciate the assistance of Dr. Ai-tao Guo for her help.

## Author Contributions

Conception and design of the research: Zhang Y, Wei-hua Y, Ruiqing T; Acquisition of data: Yang F, Yun-qiang A, Zhou W, Yu H, Xie H, Yan-ling Z, Zhu Y; Analysis and interpretation of the data: Yang F, Yun-qiang A, Zhou W, Yu H, Xie H, Yan-ling Z, Zhu Y, Xiang-chun S; Statistical analysis: Xiang-chun S; Obtaining financing: Ruiqing T; Writing of the manuscript: Zhang Y, Wei-hua Y.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

This study was funded by The Joint Fund of Guizhou Province (No. LH2017-7210) and partially funded by Science and Technology Department Academic New Seedling Project (No. 2017-5718) and 2020 Department of Education Natural Science Youth Talent project of Guizhou Province (No. Qian Jiao He KY [2021]148).

## Study Association

This article is part of the thesis of master submitted by Xiang-chun Shen, from Guizhou Medical University.

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital of Guizhou Medical University under the protocol number SCXK (Qian) 2002-0001. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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# Factors Associated with the Occurrence of Arterial Hypertension in Industry Workers of State of Rio Grande do Sul, Brazil

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## Abstract

**Background:** Hypertension is a serious and persistent public health problem and is one of the main causes of cardiovascular diseases and general mortality.

**Objectives:** This study aimed to verify the prevalence and factors associated with systemic arterial hypertension in workers from the state of Rio Grande do Sul, Brazil.

**Methods:** This is a cross-sectional study using the secondary data from 20,792 industry workers from 18 to 59 years of age. The presence of arterial hypertension was determined from systolic blood pressure  $\geq 140$ mmHg and/or diastolic blood pressure  $\geq 90$ mmHg or taking antihypertensive medication. Factors investigated included demographic, socioeconomic, behavioral, nutritional status, and family history characteristics. Poisson regression was used in multivariate analysis, adopting a significance level of  $p < 0.05$ . All analyses were stratified by sex.

**Results:** The sample included 12,349 men and 8,443 women with a mean age of 32.8 years (Standard Deviation = 9.8). The prevalence of arterial hypertension was 10.3% (95% CI: 9.8-10.7), which was significantly higher in men than in women (10.9% vs 9.4%;  $p = 0.001$ ). Arterial hypertension was associated with increased age, a low level of education, living with a partner, being overweight or obese, and having at least one relative with a history of hypertension for both sexes. Women with better socioeconomic conditions presented a lower prevalence of hypertension.

**Conclusions:** The main factors associated with hypertension included sociodemographic, nutritional, and family history characteristics. In addition, socioeconomic conditions showed an association with the occurrence of hypertension, especially among women.

**Keywords:** Hypertension; Risk Factors; Epidemiology; Heredity; Obesity; Workers; Industry.

## Introduction

Systemic Arterial Hypertension (SAH) is a serious problem in public health, as well as a risk factor for cardiovascular diseases.<sup>1-4</sup> It is estimated that the prevalence of SAH in the world population is approximately 22%.<sup>5</sup> In Latin America, Brazil presents one of the highest prevalences of SAH, with a significant difference between men (26.7%) and women (19.9%).<sup>6</sup> Among industry workers, the prevalence of SAH varies according to the geographic location and tends to be more prevalent in the Northeast region (35.1%), followed by the Midwest (19%) and the South (19.8%) regions of Brazil.<sup>7</sup>

Potential risk factors for the occurrence of SAH have been explored in different worker population groups, showing a heavy influence of sociodemographic, behavioral, and occupational factors.<sup>7-9</sup> SAH has mainly been associated with behavioral habits, such as the consumption of alcohol and tobacco; dysfunctional diet; the lack of physical exercise; as well as possible effects of the family history of the disease.<sup>10</sup> In this sense, unhealthy lifestyles can also influence the occurrence of other diseases associated with SAH, especially when related to family history and the presence of obesity.<sup>9</sup>

Cardiometabolic risk factors are normally asymptomatic and their early identification allows for preventive measures and actions to be established.<sup>11</sup> In addition, the different occupational scenarios and forms of productive management have incorporated changes in workers' daily routines.<sup>12</sup> Although prior studies have investigated the occurrence of hypertension among industry workers in Brazil,<sup>8,13</sup> no studies have been conducted in the state of Rio Grande do Sul, one of the most industrialized states of the country. In this light, the

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Manuscript received November 18, 2019, revised manuscript August 07, 2020, accepted September 09, 2020.

**DOI:** <https://doi.org/10.36660/abc.20190815>

present study seeks to verify the prevalence and investigate the factors associated with SAH in industry workers from the state of Rio Grande do Sul.

## Methods

This is a cross-sectional study, using secondary data from the “Heart Project” (“Projeto Coração”) of the Social Services of the Industrial Sector of the state of Rio Grande do Sul (SESI-RS, in Portuguese), conducted from 2006 to 2009. The sample contemplated adult workers of 18 to 59 years of age and who have worked in small (20 – 99 employees), mid-sized (100 – 499 employees), and large (> 500 employees) industries, distributed throughout the main industrialized regions of the state of Rio Grande do Sul. Although this study used secondary data, it was submitted to (CAAE: 90968018.9.0000.5344/2018) and approved by the Research Ethics Committee of Universidade do Vale do Rio dos Sinos (logged under protocol number 2.719.764). In this manner, the anonymity of the workers was preserved through a statement of responsibility submitted to the institution-data source.

## Sample

In an attempt to guarantee the representativeness of the state’s industry workers, and considering the impossibility of including all employees, a sampling process was conducted in two stages. In the first stage, a simple, random sample was selected from the industries. In the second stage, a sample of the workers registered from the industries in the first stage was obtained. The selection of the companies was carried out through a survey of their location (municipalities) and the total number of employees, including all economic activities of the Annual Report on Social Information (RAIS, in Portuguese) from 2004. To determine which municipalities should be included in the study, a list was made, contemplating the municipalities in which 80% of the industry workers of the state were concentrated, distributed according to the company size and the National Classification of Economic Activities (CNAEs, in Portuguese). Through this simple and stratified random selection, according to company size, 145 companies were selected, contemplating industries from the sectors of food and beverage (CNAE 10 and 11), leather products (CNAE 15), metal-mechanic products (CNAEs 24, 25, 28 e 29), and tobacco (CNAE 12). This process sought to contemplate a representative sample related to the population of companies, considering a 95% confidence interval (95% CI), a variance for the proportion estimator of 0.25, and a maximum error in the proportion estimates of 3.6 percentage points. This study then obtained a sample proportion of the total number of employees registered in the companies. Therefore, at the end of the two stages, the assessment of 21,341 workers was contemplated.

## Sample collection and instruments

The sample collection occurred by means of face-to-face interviews during working hours and including all of the company’s work shifts. To guarantee standardization, all of the interviewees received training on the proper procedures for data collection. All of the interviews and assessments were

conducted on company grounds. All workers had received prior permission by the companies, and the adherence of the workers to this study was fully voluntary and consented.

A standardized, pre-coded, and pre-tested questionnaire was used. The questionnaire contemplated demographic, socioeconomic, behavioral, nutritional, and hereditary information. The demographic characteristics investigated in this study were: sex, age (10-year age groups), skin color (white and non-white), and marital status (with or without partner). The socioeconomic characteristics included: monthly family income (stratified in absolute values of Brazilian Reals) and education (stratified in level of education). As regards the behavioral characteristics, this study investigated smoking (smoker, non-smoker, or ex-smoker), considering a “smoker” to be the worker who uses any type or quantity of tobacco, daily, for at least six months. “Ex-smoker” was defined as those who have been a smoker and have not used tobacco in the last six months; “non-smoker” was defined as those who had never used tobacco at any time in their lives. The consumption of alcohol, by contrast, was defined based on the regular consumption of any type of alcoholic beverage at least once a week.

As regards the regular practice of physical activity (active and inactive), this study considered regular physical activity as practices performed in a regular and constant manner. The nutritional state was evaluated by means of the Body Mass Index (BMI), obtained by measuring one’s weight and height, considering the following equation: weight (in kilograms) divided by height (in meters) squared. All workers with a BMI of between 25.0 and 29.9 kg/m<sup>2</sup> were classified as overweight, while those with a BMI of 30.0 kg/m<sup>2</sup> or more were classified as obese.<sup>14</sup> To measure the body weight in kilograms, a previously calibrated digital scale was used. The measurement of height in centimeters was carried out by using a mobile stadiometer, kept on a flat plane, with no baseboard, and propped up on a wall. The measurements of the workers were taken without shoes, with light clothes (without coats or PPEs), totally erect, and with their heels together. The family history of hypertension (mother, father, and grandparents) was reported by the participants.

The outcome variable was obtained by measuring the systolic and diastolic blood pressures, using a stethoscope and an aneroid sphygmomanometer, tested and calibrated by the National Institute of Metrology Standardization and Industrial Quality (INMETRO). The measurements were carried out in duplicate, using the average of the two observed measurements. All of the measurements were taken on the right arm, at an interval of three minutes, with the individual in a sitting position. All measurements were performed by undergraduate interns in nursing. These interns had been previously trained, considering the application of the protocol of recommendations established by the Third Brazilian Guideline on Arterial Hypertension.<sup>15</sup> The measurements were performed during working hours and before the application of the questionnaires, in an adequate physical space made available by the companies (apart from the production area and with low noise levels).

The presence of hypertension was determined by the presence of systolic arterial blood pressure  $\geq$  140 mmHg

and/or diastolic arterial blood pressure  $\geq 90$  mmHg or taking antihypertensive medication, regularly or sporadically.<sup>4,16</sup> Workers with a prior diagnosis of SAH and without current treatment (use of medication) were classified based on the worker's blood pressure measured in the present study.

### Statistical analysis

Descriptive statistics was used for the general distribution of the sample and the distribution of the outcome under study, using absolute and relative frequencies for the categorical and average variables, with their respective standard deviations, for the numerical variables. For the gross analysis, between the outcome variable (SAH) and their exposure variables (independent), Pearson's chi-squared test was used for the heterogeneity of the proportions (categorical variables) or of linear trend (ordinal variables). A possible presence of collinearity between the exposure variables was assessed through their association.

Multivariate analysis was performed by means of Poisson Regression with robust variance,<sup>17</sup> considering the values of statistical significance obtained through the Wald test for the heterogeneity of proportions (categorical variables) or of linear trend (ordinal variables). The multivariate analysis was based on the conceptual model of determination and interactions among variables,<sup>18</sup> considering two hierarchical levels of adjustment. At the first level, the adjusted analysis was performed between the demographic and socioeconomic characteristics themselves. By contrast, at the second level, the adjusted analysis was performed, including the variables of the first level with  $p < 0.20$  and the behavioral, nutritional, and family history variables. All of the analyses were stratified by sex, considering the heterogeneity of the outcome prevalence (SAH), and were conducted using the Stata program, version 12 (StataCorp LP, College Station, Texas, USA), considering a significance level of 5% ( $p < 0.05$ ).

### Results

Of the 21,341 workers eligible in this study, 489 (2.3%) were classified as losses or exclusions, as they packed information or were outside of the age group target, while for 60 workers (0.28%), it was not possible to measure their blood pressure. Thus, a total of 20,792 workers, with an average age of  $32.8 \pm 9.8$  years, was included in the final analysis, considering 12,349 men (59.4%) and 9,443 women (40.6%), with average ages of  $33.5 \pm 10.1$  years and  $31.9 \pm 9.3$  years, respectively. Regarding the industrial sectors, the present study included 4,356 workers from the food and beverage sector (20.9%), 9,692 from the leather products sector (46.6%), 6,168 from the metal-mechanic sector (29.7%), and 576 from the tobacco sector (2.8%).

Table 1 presents the general characteristics of the sample for men and women and the respective prevalence of SAH, according to the investigated variables. In the general sample, a prevalence of hypertension (SAH  $\geq 140/90$  mmHg or treatment) of 10.3% was found (95% CI: 9.8 - 10.7), given that 43.7% were not taking antihypertensive medication ( $n=931$ ). The prevalence of SAH was greater in men (10.9%; 95% CI: 10.3 - 11.4) than in women (9.4%; 95% CI: 8.8 -

10.0;  $p=0.001$ ), given that 24.3% of the men and 25.8% of the women, aged 40 years and over, presented SAH. This study also found that the women with better socioeconomic conditions presented a higher prevalence of SAH when compared to men (Table 1). No collinearity was identified between any of the independent variables, including age and marital status, as well as between BMI, family income, and level of education.

Table 2 presents the ratios of gross and adjusted prevalence, stratified among men and women, for the occurrence of SAH, according to the investigated factors. After the analysis had been adjusted, the prevalence of SAH proved to be associated with the rise in age group, a low level of education, living with a partner, being overweight or obese, and having at least one family member with a medical history of hypertension. As regards the socioeconomic factors, the lower level of education continued to be associated with a higher prevalence of SAH only among women. A directly proportional association was observed between the nutritional state and SAH in both sexes. Nonetheless, the prevalence of SAH was directly and significantly higher among those who had one of their parents, or both parents, and their grandparents, with a medical history of hypertension. Although family income, smoking, alcohol consumption, and the practice of physical activity did present a trend of association in the gross analysis, these were contradictory and all of them lost significance after the adjustment (Table 2).

### Discussion

The present study's findings point out that sociodemographic, nutritional, and family history factors are associated with the occurrence of SAH in industry workers. Moreover, this study also found that the prevalence of SAH increased according to the advance in age and the marital status, in both sexes. The unfavorable socioeconomic conditions also proved to be associated with the presence of SAH, especially among women.

The prevalence of SAH confirmed in this study was below that confirmed in other studies conducted with industry workers in Brazil.<sup>8,13</sup> This variability may potentially be explained by this study's period of data collection (2006 to 2009), by the diversity of criteria used to define the presence of SAH, in addition to the type of device and time of measurement of the SAH, making the comparisons among studies difficult.<sup>19</sup> Furthermore, male workers presented a higher prevalence of SAH when compared to women, which runs in line with a study previously conducted with industry workers.<sup>7</sup>

Although cross-sectional studies do not allow for cause-effect relationships to be established, it is possible to consider that the physiological changes related to the advance in age can increase risks in the cardiovascular system.<sup>1,20,21</sup> In this study, the prevalence of SAH was significantly higher among workers of 40 years of age and over. One similar finding was observed in a study conducted with workers from the metallurgical and steelworking sector,<sup>13</sup> illustrating that workers of over 40 years of age are a priority for SAH preventive actions and intervention.

**Table 1 – Distribution of the sample and prevalence of systemic arterial hypertension (SAH  $\geq 140/90$  mmHg or treatment) according to demographic, socioeconomic, behavioral, nutritional state, and hereditary characteristics in the sample of male and female industry workers in the state of Rio Grande do Sul, RS, Brazil, 2006-2009. (N=20.792)**

| Characteristics                            | Men (12,349) |       |         | Women (8,443) |       |         |
|--------------------------------------------|--------------|-------|---------|---------------|-------|---------|
|                                            | n (%)        | % SAH | p-value | n (%)         | % SAH | p-value |
| Age (years)                                |              |       | <0.001  |               |       | <0.001  |
| 18 to 29                                   | 5,180 (42.0) | 2.6   |         | 3,925 (46.5)  | 2.0   |         |
| 30 to 39                                   | 3,613 (29.2) | 9.5   |         | 2,622 (31.1)  | 8.6   |         |
| 40 to 49                                   | 2,593 (21.0) | 20.1  |         | 1,522 (18.0)  | 22.6  |         |
| 50 to 59                                   | 963 (7.8)    | 35.5  |         | 374 (4.4)     | 39.0  |         |
| Skin color                                 |              |       | 0.936   |               |       | 0.508   |
| White                                      | 9,595 (77.7) | 10.8  |         | 7,031 (83.3)  | 9.5   |         |
| Não White                                  | 2,754 (22.3) | 10.9  |         | 1,412 (16.7)  | 8.9   |         |
| Marital status                             |              |       | <0.001  |               |       | <0.001  |
| Without partner                            | 3,976 (32.2) | 5.8   |         | 2,724 (32.3)  | 7.0   |         |
| With partner                               | 8,373 (67.8) | 13.2  |         | 5,719 (67.7)  | 10.5  |         |
| Education                                  |              |       | <0.001  |               |       | <0.001  |
| Incomplete elementary                      | 4,039 (32.7) | 15.8  |         | 3,469 (41.1)  | 14.3  |         |
| Complete elementary                        | 2,932 (23.8) | 8.6   |         | 2,060 (24.4)  | 7.5   |         |
| Complete high school                       | 3,699 (29.9) | 7.9   |         | 2,021 (24.0)  | 5.4   |         |
| Incomplete/complete higher education       | 1,679 (13.6) | 9.5   |         | 893 (10.6)    | 3.6   |         |
| Monthly Family income (Brazilian reais)    |              |       | 0.004   |               |       | 0.002   |
| $\leq 800$                                 | 2,973 (25.3) | 10.6  |         | 2,410 (29.7)  | 10.6  |         |
| 801 to 1,200                               | 3,113 (26.4) | 10.0  |         | 2,819 (34.7)  | 9.5   |         |
| 1,201 to 1,800                             | 2,518 (21.3) | 10.0  |         | 1,578 (19.5)  | 9.9   |         |
| > 1,800                                    | 3,183 (27.0) | 12.9  |         | 1,313 (16.2)  | 7.1   |         |
| Smoking                                    |              |       | <0.001  |               |       | 0.014   |
| Non-smoker                                 | 9,051 (73.3) | 9.8   |         | 7,153 (84.8)  | 9.2   |         |
| Ex-smoker                                  | 1,267 (10.3) | 16.7  |         | 519 (6.1)     | 12.9  |         |
| Smoker                                     | 2,031 (16.4) | 12.0  |         | 771 (9.1)     | 8.4   |         |
| Alcohol consumption                        |              |       | 0.435   |               |       | 0.001   |
| Does not consume                           | 7,650 (61.9) | 10.7  |         | 7,483 (88.6)  | 9.8   |         |
| Consumes                                   | 4,699 (38.1) | 11.1  |         | 960 (11.4)    | 6.6   |         |
| Physical Activity                          |              |       | <0.001  |               |       | 0.324   |
| Active                                     | 4,419 (36.0) | 8.9   |         | 2,054 (24.5)  | 9.9   |         |
| Inactive                                   | 7,860 (64.0) | 11.9  |         | 6,347 (75.5)  | 9.2   |         |
| Nutricional State (BMI)                    |              |       | <0.001  |               |       | <0.001  |
| Normal (< 25 kg/m <sup>2</sup> )           | 5,664 (46.0) | 4.7   |         | 4,538 (53.9)  | 3.6   |         |
| Overweight (25 to 29.9 kg/m <sup>2</sup> ) | 5,014 (40.6) | 13.0  |         | 2,505 (29.8)  | 11.9  |         |
| Obese ( $\geq 30$ kg/m <sup>2</sup> )      | 1,660 (13.5) | 25.4  |         | 1,380 (16.3)  | 24.0  |         |
| Presence of hypertension in the family     |              |       | <0.001  |               |       | <0.001  |
| No                                         | 6,442 (52.2) | 7.8   |         | 3,477 (41.2)  | 4.8   |         |
| Mother or Father                           | 4,987 (40.5) | 12.5  |         | 3,950 (46.8)  | 10.3  |         |
| Mother and Father                          | 674 (5.5)    | 22.9  |         | 657 (7.8)     | 22.2  |         |
| Mother, Father, and Grandparents           | 226 (1.8)    | 25.7  |         | 349 (4.1)     | 21.2  |         |

BMI: body mass index. P-value for the chi-squared test for the heterogeneity of proportions (categorical variables) or linear trend (ordinal variables).

**Table 2** – Gross or adjusted prevalence ratios (OR) of systemic arterial hypertension (SAH  $\geq 140/90$  mmHg or treatment) according to demographic, socioeconomic, behavioral, nutritional state, and hereditary characteristics in the sample of male and female industry workers in the state of Rio Grande do Sul, RS, Brazil, 2006-2009. (N=20.792)

|              | Men (12,349)                               |                    | Women (8,443)       |                     |
|--------------|--------------------------------------------|--------------------|---------------------|---------------------|
|              | Gross PR*                                  | Adjusted PR†       | Gross PR *          | Adjusted PR †       |
| First level  | Age (years)                                | p<0.001            | p<0.001             | p<0.001             |
|              | 18 to 29                                   | 1                  | 1                   | 1                   |
|              | 30 to 39                                   | 3.66 (3.01-4.45)   | 4.32 (3.35-5.56)    | 3.79 (2.93-4.90)    |
|              | 40 to 49                                   | 7.78 (6.48-9.35)   | 11.37 (9.00-14.44)  | 9.85 (7.70-12.60)   |
|              | 50 to 59                                   | 13.7 (11.38-16.56) | 19.64 (15.24-25.31) | 17.28 (13.29-22.47) |
|              | Skin color                                 | p=0.936            | p=0.509             | -                   |
|              | White                                      | 1                  | 1                   |                     |
|              | Não White                                  | 1.01 (0.89-1.13)   | 0.95 (0.78-1.13)    |                     |
|              | Marital status                             | p<0.001            | p<0.001             | p<0.001             |
|              | Without partner                            | 1                  | 1                   | 1                   |
|              | With partner                               | 2.27 (1.98-2.60)   | 1.50 (1.28-1.76)    | 1.28 (1.09-1.51)    |
|              | Education                                  | p<0.001            | p<0.001             | p=0.001             |
|              | Incomplete elementary                      | 1.67 (1.41-1.96)   | 4.00 (2.82-5.67)    | 1.58 (1.08-2.29)    |
|              | Complete elementary                        | 0.91 (0.75-1.10)   | 2.10 (1.45-3.05)    | 1.46 (1.00-2.14)    |
|              | Complete high school                       | 0.83 (0.69-1.00)   | 1.51 (1.02-2.21)    | 1.30 (0.87-1.92)    |
|              | Incomplete/complete higher education       | 1                  | 1                   | 1                   |
|              | Monthly family income (Brazilian reais)    | p=0.005            | p=0.002             | p=0.055             |
|              | ≤ 800                                      | 0.83 (0.72-0.95)   | 1.50 (1.19-1.88)    | 1.30 (1.02-1.66)    |
|              | 801 to 1,200                               | 0.77 (0.67-0.89)   | 1.35 (1.07-1.69)    | 1.20 (0.95-1.51)    |
|              | 1,201 to 1,800                             | 0.78 (0.67-0.90)   | 1.40 (1.09-1.79)    | 1.16 (0.91-1.49)    |
| Second level | > 1,800                                    | 1                  | 1                   | 1                   |
|              | Smoking                                    | p<0.001            | p=0.014             | p=0.133             |
|              | Non-smoker                                 | 1                  | 1                   | 1                   |
|              | Ex-smoker                                  | 1.70 (1.48-1.96)   | 1.40 (1.10-1.77)    | 0.96 (0.77-1.20)    |
|              | Smoker                                     | 1.23 (1.08-1.40)   | 0.91 (0.71-1.16)    | 0.83 (0.67-1.05)    |
|              | Alcohol consumption                        | p=0.435            | p=0.002             | p=0.824             |
|              | Does not consume                           | 1                  | 1                   | 1                   |
|              | Consumes                                   | 1.04 (0.94-1.16)   | 0.67 (0.52-0.86)    | 0.98 (0.77-1.25)    |
|              | Physical Activity                          | p<0.001            | p=0.323             | -                   |
|              | Active                                     | 1                  | 1                   |                     |
|              | Inactive                                   | 1.35 (1.20-1.51)   | 0.93 (0.80-1.08)    |                     |
|              | Nutritional state (BMI)                    | p<0.001            | p<0.001             | p<0.001             |
|              | Normal (< 25 kg/m <sup>2</sup> )           | 1                  | 1                   | 1                   |
|              | Overweight (25 to 29.9 kg/m <sup>2</sup> ) | 2.78 (2.42-3.18)   | 3.34 (2.78-4.02)    | 2.04 (1.69-2.45)    |
|              | Obese (≥ 30 kg/m <sup>2</sup> )            | 5.43 (4.71-6.27)   | 6.76 (5.66-8.08)    | 3.60 (2.98-4.36)    |
|              | Presence of SAH in the family              | p<0.001            | p<0.001             | p<0.001             |
|              | No                                         | 1                  | 1                   | 1                   |
|              | Mother or Father                           | 1.61 (1.44-1.80)   | 2.17 (1.82-2.58)    | 1.78 (1.50-2.10)    |
|              | Mother and Father                          | 2.94 (2.50-3.46)   | 4.68 (3.81-5.76)    | 2.77 (2.27-3.38)    |
|              | Mother, Father, and Grandparents           | 3.31 (2.61-4.19)   | 4.47 (3.48-5.74)    | 3.22 (2.54-4.07)    |

\* P-value for the Wald test for the heterogeneity of proportions (categorical variables) or linear trend (ordinal variables) obtained by means of Poisson regression with robust variance; † Adjusted analysis by multivariate model, including the variables with p<0.20 in the gross analysis. First Level: adjustment among the sociodemographic variables; Second Level: adjustment among the variables of the first level with p<0.20 plus the behavioral, nutritional state, and hereditary variables.

Workers who reported living with a partner presented a higher prevalence of SAH. A similar finding was previously observed, in which living with a partner was associated with other morbidities and SAH.<sup>22</sup> By contrast, when analyzing the influence of the level of education on SAH, our study identified that the women with a lower level of education presented a higher probability for SAH, which was similar to previous findings in worker samples.<sup>23,24</sup> Although studies have sought to identify differences between the potential risk factors for SAH among workers of both sexes, what stands out is that the biological susceptibility related to sex or to difference in gender is not linked to the health risks inherent to the work process for both sexes.<sup>25</sup> Nevertheless, it is possible to highlight that women often occupy less prestigious positions and with lower salaries in companies,<sup>26</sup> aspects that can reflect the higher prevalence of SAH in women of lower socioeconomic classes.

In the present study, the overweight and obese workers presented a two to three-fold greater probability of having SAH. Prior studies corroborate a significant association between the nutritional state and SAH, including studies conducted with workers.<sup>12,20,27,28</sup> This finding demonstrates a possible relationship between the increase in the prevalence of SAH with the nutritional transition of the population.<sup>6,28</sup> By contrast, as regards the family history of SAH, our study confirmed a significantly higher prevalence of SAH among workers who reported a prior family history of SAH in their father, mother, or grandparents. Previous studies on the theme demonstrate a significant importance of the hereditary burden for the development of SAH.<sup>29,30</sup>

The main positive points of this study include its sample size, including workers from different industrial sectors of the state of Rio Grande do Sul. The present study adopted a standardized method of data collection, as well as all procedures necessary for the adequate measurement of one's blood pressure. It should also be emphasized that this study sought to explore the potential factors associated with the occurrence of SAH, considering the adoption of a multivariate analysis model. However, the findings of this study should be interpreted considering a few limitations. This study used secondary data, collected from 2006 to 2009, not including the collection of occupational variables. As this is a cross-sectional study, it may be subject to the presence of reverse causality among the investigated associations. The presence of bias on the part of a healthy worker or survivor cannot be totally discarded, since this study considered only active workers, that is, those who were working when this study was applied, excluding those who were on leave due to health problems, for example. Another limitation of this study is due to the lack of an intra- and inter-examiner variability analysis for the measurements of systolic and diastolic blood pressures. Finally, the analysis by industrial sector, as well as

possible sociodemographic differences between sectors, were hindered due to the broad heterogeneity of the number of workers investigated in each sector.

Although the prevalence of SAH found in our study was relatively low, it was observed that the occurrence of SAH in industry workers is influenced by sociodemographic, nutritional, and family history factors. However, further studies are warranted and should focus on identifying potential occupational risk factors (type of occupation, work shift, time of service, presence of a food program in the workplace, among others) associated with SAH, concentrating on specific measures and actions geared toward combatting the occurrence of chronic non-communicable diseases and protecting the full wellbeing of the worker.

## Conclusions

This study's findings, in the studied sample, pointed out that sociodemographic, nutritional, and family history factors are associated with the occurrence of SAH. It was found that the prevalence of SAH increased in accordance with advances in age and marital status, in both sexes. The unfavorable socioeconomic conditions were also associated with the presence of SAH, primarily among women. Such evidence can contribute to the formulation of effective interventions for the prevention of SAH, together with the policies geared toward worker health.

## Author Contributions

Conception and design of the research: Xavier PB, Cibeira GH, Germano A, Olinto MTA; Acquisition of data: Xavier PB, Cibeira GH, Germano A; Analysis and interpretation of the data and Statistical analysis: Xavier PB, Garcez A, Olinto MTA; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Xavier PB, Garcez A, Cibeira GH, Germano A, Olinto MTA.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

There were no external funding sources for this study.

## Study Association

This article is part of the thesis of doctoral submitted by Paula Brustolin Xavier, from Universidade do Vale do Rio dos Sinos (UNISINOS).

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## Is It Time to Move From Diagnosis to Active Intervention in Brazilian Workplaces? A Call for Action

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Short Editorial related to the article: Factors Associated with the Occurrence of Arterial Hypertension in Industry Workers of State of Rio Grande do Sul, Brazil

Arterial hypertension (AH) is a major contributing risk factor for heart failure, myocardial infarction, stroke, and chronic kidney disease.<sup>1</sup> According to the 2013 Brazilian National Health Survey, 21.4% (95%CI 20.8-22.0) of adults self-reported having AH; however, considering their blood pressure (BP) measurements and the use of antihypertensive medications, the rate of adults with BP greater than or equal to 140/90 mm Hg reached 32.3% (95% CI 31.7-33.0). The prevalence of AH was higher among men, and, as expected, this rate was highly affected by aging, reaching 71.7% for individuals over 70 years of age.<sup>2,3</sup>

Therefore, every study to determine the prevalence of AH is very important for prevention, treatment, and follow-up programs. Samples representing the workforce are of particular importance because they are younger, in the productive age and have a longer life expectancy.

Several studies published in Brazil<sup>4-6</sup> have assessed the prevalence of AH and other risk factors in populations of industrial workers across different areas of expertise. In these studies, the prevalence of AH ranged from 6% (stage 2), according to the VII Joint National Committee,<sup>7</sup> to 19%-35.1% in different Brazilians regions among adults of different ages (mean age of 35.4 years).<sup>8</sup>

It is well established that several risk factors contribute to the development of AH, such as obesity, alcohol abuse, physical inactivity, heredity, age, and sex, among others.<sup>2</sup>

In the article by Paula Brustolin Xavier et al.,<sup>9</sup> published in this issue of the *Arquivos Brasileiros de Cardiologia*, the authors report the prevalence of AH in a population of industrial workers in Rio Grande do Sul, Brazil, representing at least 5 sectors of distinct industrial activities. They also assess the risk factors for the development of AH. The finding of a mean

prevalence of 10.3% in people with a mean age of 32.8 years is in agreement with those previously observed.

As for the determining factors of AH, direct relationships have been observed between age and higher BP, being more frequent in men than in women, in overweight and obese people, and in those with low education and heredity for hypertension. These data are compatible with those reported in previous studies and guidelines on AH.

Regarding their work, methodological issues may affect some of the findings, especially the absence of statistically significant correlations with family income, smoking, alcohol consumption, and level of physical activity, even considering that they were obtained more than a decade ago.

First: The auscultatory method of measuring BP is certainly more prone to methodological errors and requires well-trained personnel to be consistent. Nowadays, well-validated automatic equipment is preferable for diagnosis, as recommended by recent guidelines.<sup>2</sup>

Second: The analysis of nutritional status using body mass index (BMI) can be refined with the measurement of waist circumference, which is better related to prognosis, eliminates the imprecision of BMI in estimating fat accumulation,<sup>10</sup> and seems to be more precise in relation to AH.<sup>11</sup>

In summary, the study sheds light on factors that can contribute to the incidence of AH in a defined population of industrial workers and, as such, alerts to the need for prevention, diagnosis, and guidance for a disease with high morbidity that contributes to high mortality rates. It reproduces previous data and leads to an intriguing question: Is it time to move forward from diagnosis?

At the present time, it may be appropriate to use the large databases from all regions of our country to take a step further and propose some active interventions led by the existing well-organized support organizations (SESI and SENAI, for example). Simple measures, such as workplace health promoting activities,<sup>12</sup> healthy meal planning for industries with a cafeteria, and even the offer of free healthy snacks, may have a future impact on risk factors for AH and their modification or, at least, on the personal perception of well-being.<sup>13</sup> Some initiatives in our country have produced good results and need to be expanded.<sup>14</sup> The Brazilian Society of Cardiology must lead this effort!!

### Keywords

Hypertension; Occupational Health; Epidemiology.

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DOI: <https://doi.org/10.36660/abc.20210619>

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# Association between Leisure Time Physical Activity and HDL-C in the Elsa-Brasil Study Participants: Are There Any Gender Differences in the Dose-Response Effect?

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## Abstract

**Background:** High levels of high-density lipoprotein (HDL-C) are known for their protective effect against cardiovascular diseases and the regular practice of leisure time physical activity (LTPA) may be associated with their increase.

**Objective:** To verify the existence of differences between genders in the dose-response effect regarding the association between LTPA and HDL-C in the ELSA-Brasil study cohort.

**Methods:** Cross-sectional study with data from wave 2 of 13,931 participants of both genders (7,607 women) from the Longitudinal Study of Adult Health ELSA-Brasil. The LTPA was measured using the International Physical Activity Questionnaire (IPAQ) and classified into four categories: sedentary, low active, active and very active. The discriminatory power of LTPA at different intensities analyzed for high HDL-C was tested using ROC curves. Associations, adjusted for confounders between LTPA and HDL-C were analyzed by logistic regression. A 95% confidence interval was used.

**Results:** A positive association, with a dose-response effect, was observed between LTPA and HDL-C in both men and women. With regard to intensity, only vigorous physical activity discriminated high HDL-C in men, while both walking and moderate and vigorous physical activity discriminated high HDL-C in women.

**Conclusions:** LTPA shows a positive association with gradient dose-response and HDL-C, but in men, the association is not observed for those classified as physically unfit. In women, both walking intensity and moderate or vigorous physical activity can discriminate high HDL-C levels, whereas only vigorous intensity-exercise discriminate elevated HDL-C levels in men, demonstrating that males need to do more physical activity for this benefit to be observed.

**Keywords:** Cardiovascular Diseases; Exercise; Physical Activity; Cross-Sectional Studies; HDL-Cholesterol; Epidemiology; Walking.

## Introduction

The regular practice of physical activity (PA) shows a positive association with the increase in high density lipoprotein (HDL-C) and decrease in triglyceride levels, with inconsistent changes in low-density lipoprotein levels.<sup>1</sup> In addition, higher levels of HDL-C may have benefits such as protecting against coronary artery disease, although more recent Mendelian randomization studies have suggested that HDL-C is more of a marker of cardiovascular risk than a risk factor itself.<sup>2,3</sup>

The increase of HDL-C associated with PA practice may be explained to the extent that, during PA, there is an increase in lipoprotein lipase activity (LPL), accelerating the breakdown of triglyceride-rich lipoprotein. This generates the transfer of cholesterol, phospholipids and proteins to the nascent particles of HDL-C.<sup>4</sup> However, in more physically active individuals, the HDL-C half-life may reach 6-7 days, while in the physically inactive, it is only 3-4.<sup>5</sup>

Despite this evidence, the ideal PA intensity to increase HDL-C needs to be better clarified, mainly with emphasis in possible differences between men and women as shown in previous studies about PA and cardiometabolic health.<sup>6</sup>

In a recent research carried out in participants of the Longitudinal Study of Adult Health ELSA-Brasil, the results show that there is an association between PA and higher HDL-C levels, both in men and women. Moreover, it was observed that vigorous-intensity PA practice is associated with more positive changes in lipid profiles, than only the duration

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Manuscript received May 07, 2020, revised manuscript August 13, 2020, accepted September 09, 2020

**DOI:** <https://doi.org/10.36660/abc.20200438>

of PA practice. However, this study did not analyze possible differences between men and women about the quantities (time and duration) of PA.<sup>7</sup>

The knowledge of existence of a dose-response effect between PA and HDL-C increase will contribute to the production of new information and researches on the subject, considering that public policies for PA promotion may use this information as a basis for new intervention proposals. Moreover, although the association between PA and HDL-C levels is already known, studies that demonstrate the dose-response effect in relation the possible differences between men and women are scarce in assessed literature about the subject. Studies that reaffirm the association between PA and HDL-C are still important for better understanding of this association, mainly in the analysis of possible differences between the genders regarding these findings.

The objective of study was to verify the existence of differences between the genders in the dose-response effect regarding the association between LTPA and HDL-C in the ELSA-Brasil cohort

## Methods

### Population and sample

The ELSA-Brasil is a cohort study of 15,105 active or retired civil servants aged 25 to 74 years from six higher education institutions located in the cities of Salvador, Vitória, Belo Horizonte, Rio de Janeiro, São Paulo e Porto Alegre, which has as its main objective to investigate the incidence and progression of diabetes and cardiovascular diseases and their associated factors (biological, behavioral, environmental, occupational, psychological and social), whose methodological details were previously described.<sup>8,9</sup> To date, information has been collected about participants in three opportunities: (1<sup>st</sup> wave, from 2008 to 2010); (2<sup>nd</sup> wave, from 2012 to 2014) and (3<sup>rd</sup> wave, from 2016 to 2018). For the present study, was selected all participants of the second wave (2012-2014) that answered questionnaires about PA and had complete data on the variables involved in the analysis, totaling 13,931 participants (7,607 women).

The ELSA-Brasil was approved by the National Research Ethics Commission (CONEP) and by all Research Ethics Committees of the six research centers involved. All participants signed the informed consent form and the confidentiality of the data is guaranteed.

### Data production

The data were collected by a team of interviewers and raters trained and certified by a quality control committee,<sup>9</sup> able to perform the study protocol in any ELSA-Brasil Research Center. Face-to-face interviews were conducted when applying the blocks of questionnaires to obtain information on age, level of schooling, family income and smoking. Additionally, information on anthropometric measurements of weight, height and waist circumference was collected. Body weight was obtained in the morning, after 8-12 hours of fasting and with the participant without shoes and wearing light clothes.

An electronic Toledo® scale was used to measure weight, with a capacity of up to 200 Kg. A SECA® stadiometer was used to measure height, with the participant in the standing position and strictly following the Frankfurt plan. Obesity was identified through the body mass index (BMI) by applying the equation  $BMI = \text{weight (Kg)} / \text{height (m)}^2$  adopting the following cut-off points; obesity = 0 if  $BMI < 30.0$  and obesity = 1 if  $BMI \geq 30.0$ .

### Evaluation of Physical Activity

The long version of the International Physical Activity Questionnaire (IPAQ) was used for the identification and qualification of PA, which consists of questions related to the frequency and duration of physical activities (walking, moderate PA and vigorous PA) developed at work, during commuting, in domestic activities and leisure time.<sup>10</sup> Only leisure time and commuting domains were assessed in the ELSA-Brasil. The PA was measured in minutes/week by multiplying the weekly frequency by the duration of each of the performed activities. For the study effect, only leisure-time physical activity (LTPA) was utilized, with the following categorization: 0 = physically inactive (less than 10 minutes of any PA in the week); 1 = unfit (from 10 minutes to less than 150 minutes of walking/moderate activity per week and/or from 10 minutes to less than 60 minutes of vigorous activity for week and/or from 10 minutes to less than 150 minutes per week of any combination of walking, moderate and vigorous activity); 2 = physically active (more than or equal to 150 minutes of walking/moderate activity per week and/or more than or equal to 60 minutes of vigorous activity per week and/or more than or equal to 150 minutes per week of any combination of walking/moderate and vigorous activity); 3 = very active (more than or equal to 150 minutes of vigorous activity per week, or more than or equal to 60 minutes of vigorous activity per week + 150 minutes per week of any combination between walking and moderate activity). For the dichotomized analyses, those classified as physically inactive and unfit were considered as insufficiently active, and those classified as physically active and very active as active.

### Evaluation of HDL-C

Blood collection was performed after 12 hours of overnight fasting and centrifuged and stored in cryo-tubes at -80°C in the respective research centers. To ensure the quality and standardization of the results, all samples were sent for processing and analysis in a central ELSA-Brasil laboratory located in the city of São Paulo. The HDL-C values in mg/dL were determined by a homogeneous colorimetric method using an ADVIA 1200 Siemens equipment.<sup>7</sup> HDL-C was dichotomized at 60 mg/dL and  $\geq 60$  mg/dL (high HDL-C).

### Covariates

The following categorization was adopted for the covariates: age=0 if between 34 and 50 years, age=1 if between 51 and 60 years and age=2 if  $>60$  years. Four strata were established for the level of schooling: 0 = incomplete elementary school; 1 = complete elementary school; 2 = complete high school; and 3 = complete higher education

/ postgraduation. The family income was categorized as: up to 2 minimum wages=0; from 2 to 8=minimum wages=1; from 8 to 18 minimum wages=2; and above 18 minimum wages=3. The current smoking status was categorized as no=0 and yes=1.

### Data analysis

The descriptive measures (proportions) were calculated for all categorized variables. The analysis was stratified by gender *a priori* and compared using the chi-square test. ROC (Receiver Operating Characteristic) curves were used to test the discriminatory power of different LTPA intensities (walking, moderate PA and vigorous PA) for elevated HDL-C levels.<sup>11</sup> The 95% confidence interval (95%CI) of was utilized. The associations were analyzed by logistic regression. The following variables were considered as potential confounders or effect modifiers: age, obesity, smoking at the moment of the interview, income family and level of schooling. The variables that showed  $p \leq 0.05$  and correlation coefficient  $Rho < 0.60$  in the simultaneous evaluation in the bivariate stage (tetrachoric matrix) were selected for modeling.

The verification of the effect modification was performed by stratification with the observation of stratum-specific point measures and their confidence interval. Effect modification. was indicated when the point measurement of a factor, in a specific stratum, was not contained in the confidence interval of the other factor in the same stratum. The analysis of possible confounding variables was performed using the backward procedure, using logistic regression. The analysis begins with the complete model, followed by removal of the potential confounders one by one. When a change equal to or greater than 10% in the point association between LTPA and HDL-C is observed, the variable is considered to be a confounder.<sup>12</sup> No effect-modifying variables were identified in the modeling process, and the age variable was identified as a confounder. Therefore, the best model for the analysis of an association between LTPA and HDL-C was the age-adjusted model. The dose-response effect also analyzed the association between LTPA and HDL-C. For this analysis, variables called DUMMIES were created for comparison between the reference group (physically inactive) and each of the other strata of the PA variable (insufficiently active, active and very active). The Mantel-Haenszel test was used to test the homogeneity of the odds ratio (OR) values between the strata of each variable with a significance level of 5%. The confidence interval was set at 95%. The statistical program STATA® version 12.0 was used.

### Results

A total of 6,324 men and 7,607 women was included in the analysis. The sample characteristics are shown in table 1. The women's mean age is  $55.7 \pm 8.8$  and the men's is  $55.7 \pm 9.2$ . It is also observed that men have higher family income, are more often smokers, are more active in leisure time, while the women are more obese and have a higher proportion of higher HDL-C levels. It is also observed that there are no statistically significant differences between men and women in relation to age.

Table 2 shows the discriminatory power of the different intensities of LTPA for the increase in HDL-C levels. Among men, only the vigorous PA showed statically significant areas under the ROC curves, while among women, both walking and moderate and vigorous physical activity showed statistical significance to discriminate the increase in HDL-C levels, although the areas under the ROC curves did not show high values.

The association between LTPA and HDL-C in male and female individuals is shown in Table 3. It can be observed that active men have a 38% chance of having higher HDL-C levels, while in active women the chance is 41%, compared to physically inactive men and women, respectively.

Table 4 shows that when the PA was classified into 4 categories, there was a dose-response effect in the association between LTPA and HDL-C, both in men and women. However, in male individuals, the association was found only in those classified as active and very physically active.

### Discussion

The study analyzed the existence of a dose-response effect in the association between LTPA and HDL-C increase.

Is important to point out that the study population is a cohort of civil servant volunteers, which although are not representative of the general population, represent a significant number of participants in six Brazilian capitals, a fact that embodies a strong point of the study.

The mechanisms that associate higher PA intensity and more positive lipid changes are explained by the fact that during the PA there is an increase in LPL activity and triglyceride catabolism, which results in the transfer of cholesterol, phospholipids and proteins to the nascent HDL-C particles, thus increasing its concentration.<sup>4,5</sup> In addition, the average half-life of HDL-C particles is higher in more physically active individuals, a fact that can contribute to the maximization of the reverse transport of cholesterol.<sup>5</sup>

In this context, in a study carried out with participants of ELSA-Brasil, it was demonstrated that there is a beneficial association between PA levels and a favorable lipid profile for HDL-C and triglycerides, both in men and women. Moreover, it was also observed that the higher the intensity of PA, the more positive the changes in lipid profile.<sup>7</sup>

In another study carried out with individuals living in the municipality of Caxias do Sul, state of Rio Grande do Sul, Brazil, who were over 60 years old, it was shown that those who performed physical activities of moderate intensity had reduced LDL-C and increased HDL-C levels, when compared to older adults who had low PA<sup>13</sup> levels.

According to Matsudo et al.,<sup>14</sup> there is little evidence regarding the mechanics responsible for the reduction of LDL-C and very low-density lipoprotein (VLDL-C) levels, but the main reason for the increase in HDL-C levels is the greater action of LPL in response to physical exercise, a fact that increase the catabolism of triglycerides and causes the transfer of cholesterol, phospholipids and proteins to HDL-C particles, thus increasing its levels.<sup>14</sup> Other studies have shown that physically active men and women have higher HDL-C levels and lower levels of LDL-C and VLDL-C than their physically

**Table 1 – Characteristics of the study sample**

|                                               | Men (n=6324) | Women (n=7607) | p     |
|-----------------------------------------------|--------------|----------------|-------|
| <b>Age (years) - n (%)</b>                    |              |                |       |
| 34-50                                         | 2055 (32.5)  | 2342 (30.8)    | 0.49  |
| 51-60                                         | 2182 (34.5)  | 2752 (36.2)    |       |
| >60                                           | 2087 (33.0)  | 2511 (33.0)    |       |
| <b>Family income (minimum wages) - n (%)</b>  |              |                |       |
| Up to 2                                       | 60 (0.9)     | 84 (1.1)       | <0.01 |
| From 2 to 8                                   | 2117 (33.6)  | 2545 (33.6)    |       |
| From 8 to 18                                  | 2462 (39.1)  | 3356 (44.3)    |       |
| More than 18                                  | 1657 (26.3)  | 1583 (20.9)    |       |
| <b>Education - n (%)</b>                      |              |                |       |
| Incomplete Elementary School                  | 448 (10.2)   | 261 (4.5)      | <0.01 |
| Complete Elementary School                    | 482 (10.9)   | 390 (6.7)      |       |
| Complete High School                          | 1933 (43.9)  | 2449 (42.3)    |       |
| Complete Higher Education/ Postgraduation     | 1533 (34.9)  | 2694 (46.)     |       |
| <b>Obesity - n (%)</b>                        |              |                |       |
| BMI < 30 kg/m <sup>2</sup>                    | 4763 (75.3)  | 5308 (69.8)    | <0.01 |
| BMI ≥30 kg/m <sup>2</sup>                     | 1561 (24.7)  | 22299 (30.2)   |       |
| <b>Current smoking- n (%)</b>                 |              |                |       |
| No                                            | 3290 (52.0)  | 4863 (63.9)    | <0.01 |
| Yes                                           | 3033 (48.0)  | 2744 (36.1)    |       |
| <b>Leisure time physical Activity - n (%)</b> |              |                |       |
| Physically Inactive                           | 2218 (35.1)  | 3401 (44.7)    | <0.01 |
| Insufficiently Active                         | 1089 (17.2)  | 1342 (17.6)    |       |
| Active                                        | 1749 (27.6)  | 1947 (25.6)    |       |
| Very Active                                   | 1268 (20.1)  | 917 (12.0)     |       |
| <b>High HDL-C levels</b>                      |              |                |       |
| Yes                                           | 916 (14.5)   | 3.241 (42.7)   | <0.01 |
| No                                            | 5408 (85.5)  | 4.366 (57.3)   |       |

Values for men and women were compared using the chi-square test.

**Table 2 – Areas under the ROC curves for different physical activity intensities as a discriminator for high HDL-C (≥60 mg/dL)**

| Leisure Time Physical Activity | Male              | Female             |
|--------------------------------|-------------------|--------------------|
| Walking                        | 0.52 (0.50-0.54)  | 0.52 (0.51-0.53) * |
| Moderate                       | 0.52 (0.50-0.54)  | 0.53 (0.53-0.54)*  |
| Vigorous                       | 0.54 (0.52-0.56)* | 0.53 (0.52-0.54)*  |

ROC: receiver operating characteristic; 95% CI: confidence interval of 95%. \*Area under the ROC curve with discriminatory power IM (Li-IC > 0.50). )

**Table 3 – Association between leisure time physical activity and HDL-C**

| Leisure time physical activity                                   | Male             | Female           |
|------------------------------------------------------------------|------------------|------------------|
| Insufficiently Active<br>(Physically Inactive and Little Active) | 1.00             | 1.00             |
| Active<br>(Active and Very Active)                               | 1.38 (1.20-1.59) | 1.41 (1.29-1.55) |

\* Adjusted by age

**Table 4 – Dose-response effect in the association between leisure time physical activity and HDL-C**

| Leisure time physical activity | Male             | Female           |
|--------------------------------|------------------|------------------|
| Inactive                       | 1.00             | 1.00             |
| Little Actives                 | 1.21 (0.98-1.50) | 1.15 (1.01-1.31) |
| Active                         | 1.27 (1.05-1.52) | 1.33 (1.19-1.49) |
| Very Active                    | 1.77 (1.46-2.15) | 1.81 (1.56-2.09) |

\* Adjusted by age.

inactive pairs.<sup>15</sup> Moreover, another study conducted only with female individuals, it was observed that there are significant differences in HDL-C levels in women with high, moderate and low levels of physical fitness, and the highest values were found in women with high levels of physical fitness.<sup>16</sup>

It is also important to emphasize that in our study, the intensity of LTPA was classified as walking; moderate PA; and vigorous PA. In this context, although the areas under the ROC curves do not show high values, only the vigorous PA discriminates high HDL-C in men, while in women, both the walking and moderate or vigorous PA discriminate high HDL-C levels, demonstrating that men need more intense PA to increase HDL-C levels.

Another important aspect to be highlighted in this study is that the dose-response effect between LTPA and HDL-C has significance both in women classified as little active and in women classified as active and very active. In men, the association is observed only in those classified as active and very active. Therefore, it is possible to understand that they need to practice a greater amount of PA to have a positive result regarding the HDL-C increase.

In a recent publication, also with data from the ELSA-Brasil, aiming to verify the association between LTPA and PA during commuting with cardiovascular risk scores, it was observed that only LTPA was inversely associated with cardiovascular events; moreover, the men needed a greater amount of PA (duration and intensity), also with a dose-response effect, than women to reach the benefits.<sup>17</sup>

These results can be partially explained by the fact that, in men, the resting homeostatic parameters, such as heart rate, blood pressure, glycemic levels, caloric expenditure, among others, are higher than in women, although in the postmenopausal period and with the aging process, blood pressure values may be higher in the female sex.<sup>18,19</sup> Thus, to disrupt the resting homeostasis, the men need a greater amount of PA (duration and intensity) than women, to activate the mechanisms that trigger cardiovascular protection, such as the lowering of blood pressure, reduction of glycemia and triglyceride levels, and increase in HDL-C levels (which at rest show lower levels in men).<sup>6</sup>

A possible limitation can be attributed to the information on PA, since it was obtained through questionnaires, which, despite being a widely used instrument in national and international studies, may present problems, such as memory bias. In addition, it is important to note that only LTPA was analyzed in the present study, and other domains of PA were

not considered, such as commuting, PA at work and domestic PA. Moreover, considering this is a cross-sectional study, reverse causality may limit the strength of the results.

## Conclusions

According to the results observed in this present study, it is suggested that the practice of PA discriminates and is associated with higher levels of HDL-C in adults of both genders. It is important to emphasize that men need a greater amount of physical activities (duration and intensity) for benefits to be achieved. These results are of great importance for public health, considering that public policies for the promotion of physical activities can be guided based on this information. Longitudinal studies on the subject are suggested to confirm the present results.

## Author Contributions

Conception and design of the research, Acquisition of data and Obtaining financing: Griep RH, Almeida MC, Fonseca MJM, Matos SMA; Analysis and interpretation of the data: Pitanga FJG, Griep RH, Almeida MC, Fonseca MJM, Souza AR, Silva RC, Matos SMA; Statistical analysis: Pitanga FJG, Almeida MC; Writing of the manuscript: Pitanga FJG, Souza AR, Silva RC; Critical revision of the manuscript for intellectual content: Pitanga FJG, Griep RH, Almeida MC, Fonseca MJM, Matos SMA.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

This study was partially funded by Ministério da Saúde do Brasil (Departamento de Ciência e Tecnologia) e o Ministério de Ciência e Tecnologia da Brasil (Financiadora de Estudos e Projetos and CNPq – Conselho Nacional de Pesquisa), processos nº 01 06 0010.00RS, 01 06 0212.00BA, 01 06 0300.00ES, 01 06 0278.00MG, 01 06 0115.00SP, 01 06 0071.00RJ.

## Study Association

This study is not associated with any thesis or dissertation work.

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## Physical Activity and HDL-C: Are There Gender Differences in the Dose-response Effect?

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Short Editorial related to the article: Association between Leisure Time Physical Activity and HDL-C in the Elsa-Brasil Study Participants: Are There Any Gender Differences in the Dose-Response Effect?

### HDL: Basic Functions and Cardiovascular Controversies

High-density lipoproteins (HDL) are a heterogeneous group of particles<sup>1</sup> whose primary function is to promote reverse cholesterol transport.<sup>2</sup> Evidence generated over decades has taught us that having low plasma concentrations of HDL-cholesterol (HDL-C) does not seem to be healthy. Also in 1964, Kannel et al.<sup>3</sup> demonstrated – through an analysis of the Framingham cohort – a strong inverse relationship between plasma levels of HDL-C and atherosclerotic cardiovascular disease. However, this paradigm has changed in recent years. The causal role of HDL in cardiovascular risk reduction has been challenged by Mendelian randomization studies, which failed to demonstrate reduced risk of myocardial infarction in individuals with some genetic variants that increased HDL-C.<sup>4,5</sup> In addition, the elevation of HDL-C obtained pharmacologically with cholesterol ester transporter protein (CETP) inhibitors did not lead to a reduction in cardiovascular events either.<sup>6</sup> Finally, studies showing an association of higher mortality with high and low HDL-C levels raised further questions about this situation.<sup>7</sup> Thus, today it is believed that the cardiovascular protection of HDL is, to say the least, controversial, and that HDL-C seems to act much more as a cardiovascular risk marker than as a causal factor.

### HDL-C and Physical Exercise/Physical Activity in Men and Women

Despite the controversies, weight loss, smoking cessation and physical exercise/physical activity (PA) continue to be recommended for individuals with low HDL-C.<sup>8-10</sup> However, knowledge about the dose-response on physical exercise and PA on HDL-C in men and women is somewhat sparse and controversial. Anyway, changes in plasma HDL-C concentrations

through physical training seem to be closely related to gender (men and women), intensity, frequency and duration of training.

In a systematic review that included 23 meta-analyses of randomized clinical trials, which assessed the role of physical exercise in HDL-C levels, an increase ranging from 0.27 to 5.41 mg/dL was found; however, there was great variability in exercise types, duration and intensity, and populations in the meta-analyses included, in addition to a low level of confidence.<sup>11</sup> This points to the need for more well-designed studies in this field of knowledge.

Also in the 1990s, Kokkinos et al.<sup>12</sup> suggested that favorable changes in HDL-C could be associated with higher training intensity. These researchers administered a questionnaire to more than 2,900 healthy men, non-smokers, with a mean age of 43. A 7% increase in HDL-C was observed in those individuals who ran 100–120 minutes/week for about 11 to 22 km/week compared to sedentary individuals with similar characteristics. It is suggested that gender, exercise duration and intensity are some of the factors responsible for differences in lipoprotein responses to exercise. In another study, with the ATTICA cohort population (n = 2,772, mean age 45), an association was found between PA and increased HDL-C levels in women, but not in men, after adjusting for variables such as age, smoking and body mass index.<sup>13</sup> In the cohort of Jan et al.,<sup>14</sup> with the application of a questionnaire on exercise levels, durations below or above 2.5 hours/week were correlated with an increase in HDL-C in both genders, being more pronounced in men than in women in both training durations.

Regarding a sedentary lifestyle, evidence points to worrying data related to physical inactivity in Brazil.<sup>15</sup> Over almost 30 years (1990–2017), Brazilians demonstrated a 59% risk of exposure to physical inactivity, both in 1990 and in 2017; in addition, approximately 22,500 and 32,400 deaths from all causes were attributable to physical inactivity in these years, respectively.

In this issue of Arquivos, Pitanga et al.<sup>16</sup> assessed the dose-response association of physically active time with HDL-C, and whether there were differences comparing genders in a cross-sectional analysis of participants in the Longitudinal Study of Adult Health (Elsa-Brazil). A total of 13,931 participants (average age: 55, 45% men) were analyzed. Among men, almost half were smokers, while among women this percentage was 36%. Approximately 1/4 of men and 30% of women were obese. HDL-C  $\geq$  60 mg/dL levels were considered high. Only 14.5% of

### Keywords

Cholesterol, HDL; Exercise; Cardiovascular Diseases.

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DOI: <https://doi.org/10.36660/abc.20210551>

men had HDL-C at this level, compared to approximately 43% of women. It is worth noting that, despite a higher percentage of women with high HDL-C, more than 36% of them were smokers, a fact that could change the functionality of HDL.<sup>17</sup>

The study by Pitanga et al.<sup>16</sup> also corroborates previous data<sup>15</sup> and strengthens the need for a less sedentary life among Brazilians. In this regard, PA levels during free time were measured using the International Physical Activity Questionnaire (IPAQ). A low percentage of both men and women was considered active or very active (27.6% vs. 25.6%; 20.1% vs. 12.0%, respectively); more than 30% of men and 44% of women were classified as physically inactive. The researchers found a 38% and 41% higher percentage in the chances of achieving high levels of HDL-C in active men and women, respectively, compared to inactive men and women. In men, high HDL-C was associated with greater duration and intensity of PA, while in women, PA of

smaller intensity and shorter duration was also associated with this parameter. In contrast, other authors proposed that women, rather than men, would need more training to increase HDL-C, which could be justified by a higher HDL-C among women at the baseline of studies compared to men,<sup>12</sup> since the increase in HDL-C may be more pronounced in individuals with lower baseline levels. Unfortunately, as there is no baseline HDL-C data from participants in the cohort of Pitanga et al.,<sup>16</sup> this analysis was not possible. On the other hand, the study brings interesting hypotheses that can be tested in randomized controlled trials.

The study is limited by its observational nature, its cross-sectional design, and the use of self-reported PA questionnaires, which may add some subjectivity to the information. Thus, there is still debate regarding the specific intensity and volume of training for men and women aiming at raising HDL-C.

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# Association Between Serum Elabela Levels and Chronic Totally Occlusion in Patients with Stable Angina Pectoris

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## Abstract

**Background:** The beneficial effects of Elabela on the cardiovascular system have been shown in studies.

**Objective:** To compare serum Elabela levels of chronic total occlusion (CTO) patients with control patients with normal coronary arteries, and to investigate whether there is a correlation with collateral development.

**Methods:** The study was planned cross-sectionally and prospectively. Fifty patients (28.0% female, mean age  $61.6 \pm 7.3$  years) with CTO in at least one coronary vessel and 50 patients (38% female, mean age  $60.7 \pm 6.38$  years) with normal coronary arteries were included in the study. Patients in the CTO group were divided into two groups as Rentrop 0-1, those with weak collateral development, and Rentrop 2-3 with good collateral development. In addition to the age, sex, demographic characteristics and routine laboratory tests of the patients, Elabela levels were measured.

**Results:** Demographic characteristics and laboratory values were similar in both groups. While the mean NT-proBNP and troponin were higher in the CTO group, the Elabela mean was lower ( $p < 0.05$  for all). In the multivariate regression analysis, NT-proBNP and Elabela levels were found to be independent predictors for CTO. Also, Elabela level was found to be statistically higher in Rentrop class 2-3 patients compared to Rentrop class 0-1 patients ( $p < 0.05$ ).

**Conclusion:** In our study, we showed that the average Elabela level was low in CTO patients compared to normal patients. In addition, we found the level of Elabela to be lower in patients with weak collateral development compared to patients with good collateral development.

**Keywords:** Chronic Total Occlusion; Coronary Occlusion; Peptides; Elabela; Apelin; Coronary Angiography; Angina Pectoris; Colateral Circulation.

## Introduction

Chronic Total Occlusion (CTO) is defined as an atherosclerotic complete obstruction (Thrombolysis in Myocardial Infarction (TIMI) grade 0) of flow of a coronary artery, with an estimated occlusion duration of  $\geq 3$  months.<sup>1</sup> Data on the prevalence of CTO are derived from registries of patients undergoing coronary angiography for suspected coronary artery disease (CAD); thus, the overall prevalence in the general (asymptomatic) population is unknown. The frequency of at least one CTO ranges from 30% to 50% in patients with a prior diagnosis of CAD who undergo cardiac catheterization.<sup>2</sup>

Elabela was recently discovered as a new endogenous peptidic ligand of the Apelin receptor (APJ), a G protein-coupled receptor. Elabela expression is highest in embryonic

heart tissue and then declines gradually. Elabela is mainly found in fibroblasts and endothelial cells in the heart. Elabela signaling has been demonstrated to be crucial for normal development of the cardiovascular system during embryogenesis.<sup>3</sup> The biological functions of Elabela in the body are similar to those of Apelin, the ligand of the other apelin receptor. In general, Apelin and Elabela are known for their protective effects on the cardiovascular system. Binding of this receptor and its ligands plays some regulatory roles in the cardiovascular system, central nervous system, circulatory system and many other systems.<sup>4,5</sup>

Elabela and Apelin promote angiogenesis through APJ.<sup>6</sup> Elabela and Apelin play roles in different stages of vascular morphogenesis.<sup>7</sup> Elabela is more potent than Apelin when it comes to increasing myocardial contractility and coronary vasodilation.<sup>8</sup> Although Elabela and Apelin share many similarities they function through different signaling pathways and have different biological activities. However, relatively little is known about the biological properties and functions of Elabela. Mounting evidence suggests that APJ is not the only receptor for Elabela. It was suggested that Elabela may have multiple cardioprotective effects via additional pathways.<sup>9,10</sup> Therefore, further studies are warranted to elucidate the molecular mechanisms and biological roles of Elabela and the regulation of cellular signaling pathways.

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Manuscript received June 04, 2020, revised manuscript September 08, 2020, accepted November 04, 2020

**DOI:** <https://doi.org/10.36660/abc.20200492>

There are several studies in the literature that examined the role of Apelin in the human body. However, almost all of the aforementioned studies on Elabela have been conducted in vitro or in animal models. Recently, a number of research studies in humans have been reported in the literature.<sup>11,12</sup> To our best knowledge, there is no study on the role of Elabela in human cardiovascular disease and its treatment potential. In patients with CTO, which represents a spectrum of coronary artery disease, former studies did not investigate serum Elabela levels compared to patients with normal coronary arteries. Since Elabela has effects on angiogenesis and arteriogenesis, there may be a relationship between the extent of coronary collateral development and Elabela levels. Thus, in the present study, we aimed to investigate serum Elabela levels of patients with CTO in comparison to patients with normal coronary arteries and to examine the relationship between coronary collateral development and Elabela levels.

## Method

### Study design

This was a cross-sectional study. The decision for coronary angiography was made according to a positive noninvasive stress test or high clinical suspicion for a coronary artery disease. Sample size or power was not calculated for the study. The sample size was defined for convenience. The local ethics committee approved the study protocol which was implemented in accordance with the principles established in the Declaration of Helsinki. All subjects signed written informed consent prior to initiation of the study.

### Study population

Fifty patients with CTO as demonstrated by coronary angiography and 50 patients with normal coronary arteries (control group) were included in the study. Baseline clinical and demographic characteristics of the study population, all routine laboratory parameters, and echocardiographic data were recorded in the study-specific forms that were generated for each patient. There was no difference in pharmacological treatment between Rentrop Class 0-1 and 2-3 CTO patients.

Hypertension was defined as >140/90 mmHg in repeated systemic blood pressure measurements or use of antihypertensive drugs. Diabetes mellitus was defined according to the presence of one of the following criteria: (1) fasting blood glucose  $\geq 126$  mg/dL, (2) blood glucose > 200 mg/dL at any time, (3) a history of diabetes mellitus, or anti-diabetic medication use. Hypercholesterolemia was defined as current treatment with lipid-lowering agents or a baseline total cholesterol level >200 mg/dL. Smoking was defined as regular smoking for the past 6 months. Family history of coronary artery disease was defined as the presence of coronary artery disease in first-degree relatives of males under 55 years of age or females under 65 years of age.

The study exclusion criteria were as follows: known moderate to severe valvular heart disease, chronic liver disease, chronic kidney disease (GFR <60 ml/kg/min), thyroid dysfunction, atrial fibrillation, acute coronary syndrome, malignancy, active infection, autoimmune disease, patients age  $\leq 18$  and  $\geq 85$  years.

### Laboratory parameters

Routine laboratory parameters (glucose, high-sensitivity troponin I, N-terminal pro-brain natriuretic peptide, renal function, lipid panel and complete blood count) were analyzed for all patients. Serum Elabela levels were obtained using commercially available kits (Sunred Biological Technology, Shanghai, China). Elabela-32 isoform was measured. The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to determine the level of Elabela in blood samples. To measure apelin, serum was separated from the blood by centrifugation at 3,000 rpm for 10 min and kept frozen at  $-80^{\circ}\text{C}$  until analysis. According to the manufacturer, this assay has an inter-assay coefficient of variation of less than 12% and an intra-assay coefficient of variation of less than 10%.

### Angiographic evaluation

Coronary angiography was routinely performed using the Judkins technique with 6- or 7-French right and left heart catheters without the use of nitroglycerin, adenosine, or a calcium channel blocker. Angiograms were recorded in DICOM format at 15 frames/sec and were reviewed by two experienced angiographers who had no knowledge of the patients' clinical condition. Normal coronary arteries were defined as the absence of coronary lesions. CTOs were visualized from at least two angles after selective injection of the contrast material. CTO was defined as a 100% stenosis of the luminal diameter when there was no noticeable lumen and antegrade flow for more than 3 months.<sup>1</sup> Coronary angiograms were re-evaluated for collateral circulation by two experienced interventional cardiologists who were completely blinded to the study. The coronary collateral circulation was graded using the Rentrop classification,<sup>13</sup> where grade 0=no filling of collateral vessels; grade 1=filling of side branches of the artery to be dilated via collateral channels without visualization of the epicardial segment; grade 2=partial filling of the epicardial segment by collateral vessels; and grade 3=complete filling of the epicardial segment of the artery being dilated by a collateral vessel. Patients with grade 0-1 coronary collateral development were considered as poor collateral group, and patients with grade 2-3 coronary collateral development were considered as good collateral group.<sup>14</sup> In patients with more than 1 collateral vessel filling the occluded vessel, the collateral vessel with the highest Rentrop grade was used for analysis.

### Statistical analysis

Continuous variables were analyzed for data normality using the Kolmogorov-Smirnov test. The variables following a normal distribution were presented as mean ( $\pm$  standard deviation) and those without a normal distribution were presented as median (interquartile range). The variables that showed normal distribution between the groups were compared using the unpaired Student's t-test and those without a normal distribution were compared using the Mann-Whitney U-test. Categorical variables were summarized as numbers and percentages, and compared between the groups using the Chi-square test or the Fisher's Exact test.

The receiver operating characteristics (ROC) curve was used to demonstrate the sensitivity and specificity of Elabela cut-off values for CTO. Binary logistic regression analyses were performed to determine independent predictors of CTO. Variables with an unadjusted  $p$  value  $<0.05$  in univariate analysis were included in the multivariate analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 20.0) for Windows (SPSS Inc., Chicago, Illinois, USA). A  $p$  value  $<0.05$  was considered statistically significant.

## Results

A total of 50 CTO patients and 50 patients with normal coronary arteries were included in the study. Baseline demographic and clinical characteristics of the study groups are summarized in Table 1. Comparison of the demographic features between groups showed that previous percutaneous coronary intervention was more commonly performed in the CTO group ( $p=0.006$ ). There was no statistically significant difference between groups in terms of mean age, sex, and the number of patients with hypertension, diabetes mellitus, hyperlipidemia, peripheral artery disease, heart failure, stroke, and chronic obstructive pulmonary disease (all  $p>0.05$ ).

Laboratory parameters and Elabela levels are presented in Table 2. Mean NT-proBNP and troponin levels were significantly higher in the CTO group than in the control subjects ( $p<0.05$ , for both). However, mean Elabela levels were significantly lower in the CTO group than in control subjects ( $p<0.001$ ). There were no significant differences between groups with respect to other laboratory parameters (all  $p>0.05$ ).

In CTO patients, the right coronary artery ( $n=26$ , 52%) was the most affected vessel, followed by the left anterior descending artery ( $n=20$ , 40%), the left circumflex artery ( $n=11$ , 22%) and multiple vessels ( $n=7$ , 14%).

For the prediction of CTO, the cut-off value of  $<0.9$  for Elabela had a 84.8% sensitivity and 80.0% specificity (AUC: 0.824; 95% confidence interval, 0.723-0.924;  $p<0.001$ ) in the ROC curve analysis (Figure 1).

The patients were divided into two groups based on the Rentrop classification: Rentrop 0-1 ( $n=17$ ) and Rentrop 2-3 ( $n=33$ ). The median Elabela value of the Rentrop 0-1 group (median 0.430, IQR: 0.170) with poor collateral development was lower than that of the Rentrop 2-3 group (median 0.740, IQR: 0.380) with a good collateral development ( $p<0.001$ ) (Figure 2).

The results of univariate and multivariate regression analyses are summarized in Table III. Univariate analysis showed that NT-proBNP, Elabela and troponin were independent predictors of CTO. However, in the multivariate analysis, only NT-proBNP ( $p=0.003$ ) and Elabela ( $p=0.001$ ) remained as independent predictors of CTO.

## Discussion

The main finding of our study was that CTO patients had lower serum Elabela levels compared to patients with normal coronary arteries. In addition, patients with a good coronary collateral development had higher serum Elabela levels than patients with poor coronary collateral development. To our best knowledge, our study is the first to examine the relationship between serum Elabela levels and CTO and coronary collateral development.

The human cardiovascular system contains a family of peptides called the Apelinergic system, consisting of Apelin, Elabela and APJ receptors.<sup>15</sup> Studies have shown that Apelin and the receptor system have some positive effects on atherosclerosis, myocardial infarction (MI), heart failure, and pulmonary artery hypertension.<sup>16-18</sup> Although Apelin was initially believed to be the only ligand for APJ, a new peptide they named Elabela was identified by the research conducted

**Table 1 – Baseline demographic characteristics and cardiovascular risk factors of the study population**

| Variable                                         | CTO patients (n=50) | Controls (-) (n= 50) | p     |
|--------------------------------------------------|---------------------|----------------------|-------|
| Age, years                                       | 61.6 ± 7.31         | 60,7 ± 6.38          | 0.495 |
| Female, % (n)                                    | 28.0 (14)           | 38 (19)              | 0.288 |
| Left ventricular ejection fraction, %            | 55.3 ± 7.0          | 55.7 ± 6.83          | 0.795 |
| Hypertension, % (n)                              | 70.0 (35)           | 50 (28)              | 0.147 |
| Diabetes mellitus, % (n)                         | 66.0 (33)           | 50 (25)              | 0.105 |
| Hyperlipidemia, % (n)                            | 62 (31)             | 44 (22)              | 0.071 |
| Peripheral vascular disease, % (n)               | 10.0 (5)            | 6 (3)                | 0.461 |
| Stroke, % (n)                                    | 4.0 (2)             | 2(1)                 | 0.558 |
| Heart failure, % (n)                             | 16.0 (8)            | 12 (6)               | 0.564 |
| Chronic obstructive pulmonary disease, %(n)      | 10.0 (5)            | 18 (9)               | 0.249 |
| Previous Percutaneous Coronary Intervention% (n) | 14.0 (7)            | 0 (0)                | 0.006 |
| Current smoker, % (n)                            | 58 (29)             | 48 (24)              | 0.316 |
| Family history of CAD, % (n)                     | 22.0 (11)           | 24 (12)              | 0.812 |

CAD: Coronary artery disease

**Table 2 – Laboratory parameters and Elabela levels of the study groups.**

| Variable                                     | CTO patients (n=50) | Controls (n= 50) | P      |
|----------------------------------------------|---------------------|------------------|--------|
| Fasting glucose level, mg/dL, median (IQR)   | 102.5 (28.0)        | 121 (55.0)       | 0.057  |
| Hemoglobin, g/dL                             | 13.9 ± 1.90         | 13.2 ± 1.52      | 0.107  |
| Hematocrit, %                                | 39.9 ± 5.57         | 39.3 ± 3.95      | 0.584  |
| White blood cell count, x10 <sup>3</sup> /mL | 8.2 ± 2.02          | 8.4 ± 2.40       | 0.692  |
| Platelet count, x10 <sup>3</sup> /mL         | 265 ± 82            | 271 ± 51         | 0.743  |
| Neutrophil count, x10 <sup>3</sup> /mL       | 5.4 ± 1.68          | 5.2 ± 1.57       | 0.357  |
| Lymphocyte count, x10 <sup>3</sup> /mL       | 2.2 ± 0.7           | 2.1 ± 0.6        | 0.417  |
| Monocyte count, x10 <sup>3</sup> /mL         | 0.6 ± 0.23          | 0.7 ± 0.29       | 0.640  |
| Mean platelet volume, fL                     | 8.8 ± 1.14          | 8.8 ± 1.02       | 0.933  |
| Total cholesterol, mg/dL, median (IQR)       | 206.5 (53.5)        | 216 (46.5)       | 0.955  |
| LDL-Cholesterol, mg/dL, median (IQR)         | 132.5 (40.5)        | 147 (34.5)       | 0.389  |
| HDL-Cholesterol, mg/ dL                      | 42.1 ± 9.5          | 44.6 ± 8.5       | 0.236  |
| Triglyceride, mg/dL, median (IQR)            | 173 (103.7)         | 159 (101.5)      | 0.147  |
| Urea, mg/dL                                  | 34.9 ± 13.93        | 33.4 ± 7.89      | 0.580  |
| Creatine, mg/dL,                             | 0.84 ± 0.27         | 0.78 ± 0.15      | 0.275  |
| Albumin, mg/dL                               | 3.7 ± 0.59          | 3.8 ± 0.34       | 0.424  |
| Troponin, ng/ml median (IQR)                 | 6.0 (12.0)          | 4.0 (7.0)        | 0.013  |
| Elabela, ng/mL, median (IQR)                 | 0.64 (0.40)         | 1.20 (1.14)      | <0.001 |
| CRP, mg/l, median (IQR)                      | 1.8 (1.4)           | 1.4 (2.0)        | 0.506  |
| NT-proBNP, pg/ml, median (IQR)               | 25.5 (16.5)         | 16.0(11.0)       | 0.001  |
| SYNTAX score                                 | 12.3 ± 7.1          | -                | -      |

IQR: Interquartile Range, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, CRP: C reactive protein, NT-proBNP: N-terminal pro-brain natriuretic peptide

by the Reversade team.<sup>19</sup> It has been shown in studies that Apelin and Elabela act via APJ and have similar functions. Moreover, Elabela was shown to be more potent than Apelin in producing positive cardiac effects.<sup>20</sup> Patients with stable angina were found to have significantly lower plasma Apelin levels in comparison to controls. In addition, plasma Apelin level was found to be negatively correlated with Gensini score in patients with acute coronary syndrome.<sup>21</sup> In their study, Weir et al. showed that plasma Apelin concentration was reduced in the early period after acute myocardial infarction, increased significantly over time, but remained depressed at 24 weeks.<sup>22</sup> As CTO is a late coronary event, Elabela level was similarly lower in CTO patients than in patients with normal coronary arteries.

CTO is a subgroup of atherosclerotic heart disease and is associated with negative clinical outcomes. The biological roles of Elabela in atherosclerotic diseases have recently been explored in a recent study by Li et al. who proposed Elabela as a new possible therapeutic agent for cardiovascular diseases.<sup>23</sup> Impaired endothelial function is associated with atherosclerosis. Elabela is mainly detected in fibroblasts in the heart and intact endothelial cells.<sup>3</sup> Therefore, Elabela production decreases in impaired endothelial function. In our study, low Elabela levels measured in the CTO group can be explained by the presence of impaired endothelial function.

The development of coronary collaterals is a response to chronic myocardial ischemia. Collateral vessels provide an alternative blood supply for myocardium in patients with obstructive coronary lesions. Increased coronary collateral blood flow can reduce angina symptoms and cardiovascular events and maintain the contractile function of the myocardium. There is important evidence that collateral circulatory development occurs as a result of angiogenesis and/or arteriogenesis.<sup>24</sup> Elabela signaling has been shown to have a key role in the development of normal cardiovascular system during embryogenesis. Elabela promotes angiogenesis and arteriogenesis via APJ.<sup>6,25</sup> In their study, Sharma et al. found that the Elabela-APJ signal axis induces progenitor cell migration from sinus venosus in mice and thus plays a role in the development of coronary vessels. In addition, they detected defects in coronary vessel development in mice lacking the Elabela-APJ signal.<sup>26</sup> In our study, the high serum level of Elabela in Rentrop class 2-3 patients with good collateral development compared to patients in Rentrop class 0-1 with poor collateral development can be explained by the positive effects of Elabela on angiogenesis and arteriogenesis.

Perjes et al. showed in mice that Elabela levels increased in the early post- MI period due to its cardioprotective effects but decreased later or after unsuccessful treatment.<sup>27</sup> CTO, a

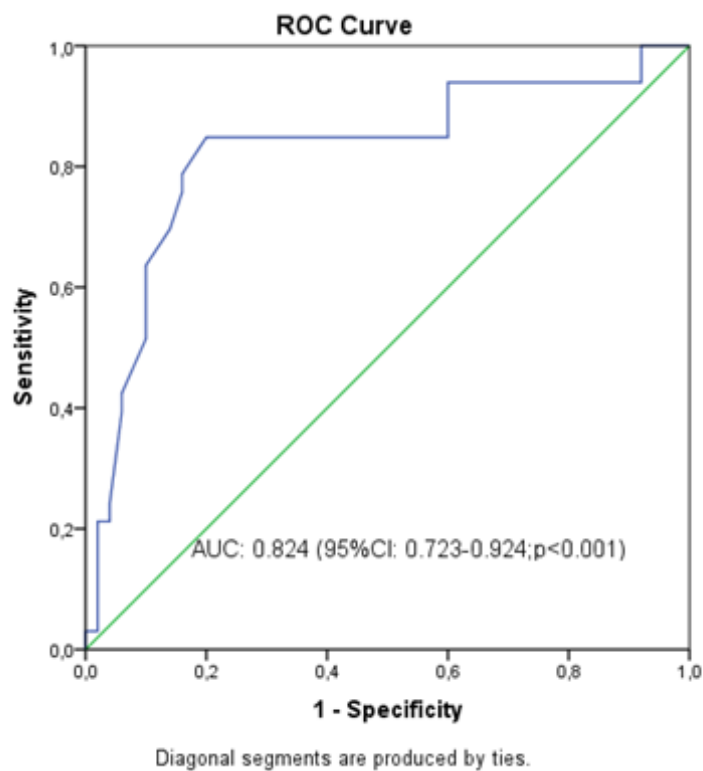


**Figure 1** – Receiver–operating characteristic curve analysis for Elabela for prediction of CTO.

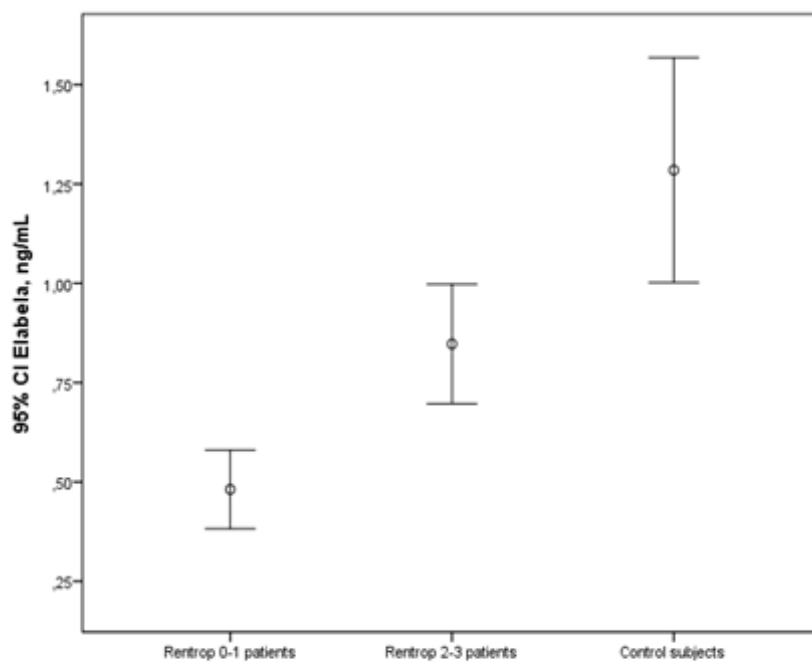


**Figure 2** – Relationship between Elabela level and Rentrop score (error bars: 95% confidence interval [CI]).

spectrum of atherosclerotic heart disease, is defined as 100% lumen diameter stenosis for more than 3 months when there is no noticeable lumen and antegrade flow.<sup>1</sup> The low level of Elabela in CTO patients as found in our study is consistent with the findings of that study

Previous studies reported that Elabela is involved in a wide range of cardiovascular conditions and diseases. Apelinergic system activity increases substantially in remodeling after myocardial infarction, in arterial hypertension and exerts beneficial effects by blocking the Renin-Angiotensin-Aldosterone system<sup>4</sup>. In addition, positive effects of Elabela on heart failure and diabetes have also been shown in studies<sup>19,28,29</sup>. In our study, there was no difference between the groups in terms of hypertension, diabetes and heart failure.

Current evidence for the cardioprotective effects of Elabela is scarce. However, in vitro and animal studies suggest that Elabela or a synthetic derivative may have therapeutic or biomarker potential for cardiovascular diseases.

### Limitations

The cross-sectional design and the sample size of the study are the main limitations of our study. Although biochemical measurements were performed in our study, we did not examine the APJ receptor level of the tissue samples. Also, Apelin and APJ measurements were not obtained and they could have provided more information about the Apelinergic system in CTO patients.

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### Conclusion

In this study, we showed decreased Elabela levels in CTO patients. We also observed a positive correlation between coronary collateral development and serum Elabela levels. Larger and more comprehensive studies are needed to establish the role of Elabela as a cardiac biomarker or therapeutic agent in humans.

### Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Yavuz F; Statistical analysis and Obtaining financing: Kaplan M; Critical revision of the manuscript for intellectual content: Yavuz F, Kaplan M.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

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## A New Pathway to Coronary Occlusion with Elabela?

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Short Editorial related to the article: Association Between Serum Elabela Levels and Chronic Totally Occlusion in Patients with Stable Angina Pectoris

Total coronary occlusion (TCO) is characterized by an obstruction with an estimated duration of more than 3 months and is present in approximately 15–18% of all coronary angiographies performed.<sup>1</sup> Clinical manifestations can range from asymptomatic, through stable angina, to varying degrees of ventricular dysfunction. This mainly depends on the degree of collateral circulation. If it is poor, it may compromise the viability of myocytes and associate with various degrees of necrosis and/or hibernating myocardium. In the presence of well-developed collaterals (Rentrop grade III), the patient may be asymptomatic and have a preserved contractile function.<sup>2</sup> Therefore, the formation of a well-developed collateral circulation, especially before vessel occlusion, is essential for the preservation of myocytes.

Despite advances in the clinical treatment of stable angina, many patients with TCO undergo interventional procedures. Of these, most are referred for coronary artery bypass grafting surgery or percutaneous coronary intervention (PCI) with more advanced techniques, but also with a higher risk of complications. The study of mechanisms potentially stimulating arteriogenesis and angiogenesis (collateral

circulation formation) opens up opportunities for the development of drugs that, in turn, would avoid unnecessary interventions and/or could benefit patients with symptoms refractory to optimized conventional clinical treatment and who are poor candidates for interventions (e.g., thin distal bed, diffuse coronary disease).

In this issue of ABC, in a cross-sectional study, Yavuz and Kaplan<sup>3</sup> observed the relationship between elabela levels with TCO and the presence of collateral circulation. There is biological plausibility to support this association. Stimulation of the apelinergic system, whether by apelin or elabela on APJ receptors, stimulates vascular proliferation,<sup>4</sup> while apelin predominantly promotes angiogenesis, that is, more capillary vascularization, which is important in peri-lesional regions. Elabela is responsible for arteriogenesis, promotes the formation of new vessels with a diameter of up to 2 mm,<sup>5</sup> which is the most important aspect for the formation of collateral circulation.<sup>2</sup>

It took approximately 30 years from the discovery of the APJ receptor to the first clinical studies,<sup>4</sup> but more time will be needed for prospective studies to prove the association between elabela and new vessel formation in adults. We may wonder whether based on studies of this system the first effective drug, which works as an agonist of a system for the treatment of chronic coronary disease, will be developed. Currently, effective drugs inhibit platelet aggregation, reducing LDL cholesterol, stabilizing atheromatous plaques, reducing myocardial oxygen consumption, but not by stimulating vascular neoformation.<sup>6</sup> A paradigm shift will be interesting, and we will have to learn how to handle such medications, whose logic may not be one involving use for an indefinite time.

### Keywords

Coronary Occlusion; Microvascular Angina; Myocytes, Cardiac; Collateral Circulation; Biomarkers (Elabela).

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DOI: <https://doi.org/10.36660/abc.20210662>

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# Heyde's Syndrome: Therapeutic Strategies and Long-Term Follow-Up

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## Abstract

**Background:** Heyde's syndrome is the association of severe aortic stenosis with episodes of gastrointestinal bleeding due to angiodysplastic lesion. Little is known about the factors associated with new episodes of bleeding and long-term outcomes. Furthermore, most data are restricted to case reports and small case series.

**Objective:** To assess the clinical, laboratory and echocardiography profile of patients with Heyde's syndrome who underwent valve intervention or drug therapy.

**Methods:** Prospective cohort of 24 consecutive patients from 2005 to 2018. Clinical, laboratory and echocardiography data were assessed, as well as those related to valve intervention and outcomes after diagnosis. A  $P < 0.05$  was used to indicate statistical significance.

**Results:** Half of the 24 patients presented with bleeding requiring blood transfusion on admission. Angiodysplasias were more frequently found in the ascending colon (62%). Valve intervention (surgical or transcatheter) was performed in 70.8% of the patients, and 29.2% remained on drug therapy. New episodes of bleeding occurred in 25% of the cases, and there was no difference between clinical and intervention groups (28.6 vs 23.5%,  $p = 1.00$ ; respectively). Mortality at 2-year and 5-year was 16% and 25%, with no difference between the groups (log-rank  $p = 0.185$  and  $0.737$ , respectively).

**Conclusions:** Patients with Heyde's syndrome had a high rate of bleeding requiring blood transfusion on admission, suggesting that it is a severe disease with high mortality risk. No difference was found between clinical and intervention group regarding the rate of rebleeding and late mortality.

**Keywords:** Aortic Stenosis; Angiodysplasia; Hemorrhage; Mortality; Thoracic Surgery; Echocardiography/methods.

## Introduction

The association between gastrointestinal bleeding due to angiodysplastic lesions and severe aortic stenosis is named Heyde's syndrome and was described by Edward Heyde in 1958.<sup>1</sup> Since then, there have been controversies on the pathogenesis of this syndrome, and the only factor that predisposes to bleeding in this population is acquired von Willebrand factor (vWF) deficiency resulting from hemodynamic stress in the stenotic aortic valve.<sup>2-6</sup>

Heyde's syndrome is described in 1.7% of patients with severe aortic stenosis and, despite its prevalence, little is known about its epidemiological aspects. Most publications related to this entity are case reports and small case series.<sup>5</sup> The indication of valve intervention in these patients follows current guidelines and, although there are no specific recommendations, some centers advocate for intervention to

reduce bleeding, regardless of the presence of symptoms or prognostic factors.<sup>7-9</sup> Therefore, the aim of this study was to evaluate clinical, laboratory, and echocardiography aspects, in addition to mortality rates and complications after valve intervention or clinical treatment, in a case series of patients with Heyde's syndrome.

## Methods

This is a prospective cohort that assessed patients with severe aortic stenosis in a tertiary care center from 2005 to 2018. Severe aortic stenosis was defined as the presence of aortic valve area  $\leq 1.0$  cm<sup>2</sup>, mean transaortic gradient  $> 40$  mmHg, or peak velocity  $> 4.0$  m/s as measured by the transthoracic echocardiography.<sup>9</sup> Patients with history of gastrointestinal bleeding and angiodysplasia documented by colonoscopy and/or upper digestive tract endoscopy were selected. Clinical, laboratory and echocardiography data were assessed, as well as those related to the indicated treatment. Exclusion criteria were: presence of other conditions that could justify bleeding (such as gastric ulcer or neoplasms), severe aortic regurgitation, or anatomically severe primary mitral valve disease. Valve intervention was indicated according to physician's choice and followed current guidelines.<sup>9,10</sup> For comparative reasons, we divided patients into two groups, according to the chosen treatment

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Manuscript received May 08, 2020, revised manuscript August 16, 2020, accepted September 09, 2020

**DOI:** <https://doi.org/10.36660/abc.20200371>

(valve intervention vs drug therapy). We assessed mortality and perioperative complications at 30 days and later through telephone contact. This study was approved by the institutional ethical research committee, and there was a request to waive the requirement for a consent form.

### Statistical analysis

Continuous and categorical variables were presented as median (interquartile range) and frequencies or percentages, respectively. The normality of variable distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were analyzed with the Mann-Whitney test, and categorical variables with the chi-square test or the Fisher's exact test, as appropriate. Five-year mortality was assessed using the Log-rank test. All tests were two-tailed, and a  $P < 0.05$  was used to indicate statistical significance. The SPSS software, version 20 (IBM, Armonk, New York, USA) was used to analyze data.

## Results

A total of 24 patients met inclusion criteria for the study. Baseline characteristics are described in Table 1. Median age was 77 [70-82] years, 50% of patients were women, and there was a high prevalence of comorbidities such as systemic arterial hypertension (79.2%), diabetes (41.7%), and coronary artery disease (41.7%). All patients presented gastrointestinal bleeding, but 50% received red blood cell transfusion on admission. Only 33.3% were using platelet antiaggregants (aspirin), and 8.3% were on anticoagulation therapy with warfarin. There was no difference between patients using aspirin vs those not using this medication with regard to bleeding requiring transfusion (62.5 vs 43.8%, respectively;  $p = 0.385$ ). The same was observed for the use of warfarin, since the only two patients using this medication did not have new episodes of bleeding.

All patients had degenerative aortic stenosis, with median mean transaortic gradient of 49 [42-57] mmHg, valve aortic area of 0.66 [0.60-0.70] cm<sup>2</sup>, and peak velocity of 4.5 [4.0-4.9] m/s. Median left ventricular ejection fraction was 64 [56-68]%. Other echocardiography characteristics are described in Table 1, as well as laboratory data. Baseline hemoglobin was 10.1 [8.2-11.4] g/dL, and 17.4% and 34.8% of patient had hemoglobin  $< 7.0$  and  $< 9.0$  mg/dL on admission, respectively. Results for the coagulogram test were normal, except for one patient on oral anticoagulant therapy with international normalized ratio (INR) of 1.7. With regard to colonoscopy and upper digestive tract endoscopy, baseline data are described in Table 2. All patients had angiodysplasia, of which 50.0% were diagnosed in colonoscopy, 33.3% in upper digestive tract endoscopy, and 16.6% in both. Lesions were most frequently found in the ascending colon (62.5%) and in the stomach (37.5%). Treatment of lesions with cauterization or argon occurred in 41.7% of the cases.

### Valve intervention vs drug therapy

Data related to intervention and to events are described in Table 3. In our study, seven (29.2%) patients remained on clinical treatment, and 17 (70.8%) underwent aortic

valve intervention, of which 70.5% received a biological prosthesis, 17.6%, a mechanical prosthesis; 11.7%, transcatheter aortic valve replacement (TAVR), and 23.5% underwent concomitant myocardial revascularization. Thirty-day and 1-year mortality in the intervention group was 11.8% and 23.5%, respectively. No differences were found between the groups with regard to baseline, laboratory and echocardiography characteristics or with regard to findings from upper digestive tract endoscopy and colonoscopy (Tables 1 and 2). Furthermore, the rate of new episodes of bleeding was similar between clinical treatment vs intervention group (28.6 vs 23.5%, respectively;  $p = 1.000$ ). Of the patients in the intervention group who had new episodes of gastrointestinal bleeding, two required red blood cell transfusion, and none of these patients had received the mechanical prosthesis. Valve intervention was indicated due to presence of symptoms in 15 (88.2%) cases, and due to bleeding requiring red blood cell transfusion in two (11.7%) cases. Deaths at 1 year resulted from infectious endocarditis in one case, sepsis in one case, and cardiogenic shock in two cases.

Three patients in the intervention group underwent another colonoscopy due to bleeding recurrence, which shown that the angiodysplastic lesions were still located at the same sites where they were found before valve intervention.

The indication for drug therapy in seven (29.2%) patients was made according to either patient's or assisting physician's choice due to age, frailty, and other comorbidities. Median follow-up after diagnosis of Heyde's syndrome was 24 [12-54] months, and overall mortality at 2-year and 5-year follow-up was 16% and 25%, respectively, with no difference between the groups (log-rank  $p = 0.185$  and 0.737, respectively).

In order to assess the impact of the long period of study inclusion, patients were divided according to the median period of study inclusion: 2005-2010 ( $n = 13$ ) and 2011-2018 ( $n = 11$ ) (Supplemental Tables 1 and 2). Only urea levels showed a significant difference between the 2005-2010 and 2011-2018 groups (67 [51-87] vs 44 [38-49] mg/dL, respectively;  $p = 0.012$ ). No differences were found with regard to other baseline characteristics, as well as with regard to 1-year mortality (15.4 vs 18.2 %, respectively;  $p = 1.000$ ) and rates of new episodes of bleeding (30.8 vs 18.2%, respectively;  $p = 0.649$ ). There was a trend of fewer indications of isolated drug therapy in the 2011-2018 group (46.2 vs 9.1 %, respectively;  $p = 0.078$ ), but with no statistical significance.

## Discussion

The main findings of the present study were: 1) 50% of the patients presented with gastrointestinal bleeding requiring red blood cell transfusion on admission, showing that Heyde's syndrome is a potential life-threatening disease; 2) there was no difference in the rates of rebleeding between patients that underwent interventional treatment vs drug therapy; 3) survival was similar between the groups, inclusive no in long-term follow-up; 4) the most frequent bleeding site was the ascending colon.

**Table 1 – Clinical, laboratory and echocardiography characteristics of the study population**

|                                                        | Total (N = 24)               | Intervention (n = 17)        | Clinical (n = 7)             | p     |
|--------------------------------------------------------|------------------------------|------------------------------|------------------------------|-------|
| <b>Clinical characteristics</b>                        |                              |                              |                              |       |
| Age (years)                                            | 77 [70-82]                   | 76 [68-81]                   | 82 [81-87]                   | 0.069 |
| Female sex, n (%)                                      | 12 (50.0)                    | 7 (41.2)                     | 5 (71.4)                     | 0.371 |
| Diabetes mellitus, n (%)                               | 10 (41.7)                    | 7 (41.2)                     | 3 (42.9)                     | 1.000 |
| Hypertension, n (%)                                    | 19 (79.2)                    | 15 (88.2)                    | 4 (57.1)                     | 0.126 |
| Atrial fibrillation, n (%)                             | 4 (16.7)                     | 3 (17.6)                     | 1 (14.3)                     | 1.000 |
| Coronary heart disease, n (%)                          | 10 (41.7)                    | 8 (47.1)                     | 2 (8.6)                      | 0.653 |
| EuroSCORE II (%)                                       | 1.78 [1.44-3.42]             | 1.71 [1.31-2.81]             | 2.41 [1.57-7.55]             | 0.371 |
| STS (%)                                                | 2.43 [1.60-4.42]             | 2.21 [1.49-3.95]             | 4.8 [1.93-6.04]              | 1.000 |
| <b>Symptoms</b>                                        |                              |                              |                              |       |
| Dyspnea (NYHA III/IV), n (%)                           | 14 (58.3)                    | 10 (58.8)                    | 4 (57.1)                     | 1.000 |
| Angina, n (%)                                          | 3 (12.5)                     | 3 (17.6)                     | 0 (0)                        | 0.530 |
| Gastrointestinal bleeding requiring transfusion, n (%) | 12 (50.0)                    | 9 (52.9)                     | 3 (42.9)                     | 1.000 |
| <b>Medications</b>                                     |                              |                              |                              |       |
| ACE inhibitors or ARB, n (%)                           | 10 (41.7)                    | 8 (47.1)                     | 2 (28.6)                     | 0.653 |
| Beta-blockers, n (%)                                   | 6 (25.0)                     | 4 (23.5)                     | 2 (28.6)                     | 1.000 |
| Platelet antiaggregant drugs, n (%)                    | 8 (33.3)                     | 5 (29.4)                     | 3 (42.9)                     | 0.647 |
| Diuretics, n (%)                                       | 17 (70.8)                    | 11 (64.7)                    | 6 (85.7)                     | 0.625 |
| Statins, n (%)                                         | 9 (37.5)                     | 6 (35.3)                     | 3 (42.9)                     | 1.000 |
| Digoxin, n (%)                                         | 3 (12.5)                     | 2 (11.8)                     | 1 (14.3)                     | 1.000 |
| Oral anticoagulation, n (%)                            | 2 (8.3)                      | 2 (11.8)                     | 0 (0)                        | 1.000 |
| <b>Echocardiography parameters</b>                     |                              |                              |                              |       |
| Mean transaortic gradient, mmHg                        | 49 [42-57]                   | 53 [42-57]                   | 42 [39-59]                   | 0.141 |
| Aortic peak velocity, m/s                              | 4.5 [4.0-4.9]                | 4.5 [4.0-5.1]                | 4.4 [4.0-4.8]                | 0.381 |
| Left ventricular ejection fraction, %                  | 64 [56-68]                   | 64 [55-68]                   | 65 [55-69]                   |       |
| Aortic valve area, cm <sup>2</sup>                     | 0.66 [0.60-0.70]             | 0.66 [0.60-0.70]             | 0.66 [0.60-0.70]             | 1.000 |
| Moderate aortic insufficiency, n (%)                   | 2 (8.3)                      | 1 (5.9)                      | 1 (14.3)                     | 0.507 |
| Moderate/severe functional mitral insufficiency, n (%) | 7 (29.2)                     | 5 (29.4)                     | 2 (28.6)                     | 1.000 |
| Moderate/severe tricuspid insufficiency, n (%)         | 3 (12.5)                     | 1 (5.9)                      | 2 (28.6)                     | 0.194 |
| <b>Laboratory data</b>                                 |                              |                              |                              |       |
| Hemoglobin, g/dL                                       | 10.1 [8.2-11.4]              | 10.4 [8.5-12.6]              | 9.1 [6.3-11]                 | 1.000 |
| Hemoglobin < 7.0 g/dL on admission, n (%)              | 4 (17.4)                     | 1 (6.3)                      | 3 (42.9)                     | 0.067 |
| Hemoglobin < 9.0 g/dL on admission, n (%)              | 8 (34.8)                     | 5 (51.3)                     | 3 (42.9)                     | 0.657 |
| Hematocrit, %                                          | 32 [25-34]                   | 32 [27-36]                   | 27 [22-33]                   | 0.657 |
| Platelets, /mm <sup>3</sup>                            | 210 000<br>[155 000-281 000] | 208 000<br>[149 000-267 500] | 270 000<br>[175 000-299 000] | 0.667 |
| Prothrombin time, s                                    | 15.3 [13.2-16.2]             | 14.6 [12.7-16.1]             | 15.9 [15.3-17.9]             | 0.193 |
| Prothrombin activity, %                                | 78.7 [71.8-92.0]             | 83.6 [73.5-92.0]             | 71.8 [63.0-89.8]             | 0.371 |
| Time ratio (PT/RT)                                     | 1.1 [1.0-1.2]                | 1.0 [1.0-1.1]                | 1.2 [1.0-1.2]                | 0.650 |
| INR                                                    | 1.1 [1.0-1.2]                | 1.0 [1.0-1.1]                | 1.2 [1.0-1.3]                | 0.137 |
| APTT, s                                                | 29.5 [28.2-33.9]             | 29.3 [28.3-31.]              | 30.0 [28.1-36.5]             | 0.361 |
| Creatinine clearance, mL/min/1.73m <sup>2</sup>        | 59 [48-75]                   | 61 [52-70]                   | 28 [28-77]                   | 1.000 |
| Urea, mg/dL                                            | 50 [41-70]                   | 47 [38-56]                   | 71 [50-138]                  | 0.193 |

ACE: angiotensin-converting enzyme; APTT: activated partial thromboplastin time; ARB: angiotensin receptor blocker; INR: international normalized ratio; NYHA, New York Heart Association; PT: prothrombin time; RT: reptilase time.

**Table 2 – Findings from colonoscopy and upper digestive tract endoscopy**

|                                              | Total (n=24) | Intervention (n = 17) | Clinical (n = 7) | p     |
|----------------------------------------------|--------------|-----------------------|------------------|-------|
| <b>Angiodysplasia, n (%)*</b>                |              |                       |                  |       |
| Ascending colon, n (%)                       | 15 (62.5)    | 9 (52.9)              | 6 (85.7)         | 0.191 |
| Transverse colon, n (%)                      | 2 (8.3)      | 0 (0)                 | 2 (28.6)         | 0.076 |
| Stomach, n (%)                               | 9 (37.5)     | 7 (41.2)              | 2 (28.6)         | 0.669 |
| Descending colon, n (%)                      | 4 (16.7)     | 1 (5.9)               | 3 (42.9)         | 0.059 |
| Duodenum, n (%)                              | 5 (20.8)     | 4 (23.5)              | 1 (14.3)         | 1.000 |
| Jejunum, n (%)                               | 4 (16.7)     | 2 (11.8)              | 2 (28.6)         | 0.552 |
| Diverticuli, n (%)                           | 13 (54.2)    | 8 (47.1)              | 5 (71.4)         | 0.386 |
| Polyps, n (%)                                | 8 (3.3)      | 7 (41.2)              | 1 (14.3)         | 0.352 |
| Cauterization or application of argon, n (%) | 10 (41.7)    | 9 (52.9)              | 1 (14.3)         | 0.172 |

\*The sum may be higher than 100% because the patients may present with angiodysplasia at more than one site.

**Table 3 – Characteristics of intervention and events at 30 days**

|                                                        | Intervention (n = 17) | Clinical (n = 7) | p     |
|--------------------------------------------------------|-----------------------|------------------|-------|
| Biological prosthesis, n (%)                           | 12 (70.5)             | -                | -     |
| Mechanical prosthesis, n (%)                           | 3 (17.6)              | -                | -     |
| Concomitant myocardial revascularization, n (%)        | 4 (23.5)              | -                | -     |
| TAVR, n (%)                                            | 2 (11.7)              |                  |       |
| 30-day mortality, n (%)                                | 2 (11.8)              | 0 (0)            | 1.000 |
| 1-year mortality, n (%)                                | 4 (23.5)              | 0 (0)            | 0.283 |
| Major stroke, n (%)                                    | 1 (5.9)               | -                | -     |
| Pericardial effusion, n (%)                            | 3 (17.6)              | -                | -     |
| Atrial fibrillation, n (%)                             | 6 (35.3)              | -                | -     |
| Reintervention, n (%)                                  | 2 (11.8)              | -                | -     |
| Gastrointestinal bleeding, n (%)                       | 4 (23.5)              | 2 (28.6)         | 1.000 |
| Gastrointestinal bleeding requiring transfusion, n (%) | 2 (11.8)              | 2 (28.6)         | 0.552 |

TAVR indicates transcatheter aortic valve replacement.

Heyde's syndrome is defined by the presence of severe aortic stenosis associated with gastrointestinal bleeding resulting from angiodysplasias and, since it was first described in 1958, its pathophysiogenesis has not been completely elucidated yet.<sup>1</sup> Angiodysplastic vessels are the most commonly found vascular anomaly in the gastrointestinal tract, and its prevalence certainly increases with age, as well as aortic stenosis prevalence.<sup>2,4,11-13</sup> However, the correlation between severe aortic stenosis and angiodysplastic lesions does not seem to be casual. Left ventricular outflow tract obstruction reduces gastrointestinal blood flow, due to flattening of arterial pulse wave parameters. This change would lead to relative splanchnic ischemia, thus favoring neoangiogenesis.<sup>4,14-17</sup> This hypothesis is corroborated by Greensteins et al.,<sup>14</sup> who studied the configuration of the pulse wave in the mesenteric vessel in patients with aortic stenosis, and by Stern et al.,<sup>15</sup> who evaluated 33 patients with non-pulsatile ventricular assist devices and observed episodes

of bleeding resulting from small bowel angiodysplasias in 13 of them. Furthermore, ischemic colonic mucosa becomes fragile, thus increasing the risk for bleeding. However, interventional treatment of aortic stenosis does not resolve angiodysplastic lesions, as documented in three of our cases, in which colonoscopy and/or upper digestive tract endoscopy was repeated after valve intervention.<sup>2</sup> Moreover, ascending colon was the most frequent site of angiodysplastic lesions, in line with the literature.<sup>12</sup>

Other factor contributing to bleeding of these lesions is acquired vWF deficiency. vWFs are multimeric glycoproteins that bind to factor VIII, contributing to formation of platelet thrombus and acting like a mediator of platelet adhesion.<sup>2,3,6,18,19</sup> In situations of shear stress due to aortic valve stenosis, vWFs changes their structure, being subjected to proteolysis mediated by the A Disintegrin and Metalloproteinase with Thrombospondin type 1 motif,

member 13 (ADAMTS13) enzyme.<sup>2,3,6,18,19</sup> Some authors suggest that aortic valve intervention (surgical or transcatheter) corrects vWF deficiency, drastically reducing the rate of new bleeding episodes.<sup>5,6,11,12,19-21</sup> Thompson et al.<sup>12</sup> assessed a 34-year cohort of 57 patients with Heyde's syndrome who underwent surgical aortic valve replacement and showed that 79% of patients did not experience new episodes of bleeding after valve intervention at a median follow-up of 4.4 [0.1-15] years. These patients had baseline characteristics similar to those of patients included in our study, but there was no control group. In our 13-year cohort with a median follow-up of 2 [1-4.5] years, 76.5% of patients did not experience new episodes of bleeding after aortic valve intervention, but there was no difference between these patients and those who remained on drug therapy, suggesting that intervention would have the same impact as drug therapy with regard to new bleeding episodes in patients with Heyde's syndrome.

Heyde's syndrome is not described in current guidelines for the management of patients with valvular heart disease. Nevertheless, due to the hypothesis that bleeding may be resolved after aortic stenosis intervention, some authors advocate for the indication of valve intervention in patients with this condition, regarding of the presence of symptoms or prognostic factors, as two patients in the present study.<sup>11,12,19-21</sup> Indication for intervention due to Heyde's syndrome is favored by the fact that this disease may lead to episodes posing high mortality risk, as it could be observed in the present study, in which half of the patients required red blood cell transfusion on admission. In situations of acute anemia, those with severe aortic stenosis are unable to increase cardiac output, due to fixed outflow obstruction, being susceptible to cardiovascular events, such as heart failure and myocardial infarction. Nevertheless, 29.2% remained on drug therapy according to either patient's or assisting physician's choice. Patients in the clinical group tended to be older, but there were no other statistically significant differences related to baseline characteristics. It is important to highlight that these patients were followed in a hospital belonging to the Brazilian public health system, in which TAVR was not a currently available therapeutic option, which justifies the high rates of conservative treatment and the few cases of TAVR.

## Limitations

The current study has limitations inherent to its design. An important aspect is the sample size, which, although being relatively small, is the largest case series of patients with Heyde's syndrome in Latin America so far. However, we are susceptible to type II error to ensure that interventional treatment is not enough to reduce events/new bleeding

episodes. Furthermore, a long period of period of study inclusion was necessary, because Heyde's syndrome is a rare disease; however, the analysis with regard to period of study inclusion did not reveal significant differences. Another limitation is the fact that some aspects, such as frailty and pulmonary artery systolic pressure, could not be assessed, due to study characteristics; similarly, vWF deficiency was not assessed either. Moreover, patients included in the last year had a shorter follow-up time, which may have an impact on the analysis of long-term survival, despite statistical adjustment by follow-up time.

## Conclusion

In our cohort, patients with Heyde's syndrome showed a high rate of bleeding requiring blood transfusion at admission, suggesting that it is a severe disease with high risk of mortality. No differences were found between clinical and intervention groups with regard to rates of rebleeding and long-term mortality. Prospective studies are needed to confirm whether valve intervention reduces the rate of new bleeding episodes and whether Heyde's syndrome alone should be a reason to indicate valve intervention. Nevertheless, the rarity of this condition hamper the conduction of these studies.

## Author Contributions

Conception and design of the research: Rosa VEE, Fernandes JRC, Santis A, Spina GS, Sampaio RO, Tarasoutchi F; Acquisition of data: Rosa VEE, Fernandes JRC, Santis A, Spina GS, Paixão MR, Pires JT, Betttega M, Accorsi TAD, Sampaio RO, Tarasoutchi F; Analysis and interpretation of the data: Rosa VEE, Ribeiro HB, Tarasoutchi F; Statistical analysis: Rosa VEE, Ribeiro HB; Writing of the manuscript: Rosa VEE; Critical revision of the manuscript for intellectual content: Rosa VEE, Ribeiro HB, Fernandes JRC, Santis A, Spina GS, Paixão MR, Pires JT, Betttega M, Accorsi TAD, Sampaio RO, Tarasoutchi F.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

There were no external funding sources for this study.

## Study Association

This study is not associated with any thesis or dissertation work.

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## Should Patients with Heyde's Syndrome Undergo Early Valve Intervention?

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Short Editorial related to the article: Heyde's Syndrome: Therapeutic Strategies and Long-Term Follow-Up

The epidemiological profile of patients with aortic stenosis has changed with the aging of the population, characterized by an increase in associated comorbidities.<sup>1</sup> Thanks to the revolution in percutaneous aortic valve treatment, many patients who previously would have limited survival and quality of life have benefited from the possibility of curative treatment. On the other hand, the clinical challenges that arise in this population reinforce not only the consolidated relevance of the heart team but also of other specialties such as oncology and hematology.

The interesting study published in the current issue reinforces the importance of the association between Heyde's syndrome and aortic stenosis, with increased bleeding in this population. However, it is important to highlight in this context the frequently associated comorbidities that may contribute to eventual digestive bleeding, such as the association between aortic stenosis and neoplasm, since both share the same risk factors, particularly colon cancer neoplasm.<sup>2</sup> This one presents with cardinal clinical signs: anemia and low gastrointestinal bleeding. In this context, the exclusion of neoplasm is mandatory, even in the suspicion of Heyde's Syndrome. We can also describe other frequently associated comorbidities<sup>3</sup> that add bleeding risk due to the therapy used, such as coronary artery disease, which usually uses antiplatelet therapy, or dual anti-aggregation after percutaneous coronary intervention with a drug-eluting stent.

Another example is the increased prevalence of atrial fibrillation.<sup>4</sup> In this scenario, when Heyde's Syndrome is present, there is an intrinsic maximization of bleeding once anticoagulation is used. Another clinical condition that is growing in the elderly population is cardiac amyloidosis, mainly by transthyretin. Another clinical condition growing in the elderly population is cardiac amyloidosis, mainly caused by transthyretin. The association with severe

aortic stenosis is more common than previously thought, ranging between 12 and 16%.<sup>5,6</sup> Like aortic stenosis, its prevalence is higher in the elderly population; amyloid fiber acts directly in the coagulation cascade, favoring the emergence of spontaneous hemorrhagic events.<sup>7</sup> Finally, not related to increased bleeding, but the impact that this may cause, the frailty of the patient with aortic stenosis.<sup>8</sup> A patient with severe aortic stenosis, considered frail, has a less organic reserve to withstand any severe bleeding. It is known that the need for blood transfusion negatively impacts the morbidity and mortality of this population.<sup>9</sup>

The work of Rosa et al.<sup>10</sup> reinforces the importance of a neglected association with a high rate of severe bleeding and the need for transfusion on admission, with an increased risk of mortality. The current recommendation for screening colonoscopy for colorectal cancer has been reduced to 45 years according to the U.S. Preventive Services Task Force. In addition, access to endoscopic procedures is not massively available to a large part of the population in our country, which increases risk since the diagnoses of angiodysplasia and neoplasia of the digestive tract are not routinely made. The article's questioning is valid for several aspects: it reinforces the importance of actively researching angiodysplasia in this population. Therefore, it justifies a new look at the usual indications for intervention in aortic stenosis. Another point of weighting is the judicious use of platelet anti-aggregation in this population. Another interesting aspect raised in this study is the indication of valve intervention in these patients, regardless of the presence of symptoms or complicating factors, but this is still controversial. Finally, given the unique clinical fragility of a patient with severe aortic stenosis, it is always important to refer them to reference centers with access to multispecialty and more assertive decision-making.

### Keywords

Aortic Valve Stenosis; Gastrointestinal Hemorrhage/complications; Percutaneous Coronary Intervention; Comorbidities; Mortality.

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**DOI:** <https://doi.org/10.36660/abc.20210734>

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# Treated Hypertensive Patients Assessed by Home Blood Pressure Telemonitoring. TeleMRPA Study

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## Abstract

**Background:** Hypertensive patients undergoing treatment and assessed only by casual blood pressure (BP) measurement may be subject to mistaken decisions.

**Objective:** To assess BP behavior by measuring its levels at the office (casual) and at home (HBPM), the behavior of different classes of antihypertensive drugs, and the prevalence of uncontrolled white-coat hypertension (UCWCH) and uncontrolled masked hypertension (UCMH).

**Methods:** Cross-sectional study assessing patients who underwent BP monitoring in the TeleMRPA platform between 2017 and 2019. The exclusion criteria were: use of no antihypertensive drug; combined use of 3 or more antihypertensive drugs; and use of spironolactone and alpha-2 agonist. The variables analyzed were: age, sex, body mass index (BMI), number of valid BP measurements, means of systolic and diastolic blood pressure (SBP and DBP, respectively) obtained from HBPM and casual measurement, and the classes of antihypertensive drugs. Paired and unpaired t tests, as well as chi-square test, were used. The 5% significance level was adopted.

**Results:** This study selected 22 446 patients, 6731 of whom met the inclusion criteria [61.3%, female sex; mean age, 57.8 ( $\pm$ 12.6) years; mean BMI, 29.0 ( $\pm$ 5.1) kg/m<sup>2</sup>]. Mean SBP and DBP were 6.6 mm Hg ( $p$ <0.001) and 4.4 mm Hg ( $p$ <0.001) higher in casual measurement than in HBPM. The rates of BP control were 57.0% in casual measurement and 61.3% in HBPM ( $p$ <0.001), and the prevalence of UCWCH and UCMH was 15.4% and 11.1%, respectively. Renin-angiotensin-aldosterone system blockade was observed in 74.6% of the patients, and 54.8% were on single-drug therapy.

**Conclusions:** HBPM should be considered for the follow-up of treated hypertensive patients because of the high prevalence of UCWCH and UCMH. Antihypertensive drugs behaved differently in HBPM.

**Keywords:** Hypertension; Antihypertensive Agents; Blood Pressure; Study Blood Pressure Monitoring Home; TeleMRPA; Prevalence.

## Introduction

Casual blood pressure (BP) measurement of hypertensive patients for both diagnosis and control assessment has important flaws and can lead to misinterpretation.<sup>1,2</sup>

The pharmacological treatment of systemic arterial hypertension (SAH) and the consequent reduction in BP

levels are known to significantly decrease the incidence of major cardiovascular outcomes.<sup>3,4</sup> Nevertheless, most epidemiological data regarding the prevalence of SAH in Brazil derive from epidemiological questionnaires, such as the Brazilian Health Survey (*Pesquisa Nacional de Saúde* – 21.4%)<sup>5</sup> and VIGITEL (24.7%),<sup>6</sup> and most data concerning BP control have been obtained via casual measurement.<sup>7</sup>

Therefore, the efficacy of antihypertensive drugs and proper BP control of patients undergoing treatment should be assessed by using more accurate methods than casual measurement, such as ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM).<sup>8-10</sup>

This is the first study with many hypertensive patients treated with different classes of antihypertensive drugs

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Manuscript received January 29, 2020, revised manuscript August 19, 2020, accepted September 09, 2020

**DOI:** <https://doi.org/10.36660/abc.20200073>

and assessed by use of ABPM and telemedicine, aiming at investigating: whether the BP levels measured at the doctor's office and at home differ; whether the different classes of antihypertensive drugs behave differently when BP is measured at home; and the prevalence of uncontrolled white-coat hypertension (UCWCH) and of uncontrolled masked hypertension (UCMH).

## Methods

This study was submitted to the Committee on Ethics and Research of the Hospital das Clínicas da Universidade Federal de Goiás (# CAEE 99691018.7.0000.5078) and was approved.

This is a cross-sectional study assessing patients who underwent BP measurement in the TeleMRPA platform (www.telemrpa.com) from May 2017 to September 2019. The platform has been developed as a remote diagnosis tool for BP telemonitoring, and its characteristics allow the analysis and filtering of a database according to the scientific questions investigated. The mathematical algorithm used allows the protection of the patients' personal data, as well as of the data from the clinics or healthcare units, for the interpretation of the tests and the construction of research projects. Because it is not a software but a platform that can be accessed from any computer, tablet or smartphone, the input of BP measurement data can be performed remotely and in a simple way.

This study included patients aged 18 years and over, managed with antihypertensive drugs in a single-drug therapy strategy or a combination of two different classes of antihypertensive drugs. The exclusion criteria were as follows: use of no antihypertensive drug; combined use of three or more antihypertensive drugs; and use of spironolactone and alpha-2 agonist as a single-drug therapy (Figure 1).

The following data of the TeleMRPA platform were used: sex (male/female); age (in years, calculated from

the birth date); body mass index (BMI); number of valid BP measurements at home; systolic and diastolic blood pressure (SBP and DBP, respectively) obtained from HBPM and casual measurement; and class of antihypertensive drug used.

To calculate BMI, weight and height were measured and the Quetelet's index used.<sup>11</sup> On the first visit to the doctor's office, the patient received a BP device for home BP measurement in addition to instructions on its proper management.<sup>3</sup> On that same day, two BP measurements were taken at the office and, in the following four days, the patient (and/or caregiver) took BP measurements at home according to a protocol. Casual BP measurement was defined as the mean of the two BP measurements taken at the office, while home BP measurement was defined as the mean of the 24 BP measurements taken from the second to the fifth day (Figure 2).<sup>12,13</sup>

Validated automated Omron, Geratherm and Microlife devices were used.

Data were exported from the TeleMRPA platform to excel. All classes of drugs described in the platform were reviewed and encoded by two work teams. Then, the databases were crossed for identification of discrepancies, which, when present, were reviewed by the entire team and the coordination.

## Statistical analysis

For data analysis, the software Stata, version 14.0, was used. Descriptive statistics with means and standard deviation was used for normally distributed continuous variables, and absolute and relative frequencies, for categorical variables. Kolmogorov-Smirnov test was used to assess the data distribution of the variables. The BP levels obtained from HBPM and casual measurement were compared by using paired *t* test. To compare the BP levels according to the drugs used, unpaired *t* test was applied, while patients reaching and not reaching BP

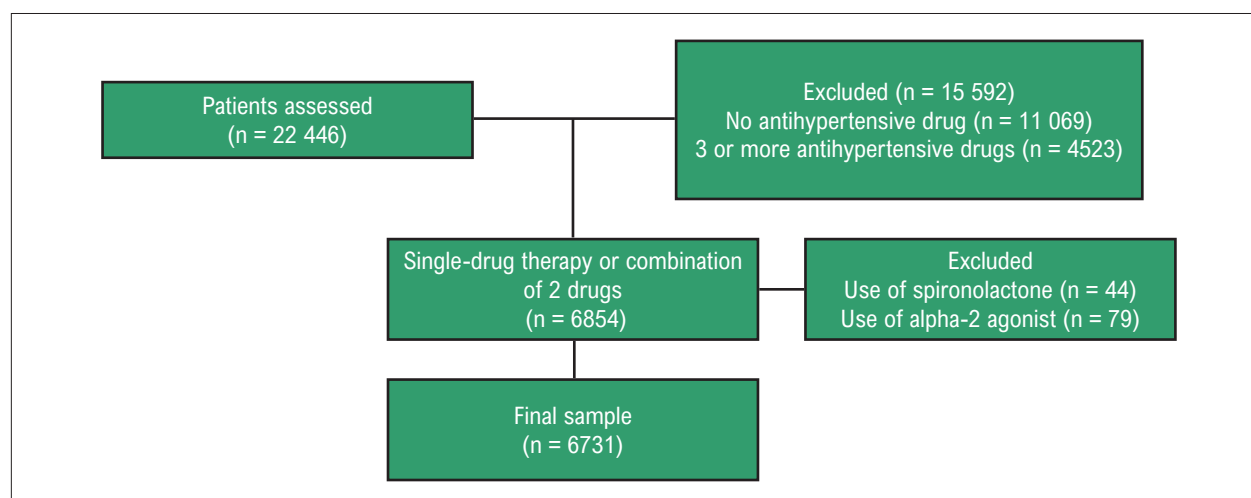


Figure 1 – Flowchart of the study's sample selection. Source: the authors.

| 1 <sup>st</sup> day Office   | HBPM                                         | 2 <sup>nd</sup> day – Home | 3 <sup>rd</sup> day – Home | 4 <sup>th</sup> day – Home | 5 <sup>th</sup> day – Home |
|------------------------------|----------------------------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| Any time<br>***/**<br>***/** | Morning<br>Before breakfast                  | ***/**                     | ***/**                     | ***/**                     | ***/**                     |
|                              |                                              | ***/**                     | ***/**                     | ***/**                     | ***/**                     |
|                              | Evening<br>Before dinner or 2<br>hours after | ***/**                     | ***/**                     | ***/**                     | ***/**                     |
|                              |                                              | ***/**                     | ***/**                     | ***/**                     | ***/**                     |
|                              |                                              | ***/**                     | ***/**                     | ***/**                     | ***/**                     |
|                              |                                              | ***/**                     | ***/**                     | ***/**                     | ***/**                     |

Figure 2 - Protocol of home blood pressure monitoring (HBPM) according to the Brazilian guidelines (\*\*\*/\*\*: blood pressure measurement).<sup>8,9</sup>

goals in casual measurement and HBPM were compared by using chi-square test. The 5% significance level was adopted for all analyses.

## Results

This study assessed 6731 patients, 61.3% of the female sex, mean age of 57.8 ( $\pm 12.6$ ) years, and mean BMI of 29.0 ( $\pm 5.1$ ) kg/m<sup>2</sup>. The BP levels taken casually were higher than those taken at home, and this behavior was seen with the use of single-drug therapy or of a combination of drugs, and for all drug classes (Table 1). The mean number of valid BP measurements was 23.5 ( $\pm 1.6$ ). The differences in the mean SBP and DBP levels were 6.6 mm Hg ( $p < 0.001$ ) and 4.4 mm Hg ( $p < 0.001$ ), respectively. Those differences characterize the white-coat effect and maintained statistical significance in all treatment strategies.

Regarding the drug treatment strategy, 54.8% of the patients were on single-drug therapy and 45.2% were on combinations of two drugs. Renin-angiotensin-aldosterone system (RAAS) blockers were the most frequent option, and 58.7% of the patients were using angiotensin receptor blockers (ARB), while 15.9% were on angiotensin converting enzyme inhibitors (ACEI) (Table 1).

When assessing BP control according to the goals 'lower than 140 mm Hg and 90 mm Hg' for casual measurement, and 'lower than 135 mm Hg and 85 mm Hg' for HBPM, according to current guidelines,<sup>3,4</sup> our rates were 57.0% and 61.3%, respectively ( $p < 0.001$ ). The prevalence of UCWCH was 15.4% and that of UCMH, 11.1% (Table 2).

The comparisons of SBP and DBP obtained via HBPM according to the different classes of antihypertensive drugs are shown in Table 3 (single-drug therapy) and Table 4 (combinations of two drugs).

## Discussion

This study contributes to the analysis in clinical practice of a significant number of hypertensive patients undergoing drug treatment, assessed by use of casual BP measurement and HBPM. Our findings confirm that lower mean BP levels are observed in HBPM regardless of the use of single-drug therapy or drug combination or even of the class of the antihypertensive drug prescribed. A high rate of BP control was found, higher with HBPM, in addition

to a significant prevalence of UCWCH and UCMH, with potential prognostic implications, reinforcing the need for out-of-the-office BP measurement as a parameter for proper management and follow-up of hypertensive patients.

Regarding the characteristics of the sample studied, it is worth emphasizing the population's mean age close to 60 years and increased BMI, which are relevant aspects that make SAH treatment as well as SAH control more difficult.<sup>14-16</sup>

In addition, although the latest national and international guidelines recommend the combination of drugs as the preferred strategy for most hypertensive patients, 54.8% of our sample were on single-drug therapy.<sup>3,4,17,18</sup> The analysis of the classes of antihypertensive drugs used evidenced the preference for the RAAS blockade strategy, which was observed in 74.6% of the patients, and a 3.7-time greater frequency of ARB use as compared to ACEI use. Other classes of antihypertensive drugs had a low frequency of use in single-drug therapy. The combination of ARB or ACEI with diuretics (DIUR) or calcium channel blockers (CCB) was preferred, which is in accordance with the current recommendations.<sup>19,20</sup>

The SBP and DBP levels were always higher and statistically significant in the measurements taken in the office than at home, regardless of the antihypertensive drug class and of the single-drug or combination strategy. On average, the differences were 6.6 mm Hg for SBP ( $p < 0.001$ ) and 4.4 mm Hg for DBP ( $p < 0.001$ ), and these differences remained at a higher or lower intensity for all drugs used. This evidences the need to consider the UCWCH as a frequent phenotype among patients treated, which can induce the use of higher doses of drugs than required when assessing hypertensive patients treated based only on BP measurements taken at the office.<sup>2,8,9,21</sup> In our sample, the prevalence of UCWCH was 15.4% and that of UCMH, 11.1%, meaning a 26.5% misinterpretation of proper BP control with the therapeutic strategy.

The UCWCH is even more relevant if we consider that, from the HBPM perspective, more patients reached the BP goal as compared to those assessed via casual measurement (61.3% vs 57%,  $p < 0.001$ ), reinforcing the thesis that, with home measurements, more proper adjustments to BP levels can be obtained daily. It is worth considering that, differently from what we imagined,

**Table 1** – Sample description according to the antihypertensive drug used, and comparison between the methods used to measure blood pressure, casual and home blood pressure monitoring (HBPM), total and according to drug strategy, n= 6731

| Variable                       | n    | %    | HBPM         | Casual       | p      |
|--------------------------------|------|------|--------------|--------------|--------|
| <b>Total</b>                   |      |      |              |              |        |
| SBP                            | 6731 | 100  | 126.2 ± 15.3 | 132.8 ± 19.6 | <0.001 |
| DBP                            |      |      | 79.6 ± 9.7   | 84.0 ± 11.6  | <0.001 |
| <b>ARB</b>                     |      |      |              |              |        |
| SBP                            | 2254 | 33.5 | 127.1 ± 15.2 | 133.5 ± 19.2 | <0.001 |
| DBP                            |      |      | 80.4 ± 9.6   | 84.9 ± 11.6  | <0.001 |
| <b>ACEI</b>                    |      |      |              |              |        |
| SBP                            | 595  | 8.8  | 124.7 ± 14.2 | 130.2 ± 18.1 | <0.001 |
| DBP                            |      |      | 79.3 ± 9.0   | 83.0 ± 10.5  | <0.001 |
| <b>CCB</b>                     |      |      |              |              |        |
| SBP                            | 196  | 2.9  | 127.2 ± 13.1 | 134.0 ± 17.4 | <0.001 |
| DBP                            |      |      | 80.2 ± 9.5   | 84.4 ± 11.2  | <0.001 |
| <b>Diuretic</b>                |      |      |              |              |        |
| SBP                            | 173  | 2.6  | 123.1 ± 13.8 | 132.2 ± 19.1 | <0.001 |
| DBP                            |      |      | 79.1 ± 9.3   | 85.5 ± 10.6  | <0.001 |
| <b>Beta-blocker</b>            |      |      |              |              |        |
| SBP                            | 474  | 7.0  | 123.2 ± 15.2 | 130.6 ± 19.4 | <0.001 |
| DBP                            |      |      | 77.7 ± 10.0  | 82.4 ± 11.2  | <0.001 |
| <b>ARB + CCB</b>               |      |      |              |              |        |
| SBP                            | 683  | 10.1 | 127.1 ± 14.6 | 133.6 ± 19.1 | <0.001 |
| DBP                            |      |      | 79.0 ± 9.7   | 83.2 ± 11.8  | <0.001 |
| <b>ACEI + CCB</b>              |      |      |              |              |        |
| SBP                            | 332  | 4.9  | 126.2 ± 12.6 | 132.4 ± 16.3 | <0.001 |
| DBP                            |      |      | 79.9 ± 8.9   | 83.8 ± 10.4  | <0.001 |
| <b>ARB + diuretic</b>          |      |      |              |              |        |
| SBP                            | 1015 | 15.1 | 125.2 ± 16.2 | 132.8 ± 21.1 | <0.001 |
| DBP                            |      |      | 79.6 ± 9.6   | 84.5 ± 12.1  | <0.001 |
| <b>ACEI + diuretic</b>         |      |      |              |              |        |
| SBP                            | 151  | 2.2  | 124.6 ± 15.8 | 132.7 ± 20.0 | <0.001 |
| DBP                            |      |      | 78.8 ± 9.5   | 84.0 ± 11.1  | <0.001 |
| <b>Beta-blocker + ACEI</b>     |      |      |              |              |        |
| SBP                            | 134  | 2.1  | 127.6 ± 17.1 | 133.9 ± 21.9 | <0.001 |
| DBP                            |      |      | 79.0 ± 10.4  | 82.4 ± 13.2  | <0.001 |
| <b>Beta-blocker + ARB</b>      |      |      |              |              |        |
| SBP                            | 475  | 7.1  | 129.5 ± 18.0 | 135.5 ± 22.3 | <0.001 |
| DBP                            |      |      | 79.1 ± 10.6  | 83.0 ± 12.7  | <0.001 |
| <b>Beta-blocker + diuretic</b> |      |      |              |              |        |
| SBP                            | 137  | 2.0  | 122.0 ± 14.9 | 130.9 ± 21.0 | <0.001 |
| DBP                            |      |      | 78.1 ± 8.3   | 84.0 ± 11.3  | <0.001 |
| <b>Beta-blocker + CCB</b>      |      |      |              |              |        |
| SBP                            | 65   | 1.0  | 125.5 ± 16.4 | 131.9 ± 21.6 | <0.001 |
| DBP                            |      |      | 77.4 ± 10.7  | 82.1 ± 12.1  | <0.001 |
| <b>CCB + diuretic</b>          |      |      |              |              |        |
| SBP                            | 45   | 0.7  | 130.8 ± 14.6 | 137.1 ± 18.6 | <0.001 |
| DBP                            |      |      | 81.7 ± 11.0  | 86.3 ± 13.1  | <0.001 |

Paired t test. ARB: angiotensin receptor blocker; ACEI: angiotensin-converting-enzyme inhibitor; CCB: calcium channel blocker; SBP: systolic blood pressure; DBP: diastolic blood pressure. Source: the authors.

**Table 2 – Blood pressure (BP) control assessed via casual measurement (< 140 and <90 mm Hg) and home blood pressure monitoring (HBPM: < 135 and < 85 mm Hg), n= 6731**

|                         | BP goal in casual measurement |                         | Total         |          |
|-------------------------|-------------------------------|-------------------------|---------------|----------|
|                         | <140 and <90 mm Hg            | ≥ 140 and/or ≥ 90 mm Hg |               |          |
| BP goal in HBPM         |                               |                         |               |          |
| < 135 and < 85 mm Hg    | 3093 (45.9%)                  | 1034 (15.4%)*           | 4127 (61.3%)  | p< 0.001 |
| ≥ 135 and/or ≥ 85 mm Hg | 744.9 (11.1%)†                | 1860 (27.6%)            | 2604 (38.7%)  |          |
| Total                   | 3837 (57.0%)                  | 2894 (43.0%)            | 6731 (100.0%) |          |

Chi-square test. \*Uncontrolled white-coat hypertension, †uncontrolled masked hypertension. Source: the authors.

**Table 3 – Significance values (p) of the comparisons of systolic blood pressure and diastolic blood pressure obtained from home blood pressure monitoring, according to the different classes of antihypertensive drugs in single-drug therapy, n= 6731**

| Drugs |                 |       |       |        |        |
|-------|-----------------|-------|-------|--------|--------|
|       | SBP comparisons | ACEI  | CCB   | DIUR   | BB     |
| ARB   |                 | <0.01 | 0.987 | <0.001 | <0.001 |
| ACEI  |                 | -     | 0.035 | 0.060  | 0.095  |
| CCB   |                 | -     | -     | <0.001 | 0.002  |
| DIUR  |                 | -     | -     | -      | 0.630  |
| BB    |                 | -     | -     | -      | -      |
|       | DBP comparisons | ACEI  | CCB   | DIUR   | BB     |
| ARB   |                 | 0.009 | 0.737 | <0.001 | <0.001 |
| ACEI  |                 | -     | 0.231 | 0.115  | 0.005  |
| CCB   |                 | -     | -     | 0.028  | 0.002  |
| DIUR  |                 | -     | -     | -      | 0.557  |

Unpaired t test. ARB: angiotensin receptor blocker; ACEI: angiotensin-converting-enzyme inhibitor; CCB: calcium channel blocker; DIUR: diuretic; BB: beta-blocker; SBP: systolic blood pressure; DBP: diastolic blood pressure. Source: the authors.

UCWCH can be found in elevations of the SBP or DBP component via casual measurement and in all age ranges.<sup>21</sup> Another phenotype to be considered is UCMH, still one of the major doubts in SAH treatment: how to manage patients with controlled BP at the office but with elevated BP levels taken at home, and which would be the BP goals for HBPM?<sup>22</sup>

When comparing the classes of antihypertensive drugs, significant differences were found regarding the reduction in BP levels. However, one limiting factor should be considered: because this study was not randomized for the comparison of antihypertensive drug classes, the doses used and the patients' characteristics, those differences should be carefully analyzed. Those findings are in accordance with those of other publications, mainly meta-analyses of randomized studies, which had already described differences in drug potency depending on the doses used and indications but based on casual BP measurement.<sup>23-25</sup> In this study, the different classes of antihypertensive drugs seem to have different potencies when assessed via HBPM, reinforcing the need for patient's individualization when choosing the best treatment strategy.

From our viewpoint, a relevant aspect in this study is the higher prevalence of ARB use as the strategy for RAAS blockade and its combination with CCB and DIUR. The preference for RAAS blockade to treat SAH might have been based on the literature evidence of significant BP reduction, cardiovascular protection, and low incidence of side effects with the use of that drug class, in both single-drug and combination therapy.<sup>26,27</sup>

## Conclusions

For hypertensive patients undergoing treatment, the proper BP control assessment should be based not only on measurements taken at the office but at home as well.

The different classes of antihypertensive drugs behave differently regarding BP reduction even for HBPM, and this finding should be further investigated in prospective randomized trials.

The high prevalence of UCWCH and UCMH found suggests that, when the therapeutic decision is based only on measurements taken at the office, the BP management might be inappropriate, with a potential impact on the management and follow-up of hypertensive patients.

**Table 4 – Significance values (p) of the comparisons of systolic blood pressure and diastolic blood pressure obtained from home blood pressure monitoring according to the different combinations of two antihypertensive drugs, n= 6731**

| Combination of 2 drugs |               |               |                |              |                  |                  |              |                  |
|------------------------|---------------|---------------|----------------|--------------|------------------|------------------|--------------|------------------|
| SBP comparisons        | ACEI with CCB | ARB with DIUR | ACEI with DIUR | BB with ACEI | BB with ARB      | BB with DIUR     | BB with CCB  | CCB with DIUR    |
| ARB with CCB           | 0.358         | <b>0.018</b>  | 0.070          | 0.713        | 0.012            | <b>&lt;0.001</b> | 0.419        | 0.099            |
| ACEI with CCB          | -             | 0.317         | 0.239          | 0.332        | <b>0.004</b>     | <b>0.001</b>     | 0.696        | <b>0.023</b>     |
| ARB with DIUR          | -             | -             | 0.671          | 0.117        | <b>&lt;0.001</b> | <b>0.026</b>     | 0.894        | <b>0.024</b>     |
| ACEI with DIUR         | -             | -             | -              | 0.132        | <b>0.003</b>     | 0.144            | 0.714        | 0.021            |
| BB with ACEI           | -             | -             | -              | -            | 0.276            | 0.004            | 0.417        | 0.263            |
| BB with ARB            | -             | -             | -              | -            | -                | <b>&lt;0.001</b> | 0.093        | 0.641            |
| BB with DIUR           | -             | -             | -              | -            | -                | -                | 0.129        | <b>&lt;0.001</b> |
| BB with CCB            | -             | -             | -              | -            | -                | -                | -            | 0.087            |
| DBP comparisons        | ACEI with CCB | ARB with DIUR | ACEI with DIUR | BB with ACEI | BB with ARB      | BB with DIUR     | BB with CCB  | CCB with DIUR    |
| ARB with CCB           | 0.133         | 0.195         | 0.800          | 0.995        | 0.842            | 0.270            | 0.204        | 0.077            |
| ACEI with CCB          | -             | 0.581         | 0.190          | 0.319        | 0.243            | <b>0.030</b>     | <b>0.040</b> | 0.239            |
| ARB with DIUR          | -             | -             | 0.317          | 0.485        | 0.366            | 0.065            | 0.072        | 0.166            |
| ACEI with DIUR         | -             | -             | -              | 0.856        | 0.725            | 0.475            | 0.343        | 0.087            |
| BB with ACEI           | -             | -             | -              | -            | 0.903            | 0.397            | 0.313        | 0.145            |
| BB with ARB            | -             | -             | -              | -            | -                | 0.264            | 0.216        | 0.125            |
| BB with DIUR           | -             | -             | -              | -            | -                | -                | 0.644        | <b>0.020</b>     |
| BB with CCB            | -             | -             | -              | -            | -                | -                | -            | <b>0.043</b>     |

Unpaired t test. ARB: angiotensin receptor blocker; ACEI: angiotensin-converting-enzyme inhibitor; CCB: calcium channel blocker; DIUR: diuretic; BB: beta-blocker; SBP: systolic blood pressure; DBP: diastolic blood pressure. Source: the authors.

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### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

This study was partially funded by EMS

### Study Association

This study is not associated with any thesis or dissertation work.

### Erratum

In Original Article "Treated Hypertensive Patients Assessed by Home Blood Pressure Telemonitoring. TeleMRPA Study", with DOI number: <https://doi.org/10.36660/abc.20200073>, published in the Journal Arquivos Brasileiros de Cardiologia, 117(3):520-527, on page 520, change the institution of Dr. Roberto Dischinger Miranda from: Universidade Federal de São Paulo Escola Paulista de Medicina, São Paulo, SP - Brasil to: Seção Cardiovascular, Disciplina de Geriatria e Gerontologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP - Brasil and add for Dr. Roberto Dischinger Miranda the institution Hospital Israelita Albert Einstein. Thus, institution 7 became: Escola de Ciências Sociais e da Saúde - Pontifícia Universidade Católica de Goiás, Goiânia, GO - Brazil; institution 8 became: Estratégia de Saúde da Família - Secretaria Municipal de Saúde Campos do Jordão, Campos do Jordão, SP - Brazil; institution 9 became: Procape / MCor, Recife, PE - Brazil and institution 10 became: Centro Universitário CESMAC - Hospital do Coração, Maceió, AL - Brazil.

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## The New Paradigm of Blood Pressure Measurement

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Short Editorial related to the article: Treated Hypertensive Patients Assessed by Home Blood Pressure Telemonitoring. TeleMRPA Study

Hypertension (HTN) is the leading preventable risk factor for cardiovascular disease (CVD) and all-cause mortality worldwide.<sup>1,2</sup>

Accuracy in blood pressure (BP) measurement is essential for the diagnosis, risk stratification, and adequate treatment of HTN. The evidence shows that the traditional casual assessment of BP in the doctor's office is not, in most cases, the best tool for diagnosis or clinical decision-making in individuals with high BP, or even for monitoring response to antihypertensive treatment.<sup>3,4</sup>

Recent guidelines have advocated the broader use of outpatient and home BP measurements in the initial assessment of patients with high BP, as well as in the follow-up of patients with known HTN.<sup>4-8</sup> Outpatient and home BP measurements have been shown to be effective strategies to detect common confounding intermediate phenotypes, such as white coat hypertension and masked hypertension, which are poorly demonstrated by office measurements. Furthermore, monitoring BP in the patient's usual environment has been found to correlated more strongly with the risk of major clinical outcomes and target organ damage.<sup>3,4,9,10</sup>

In the literature and international clinical medical practice, two broad types of out-of-office BP assessment are described: ambulatory blood pressure monitoring (ABPM), in which the device is programmed to obtain automatic measurements at preset intervals over a 24-hour period; and home BP measurement, in which patients themselves obtain measurements at predetermined or random times and BP values are manually recorded. In Brazil, although ABPM is done as in other countries, household BP measurement is usually done in two different ways: one unstructured, which we call self-measurement of BP (SMBP), and a peculiar form of recording quite common in our country, home blood pressure monitoring (HBPM), based on the use of semi-automatic sphygmomanometers which stores measurements and, according to a protocol defined in clinical guidelines, must be capable of issuing structured reports.<sup>3,4</sup>

### Keywords

Cardiovascular Diseases/mortality; Blood Pressure; Hypertension; Blood Pressure Monitoring; Ambulatory/ methods; Telemedicine; Meta-Analysis.

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**DOI:** <https://doi.org/10.36660/abc.20210592>

This issue of ABC Cardiol carries the original article "Treated Hypertensive Patients Assessed by Home Blood Pressure Telemonitoring. TeleMRPA Study", by Barroso et al.,<sup>11</sup> which assesses the findings of a database of measurements performed in different Brazilian locations and collected in a central platform for remote analysis via telemedicine.<sup>11</sup>

Although there are no head-to-head comparisons of SMBP and HBPM, the structured method (HBPM) is believed to be more reproducible, although freeform measurement (SMBP) is less costly and can be performed habitually and frequently as an adjunct to follow-up.<sup>3</sup> There are also substantial differences between HBPM and ABPM. HBPM is performed by patients at home, in the seated position, while ABPM is performed under a variety of conditions at home or at work, during routine activities of daily living, and with no periods of rest prior to each measurements. In addition, ABPM allows analysis of overnight BP during sleep, which adds greater prognostic value to this method.<sup>4</sup> Average waking BP values, however, have considered comparable whether measured by home-based methods or by ABPM.<sup>4</sup> There is evidence that elevated mean BP values in either one of the two methods (either ABPM or HBPM) is associated with greater cardiovascular risk (CVR) than normal values evidenced by both methods. However, when mean BP was elevated in both ABPM and HBPM, the CVR was even higher. Thus, the two methods should be considered not as competitive, but as complementary techniques for BP assessment.<sup>12,13</sup>

A study carried out in Ohasama, Japan, originally revealed that home BP had greater predictive value for mortality than casual BP in the general population.<sup>14</sup> Prospective studies have since proven the superiority of home measurements over casual BP in predicting CVR.<sup>14</sup> A meta-analysis provided further evidence that home BP may be a better predictor of CVD and cardiovascular death, allowing for a more accurate stratification of CVR than casual BP measurement, particularly in cases of masked hypertension.<sup>15</sup> Considering surrogate endpoints, a meta-analysis showed that elevated home BP measurements correlated more significantly with subclinical target organ damage, assessed mainly by the left ventricular mass index on echocardiography, when compared to casual BP, having a predictive value similar to that of MAP.<sup>16</sup>

In view of its greater diagnostic accuracy and prognostic capacity, home BP measurement also plays an important role in the follow-up of antihypertensive treatment, as it is superior to casual BP in conditions such as white coat hypertension and masked uncontrolled hypertension in treated patients, as well as for monitoring response to drug titration.<sup>17</sup> In addition, HBPM imposes fewer restrictions on daily activities and is more comfortable during sleep than ABPM.<sup>3,4</sup> There is also evidence that the combination

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of home BP measurement and remote telemonitoring was superior to casual BP measurement for treatment control of patients with known hypertension.<sup>18</sup>

Given these many restrictions on casual measurement and in an attempt to ascertain the accuracy of office BP measurement, the *Systolic Blood Pressure Intervention Trial* (SPRINT) used a method that included a rest period before each measurement and averaged multiple readings obtained at each visit for analysis. The protocol also included the use of an appropriately sized cuff, proper patient positioning, back support, feet flat on the floor, arm supported at heart level and cuff placed on a bare arm, with self-measurement performed under the supervision of the investigators.<sup>19</sup> Although arguments have emerged that the BP measurement technique used in the SPRINT trial is atypical, this protocol followed the recommendations of most clinical practice guidelines and was similar to that adopted in many previous trials, in addition to serving as a model for future studies and strengthening guidance regarding the most appropriate technique for office BP measurement.<sup>19</sup>

In the study by Barroso et al.,<sup>11</sup> who used telemonitoring to evaluate HBPM values of 6,731 patients with hypertension undergoing pharmacological treatment (61.3% female; mean age 57.8±12.6 years; mean BMI 29.0±5.1 kg/m<sup>2</sup>), mean systolic BP values were 6.6 mmHg ( $p<0.001$ ) higher and diastolic BP 4.4 mmHg higher ( $p<0.001$ ) than on casual measurement. Comparatively, the prevalence of controlled HTN was 61.3% by HBPM versus 57.0% by casual BP measurement

( $p<0.001$ ). The study also showed a 15.4% prevalence of the white coat effect and 11.1% prevalence of uncontrolled masked hypertension in the evaluated population.<sup>11</sup>

A previously published interim analysis of the same database, involving 1273 participants with prehypertension and stage 1 HTN, had found white coat hypertension in 21.9% and masked hypertension in 11.4%, as well as disagreement with the diagnosis of hypertension by casual BP measurement in 33.3% of patients.<sup>20</sup>

By revealing the reality of HBPM in our country, this study makes an important contribution to the body of evidence that demonstrates the benefits of this method in evaluating the response to HTN treatment, highlighting the need for broader use of this tool in the follow-up of hypertensive patients.

Given the evidence of the importance of monitoring of BP, it is necessary to reflect on the emerging devices of BP measurement outside the office, many of which are wearable, providing the possibility of unlimited recording, storage, and digital analysis. New digital monitors, which now even dispense the use of inflatable armbands or cuffs, offer greater convenience, and although many have yet to be validated, these are already being used in randomized clinical trials. In addition, the advent of artificial intelligence expands the possibilities of analysis of the enormous body of BP records provided by such devices, which, together with other variables, should bring about a true revolution in knowledge about HTN in the very near future.<sup>21</sup>

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# Predictors of Total Mortality and Serious Arrhythmic Events in Non-Ischemic Heart Failure Patients: The Role of Galectin-3

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## Abstract

**Background:** Risk stratification remains clinically challenging in patients with heart failure (HF) of non-ischemic etiology. Galectin-3 is a serum marker of fibrosis that might help in prognostication.

**Objective:** To determine the role of galectin-3 as a predictor of major arrhythmic events and overall mortality.

**Methods:** We conducted a prospective cohort study that enrolled 148 non-ischemic HF patients. All patients underwent a comprehensive baseline clinical and laboratory assessment, including levels of serum galectin-3. The primary outcome was the occurrence of arrhythmic syncope, appropriate implantable cardioverter defibrillator therapy, sustained ventricular tachycardia, or sudden cardiac death. The secondary outcome was all-cause death. For all statistical tests, a two-tailed p-value < 0.05 was considered significant.

**Results:** In a median follow-up of 941 days, the primary and secondary outcomes occurred in 26 (17.5%) and 30 (20%) patients, respectively. Serum galectin-3 > 22.5 ng/mL (highest quartile) did not predict serious arrhythmic events (HR: 1.98, p=0.152). Independent predictors of the primary outcome were left ventricular end-diastolic diameter (LVEDD) > 73 mm (HR: 3.70, p=0.001), exercise periodic breathing (EPB) on cardiopulmonary exercise testing (HR: 2.67, p=0.01), and non-sustained ventricular tachycardia (NSVT) > 8 beats on Holter monitoring (HR: 3.47, p=0.027). Predictors of all-cause death were galectin-3 > 22.5 ng/mL (HR: 3.69, p=0.001), LVEDD > 73 mm (HR: 3.35, p=0.003), EPB (HR: 3.06, p=0.006), and NSVT > 8 beats (HR: 3.95, p=0.007). The absence of all risk predictors was associated with a 91.1% negative predictive value for the primary outcome and 96.6% for total mortality.

**Conclusions:** In non-ischemic HF patients, elevated galectin-3 levels did not predict major arrhythmic events but were associated with total mortality. Absence of risk predictors revealed a prevalent subgroup of HF patients with an excellent prognosis.

**Keywords:** Heart Failure; Arrhythmias Cardiacs; Galectin-3; Apoptosis; Defibrillators, Implantable; Death Sudden; Mortality.

## Introduction

Despite impressive therapeutic advances, heart failure (HF) is associated with persistently elevated death rates,<sup>1</sup> and approximately 30% of the overall mortality in HF patients is attributed to sudden cardiac death (SCD).<sup>2,3</sup> Implantable cardioverter defibrillators (ICD) are an established treatment strategy to prevent SCD, particularly in HF due to coronary artery disease, as several clinical trials have demonstrated their unquestionable beneficial effects in clinical outcomes.<sup>4-6</sup> However, there is an ongoing debate on the overall efficacy of ICD implantation in patients with non-ischemic

cardiomyopathy (NICM). Clinical studies addressing this specific scenario had conflicting results. In the DEFINITE and DANISH trials, which enrolled only NICM patients, all-cause mortality reduction was not achieved, although SCD decrease was detected.<sup>7,8</sup>

This heterogeneity in efficacy can be partly explained by the disparity in SCD risk for different HF etiologies. Ischemic heart disease is notably associated with an increased risk of life-threatening arrhythmias, attributable mostly to the presence of fibrotic scars involved in arrhythmogenesis.<sup>6</sup> Myocardial fibrosis, nonetheless, is ubiquitous in HF, irrespective of etiology, and has been consistently associated with risk of SCD.<sup>9-12</sup> Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging is a non-invasive diagnostic tool that identifies myocardial fibrosis and has been proposed as a potential predictor of arrhythmic events and mortality in NICM.<sup>12,13</sup> Clinical use of LGE-CMR is limited because of its costs, contraindications in common HF scenarios, and restricted availability worldwide. A

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Manuscript received April 20, 2020, revised manuscript September 05, 2020, accepted September 30, 2020

**DOI:** <https://doi.org/10.36660/abc.20200353>

simple serum biomarker capable of identifying the burden of myocardial fibrosis could potentially help stratify the risk of SCD, with broader application.<sup>14,15</sup> Galectin-3 has been recently evaluated as a biomarker of cardiac remodeling and fibrosis, as its production is directly involved in the initiation and progression of tissue scarring.<sup>15</sup> Preliminary studies have demonstrated that high serum galectin-3 levels predict sustained ventricular arrhythmias in HF patients at high risk for SCD and major cardiac events in dilated and hypertrophic cardiomyopathy.<sup>10,16</sup>

The present study aimed to assess whether levels of galectin-3 predict arrhythmic events and total mortality in a NICM patient cohort, thus adding predictive value beyond other known risk markers.<sup>17</sup>

## Methods

We performed a prospective observational study that enrolled adult patients under optimized HF treatment in a dedicated HF outpatient clinic at Hospital de Clínicas de Porto Alegre (Porto Alegre, RS, Brazil) from March 2011 to November 2017. Participants had a previous diagnosis of systolic HF of non-ischemic etiology. Systolic HF was defined as LVEF < 40%. Although the inclusion criteria allowed assessing LVEF by either two-dimensional transthoracic echocardiography or CMR, all patients participating in the current protocol were initially evaluated by echocardiography, preferably by Simpson's biplane method. Non-ischemic etiology was defined as the absence of atherosclerotic coronary lesions > 75% on coronary angiography or absence of necrotic or ischemic areas on cardiac single-photon emission computed tomography (SPECT) or LGE-CMR. Exclusion criteria were history of SCD, previous cardiogenic syncope, previous sustained ventricular tachycardia (VT), advanced cerebrovascular disease, or life expectancy lower than one year due to non-cardiovascular diseases. The study protocol was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre, and written informed consent was obtained from all participants. Study protocol procedures involved a detailed clinical evaluation, routine laboratory tests, including B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), non-invasive cardiac exams, and invasive electrophysiological study (EPS). Non-invasive cardiac exams consisted of routine resting electrocardiogram (EKG), 24 h continuous EKG recording (Holter), and cardiopulmonary exercise testing (CPET). During invasive EPS, blood was drawn for galectin-3 analysis.

### EKG and 24 h Holter monitoring

Twelve-lead EKG was performed with a digital device (Mortara ELI 350, Mortara Instrument, Milwaukee, Wisconsin, USA), and 24 h Holter monitoring was carried out using a digital record (SEER Light) and analyzed with the GE Marquette MARS (GE Healthcare, Wauwatosa, Wisconsin, USA) software by an experienced cardiologist. Non-sustained VT (NSVT) was defined as a run of 3 or more consecutive premature ventricular beats  $\geq 100$  bpm.

### Cardiopulmonary exercise testing (CPET)

CPET was performed on a standard treadmill (INBRAMED™ KT 10200, Porto Alegre, Brazil) with a calibrated computer-based gas analyzer (Cortex Biophysik Metalyzer 3B Stationary CPX system, M13B2.1, Leipzig, Germany). A ramp-staged protocol was used, starting at 2.4 km/h with 1–2% inclination, followed by progressive speed increments of 0.1–0.12 km/h every 20 s and slope increments of 0.5–1.0% every 60 s, until volitional fatigue was reached. Traditional CPET variables were evaluated: peak oxygen consumption (peak  $\text{VO}_2$ ), carbon dioxide production ( $\text{VCO}_2$ ), minute ventilation (VE), respiratory exchange ratio (RER),  $\text{VE}/\text{VCO}_2$  slope, and exercise periodic breathing (EPB). EPB was defined based on the following criteria: (1) 3 or more regular oscillations, clearly discernible from inherent data noise, (2) regularity, defined by the standard deviation (SD) of 3 consecutive cycle lengths (time between 2 consecutive nadirs) within 20% of the average, and (3) minimal average amplitude of ventilatory oscillation of 5 L (peak value minus the average of 2 in-between consecutive nadirs).

### Invasive electrophysiological study

Patients were sedated with midazolam and fentanyl and locally anesthetized with lidocaine. A quadripolar diagnostic catheter was introduced via the right femoral vein and positioned under fluoroscopy in the right ventricular apex. The EP-Tracer system (CardioTek™, Maastricht, Netherlands) was used for programmed ventricular stimulation (PVS), using an output pulse amplitude twice the threshold and pulse width of 1 ms. Stimulation protocol consisted of up to 3 extrastimuli (S2/S3/S4) delivered after a 10-beat drive train. Ten-millisecond decrements in the extrastimulus coupling interval were applied after each cycle until either ventricular refractoriness or a 200 ms coupling interval was reached. This process was repeated under 3 different basal cycle lengths (600, 500, and 400 ms). Sustained VT was defined as monomorphic or polymorphic tachycardia with either  $\geq 30$ s duration or hemodynamic collapse. When no sustained VT was induced, PVS was repeated with up to 2 extrastimuli (S2/S3) after intravenous isoproterenol infusion (1–4 mcg/min). Induction of monomorphic or polymorphic VT or ventricular fibrillation (VF) with triple extrastimuli was considered a true positive finding in the current analysis. In patients with a previously implanted permanent pacemaker, a non-invasive EPS was performed using the pacemaker programmer under the same protocol.

### Serum galectin-3 measurement

A 20 mL blood sample was taken through the venous sheath before the invasive EPS. The blood sample was centrifuged in a dedicated research laboratory and stored under  $-70^\circ\text{C}$ . Galectin-3 was measured in duplicate using an ELISA assay (BG Medicine, Waltham, USA).

### Natriuretic peptides measurement

In the HF outpatient clinic where the patients were followed up, both BNP and NT-proBNP levels were available during the study period. For the current analysis, we defined patients with elevated natriuretic peptide levels as those in the highest quartile of any of them.

## Follow-up and outcomes

Patients had outpatient visits at 3, 6, 18, 24, 30, and 36 months. Those who did not attend follow-up visits were contacted by telephone or received home visits. ICD implantation was decided by the clinical cardiology team involved in routine care, with no interference from the researchers. The primary outcome of the protocol consisted of arrhythmic events (SCD, sustained VT, cardiac syncope, or appropriate ICD therapy). ICD shocks were considered appropriate if caused by VT or VF. There was no ICD standardized programming protocol for tachycardia therapy, but the VF zone was typically set to >200 bpm with at least 1 train of antitachycardia pacing (ATP) prior to shock, while the VT zone was typically set to >180 bpm with at least 3 trains of ATP prior to shock. The secondary outcome of the study was all-cause death. Outcomes were adjudicated by two independent researchers blinded for the baseline assessment. Discordant cases were defined by consensus.

## Statistical analyses

Data are expressed as mean $\pm$ SD or median and interquartile range (IQR) for continuous variables according to data normality, or as absolute numbers and percentage for categorical variables. Continuous data were added to the regression model and categorized based on quartiles of distribution into 2 groups: patients with values below the 75<sup>th</sup> percentile (<quartile 3[Q<sub>3</sub>]) and patients with values above or equal to the 75<sup>th</sup> percentile ( $\geq$  Q<sub>3</sub>). The Shapiro-Wilk test was used to determine the normality of all continuous variables. Groups were compared using the unpaired Student's *t*-test for continuous variables and the chi-square test or Fischer's exact test for categorical variables. Non-normally distributed variables were compared by the Mann-Whitney U test. For the CPET missing values (*n*=13), data were imputed according to five multivariate models, built from variables capable of predicting EPB, based on previously validated imputing strategies from Rubin,<sup>18</sup> which provide input values without losing data accuracy. The survival rate and survival free from serious arrhythmic events in the two groups were determined by the Kaplan-Meier method, and the difference between them was analyzed using the log-rank test. Cox regression was adopted for univariate and multivariate analyses of potential predictors of primary and secondary outcomes. A two-tailed *p*-value of 0.05 or less was considered statistically significant. Based on a 26% incidence of ICD therapies from a cohort study comprising NICM and ischemic HF, a sample size of 142 patients was calculated (80% statistical power and two-tailed *p*-value<0.05). All analyses were performed using the SPSS statistical software (version 19; Chicago, USA).

## Results

### Patient characteristics

We enrolled 148 of the 296 HF outpatients screened. Most were male (59.5%), with a mean age of 54.8 $\pm$ 13 years. HF etiology was idiopathic cardiomyopathy in 45.4% of cases, hypertensive cardiomyopathy in 16.9%, and alcoholic cardiomyopathy in 12.2%. Most subjects were classified in

New York Heart Association (NYHA) functional class I or II (42.6% and 39.9%, respectively), and the mean LVEF was 27.4 $\pm$ 7.5%. Pharmacological treatment was optimized in the majority of patients: 97% were on a beta-blocker and either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, 70% were taking spironolactone, and 81% were using digoxin. Table 1 describes clinical characteristics of the whole cohort stratified by galectin-3 levels.

## Follow-up and outcomes

Median follow-up was 941 days (IQR: 440–1241 days). All patients had at least two follow-up visits, and only three could not be reached. The primary outcome (Table 2) occurred in 26 patients (17.5%): SCD in 13 (8.7%), cardiac syncope in 5 (3.3%), appropriate ICD therapy in 7 (4.7%), and sustained VT in 1 (0.7%). During follow-up, 30 (20.2%) patients died, and 10 of these deaths were adjudicated as cardiovascular death (6.7%). Eight patients (5.4%) underwent heart transplant. There were 81 hospital admissions for decompensated HF. Forty-eight patients underwent device implant: 17 ICDs with cardiac resynchronization therapy (CRT-D), 19 single-chamber ICDs, 5 cardiac resynchronization therapy with pacemaker (CRT-P), 4 dual-chamber ICDs, and 4 single-chamber pacemakers.

## Galectin-3 levels

Mean galectin-3 level was 19 $\pm$ 9.4 ng/mL, and the median was 16 ng/mL (IQR: 13.1–22.5). Clinical data stratified by the upper quartile of galectin-3 levels (>22.5 ng/mL) are shown in Table 1. Galectin-3 levels did not differ in patients with or without the primary outcome, and quartiles of galectin-3 (>22.5 ng/mL) also did not differentiate patients with serious arrhythmic events (7 [19.4%] patients in the upper quartile versus 19 [17%] patients in lower quartiles; *p*=0.73). However, galectin-3 levels stratified by quartiles were significantly different for overall mortality (13 [36.1%] patients in the upper quartile versus 17 [15.2%] patients in lower quartiles; *p*=0.007) and for HF hospitalization (50 [34%] patients in the upper quartile versus 31 [21%] patients in lower quartiles; *p*<0.001) during follow-up.

## Univariate and multivariate analyses

In univariate analyses, significant predictors of major arrhythmic events (Table 2) were the highest quartile of left ventricular end-diastolic diameter (LVEDD) on echocardiography (hazard-ratio — HR: 4.13, *p*<0.001), the highest quartile of the VE/VCO<sub>2</sub> slope (HR: 2.32, *p*=0.03), the presence of EPB on CPET (HR: 3.37, *p*=0.03), the highest quartile of the HV interval on invasive EPS (HR: 2.23, *p*=0.04), and NSVT>8 beats on Holter monitoring (HR: 3.27, *p*=0.03). In this analysis, galectin-3 levels, both continuous and stratified by quartiles, were not significant predictors of the primary outcome (HR: 1.13, *p*=0.78). In the multivariate Cox regression model, variables that remained significantly associated with serious arrhythmic events were LVEDD (HR: 3.70, *p*=0.001), presence of EPB (HR: 2.67, *p*=0.01), and NSVT>8 beats (HR: 3.47, *p*=0.027). Similar results were obtained using LVEDD indexed to body surface area (LVEDD>40 mm/m<sup>2</sup> representing the 75<sup>th</sup> percentile; HR: 3.34; 95% confidence interval 1.50–7.45; *p*=0.003).

**Table 1 – Clinical characteristics according to galectin-3 levels**

|                           | All patients<br>(n=148) | Upper quartile<br>GAL-3>22.5 ng/mL<br>(n=36) | Lower quartiles<br>GAL-3≤22.5 ng/mL<br>(n=112) | p-value |
|---------------------------|-------------------------|----------------------------------------------|------------------------------------------------|---------|
| Age (years)               | 54.8±12.7               | 63±9.3                                       | 52.2±12.6                                      | <0.001  |
| Male gender (%)           | 88 (59.5)               | 20 (55.6)                                    | 68 (61.3)                                      | 0.54    |
| NYHA class (%)            |                         |                                              |                                                |         |
| I                         | 63 (42.6)               | 11 (30.6)                                    | 51 (46)                                        | 0.12    |
| II                        | 59 (39.9)               | 15 (41.7)                                    | 44 (40)                                        |         |
| III                       | 26 (17.6)               | 10 (28.8)                                    | 16 (14.4)                                      |         |
| IV                        | 0                       | 0 (0)                                        | 0 (0)                                          |         |
| Etiology (%)              |                         |                                              |                                                |         |
| Idiopathic                | 67 (45.3)               | 13 (36.1)                                    | 54 (48.6)                                      | 0.38    |
| Hypertensive              | 25 (16.9)               | 7 (19.4)                                     | 18 (16.2)                                      |         |
| Alcoholic                 | 18 (12.2)               | 4 (11.1)                                     | 14 (12.6)                                      |         |
| Chagas disease            | 7 (4.7)                 | 3 (8.3)                                      | 4 (3.6)                                        |         |
| Valvular                  | 4 (2.7)                 | 2 (5.6)                                      | 2 (1.8)                                        |         |
| Other                     | 27 (18.2)               | 7 (19.5)                                     | 19 (17.1)                                      |         |
| Physical examination      |                         |                                              |                                                |         |
| SBP (mmHg)                | 119.3±21.6              | 122.6±22.5                                   | 118.1±21.3                                     | 0.28    |
| DBP (mmHg)                | 74.7±12.7               | 74.6±13                                      | 74.8±12.8                                      | 0.95    |
| Laboratory tests          |                         |                                              |                                                |         |
| Hemoglobin (g/dL)         | 13.4±1.6                | 12.6±1.9                                     | 13.6±1.4                                       | 0.008   |
| Lymphocytes (/mm³)        | 2099.2±848              | 1825±787                                     | 2193±852                                       | 0.02    |
| Creatinine (mg/dL)        | 1.1±0.73                | 1.6±1.1                                      | 1.0±0.4                                        | 0.002   |
| Sodium (mEq/L)            | 140±2.8                 | 140±2.9                                      | 140±2.8                                        | 0.86    |
| Potassium (mEq/L)         | 4.6±0.4                 | 4.6±0.4                                      | 4.6±0.3                                        | 0.82    |
| Uric acid (mg/dL)         | 7.5±2.2                 | 8.6±2.4                                      | 7.1±2.1                                        | <0.001  |
| Glucose (mg/dL)           | 118±49.6                | 117.5±40.3                                   | 118.4±52.6                                     | 0.92    |
| Total cholesterol (mg/dL) | 180.6±42.6              | 188.4±42.6                                   | 177.3±41                                       | 0.16    |
| LDL (mg/dL)               | 104.7±37.2              | 110.5±37.6                                   | 102.3±36.8                                     | 0.26    |
| Galectin-3 (ng/mL)        | 19±9.4                  | 31.6±10.7                                    | 14.9±10.7                                      | <0.001  |
| BNP (pg/mL)               | 116.4 (59.7–295)        | 158 (77–289)                                 | 106.6 (53–298)                                 | 0.30    |
| NT-proBNP (pg/mL)         | 1145 (392–2590)         | 4776 (1549–15852)                            | 741 (314–2291)                                 | 0.005   |
| Echocardiography          |                         |                                              |                                                |         |
| LVEF (%)                  | 27.4±7.5                | 27.3±7.6                                     | 27.4±7.5                                       | 0.97    |
| Left atrium (mm)          | 47.3±6.6                | 48.7±7                                       | 46.9±6.4                                       | 0.15    |
| LVEDD (mm)                | 67.5±10.2               | 65.3±7                                       | 68.2±11                                        | 0.13    |
| LVESD (mm)                | 58.7±10.1               | 56.6±8.5                                     | 59.4±10.6                                      | 0.15    |
| EKG                       |                         |                                              |                                                |         |
| Atrial fibrillation       | 22 (14.9)               | 8 (22)                                       | 14 (12.6)                                      | 0.16    |
| LBBB                      | 60 (40.8)               | 18 (50)                                      | 42 (37.8)                                      | 0.46    |
| 24-hour Holter monitoring |                         |                                              |                                                |         |
| NSVT (%)                  | 54 (36.5)               | 12 (33.3)                                    | 42 (38.5)                                      | 0.57    |
| NSVT>8 beats              | 11 (7.4)                | 1 (8.3)                                      | 9 (21.4)                                       | 0.54    |

## Continuation

### Cardiopulmonary exercise testing

|                                  |           |           |           |        |
|----------------------------------|-----------|-----------|-----------|--------|
| Peak VO <sub>2</sub> (mL/kg/min) | 18±5.1    | 14.7±4.3  | 19±4.9    | <0.001 |
| VE/CO <sub>2</sub> slope         | 41.5±11.7 | 44.3±12.5 | 40.8±11.5 | 0.14   |
| EPB (%)                          | 26 (17.5) | 3 (8.3)   | 23 (20.5) | 0.14   |

### EPS (%)

|                          |            |           |           |      |
|--------------------------|------------|-----------|-----------|------|
| No induction             | 129 (87.2) | 34 (94.4) | 94 (84.7) | 0.10 |
| SMVT                     | 10 (6.8)   | 0         | 10 (9)    |      |
| SPVT                     | 5 (3.4)    | 1 (2.8)   | 4 (3.6)   |      |
| Ventricular fibrillation | 3 (2)      | 0         | 3 (2.7)   |      |
| HV interval (ms)         | 52.6±10.4  | 54.2±11.3 | 52.2±10.1 | 0.34 |

### Medication

|                         |            |           |            |       |
|-------------------------|------------|-----------|------------|-------|
| Beta-blocker (%)        | 144 (97.3) | 36 (100)  | 107 (96.4) | 0.57  |
| ACEi or ARB (%)         | 144 (97.3) | 32 (88.9) | 111 (99.1) | 0.003 |
| Spironolactone (%)      | 103 (69.6) | 21 (58.3) | 82 (73.9)  | 0.07  |
| Digoxin (%)             | 121 (81.8) | 31 (86.1) | 90 (81.1)  | 0.49  |
| Antiarrhythmic drug (%) | 8 (5.4)    | 1 (2.8)   | 7 (6.3)    | 0.41  |

Data expressed as mean±standard deviation, median (Q1–Q3), or absolute numbers (percentage). GAL-3: galectin-3; NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; EKG: electrocardiography; NSVT: non-sustained ventricular tachycardia; VO<sub>2</sub>: oxygen consumption; VE/CO<sub>2</sub> slope: ventilatory efficiency; EPB: exercise periodic breathing; EPS: electrophysiological study; SMVT: sustained monomorphic ventricular tachycardia; SPVT: sustained polymorphic ventricular tachycardia; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LBBB: left bundle branch block.

**Table 2 – Univariate analysis and Cox proportional hazard model for the primary outcome (major arrhythmic events)**

|                                      | Univariate analysis |           |        | Multivariate analysis |           |       |
|--------------------------------------|---------------------|-----------|--------|-----------------------|-----------|-------|
|                                      | HR                  | 95%CI     | p      | HR                    | 95%CI     | p     |
| Galectin-3 (for each 1 ng/mL)        | 1.003               | 0.97–1.04 | 0.877  |                       |           |       |
| Galectin-3>22.5 ng/mL                | 1.13                | 0.47–2.70 | 0.787  |                       |           |       |
| Atrial fibrillation                  | 1.86                | 0.75–4.60 | 0.182  |                       |           |       |
| LVEF<20%                             | 0.69                | 0.21–2.30 | 0.691  |                       |           |       |
| LVEDD>73 mm                          | 4.13                | 1.91–8.90 | <0.001 | 3.70                  | 1.69–8.1  | 0.001 |
| Peak VO <sub>2</sub> <14.2 mL/kg/min | 1.69                | 0.75–3.90 | 0.203  |                       |           |       |
| VE/CO <sub>2</sub> slope>48.4        | 2.32                | 1.05–5.10 | 0.037  |                       |           |       |
| EPB                                  | 3.37                | 1.52–7.40 | 0.030  | 2.67                  | 1.19–6.0  | 0.017 |
| HV interval>59 ms                    | 2.23                | 1.01–4.90 | 0.047  |                       |           |       |
| NSVT>8 beats                         | 3.27                | 1.11–9.70 | 0.030  | 3.47                  | 1.15–10.5 | 0.027 |
| Positive EPS                         | 1.58                | 0.54–4.60 | 0.403  |                       |           |       |
| Elevated natriuretic peptides        | 2.75                | 1.26–6.01 | 0.011  |                       |           |       |

HR: hazard ratio; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; peak VO<sub>2</sub>: peak oxygen consumption; NSVT: non-sustained ventricular tachycardia; EPB: exercise periodic breathing; EPS: invasive electrophysiological study.

Predictors of total mortality in univariate analyses were similar, but also included the highest quartile of galectin-3 levels (HR: 2.20,  $p=0.03$ ), peak  $\text{VO}_2$  (HR: 0.92,  $p=0.04$ ), and the highest quartile of the HV interval (HR: 2.80,  $p=0.005$ ). Independent predictors of total mortality in the multivariate model (Table 3) were the highest quartile of galectin-3 (HR: 3.69,  $p=0.001$ ), the highest quartile of LVEDD (HR: 3.35,  $p=0.003$ ), the presence of EPB (HR: 3.06,  $p=0.006$ ), and NSVT $>8$  beats (HR: 3.95,  $p=0.007$ ). Similar results were obtained using LVEDD indexed to body surface area (LVEDD $>40$  mm/m<sup>2</sup> representing the 75<sup>th</sup> percentile; HR: 3.77; 95% confidence interval 1.77–8.02;  $p=0.001$ ).

### Predictive values

Positive predictive values (PPV) for the primary outcome were low for individual parameters (Table 4); the only variable associated with the highest PPV was EPB (38.4%), while the one with the greatest negative predictive value (NPV) was LVEDD $>73$ mm (88.3%). Ninety patients (61% of the study sample) presented none of the 3 variables independently associated with the primary outcome, leading to an NPV of 91.1%. Similar findings were observed for total mortality: NSVT $>8$  beats was the predictor associated with the highest PPV (45.5%), while HV interval $>59$  ms showed the highest NPV (84.9%). Patients without any of the 5 variables independently associated with risk had an NPV of 96.3% for all-cause death.

Figure 1 demonstrates the survival curves for different levels of galectin-3, adjusted for the other predictors of all-cause mortality in the Cox regression model ( $p<0.001$ ). Figure 2 shows the Kaplan-Meier survival curve for the primary outcome stratified by the number of predictor variables (LVEDD, EPB, NSVT $>8$  beats; log-rank  $p$  value $<0.001$ ).

Figure 3 depicts the Kaplan-Meier survival curve for all-cause mortality stratified by the number of risk markers (galectin-3 $>22.5$  ng/mL, LVEDD $>73$ mm, EPB, NSVT $>8$  beats, HV interval $>59$  ms). HF patients with more than 3 risk factors had an ominous prognosis, with a mortality rate $>80\%$  after 3 years of follow-up.

### Discussion

In this prospective cohort of NICM HF patients, galectin-3 levels were not an independent predictor of major arrhythmic events (SCD, cardiac syncope, sustained VT, or ICD appropriate therapy). However, higher galectin-3 levels were independently associated with overall mortality. Previously, we had identified 3 clinical predictors of arrhythmic events (LVEDD, EPB, and NSVT on 24-hour Holter monitoring), which were confirmed by the current analysis.<sup>17</sup> In a clinical scenario in which ICD implants are under scrutiny, our data may help select which patients would most benefit from an invasive and costly therapy. Serum levels of galectin-3 may be used to further stratify risk and help in prognostication.<sup>18</sup>

Galectins are a large family of lectins that bind to  $\beta$ -galactosides. Primarily located in the cytoplasm, they can also be found in the nucleus or the extracellular matrix. Extracellular galectin-3 exhibits numerous autocrine and paracrine effects, including cell adhesion, activation and chemoattraction of certain cell types, mainly those related to the extracellular matrix. Galectin-3 affects various biological processes, such as cellular homeostasis, immune responses, organogenesis, and angiogenesis.<sup>19</sup> Henderson et al. reported that disruption of the galectin-3 gene blocked hepatic stellate cell activation and collagen expression in the liver, attenuating hepatic fibrosis.<sup>20</sup> Aldosterone led to galectin-3 expression

**Table 3 – Univariate analysis and Cox proportional hazard model for the secondary endpoint (total mortality)**

|                                   | Univariate analysis |           |       | Multivariate analysis |            |       |
|-----------------------------------|---------------------|-----------|-------|-----------------------|------------|-------|
|                                   | HR                  | 95%CI     | p     | HR                    | 95%CI      | p     |
| Galectin-3 (for each 1 ng/mL)     | 1.024               | 0.99–1.05 | 0.057 |                       |            |       |
| Galectin-3 $>22.5$ ng/mL          | 2.20                | 1.07–4.50 | 0.033 | 3.69                  | 1.7–8.19   | 0.001 |
| Atrial fibrillation               | 0.98                | 0.34–2.80 | 0.980 |                       |            |       |
| LVEF (for each 1%)                | 0.96                | 0.91–1.01 | 0.098 |                       |            |       |
| LVEF $<20\%$                      | 1.40                | 0.57–3.40 | 0.461 |                       |            |       |
| LVEDD $>73$ mm                    | 3.02                | 1.44–6.30 | 0.003 | 3.35                  | 1.53–7.34  | 0.003 |
| Peak $\text{VO}_2$ (mL/kg/min)    | 0.92                | 0.86–0.99 | 0.042 |                       |            |       |
| Peak $\text{VO}_2<14.2$ mL/kg/min | 1.20                | 0.53–2.70 | 0.656 |                       |            |       |
| VE/ $\text{VO}_2$ slope $>48.4$   | 1.92                | 0.89–4.10 | 0.092 |                       |            |       |
| EPB                               | 2.91                | 1.36–6.20 | 0.006 | 3.06                  | 1.38–6.77  | 0.006 |
| HV interval $>59$ ms              | 2.80                | 1.36–5.80 | 0.005 | 1.98                  | 0.95–4.13  | 0.068 |
| NSVT $>8$ beats                   | 3.31                | 1.26–8.70 | 0.015 | 3.95                  | 1.45–10.73 | 0.007 |
| Positive EPS                      | 0.95                | 0.29–3.10 | 0.993 |                       |            |       |
| Elevated natriuretic peptides     | 3.44                | 1.67–7.06 | 0.001 |                       |            |       |

HR: hazard ratio; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; peak  $\text{VO}_2$ : peak oxygen consumption; EPB: exercise periodic breathing; NSVT: non-sustained ventricular tachycardia; EPS: invasive electrophysiological study.

## Original Article

**Table 4 – Positive and negative predictive values according to risk factors**

| Primary outcome (major arrhythmic events) |                         |                      |                  |                  |
|-------------------------------------------|-------------------------|----------------------|------------------|------------------|
|                                           | All patients<br>(n=148) | With event<br>(n=26) | PPV% (95%CI)     | NPV% (95%CI)     |
| LVEDD>73 mm                               | 36                      | 13                   | 36.1 (24.9–49)   | 88.3 (83.7–91.8) |
| EPB                                       | 26                      | 10                   | 38.4 (24.2–54.9) | 86.8 (82.9–90)   |
| NSVT>8 beats                              | 11                      | 4                    | 36.3 (15.2–64.4) | 83.7 (81.2–85.9) |
| Absence of all three                      | 90                      | 8                    |                  | 91.1 (85.4–94.8) |
| Secondary outcome (total mortality)       |                         |                      |                  |                  |
|                                           | All patients<br>(n=148) | With event<br>(n=30) | PPV% (95%CI)     | NPV% (95%CI)     |
| GAL-3>22.5 ng/mL                          | 36                      | 13                   | 36.1 (24.6–49.4) | 84.8 (80.1–88.5) |
| LVEDD>73 mm                               | 36                      | 12                   | 33.3 (22.1–46.8) | 83.9 (79.3–87.6) |
| EPB                                       | 26                      | 10                   | 38.4 (24.3–55.2) | 83.6 (79.6–86.9) |
| NSVT>8 beats                              | 11                      | 5                    | 45.5 (21.4–71.8) | 81.4 (78.8–83.8) |
| HV interval>59 ms                         | 35                      | 13                   | 37.1 (25.3–50.7) | 84.9 (80.3–88.6) |
| Absence of all five                       | 55                      | 2                    |                  | 96.3 (85.2–99.0) |

GAL-3: galectin-3; LVEDD: left ventricle end-diastolic diameter; EPB: exercise periodic breathing; NSVT: non-sustained ventricular tachycardia.

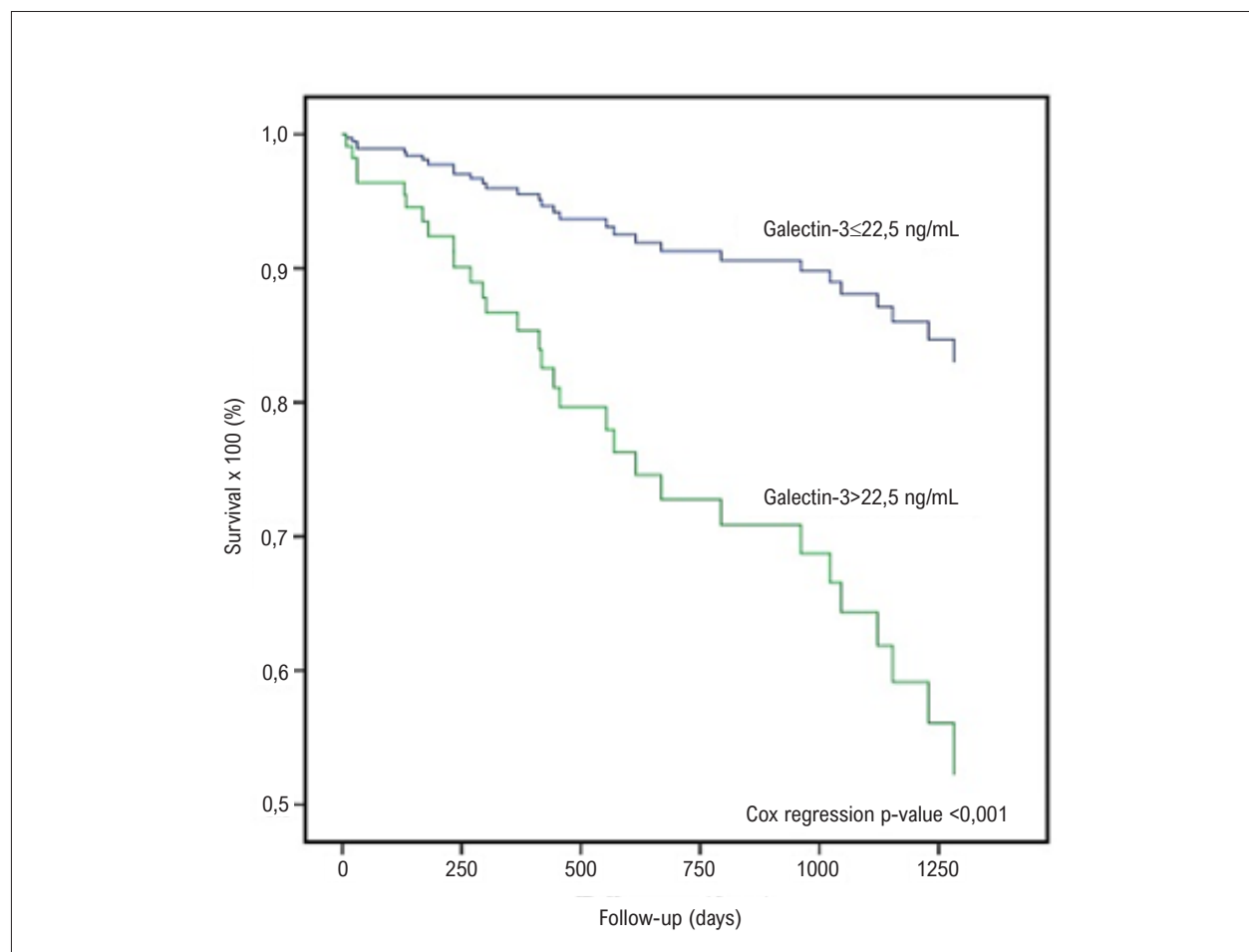


**Figure 1 – Kaplan-Meier survival curve for total mortality according to levels of serum galectin-3.**

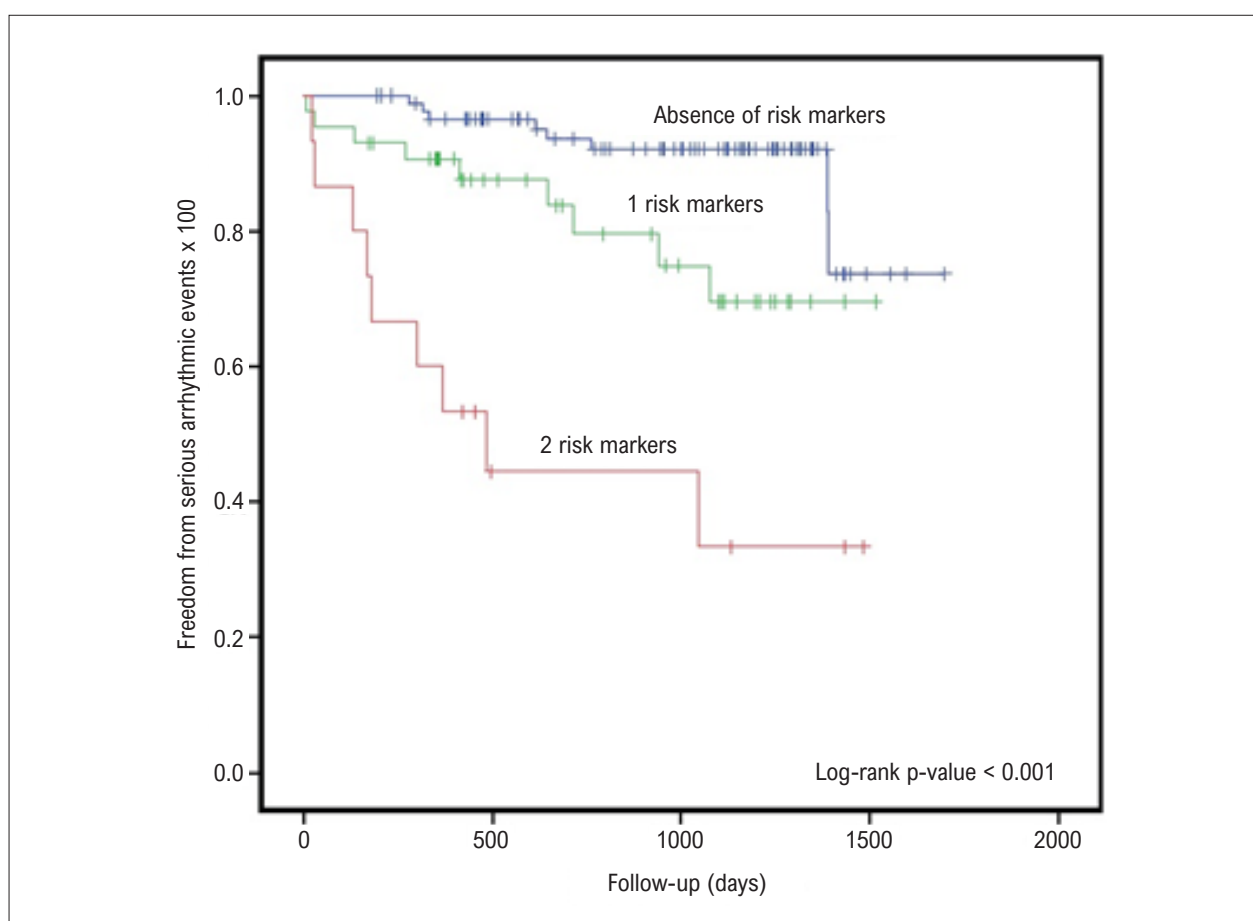


**Figure 2** – Kaplan-Meier survival curve for the primary outcome (serious arrhythmic events) stratified by the number of risk factors (dilated left ventricular end-diastolic diameter, exercise periodic breathing on cardiopulmonary exercise testing, and non-sustained ventricular tachycardia on Holter monitoring).

in the aortic tunica media in animal models and, in turn, its overexpression increased type I collagen production.<sup>21</sup>

The role of galectin-3 as a predictor of future clinical events has been partially assessed in several cardiovascular scenarios. Higher galectin-3 levels were related to new-onset atrial fibrillation (AF) 3–5 days after ST-segment elevation myocardial infarction.<sup>22</sup> Recent reports have also indicated the association of galectin-3 levels with paroxysmal AF<sup>23</sup> and persistent AF.<sup>24</sup> Concentrations of sST2 and galectin-3 were significantly higher in hypertrophic cardiomyopathy patients than in controls, but neither marker had a significant relationship with SCD risk, history of syncope, or family history of SCD.<sup>25</sup>

The predictive role of galectin-3 has also been assessed in studies of mixed HF etiologies, but few have explored its role as a predictor of arrhythmic events specifically in non-ischemic HF patients. Francia et al. investigated 75 HF patients who underwent ICD implantation and found that galectin-3 levels were higher in those with VR or VF. Most of their sample (60%), however, had an ischemic etiology.<sup>16</sup> Hu et al.<sup>10</sup> assessed both galectin-3 levels and LGE on CMR in a prospective cohort that enrolled patients with NICM (46% with dilated cardiomyopathy and 56% with hypertrophic cardiomyopathy). Both galectin-3 levels and the presence of LGE were independent predictors of

major cardiac events. No specific analysis related to arrhythmic risk or total mortality was performed.<sup>10</sup> Recently, Competence Network Heart Failure investigators evaluated the role of sST2 and galectin-3 in patients with non-ischemic dilated cardiomyopathy and obtained intriguing results. While sST2 was associated with cardiac and overall mortality, galectin-3 levels had no impact on the risk of future events as a continuous variable, but the intermediate tertile of galectin-3 was significantly associated with a better prognosis.<sup>26</sup> Nonetheless, our findings suggest that elevated galectin-3 levels might not predict arrhythmic risk in a selected sample of non-ischemic HF patients but could be an important marker of overall mortality. These results are in agreement with a meta-analysis of 9 studies that included a heterogeneous group of HF patients and reported that, for every 1 ng/mL of galectin-3 elevation, the mortality rate increased by 28%.<sup>27</sup>

In the current analysis, the absence of all independent predictors of risk for arrhythmic events (Figure 2) or total mortality (Figure 3) revealed a subgroup of patients with excellent prognosis in a follow-up of up to four years. These results strengthen our previous findings<sup>17</sup> and point out that better risk stratification is feasible in non-ischemic HF patients.

Some methodological aspects of our protocol deserve consideration. We lost contact with only three patients, so they

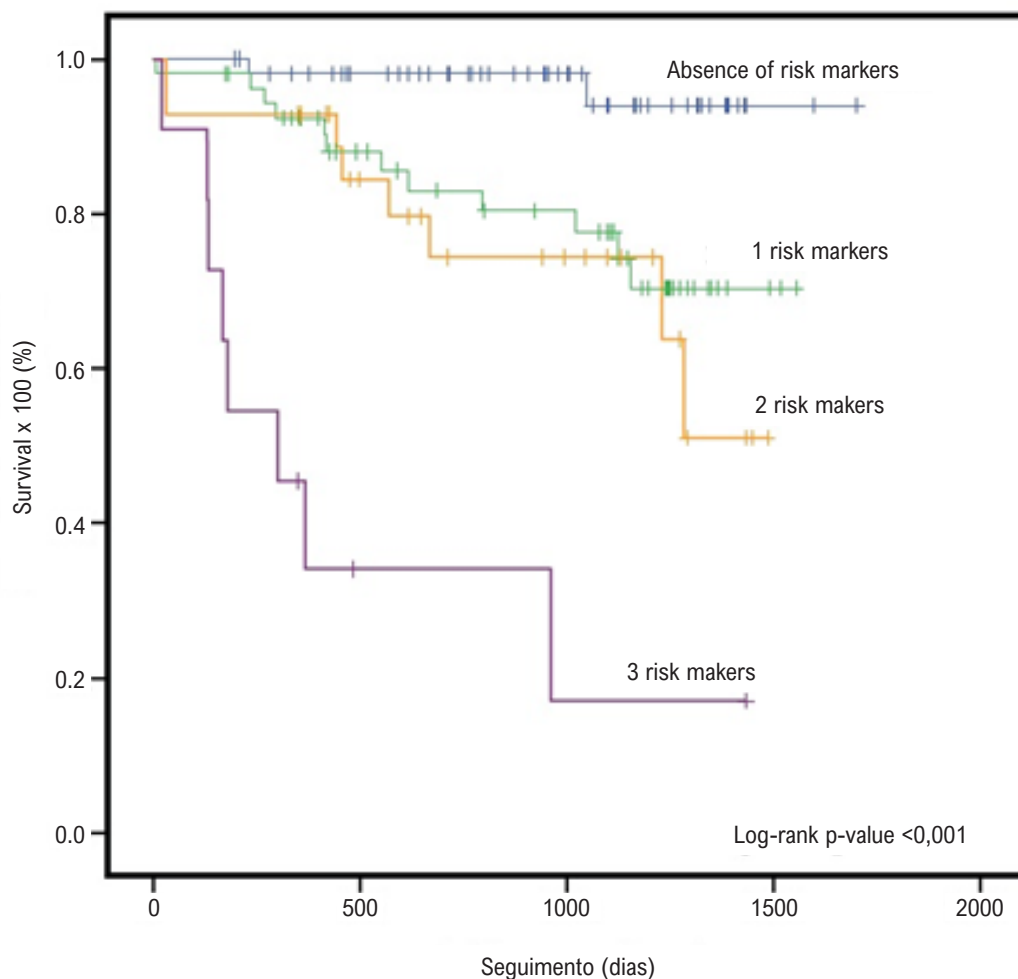


**Figure 3** – Kaplan-Meier curve for the secondary outcome (total mortality) stratified by the number of risk factors (elevated levels of galectin-3, dilated left ventricular end-diastolic diameter, exercise periodic breathing on cardiopulmonary exercise testing, non-sustained ventricular tachycardia on Holter monitoring, and increased HV interval).

were censored in the last visit. Asymptomatic ventricular arrhythmias could not be detected, as only 48 patients of our cohort underwent device implantation. LGE-CMR has been suggested as a valid tool for prognosis stratification of HF, but only a few of our patients underwent CMR, precluding its analysis as a prognostic factor in this cohort. CMR, however, is not widely available to most HF patients worldwide. We acknowledge that our sample size and number of events are relatively small, and as such, our results should be considered hypothesis-generating. Still, most previous studies had similar or smaller sample sizes. Finally, our findings deserve future prospective validation before broad clinical applicability can be proposed.

## Conclusion

In this prospective cohort of non-ischemic HF patients on optimized medical treatment, galectin-3 levels did

not predict major arrhythmic events. Three variables were confirmed as risk markers for the primary outcome: LVEDD > 73 mm, EPB on CPET, and NSVT > 8 beats on Holter monitoring. Elevated galectin-3 levels were independently associated with total mortality. Absence of all risk predictors revealed a substantially prevalent subgroup of patients with an excellent prognosis. In the current scenario of uncertainty about ICD advantages in NICM HF patients, our results might help establish future strategies to identify the patients who would most benefit from ICDs.

## Author Contributions

Conception and design of the research: Kochi AN, Pimentel M, Zimmerman LI, Rohde LE; Acquisition of data: Kochi AN, Zimmerman T; Analysis and interpretation of the data: Kochi AN, Pimentel M, Andrades M, Zimmerman T, Rohde

LE; Statistical analysis: Kochi AN, Rohde LE; Obtaining financing: Rohde LE; Writing of the manuscript: Kochi AN; Critical revision of the manuscript for intellectual content: Pimentel M, Andrade M, Zimmerman LI, Rohde LE.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

This study was partially funded by FIPE-HCPA

### Study Association

This article is part of the thesis of master submitted by Adriano Nunes Kochi, from Programa de Pós-graduação em Ciências da Saúde; Cardiologia. e Ciência Cardiovasculares.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre under the protocol number 59122016 0 0000 5327. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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## The Challenge of Assessing Sudden Cardiac Death Risk in Patients with Nonischemic Heart Failure

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Short Editorial related to the article: Predictors of Total Mortality and Serious Arrhythmic Events in Non-Ischemic Heart Failure Patients: The Role of Galectin-3

Sudden cardiac death (SCD) accounts for approximately 50% of deaths in patients with ischemic and nonischemic heart disease in the presence of severe left ventricular systolic dysfunction.<sup>1</sup> Many clinical trials<sup>2-8</sup> have evaluated the effectiveness of implantable cardioverter defibrillators (ICDs) in primary prevention of SCD in the last 20 years.

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)<sup>2</sup> and the Sudden Cardiac Death in Heart Failure (SCD-HeFT)<sup>3</sup> defined the principles for indication<sup>1,4</sup> of ICDs in primary prophylaxis of SCD of patients with heart failure (HF) of ischemic etiology. On the other hand, clinical trials evaluating patients with HF of nonischemic origin<sup>3,5-8</sup> have shown heterogeneous results and, so far, there are uncertainties on the best candidates for this type of therapy.

The SCD-HeFT<sup>3</sup> evaluated the use of ICDs in the prophylaxis of SCD in patients with HF of ischemic and nonischemic origin. Despite the benefits of ICDs observed in the nonischemic subgroup, the results were inconsistent. In the DEFINITE,<sup>5</sup> the use of ICD did not promote a significant reduction in mortality. The AMIOVIRT<sup>6</sup> and the CAT<sup>7</sup> had small sample sizes and short follow-up, yielding inconclusive results.

A meta-analysis<sup>8</sup> of these four studies, published in 2010, described favorable results for the use of ICDs in this group of

patients, which has supported the indication of these devices in the guidelines.<sup>1,4</sup> However, in 2016, the DANISH<sup>9</sup> study reopened the discussion as it did not demonstrate a reduction in mortality of nonischemic HF patients with the use of ICDs. Despite the critics received,<sup>10</sup> the study reinforced the need for establishing the best predictors of response to ICD implantation.

In this issue of the Arquivos Brasileiros de Cardiologia, Kochi et al.<sup>11</sup> evaluated the role of galectin-3 in predicting severe arrhythmic events and all-cause mortality in patients with HF of nonischemic etiology.<sup>11</sup> This molecule has been investigated as a prognostic marker in patients with HF and myocardial fibrosis.<sup>4,12,13</sup> Fibrosis is a known substrate for ventricular arrhythmias, and the quantification of ventricular dysfunction using biomarkers that identify these changes would help the selection of patients at high risk of SCD.

Despite the elegant study rational and design, galectin-3 could not predict SCD neither as a continuous variable nor when stratified in quartiles. However, the highest quartile was associated with higher all-cause mortality.

The prediction of risk of SCD in nonischemic heart failure patients is still a challenge, and studies determining which patients would benefit most from the use of ICD are still needed.

### Keywords

Heart Failure/physiopathology; Death, Sudden, Cardiac; Ventricular Dysfunction, Left; Galectin 3; Endomyocardial Fibrosis; Mortality; Biomarkers.

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**DOI:** <https://doi.org/10.36660/abc.20210633>

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## Myocardial Injury after Non-cardiac Surgery – State of the Art

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### Abstract

Approximately 300 million non-cardiac surgeries are performed annually worldwide and adverse cardiovascular events are the main cause of morbidity and mortality in the peri- and postoperative period. Myocardial injury after non-cardiac surgery (MINS) is a new clinical entity associated with adverse cardiovascular outcomes. MINS is defined as myocardial injury that can result in necrosis due to ischemia, marked by increase in biomarker levels. It has prognostic relevance and occurs within up to 30 days after non-cardiac surgery. The diagnostic criteria for MINS are an elevated postoperative measure of troponin judged as secondary to myocardial ischemia, i.e., with no evidence of a non-ischemic etiology, during or within 30 days after non-cardiac surgery, and without the requirement of an ischemic symptom or electrocardiographic finding of ischemia. Recently, patients at higher risk for MINS have been recognized using clinical variables and biomarkers and established protocols for greater surveillance in relation to electrocardiographic monitoring and cardiac troponin dosage. Elderly patients with previous atherosclerotic disease need to measure troponin daily in the postoperative period. The aim of the present work is to describe this new public health problem, its clinical impact and contemporary therapeutic approach.

### Introduction

Approximately 300 million non-cardiac surgeries are performed annually in the world and adverse cardiovascular events are the main cause of morbidity and mortality in the peri- and postoperative period.<sup>1</sup> Myocardial injury after non-cardiac surgery (MINS) is a new clinical entity, distinct from myocardial infarction (AMI) that occurs in the postoperative period, associated with adverse cardiovascular outcomes as shown in the international VISION registry.<sup>2</sup> MINS is defined as myocardial injury that can result in necrosis secondary to ischemia, with elevation of biomarkers. It has prognostic relevance and occurs in the period of up to thirty days after non-cardiac surgery.<sup>3</sup> MINS has an estimated incidence of eight

million patients per year and is independently associated with the risk of death and cardiovascular complications in the initial postoperative period<sup>4,5</sup> (Figure 1).

The prognostic relevance can be demonstrated by the association of the proposed diagnostic criteria with the risk of mortality at 30 days<sup>6</sup> and up to two years after non-cardiac surgery.<sup>7</sup>

MINS does not include perioperative myocardial injury due to non-ischemic causes, such as sepsis, atrial fibrillation, pulmonary embolism, and renal failure, or chronically elevated troponin levels.<sup>6,7</sup>

The diagnostic criteria for MINS are high troponin levels within 30 days after non-cardiac surgery judged as secondary to myocardial ischemia, i.e., with no evidence of a non-ischemic etiology, and without the requirement of an ischemic symptom or ischemia electrocardiographic finding.<sup>6</sup>

Although MINS is a common and increasingly recognized postoperative phenomenon, its incidence, risk factors, pathophysiology and clinical implications are not yet fully defined.<sup>8</sup> Cardiovascular complications are a cause of morbidity and mortality in patients undergoing non-cardiac surgery and studies have shown that the incidence of perioperative AMI corresponds to 6.2% of all surgeries performed. The pathophysiology of cardiovascular events in the postoperative period is complex and involves, among others, anesthetic induction, bleeding, anemia, hypoxia and pain in the postoperative period, causing elevation of catecholamines and cortisol production and a state of hypercoagulability.<sup>8</sup> Recently, patients at higher risk for MINS have been identified by clinical variables and biomarkers, as well by surveillance protocols in relation to electrocardiographic monitoring and cardiac troponin dosage. Thus, it is suggested that elderly patients with previous atherosclerotic disease need to measure troponin for three days postoperatively.<sup>6</sup>

Predicting cardiac complications after non-cardiac surgery is difficult and inaccurate, and troponin measurements seem to play an important role in this scenario. Studies have shown that high-sensitivity troponin (Hs-cTn) can be detected in most adult patients before non-cardiac surgery and that higher values are associated with increased risk. Therefore, the use of Hs-cTn can improve the prediction of cardiac complications after non-cardiac surgery.<sup>9,10</sup>

Despite the increase in the literature on the subject and scientific evidence, MINS is poorly recognized, as there is currently no global consensus on its definition or diagnostic criteria. Many studies have used different terminologies, such as POMI<sup>11</sup> (perioperative myocardial infarction/postoperative period) or PMI<sup>12</sup> (perioperative myocardial injury) to describe the phenomenon. In addition, the cutoff points of troponin

### Keywords

Myocardial Contusions; Biomarkers; Preoperative Care.

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Manuscript received April 12, 2020, revised manuscript August 27, 2020, accept November 04, 2020

**DOI:** <https://doi.org/10.36660/abc.20200317>

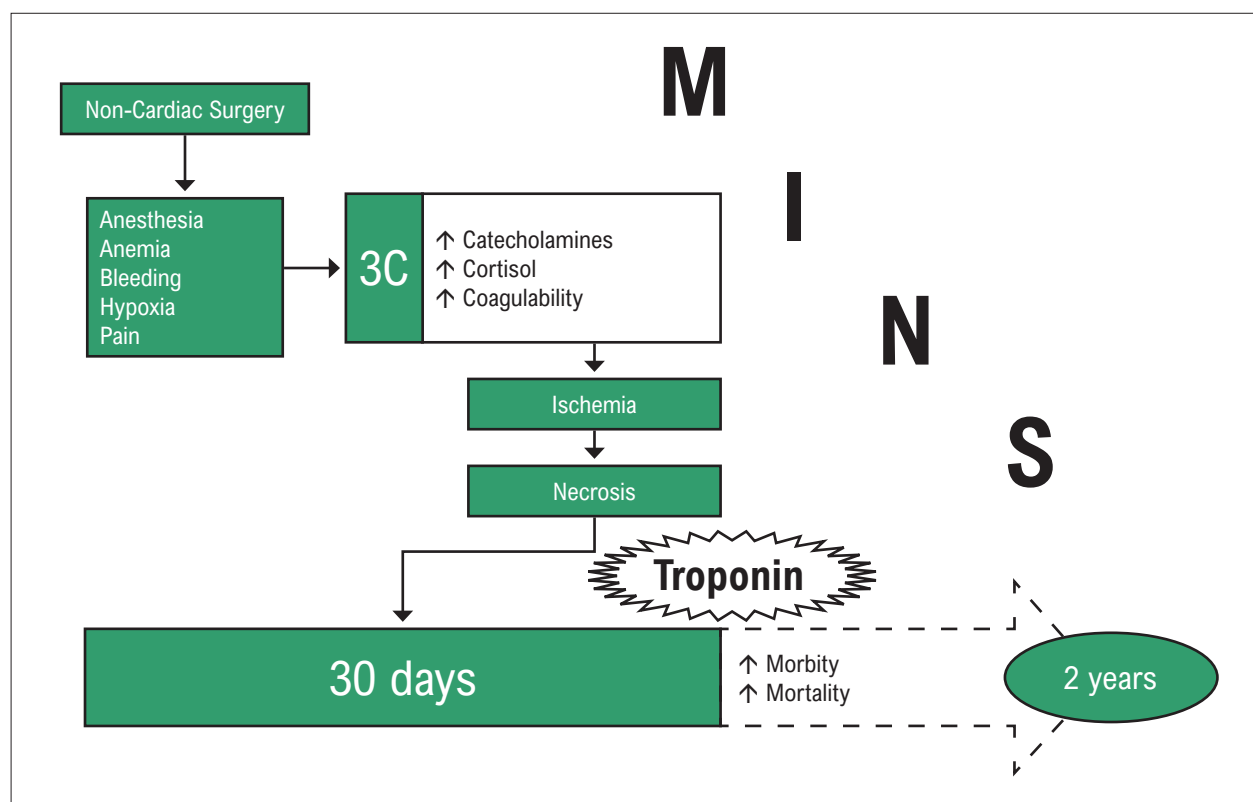


Figure 1 – Scheme of the development of myocardial injury after non-cardiac surgery (MINS).

levels for diagnostic purposes have varied among studies, depending on the troponin subtype and the assay used (Table 1). Also, the presence of MINS has drawn little attention among cardiologists and hospitalists in clinical practice, regarding its diagnosis, clinical implications and prognosis.<sup>13,14</sup> The aim of this article is to describe this new clinical problem with repercussions on public health and the contemporary therapeutic approach.

To structure this review article, two databases (Pubmed and Scielo) were searched, using the keywords in English “myocardial injury AND non-cardiac surgery”. The survey took place in January 2020. Prospective and retrospective studies were included, and clinical cases and abstracts presented at conferences were excluded. The eligibility of each study was independently assessed by two investigators. Divergent opinions regarding the relevance of the articles were resolved by consensus.

### Myocardial injury after non-cardiac surgery

#### Epidemiological aspects

Cardiac death is the leading cause of postoperative mortality in the first 30 days after surgery.<sup>15</sup> It is estimated that among all surgeries performed in the world, approximately 100 million involve patients aged 45 years and over, nearly 1.1 million (1.1%) of these have a AMI with ischemic symptoms in the perioperative period, 2.2 million (2.2%) have an asymptomatic AMI, and 4.6 million (4.6%) have MINS. Thirty-day mortality

rates in these three groups are 9.7%, 12.5% and 7.8%, respectively, which corresponds to more than 750 thousand deaths due to myocardial ischemia annually and thus a new global public health challenge.<sup>16</sup>

Patients diagnosed with MINS are older than those without the disease and the incidence of MINS is slightly higher in men (17.7%) than in women (16.2%).<sup>1</sup> Also, patients who develop MINS have more atrial fibrillation, heart failure, coronary artery disease, chronic kidney disease and have a higher preoperative heart rate.<sup>17</sup> More than 90% of patients with MINS do not present elevation of the ST segment or any other symptom of ischemia.<sup>4</sup>

Smilowitz & Berger<sup>8</sup> carried out a meta-analysis involving 169 studies, showing that the incidence of MINS was 17.9% of non-cardiac surgeries. Among the 139 studies that systematically measured cardiac biomarkers in all surgical patients, MINS occurred in 19.6% of patients. Among the other 30 studies, without biomarker measurements, the incidence of MINS was 9.9%.<sup>1</sup> MINS occurs more frequently in urgent procedures than in elective procedures (32.7% vs. 16.6%). The incidence also varies according to the subtype of non-cardiac surgery; the incidence of MINS was 20.1% and 18.0% in vascular surgeries and orthopedic surgeries, respectively.

#### Risk factors

Studies have reported the prevalence of cardiovascular disease or at least one cardiovascular risk factor among

**Table 1 – Criteria for the characterization of myocardial injury, myocardial injury after noncardiac surgery (MINS), perioperative myocardial injury, and perioperative/postoperative myocardial infarction**

|                                                                  | Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Myocardial Injury <sup>32</sup>                                  | <ul style="list-style-type: none"> <li>• Evidence of elevated cardiac troponin values with at least one value above the 99<sup>th</sup> percentile upper reference limit;</li> <li>• Clinical manifestations do not have to be present;</li> <li>• The myocardial injury is considered acute if there is a rise and/or fall of cardiac troponin values;</li> <li>• Cardiac biomarker release without evidence of myocardial ischemia;</li> </ul>                                                                               |
| myocardial injury after noncardiac surgery (MINS) <sup>32</sup>  | <ul style="list-style-type: none"> <li>• Defined as myocardial cell injury during the first 30 days after noncardiac with ischemic etiology and is independently associated with mortality;</li> <li>• Absence of other non-ischemic conditions;</li> </ul>                                                                                                                                                                                                                                                                    |
| Perioperative myocardial injury <sup>12)</sup>                   | <ul style="list-style-type: none"> <li>• Commonly does not exhibit typical symptoms of myocardial ischemia;</li> <li>• Electrocardiography has very low sensitivity for diagnosis;</li> <li>• Detection and quantification of acute cardiomyocyte injury by measuring cardiac troponin;</li> <li>• Defined as an absolute increase in high-sensitivity troponin of <math>\geq 14</math> ng/L above preoperative values;</li> <li>• After noncardiac surgery, strongly associated with 30-day mortality</li> </ul>              |
| Perioperative/ postoperative myocardial infarction <sup>49</sup> | <ul style="list-style-type: none"> <li>• Defined as an elevated cardiac biomarker or enzyme levels (with separate definitions for troponin or creatine kinase MB fraction), and one or more of the following:</li> <li>• Ischemic symptoms;</li> <li>• Electrocardiographic changes in two contiguous leads (i.e., development of pathologic Q waves, ST-segment elevation, ST-segment depression, or T-wave inversion);</li> <li>• coronary artery intervention, or evidence of AMI on cardiac imaging or autopsy;</li> </ul> |

individuals undergoing non-cardiac surgery.<sup>1</sup> Patients with MINS were more likely to have high blood pressure, coronary artery disease, previous MI, heart failure, and chronic kidney disease compared to patients without MINS<sup>1</sup> (Figure 2).

The risk of MINS is higher in individuals undergoing urgent or emergency surgery, open surgery, transfusions, prolonged surgery time, mean arterial pressure < 65 mmHg, heart rate  $\geq 110$  bpm and use of vasopressors in the perioperative period.<sup>1,5</sup>

The relationship between the type of anesthesia and MINS remains uncertain. While sevoflurane has been associated with lower MINS rates than propofol (11.7% vs. 29.0%,  $p = 0.018$ ) in one study,<sup>18</sup> other studies have shown no benefit from volatile anesthetics in relation to the occurrence of MINS.<sup>19,20</sup>

It is important to identify patients at high risk of serious adverse cardiac events based on preoperative assessment and low functional capacity (< 4 METs). Guidelines recommend evaluating those patients with known cardiovascular disease or aged 45 years or older who have undergone surgery that requires at least one night of hospitalization.<sup>21</sup>

Cost and accessibility are considered important determinants of the method used, and prospective observational studies have assessed the prognostic capability of the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) to predict major cardiovascular events after non-cardiac surgery. In patients aged 45 years or older with significant cardiovascular disease or with a Revised Cardiac Risk Index (RCRI) score  $\geq 1$  it is recommended to measure BNP or NT-proBNP before surgery to improve the estimate perioperative cardiac risk instead of imaging and noninvasive cardiac stress testing.<sup>21</sup>

Pre-existing lung diseases contribute to perioperative morbidity and mortality at a similar intensity to cardiac complications.<sup>23</sup> Complication rates are higher in abdominal, thoracic, and head and neck surgeries due to the impact on respiratory mechanisms.<sup>24</sup>

Most patients undergoing vascular surgery have multiple risk factors and comorbidities and there is growing evidence that traditional cardiovascular risk factors are also associated with venous thromboembolism, which would increase the risk of MINS. According to large prospective cohort studies, MINS influences in the short and long term all causes of mortality after vascular surgery.<sup>25</sup>

### Pathophysiology

The pathophysiology of MINS is not yet fully defined. It is not clear about the predominance of thrombosis or ischemia, although most cases occur in patients with underlying atherosclerotic disease.<sup>4</sup> Two distinct pathophysiological mechanisms can be considered in patients with MINS: rupture, fissure, or erosion of the coronary plaque with consequent intraluminal thrombosis that is equivalent to type 1 acute MI (type 1 AMI) and an imbalance between myocardial oxygen supply and/or demand and presence of unstable plaques that characterizes type 2 acute MI (type 2 AMI). Studies suggest that both mechanisms play an important role in the pathophysiology of MINS in the perioperative period.<sup>26-28</sup>

MINS confirmation is made based on elevated troponin levels, according to large prospective cohort studies that evaluated post-operative troponin levels in adults undergoing non-cardiac surgery. MINS does not include perioperative myocardial injury secondary to a documented non-ischemic etiology, including paroxysmal atrial fibrillation, sepsis, pneumonia, and pulmonary embolism.<sup>6</sup>

The OPTIMUS<sup>29</sup> study evaluated 30 patients who had a MI without ST elevation (STEMI) after non-cardiac surgery and 30 paired patients who had a non-operative STEMI. The study patients underwent cardiac catheterization and optical coherence tomography on average two days after the diagnosis of AMI. Intracoronary occlusive thrombus as the

## Review Article

| Risk Factors for Myocardial Injury after Non-Cardiac Surgery (MINS) |                                        |                   |
|---------------------------------------------------------------------|----------------------------------------|-------------------|
| Preoperative                                                        | Peroperative                           | Postoperative     |
| • Age ≥65 years                                                     | • Anesthesia (sympathetic stimulation) | • Hypotension     |
| • Male                                                              | • Hypotension                          | • Bleeding        |
| • Chronic kidney disease                                            | • Tachycardia                          | • Tachycardia     |
| • Peripheral arterial disease                                       | • Hypothermia                          | • Hypoxemia       |
| • Chronic coronary artery disease and recent <i>stent</i>           |                                        | • Pain            |
| • Chronic cerebrovascular disease and recent stroke                 |                                        | • Troponin dosage |
| • Diabetes mellitus                                                 |                                        |                   |
| • Hypertension                                                      |                                        |                   |
| • Severe aortic stenosis                                            |                                        |                   |
| • Urgent and emergency surgeries                                    |                                        |                   |
| • NT-pro BNP high dosage                                            |                                        |                   |

**Figure 2** – Risk factors for myocardial injury in non-cardiac surgery in the pre-, peri- and postoperative periods; NT-proBNP: N-terminal prohormone of brain natriuretic peptide. Adapted from Devereaux & Szczeklik W.<sup>6</sup>

cause of AMI was present in 13% of cases of perioperative MI compared to 67% of cases of MI not related to surgery ( $p < 0.001$ ). The culprit lesions showed fibroatheroma in 60% of the perioperative cases and 67% of the non-operative cases ( $p = 0.52$ ). The OPTIMUS study excluded patients with STEMI. Large prospective studies suggest that STEMI accounts for 11% to 21% of perioperative MIs.<sup>5,30</sup>

The VISION study<sup>31</sup> was a prospective cohort study of 955 patients from 12 centers in eight countries, who underwent coronary computed tomographic angiography (CTA) before non-cardiac surgery. Of the 71 patients (7%) who had AMI in the preoperative period, in 4% CTA showed normal coronaries.<sup>6,31</sup> Obstructive or extensive coronary artery disease was present in 72% of patients who had AMI in the perioperative period, and the remaining 24% had at least one coronary plaque with stenosis less than 50%.<sup>6</sup>

Studies have shown that a substantial number of patients undergoing non-cardiac surgery have important myocardial injuries that will not meet the universal definition of MI. The OPTIMUS<sup>29</sup> and VISION<sup>31</sup> studies excluded patients who had perioperative myocardial injury that did not meet the definition criteria for MI.<sup>32</sup> Both studies showed that thrombosis was present in one third of the cases and in the other patients, the imbalance between oxygen supply and demand was possibly the responsible for perioperative myocardial injury. Therefore, these data suggest that nearly one third of MINS cases are caused by thrombosis. Almost all these patients had underlying coronary stenosis that predispose patients to future thrombotic events, which would facilitate the establishment of effective therapeutic interventions.<sup>6</sup>

MINS has been consolidated for patients with increased troponin in the postoperative period in the absence of the criteria for the fourth universal definition of MI.<sup>32</sup> These patients may progress with chest pain and/or

electrocardiographic changes typical of MI. In addition, cardiovascular and cerebrovascular complications have been observed in in-hospital and out-hospital patients with MINS. The pathophysiological mechanisms of MINS involve elevations of troponin in the first days after surgery and are strongly associated with mortality at 30 days and in the long run. Also, although higher concentrations of troponin in the postoperative period are better associated with cardiac complications such as type 2 MI, low troponin elevations are rarely associated with evident signs of cardiac abnormalities in the postoperative period.<sup>33,34</sup> These data were demonstrated in the VISION study, in which a troponin of 0.02ng/mL was independently associated with mortality from non-vascular causes (RR 3.25, 95% CI 1.78-5.94), but not with vascular causes (RR 1.65, 95% CI 0.74-3.67).<sup>35</sup> Regardless of whether patients have a vascular or non-vascular death, MINS as a response to the stress of surgery may be a predictor of adverse events.<sup>16</sup>

### MINS diagnosis and mechanisms

Postoperative myocardial injury does not occur at random and is more likely in cardiovascular disease patients. If, on the one hand, the type, duration, and extent of surgery are factors that contribute to the occurrence of MINS, the baseline risk is a much stronger determinant of MI risk and mortality. The assessment of preoperative cardiac risk can help guide patient selection, treatment decisions such as, open *versus* endoscopic procedure and the intensity and duration of postoperative follow-up.<sup>4</sup>

Preoperative risk estimation generally uses a combination of risk assessment tools, non-invasive cardiac tests and, more recently and apparently more promising, the use of biomarkers.

Understanding the physiological changes due to surgical stress and the use of anesthesia is necessary to assess perioperative risk. The response to surgical stress is activated in the hypothalamus by the site of tissue damage, which results in endocrine (increased levels of cortisol and antidiuretic hormone), metabolic (catabolism of carbohydrates, fat, and proteins) and inflammatory (release of cytokines) responses.<sup>24</sup>

Physicians often use patient information to assess exercise tolerance as an approximate index of physical fitness. However, patients generally have little ability to estimate their tolerance to exercise, and perhaps that is why physicians also underestimate exercise tolerance. However, poor estimates of exercise tolerance probably do not matter much, because even the cardiopulmonary test poorly predicts preoperative cardiovascular risk.<sup>36</sup>

Epidemiological studies have investigated several criteria for the diagnosis of MINS and demonstrated their association with 30-day mortality.<sup>6</sup> These studies established the following diagnostic criteria for MINS: (1) elevated postoperative troponin levels considered as a result of myocardial ischemic injury in the absence of other non-ischemic conditions such as Pulmonary Tromboembolism (PTE), sepsis, myocarditis, Takotsubo cardiomyopathy; (2) within thirty days after non-cardiac surgery; (3) and without the requirement of symptoms or electrocardiographic changes of ischemia<sup>3,15</sup> (Table 2).

These studies also established perioperative troponin thresholds for MINS: (1) a troponin T > 0.03 ng/mL<sup>11</sup> and (2) elevation in highly sensitive troponin T (hsTnT) from 0.02 to < 0.065 ng/mL with an absolute change of at least 0.005 ng/mL (which was independently associated with 30-day mortality), or hsTnT > 0.065 ng/mL.<sup>3</sup> Although no study has established ideal thresholds for troponin I for MINS, there is no preference for troponin T over I. Until research establishes troponin I thresholds for MINS, clinicians must define an elevation as any value above the 99<sup>th</sup> percentile upper reference limit for each troponin I assay.<sup>6</sup>

The elevation of troponin remains controversial in specific surgical populations, such as elderly patients with hip fractures. Some studies have reported an increase in short and long-term mortality,<sup>37,38</sup> while others showed no change.<sup>39,40</sup> An observational cohort study<sup>41</sup> on this type of population included 312 patients and showed that the isolated increase in troponin was not predictive of death and/or readmission or any other outcome, including postoperative complications, hospitalization, intensive care unit (ICU) admission, or functional status.

Prospective studies evaluating adults undergoing non-cardiac surgery and troponin measurements after surgery demonstrate that 13% to 18% develop MINS within 30 days of surgery.<sup>3,12</sup> Among these individuals who develop MINS, 22% to 29% met the criteria for the universal definition of MI.<sup>32</sup> Most of the perioperative MI and MINS occur in the first 48 hours after surgery, and the perioperative MI can occur without ischemic symptoms. This disparity can be explained, in part, by the use of narcotics and sedatives after surgery.<sup>6</sup>

Considering that most of MINS' cases will go unnoticed without troponin monitoring, the recommendation is to measure the biomarker levels in at-risk patients on days 1, 2 and 3 after non-cardiac surgery while the patient is in the hospital.<sup>6</sup> Based on the cost-consequence analysis of the VISION study, we can define patients at risk those who are older than 65 years or with a history of atherosclerotic disease.<sup>42</sup> (Figure 3)

BNP and NT-proBNP are biomarkers released into the systemic circulation in response to the stretching of the left atrial myocardium. They are also released in response to ischemia, inflammation, and neuroendocrine stimuli. Preoperative concentrations of natriuretic peptides are strong predictors of perioperative cardiac events, including mortality, MI and heart failure.<sup>43</sup> In patients undergoing vascular surgery, measurement of natriuretic peptides for preoperative risk assessment substantially improves predictions based on tools such as the RCRI.<sup>22</sup> Recently, a sub-analysis of the VISION registry showed that in individuals over 45 years, NT-proBNP dosing in the preoperative period identified individuals at greatest risk for MINS and promoted incremental value on the RCRI scale by identifying individuals at greatest risk cardiovascular.<sup>44</sup>

Rodseth et al.<sup>45</sup> conducted a systematic review of 2,179 patients and showed that elevated preoperative BNP in concentrations higher than 92ng/L or concentrations of preoperative NT-proBNP higher than 300ng/L were strong predictors of death or non-fatal MI within 30 days after surgery (OR, 3.4 [95% CI 2.6–4.5; p < 0.001]) and 180 days or more after surgery (OR 2.6 [95% CI 2.0–3.4; p < 0.001]). A model using preoperative BNP correctly reclassified 16% more high-risk patients and 15% more low-risk patients than a model based only on preoperative baseline risk factors. Adding BNP or NT-proBNP measurements, it was observed that high preoperative values increase the predictive capacity of a composite outcome of death and non-fatal MI in 30 days (adjusted OR, 3.7 [95% CI 2, 2–6.2])

**Table 2 – Elevation of troponin in the first postoperative days and mortality in 30 days**

| Troponin T (ng / mL) | Patients n (%) | Deaths 30 days after surgery n (%) | Adjusted HR (CI 95%) |
|----------------------|----------------|------------------------------------|----------------------|
| < 0.01               | 13,376 (88.4)  | 134 (1.0)                          | 1.0                  |
| 0.02                 | 494 (3.3)      | 20 (4.0)                           | 2.41 (1.33-3.77)     |
| 0.03 -0.29           | 1,121 (7.4)    | 105 (9.3)                          | 5.00 (3.72-6.76)     |
| ≥ 0.30               | 142 (0.9)      | 24 (16.9)                          | 10.48 (6.25-16.62)   |

HR: hazard ratio. Adapted from Devereaux et al.<sup>35</sup>

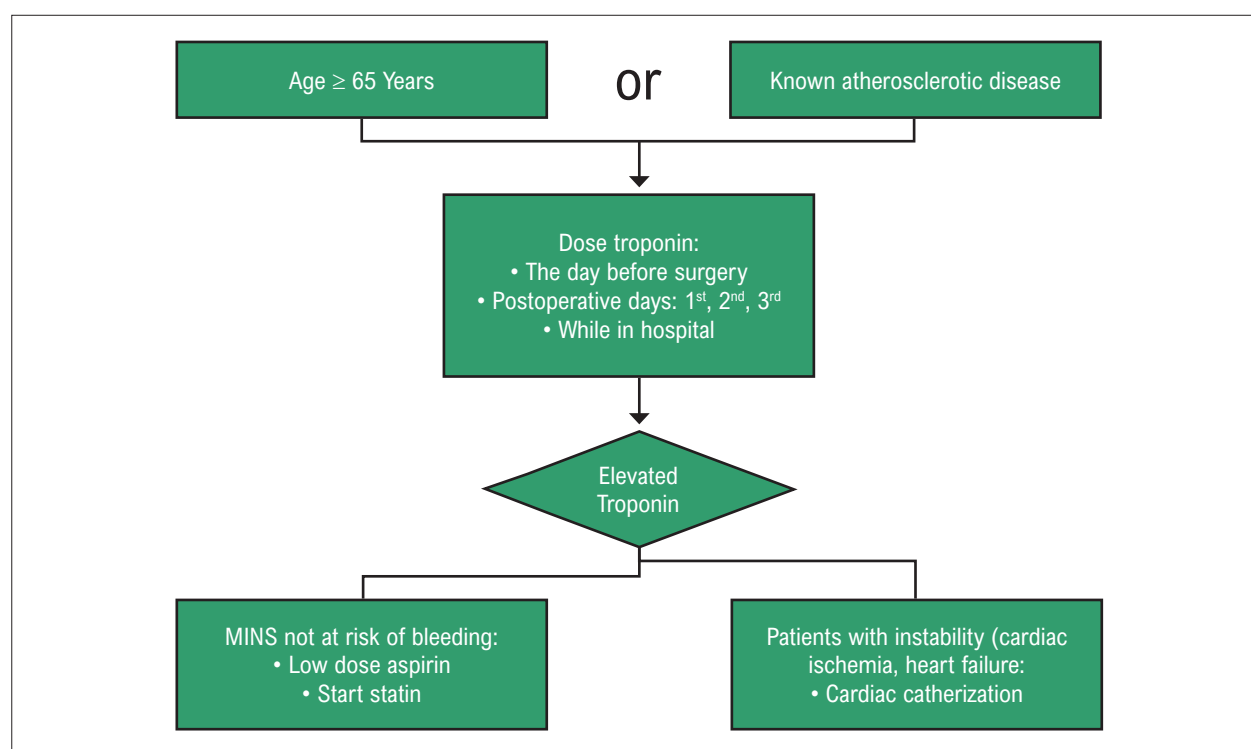


**Figure 3** – Evaluation for patients undergoing non-cardiac surgery. Adapted from Devereaux & Szczeklik W.<sup>6</sup>

and 180 days (adjusted OR 2.2 [95% CI 1.9– 2.7]) after non-cardiac surgery.<sup>45</sup>

European Society of Anesthesiology guidelines for preoperative risk assessment of non-cardiac surgery recommend preoperative measurement of natriuretic peptides in high-risk patients scheduled for general or orthopedic surgery and in intermediate and high-risk patients scheduled for vascular surgery or chest surgery.<sup>46</sup>

The Canadian Society of Cardiology Guidelines for Noncardiac Surgery<sup>21</sup> recommend measuring BNP or NT-proBNP before surgery to improve the estimate of perioperative cardiac risk in patients 65 years of age or older. In those aged 45 to 64 years with significant cardiovascular disease or an RCRI score  $\geq 1$ . In addition, patients with high concentrations of biomarkers must have troponin measured in the first two postoperative days.<sup>21</sup>

The Third Guideline for Perioperative Cardiovascular Evaluation of the Brazilian Society of Cardiology recommends for those patients of intermediate or high risk, the active search for the occurrence of cardiovascular events, through monitoring in a semi-intensive unit or ICU environment. The risk of an event of ischemic nature requires electrocardiographic monitoring and measurement of myocardial injury markers (troponin) until the third day after surgery, a period in which most cardiovascular events are concentrated.<sup>47</sup>

## Treatment

The complexity of the mechanisms that contribute to perioperative MI makes it difficult to treat MINS. Some of the

treatment options established for the non-operative scenario, such as the use of antiplatelet agents, pose a high risk due to the possibility of postoperative bleeding. In addition, there is little data from randomized clinical trials on the treatment of MINS.<sup>16</sup>

## Preoperative therapy for MINS prevention

A point that remains relatively unaddressed at MINS is prevention. The proposed mechanisms of MI in the perioperative period include fissures or rupture of the atherosclerosis plaque, in a condition characterized by hypotension, tachycardia, high catecholamine levels and arrhythmias. In the prevention of MINS, a balance must be struck between providing adequate antithrombotic coverage without increasing the risk of bleeding and minimizing the adverse effects of increased sympathetic impulse, avoiding hypotension.<sup>14</sup>

To date, perioperative patient care has largely focused on the prevention of MI, and few studies have attempted to determine the impact of secondary preventive therapies for MI in patients with isolated troponin elevation.<sup>48</sup>

In the past, beta-blockers were recommended in patients at vascular risk who underwent cardiac surgery of intermediate or high risk. However, after the publication of the POISE trial<sup>49</sup> that evaluated the preoperative use of beta-blockers, the risk-benefit ratio was considered unfavorable. The POISE study recruited 8,351 patients and demonstrated that metoprolol significantly reduced the incidence of MI compared to placebo, but significantly increased the risk of stroke and clinically important bradycardia. In addition, the metoprolol group had a significantly higher risk of mortality

compared to placebo. So, the main preoperative strategy of using beta-blockers proved to be ineffective and even dangerous for those patients who are not yet taking the drug to treat their pre-existing cardiac conditions.<sup>49</sup> In patients with proven, or at high-risk of, coronary heart disease, it is appropriate that they receive beta-blockers for long-term outcome benefits, irrespective of any impending surgery.<sup>50</sup>

Perioperative observational data suggest that patients with MINS benefit from aspirin and statin therapy. Although the use of aspirin would aim to avoid a state of postoperative hypercoagulability that can result in ischemic events, the role of aspirin in preventing MINS remains controversial.<sup>10</sup> In a substudy of 415 patients who had a perioperative MI in the POISE trial, a multivariate analysis demonstrated a lower risk of death at 30 days in patients using aspirin and statins.<sup>6</sup> On the other hand, the results of the POISE 2 study showed that aspirin did not result in an improvement in the rate of cardiovascular events and mortality within 30 days, instead causing a significant increase in bleeding compared to placebo. The authors postulated that the increase in cardiovascular events may be related to increased bleeding, causing a supply and demand failure.<sup>51</sup>

However, the POISE 2 study<sup>51</sup> has some shortcomings that potentially limit its applicability. For example, the time of aspirin administration in the preoperative period has not been standardized. Based on the inclusion criteria, aspirin would have been indicated for secondary prevention in most patients in the study. Withdrawing aspirin in these patients may have put them at increased risk for cardiac events and stroke, as withdrawal from aspirin treatment results in increased thromboxane A2 levels and decreased fibrinolysis.<sup>52</sup>

Observational study by Foucrier et al.<sup>53</sup> included 66 patients who had troponin elevation after vascular surgery and 132 paired controls who did not have troponin elevation after surgery. The primary outcome was the occurrence of a major cardiac outcome, that is, MI, coronary revascularization, or pulmonary edema with hospitalization in one year. Intensification of cardiovascular medication was defined as the introduction or increase of the dose of at least one of the following four medications – antiplatelet agents, statins, beta-blockers, and angiotensin-converting enzyme inhibitors. Patients without intensified cardiovascular treatment had an RR of 1.77 (95% CI 1.13–2.42) for the primary outcome, compared to the matched control group. On the other hand, patients who received intensification of cardiovascular treatment had a similar risk for the primary outcome compared with the control group (RR 0.63; 95% CI 0.10–1.19).<sup>53</sup> Also, a meta-analysis demonstrated that interruption of aspirin in the perioperative period in patients with or without risk of ischemic heart disease was associated with a three-time greater risk of serious adverse cardiac events.<sup>54</sup>

Cardiovascular complications are the most important cause of perioperative morbidity and mortality among patients undergoing vascular surgery. The protective effects related to the use of statins seem to be based on lipid-lowering and other properties of these drugs, such as improvement in endothelial function, in hemostasis and inflammation, which result in coronary plaque stabilization. Clinical trial showed that the incidence of cardiovascular events in the first six

months after surgery, including death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina, can be reduced with perioperative use of atorvastatin in patients who must undergo vascular surgery, regardless of their serum cholesterol concentration.<sup>55</sup>

The Third Guideline for Perioperative Cardiovascular Evaluation of the Brazilian Society of Cardiology recommends that for patients receiving aspirin for secondary prevention, the medication should be kept at the maximum dose of 100mg per day. Meta-analysis data suggest that this relationship is favorable for the majority of patients in the perioperative period. Neurosurgeries, due to the high morbidity and mortality of related bleeding, are an indication for aspirin suspension seven days before surgery.<sup>47</sup>

The main guidelines recommend the continuation of statin therapy in the perioperative period, and the initiation of statins in patients undergoing vascular surgery.<sup>21,47,56,57</sup> The VISION study showed that patients who took statins preoperatively had significantly lower rates of MINS and all-cause mortality. Statins should be started at least two weeks before surgery to promote the plaque-stabilizing effects and anti-inflammatory action.<sup>14</sup>

The latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not recommend coronary revascularization before non-cardiac surgery.<sup>57</sup> Preoperative coronary artery revascularization did not reduce long-term mortality or postoperative MI compared to drugs in a study with more than 5,000 patients undergoing vascular surgery.<sup>58</sup> Myocardial revascularization surgery and percutaneous coronary intervention are procedures associated with a significant risk.<sup>59</sup> Patients with coronary stents after percutaneous coronary intervention are at risk of in-stent thrombosis during surgery, especially if antiplatelet drugs are discontinued in the perioperative period. Revascularization before non-cardiac surgery is recommended only for patients in whom revascularization is indicated regardless of surgery.<sup>57</sup>

In the perioperative phase, to prevent cardiovascular events, the anesthesiologist must limit hypothermia and immediately treat hypotension and tachycardia, possibly avoiding beta-blockers.<sup>48</sup>

### Postoperative care

In the postoperative period, hypotension, tachycardia, hypoxia, bleeding, and pain promote an imbalance in the supply and consumption of oxygen in the myocardium, increasing the risk of injury, and must be detected and corrected early.<sup>48</sup>

In the management of MINS, the use of aspirin and statin may be recommended in patients who do not meet the criteria for acute coronary syndrome, as this has been shown to improve results.<sup>21</sup> Theoretically, beta-blockers may have a role in the management of the imbalance between oxygen supply and demand that results in MINS. However, the benefits of using beta-blockers and angiotensin-blocking agents should be weighed against the risk of hypotension, which can accentuate myocardial damage.<sup>14</sup> Additional studies are needed to provide more robust evidence on the use of these drugs. Patients who meet the criteria for acute coronary syndrome should be treated according to current clinical practice guidelines.<sup>14</sup> Invasive procedures to

investigate obstructive coronary disease in patients with MINS would not be indicated, except for patients who present criteria for STEMI or patients with hemodynamic or electrical instability.

The MANAGE study examined the use of dabigatran for the treatment of MINS. The authors found that subjects in the intervention arm had lower rates of major vascular events ( $n = 97$ ; 11% - patients assigned to dabigatran vs 133 - 15% - in placebo group,  $p = 0.0115$ ), with similar bleeding complications compared to the placebo arm ( $n = 29$  patients; 3% - dabigatran group vs.  $n = 31$ ; 4% - placebo group,  $p = 0.76$ ).<sup>7</sup> However, the study has some limitations in its design and results. The study ended early, the primary outcome was modified in the middle of the study, and drug discontinuation rates were high. Despite its deficiencies, the study paves the way for further research in this area.<sup>14</sup>

## Conclusions

MINS represents a new clinical entity characterized today as an emergent health problem in view of the growing number of non-cardiac surgeries and their high prevalence. MINS is a marker of future vascular events and its early detection with the use of biomarkers should be performed in all medium or large surgeries in individuals aged 65 years or over and in

those with previous atherosclerotic disease regardless of age. Multicenter registries and clinical trials have been progressively developed with the aid of perioperative medicine aiming at improving cardiovascular surveillance and treatment of this group of patients.

## Author contributions

Conception and design of the research, writing of the manuscript and critical revision of the manuscript for intellectual content: Jorge AJL, Mesquita ET, Martins WA.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Fontes de financiamento

There were no external funding sources for this study.

## Vinculação acadêmica

This study is not associated with any thesis or dissertation work.

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## Reduced Systemic Nitric Oxide Bioavailability Parallels Microvascular Endothelial Dysfunction during Cardiopulmonary Bypass

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### Introduction

Cardiopulmonary bypass (CPB) is currently performed in infants and newborns for surgical correction of congenital heart diseases (CHDs).<sup>1</sup> CPB exposes the body to extreme, nonphysiologic conditions that initiate a systemic inflammatory response accompanied by vasomotor dysfunction, and can lead to multiple organ dysfunction.<sup>2</sup> Additionally, CPB has been linked to activation and injury of endothelial cells, which is associated with global inflammatory response, triggering of the coagulation system and subsequent organ dysfunction, not only in adult patients, but particularly in infants and newborns.<sup>3</sup>

Systemic microvascular dysfunction during CPB results in inadequate blood flow, organ perfusion and oxygen delivery to the tissues.<sup>4</sup> We have shown, using laser Doppler perfusion monitoring (LDPM) (a non-invasive method coupled with local heating of the skin), that the microcirculatory bed of the skin of the forehead is an appropriate model for the study of microvascular reactivity and tissue perfusion in cardiovascular surgery with CPB in adults.<sup>5</sup> Actually, local thermal hyperemia (LTH) is a useful method in the evaluation of systemic microvascular endothelial function.<sup>5,6</sup> In addition, using LDPM, we demonstrated that microvascular dysfunction and hypoperfusion occur during CPB in surgical correction of congenital heart disease in infants and children, despite adequate macrohemodynamic parameters.<sup>7</sup> The mismatch between macro- and microcirculation in severely ill patients with septic or cardiogenic shock, which can be misleading to an adequate clinical management of these patients, has also stimulated the search for new methods to monitor microcirculatory perfusion in the intensive care units.<sup>8</sup>

Of note, the release of nitric oxide (NO) from the constitutive endothelial isoform of nitric oxide synthase (eNOS) is reduced during CPB in adult patients.<sup>9</sup> NO is a potent endothelium-derived endogenous vasodilator, and its depletion during CPB under non-pulsatile flow can lead to vasoconstriction, and consequently reduced organ perfusion. Plasma NOx ( $\text{NO}_2^- / \text{NO}_3^-$ ), steady

metabolites of NO, which have been used as markers of systemic NO bioavailability, as their levels reflect changes in eNOS activity in humans.<sup>10</sup> Therefore, the aim of the present study was to investigate whether a reduction of NO systemic bioavailability is associated with endothelial-dependent microvascular dysfunction in infants and children, during on-pump cardiac surgery for the correction of acyanotic CHD.

### Methods

This longitudinal observational study included 47 consecutive pediatric patients with acyanotic heart defects, aged between 1 month and 9 years, undergoing corrective cardiac surgery at a tertiary public Brazilian hospital. The study was undertaken according to the Declaration of Helsinki and was approved by the ethics committee of the institution. Parents or legal tutors of the study participants gave written informed consent. The anesthetic procedures occurred under CPB, with mild to moderate hypothermia (32-34° C). Mean arterial pressure was kept between 45-60 mmHg.

### Assessment of microvascular flow and reactivity

Skin microvascular reactivity was evaluated using a single-point LDPM system (Periflux 5001, Perimed, Järfälla, Sweden), which measures microvascular flow using a heating laser probe (PF 457, Perimed). The microvascular perfusion changes were registered in arbitrary perfusion units (APU=10 mV). The probe was positioned on the forehead at the beginning of the anesthetic procedures, and baseline microvascular flow was measured during 20 minutes of local heating of the laser probe to 42 °C (LTH). The maximal vasodilation was expressed as cutaneous vascular conductance (CVC), calculated as the ratio of the microvascular flow, in APU, to the mean arterial pressure (APU/mmHg). Mean of values of microvascular flow (in APU) before and during CPB were used in the calculations. After the baseline evaluation, the microvascular response to LTH was also recorded after induction of general anesthesia and 15 minutes after the beginning of CPB.

### Evaluation of systemic bioavailability of NO

Systemic nitric oxide bioavailability was evaluated using plasma NOx ( $\text{NO}_2^- / \text{NO}_3^-$ ) concentrations, which have been used as an index of *in vivo* NO formation. Total plasma NOx concentrations were determined after induction of anesthesia and immediately after conclusion of CPB using a colorimetric assay (Cayman Chemical Company, Ann Arbor, Michigan, USA) with a 2.5  $\mu\text{M}$  sensitivity and a 2.7% intra-assay coefficient of variation. Each plasma sample was measured in duplicate.

### Keywords

Laser-Doppler Flowmetry; Nitric Oxide; Cardiopulmonary Bypass.

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Manuscript received September 20, 2020, revised manuscript February 03, 2021, accepted March 24, 2021

**DOI:** <https://doi.org/10.36660/abc.20201040>

## Research Letter

### Statistical analysis

Results are presented as medians (interquartile range). Shapiro-Wilk was used to test the normality of the data. Results were analyzed with two-tailed Wilcoxon matched-pairs signed rank test using GraphPad Prism 7.0 software (GraphPad Software INC., San Diego, California, USA). A p-value < 0.05 defined statistical significance.

### Results

Baseline clinical characteristics of the patients included in the study and the surgical parameters are depicted in Table 1. Mean arterial pressure values were  $58.4 \pm 11.5$  mmHg before and  $50.9 \pm 8.4$  mmHg during CPB ( $p=0.01$ ).

Before CPB, patients' plasma NOx levels were  $51.4$  ( $24.2$ - $75.8$ )  $\mu\text{M}$ , which were significantly reduced to  $45.1$  ( $31.0$ - $66.5$ )  $\mu\text{M}$  after CPB ( $p=0.03$ ; Figure 1A).

Median baseline microvascular conductance before CPB [ $0.47$  ( $0.35$ - $0.64$ ) APU/mmHg] did not change significantly [ $0.48$  ( $0.28$ - $0.66$ ) APU/mmHg] during CPB ( $p=0.85$ ). On the other hand, the endothelial-dependent increase in microvascular conductance, induced by thermal hyperemia, was significantly blunted during CPB, when

**Table 1 – Clinical characteristics and surgical data of patients (n=47)**

| Parameters                                |                 |
|-------------------------------------------|-----------------|
| Male gender n (%)                         | 19 (40.4)       |
| Age (months)                              | 16 (9 - 54)     |
| Weight (Kg)                               | 8 (6 - 16)      |
| CPB time (min)                            | 85 (75 - 105)   |
| Temperature during CPB (°C)               | 32 (32-33)      |
| Pump flow rate (mL/Kg/min)                | 150 (120 - 150) |
| Aortic cross-clamping time (min)          | 67 $\pm$ 28     |
| Type of cardiopathy n (%)                 |                 |
| Atrial septal defect                      | 3 (6.4)         |
| Ventricular septal defect                 | 16 (34)         |
| Atrioventricular canal (partial or total) | 15 (32)         |
| Aortic arch interruption                  | 1 (2.1)         |
| Truncus arteriosus                        | 1 (2.1)         |
| Mixed lesions                             | 11 (23.4)       |
| RACHS-1 score n (%)                       |                 |
| Risk category 1                           | 3 (6.4)         |
| Risk category 2                           | 21 (44.7)       |
| Risk category 3                           | 21 (44.7)       |
| Risk category 4                           | 2 (4.2)         |

Dados apresentados em média  $\pm$  desvio padrão ou medianas (percentis 25 - 75) para valores que não apresentaram distribuição gaussiana (teste de normalidade de Shapiro-Wilk); BCP: bypass cardiopulmonar; RACHS-1: escore de risco ajustado para cirurgia de cardiopatia congênita

compared to values obtained before CPB (Figure 1B). Maximum absolute values of microvascular conductance during LTH before CPB [ $1.97$  ( $1.04$ - $3.89$ ) APU/mmHg], were markedly reduced to [ $0.74$  ( $0.54$ - $1.32$ ) APU/mmHg] during CPB ( $p<0.0001$ ; Figure 1B). Percentage increases of microvascular conductance induced by LTH were also markedly reduced, from [ $313$  ( $171$ - $604$ ) %] before CPB to

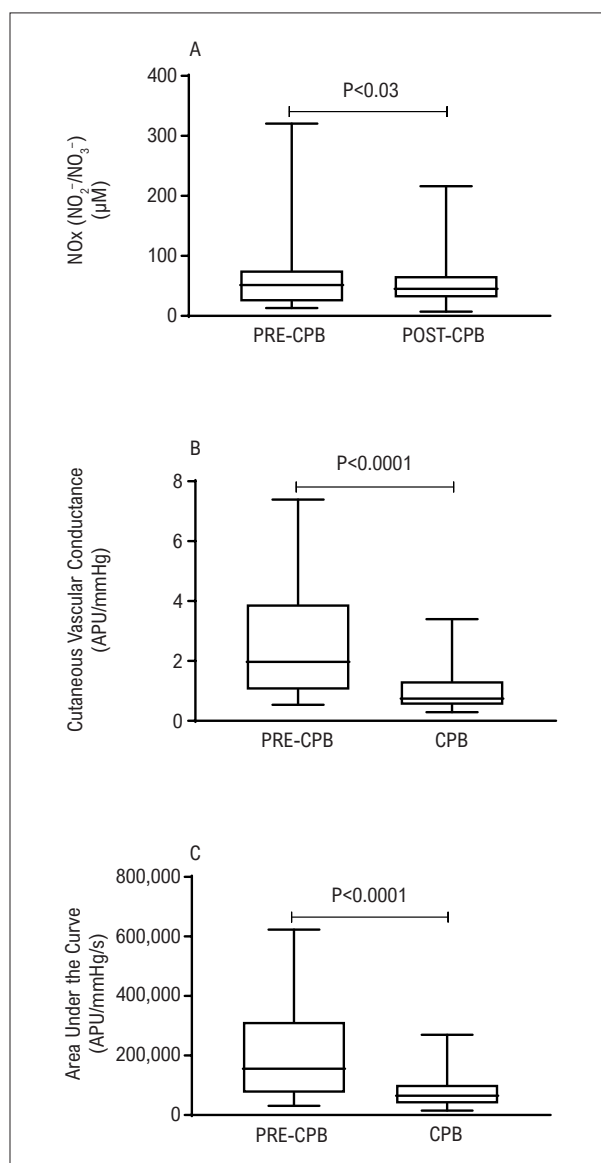


**Figure 1 – (A)** Total plasma levels of NOx ( $\text{NO}_2$  /  $\text{NO}_3$ ) before (PRE-CPB) and after the termination of cardiopulmonary bypass (POST-CPB). **(B)** Peak values of skin microvascular vasodilator responses induced by local thermal hyperemia, expressed as cutaneous vascular conductance [arbitrary perfusion units (APU)/mean arterial pressure (mmHg)] before (PRE-CPB) and 15 minutes after the beginning of CPB. **(C)** Area under the curve of vasodilator responses induced by local thermal hyperemia before (PRE-CPB) and 15 minutes after the beginning of CPB. Values are expressed as box and whisker plots where the center line denotes the median value, the box contains the 25<sup>th</sup> to 75<sup>th</sup> percentiles of dataset and whiskers mark the maximum and minimum values. Results were analyzed using the Wilcoxon matched-pairs signed rank test

[74 (8-156) %] during CPB ( $p < 0.0001$ ). The area under the curve (AUC) of microvascular vasodilation induced by LTH showed a similar pattern of response. Maximum increases in AUC induced by LTH before CPB [155,552 (75,323-313,040) APU/mmHg/s] were significantly reduced to [64,676 (38,753-101,423) APU/mmHg/s] during CPB ( $p < 0.0001$ ; Figure 1C).

## Discussion

NO has a key role in the regulation of endothelial function and microvascular inflammation.<sup>11</sup> CPB induces a generalized inflammatory response, triggered at least in part by ischemia-reperfusion injury, which contributes to myocardial dysfunction and reduced cardiac output, and is related to NO metabolism, among other mechanisms.<sup>12</sup> The current study shows a reduction of NO during CPB in children, which parallels the objective evidence of microvascular dysfunction. This underscores prior evidence of NO reduction during cardiac surgery,<sup>13</sup> what has led to studies using NO administration to reduce bypass-induced inflammation in children undergoing cardiac surgery.<sup>14</sup> Therefore, data from this study may support the use of microcirculatory monitoring during CPB, with guided therapeutic interventions.

## Conclusions

The impairment of microvascular endothelial function during CPB in cardiac surgery for the correction of congenital heart defects appears to be related to a reduced systemic bioavailability of NO, resulting from the inflammatory and pro-oxidative response typical of this surgical procedure.

It is important to note that our study had a cross-sectional experimental design; thus, microcirculatory reactivity in our population was evaluated without any intervention. Nevertheless, considering that our results pointed out to the existence of an association between CPB and systemic NO depletion in infants and children, we intend to extend our clinical research with drug interventions - such as sodium nitroprusside, a NO donor drug - utilized for optimizing microcirculation during CPB, to investigate their putative beneficial effects on microcirculatory alterations. For the

moment, LDPM reflected changes in microvascular perfusion and reactivity that correlated well with shifts in flow patterns, perfusion pressure and endothelial dysfunction, triggered by the systemic inflammatory response syndrome.

Finally, we suggest that the use of microcirculatory monitoring during cardiac surgery, with the implementation of microcirculatory/tissue perfusion variables in routine care during CPB, together with appropriate therapeutic microcirculatory intervention, has the potential to improve outcomes in pediatric cardiac surgery.

## Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Ugenti V, Romano AC, De Lorenzo A, Tibirica E; Acquisition of data: Ugenti V, Romano AC; Statistical analysis: Ugenti V, Tibirica E; Obtaining financing: Tibirica E; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Ugenti V, De Lorenzo A, Tibirica E.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

This study was funded by FAPERJ and CNPq.

## Study Association

This article is part of the thesis of master submitted by Viviana Ugenti, from Instituto Nacional de Cardiologia.

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Nacional de Cardiologia under the protocol number 26613714.3.0000.5272. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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## The Congenital Heart Disease Diagnosis List for the eleventh iteration of the International Classification of Diseases (ICD11): Translation to Brazilian Portuguese

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### Background

The International Society for Nomenclature of Pediatric and Congenital Heart Disease (ISNPCHD) is an organization composed by specialists in Pediatric Cardiology, Cardiac Surgery and Morphology. It was created aiming at unifying the terminology of congenital and acquired pediatric heart disease across the world. The unified lexicon allows for inter-institutional and international diagnostic comparisons and exchange of information on the outcomes of children and adults with congenital heart defects<sup>1</sup>.

Initially gathering annually, as the “The International Nomenclature Working Group for the Mapping and Coding of Nomenclatures for Pediatric and Congenital Heart Disease”,<sup>1</sup> the members decided to create, in 2005, the International Society (ISNPCHD), extending the membership to incorporate professionals from underrepresented areas of the world.

Over time, three working groups of the ISNPCHD were created: the Definitions Working Group,<sup>1</sup> the Mapping and Coding Group (or Nomenclature Working Group) and the Archiving Working Group.

The initial tasks of the Society were accomplished with the development of the International Pediatric and Congenital Cardiac Code (IPCCC), a list of diagnoses and procedures, each linked to a six-digit numeric code, and the bidirectional cross-mapping between “The European Paediatric Cardiac Code of the Association for European Paediatric and Congenital Cardiology” and “The nomenclature system of the International Congenital Heart Surgery Nomenclature and Database Project”. The IPCCC numerical code was derived from “The European Paediatric Cardiac Code” and served as the backbone for the mapping process.

The IPCCC codes and lists (in English) are freely available for download from the Society’s website at <http://www.IPCCC.net>.

### Keywords

Heart Defects Congenital; Terminology as Topic; International Classification of Diseases.

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Manuscript received February 17, 2021, revised manuscript April 01, 2020, accepted May 12, 2021.

**DOI:** <https://doi.org/10.36660/abc.20210143>

During the preparation of the eleventh iteration of the International Classification of Diseases (ICD11) of the World Health Organization (WHO), in 2007 the members of the ISNPCHD were given the mission of revising the existing list of diagnoses for pediatric and congenital heart disease from the previous ICD version. The ISNPCHD group was also expected to update the list according to the nomenclature consensus that has been built among specialists since the creation of the Nomenclature Committee.<sup>2</sup>

While the ICD9 and ICD10 versions had respectively only 29 and 73 terms devoted to the congenital malformations of the circulatory system, the intention was to expand the number of diagnoses in order to cover most of the frequent cardiovascular malformations, which resulted in more than 300 terms in the 11<sup>th</sup> version of the ICD. Of course, the rarest lesions were not included in the new ICD list, because their uncommon occurrence is not worth reporting in vital statistics. Such rare lesions (among many others, “intra-avalvular mitral ring” is an example) should be included under the generic upper level category (“congenital anomaly of the mitral valve”, in the abovementioned example).

### Methods

**The ICD11 list for Congenital Heart Defects (access the supplementary material at the end of the article)**

Officially starting in Japan, 2007, at least one session of each ISNPCHD annual meeting was devoted to the discussion of the ICD11 list, following the hierarchy of terms from the IPCCC, already developed and maintained by the group and mapped to the two main diagnosis’ lists currently in use, the ones from the European Society of Cardiology and the Society of Thoracic Surgeons, as previously explained.

Besides the organization of the list into six hierarchical levels, the terms were mapped to the IPCCC code and to the previous ICD10 alphanumeric code of the WHO. Also, a definition and a list of synonyms and commonly used abbreviations were provided for each diagnosis.

Reaching a consensus on the definitions was the most contentious part of the process and of fundamental importance, since the goal was to provide a clear comprehension of the morphological diagnosis to coders all over the world.

The list of 324 diagnoses with their respective IPCCC codes were presented at the Nomenclature Summit of the World Congress of Pediatric Cardiology in Barcelona, 2017 and published in the journal ‘Cardiology in the Young’ in the same year.<sup>2</sup>

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The final product was then, together with the complete ICD11 list, released by the WHO in 2018 (<https://icd.who.int/dev11/f/en>), under “Developmental anomalies / Structural developmental anomalies primarily affecting one body system / Structural developmental anomalies of the circulatory system / Structural developmental anomaly of the heart or great vessels”. The 11<sup>th</sup> version is meant to be implemented in January 2022. Meanwhile, the country members will prepare for its implementation, including the translation work, etc. There have been many major changes in the system, including an increase in the number of chapters. The new coding system is not similar to the one used in the ICD10, as discussed in the document accessed electronically on October 19, 2020: <https://www.icd10monitor.com/icd-11-hurry-up-and-wait>.

### Addition of new terms to the list

After the completion of the congenital heart disease list of terms by the ISNPCHD, 94 new terms were added by the WHO staff. These terms are currently under analysis by the ISNPCHD members, who will eventually decide regarding their maintenance in the ICD11 list, their removal (because of scientific incorrectness) or replacement in other sections of the ICD11.

### Translation of the ICD11 list for Congenital Heart Defects to other languages

As it appears at the WHO/ICD webpage, “ICD, as an international standard, has to be multilingual.”

The priority for multilingual representation of the ICD11 will be the 6 Official United Nations Languages: English, French, Spanish, Russian, Chinese, Arabic.

In an initiative aimed at accelerating the use of ICD11 congenital heart disease terms by non-English speaking Health teams, in 2019 Béland et al.<sup>3</sup> prepared and published the French translation of the ICD11 list for congenital heart defects in the Canadian Journal of Cardiology.

In 2018, given the lack of a translation to the Portuguese language, we embraced the task, and the final product is presented here.

### Some particular aspects of the translation of the ICD11 terms into Brazilian Portuguese

Brazil is currently the country in the world with the largest number of Portuguese-speaking people as their native language. Portuguese is currently the sixth language by number of native speakers, which comprises 2.87% of the world's population

(Wikipedia, accessed in October 19<sup>th</sup>, 2020: [https://en.wikipedia.org/wiki/List\\_of\\_languages\\_by\\_number\\_of\\_native\\_speakers](https://en.wikipedia.org/wiki/List_of_languages_by_number_of_native_speakers)).

Nevertheless Portuguese is not considered an official language by the WHO (WHO webpage, accessed on October 19, 2020: <https://www.who.int/about/who-we-are/multilingualism>) and still does not have a platform at the ICD site.

Moreover, the number of Pediatric Cardiologists associated to the Department of Pediatric Cardiology of the Brazilian Society of Cardiology in 2020 surpasses 750,

what clearly highlights the importance of maintaining this community updated with the nomenclature of congenital heart defects.

Although the billing process of the Unified Health System (SUS) of the Brazilian Ministry of Health is currently based on the 10<sup>th</sup> version of the ICD, the quality of the improvements included in the new version (ICD11), together with the possibility of mapping the new terms to the previous ICD list, makes it fundamental to make the new Portuguese list available.

Not only the diagnostic terms, but definitions, commentaries and synonyms, which are all available at the ICD/WHO website, were translated in this new list, as well.

During the translation, some decisions were made in order to facilitate the comprehension and the search/retrieval process. Some examples are:

- A few diagnostic terms were maintained in English, in parenthesis after the term in Portuguese, due to their widespread use among the Brazilian cardiologists (examples: *crisscross*, *sling*).
- Maintenance of Latin terms when of common use, similarly to the previous decisions (examples: *truncus*, *ostium primum*).
- Maintenance of eponyms (*Fallot*, *Ebstein*) as they appear in the English version of the diagnosis list.

-Non-translation of some English terms, since they make no sense in Portuguese (example: upstairs-downstairs ventricle).

- Last but not least, we have to discuss the use of the word “communication” between chambers as the most preferred term in Romance languages like Portuguese, Italian, French and Spanish, over the term “septal defect” commonly applied in English and other Germanic languages. It is easy to understand that not all interatrial communications are caused by defects within the anatomic atrial septum, with “coronary sinus defect” being an example. Likewise, not all the interventricular communications coincide with what we call a ventricular septal defect.<sup>4</sup> Especially when there is overriding of an arterial trunk, the interventricular communication is the plane of space between the overriding valve and the top of the trabecular septum. This area is the outflow for the left ventricle, but the hole closed by the surgeon, what we usually call the ventricular septal defect, is the right border of this plane, as in Tetralogy of Fallot. In our translation, we decided to maintain “*comunicação interventricular*” (interventricular communication) in all the places where the term “ventricular septal defect” was found.

### Future perspectives for the translation of ICD11 terms into Portuguese

As previously mentioned, in Brazil the Unified Health Insurance System (SUS) is currently the main tool used by the Ministry of Health for the billing process in public hospitals. Although the implantation of ICD11 by the Government does not seem to be on the horizon in the short or middle term in our country, we should not hinder the access of professionals who care for children and adults with congenital heart disease to an updated system of nomenclature of cardiac defects in Portuguese.

We submitted our translated list of terms to the WHO in 2019. However, we were recently informed that our work has not yet been incorporated due to the lack of a Portuguese platform in their website. Our decision to publish the list, in a local Journal of Cardiology and also electronically on the website of the Brazilian Society of Cardiology/ Department of Pediatric Cardiology, aims to give access to specialized professionals and services to the new coding system and nomenclature, thus enhancing their capabilities to exchange data about prevalence, treatment and prognosis of congenital heart disease in Portuguese-speaking countries.

As the next step in this process, we plan to develop an application to cross-map the ICD10 and ICD11 codes and the IPCCC, so that even if the official system does not change regarding billing purposes, the Pediatric Cardiologists and Surgeons can have a parallel and updated coding system to be used in daily practice.

### The process of translation

It all started during a conversation between the authors, and the decision was accelerated by the fortuitous visit of one of us (VDA) to the beautiful city of Recife - where the other one of us (SSM) lives - during the last week of 2018. Encouraged by the astonishing view of the Atlantic ocean in Northeast Brazil, we met *tête-à-tête* during 5 days, and completed the task during computer meetings along the year of 2019, even when virtual conferences were not yet a common practice as they are now in the COVID19 pandemic era.

After the translation, the list was checked for consistency and grammatical corrections by a professional in the area.

We do hope the result of our effort is welcomed by the Portuguese-speaking scientific community and that it

can facilitate the exchange of data between the numerous health institutions in the country, thus providing background to research focused in the wellbeing of our patients with congenital heart defects.

### Acknowledgements

We are indebted to Sergio Dortas and his team for the grammatical corrections and to Drs Marie J Béland and Rodney Franklin for their scientific advice.

### Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript; Critical revision of the manuscript for intellectual content: Vera D. Aiello, Mattos SS.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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### \*Supplemental Materials

For additional information, please click here.



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## Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis – 2021

**Development:** The Brazilian Society of Cardiology's Department of Heart Failure (Departamento de Insuficiência Cardíaca – DEIC) and the Study Group on Cardiomyopathies (Grupo de Estudos em Miocardiopatias – GEMIC) of the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia – SBC)

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**DOI:** <https://doi.org/10.36660/abc.20210718>

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**How to cite this statement:** Simões MV, et al. Posicionamento sobre Diagnóstico e Tratamento da Amiloidose Cardíaca – 2021. Arq Bras Cardiol. 2021; 117(3):561-598

**Note:** These statements are intended to support, not replace, the clinical judgment of physicians who, ultimately, must determine the appropriate treatment for their patients.

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# Statement

## Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis – 2021

The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these statement, 2020/2021.

| Expert                            | Type of relationship with industry                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Acary Souza Bulle Oliveira        | Nothing to be declared                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| André Schmidt                     | <p>Financial declaration</p> <p>A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry:</p> <p>- Bayer: Anticoagulants.</p> <p>Other relationships</p> <p>Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry:</p> <p>- Sanofi: Anticoagulants.</p>                                                                                                                                                                                                                                                                                                                                        |
| Andréia Biolo                     | Nothing to be declared                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Aristóteles Comte de Alencar Neto | Nothing to be declared                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Aurora Felice Castro Issa         | Nothing to be declared                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Bruno Vaz Kerges Bueno            | <p>Financial declaration</p> <p>A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry:- Pfiser: Eliquis; Alnylam: Patisiran.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Carlos Eduardo Rochitte           | Nothing to be declared                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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# Statement

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| Silvia Marinho Martins Alves | Nothing to be declared                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

## Statement

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## 1. Introduction

Significant advances in understanding cardiac amyloidosis (CA) have been made in recent years, leading to a thorough reformulation of its clinical significance. In addition to convincing evidence that CA is a relatively common cause of heart failure with preserved ejection fraction (HFpEF), we are witnessing the emergence of specific therapies that can change the course of the disease and prolong the survival of affected patients.

In parallel, relevant advances in cardiovascular imaging techniques have greatly contributed to earlier and more accurate identification of the disease. Cardiac scintigraphy with bone-seeking radiotracers has allowed non-invasive diagnosis of transthyretin (TTR) cardiac amyloidosis (ATTR-CA), eliminating the need for endomyocardial biopsy, which has greatly simplified the diagnostic flow.

Thus, we aim to present the most current recommendations for the diagnosis, prognostic staging, and treatment of CA based on a critical review of the current scientific evidence.

In this position paper, the recommendations and levels of evidence are classified according to the following parameters:

### Grades of recommendation:

**Grade I** – Conclusive evidence or, in its absence, general consensus that the procedure is safe and useful/effective

**Grade IIa** – Conflicting evidence and/or divergence of opinion about the procedure's safety and usefulness/effectiveness. The weight of evidence/opinion favors it and most studies/experts approve it

**Grade IIb** – Conflicting evidence and/or divergence of opinion about the procedure's safety and usefulness/effectiveness. Its safety and usefulness/efficacy are less well established, and opinion is not predominantly in its favor

**Grade III** – Evidence and/or consensus that the procedure is not useful/effective and, in some cases, may be harmful

### Levels of evidence:

**Level A** – Data obtained from several large randomized studies or concordant and/or robust meta-analysis of randomized clinical trials

**Level B** – Data obtained from less robust meta-analysis, from a single randomized study, or from non-randomized (observational) studies

**Level C** – Data obtained from a consensus of expert opinion

## 2. General Concepts

Systemic amyloidosis is caused by tissue deposition of fibrillar and insoluble protein aggregates in different organs, including the heart, which leads to organ dysfunction.<sup>1</sup> More than 30 types of amyloidogenic proteins have been described,<sup>2</sup> and five of them can affect the heart (immunoglobulin heavy and light chain (AL), TTR, amyloid A, and apolipoprotein A1), with the AL and ATTR types accounting for 95% of all CA cases, both in its wild type (ATTRwt) and hereditary/variant (ATTRv) forms.<sup>3-7</sup>

TTR is a protein composed of four monomers, which circulate as a tetramer.<sup>8</sup> It acts as a thyroxine and retinol (vitamin A) transporter under physiological conditions. The limiting step in the amyloid fibril formation rate is the tetramer's dissociation into monomers, which may involve proteolysis. Subsequently, partial denaturation of the monomer allows for incorrect assembly in various aggregate structures. Amyloidosis through mutation of the TTR gene (ATTRv) has an autosomal dominant character. This gene is

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located on chromosome 18, and more than 140 mutations of it have been described. By producing less stable TTR, aggressive and systemic amyloid deposition occurs.<sup>9</sup>

In ATTRwt, the amino acid sequence is normal and the process by which the wild-type protein becomes unstable and aggregates into amyloid fibrils is not completely clear. However, aging appears to be involved in its pathophysiology.<sup>8,9</sup>

In the AL form, amyloidogenic light chains originate from plasma cells or, less frequently, abnormal B lymphocytes. Thus, it is a clonal and neoplastic hematologic disease. In the heart, the deposition of amyloid fibrils causes structural damage by increasing cardiac and vascular rigidity, impairing cardiac contraction and relaxation and creating conduction disturbances. In parallel, circulating light chains are directly toxic to the myocardium through lysosomal dysfunction, defective autophagy, production of reactive oxygen species, cell and mitochondrial dysfunction, alterations in cardiomyocyte calcium homeostasis and, finally, cell death.<sup>10</sup>

Figure 1 represents the physiopathogenesis of transthyretin (TTR) and light chain (AL) cardiac amyloidosis.

Different subtypes of amyloidosis can lead to overlapping clinical manifestations and, once diagnosed, it is essential to correctly characterize the precursor protein to determine a specific treatment.<sup>11-13</sup>

Depending on the affected organs and degree of dysfunction, a wide spectrum of clinical manifestations can be observed, with a progressive and potentially fatal evolution. The main organs affected by systemic amyloidosis are the

heart, kidneys, eyes, central and peripheral nervous system, and liver. Nonspecific clinical manifestations are frequently observed and include fatigue, weight loss, peripheral edema and orthostatic hypotension. For this reason, late diagnosis is common. Thus, knowledge of the disease and a high degree of clinical suspicion are necessary to complete the diagnosis.

In ATTRv, depending on the mutation, the clinical picture is dominated by neuropathy or heart disease. In ATTRwt, heart disease is the main clinical manifestation, occurring mainly in elderly men who develop HFpEF without previously known risk factors.

Some extracardiac alterations may precede CA by several years, especially bilateral carpal tunnel syndrome and spontaneous rupture of the biceps tendon. It is essential to recognize such signs as part of the clinical picture of amyloidosis, which could lead to earlier diagnosis and specific treatments that could prevent the progression of heart disease.<sup>14,15</sup>

There is a higher incidence of ATTRwt in older patients, usually those over 70 years of age. However, since the clinical manifestations of ATTRv also usually occur in older adults, age should not be taken into account when differentiating between the two forms of ATTR. Regarding sex, there is a strong predominance (80% to 90%) of ATTRwt in men.

Regarding ATTRv, V30M is the most widespread mutation worldwide, being endemic in Portugal, Sweden, and Japan. It is probably the most common form in Brazil. Another common mutation is V122I, which is

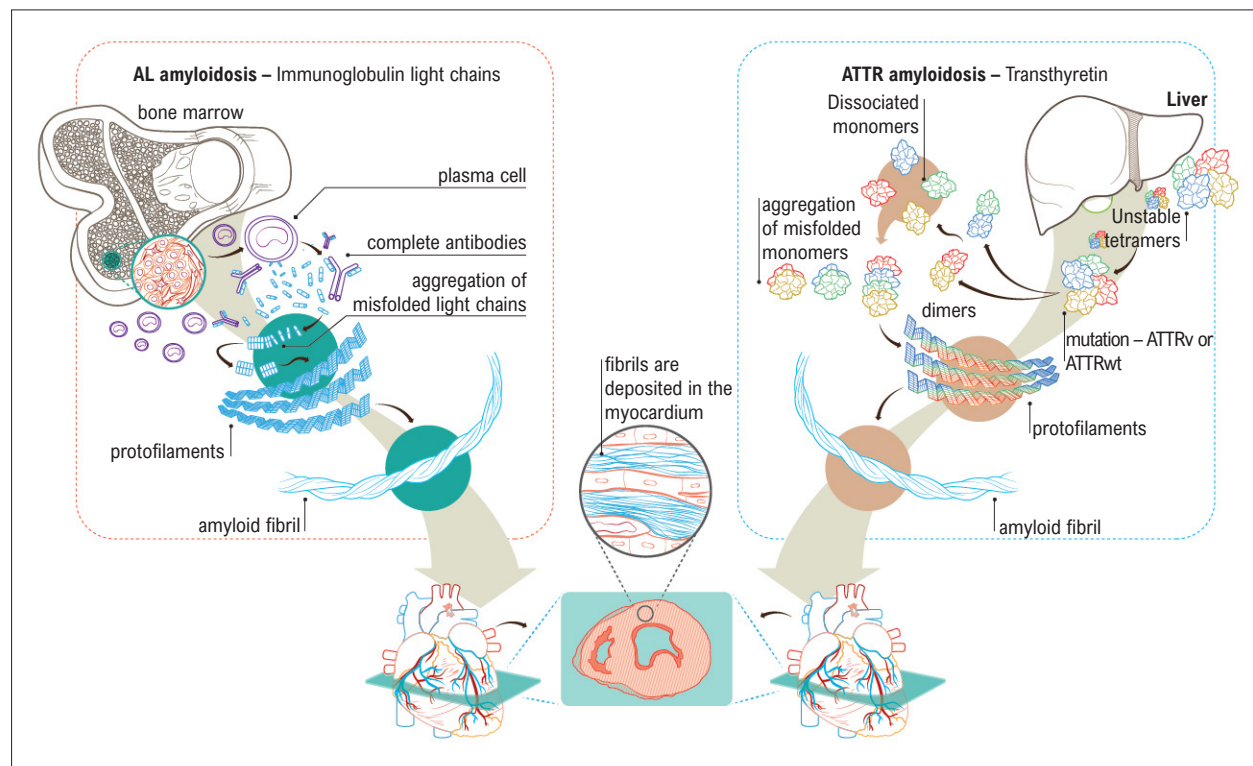


Figure 1 – Physiopathogenesis of cardiac amyloidosis.

present in 3.4% of African-Americans and is related to the development of heart disease in patients over 60 years of age.<sup>7,9,16,17</sup>

Table 1 summarizes the demographic and clinical characteristics of the AL, ATTRv, and ATTRwt subtypes.

The incidence of AL-CA is 6-10/million people/year and it is considered the main cause of CA.<sup>18</sup> With the development of less invasive CA diagnosis techniques for ATTR<sup>19</sup> and the prospect of more effective treatments, the number of diagnosed cases, especially of ATTRwt, has been increasing significantly.<sup>20</sup> AL is currently the most common cause of CA. Studies have found ATTR deposits in the heart of 13% of HFpEF patients<sup>21</sup> and in 25% of autopsied older adults,<sup>22,23</sup> mainly males.<sup>24</sup>

Thus, CA could be considered an underdiagnosed condition, rather than a rare disease. Recent data from the USA indicate a progressive increase in CA prevalence (from 18 to 55.2/100,000 person-years),<sup>25</sup> which supports this idea. The patient's journey to diagnosis is long; it is estimated that there is a delay of more than 2 years from symptom onset to diagnosis, with the involvement of an average of five different professionals.<sup>26</sup> Thus, it is essential to disseminate knowledge about CA; clinicians and cardiologists must give greater consideration to this entity, aiming at earlier diagnosis and adequate therapeutic guidance, thus improving patient prognosis and survival.

Regarding prognosis, AL affects multiple organs and is more aggressive than other subtypes. Late diagnosis is associated with high early mortality in the first 6 to 12 months due to advanced heart disease complications.<sup>7,8</sup> The median estimated survival for ATTRwt is 3.6 years, while the prognosis for ATTRv depends on the mutation. In cases of neurological phenotype, the progression of

neuropathy leads to sensorimotor disability, although mortality is more associated with cardiac impairment.<sup>12,13</sup>

### 3. Neurological Manifestations

Mutations in the TTR gene are associated with a wide variety of clinical manifestations, which reflect the deposition of the variant protein in different types of tissues. Cardiac and peripheral nervous system tissue are the most frequent; the former is particularly associated with the V122I mutation, and the latter with the V30M mutation.<sup>27</sup>

In this chapter, we will describe the main neurological manifestations suggestive of ATTRv.

Neurological manifestations in ATTRv can be divided into peripheral neuropathy, ie, late manifestations of central nervous system involvement linked to amyloid angiopathy, and central nervous system manifestations associated with oculoleptomeningeal infiltration.

#### 3.1. Peripheral Neuropathy

The involvement of the peripheral nerves in ATTRv is typically mixed sensory and motor length-dependent axonal neuropathy, ie, it initially affects more distal segments of the limbs, especially the lower ones, progressing to the proximal segments and upper limbs.<sup>28,29</sup>

In its early onset form (< 50 years of age), it is usually associated with the ATTRv V30M (V50M) mutation, and thin fibers with little or no myelination (autonomic, heat, cold, and pain) are initially affected. This is followed, in the degree that the disease progresses, by thick fibers, which are very myelinated and responsible for vibratory, postural-kinetic, and motor sensitivity. The initial symptoms are erectile dysfunction, early satiety, nausea, vomiting,

**Table 1 – Demographic and clinical presentation aspects, comparative between the forms AL, ATTRv and ATTRwt**

| Demographic Aspects                    | AL                                               | ATTRv                                                                          | ATTRwt                      |
|----------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------|
| Starting age (years)                   | > 60 years                                       | Depends on the genotype                                                        | > 70 years                  |
| Sex                                    | Slightly predominant in men                      | No predominance                                                                | Predominant in men          |
| Ethnic origin                          | None                                             | Most frequent mutation: African-Americans = Val122Ile<br>Portuguese = Val30Met | None                        |
| Prevalence/Incidence                   | 10 cases/million people/year, increases with age | Variable according to genotype                                                 | Unknown, increases with age |
| <b>Clinical aspects</b>                |                                                  |                                                                                |                             |
| HFpEF                                  | ✓                                                | ✓                                                                              | ✓                           |
| Peripheral and/or autonomic neuropathy | ✓                                                | ✓                                                                              | -                           |
| Proteinuria                            | ✓                                                | -                                                                              | -                           |
| Periorbital hyperpigmentation          | ✓                                                | -                                                                              | -                           |
| Macroglossia                           | ✓                                                | -                                                                              | -                           |
| Bilateral carpal tunnel syndrome       | ✓                                                | -                                                                              | ✓                           |
| Spontaneous biceps tendon rupture      | -                                                | -                                                                              | ✓                           |

HFpEF: heart failure with preserved ejection fraction.

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diarrhea, constipation, alternating diarrhea with constipation, orthostatic hypotension, syncope, arrhythmias, altered atrioventricular conduction, dry eye, urinary retention or incontinence, neuropathic pain, lost sensitivity to heat and cold, and significant weight loss. The initial phase can include painless lesions, plantar perforating ulcers and their repercussions, such as localized infections, cellulitis, osteomyelitis, and even septicemia. After a few years, gait instability and muscle atrophy appear, always evolving from distal to proximal segments.<sup>28,29</sup>

In its late forms, neuropathy compromises all types of fibers, although dysautonomia is not as important, at least in the initial phase. These forms can be associated with V30M or a number of other mutations, and the evolution is usually more aggressive. In a Brazilian study, 26% of ATTRv patients with V30M had late onset.<sup>30</sup>

Bilateral carpal tunnel syndrome is a frequent manifestation in ATTRv and may be the initial manifestation. Although it can be associated with any mutation, it is particularly important in some of them, including TTR V122I. This mutation appears to be frequent in Brazil and is associated with heart disease, which it can precede by several years.<sup>31</sup>

### 3.2. Central Nervous System Manifestations

Prolonging survival, which was initially associated with liver transplantation and is currently possible with new drugs, has enabled the appearance of previously uncommon manifestations. The long-term production of TTR by the choroid plexus (only 2% of the total) is associated with both amyloid angiopathy and meningeal infiltration. Amyloid angiopathy manifests as focal stroke-like, transient ischemic attack-like, or aura-like episodes, as well as an irritative epileptic type. In more severe cases, ischemia or even intracranial hemorrhaging can occur. The following neurological manifestations stand out: hearing impairment, migraine, dementia, cerebellar syndrome, myelopathy, and radiculopathy.

Some rare mutations have a predilection for oculocerebral involvement and lead to oculoleptomeningeal amyloidosis (ATTR Y69H: oculocerebral; Val30Gly: oculoleptomeningeal).<sup>32</sup>

**Stages of neuropathy:** The Coutinho stages for ATTRv are classified according to polyneuropathy. In stage 1

sensorimotor polyneuropathy affects gait, but walking support is not necessary. In stage 2, one or more support devices are needed for walking. In stage 3, the patient is confined to bed or a wheelchair.

### 3.3. Genetic Analysis

ATTRv is a disease of autosomal dominant inheritance but variable penetrance. It is mutation- and age-dependent, as well as regionally influenced.<sup>33</sup> The V30Met mutation, for example, has an 80% and 91% penetrance in Portugal in individuals aged 50 and 70 years, respectively. On the other hand, in Sweden, the values are 11% and 36%, respectively, for the same age groups.

At least 140 different mutations have been described to date, but not all are pathogenic. Some polymorphisms are well-defined, while the significance of others is still indeterminate.<sup>34</sup> This suggests that the diagnostic test must always include complete TTR gene sequencing and that care must be taken regarding the interpretation of rare or undescribed variants. Among pathogenic mutations, some predominantly cause neuropathy (V30Met), heart disease (V122I), or both (Leu58His) (Figure 2).<sup>35</sup> It should be considered, however, that the genotypic/phenotypic correlation is not strict.

A special topic among genetic aspects is pre-symptomatic testing, ie, testing the relatives of individuals known to be affected. Unlike diagnostic testing, it must be performed by specialized personnel and there must be a support team, including a psychologist. It must include a preparation phase, pre-diagnosis, genetic testing and a post-result support phase. Such testing should not be performed on children and should only be applied to individuals who expressly state that it is their wish and are considered psychologically prepared for the results.<sup>36</sup>

## 4. Cardiovascular Manifestations

CA progresses as the cardiac extracellular matrix is infiltrated by amyloid fibrils, resulting in a progressive increase in the thickness of the ventricular wall and a marked increase in chamber stiffness, resulting in impaired diastolic function, which leads to heart failure with restrictive physiology.<sup>37</sup> Systolic function is also compromised and is usually indicated

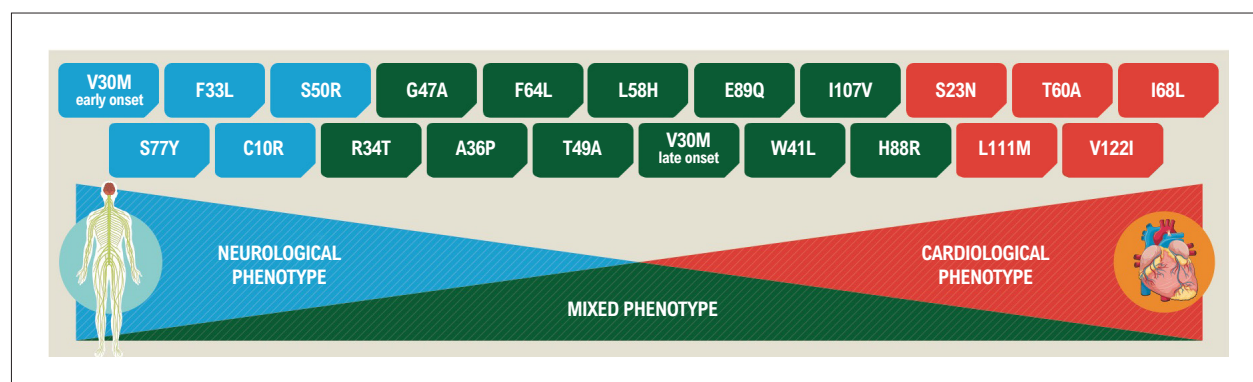


**Figure 2** – Distribution of hereditary transthyretin amyloidosis mutations associated with neurological, cardiological, and mixed phenotypes.

by abnormal longitudinal tension despite normal ejection fraction, which may be preserved until the late stages of the disease.<sup>38-40</sup> Atrial amyloid infiltration is frequent, leading to contractile dysfunction. Deposits can also occur in the heart valves, usually without causing major dysfunctions, as well as in the perivascular region.<sup>3</sup>

Thus, the most frequent clinical manifestation is heart failure syndrome, most commonly with preserved ejection fraction (HFpEF), although a drop in ejection fraction can occur in more advanced stages of the disease. The clinical syndrome may present predominant left HF symptoms with pulmonary congestion (dyspnea, orthopnea, paroxysmal nocturnal dyspnea), right HF symptoms (edema, ascites, hepatomegaly, increased abdominal volume, early satiety, severe fatigue), or both sets of symptoms. Cardiac amyloidosis should be considered in the differential diagnosis of HFpEF etiology in older men,<sup>41</sup> particularly when there is no apparent history of systemic arterial hypertension or the thickness of the interventricular septum increases  $\geq 12$  mm, which raises the possibility of infiltrative cardiomyopathy.<sup>21</sup>

Syncope and orthostatic hypotension are common symptoms and indicate the presence of dysautonomia. One typical clinical aspect that may raise the suspicion of amyloidosis is the need for dose reduction or discontinuation of antihypertensive drugs in patients previously diagnosed with systemic arterial hypertension, especially beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.<sup>15</sup>

Amyloid infiltration can also occur, causing cardiac conduction system disease from the early stages, with variable degrees of atrioventricular block, which results in high-risk bradycardia in some cases, requiring pacemaker implantation. Another important change is the hardening of the atrial walls, which leads to high rates of atrial arrhythmias, including atrial fibrillation, as well as atrial thrombi, with cardioembolic stroke being a common clinical manifestation, even in individuals with sinus rhythm. Complex ventricular arrhythmias seem to be frequent in advanced stages of the disease, an aspect that is best documented in AL amyloidosis.

## 4.1. Increased Suspicion of Cardiac Amyloidosis

CA, particularly the ATTR type, is often underdiagnosed due to factors associated with the medical evaluation, in addition to the characteristics of the disease itself, including: fragmented knowledge among different specialties and subspecialties, a scarcity of centers and specialists dedicated to the management of this disease, the mistaken belief that CA is a rare and incurable disease, and the phenotypic and genotypic heterogeneity of ATTR-CA.<sup>42</sup> It should be pointed out that early CA diagnosis is critical, since the prognosis rapidly worsens with continued amyloid protein deposition and increasing organ dysfunction.

Thus, recognizing “red flags” can help diagnose CA in HF patients,<sup>35,43</sup> the most relevant of which are summarized in Table 2.

**Table 2 – Clinical clues that should raise suspicion of cardiac amyloidosis in patients with manifestations of heart failure**

|                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical history and physical examination</b>                                                                                                                            |
| HFpEF, particularly in men > 65 years of age                                                                                                                                |
| Intolerance to ACEi/ARB/ARNi and/or beta-blockers                                                                                                                           |
| Unexplained LV block with prior pacemaker implantation                                                                                                                      |
| Bilateral carpal tunnel syndrome                                                                                                                                            |
| Spinal canal stenosis                                                                                                                                                       |
| Biceps tendon rupture                                                                                                                                                       |
| Unexplained sensorimotor polyneuropathy (paraesthesia, neuropathic pain, weakness)                                                                                          |
| Autonomic dysfunction (postural hypotension, alternating diarrhea with constipation, erectile dysfunction)                                                                  |
| Spontaneous/minimal trauma periorbital purpura                                                                                                                              |
| Macroglossia                                                                                                                                                                |
| Vitreous opacity and pupillary changes                                                                                                                                      |
| Family history of cardiomyopathy or polyneuropathy                                                                                                                          |
| <b>Imaging examinations</b>                                                                                                                                                 |
| Infiltrative phenotype on echocardiogram (IVS $\geq 12$ mm), biventricular hypertrophy, myocardial hyperrefringence, valve thickening, thickening of the interatrial septum |
| Concentric thickening of the LV walls with reduced or normal QRS amplitude in proportion to the increase in LV wall thickness                                               |
| <b>Combined clues</b>                                                                                                                                                       |
| Low flow/low gradient aortic stenosis in patients > 60 years of age                                                                                                         |
| Clinical presentation of late-onset hypertrophic cardiomyopathy in patients > 60 years of age                                                                               |

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNi: Angiotensin receptor neprilysin inhibitor; HFpEF: heart failure with preserved ejection fraction; IVS: interventricular septum; LV: left ventricle.

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Bilateral carpal tunnel syndrome, often one of the first indicators of ATTR-CA, is the most common non-cardiac manifestation and can precede symptoms of HF by several years. A recent study found that approximately 50% of individuals with ATTRwt had carpal tunnel syndrome 5 to 7 years prior to diagnosis.<sup>44</sup> Lumbar stenosis and atraumatic rupture of the biceps tendon have also been identified as clinical manifestations of extracardiac deposition in ATTRwt. Biceps tendon rupture may occur in up to 33% of ATTRwt cases.<sup>45</sup> On the other hand, macroglossia and periorbital purpura are highly specific to AL-CA, although they occur in only 15% of cases.<sup>46</sup> Sensorimotor polyneuropathy or dysautonomia in HF patients should raise suspicion of CA.<sup>47,48</sup>

Other warning signs may emerge from typical changes in routine complementary cardiac examinations, which are covered as specific topics in this document.

It should also be pointed out that CA can often simulate other heart diseases. Amyloidosis should be considered one possible etiology for patients with a hypertrophic cardiomyopathy phenotype, particularly if it developed after 60 years of age. The asymmetrical pattern of myocardial hypertrophy in ATTR-CA patients differs from that of AL-CA patients, which is usually symmetrical. In a study that compared 263 confirmed ATTR-CA patients with 50 AL-CA patients, among the ATTR cases, asymmetric hypertrophy was present in 79%, symmetric hypertrophy in 18%, and no myocardial hypertrophy in 3%.<sup>49</sup>

Older patients with severe low-flow/low-gradient aortic stenosis may have CA in 10% to 15% of cases, with an unfavorable prognosis.<sup>50</sup>

## 5. Additional Diagnostic Examinations

### 5.1. Electrocardiogram

The electrocardiogram (ECG) is an essential test for diagnostic assessment and therapeutic planning, and its interpretation in conjunction with clinical and echocardiographic information is important. Although low-voltage ECG has great specificity in diagnosing myocardial infiltration secondary to CA, this is not the most prevalent finding. A lack of R-wave progression in precordial leads, which simulates an electrically inactive anteroseptal zone (pseudoinfarction pattern) is a much more frequent finding, with a prevalence of 60% to 70% in confirmed CA diagnoses, regardless of the type (Figure 3).

In ATTR-CA, less than 40% of patients with a biopsy-confirmed diagnosis have low-voltage ECG.<sup>51</sup>

Thus, without low-voltage ECG criteria or signs of left ventricle (LV) overload, diagnostic suspicion of CA should not be ruled out, especially ATTR-CA. Disproportionate voltage in relation to myocardial thickness is also an important warning sign, reaching a prevalence of 73% to 80% in CA patients, regardless of type.<sup>52,53</sup>

Among cardiac rhythm alterations, atrial fibrillation is more prevalent in ATTR patients, as well as atrioventricular blocks.

### 5.2. Echocardiogram

Echocardiography should be performed in all patients with clinical suspicion of the disease. Classic CA findings are usually present at an advanced stage of the disease and

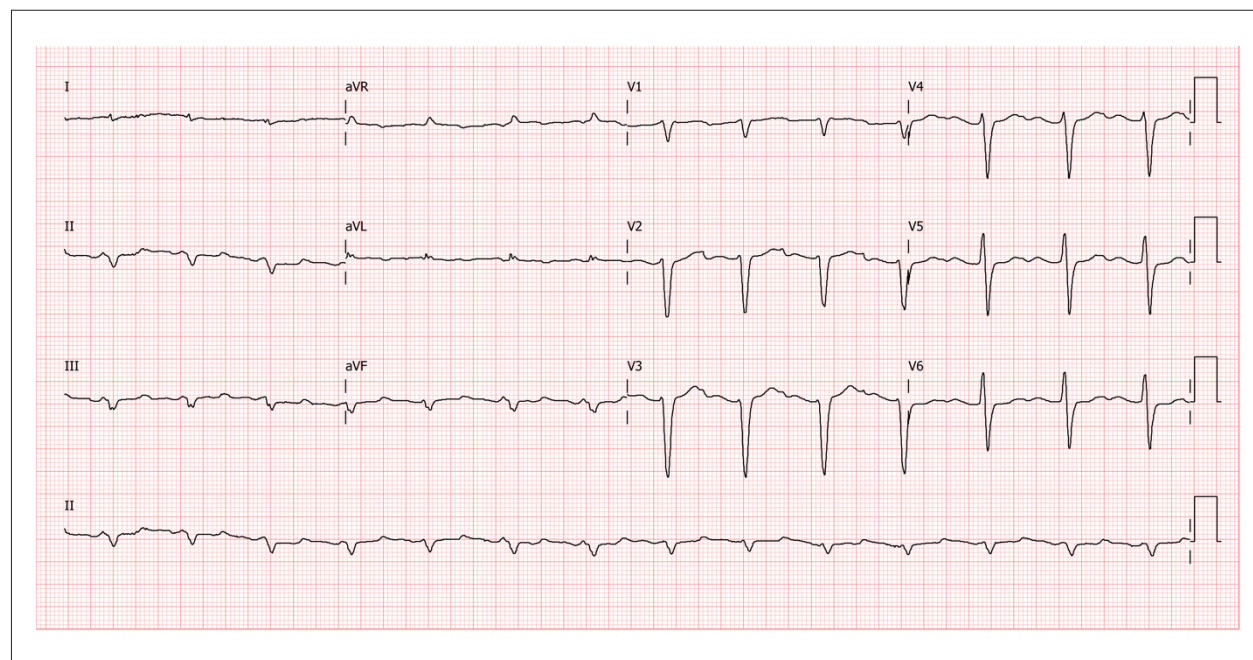


**Figure 3** – Sample electrocardiogram image from a patient with wild-type transthyretin cardiac amyloidosis, showing low voltage in peripheral leads, no R-wave progression in precordial leads V1 to V3 (pseudoinfarction pattern) and first degree atrioventricular block. (Image from the authors' personal archive)

characterize a restrictive, infiltrative-type cardiomyopathy. The dimensions of the LV are not increased, volumes are normal or reduced, and there is a thickening of the ventricular walls. Increased atrial dimensions are common, reflecting early and progressive diastolic dysfunction, with increased filling pressures. Atrioventricular valves may be thickened and mitral and tricuspid regurgitations are functional. There may also be signs suggestive of infiltration of the interatrial septum, as well as an increase in the pulmonary artery systolic pressure. The right ventricle (RV) may also be affected. Pleural and pericardial effusions are very common and, in cases involving intense tissue infiltration, a granular sparkling appearance can be observed (Figure 4)<sup>35,54</sup>

The LV ejection fraction is normally preserved until the more advanced stages of CA, although the longitudinal contractile function is reduced early.<sup>55</sup> Quantitatively, systolic function can be assessed in 2D mode by calculating LV stroke volume and ejection fraction, as well as by Doppler-derived techniques such as estimating left ventricular dP/dt.<sup>56</sup>

Assessing the ventricular diastolic filling pattern is essential and often demonstrates some degree of diastolic dysfunction. In the initial phases, alterations compatible with type I diastolic dysfunction can be observed (inversion of the mitral inflow E/A wave ratio, prolongation of the isovolumetric relaxation time, and early diastolic deceleration. In tissue Doppler recording of myocardial velocities, E' wave deceleration may be observed (Figure 5).

As the disease progresses, a pseudonormal pattern of diastolic dysfunction (normal E/A wave ratio and normal deceleration time) may develop as a result of increased left atrial pressure.

In more advanced phases of the disease, there is a restrictive pattern of ventricular filling (E/A wave ratio > 2, decreased relaxation time, and an increased deceleration slope of the E-wave).

Analyzing myocardial deformation allows the early identification of signs of myocardial dysfunction in relation to LV ejection fraction.<sup>57-59</sup> Global longitudinal strain – a function predominantly performed by the endocardium – is reduced early.<sup>60</sup> Regional myocardial deformation also frequently presents an apical sparing (“cherry on top”) pattern.<sup>61,62</sup> This aspect is best visualized in a parametric (“bull’s eye”) image of the LV (Figure 6).

Other analyses of myocardial deformation, such as RV systolic function,<sup>63</sup> atrial function,<sup>65</sup> and estimating myocardial work,<sup>59</sup> have been applied to CA patients and have shown good diagnostic accuracy.

## 5.3. Cardiac Magnetic Resonance

Cardiovascular magnetic resonance (CMR) allows accurate assessment of myocardial tissue changes in CA.<sup>65</sup> Classically, the deposition of myofibrils leads to an increase in the thickness of the LV myocardial wall and the interatrial septum, which can be visualized by the morphological techniques of CMR.<sup>66,67</sup> Another tissue change is increased total water content in the myocardium, which may be derived from increased extracellular volume, a direct result of protein deposition and the water it attracts through osmosis, as well as from the increased intracellular water in myocytes suffering the cytotoxic effects of the deposition or even from decreased myocardial perfusion (increased distance from the capillaries and/or obstruction by the deposition).

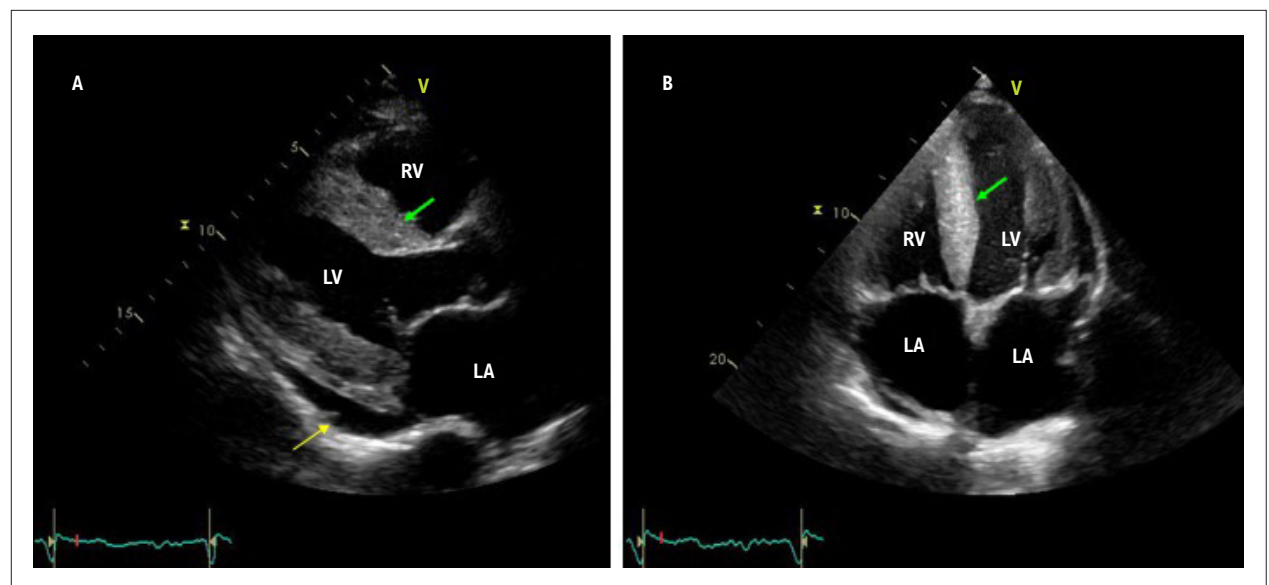


**Figure 4** – Classic echocardiographic presentation of cardiac amyloidosis. In A, the longitudinal parasternal projection shows a normal-sized left ventricle (LV) with increased wall thickness and a granular aspect in the interventricular septum (green arrow). There are also signs of left atrium (LA) enlargement and mild pericardial effusion (yellow arrow). In B, the apical projection shows large atria, normal-sized ventricles, and increased wall thickness, as well as a granular aspect in the interventricular septum (green arrow). The mitral and tricuspid valves are slightly thickened. LV: left ventricle; RV: right ventricle; LA: left atrium. (Images from the authors' personal archive).

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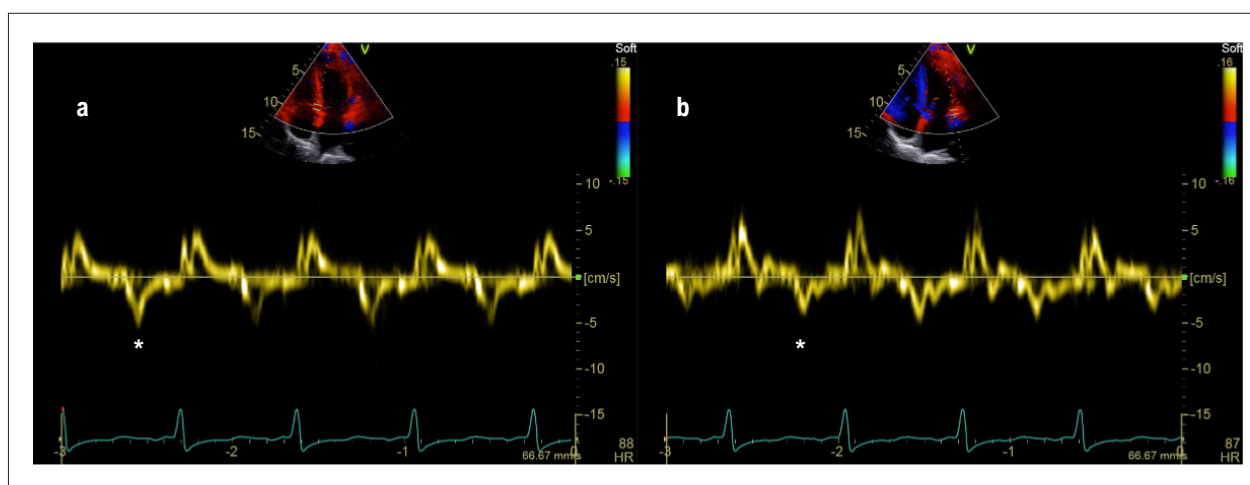


**Figure 5** – Tissue Doppler images of the mitral annulus. There is E' wave(\*) deceleration in both the medial (a) and lateral (b) mitral annulus. Both speeds are below 4 cm/s (right ventricle > 8 cm/s). (Images from the authors' personal archive).

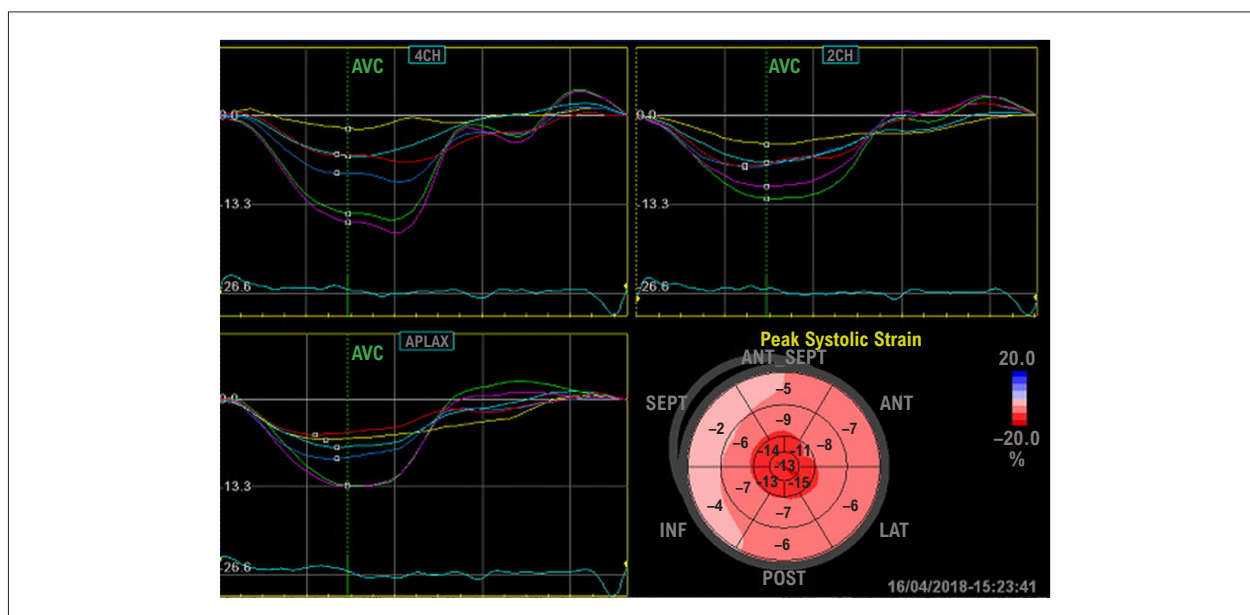


**Figure 6** – Analyses of global and regional LV myocardial deformation in a patient with cardiac amyloidosis, showing the parametric graphical representation (bull's-eye), apical segments in dark red (preserved values), and basal segments in light red (reduced values) in the “cherry-on-top” pattern. (Image from the authors' personal archive)

The global increase in myocardial tissue water content leads to an increase in mean hydrogen relaxation time, whether T1 (longitudinal) or T2 (transverse).<sup>68</sup> However, the most dramatic and relevant myocardial tissue change in CA is the extreme increase in myocardial extracellular volume, which occurs in the clinical stages of the disease, not only due to the deposition of amyloid fibrils, but also to myocardial fibrosis repair.

Thus, the combination of myofibril deposition and interstitial fibrosis can be detected easily and precisely, and can even be quantified by late enhancement (LE) techniques<sup>67,69</sup> and by calculating the extracellular myocardial volume.<sup>70-72</sup>

As an example, normal values for myocardial extracellular space are approximately 25%, while in CA they can reach 60% (mainly in ATTR-CA).<sup>72,73</sup>

The CMR contrast medium is based on gadolinium, which is bound to a macromolecular chelator that does not allow it to pass through the entire cell membrane. Thus it is distributed exclusively in the myocardial extracellular volume. The distribution pattern in the LE image can raise suspicion of CA (global subendocardial, apical non-involvement of the LV, and distribution outside the coronary vascular territory).<sup>67</sup>

### 5.3.1. Assessment of Cardiac Morphology and Function

CA can modify the appearance of all cardiac chambers.<sup>74,75</sup> Changes in the atrial plane can be observed the initial stages, including dilation and apparent thickening of the interatrial septum, which, in most cases, consists of fat.<sup>74</sup> In later stages of cardiac impairment, when atrial function decreases, signs of slow flow and thrombi in the left atrial appendage can be seen, which may not appear in cardiovascular magnetic resonance imaging if there are artifacts related to rhythm or if specific series are not used for this purpose.

CA is also commonly associated with increased myocardial thickness, which is, in most cases, more expressive than in cases secondary to hypertension. The thickness of the cardiac muscle is generally greater in ATTR-CA than AL-CA.<sup>52,76</sup> The increased thickness may be concentric or eccentric,<sup>74,75</sup> and may involve the RV.<sup>74,75</sup> The ejection fraction may be preserved for a long time, and the earliest changes in ventricular function include diastolic restriction and changes in ventricular strain.<sup>75,76</sup>

As a result of diastolic dysfunction, it is not uncommon to observe pericardial or pleural effusions.<sup>74</sup> Assessing morphological characteristics with cardiovascular magnetic resonance imaging (Figure 7) is helpful and can suggest the diagnosis. However, tissue characterization is usually performed with LE and T1 mapping techniques, which we will discuss below in other sections.

### 5.3.2. Assessment with Late Enhancement

The LE technique after gadolinium contrast injection has been widely recognized as a pillar of CA imaging diagnosis.<sup>77,78</sup> When crossing the interstitial space in normal tissue, gadolinium contrast medium is not delayed and the agent quickly diffuses, leaving normal tissue dark. When there is amyloid deposition in the interstitial space, it begins to slow the transit of the gadolinium-based contrast agent, and the myocardium “shines” in the dedicated sequences, for which an anatomopathological correlation has been demonstrated.<sup>65</sup> Subendocardial, transmural and focal patterns of amyloid infiltration have been described, the latter being less frequent (Figure 8).<sup>67</sup> A recent meta-analysis found that LE

had a sensitivity and specificity of 85% and 92%, respectively, for amyloidosis.<sup>79</sup>

In a series of 250 patients with different forms of amyloidosis, LE with a transmural pattern was associated with a 5.4 times greater risk of death (CI: 2.1-13.7;  $p < 0.0001$ ).<sup>80</sup> In addition, LE has an incremental prognostic effect for cardiac markers in AL-CA<sup>81</sup> or in isolation.<sup>82</sup>

### 5.3.3. T1 Mapping

Different groups have investigated the utility of cardiovascular magnetic resonance-derived T1 maps to improve diagnostic and prognostic performance in CA.<sup>70,71,73,83,84</sup> Both native T1 data, which do not require a contrast agent, as well as extracellular volume data have effectively identified patients with CA, who show markedly higher native T1 and extracellular volume values than healthy controls.<sup>70,73,83</sup> These changes can be detected before LE.<sup>70,72,73</sup> Therefore, combining native T1 mapping and extracellular volume measurements can help determine the amyloid burden and confirm the diagnosis of CA.<sup>85,86</sup>

### 5.4. Cardiac Scintigraphy with Bone-seeking Radiotracers

Technetium-99m-labeled bisphosphonate-derived radiotracers, originally developed for bone imaging, have found a new role as a non-invasive diagnostic tool for ATTR-CA.<sup>1-7</sup> Bone radiotracers safely allow non-invasive diagnosis of ATTR-CA once the presence of monoclonal gammopathy is excluded.<sup>91</sup>

The main <sup>99m</sup>Tc-labeled bone radiotracers used in ATTR-CA diagnosis are <sup>99m</sup>Tc-pyrophosphate, <sup>99m</sup>Tc-DPD (3,3-diphosphono-1,2-propanedicarboxylic acid), and <sup>99m</sup>Tc-HMDP (99mTc-labeled hydroxymethylene diphosphonate).<sup>1-7</sup> <sup>99m</sup>Tc-pyrophosphate is the only one of these available in Brazil. It should be pointed out that although <sup>99m</sup>Tc-MDP (99mTc-labeled methylene diphosphonate) has proven efficient for bone scintigraphy, it has low sensitivity for diagnosing ATTR-CA and should not be used for this purpose.<sup>89</sup>

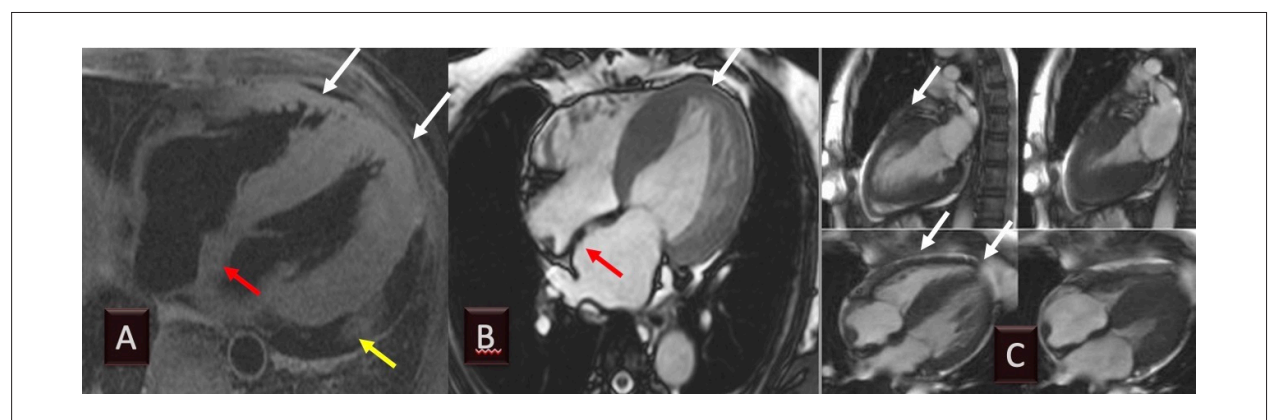


**Figure 7** – Example of cardiovascular magnetic resonance imaging of transthyretin amyloidosis, showing pericardial effusion (A, yellow arrow and C), increased atrial dimensions (A and B), and increased interatrial septum (A and B, red arrows) and ventricular wall thickness (A to C, white arrows). Diastolic function is reduced, but contractility may be preserved until the later stages of the disease. (Image from the authors' personal archive).

## Statement

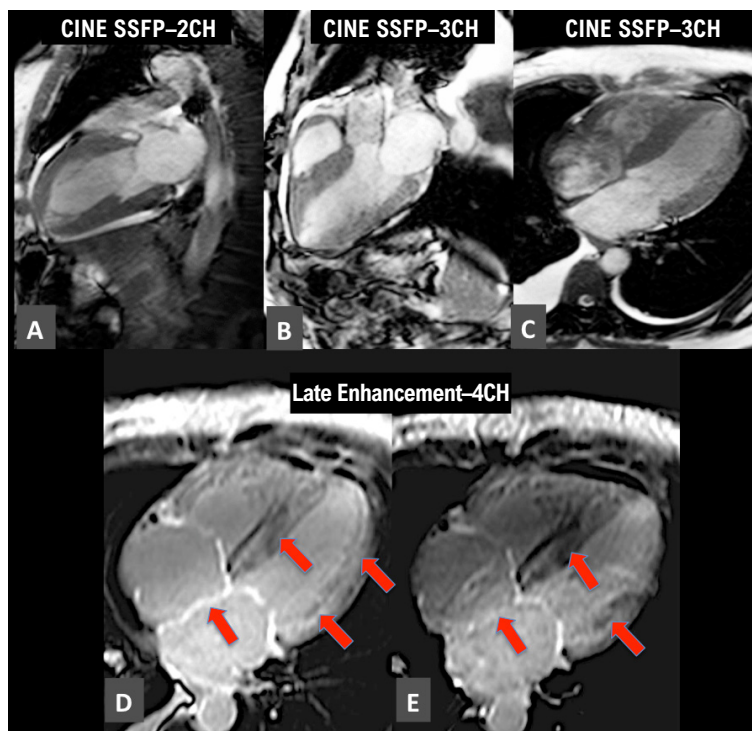


**Figure 8** – Example of a patient with ATTR transthyretin with concentric hypertrophy of the left ventricle and enlargement of both atria in cine images (A to C). Late enhancement shows a predominantly diffuse transmural pattern (red arrows, D and E). (Image from the authors' personal archive).

Although the structural component of the amyloid deposition to which  $^{99m}\text{Tc}$ -pyrophosphate binds in the heart is unknown, it is widely accepted that a calcium-dependent uptake mechanism is involved.<sup>93</sup> Several binding sites have been found in animals: microcalcifications, calcium deposits, intracellular pyrophosphate, and intracellular macromolecules. The mechanism of  $^{99m}\text{Tc}$ -pyrophosphate uptake in the myocardium is probably related to the presence of microcalcifications.<sup>88</sup> ATTR-CA involves more microcalcifications than AL-CA and has greater  $^{99m}\text{Tc}$ -pyrophosphate uptake, while AL-CA has little or no affinity for bone radiotracers. In addition, ATTR-CA has a more indolent evolution, providing more microcalcifications and, consequently, greater radiotracer accumulation.

Although the echocardiogram and cardiac magnetic resonance findings may be indicative of CA, they cannot differentiate ATTR-CA from AL-CA. This is the main advantage of  $^{99m}\text{Tc}$ -pyrophosphate cardiac scintigraphy: it is a simple, easy, widely available method with low dosimetry that can differentiate ATTR-CA from AL-CA noninvasively and with high specificity, and thus guide treatment. This differentiation is useful, since AL-CA and ATTR-CA have completely different prognostic and therapeutic implications.

The role of bone radiotracers in ATTR diagnosis was recently re-evaluated by an international group of several centers with expertise in CA: in a cumulative analysis of 1,217 patients, 867 with biopsy-confirmed amyloidosis and 360 with non-amyloid cardiomyopathy, scintigraphy was highly

sensitive (99%) and specific (86%) for ATTR-CA.<sup>19</sup> This study further demonstrated that the combined finding of positive bone radiotracer scintigraphy in patients with no evidence of detectable monoclonal protein in urine or serum (serum free light chain analysis and electrophoresis with immunofixation) was 100% specific for ATTR-CA, leading the authors to conclude that scintigraphy allows for accurate detection without the need for cardiac biopsy.<sup>19</sup> Another recent study with pooled cases from three U.S. centers showed that, among a total of 171 patients (121 ATTR, 34 AL, and 16 non-amyloid HFpEF),  $^{99m}\text{Tc}$ -pyrophosphate had an 88% sensitivity and 88% specificity for ATTR when only visual assessment was used (score  $\geq 2$ ).<sup>94</sup> When semiquantitative analysis was used (heart/contralateral ratio  $> 1.6$ ), its sensitivity and specificity were 91% and 92%, respectively, for detecting ATTR. Furthermore, when considering all variables, a heart/contralateral ratio  $\geq 1.6$  was predictive of worse survival in ATTR-CA patients.<sup>94</sup> Vranian et al.<sup>95</sup> also demonstrated that, in patients with suspected CA, the intensity of cardiac  $^{99m}\text{Tc}$ -pyrophosphate uptake was predictive of overall mortality and hospitalization for HF. In these studies, combined assessment of the intensity of radiotracer uptake in the myocardium (heart/contralateral ratio) with anatomical, functional and biomarker variables improved risk stratification.

### 5.4.1. Recommended Technical Aspects for Image Acquisition

No preparation required. Images are obtained after intravenous administration of 10 to 25 mCi (370 to

925 Mbq) of  $^{99m}\text{Tc}$ -pyrophosphate (dosimetry: 3.2 mSv for the whole body for 15 mCi). Flat and single photon emission computed tomography (SPECT) images of the chest are taken 1 and 3 hours after administration of the radiopharmaceutical.

- **Planar chest images:** can be obtained in the anterior, left anterior oblique, and left lateral projections using  $^{99m}\text{Tc}$  photopic (140 keV, 15% window), low energy/high resolution collimator and a  $256 \times 256$  matrix, 500,000–750,000 counts.
- **SPECT chest images:** obtained with a  $128 \times 128$  matrix ( $64 \times 64$  is acceptable), 180-degree rotation from right anterior oblique to left posterior oblique (360-degree is acceptable), 1 image every 3 to 6 degrees. If available, SPECT/CT images (SPECT combined with computed tomography) provide greater confidence for interpreting the images.
- **Minimum recommended images:** 1 h SPECT and 1 h and 3 h flat images in the anterior projection. The use of SPECT images is recommended to differentiate diffuse uptake of the radiopharmaceutical in the myocardium from its persistence in the blood pool, focal uptake by myocardial infarction, and bone overlay. In addition, 1 h and 3 h flat images are useful for quantifying and monitoring the blood pool washout, which is variable, eg, much slower in patients with renal failure.

## 5.4.2. Image Analysis

- **Semiquantitative analysis (1 h planar image):** For  $^{99m}\text{Tc}$ -pyrophosphate, the semiquantitative analysis was defined as the ratio between uptake in the cardiac projection and uptake in the contralateral hemithorax, measured in a planar 1 h image in the anterior view. To do this, a circular (or elliptical) area of interest is drawn over the cardiac projection without including the sternum, avoiding the inclusion of both the adjacent lung and areas of focal uptake in the costal arches. An identical (“mirror”) area of interest is placed in the contralateral hemithorax following the same procedure. The count within the cardiac area of interest is divided by the count in the contralateral area of interest, thus obtaining the heart/contralateral (H/CL) ratio.  $\text{H/CL} \geq 1.5$  at 1 h identifies ATTR-CA with high accuracy if systemic AL-CA has been excluded<sup>90,91</sup> (Figure 9).
- **Visual graduation (3 h image):** visual grading is performed by comparing cardiac uptake with physiological uptake in adjacent costal arch, and can be performed with planar images in the anterior projection, in SPECT images, or even in whole-body images obtained 3 h after injecting the radiopharmaceutical. Uptake intensity is defined as grade 0 (no myocardial uptake), grade 1 (myocardial uptake lower than that of adjacent costal arch), grade 2 (uptake similar to that of costal arch), and grade 3 (greater than that of the costal arch). Grades 2 or 3 are strongly suggestive of ATTR if monoclonal gammopathy has been excluded (Figure 9).

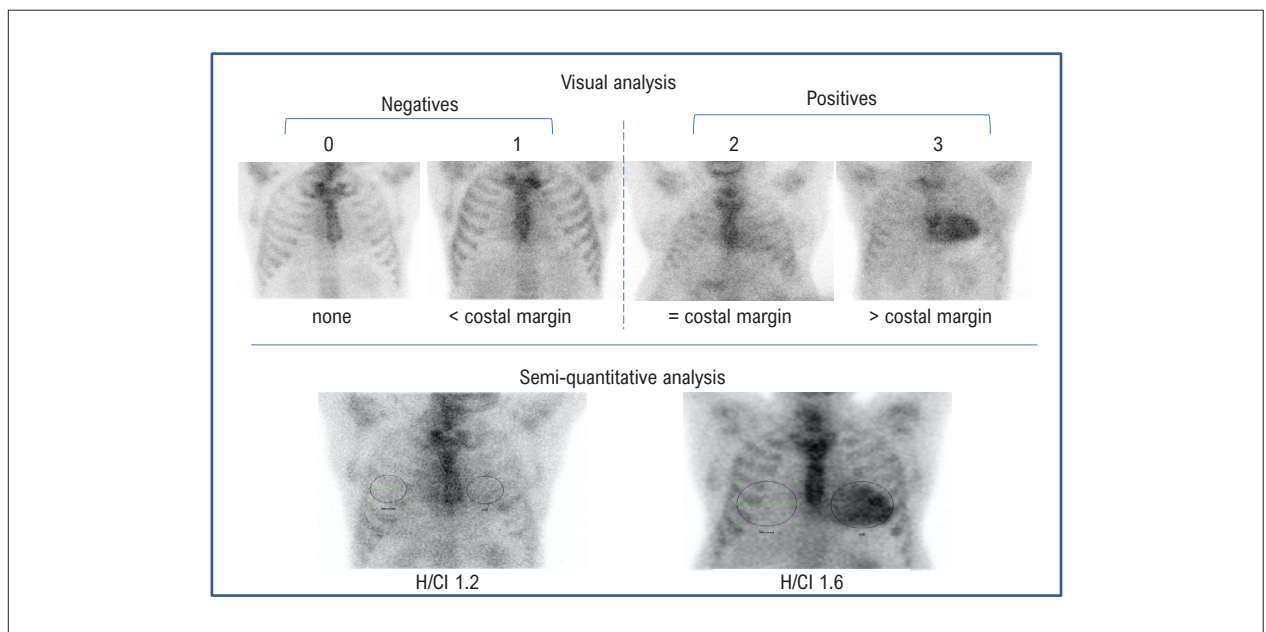


**Figure 9** –  $^{99m}\text{Tc}$ -pyrophosphate cardiac scintigraphy in patients with suspected cardiac amyloidosis (flat images in anterior chest view taken 3 h after administration) showing negative and positive transthyretin (ATTR) amyloidosis cases. Visual analysis: images on the left: negative ATTR cases (grades 0 and 1); images on the right: positive ATTR cases (grades 2 and 3). Semi-quantitative analysis: on the left, negative ATTR case (heart/contralateral ratio = 1.2 – in this case, the SPECT images showed activity in the blood pool and not in the heart walls); on the right, positive ATTR case (heart/contralateral ratio = 1.6 – SPECT imaging confirmed uptake in the left ventricle walls).

In visual interpretation, cardiac uptake equal to (grade 2) or greater (grade 3) than that of the costal margins is important for ATTR diagnosis. In semiquantitative analysis, heart/contralateral count ratios  $\geq 1.5$  in 1 h images and  $\geq 1.3$  in 3 h images are considered highly suggestive of ATTR when confirmed by SPECT images. (Images from the authors' personal files)

## Statement

### 5.4.3. False-Positive ATTR

The operational characteristics of bone scintigraphy are very favorable for use in clinical diagnosis, with a specificity of 100% for ATTR when the uptake is grade 2 or 3 and there is no monoclonal gammopathy. However, it must be pointed out that failure to exclude monoclonal gammopathy (either due to inappropriate use or to misinterpretation of laboratory tests) entails a risk of inaccurate diagnosis. The most common cause of ATTR misdiagnosis is AL-CA. Recent studies indicate that up to 22% of patients with AL-CA may have grade 2 or 3 uptake in  $^{99m}\text{Tc}$ -pyrophosphate scintigraphy.<sup>6</sup> It should also be pointed out that SPECT imaging is crucial to differentiate abnormal myocardial uptake from residual uptake in the blood pool (Figure 10). Table 3 lists the main causes of false-positive diagnosis with  $^{99m}\text{Tc}$ -pyrophosphate scintigraphy.

Finally, scintigraphy is not recommended for patient follow-up, since there is no current evidence of a correlation between a change in image pattern and disease progression or response to treatment.<sup>87,90</sup>

Table 4 summarizes the main findings and practical guidelines for image acquisition and analysis in CA diagnosis.

### 5.5. Biomarkers

No specific laboratory marker can be used to diagnose CA.

Troponin and natriuretic peptides have been found useful for assessing cardiac damage due to amyloidosis and are non-invasive, accessible, and relatively low-cost diagnostic aids.<sup>96</sup> When these biomarkers detect persistent changes, it is a warning sign of cardiac damage due to amyloidosis.

#### 5.5.1. Natriuretic Peptides

Analysis of data from the THAOS (Transthyretin Amyloidosis Outcomes Survey) registry showed that natriuretic peptide levels can be used as a diagnostic aid, with higher values observed in mutations associated with amyloid cardiomyopathy, such as V122I and late-onset V30M, than in those predominantly associated with neurologic manifestations, such as early-onset V30M. Higher levels of biomarkers were also observed in ATTRwt than ATTRv. However, it was observed that even in patients with a predominantly neurological phenotype, 45% to 90%

had altered levels of these biomarkers, indicating some degree of subclinical myocardial involvement.<sup>97</sup>

Higher NT-proBNP values have been observed in AL-CA than ATTR-CA. This is because amyloidogenic light chains modulate p38 mitogen-activated protein kinase, which directly promotes NT-proBNP expression. Thus, despite the same degree of hemodynamic changes in both forms of amyloidosis, serum levels of NT-proBNP may be higher in AL-CA.<sup>98</sup>

Of note, patients with HFpEF due to ATTR have disproportionately high NT-ProBNP values with respect to HF severity compared to patients with non-amyloid HFpEF.<sup>99</sup>

#### 5.5.2. Troponins

Mild and persistent elevation of troponin levels is frequently observed and suggests subclinical myocardial damage in several non-ischemic cardiomyopathies.<sup>100</sup> However, it has been reported that levels are higher in CA than in other forms of cardiomyopathy.<sup>21</sup> A study of patients with hypertrophic cardiomyopathy who underwent endomyocardial biopsy identified markedly higher troponin levels in CA patients than in those with amyloid-free heart disease and had high diagnostic sensitivity.<sup>101</sup>

Several mechanisms have been postulated to explain the elevated troponin levels in these patients: myocardial ischemia, increased wall stress, direct myocyte damage by inflammatory cytokines and/or oxidative stress, neurohormonal activation, and microvascular dysfunction in heart failure. Microvascular dysfunction in amyloidosis is presumably caused by interstitial and perivascular deposition, increased ventricular filling pressure, and endothelial dysfunction due to immunoglobulin-induced toxicity in AL-CA. In addition, it has also been found that light chains have a direct cardiotoxic effect, regardless of extracellular deposition of fibrils, which might explain the higher troponin levels in AL-CA than in ATTR-CA, in which mild and persistent elevation is usually observed.<sup>101</sup>

It is important to point out that many ATTR patients have comorbidities, such as ischemic cardiomyopathy, which can cause altered troponin values. Therefore, troponin levels should not be used to rule out or confirm cardiac involvement. Rather, they should serve as a potential warning sign for the disease, which can be better evaluated through more specific tests.

#### 5.5.3. New Biomarkers

A number of other biomarkers have been studied, some with high specificity for amyloidosis subtypes, such as retinol-binding protein 4 for hereditary amyloidosis through the Val142Ile mutation. However, further studies are necessary, as is the commercial availability of tests for routine analysis.<sup>102</sup>

**Table 3 – Causes of false-positive  $^{99m}\text{Tc}$ -pyrophosphate scintigraphy (myocardial  $^{99m}\text{Tc}$ -pyrophosphate uptake that is not associated with amyloid transthyretin)**

|                                              |
|----------------------------------------------|
| 1. Light-chain cardiac amyloidosis           |
| 2. Capture in blood pool (planar images)     |
| 3. Rib fractures (planar images)             |
| 4. Myocardial infarction (acute or subacute) |
| 5. Hydroxychloroquine cardiotoxicity         |
| 6. Rare forms of cardiac amyloidosis         |

Source: adapted from Hanna et al.<sup>91</sup>

## 6. Rational Diagnostic Approach to Cardiac Amyloidosis

Recent evidence indicates that CA, particularly the ATTRwt form, is more prevalent than previously estimated, and this is due in part to widespread underdiagnosis and the fact that this disease

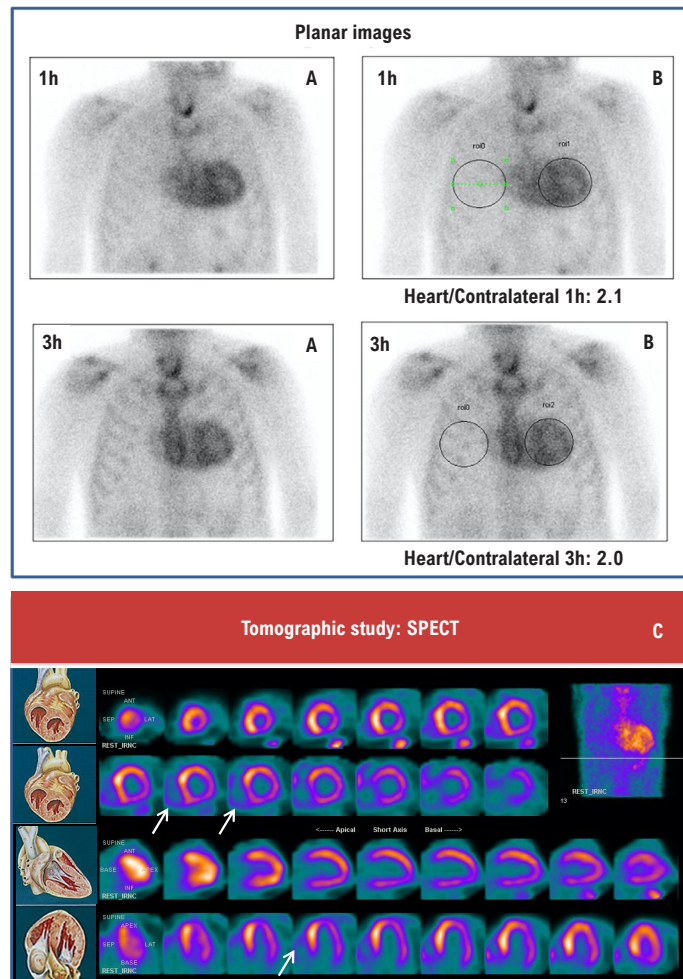


**Figure 10** – Illustrative images of a 76-year-old male patient with ATTRv (VAL30MET) cardiac amyloidosis. Cardiac scintigraphy with  $^{99m}\text{Tc}$ -pyrophosphate (flat images A and B) showed intense radiotracer uptake in the 1 h and 3 h images. Visual analysis (A) showed grade 3 uptake in both 1 h and 3 h images (myocardial uptake intensity greater than that of the costal margins). The semiquantitative analysis (B) showed a 2.1 heart/contralateral ratio at 1 h 2.0 and at 3 h. Single photon emission computed tomography (SPECT) showed radiopharmaceutical uptake in all left ventricle walls and confirmed right ventricle involvement, as shown in the flat images (arrows). The  $^{99m}\text{Tc}$ -pyrophosphate cardiac scintigraphy findings are highly suggestive of ATTR-CA. (Images from the authors' personal files).

mimics other heart diseases, such as hypertrophic cardiomyopathy, non-amyloid HFpEF, and low-flow/low-gradient aortic stenosis.<sup>42</sup> These factors indicate that high suspicion of the disease in different clinical scenarios is needed for a more rational diagnostic process.<sup>54</sup> Figure 11 shows a diagnostic algorithm for CA, whose steps are discussed below. The main recommendations and classes of evidence for diagnosis are listed in Table 5.

The **first and most important step** is clinical suspicion, which is based on clinical history, a physical examination (see Table 2) with findings suggestive of CA in ECG, echocardiogram, and CMR (see Table 4).

**Thus, in cases with high clinical suspicion, an investigation of immunoglobulin monoclonal light chains should be performed** for effective screening of AL-CA, given that an AL-CA

diagnosis is a medical emergency, and treatment delay should be avoided, since it is associated with a markedly worse prognosis.

Protein electrophoresis is not an adequate screening test since this method may not detect the monoclonal component in blood and/or urine. Thus, it is important to carry out immunofixation in blood and urine, which increases the detection sensitivity for clonal light chains to around 90%.<sup>103</sup> Adding the serum free light chain ratio, which detects an abnormal relationship between kappa/lambda chains ( $> 1.65$  or  $< 0.26$ ), increases the detection sensitivity to  $> 99\%$ .<sup>103,104</sup> Therefore, electrophoresis with immunofixation in blood and urine associated with free light chain ratio analysis represents the best non-invasive method for detecting clonal light chains, which indicate the presence of AL.

# Statement

**Table 4 – Summary of the main findings suggestive of cardiac amyloidosis in complementary examinations**

| Examinations - results suggestive of cardiac amyloidosis                                                                                                                                                                                                                                                                                                       | Practical tips - diagnostic details                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Electrocardiogram</b>                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |
| Pseudoinfarction pattern<br>QRS voltage disproportionate to degree of wall thickening<br>Low voltage of QRS complexes<br>Atrial arrhythmias - atrial fibrillation<br>Conduction disorders                                                                                                                                                                      | A classic low voltage pattern is common in AL-CA (up to 70% of cases) but uncommon in ATTR-CA (only 30% of cases)<br>The ECG results should be interpreted together with clinical and echocardiographic data<br>BAV or AF can be an initial manifestation of CA                                                        |
| <b>Echocardiogram</b>                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                        |
| Increased ventricular thickness (IVS > 12 mm)<br>Granular/hyperrefringent appearance of thickened myocardium<br>Thickening of both the RV and LV walls+<br>Biatrial dilation<br>Valve and thickening of the interventricular septum<br>Diastolic dysfunction (restrictive pattern)<br>Longitudinal myocardial deformation with relative apical sparing pattern | In addition to structural and functional information from conventional echocardiography, myocardial deformation analysis is important to identify myocardial dysfunction, even with normal EF and an apical sparing pattern                                                                                            |
| <b>Cardiac Magnetic Resonance</b>                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                        |
| High native T1 values<br>Marked increase in extracellular volume<br>Diffuse transmural or subendocardial delayed enhancement<br>Late enhancement in atrial walls<br>Increased RV/LV wall and interatrial septum thickness                                                                                                                                      | In addition to structural and functional cardiac information, which can be very suggestive, late enhancement information, T1 mapping and extracellular volume are important indicators of CA<br>CMR cannot differentiate between AL-CA and ATTR-CA<br>CMR may help identify other forms of infiltrative cardiomyopathy |
| <b>Cardiac scintigraphy with bone radiotracer</b>                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                        |
| Myocardial uptake ≥ bone uptake (grade 2 or 3)<br>Heart/contralateral uptake ratio ≥ 1.5<br>99mTc-pyrophosphate uptake in heart walls confirmed by SPECT imaging                                                                                                                                                                                               | In Brazil, only 99mTc-pyrophosphate is available for this purpose<br>In the absence of light chains, positive 99mTc-pyrophosphate scintigraphy diagnoses ATTR-CA without the need for EMB<br>Up to 30% of AL-CA may show positive scintigraphy<br>Negative 99mTc-pyrophosphate scintigraphy does not rule out CA       |

AF: atrial fibrillation; BAV bicuspid aortic valve; EMB: endomyocardial biopsy; CA: cardiac amyloidosis; CMR: Cardiac Magnetic Resonance; ECG: electrocardiogram; EF: ejection fraction; IVS: interventricular septum; GLS: global longitudinal strain; LV: left ventricle; SPECT: single photon emission computed tomography; RV: right ventricle.

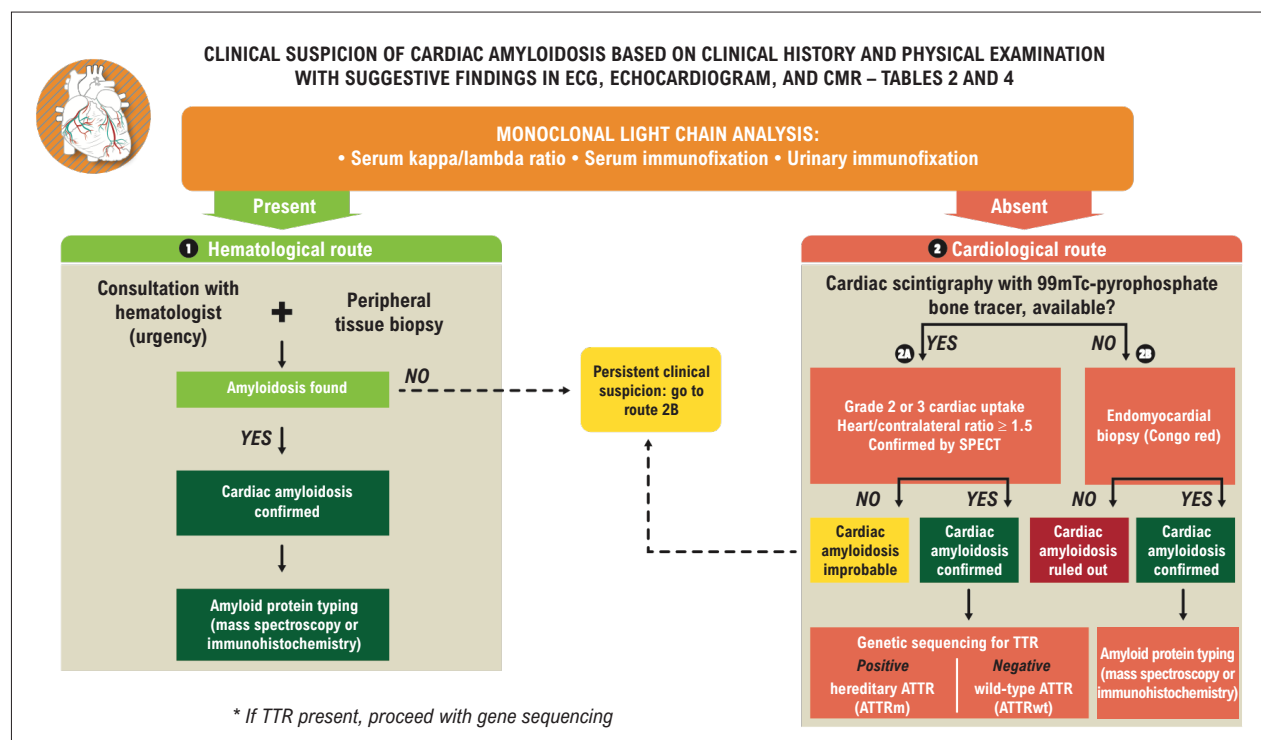


**Figure 11 – Flowchart for diagnosing cardiac amyloidosis.**

**Table 5 – Recommendations for cardiac amyloidosis diagnostics**

| Indication                                                                                                                                                                          | Recommendation class | Level of evidence (references) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|--------------------------------|
| Begin CA investigation in patients with signs and symptoms of HF and one or more warning sign of the disease (see Table 2)                                                          | I                    | C                              |
| Whenever available, perform echocardiography with analysis of LV myocardial strain, and/or CMR with LE and T1 mapping for patients with suspected CA                                | I                    | B<br>(ref. 60, 61, 62)         |
| For suspected CA, continue the diagnostic investigation with serum and urine immunofixation tests and kappa/lambda light chain ratio measurement to assess the possibility of AL-CA | I                    | B<br>(ref. 19)                 |
| When available, perform cardiac scintigraphy with a bone-seeking radiotracer* to diagnose ATTR-CA, after AL type has been excluded (light-chain negative)                           | I                    | B<br>(ref. 19, 94, 95)         |
| Perform EMB to diagnose CA in cases with high clinical suspicion of the AL form (light-chain positive) when the peripheral tissue biopsy is negative                                | I                    | B<br>(ref. 108)                |
| Perform amyloid protein typing in EMB using immunohistochemistry or mass spectroscopy, when available, when the CA type is indeterminate or conflicts with the clinical suspicion   | I                    | C                              |
| Perform EMB to confirm CA diagnosis in suspected cases of ATTR when bone scintigraphy is not available                                                                              | I                    | B<br>(ref. 19)                 |
| Perform EMB to confirm CA diagnosis when there is high suspicion of ATTR, but bone scintigraphy is indeterminate                                                                    | I                    | C                              |
| Perform genetic sequencing in patients diagnosed with ATTR to differentiate ATTRv from ATTRwt                                                                                       | I                    | B<br>(ref. 33)                 |

\* Radiotracers that can be used for this purpose include <sup>99m</sup>Tc-pyrophosphate, <sup>99m</sup>Tc-DPD (3,3-diphosphono-1,2-propanedicarboxylic acid) and <sup>99m</sup>Tc-HMDP (hydroxymethylene diphosphonate); of these, only <sup>99m</sup>Tc-pyrophosphate is available and approved for use in Brazil. AL: light-chain amyloidosis; ATTR: transthyretin amyloidosis; ATTRv: hereditary ATTR; ATTRwt: wild-type ATTR; CA: cardiac amyloidosis; EMB: endomyocardial biopsy; HF: heart failure; LV: left ventricle; LE: late enhancement

The patients with positive results for monoclonal light chains must be referred to a hematologist (following the **hematological route** on the algorithm), and a tissue biopsy must be performed, which is fundamental for confirming amyloid protein deposition and definition of the therapeutic strategy.

## 6.1. Hematological Route

### 6.1.1 Hematologist Participation and Peripheral Tissue Biopsy

An AL-CA diagnosis must be confirmed by biopsy. Abdominal fat biopsy, a simple and safe method, is preferred initially.<sup>105</sup>

Congo red staining with birefringence under polarized light is used to determine tissue amyloid protein. In cases of systemic amyloidosis, ie, affecting numerous organs or tissues, abdominal fat biopsy with this stain has a sensitivity of 60-80% and a specificity of 90-100% for diagnosing amyloidosis,<sup>106</sup> as well as a strong association with the total body load of amyloid deposition.<sup>37</sup> However, in cases of localized amyloidosis, ie, restricted to one organ or tissue, a subcutaneous fat tissue biopsy is seldom positive.<sup>107</sup> In general, there is a higher chance of positive extracardiac biopsy results when the site is abdominal fat and the amyloidosis is AL. AL is followed by ATTRv and ATTRwt in this regard.<sup>37</sup> In a series of 131 patients whose ATTR-CA

diagnosis was confirmed by endomyocardial biopsy, the abdominal fat biopsy was positive in 67% of ATTRv patients but only in 14% of ATTRwt patients.<sup>8</sup> Therefore, although abdominal fat is the preferred initial site for extracardiac biopsies, a negative result should not exclude the diagnosis, and an endomyocardial biopsy should be performed.<sup>37</sup> In these cases, biopsy of the affected organ has 100% sensitivity and specificity.

It should be pointed out that although Congo red staining can confirm amyloid infiltration in tissue, it cannot identify the type of precursor protein. In addition, 40% of ATTR patients may have a monoclonal gammopathy of undetermined significance, presenting positive results in a monoclonal light chain analysis.<sup>109</sup>

In light of these aspects, since identifying the amyloid deposition type is fundamental for appropriate treatment, immunohistochemistry or, preferably, laser microdissection and mass spectrometry of the amyloid biopsy material must be performed. Immunohistochemistry remains the most widely available method for identifying the deposition type. However, when the amyloidosis is light chain, the results are not always conclusive; they may be positive for more than one type of antiserum, usually TTR and kappa or lambda chain. Thus, mass spectrometry has become the new gold standard for identifying amyloid deposition type.<sup>37,54,110</sup>

# Statement

For **negative monoclonal light chain results**, ie, when ATTR is more likely, although other rare forms of CA may also be diagnosed, the investigation should follow the **cardiological route**, taking two sub-routes according to the availability of scintigraphy with bone markers.

## 6.2. Cardiological Route

When **scintigraphy with bone tracers (sub-route 2A)** is available and monoclonal light chains are absent, grades 2 or 3 cardiac uptake (equivalent to or greater than that of the costal arches) and a  $\geq 1.5$  H/CL uptake ratio, with SPECT imaging showing that the increased uptake is in the ventricular walls, confirms ATTR-CA without the need for endomyocardial biopsy. TTR gene sequencing should then be performed to determine whether the ATTR is hereditary or wild type.

Differentiating between hereditary and wild-type ATTR has prognostic and therapeutic implications and is also important for family screening and genetic counseling.

When cardiac scintigraphy with bone tracers is negative and is associated with an absence of monoclonal light chains, CA is unlikely. However, when clinical suspicion persists, based mainly on the results of other imaging methods highly suggestive of amyloidosis, endomyocardial biopsy can have a relevant diagnostic role and should be performed. Such cases could indicate ATTRv involving mutations and amyloid deposits, to which bone tracers do not adhere, such as early-onset V30M and P64I, in addition to other unusual types of amyloidosis.<sup>111</sup>

When **bone scintigraphy is unavailable (sub-route 2B)**, endomyocardial biopsy is recommended to clarify the diagnosis.

## 7. Prognosis and Staging

### 7.1. AL-CA

AL-CA patients have faster-forming and more toxic amyloid deposits than ATTR-CA patients. As a consequence, monthly increases of 1.45 to 2.16 mm can be observed in myocardial thickness, which are associated with higher elevations of biomarkers, such as troponin and BNP,<sup>112</sup> as well as the development of HF symptoms and death within an average of 6 months after diagnosis.<sup>113</sup>

Recent technological and laboratory advances indicate that the main prognostic determinant in AL-CA is the extent of amyloid deposition in the heart.<sup>114</sup> The most widely used staging criteria were developed by the Mayo Clinic (shown in

Table 6), which consider individuals to be at higher risk when troponin T  $\geq 0.025$  ng/mL, NT-ProBNP  $\geq 1,800$  pg/mL, and the difference between the light chains  $\geq 18$  mg/dL.<sup>115</sup>

Additionally, echocardiographic findings such as a marked increase in wall thickness, diastolic dysfunction, LV dysfunction, valve thickening, and reduction in LV global longitudinal strain, combined with BNP and troponin biomarkers and hematological status, are predictors of higher mortality.<sup>116</sup> Myocardial elastography, a new non-invasive myocardial assessment technique that assesses heart stiffness, has shown a good correlation with ventricular mass, myocardial thickness, biomarkers such as BNP, filling pressures, worsening functional class, and diastolic dysfunction.<sup>117</sup>

CMR also provides data that correlates with survival in CA patients.<sup>84,119-121</sup> The presence and extent of myocardial fibrosis, detected by late gadolinium enhancement, indicate poor prognosis.<sup>118-119</sup> A recent study found that T1 mapping measurements  $> 1,044$  ms and extracellular volume measurements (calculated in the equilibrium phase)  $> 0.45$  are associated with 5.84 and 3.48 times higher cardiovascular mortality, respectively.<sup>9,10</sup>

Biomarkers not only play a role in staging these patients, but also enable treatment response assessment, which is always a challenge in clinical practice, especially for AL-CA, since chemotherapy can be an additional factor in myocardial damage. What has been well established in the literature is the agreement between lower NT-proBNP levels and hematologic response to treatment, as well as improvement in New York Heart Association (NYHA) functional class. The reverse is also true, such as increased levels of NT-proBNP and troponin and reduced ejection fraction. (see Table 9 regarding AL-CA treatment)

### 7.2. ATTR-CA

ATTR-CA has a more benign profile and is associated with longer survival than AL-CA.<sup>121</sup> In addition to the specific type of amyloid deposition, other factors such as genotype, clinical data, laboratory biomarkers, and radiological findings can guide therapeutic planning and determine prognosis.<sup>13</sup>

In cases of hereditary ATTR, the genetic profile determines the clinical phenotype and evolution of the disease, although the gene's distribution may vary in different populations. Thus, the survival time for pathogenic variants with predominantly myocardial involvement, such as V122I, is shorter than for ATTRwt and mixed or predominantly neuropathic variants such as V30M.<sup>20,122,123</sup>

**Table 6 – Prognostic staging of light-chain amyloidosis according to revised Mayo Clinic criteria<sup>115</sup>**

| Biomarker cut-off values                                                        | Staging<br>(number of biomarkers with high values) | Mean survival |
|---------------------------------------------------------------------------------|----------------------------------------------------|---------------|
| Troponin T $\geq 0.025$ ng/mL<br>NT-proBNP $> 1,800$ pg/mL<br>dFLC $> 18$ mg/dL | Stage I: no biomarkers                             | 94 months     |
|                                                                                 | Stage II: 1 biomarker                              | 40 months     |
|                                                                                 | Stage III: 2 biomarkers                            | 14 months     |
|                                                                                 | Stage IV: 3 biomarkers                             | 6 months      |

dFLC: difference in serum free light chains; NT-proBNP: N-terminal pro-B-type-natriuretic peptide.

From a clinical point of view, the onset and duration of HF symptoms have prognostic value.<sup>124</sup> It has been determined that the longer the clinical decompensation and the more advanced the NYHA functional class, the lower the survival.<sup>125,126</sup> The median survival observed for each functional class is: I = 4.6 years, II = 4.1 years, III = 2.1 years and IV = 1.3 years. Although sex, age at diagnosis, and comorbidities such as aortic valve disease or tachyarrhythmias do not have a direct effect on mortality, a greater association with unfavorable cardiac outcomes has been observed in older men with associated diseases.<sup>127</sup>

The results of inexpensive, quick, and easy-to-interpret laboratory tests have been used in different proposals for staging the disease, being closely correlated with life expectancy. (Table 7).<sup>128-130</sup> Serum levels of troponins T and I, NT-proBNP, and glomerular filtration rate reflect the toxicity of amyloid deposition in target organs by direct action, as well as oxidative stress and inflammation processes.<sup>131</sup> Recommendations for CA risk stratification/staging and treatment response monitoring are shown in Table 8.

Imaging findings, such as echocardiography, cardiac scintigraphy with technetium-pyrophosphate (<sup>99m</sup>Tc-PYP), and CMR, provide complementary data that facilitate prognostic stratification.<sup>9,80,94,132-134</sup> (Table 9). The increasing quality of the images, associated with greater quantitative detailing of amyloid deposits, has reduced the need for myocardial biopsy as a predictor of disease.<sup>9</sup>

## 8. Treatment

CA treatment consists of specific measures aimed at reducing or preventing the progression of amyloid fibril deposition. These measures will be addressed separately for AL-CA and ATTR-CA. General measures are also needed to manage the resultant clinical and hemodynamic abnormalities, including heart failure and cardiac rhythm disturbances, which apply to both AL-CA and ATTR-CA.

### 8.1. Specific Therapy for AL-CA

AL-CA is caused by the aberrant production of kappa or lambda immunoglobulin light chains (*kappa* or *lambda*). Thus, specific treatment is based on eliminating this light chains production by eradicating plasma cell clones in bone marrow. The rapid reduction and, ideally, normalization of light chain levels (hematologic response) is a primary goal in AL-CA treatment. The reversal of damage to tissues and organs affected by amyloid deposits (organ response) is the second major objective of treatment. Further goals include improved quality of life and overall survival.<sup>135</sup>

After the diagnosis of systemic AL-CA has been confirmed, the therapeutic plan must be defined by the hematologist. However, the identification and management of organ dysfunction is essential, as is multidisciplinary work, including joint follow-up with a cardiologist and other specialists (see Table 12). Cardiac involvement is the main prognostic factor in AL-CA, determining not only survival, but also tolerance to cytotoxic treatment. The impact of cardiac impairment on survival has been well established in the literature, and validated staging systems can help with patient risk

stratification. These systems are used together with other parameters to determine therapeutic strategies.<sup>135</sup>

Survival in AL-CA is related to the production of amyloidogenic light chains and target organ damage, especially to the heart. Thus, staging includes biomarkers related to these factors,<sup>104,115,136</sup> as described above (see Table 5).

The value of this prognostic stratification has been confirmed in individuals treated with autologous hematopoietic stem cell transplantation (HSCT), as well as in those treated without this procedure. The median survival for stage I, II, III, and IV patients is 55, 19, 12 and 5 months, respectively, in patients who did not receive or failed HSCT, and 97, 58 and 22 months, respectively for stages II, III and IV, in patients who underwent HSCT.<sup>115</sup>

Low-risk patients are candidates for high-dose chemotherapy followed by autologous HSCT (Table 12). This is considered the most effective current strategy to eradicate plasma cell clones.<sup>135</sup> Intermediate-risk patients usually receive chemotherapy at conventional doses and, if they show clinical and laboratory improvement, they can become candidates for autologous HSCT. Finally, older or frail patients with multiple affected organs or patients with advanced cardiomyopathy are treated with chemotherapy at adjusted doses and have a poor prognosis, since they generally cannot tolerate the treatment.<sup>135</sup>

Three months after the end of treatment, the hematological and organ responses must be evaluated with specific tests for monoclonal gammopathy and each affected organ. The hematological and organ response criteria are summarized in Tables 10 and 11.<sup>136,137</sup>

Even when a complete hematological response occurs, dysfunction improves more slowly, and may take months or even years to appear after the light chain ratio has been normalized.<sup>19</sup>

#### 8.1.1. Treating Patients Eligible for Autologous Hematopoietic Stem Cell Transplantation

Only 20% of patients diagnosed with AL amyloidosis are eligible for HSCT, although this number could increase with organ response after induction regimens with effective anti-cancer therapies (bortezomib and daratumumab).<sup>135,139,140</sup>

HSCT eligibility assessment is central to therapeutic success in this strategy. A single prospective randomized study compared HSCT with conventional chemotherapy, finding no overall survival benefit compared to a less intensive strategy. However, in this study the high mortality rate associated with HSCT (24%) was related to the inclusion criteria, the inexperience of the transplant center and the use of a subtherapeutic dose of melphalan.<sup>141</sup>

Since the literature provides no precise well-established prospectively validated HSCT eligibility criteria, each center establishes its own. Although subjective assessment is relevant, HSCT can be guided by certain factors: "physiological age" ≤ 70 years, creatinine clearance > 30 mL/min (except for patients on chronic dialysis), troponin T < 0.06 ng/mL, Eastern Cooperative Oncology Group performance scale ≤ 2, NYHA functional class I or II, and systolic blood pressure > 90 mmHg.

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**Table 7 – ATTR amyloidosis staging proposals involving biomarkers**

| Staging proposal       | CA form         | Biomarker cutoff points                          | Staging                                                                                                                                                                           | Mean survival (months)                                |
|------------------------|-----------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Grogan et al. (2016)   | ATTRwt          | NT-proBNP > 3,000 ng/L<br>Troponin-T > 0.05 µg/L | Stage I<br>NT-proBNP < 3,000 ng/L<br>cTnT < 0.05 µg/L<br>Stage II<br>NT-proBNP or cTnT above the cutoff point<br>Stage III<br>NT-proBNP and cTnT above the cut-off point          | Stage I = 66<br>Stage II = 40<br>Stage III = 20       |
| Gillmore et al. (2018) | ATTRwt<br>ATTRv | NT-proBNP > 3,000 ng/L<br>eGFR < 45 mL/min       | Stage I<br>NT-proBNP ≤ 3,000 ng/L<br>eGFR > 45 mL/min<br>Stage II<br>NT-proBNP > 3,000 ng/L OR<br>eGFR < 45 mL/min<br>Stage III<br>NT-proBNP > 3,000 ng/L AND<br>eGFR < 45 mL/min | Stage I = 69.2<br>Stage II = 46.7<br>Stage III = 24.1 |

ATTR transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; cTnT cardiac troponin T level; eGFR: estimated glomerular filtration rate; ATTRv: hereditary ATTR amyloidosis; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

**Table 8 – Recommendations for risk stratification/staging of cardiac amyloidosis and monitoring treatment response and/or disease progression**

| Recommendation                                                                                                                    | Recommendation class | Level of evidence (references) |
|-----------------------------------------------------------------------------------------------------------------------------------|----------------------|--------------------------------|
| Stratify the risk of CA patients using validated staging systems, including biomarkers such as BNP/NT-ProBNP and/or troponins     | I                    | B<br>(ref. 128-130)            |
| Monitor CA progression and/or response to specific treatments using echocardiogram or cardiac magnetic resonance and biomarkers** | I                    | C                              |

\*\* The periodicity of the evaluation depends on the type of amyloidosis and the patient's clinical evolution.

**Table 9 – Imaging parameters that have prognostic value in transthyretin cardiac amyloidosis**

| Echocardiogram                                                      | <sup>99m</sup> Tc-pyrophosphate scintigraphy | Cardiac Magnetic Resonance                                                                                   |
|---------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| ↓ LVEF<br>↓ MCF<br>↓ GLS<br>Apical sparing<br>↓ SVI <sup>(17)</sup> | H/CL ratio ≥ 1.6                             | TAPSE<br>↓ Indexed ejection volume<br>↑ Late gadolinium enhancement<br>↑ Extracellular volume<br>↑ Native T1 |

LVEF: left ventricular ejection fraction; MCF: myocardial contraction fraction (MCF = SV/ LV volume); GLS: global longitudinal strain; SVI: stroke volume index; H/CL: heart-to-contralateral ratio; TAPSE: tricuspid annular plane systolic excursion.

Adequate pre-treatment risk stratification, concomitant with the development of better supportive conditions, such as antibiotic therapy and intensive care, has led to a reduction in HSCT-associated mortality in recent decades, with rates of 2.4% to 3.4% in retrospective analyses.<sup>142-148</sup>

Therefore, HSCT should be recommended as the first-line therapy in eligible patients (Table 12). This recommendation is due to the achievement of high hematological response rates, leading to reduced production and potential reabsorption of amyloid fibrils, with consequent improvement in organ dysfunction and performance status, as well as increased survival and quality of life. As an example, in a series of 672

AL-CA patients undergoing HSCT, 84% had a hematologic response, 39% of which were a complete response, and survival was > 50% at 15 years.<sup>146,147,149</sup>

An upfront HSCT can be performed soon after diagnosis in patients with < 10% clonal plasma cells in the bone marrow or when preceded by induction therapy with regimens containing bortezomib and/or anti-CD38 monoclonal antibody. The latter should be considered when there is an association with multiple myeloma, a predictable delay in HSCT, poor performance that may improve with induction therapy, and > 10% infiltration of the bone marrow by clonal plasma cells, which is associated with worse prognosis.<sup>135,150</sup>

**Table 10 – Criteria for determining hematological response to treatment**

|                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Complete response:</b> normalization of the serum free light chain ratio, immunofixation in blood, and negative urine (no clonal component)                                                                                                                                                        |
| <b>Very good partial response:</b> reduction in the difference between involved and uninvolved free light chains to < 40 mg/L                                                                                                                                                                         |
| <b>Partial response:</b> > 50% reduction in the difference between involved and uninvolved free light chains                                                                                                                                                                                          |
| <b>No response:</b> partial response not obtained                                                                                                                                                                                                                                                     |
| <b>Progressive disease:</b> free light chain increase of 50% or to > 100 mg/L. In patients with a complete response, the reappearance of a clonal component in immunofixation or free light chains; in patients with a partial response, a 50% increase in the monoclonal component in blood or urine |

The main regimens used as pre-transplant therapy are cyclophosphamide, bortezomib and dexamethasone (CyBorD) and daratumumab, bortezomib, cyclophosphamide and dexamethasone (Dara-CyBorD).<sup>139</sup>

Given that new therapies for treating AL amyloidosis are emerging and the scarcity of randomized studies on transplantation, further studies will be needed to determine whether HSCT will remain the most effective therapy in coming decades.

### 8.1.2. Treating Patients Ineligible for HSCT/Conventional Chemotherapy

Most patients diagnosed with AL-CA are not eligible for higher intensity autologous HSCT therapy due to comorbidities, such as advanced heart disease, renal failure, the involvement of more than two organs, or advanced age. Thus, in this group of patients, chemotherapy with anti-cancer medications is the basis of treatment (Table 12). The regimens are similar to those for multiple myeloma.

The CyBorD regimen was found to be highly effective (81% to 94%), well tolerated, and capable of producing a rapid hematological response (within 3 months) in two retrospective studies with small samples (n = 17 and 43). Two-year overall survival reached 92% in these studies.<sup>151,152</sup> The largest sample to have been tested with this regimen included 230 patients, 60% of whom had a hematologic response, and 23% of whom had a complete response. However, cardiac and renal organ responses were observed in only 17% and 25% of patients, respectively. A lower hematologic response rate was observed among patients with advanced heart disease (42% global and 14% complete), with a median overall survival of 7 months for this group.<sup>153</sup> Since the CyBorD regimen may make patients who are initially ineligible for autologous HSCT eligible (after hematologic response and clinical improvement), it should be considered when developing the therapeutic plan.<sup>153-155</sup>

Two recent randomized studies tested chemotherapy combinations as new treatments of choice in AL-CA patients who are ineligible for HSCT. The first compared a regimen of bortezomib, melphalan and dexamethasone to melphalan and dexamethasone, finding that adding bortezomib resulted in a higher overall hematologic response rate after

**Table 11 – Criteria for determining organ response to treatment**

|                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Cardiac response:</b> > 30% reduction and > 300 ng/L in patients with NT-proBNP ≥ 650 ng/L, or functional improvement of at least two classes according to New York Heart Association criteria                                                                                                                                                                                       |
| <b>Renal response:</b> decrease in proteinuria ≥ 50% (reduction of at least 0.5 g/24 h) at 6 months without a ≥ 25% worsening in estimated glomerular filtration rate. Recent retrospective analyses suggest that a ≥ 30% reduction in proteinuria is associated with better prognosis, although this criterion has not yet been incorporated into formal recommendations <sup>18</sup> |
| <b>Liver response:</b> ≥ 50% reduction in alkaline phosphatase and ≥ 2 cm reduction in liver size                                                                                                                                                                                                                                                                                       |
| <b>Peripheral nervous system:</b> improvement in nerve conduction speed according to electroneuromyography                                                                                                                                                                                                                                                                              |

3 months (79% vs. 52%), a greater cardiac organ response (38% vs. 28%), and improved overall survival, with a 2-fold reduction in mortality.<sup>156</sup> The largest randomized trial for AL-CA (ANDROMEDA) associated an anti-CD38 monoclonal antibody (daratumumab) with the CyBorD regimen, finding promising results.<sup>139</sup> The Dara-CyBorD group had an overall hematologic response of 92%, compared to 77% in the CyBorD group, with an OR of 53% vs. 18%, which took a median of 2 months to achieve. Better organ function was also observed in the group that received the monoclonal antibody, with improved progression-free survival. Importantly, advanced heart disease patients (classified as stage IIIb) were excluded from both of these randomized studies, and treatment for this group remains a challenge in clinical practice.

## 8.2. ATTR-specific Therapies

Several steps in the pathophysiological process of amyloid fibril formation and deposition in cardiac tissue are potential therapeutic targets in ATTR-CA, as illustrated in Figure 12, including: 1) liver transplantation; 2) TTR tetramer stabilizers; 3) hepatic TTR synthesis inhibitors; and 4) the degradation and resorption of deposited amyloid fibrils.

### 8.2.1. Liver Transplantation

In the past, liver transplantation has been proposed as a treatment for patients with ATTRv-associated polyneuropathy.<sup>157</sup> Liver transplantation, which removes the source of mutated TTR molecules, is associated with increased survival, with a reported 20-year survival rate of 55.3%. However, TTR deposition may continue after liver transplantation and is associated with heart disease progression, probably because the accumulated amyloid fibrils in the myocardium promote additional deposition of wild-type TTR over time.<sup>158,159</sup> Thus, heart and liver transplantation may be possible and appears to be associated with better prognosis than the transplantation of either organ alone.<sup>160</sup> Considering the reduced availability of organs and transplant centers, in addition to the risks posed by lifelong immunosuppression, the development of new therapies capable of blocking hepatic TTR synthesis should replace liver transplantation as a means of suppressing TTR production.

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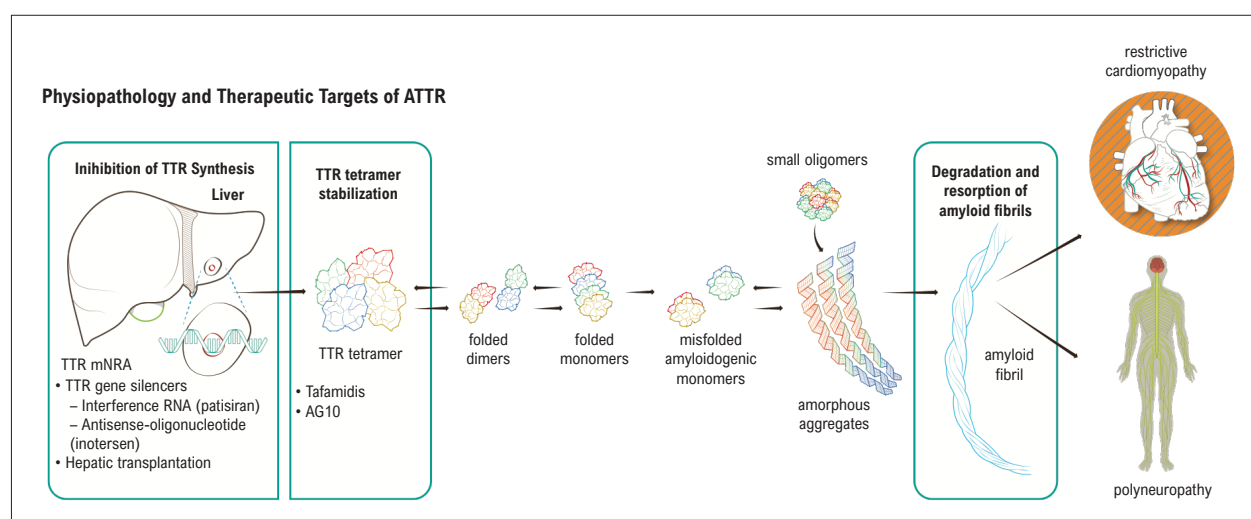


**Figure 12** – The pathophysiological process of amyloid fibril deposition in ATTR and recognized therapeutic targets.

## 8.2.2. Selective Transthyretin Kinetic Stabilizers

### 8.2.2.1. Tafamidis

Tafamidis is a small molecule that selectively inhibits the dissociation of TTR tetramers by binding to thyroxine binding sites, thereby effectively inhibiting the cascade that results in amyloid fibril formation.<sup>161</sup> When tested in a phase 3 clinical trial, tafamidis was effectively reduced the progression of neurological manifestations in patients with early-stage ATTRv polyneuropathy.<sup>162</sup>

Tafamidis is the only drug to have been specifically tested in CA patients in a prospective, randomized, placebo-controlled, multicenter clinical trial (ATTR-ACT).<sup>163</sup> This phase 3 trial included 441 patients (18 to 90 years of age) diagnosed with hereditary or wild-type ATTR cardiomyopathy who were characterized by a history of heart failure, interventricular septal thickness > 12 mm on echocardiography, TTR amyloid deposits (confirmed by biopsy or positive bone marker scintigraphy), NT-Pro-BNP > 600 pg/mL, and > 100 meters walked in the 6-minute walk test. The main exclusion criteria were: NYHA functional class IV, AL-CA, and GFR < 25 mL/min/1.73 m<sup>2</sup>. The patients were randomized to receive tafamidis 80 mg/day, tafamidis 20 mg/day, or placebo in a 2:1:2 proportion. The study's primary endpoint was hierarchically assessed all-cause mortality, followed by the frequency of cardiovascular hospitalization over 30 months of follow-up. The main secondary outcomes were change in 6-minute walk test results and quality of life scores according to the Kansas City Cardiomyopathy Questionnaire. The tafamidis 80 and 20 mg groups were merged for the statistical analysis, and the results indicated that these patients (n = 264) had a 30% lower relative risk of all-cause mortality (RR = 0.70 [95% CI: 0.51-0.96]), 32% fewer cardiovascular hospitalizations (RR = 0.68 [95% CI: 0.56-0.81]), a lower rate of decline in 6-minute walk test results (p < 0.001), and a lower rate of decline in Kansas City Cardiomyopathy Questionnaire scores (p < 0.001) than the

placebo group (n = 177). The Kaplan-Meier survival curves showed that tafamidis resulted in lower all-cause mortality, with the curves diverging after approximately 18 months of treatment, a result that agrees with the concept that tafamidis modifies the natural history of the disease. Tafamidis was well tolerated, with a similar incidence of adverse effects in the treatment and placebo groups. In the patient subgroup analysis, tafamidis was associated with lower all-cause mortality than placebo independently of NYHA functional class or ATTR genotype (hereditary or wild-type). However, patients in NYHA functional class III at the time of inclusion who were allocated to the tafamidis group had higher rates of hospitalization than the placebo group, a result likely explained by longer survival during a more severe disease phase. This subgroup analysis demonstrates the need for a trial with a large enough sample size to specifically assess the effect of tafamidis in ATTR patients with more advanced symptoms of heart failure.

More recently, an open-label extension study of ATTR-ACT found that 80 mg/day of tafamidis resulted in significantly higher survival than 20 mg/day (RR = 0.70 [95%CI: 0.50 - 0.979], p = 0.0374).<sup>164</sup>

Based on this evidence, tafamidis 80 mg/day is recommended for patients with ATTRv or ATTRwt, with NYHA I to III HF, without severe renal dysfunction, and who are beginning therapy at the earliest stages of the disease (Table 12). In Brazil, tafamidis 80 mg/day was approved by the Brazilian Health Regulatory Agency for treating ATTR-CA.

### 8.2.2.2. AG10

AG10 is a selective TTR tetramer stabilizer designed to mimic the structural influence of a super-stabilizing mutation (T119M), which significantly reduces the dissociation rate of tetramers.<sup>165</sup> This agent was evaluated in a multicenter, phase 2, randomized, double-blind, placebo-controlled trial that included 49 patients with symptomatic ATTR cardiomyopathy

and NYHA functional class II or III. The treatment was well tolerated and resulted in almost complete TTR stabilization.<sup>166</sup> There is an ongoing phase 3 multicenter clinical trial testing the effects of AG10 in CA patients. (ClinicalTrials.gov – Identifier: NCT03860935).

### 8.2.3. Inhibitors of Hepatic TTR Synthesis

Therapies based on silencing the expression of genes that encode hepatic TTR production are very promising, including RNA interference (patisiran) and antisense oligonucleotide (inotersen) strategies. Both drugs have been tested in multicenter phase 3 trials in patients with ATTRv polyneuropathy and were shown to be effective in reducing the progression of neurological manifestations.<sup>167,168</sup> Post-hoc analyses of subgroups of CA patients in these studies suggest positive effects on the progression of cardiomyopathy. Both classes of gene expression silencers are currently being tested in multicenter phase 3 trials in ATTR-CA patients (ClinicalTrials.gov Identifiers: NCT03997383 and NCT04136171).

### 8.2.4. Degradation and Resorption of Amyloid Fibrils

In vitro and experimental studies have shown that certain compounds based on hydrophobic molecules promote the degradation of amyloid tissue deposits, allowing their resorption through the macrophage system.<sup>169</sup> Experimental studies have found that doxycycline, an antibiotic of the tetracycline family, is one such compound,<sup>170</sup> having synergistic effects with tauroursodeoxycholic acid.<sup>171</sup> Although promising in preclinical studies, clinical experience with this approach is limited and has not established its efficacy or provided recommendations for its use.

## 9. Heart Failure Syndrome Management

In addition to specific therapy for amyloidosis, supportive treatment for HF may be necessary. CA initially presents as HFpEF and a restrictive pattern of LV filling, which could lead to disease progression and reduced EF. This pathophysiological mechanism could explain the difficulties in clinical management of CA patients when using HFREF medications.<sup>20,21</sup>

Maintaining euvolemia through water restriction and medications is the focus. Loop diuretics, the most frequently used medication, are indicated to reduce pulmonary and systemic congestion, and they may be associated with aldosterone antagonists (Table 12). Using diuretics to achieve euvolemia can be a challenge, since excessive dosage can impair renal function and/or result in low cardiac output due to reduced preload in hearts with already reduced stroke volume.<sup>172,173</sup> Furthermore, in patients with autonomic polyneuropathy, hypotension may impede diuretic use due to unstable preload conditions.<sup>172</sup>

Regarding HFREF drugs, there is no scientific evidence that neurohormonal antagonists such as angiotensin II-converting enzyme inhibitors, angiotensin II receptor blockers, and beta blockers, or even substances recently described as neprilysin inhibitors, angiotensin II receptor antagonists, and SGLT2

inhibitors, have any effect on CA, and they also involve the risk of hypotension and autonomic dysfunction. In a retrospective, single-center study of 99 CA patients (33% AL-CA and 67% ATTR-CA), Aimo et al.<sup>173</sup> observed that an association of angiotensin II-converting enzyme inhibitors/angiotensin II receptor blockers and mineralocorticoid antagonists can be used safely and with gradual dose adjustments if there are no contraindications, as well as that tolerance for beta-blockers is lower in AL-CA patients with left or right ventricular dysfunction. Beta-blockers and non-dihydropyridine calcium channel blockers are usually not well tolerated, because, due to the low ejected systolic volume, cardiac output is maintained through increased heart rate. In addition, non-dihydropyridine calcium channel blockers should be avoided in AL-CA patients, since they bind to amyloid fibrils, which can result in advanced blocks and cardiogenic shock.<sup>172,173</sup>

### 9.1. Arrhythmia Management

Arrhythmias are very common in CA patients and are usually symptomatic and poorly tolerated. Arrhythmia assessment in this population should involve three different situations: atrial arrhythmias, ventricular arrhythmias, and conduction system disease.

#### 9.1.1. Atrial Arrhythmia and Anticoagulants

Amyloid deposition leads to atrial thickening, including changes in atrial relaxation and increased intracavitary pressure, which produces atrial dilatation that, in association with atrial fibrosis, predisposes patients to atrial fibrillation (AF) or other atrial arrhythmias. The prevalence of AF in CA patients can range from 11% to 71%, being even higher in ATTR-CA, possibly because it affects older men.<sup>174,175</sup>

Managing AF in these patients is generally difficult, since they usually cannot tolerate drugs such as beta-blockers, non-dihydropyridine calcium channel blockers or digitalis due to the fact that they cause postural hypotension and HF decompensation. Given the need for these medications, it is advisable to use low doses with careful hemodynamic monitoring, in addition to serum level control, if digoxin is used. Regarding rhythm control, a retrospective analysis found no difference in survival between patients who received antiarrhythmic drugs and those treated with frequency control alone.<sup>176</sup> Recent data suggest that catheter ablation may be associated with lower mortality in CA patients, especially when performed early. However, these data are from small retrospective observational studies that also had a high rate of AF recurrence.<sup>177</sup>

Finally, the reduced contractility caused by amyloid infiltration in atrial tissue may also contribute to thrombus formation. Autopsy studies have found that up to 33% CA patients have intracavitary thrombi,<sup>178</sup> while retrospective studies have found a prevalence of 15 to 33%.<sup>179,180</sup> Therefore, anticoagulation is indicated in CA patients who develop AF, regardless of risk score calculations (Table 12). In addition, left atrial thrombus has been described in up to 30% of patients who underwent transesophageal echocardiography prior to a planned electrical cardioversion, even with adequate

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anticoagulation.<sup>181,182</sup> Thus, a transesophageal echocardiogram is recommended for every electrical cardioversion candidate. The role of anticoagulation in patients in sinus rhythm is still uncertain. However, even in sinus rhythm, changes in atrial contractility are common and are associated with atrial thrombus formation, especially in AL-CA patients.<sup>180,182</sup>

### 9.1.2. Ventricular Arrhythmias

Ventricular arrhythmias are frequent in CA patients, especially AL-CA. Previous studies have detected complex ventricular arrhythmias in at least 50% of AL-CA patients, in whom non-sustained ventricular tachycardia was the most frequent arrhythmia and was associated with lower survival.<sup>183,184</sup>

In this context, implantable cardioverter-defibrillators (ICD) may have a role in preventing sudden death in CA patients. ICD may benefit patients with unstable ventricular tachycardia or who have survived cardiac arrest without a reversible cause and a life expectancy > 1 year with significant quality.<sup>185-187</sup>

However, recommending ICD as primary prevention is difficult for a number of reasons. The first is that most causes of sudden death are related to electromechanical dissociation and not ventricular arrhythmias.<sup>188</sup> The second reason is the historically low life expectancy of CA patients, especially those with AL-CA. Finally, traditional risk stratification tools, such as reduced EF, do not really seem applicable to CA patients, since severe systolic dysfunction is associated with the late stages of the disease, in which pump failure predominates as the cause of death. The challenge is, therefore, to identify at-risk patients in the early stage of the disease when arrhythmia predominates and can potentially be corrected with ICD. Prospective studies are necessary to determine when ICD can be beneficial in CA patients.<sup>189</sup>

### 9.2. Conduction Disorders

Conduction-system disease is highly prevalent among CA patients, with atrioventricular conduction being more commonly affected than the sinus node. The involved pathophysiology has not yet been fully defined, although small studies have suggested that the amyloid protein conduction system is involved.<sup>190</sup> There is evidence that these changes are the cause of death in a considerable number of CA patients,<sup>191</sup> for whom pacemakers are often indicated, especially ATTR-CA patients.<sup>178</sup> In a Colombian cohort, a pacemaker was indicated in 43% of ATTRwt patients and 36% of ATTRv patients.<sup>192</sup> Pacemaker use in this population should follow traditional implantation recommendations.<sup>193</sup>

### 9.3. Therapeutic Options in Advanced Heart Failure

In advanced HF associated with CA, advanced support strategies, such as mechanical circulatory assistance and transplantation, present challenges, especially since it is a multisystem disease. Moreover, due to the reduced size of the left ventricular cavity and the frequent involvement of the right ventricle, the use of long-term mechanical circulatory assistance devices may be limited.<sup>193,194</sup> Although heart transplantation has historically had a lower survival curve in

CA,<sup>191</sup> the most recent results indicate that it is similar to other etiologies.<sup>195</sup> This change is related to better patient selection and specific strategies, such as double transplantation for ATTRv patients and heart transplantation prior to bone marrow transplantation in AL-CA.<sup>196</sup>

Table 12 summarizes the recommendations for CA treatment.

## 10. Centers of Excellence/Reference and New Treatment Remuneration Models

Access to care and a sustained commitment to improving care quality are fundamental for achieving excellent results, which are critical for complex diseases such as CA. Developing a course of care that provides the right care at the right time for CA requires the involvement of public and private health care managers, health professionals, and everyone involved in the care of these patients.

CA, particularly AL-CA, must be approached with a view to rapid diagnosis, and multidisciplinary teams with proven experience and clinical protocols based on the best scientific evidence must be available. In addition, comprehensive care and the monitoring and publishing of care results should be promoted. An integrated and collaborative practice model should be observed at these reference centers, with a telemedicine structure to support diagnosis at more distant centers, patient monitoring, and clinical research, which is the basis for emerging therapies. Such initiatives have been undertaken at a number of centers worldwide, including some in Brazil.<sup>187-199</sup>

Additionally, such reference centers should contribute to a National Registry of Cardiac Amyloidosis, allowing better insight into regional epidemiology and care quality, in addition to measuring patient-centered clinical outcomes and contributing to new public policies.

New financing models for high-cost rare disease treatments have been discussed, tested in pharmacoeconomic studies, and implemented around the world.<sup>200</sup> A risk-sharing strategy for pharmaceutical companies, funders, and healthcare providers must involve clinical research, being based on outcome assessment and the impact of clinical protocols. This new paradigm is under development in Brazil for rare diseases, and it can be used for CA.<sup>201,202</sup> Ensuring the sustainability of the health system and access to excellent treatment for CA patients will increasingly involve the Brazilian Society of Cardiology and its scientific departments/study groups. The Society is promoting debate on good care practices in all of these critical dimensions in order to build a health system that focuses on patient needs and fights waste.

An assessment of new treatments for rare diseases by the National Commission for Technological Incorporation in the Unified Health System (CONITEC) indicated that approximately 52% of the evaluated medicines have already been incorporated. In our vision we are building a new, technologically-based scenario developed through robust data with the support of clinical protocols and reference centers that can replace the current model, where access is sought through judicialization, which has a heavy impact on the federal budget.<sup>197</sup>

**Table 12 – Recommendations for cardiac amyloidosis treatment**

| Recommendation                                                                                                                                                                                  | Recommendation class | Level of evidence (references) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|--------------------------------|
| <b>Recommendations for heart failure treatment</b>                                                                                                                                              |                      |                                |
| Loop diuretics to control congestive manifestations                                                                                                                                             | I                    | C                              |
| Avoid substances that cause bradycardia, except in special situations                                                                                                                           | I                    | C                              |
| Routine use of HFrEF drugs: beta-blockers, ACEi, ARB, ARNi, SGLT2i, MRA                                                                                                                         | III                  | C                              |
| Oral anticoagulation for patients with CA and atrial fibrillation, regardless of the calculated risk of stroke or systemic embolism                                                             | I                    | C                              |
| For patients with a confirmed diagnosis of CA, offer referral to a specialized center                                                                                                           | I                    | C                              |
| <b>Recommendations for specific ATTR-CA treatment</b>                                                                                                                                           |                      |                                |
| Tafamidis 80 mg/day for ATTRv or ATTRwt CA with heart failure (NYHA FC I to III) and no severe renal dysfunction in order to reduce mortality, disability progression, and quality-of-life loss | I                    | B<br>(ref. 162, 163)           |
| <b>Recommendations for specific AL-CA treatment</b>                                                                                                                                             |                      |                                |
| Joint assessment with hematologist in suspected or confirmed AL-CA cases to determine treatment:                                                                                                |                      |                                |
| Consider HSCT for eligible AL-CA patients, ie, no severe comorbidities, advanced heart disease, or severe renal failure, having no more than two affected organs, and not of advanced age       | I                    | B<br>(ref. 147, 148, 149)      |
| Initiate chemotherapy with anti-cancer medications in AL-CA patients who are ineligible HSCT                                                                                                    | I                    | A<br>(ref. 139,156)            |

ACEi: angiotensin converting enzyme inhibitor; ARNi Angiotensin–neprilysin inhibitor; ARB: angiotensin-II receptor blocker; CA: cardiac amyloidosis; FC: functional class; HSCT: hematopoietic stem cell transplantation; MRA: mineralocorticoid receptor antagonist.; NYHA: New York Heart Association; SGLT2i: sodium-glucose cotransporter 2 inhibitor

## 11. Knowledge Gaps and Future Perspectives

Despite recent advances in CA research, there are still numerous knowledge gaps to be filled regarding this complex and multifaceted disease. Both the diagnosis and treatment of amyloidosis are evolving, which is exemplified by the 638 studies registered in the clinicaltrials.gov site that have recently been completed or are in progress.

Current cardiovascular imaging for CA diagnosis involves cardiac scintigraphy with bone-seeking radiotracers, such as <sup>99m</sup>Tc-pyrophosphate, which allows molecular images of amyloid fibril deposition in the myocardium. Although not yet available in Brazil, another promising technique is PET imaging with <sup>18</sup>F-Flortetapir in peripheral nerves and/or other extracardiac sites.<sup>203,204</sup> Elastography, ultrasound, and CMR are also being used to assess the degree of myocardial fibrosis and may be additional and promising tools to aid in diagnosis and prognosis.

Recent studies have focused on transcriptome analysis, seeking differences in expression between healthy and sick individuals by means of molecular analysis and integrative genomics. The transcriptome of AL-CA patients is similar to that of patients with monoclonal gammopathy of undetermined significance. Furthermore, the level of circulating microRNA, which is known to correlate with cardiac damage, is increased in AL patients. Through principal component analysis, highly overlapping phenotypic profiles have been found between AL, monoclonal gammopathy of undetermined significance, and multiple myeloma.<sup>205,206</sup>

Additionally, using artificial intelligence to analyze data in medical databases is a promising strategy for identifying individuals with warning signs. This strategy could lead to earlier CA diagnosis and reduce treatment delay.

New therapies specifically for ATTR-CA are under intense investigation. TTR gene silencing therapies that have been found effective for hereditary amyloid polyneuropathy are currently being tested in ATTR-CA patients in large multicenter studies. The APOLLO-B study is testing the RNA interference agent patisiran (ClinicalTrials.gov Identifier: NCT03997383). The CARDIO-TTRransform clinical trial is testing antisense oligonucleotide technology in a new second-generation drug, AKCEA-TTR-LRx (ClinicalTrials.gov Identifier: NCT04136171).

Since amyloid deposition has arrhythmogenic potential and can damage the conduction system, implantable devices such as pacemakers or defibrillators are frequently used to reduce mortality and increase survival in this population. On the other hand, individuals with CA and atrial fibrillation or flutter are at high risk for cardioembolic events, and treatment with anticoagulants has been recommended. Although there is a pathophysiological rationale for using these interventions in CA patients, they must still be tested in appropriate clinical trials, and this is an important area for future clinical investigation. In addition, heart transplantation has proven to be a safe strategy in these patients, although artificial ventricles and combined therapies must still be assessed in clinical trials.

To define the best treatment options and combinations for this disease, we must wait for the results of studies that are

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testing different interventions and specific therapies, bearing in mind that: 1) we are not fully aware of the details of the disease's pathophysiology; 2) we lack a broad understanding of how medications work in this disease; 3) we still do not have an accurate, detailed and long-term assessment of the risks and benefits of different treatments; 4) and we also do not know the dose-response relationship of different medications for this clinical scenario.

Thus, we believe that the following basic steps are relevant and should be implemented:

- 1) Creating new centers of reference/excellence in CA.
- 2) Training professionals in early CA recognition and referral to specialized centers.
- 3) Promoting the development of a National Registry of Cardiac Amyloidosis.
- 4) Discussing the safety and care quality challenges involved in the journey of CA patients.
- 5) Discussing new remuneration and care models for CA.
- 6) Encouraging clinical research on CA in Brazil.

### Errata

September 2021 Issue, vol. 117 (3), pages 561-598

In "Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis – 2021", com número de DOI: <https://doi.org/10.36660/abc.20210718>, published in the Journal Arquivos Brasileiros de Cardiologia, 117(3):561-598, on page 561, author Flávio Henrique Valicelli, institution number 1, after the author Carlos Eduardo Rochitte was included. On page 564, the conflict of interest was included: "Nothing to be declared", under the name Fernando Bacal.

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# Statement

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## Position Statement on Hypertension and Spirituality – 2021

**Development:** Department of Arterial Hypertension of the Brazilian Society of Cardiology (Departamento de Hipertensão Arterial da Sociedade Brasileira de Cardiologia – DHA-SBC)

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**How to cite this Statement:** Nobre F, Esporcatte R, Brandão AA, Álvaro Avezum Jr. A, Feitosa ADM, Amodeo C, et al. Position Statement on Hypertension and Spirituality – 2021. Arq Bras Cardiol. 2021; 117(3):599-613.

**Note:** These statements are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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## Position Statement on Hypertension and Spirituality – 2021

The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these statement, 2020/2021.

| Expert                           | Type of relationship with industry                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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# Statement

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## 1. Basic Concepts about Spirituality and Forms of Evaluation

The definitions of spirituality and religiosity vary in different cultural and religious environments.<sup>1</sup> There is a diversity of concepts without a clear definition, and the term is used inaccurately and inconsistently, which impedes measurement.<sup>2</sup>

The Brazilian Society of Cardiology's Department of Spirituality Studies and Cardiovascular Medicine considers spirituality "a set of observable and measurable moral, mental, and emotional values that are motivated by the will and guide thoughts, behaviors, and attitudes in intra- and interpersonal relationships".<sup>3</sup> Spirituality should be valued and is applicable to all individuals, regardless of religious affiliation, including atheists, agnostics and those with no religious affiliation or who do not observe its precepts.<sup>4</sup>

Religiosity is the degree to which an individual believes in, follows and practices a religion. It can be organized (participation in church, temple, or religious services) or non-organized (praying, reading books or watching religious programs on one's own initiative).<sup>3</sup> Koenig describes religion as an "organized system of beliefs, practices, and symbols designed to facilitate closeness to the transcendent or the Divine and foster an understanding of one's relationship and

responsibilities with others living in community".<sup>1,5</sup> Religion is a multidimensional construct that includes beliefs, behaviors, dogmas, rituals, and ceremonies that can be performed or practiced privately or publicly, that is in some way derived from established traditions developed within a community.

Coping, or religious coping, is an important mechanism for understanding how religiosity/spirituality can affect health: it is the use of religiosity as a means of adapting to physical, psychological, and social challenges in diseases and health changes.

## 2. Scales for Assessing Religiosity and Spirituality

Spirituality/religiosity can be assessed in the "spiritual history", which is a set of questions that allows patients to share their spiritual and religious values, identifying possible spiritual issues that may interfere with the therapy. It is always necessary to focus on patients and be guided by what they reveal.<sup>6</sup> This component of the medical history should be evaluated in all patients who seek medical care; spiritual anamnesis should also be performed with all inpatients and outpatients, especially in those with chronic diseases.

Many patients are religious/spiritual, and their beliefs help them cope with disease and face adverse life situations, although certain situations can involve points of conflict with medical practice. During periods of hospitalization or chronic illness, patients are removed from communities and are unable to practice their religion. In addition, their personal beliefs can affect health-related decisions, sometimes interfering with fundamental aspects of treatment.<sup>7,8</sup>

Studies show that most patients would like their doctors to ask about religiosity/spirituality and that doing so would lead to greater empathy and trust,<sup>9</sup> which would result in more humanized care<sup>10</sup> and greater participation by both parties.<sup>7,8</sup>

The objectives of evaluating religiosity/spirituality as a social and demographic factor include: understanding the patient's beliefs, identifying aspects that might interfere with health care, assessing individual/social/family spiritual strength to cope with the disease, offer empathy and support, and help the patient accept the disease, as well as identifying conflict or suffering that requires evaluation by a trained professional.<sup>11,12</sup> Although the topic can be approached in a number of ways, the most important point is to do so with sensitivity, without imposing or promoting specific beliefs or practices. Religion should not be prescribed, forced, or encouraged, so as not to add guilt to the disease burden. Common sense should be the rule. In extreme situations, such as serious accidents or acute myocardial infarction, discussing religion can lead to stress and even worsen the patient's condition.<sup>13,14</sup>

Naturally, when the physician has not adequately prepared for this type of approach or when the patient refuses it, it should not be performed. For non-religious or adverse patients, it is necessary to understand how they face and live with the disease, what fosters purpose and meaning in their lives (family, friends, hobbies, etc.), and what cultural beliefs may impact their treatment.<sup>15</sup>

## 2.1. Scales and Instruments

The various psychometric instruments can be divided into different categories:<sup>16,17</sup>

### 2.1.1. Spiritual Inventory

These brief and easy to apply measures are used to determine the presence of spiritual needs that require deeper evaluation (Chart 1).

### 2.1.2. Instruments for Taking a Spiritual History

These instruments allow a broader assessment of the different domains of religiosity/spirituality that can affect clinical evolution, posture, self-care, and physical, mental, and spiritual well-being in the face of disease. They are well-structured and cover different domains, but they should be applied from memory, informally, throughout the conversation. They should serve as a guide, not being viewed rigidly but as a continuous learning process that is part of anamnesis. Several instruments have been validated for data collection, whether to assess religiosity/spirituality or for research purposes.

### 2.1.3. Religiosity Scales

The Duke University Religion Index (DUREL)<sup>21</sup> is a five-item scale that measures three dimensions of religious involvement: The first item assesses organizational religiosity, the second assesses non-organizational religiosity, and items 3, 4 and 5 assess intrinsic religiosity. The DUREL is succinct and easy to apply, has been validated for use in Brazil<sup>22</sup> and addresses the main areas of religiosity. The DUREL's dimensions have been shown to be related to several indicators of social support and health.<sup>22</sup>

### 2.1.4. Instruments for Assessing Spiritual History

Based on previously validated scales, these instruments involve a set of questions in different domains that are associated with health outcomes. The main scales include: FICA,<sup>23</sup> FAITH,<sup>24</sup> SPIRIT,<sup>25</sup> and HOPE.<sup>26</sup> FICA, which was created by physicians and has shown the best psychometric properties, can be used in different situations. It assesses four dimensions (faith/beliefs, importance/influence, community, and address) and is easily applied and memorized.<sup>27</sup>

Even with complete respect for the patient's beliefs and without proselytizing, religious issues can prove complex and involve conflict. They must be handled with empathy

and understanding. When conflict is evident, a visit by the religious leader should be considered.

Once spiritual tools are identified, patients should be encouraged to use them as a way of preventing disease. Such practices, beyond prayer and meditation, can include reading, music, etc. Patients must be encouraged to find spiritual aspects that, together with standard treatment, can improve disease outcomes. In serious illnesses, physicians can help patients find meaning and acceptance by coping with the situation using their spiritual resources in the best possible way. Often, through such interactions, alternatives and adjustments to the therapeutic plan emerge in which patient autonomy and patient-centered care are strengthened.<sup>27,28</sup>

## Main messages

### Concepts

**Spirituality** is a set of observable and measurable moral, mental, and emotional values that are motivated by the will and guide thoughts, behaviors and attitudes in intra- and interpersonal relationships.

**Religiosity** is how much an individual believes in, follows and practices a religion.

### Practical application

If the professional and patient are willing and able, religiosity/spirituality should always be assessed.

The assessment must be performed through questionnaires developed for use by health professionals.

### How to proceed after obtaining the spiritual history

Information about the spiritual dimension can broaden our understanding of the impact of religiosity/spirituality on the course of the disease and identify patient demands in this area.

## 3. Mechanisms Involving Spirituality and the Pathophysiology of Arterial Hypertension

Arterial hypertension (AH) is characterized as a multifactorial and multigenic disease that mainly affects the vascular system (small and large arteries), leading to progressive and, after a certain point, irreversible damage to the so-called target organs (heart, kidneys and brain).<sup>29</sup> Neural, hormonal, renal and vascular biological mechanisms participate and interact in different ways to result in sustained elevation of blood pressure (BP). Multiple factors are involved in and influence biological systems, such as: genetic, environmental, humoral, hemodynamic, neural, endocrinal, anatomical, and adaptive factors. More recently, inflammation and the production of reactive oxygen species have been implicated in several of these factors on cellular and molecular levels.<sup>30</sup>

**Chart 1 – Types of spiritual inventory**

| Tracking tools                                                      | Spiritual Domains Evaluated                                                              |
|---------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| "Rush" protocol for tracking religiosity/spirituality <sup>17</sup> | The importance of religiosity/spirituality in the disease; strength or spiritual comfort |
| "Are you at peace?" <sup>18</sup>                                   | Inner peace                                                                              |
| "Do you feel spiritual pain or suffering?" <sup>19</sup>            | Spiritual pain/suffering                                                                 |
| Spiritual Injury Scale <sup>20</sup>                                | Guilt, anger, sadness, feeling of injustice, fear of death                               |

# Statement

The mechanisms involved in BP control depend on intrinsic and extrinsic stimuli. In situations of stress, the sympathetic nervous system is activated, which discharges vasoactive substances that facilitate the onset of AH.<sup>30</sup> In situations of stress and anxiety, dietary errors, such as excessive intake of carbohydrates, fat and salt, also contribute to increased BP. Thus, human beings must be understood as biopsychosocial beings, and these dimensions are strongly interrelated. It is recognized that spirituality has an influence on this triad, participating in its balance.<sup>3</sup>

Long-term activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, altered renal mechanisms, sodium retention, and vascular alterations (represented by endothelial dysfunction and alterations of the vascular smooth muscle layer) are interrelated and are strongly implicated in the development and in the maintenance of AH through a sustained increase in peripheral vascular resistance, increased levels of inflammatory markers, and target organ damage.<sup>30</sup>

Studies have investigated the relationship between various dimensions of religiosity/spirituality and BP, and most show an association with lower BP values and lower rates of AH,<sup>1,31</sup> especially reduced diastolic BP.<sup>4</sup> It is possible that individuals who are more connected with religiosity/spirituality have more positive feelings (love, peace, forgiveness) than negative feelings (fear, anxiety, depression) and this aspect promotes reduced sympathetic nervous system activity and cortisol levels. However, the studies are not completely conclusive.<sup>1,31,32</sup>

For coping with stress, religiosity/spirituality has been associated with a lower incidence of AH, especially in the presence of higher stress levels<sup>33</sup> and reduced C-reactive protein levels in African-American populations.<sup>34</sup>

A meta-analysis of 87 studies investigated the impact of religiosity/spirituality practices on physiological health markers, finding an inverse association between religiosity/spirituality measures, particularly participation in religious services, intrinsic religiosity, prayer, and meditation and lower stress, BP, and inflammatory markers (C-reactive protein), although the effect size was small and there was substantial heterogeneity among the studies, which suggests the presence of confounding factors.<sup>35</sup>

## Main messages

### Concepts

Clinical studies investigating the relationship of religiosity/spirituality with blood pressure and biological markers are observational, with most suggesting an association with lower blood pressure values, lower levels of inflammatory markers, reduced sympathetic activity, and reduced cortisol levels.

### Practical aspects

Spirituality/religiosity practices, especially participation in worship services, intrinsic religiosity, prayers, and meditation, are inversely associated with physiological markers, such as stress level, blood pressure, and inflammatory markers (C-reactive protein).

## 4. The Association between Spirituality, High Blood Pressure, and Evidence in Primary Prevention

Although studies about the influence of psychological and religious/spiritual factors on high BP have provided further insight into the incidence and prevalence of AH, their results are not in agreement.<sup>36</sup>

Objectively measuring feelings such as forgiveness, optimism, pessimism, hostility, empathy, peaceful states, and the emotional stress involved in spirituality is difficult. An individual's degree of spirituality can often be quantified by the frequency of activity in a religious community or time spent reading about themes in the chosen religion. Thus, following other studies, we will present evidence of religiosity/spirituality indistinctly at certain points.

The Chicago Community Adult Health Study found that a greater religiosity was not a protective factor against AH. However, lower diastolic BP values were found in individuals with a propensity for forgiveness, compared to those without it.<sup>37</sup>

Similarly, the Study of Women's Health Across the Nation, which involved 1,658 participants and used the Daily Spiritual Experiences Scale, found no significant difference between daily experiences of spirituality and the prevalence/incidence of AH in 3 years of follow-up.<sup>38</sup>

In another population-based longitudinal cohort study of older adults, Koenig et al. found a strong cross-sectional relationship between religious involvement and lower BP. However, in longitudinal follow-up, the BP reduction was not significant.<sup>39</sup>

On the other hand, the Black Women's Health Study, a large cohort study that followed up 59,000 African-American women for 23 years, found that the intense religious/spiritual involvement when coping with stressful events was associated with a lower risk of developing AH than no involvement. The association was stronger among women who reported higher levels of perceived stress. However, frequent prayer was associated with a higher risk of AH.<sup>33</sup>

A Brazilian study found that the prevalence of AH in highly religious communities was lower than the national average.<sup>40</sup> Holt-Lunstad et al. monitored ambulatory blood pressure in a cohort of 100 outpatients, finding that a high level of spirituality was associated with lower BP values.<sup>41</sup>

The NHANES III survey collected data on BP, reported frequency of attendance at religious services, and history of AH treatment from 14,475 American men and women aged 20 years or older. Compared to participants who never participated, the systolic BP of those who attended weekly services was 1.46 mmHg lower (95% CI, 2.33, 0.58 mmHg,  $p < 0.01$ ), while that of participants who attended services more than 52 times/year was 3.03 mmHg lower (95% CI, 4.34, 1.72 mmHg,  $p < 0.01$ ). No significant gender effect was observed, and these estimates were adjusted for a significant interaction between age and less-than-weekly frequency (1 to 51 times) ( $p < 0.05$ ).<sup>42</sup>

Bell et al. studied the interrelationship between race/ethnicity, religious service attendance, and AH in non-Hispanic whites and blacks, and Mexican-Americans (N = 12,488). Compared with those who never attended religious services, whites who attended services weekly were less likely to have AH, as were blacks who attended more than once a week. However, there was no relationship between attending services and AH among Mexican-Americans, which suggests that these benefits are not the same for everyone.<sup>43</sup>

A cross-sectional study of 1,384 adult Tibetan Buddhists from two Buddhist institutes in Sichuan Province, China also included 798 adults from nearby towns and cities. The risk of AH was significantly lower (38%) in Buddhists than non-Buddhists. In a subgroup of 570 Buddhists, longer participation in Buddhist activities was associated with a lower prevalence AH, as well as lower BP.<sup>44</sup> In a longitudinal study, Timio et al. compared the BP of nuns in a secluded order with lay women over 30 years of follow-up. Although baseline data were similar for all variables, at the end of follow-up systolic and diastolic BP were significantly higher observed in the lay women.<sup>45</sup> Thus, these studies suggest that religiosity/spirituality has a protective role in AH, which is mediated by behaviors that could be applied to the general population.<sup>44,45</sup>

In a study that examined hostility and the risk of cardiovascular disease (CVD) in young Hispanics, Sethness et al. found that aggressive feelings were associated with higher BP.<sup>46</sup>

In the Biopsychosocial Religion and Health Study (N = 9,581), lifestyle factors such as vegetarianism and regular exercise were important predictors of lower AH rates; intrinsic religiosity, even after controlling for these factors, was as strongly related to lower AH rates as lifestyle factors. This study demonstrated that, in addition to the positive effects of lifestyle choices, religion can have a direct positive effect on AH.<sup>47</sup>

The Nurses' Health Study II evaluated 44,281 non-hypertensive women, observing that attendance at religious services had a modest inverse association with AH in a dose-response effect, ie, the higher the frequency, the lower the incidence of AH. The risk rate for those who attended more than once a week, compared to those who never or almost never attended, was 0.91 (95% CI, 0.86, 0.97).<sup>48</sup>

## Main messages

### Concepts

Studies on the influence of psychological and religious/spiritual factors on high blood pressure have sought to determine how these factors participate in hypertension, but their results disagree. In the prospective Nurses' Health Study II trial, women who attended religious services were less likely to develop high blood pressure.

### Practical aspects

Although studies do not completely agree about whether religiosity/spirituality results in a lower occurrence of arterial hypertension, some have found lower systolic blood pressure values and a lower incidence of arterial hypertension among practitioners, which was directly associated with the frequency of religious activity.

## 5. High Blood Pressure, Spirituality and Other Psychosocial Determinants

Psychosocial factors must be considered in an individual's risk profile. Prospectively following large samples with standard BP measures and psychosocial variables can establish the relationship between psychosocial factors and AH occurrence.<sup>49</sup> However, although such epidemiological studies provide evidence about psychosocial influence, they do not provide data on pathophysiological mechanisms. Differences in the magnitude or pattern of reactions to behavioral stimuli could be related to the risk of developing AH.

Experimental studies can assess the impact of psychological stimuli under carefully controlled conditions. However, they have important limitations, since only acute responses are registered. A third type of investigation is assessing daily BP measurement in relation to psychosocial conditions and verifying their impact. The difficulty with this method is that daily BP is affected by a wide range of factors, such as exercise, diet, and other lifestyle habits. The model must receive adequate statistical treatment to distinguish the influence of psychosocial factors.<sup>49</sup> Thus, different study types have both strengths and limitations. To assess the influence of psychosocial factors, it is necessary to integrate different approaches.

### 5.1. Psychosocial Characteristics

A number of psychological characteristics have been associated with AH, including anxiety, anger, hostility, mental health, social problems, work-related difficulties, and depression.<sup>49,50</sup> However, the most consistent evidence is related to anger and hostility traits.<sup>49</sup>

Anger-related traits may not be apparent all the time, but they do reveal themselves when people are confronted or feel threatened. Anger is considered relevant to the development of AH or in individuals who experience chronic stress due to their living or work conditions. Using arterial blood pressure monitoring, Casagrande et al. demonstrated that sustained feelings of anger contribute to a lack of nocturnal decline in blood pressure, which is related to a worse prognosis.<sup>51</sup>

In another study, 60 boys aged 12-16 assigned to challenging mental tasks were evaluated for physiological and subjective measures before and after the task.<sup>52</sup> The boys, who were classified as having or not having a disposition towards anger inhibition, did not differ in resting conditions. However, in response to the task, boys who reported high levels of anger inhibition had a greater systolic blood pressure response. Interestingly, this was the pattern among participants with a family history of AH, which suggests that genetic factors also interact with psychological traits and situational dispositions that can influence the risk of AH.

### 5.2. Study Characteristics

Studies have shown that certain types of work are associated with AH risk. The highest risk is when the demands of the job outweigh the rewards.<sup>49</sup> A case-control study involving 30- to

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60-year-old men working at different locations in New York showed that job stress was an independent determinant of AH after controlling for age, body mass index, type A personality, 24-hour urinary excretion of sodium, physical activity at work, education, smoking, and alcohol consumption.<sup>53</sup> After 3 years, those with persistently high job stress levels had higher BP. This response may be related to the rhythm of task performance and its relationship with baroreflex suppression when the demand level is minimal.<sup>49</sup>

Job insecurity can generate anger and psychological ailments such as that arising from working in companies with high layoff rates cause apprehension among employees.<sup>50</sup> Interestingly, workload does not seem related to higher BP.<sup>50</sup>

The CARDIA study, which evaluated 8,395 white-collar workers in Canada, looked at both cumulative exposure and new workload. After 7.5 years of follow-up, higher BP was observed among workers with low social support levels at work.<sup>54</sup> An observational study also found that a considerable pay raise can reduce the risk of hypertension by 16%.<sup>50</sup>

### 5.3. Isolation and Social Support

Social support helps us deal with life and its adversities, while isolation, defined in terms of the size and composition of the social network (eg, marital status, the number of friends and close relatives, and religious or other groups) has been associated with cardiovascular disease and mortality.<sup>49</sup> Isolation or low social support is associated with higher BP.<sup>49</sup> Social relationships are important sources of emotional and practical support and can moderate the psychological effects of stress. Lack of support and relationships not only leaves a person without these resources, but can be a major source of stress.

Among the various elements of the social network, marriage is often the central relationship in people's lives. Married individuals tend to have better health outcomes than those who live alone, while other sources of support do not fully offset the effects of loneliness. However, relationships can also be a source of conflict, and the stress associated with unhappy or strained marriages has been associated with harmful cardiovascular effects. Acute episodes of marital conflict have been shown to induce elevations in BP.<sup>54</sup>

### 5.4. Mental Health

Patients who re-experience symptoms related to a previous trauma have significantly higher rates of AH.<sup>50</sup> One study found that perceived stress can be considered a risk factor for AH in women with low-income occupations. Studies that address the relationship between stress and AH should highlight possible interactions between sex and occupational status.<sup>55</sup>

Suffering racism can adversely affect health; data from the Black Women's Health Study indicated that there may be an association between experiences of racism and an increased incidence of AH.<sup>56</sup>

Acute stress promotes a transient increase in BP, but there is no consistent evidence that this effect results in sustained AH. Chronic stress and, especially, a maladaptive stress response are likely involved in the development of AH.<sup>57</sup> A meta-analysis of cohort studies evaluated the effect of emotional stress on BP, finding that a BP increase was 21% more likely in individuals who had more intense responses to stressful tasks (odds ratio [OR]: 1.21; 95% CI, 1.14-1.28;  $p < 0.001$ ). Although the effect magnitude was small, the results suggest the relevance of controlling psychological stress to prevent increased BP.<sup>58</sup>

### 5.5. Depression and Sleep Disorders

The association between depression and the risk of developing AH has been assessed in two studies, whose results were inconsistent. In the Whitehall cohort study, participants in the "increasing depression" group (characterized by an increase in depressive episodes over the years) had a 25% lower risk of AH at 35 to 39 years of age compared to the "low/transient depression" group. However, there was a faster age-related increase in AH in the "increasing depression" group, corresponding to a 7% higher risk of AH with each 5-year increase in age. Thus, the risk of AH in participants in the "rising depression" group at the end of follow-up was substantially higher than in the "low/transient depression" group, and this pattern was more significant in men than in women. This study suggests that the risk of AH increases with repeated depressive episodes and becomes evident in later adulthood.<sup>59</sup>

NHANES I 1982-1992<sup>60</sup> examined the effects of sleep duration and insomnia on the association between depression and AH. However, as in the previous study, the results depended on the age of the cohort. Depressed individuals aged 32 to 59 years had a 44% higher risk of AH in the 10-year follow-up (OR: 1.44, CI: 1.15-1.80). Individuals who reported sleeping 5 hours or less per night were 50% more likely to develop AH than those who slept 7 to 8 hours per night (OR: 1.50, CI: 1.11-2.02). There was no association between depression, sleep quality, and AH in participants aged 60 to 86 years.

All studies show a direct relationship between sleep disturbances and the incidence of AH. In the Penn State Cohort, the risk of AH in people with short sleep duration or sleep disorders was significantly higher, but it became marginally significant after controlling for obesity (OR: 1.6, 95% CI, 0.9- 2.8). Chronic insomnia is associated with an increased risk of AH. Thus, it is possible that sleep duration is a determinant of AH.<sup>61</sup>

### 5.6. Personality

There are controversial results about the relationship between personality and AH risk. The type D personality, characterized by high levels of negative affectivity and high inhibition, was not found to be associated with elevated systolic and/or diastolic blood pressure. However, lower levels of awareness, characterized by disorganization, irresponsibility, indiscipline, negative emotions, and overreaction to stress have been associated with AH.<sup>50</sup>

## Main messages

### Concepts

Psychosocial factors that affect BP behavior and, thus, in AH onset include: personality, type of work, social isolation, mental health, depression, and sleep disorders

### Practical aspects

These conditions must be assessed to determine when they can interfere in BP behavior and AH control.

## 6. Spirituality in Blood Pressure Treatment Adherence

Beside non-drug treatments, AH is treated with antihypertensive drugs of recognized efficacy and effectiveness.<sup>3,29,62</sup> Controlling BP modifies the natural history of the disease, reducing morbidity and mortality. However, a barrier to this objective in patients worldwide is lack of adherence to lifestyle changes or prescribed medications.<sup>3,29,62</sup> Religiosity/spirituality has been recognized as a cultural aspect that interferes with the attitudes of individuals.<sup>63-68</sup>

For more than 4 decades, countless studies have found that spirituality, which in its broadest sense permeates aspects of religiosity itself, but mainly promotes self-knowledge, self-confidence, resilience, belief in the possibility of self-determination, and a positive vision of the world and the future, is associated with better adherence to the advice of health professionals.<sup>63,66,69,70</sup>

Spirituality has a strong influence on certain lifestyle habits that are directly related to hypertension and the quality of life of hypertensive patients.<sup>31,71</sup> Several clinical studies have shown that transcendental meditation (TM) helps reduce BP in hypertensive patients.<sup>72,73</sup> A meta-analysis of these randomized studies showed that TM reduces BP between 4 and 6 mmHg in a dose-dependent manner (ie, more sessions lead to greater BP reduction).<sup>74</sup>

A major clinical trial randomized 201 African-Americans with coronary artery disease to either a TM or a health education program. In a mean follow-up of 5 years, there was a 48% risk reduction in the primary outcome of death, stroke, or acute myocardial infarction (OR: 0.52, 95% CI, 0.29-0.92,  $p = 0.025$ ). There was also a reduction in mean systolic BP (5 mmHg), as well as anger expression according to specific scales ( $p < 0.05$ ). The study's conclusion was that TM can be beneficial in the AH management and in secondary prevention of stroke.<sup>75</sup>

Yoga-based interventions have been studied in CVD management. A meta-analysis of 17 studies showed that yoga was associated with a significant reduction in systolic and diastolic blood pressure, especially if all three elements of yoga are used (breathing, posture, and meditation).<sup>76</sup>

Although evidence about the direct impact of religiosity/spiritual-based interventions on AH is less robust, a significant amount of data has shown a beneficial association between religious activity (religious affiliation, organized or private

religious services) or spiritual characteristics (tendency toward optimism, gratitude, and positive emotions) and a lower incidence of AH or better BP control in already hypertensive individuals.<sup>77,78</sup>

The Black Women's Health Study found that religiosity/spirituality helps them cope with everyday life situations and contributes to BP control.<sup>33</sup>

Although the relationships between religiosity/spirituality and adherence to drug treatment in chronic diseases may vary according to the population, in general, it has a positive influence.<sup>1,79-82</sup> Spirituality can lead to improved adherence to medications through better control of negative feelings, such as anxiety, stress and depression.<sup>65</sup>

Small qualitative studies have found that African-American women believe that spirituality helped them adhere to drug treatment.<sup>83,84</sup> On the other hand, in Ghanaian women, religiosity/spirituality was associated with worse adherence to AH treatment due to the hope of a divine cure.<sup>85</sup>

Other studies have found no correlation between religiosity/spirituality and treatment adhesion, not even considering patient trust in the physician. However, trust in the physician has been associated with greater adherence to antihypertensive medications.<sup>67,86</sup> Other factors may also influence treatment adherence, such as self-efficacy, cultural beliefs and knowledge about the disease.<sup>87</sup>

Health professionals must understand the importance of religiosity/spirituality, recognize and value cultural aspects, and respect their patients' beliefs and hopes. This apparently simple attitude can provide new opportunities for successful treatment of chronic disease patients, since such conditions require greater discipline, perseverance, and faith.

## Main messages

### Concepts

A significant amount of data indicates a beneficial association between religious (religious affiliation, organized or private religious services) or spiritual aspects (tendency toward optimism, gratitude, and positive emotions) and a lower incidence of AH or better BP control in already hypertensive individuals. It has been demonstrated for over 4 decades that religiosity, self-knowledge, self-confidence, resilience, belief in the possibility of self-determination, and a positive vision of the world and the future, is associated with better adherence to the advice of health professionals

### Practical aspects

Health professionals must understand the importance of religiosity/spirituality, recognize and value cultural aspects and respect their patients' beliefs and hopes. This apparently simple attitude can provide new opportunities for successful treatment of chronic disease patients, since such conditions require greater discipline, perseverance, and faith.

## 7. Spirituality and Relevant Cardiovascular Events

Observational studies have been investigating the association between spirituality, religiosity, and clinically relevant outcomes in different areas of health (especially CVD) since the 1980s.<sup>88</sup>

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The InterHeart study evaluated risk factors independently associated with acute myocardial infarction in 52 countries, including Brazil, finding that 90% of population attributable risk was associated with nine modifiable risk factors: dyslipidemia, smoking, abdominal obesity, diabetes, hypertension, sedentarism, unhealthy diet, alcohol use, and psychosocial factors. Psychosocial risk factors (stress and depression) accounted for 33% of the population attributable risk for acute myocardial infarction, an impact greater than that of established risk factors such as hypertension and diabetes.<sup>89</sup> In addition, InterStroke assessed independent risk factors for stroke. Following the same InterHeart strategy, the study found that stress and depression were responsible for 17% of the population attributable risk for stroke worldwide.<sup>90</sup>

In 2000, a meta-analysis of 42 studies, including approximately 126,000 individuals, found that religious involvement was associated with a lower all-cause mortality rate.<sup>91</sup> Subsequent studies have shown an inverse association between mortality and frequency of attendance at religious services, and that this association was substantially mediated by health behaviors and other risk factors.<sup>42,92</sup>

Two large cohort studies published in 2016 and 2017 reinforced these findings. In the Black Women's Health Study, which included 36,613 African-American women, the mortality rate was 46% lower among those who attended religious services several times a week than among those who did not attend. There was no association between daily prayer, religious confrontation, or self-identification as a very religious/spiritual person with mortality.<sup>93</sup>

The Nurses' Health Study, which followed up more than 74,000 nurses for up to 8 years, found that attendance at religious services at least once a week was associated with 33% lower all-cause mortality, as well as substantially lower mortality from CVD and cancer, than not attending.<sup>94</sup>

On the other hand, in a cohort of 2,068 acute coronary syndrome patients, there was no association between comfort from religion, prayers for their own health, or the prayers of others on their behalf, and survival in up to 2 years of follow-up.<sup>95</sup> However, patients who prayed for their own health and those who were aware that others were interceding for them experienced improved health-related quality of life over time.<sup>96</sup> The Multiethnic Study of Atherosclerosis found no consistent patterns of association between measures of religiosity and the presence/extent of subclinical CVD at baseline or CVD incidents over 4 years.<sup>97</sup> The findings are conflicting about the association between religiosity/spirituality and CV risk factors. The Women's Health Initiative study, which included more than 43,000 menopausal women, found a higher CV risk in patients with private spiritual activity, such as prayer, Bible reading, or meditation.<sup>98</sup> In a Japanese cohort of 36,965 individuals, the more religious were significantly more likely to have better health habits and fewer CV risk factors, except for a higher prevalence of overweight/obesity

at baseline. Religiosity was also associated with better health habits over time and less likelihood of developing diabetes, but not of developing AH or dyslipidemia.<sup>99</sup>

## Main messages

### Risk of coronary artery disease and aspects related to religiosity/spirituality

In the InterHeart study, psychosocial risk factors (stress and depression) accounted for 33% of the population attributable risk for acute myocardial infarction.

### Risk of stroke and aspects related to religiosity/spirituality

In the InterStroke study, psychosocial factors (stress and depression) accounted for 17% of the population attributable risk for stroke.

### Practical aspects

Although the results do not agree regarding the benefits of religiosity/spirituality on cardiovascular health, some studies have shown a reduction in cardiovascular events and mortality in those individuals with religious/spiritual practices.

## 8. Perspectives, Knowledge Gaps and Conclusion

The concepts of evidence-based medicine have been gradually applied in the domain of spirituality and CVD research. Although the available scientific evidence can be considered promising, robust observational and randomized studies with adequate statistical power are still needed to confirm the benefits of spirituality in clinically relevant outcomes. Thus, scientific evidence about spirituality and CV medicine could influence and modify clinical practice and patient prognosis.

For strength and robustness, this position paper sought data on AH and spirituality from diverse areas of research. Health professionals must approach the spirituality of their patients according to well-defined criteria for action.

As a strictly evidence-based review, we did not find conclusive evidence that religiosity/spirituality is "a safe and useful/effective procedure" (ie, data obtained from several large studies and concordant and/or robust meta-analysis of randomized clinical trials: grade of recommendation I and level of evidence A). However, neither did we find evidence and/or consensus that "the procedure is not useful/effective and, in some cases, harmful" (ie, grade of recommendation III and level of evidence C).

What is important is these concepts are implemented with scientific support, offering physicians a way to expand their performance and offer patients resources for dealing with disease, illness, and life in addition to indispensable traditional medical approaches.

Thus, it is our duty to offer the fullest sense of health, ie, physical, social, emotional, psychological, and spiritual well-being, applying spiritual concepts sparingly and sensitively to the patients entrusted to our care.

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## Statement

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