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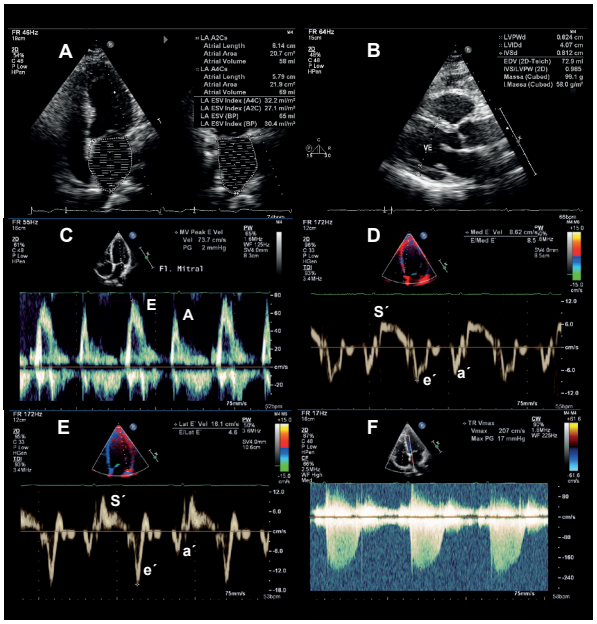

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Quality of Oral Anticoagulation in Atrial Fibrillation Patients at a Tertiary Hospital in Brazil

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Abstract

Background: Atrial fibrillation (AF) affects 0.5% to 2.0% of the general population and is usually associated with cardiac structural diseases, hemodynamic damage, and thromboembolic complications. Oral anticoagulation prevents thromboembolic events and is monitored by the international normalized ratio (INR).

Objectives To evaluate INR stability in nonvalvular AF patients treated with warfarin anticoagulation, to evaluate thromboembolic or hemorrhagic complications, and to identify the group at higher risk for thromboembolic or hemorrhagic events.

Methods: Data from the medical records of 203 patients who received medical care at a tertiary hospital in Brazil were reviewed, and the time in therapeutic range (TTR) was calculated using the Rosendaal method. The possible TTR influencing factors were then analyzed, and the relationship between the TTR and thromboembolic or hemorrhagic events was calculated. The level of significance was 5%.

Results: The mean TTR was 52.2%. Patients with INR instability in the adaptation phase had a lower mean TTR (46.8%) than those without instability (53.9%). Among the studied patients, 6.9% suffered hemorrhagic events, and 8.4% had a stroke. The higher risk group for stroke and bleeding consisted of patients with INR instability in the adaptation phase.

Conclusions: The quality of anticoagulation in this tertiary hospital in Brazil is similar to that in centers in developing countries. Patients with greater INR instability in the adaptation phase evolved to a lower mean TTR during follow-up, had a 4.94-fold greater chance of stroke, and had a 3.35-fold greater chance of bleeding. Thus, for this patient group, individualizing the choice of anticoagulation therapy would be advised, considering the cost-benefit ratio.

Keywords: Atrial Fibrillation; Hemorrhage; Warfarin; Stroke.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting from 0.5% to 2.0% of the general population.[1,2] Its prevalence increases with age, and it is generally associated with cardiac structural diseases, causing hemodynamic damage and thromboembolic complications with major economic implications and a significant impact on morbidity and mortality.[2-4]

The rate of stroke in nonvalvular AF patients is approximately 5% per year, which is 5 to 7-fold greater than that in patients without AF.[5] To prevent such cerebral embolic events, oral anticoagulation (OAC) is employed. Anticoagulation (with vitamin K antagonists (VKA), notably warfarin) in AF patients, regardless of clinical presentation, reduces stroke incidence by approximately 65% to 80%, diminishing the annual risk of stroke to 1.4% versus the 4.5% risk with placebo.[6,7]

The absorption, pharmacokinetics, and pharmacodynamics of warfarin may be influenced by genetic factors, diet, and drug interactions; these influential factors are capable of potentializing or decreasing the anticoagulating effect. The OAC goal is to effectively minimize thromboembolic risk without a significant impact on hemorrhage rates. This goal was achieved with an international normalized ratio (INR) of approximately 2.5 (2.0-3.0)[8,9] for nonvalvular AF patients.

VKA anticoagulation demands constant monitoring through the INR, which starts as early as 5 to 7 days after the onset of treatment and should be reevaluated at anytime if there is an alteration in diet or anticoagulant dosage and when introducing or withdrawing other drugs. The anticoagulation adaptation phase includes the first

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6 months of treatment. After the INR reaches stability, monitoring may be carried out every 4 weeks.

Long-term anticoagulation is not an easy task, and adherence to treatment is paramount in order to avoid hemorrhagic and thromboembolic complications in patients.

Low patient adherence to doctor's recommendations and poor doctor adherence to the guidelines are current challenges to effective oral anticoagulation treatment. The literature shows that no more than 50% of patients with OAC recommendations receive a prescription, and only 50-55% of those find themselves within the desirable range of OAC, with 30-40% unprotected (INR < 2.0) and 10-15% surpassing the upper INR limit of 3.0.[10]

The most employed tool currently used to evaluate anticoagulation quality in VKA users is calculating the time in therapeutic range (TTR).

This method, described by Rosendaal in 1993, uses a linear interpolation to assign an INR value to each day of the interval between the recorded measurements.[11]

Studies show that TTR values below 60% are related to a greater risk of death from all causes, major bleeding, stroke, and systemic thromboembolism.[12] In Brazil, there have been only a few studies employing the TTR method to evaluate the anticoagulation quality with VKA.

This study aimed to evaluate INR stability among permanent and nonvalvular AF patients who were anticoagulated with VKA and who are currently undergoing follow-up in the specialized anticoagulation outpatient clinic of the Clinical Hospital of the School of Medicine of Botucatu (HC-FMB-UNESP). This study also aimed to evaluate the thromboembolic and hemorrhagic complications in these patients and to identify the group at greater risk for thromboembolic or hemorrhagic events.

Patients and methods

This is a retrospective, longitudinal study in which 203 permanent and nonvalvular AF patients over 18 years of age, who had received follow-up for at least 24 months in the anticoagulation outpatient clinic of HC-FMB-UNESP between January 2009 and January 2015, were included. Patients who stayed for more than two consecutive months without doctor´s appointments in the outpatient clinic were excluded.

All procedures were submitted and approved by the Research Ethics Committee (CEP) of Botucatu Medical School (logged under protocol number 445.651).

The clinical and demographic variables, the occurrence of thromboembolic events (ischemic stroke, transitory ischemic accident, and peripheral emboli), and the occurrence of important hemorrhagic events, such as major bleeding (requiring medical treatment and/or blood transfusion) and life-threatening bleeding, were obtained through a review of patient medical records.

The TTR was calculated for each patient by dividing the time the patient remained with an INR within the range considered acceptable (2.0 to 3.0) by the patient's total follow-up time and multiplying the result of this division by 100% in order to evaluate the anticoagulation quality and the factors that might influence TTR. The relation between TTR and the occurrence of hemorrhagic or thromboembolic events were also analyzed.

Statistical analysis

Continuous variables with normal and non-normal distributions are presented as mean and standard deviation or median and ^{25th} and ^{75th} percentiles. The normality of numerical variables was assessed using the Shapiro-Wilk test. Categorical variables are presented as absolute values and percentages. The calculation of the TTR value followed the method described by Rosendaal in 1993. Thus, the TTR value was defined as: TTR= 100% x (total follow-up time with INR between 2 to 3) / total follow-up time, the total follow-up time with INR between 2 and 3 was calculated by having the time between two INR measurements (M1 and M2) and assigning one half of the time to the M1 value and the other half of the time to the value M2, and so on for all INR measurements made for a given patient. At the end of this process, it is possible to obtain the sum total of the time a patient spent with his INR between 2 and 3 and divided this time by the total time that this patient received follow-up.[11] Multiple logistic regression models were adjusted to explain the chance of stroke and bleeding as a function of TTR and other clinical variables that were statistically significant with $p < 0.20$ in the bivariate associations. In the final multiple regression model, associations were considered significant when $p < 0.05$. The analysis was performed with SPSS v21.0 software.

Results

A total of 203 patients with permanent and nonvalvular AF who were followed up in the anticoagulation outpatient clinic from January 2009 to January 2015 (for a minimum of 2 years and a maximum of 10 years) were evaluated through a review of their medical records. The guidelines of the American College of Chest Physicians[13] were used to monitor patients with anticoagulant therapy, and the patients had an average of 43 outpatient visits.

Clinical and demographic variables from these patients were analyzed and are presented in Table 1.

Using the linear interpolation method proposed by Rosendaal, the TTR of each patient was calculated, obtaining a median TTR of 53 (10-88) and a mean of 52.21% (Figure 1).

The factors that influenced the TTR value in this population were analyzed, and the instability of the INR in the adaptation phase presented an inverse relationship with the final value of the TTR. Patients who presented an unstable INR in the adaptation phase (INR out of therapeutic level more than 60% of the time in the first 6 months of treatment) had a lower mean TTR (46.83%) than patients without instability (53.88%) (Figure 2).

Table 1 – Clinical and demographic characteristics of all patients (n=203 patients)

Variables	n	%
Age (years)	68 ± 9.7	
Nonwhite race	11	5.4
CHA2DS2VASc	3 (3-4)	
Heart failure	78	38.4
Hypertension	175	86.2
Age 75 years or older	67	33.0
Diabetes mellitus	53	26.1
Previous stroke or TIA	35	17.2
MI, AoP, or PAD	52	25.6
Age between 65 and 74 years	66	32.5
Male	114	56.2
Number of visits	42 (26-63)	
HAS-BLED	2 (1-3)	
Previous bleeding	2	1.0
Altered renal function	22	10.8
Altered liver function	1	0.5
Alcoholism	9	4.4
Hyperlipidemia	82	40.4
Smoking	67	33.0
Sedentary lifestyle	132	65.0
Antiplatelet use	26	12.8
INR instability during adaptation	48	23.6
TTR (%)	52 ± 17.2	
TTR under 60%	129	63.5
TTR under 65%	148	72.9
TTR under 70%	171	84.2
Stroke during anticoagulation	17	8.4
Bleeding during anticoagulation	14	6.9
Stroke or bleeding during anticoagulation	30	14.8

Continuous variables are presented as mean ± standard deviation when normally distributed and median and interquartile range (25%-75%) when non-normally distributed. Categorical variables are presented in absolute values and percentages. TIA: transitory ischemic attack; MI: previous myocardial infarction; AoP: aortic plaque; PAD: peripheral artery disease; INR: international normalized ratio; TTR: time in therapeutic range.

Among the 203 studied patients, 14 (6.9%) suffered hemorrhagic events, and 17 (8.4%) suffered ischemic stroke. When the relationship between the occurrence of major events (stroke and bleeding) and TTR value was analyzed, it was concluded that a low TTR (<60%) was associated with a greater occurrence of stroke (Figure 3).

Another factor associated with a greater occurrence of stroke was INR instability in the adaptation phase. Among patients with unstable INR during the adaptation period, the stroke risk was

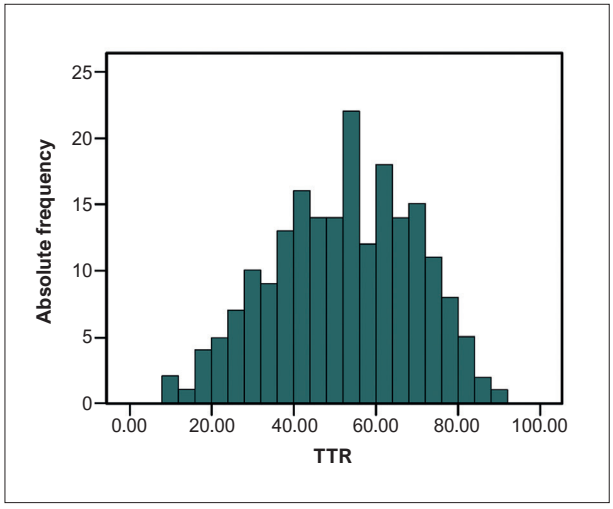

Figure 1 – *Histogram of TTR values.*

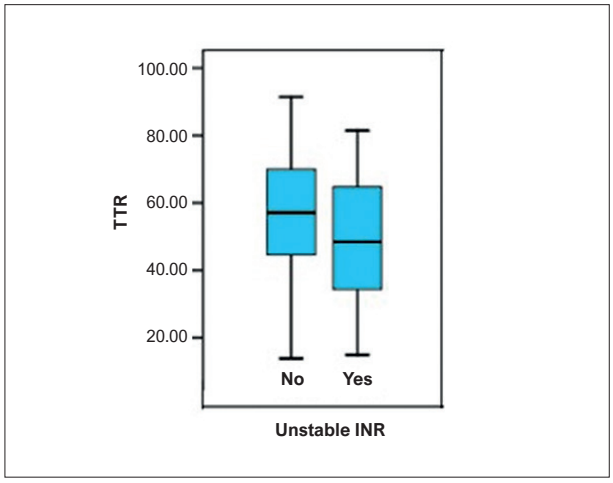

Figure 2 – *Box-plot of TTR values according to instability during the adaptation phase.*

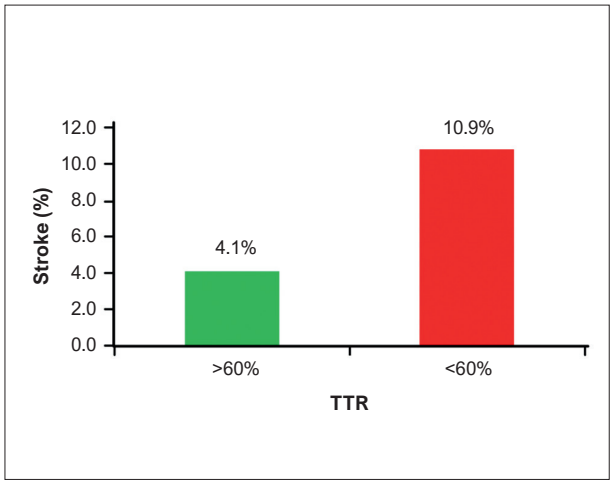

Figure 3 – *Percentage of patients with stroke according to TTR value during follow-up.*

4.94-fold greater (OR=4.94 (1.62 – 15.02); p = 0.005) than that in those without instability (Tables 2 and 3).

In the analysis of the factors related to bleeding, it was perceived that patients with INR instability during the adaptation phase had a 3.35-fold greater chance of bleeding than those without instability (Tables 4 and 5).

Discussion

In this study, performed at a public hospital, the individual TTRs were calculated, and the mean value was 52.2%. This average TTR is slightly smaller than that described in a private hospital study, which presented a mean TTR of 56.6% (± 18,9).[14] The literature considers TTR levels over 60% an indicator of good anticoagulation quality,[15] and in the present study, only 36.5% of patients found themselves with a TTR over 60%. The SPORTIF III and V study,[12] which included 3,587 patients, showed that patients with a TTR under 60% presented higher mortality (4.20%) and major bleeding (3.85%) rates when compared with the group with a TTR between 60% and 75% (1.84% and 1.96%, respectively), as well as with the group with a TTR over 75% (1.69% and 1.58%, respectively). Although it is related to a smaller occurrence of adverse events, such as bleeding or thromboembolic events, a TTR over 60% is not easily achieved in developing countries such as Brazil. The ROCKET AF study[16] carried out with 6,983 patients from 1,178 centers from 45 countries demonstrated that the TTR, calculated according to the Rosendaal method, varies according to region, with a mean TTR of 50.4% for patients from East Asia, 35.9% for patients from India, 49.7% for patients from East Europe, 54.8% for patients from South Africa and 55.2% for patients from Latin America, 63.2% for patients from Western Europe, and 64.1% for patients from Canada/United States. A higher TTR was found among those patients followed up in a specialized anticoagulation outpatient care facility.[15,17]

In the present study, the clinical and demographic characteristics of patients were evaluated, along with the TTR value, and an association between INR instability in the anticoagulation adaptation phase and a lower TTR was found, meaning that patients with unstable INR values during the adaptation phase presented a lower TTR (46.83%) during the entire treatment.

This study also established a relationship between low TTR and the occurrence of stroke, showing that the worse the anticoagulation quality, the greater the chance of stroke. The patients with a mean TTR under 60% presented a 2.88-fold greater chance of stroke than those with a mean TTR over 60%. Another finding of this study was that patients who presented an unstable INR during the adaptation phase had a 4.94-fold greater risk of stroke and a 3.35-fold greater risk of bleeding than those who did not have INR instability.

Regarding the occurrence of bleeding, we did not find a statistically significant relationship with a low mean TTR. This finding may be related to the fact that patients who maintained a lower TTR in this study mainly presented INR measures below the therapeutic range and, therefore, with greater predisposition to stroke than bleeding.

The mean TTR value and the occurrence of events are related to the adherence to anticoagulation therapy, and some factors lead to a nonadherence to VKA. INR instability, in addition to a narrow therapeutic range, variable metabolism, and potential diet and drug interactions, is a well-established limitation of VKA. This fact pushed the emergence of new anticoagulation therapies, and several important studies on direct oral anticoagulants (DOAC) were published.[18-20] These studies revealed a similar impact of reducing thromboembolic events when compared to warfarin, but the DOACs had similar or superior safety profiles. In addition, as DOACs reach the onset of an anticoagulation effect more quickly than AVK, and their actions are more predictable, there is less need for frequent therapeutic monitoring, which contributes to greater persistence with any DOAC than for VKA, as seen by Aya F. Ozaki et al.[21]

Although VKA has the previously described limitations, the disseminated use of DOAC in developing countries is challenged by cost limitations, as the costs are still extremely high. However, several studies in Europe, the United States, Canada, China, and South Africa were published to evaluate cost-effectiveness, in which each DOAC was individually compared with warfarin. In all of these, it was clear that the DOAC presented a greater cost-effectiveness than warfarin.[22]

According to a study carried out in Brazil, the monthly cost in dollar per patient who received anticoagulation with warfarin is $54.26, considering the expenses of health professionals involved in the anticoagulation outpatient visits, laboratory costs for INR monitoring, warfarin acquisition, and indirect costs, such as days of work missed and transportation to clinic. The mean monthly costs of apixaban, dabigatran, and rivaroxaban for public institutions (from January 1st to August 19th, 2015) were $49.87, $51.40, and $52.16, respectively, showing that the cumulative costs per patient followed up in an anticoagulation clinic are higher for warfarin than for DOACs.[23]

However, when exclusively evaluating AF patients, warfarin costs were similar to DOAC.[23] In this case, the comfort and better adherence to treatment provided by a DOAC, since the patient does not need anticoagulation level monitoring, the fast onset and end of the anticoagulation effect, low drug interaction, absence of diet interaction, and, most importantly, the reduction in cerebral hemorrhagic events should be taken into account, especially in some specific patient groups, such as those with INR instability during the adaptation phase, which would most likely benefit from the efficacy and safety of a DOAC.

Study limitations

The main limitations of this study are the sample size, which may be small for the purposes of the study, and the failure to address aspects of adherence to the use of VKA.

Conclusion

The results of this study allow us to conclude that the TTR of patients who received follow-up at the anticoagulation outpatient clinic of the Clinical Hospital of the School of Medicine of Botucatu (HC-FMB-UNESP), from January 2009 to January 2015, was below what is described as ideal in the literature, as occurs in other developing countries. It can also be concluded that the instability of the INR in the adaptation phase was a causal factor for both a low TTR and

Table 2 – Logistic regression for stroke risk (bivariate associations)

Variables	OR	95% CI		p
CHA2DS2VASc	1.29	0.92	1.81	0.135
Heart failure	1.13	0.41	3.11	0.808
Hypertension	2.08	0.00	.	0.998
Age 75 years or older	0.60	0.19	1.92	0.390
Diabetes mellitus	1.61	0.57	4.60	0.371
Previous stroke or TIA	2.95	1.01	8.62	0.047
MI, AoP, or PAD	1.23	0.41	3.68	0.708
Age among 65 and 74 years	0.85	0.29	2.53	0.776
Male	0.67	0.25	1.82	0.432
HAS-BLED	1.31	0.79	2.18	0.288
Previous bleeding	0.00	0.00	.	0.999
Altered renal function	1.11	0.24	5.20	0.898
Altered liver function	0.00	0.00	.	1.000
Alcoholism	1.39	0.16	11.83	0.763
Hyperlipidemia	0.79	0.28	2.23	0.655
Smoking	2.48	0.91	6.76	0.075
Sedentary lifestyle	1.32	0.45	3.91	0.616
Antiplatelet use	0.90	0.19	4.18	0.893
INR instability during adaptation	3.24	1.18	8.95	0.023
TTR	0.99	0.96	1.02	0.348
TTR under 60%	2.88	0.80	10.38	0.106
TTR under 65%	2.99	0.66	13.52	0.155
TTR under 70%	2.08	0.00	.	0.998

TIA: transitory ischemic accident; MI: previous myocardial infarction; AoP: aortic plaque; PAD: peripheral artery disease; INR: international normalized ratio; TTR: time in therapeutic range.

Table 3 – Logistic regression for stroke risk (parsimonious model)

Variable	OR	95% CI		p
CHA2DS2VASc	1.62	1.04	2.53	0.031
Smoking	3.38	1.14	10.06	0.028
INR instability during adaptation	4.94	1.62	15.02	0.005

INR: international normalized ratio.

Table 4 – Logistic regression for bleeding risk (bivariate associations)

Variables	OR	95% CI		p
CHA2DS2VASc	1.01	0.69	1.47	0.979
Heart failure	0.25	0.05	1.14	0.073
Hypertension	2.17	0.27	17.25	0.465
Age 75 years or older	1.14	0.37	3.54	0.823
Diabetes mellitus	2.27	0.75	6.87	0.148
Previous stroke or TIA	0.35	0.04	2.77	0.321
MI, AoP, or PAD	0.78	0.21	2.91	0.711
Age between 65 and 74 years	1.61	0.54	4.85	0.395
Male	0.56	0.19	1.69	0.304
HAS-BLED	2.41	1.38	4.21	0.002
Previous bleeding	14.46	0.86	244.62	0.064
Altered renal function	3.80	1.08	13.36	0.037
Altered liver function	0.00	0.00	.	1.000
Alcoholism	1.74	0.20	15.00	0.614
Hyperlipidemia	0.81	0.26	2.50	0.712
Smoking	1.57	0.52	4.74	0.420
Sedentary lifestyle	3.45	0.75	15.87	0.112
Antiplatelet use	1.15	0.24	5.44	0.864
INR instability during adaptation	3.61	1.20	10.88	0.023
TTR	1.01	0.98	1.04	0.642
TTR under 60%	0.75	0.25	2.25	0.607
TTR under 65%	0.65	0.21	2.03	0.455
TTR under 70%	1.13	0.24	5.32	0.875

TIA: transitory ischemic accident; MI: previous myocardial infarction; AoP: aortic plaque; PAD: peripheral artery disease; INR: international normalized ratio; TTR: time in therapeutic range

Table 5 – Logistic regression for bleeding risk (parsimonious model)

Variables	OR	95% CI		p
Diabetes mellitus	2.28	0.71	7.25	0.162
Altered renal function	2.57	0.68	9.64	0.160
INR instability during adaptation	3.35	1.06	10.57	0.039

INR: international normalized ratio.

a higher occurrence of ischemic stroke and bleeding in the population studied.

Author contributions

Conception and design of the research: Malagutte KNC, Hueb JC, Okoshi K, Nunes HRC, Martin LC, Bazan R, Bazan SGZ; Acquisition of data: Malagutte KNC, Silveira CFSP, Reis FM, Rossi DAA; Analysis and interpretation of the data: Malagutte KNC, Silveira CFSP, Reis FM, Rossi DAA, Hueb JC, Okoshi K, Nunes HRC, Martin LC, Bazan R, Bazan SGZ; Statistical analysis: Nunes HRC; Writing of the manuscript: Malagutte KNC, Silveira CFSP, Reis FM, Rossi DAA, Hueb JC, Okoshi K, Martin LC, Bazan R, Bazan SGZ; Critical revision of the manuscript for intellectual content: Bazan SGZ.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Karina Nogueira Dias Secco Malagutte, from Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Unesp.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Medicina de Botucatu under the protocol number 445.651. 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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Anticoagulation Therapy with Warfarin: A Reality of Brazilian Public Health that Lacks Structure for Better Control

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Short Editorial related to the article: Quality of Oral Anticoagulation in Atrial Fibrillation Patients at a Tertiary Hospital in Brazil

The increase in longevity in recent decades has led to a progressive increase in the prevalence of atrial fibrillation (AF) worldwide.[1,2]

As a result, anticoagulation therapy has become increasingly indicated in preventing thromboembolic events. The need for continuous use drove the preference for oral anticoagulants, historically represented by antivitamin K (VKA) drugs and, more recently, by new anticoagulants (anti-factor X). Among these, a VKA, warfarin, is the most prominent for its low cost.

However, because warfarin has a narrow therapeutic window, its use requires a balance between avoiding underdoses that cannot prevent thromboembolic events and overdoses that can cause bleeding. This handling of warfarin is hampered by the enormous inter-individual variability of drug response and a large number of interactions with other drugs and foods.[3]

Warfarin is among the ten drugs most related to dispensing errors. In the United States and Australia, oral anticoagulants are among the five classes most related to serious events secondary to medication use.[4]

In Brazil, the Institute for Safe Practices in the Use of Medicines (IPSM) includes warfarin as a high surveillance drug and potentially dangerous use.[5] The ideal dose of warfarin adjustment is monitored by the International Normalized Ratio (INR), and the drug efficiency is estimated by the time in the therapeutic range (TTR), period of INR with values between 2.0 and 3.0. There are few data on TTR in patients with AF in community practice, but this tool needs to be increasingly disseminated.

The use rate of warfarin in the public health network in Brazil is high, and the cost-effectiveness is controversial.[6] There are serious practical barriers to its use in our country: low adherence caused by limited financial resources and/or low sociocultural status, as well as the complexity of drug handling by health professionals. In this sense, there is evidence that Brazilian physicians are unfamiliar with the proper administration of warfarin to patients.

Colet et al.[7] reported the low knowledge of public health professionals at a public hospital in the Rio Grande do Sul about using warfarin. The authors found no institutional strategy to address the issue and suggest that health services include education programs for those most vulnerable to adverse events to increase patient safety.

Pokorney et al.[8] reported specific findings of warfarin anticoagulation in 5,210 patients from the American AF Registry (ORBIT-AF). Over 18 months, the mean TTR was 65% ± 20%, with a median of 68%. Patients with TTR ≤ 53% were more often female and had less college education than patients with higher TTR. Patients with diabetes mellitus, renal failure, or cardiomyopathy were also less likely to have an elevated TTR. However, the striking finding of this study was the association of TTR values significantly higher ($p < 0.0001$) among patients seen in the clinic of anticoagulation (69%) versus general outpatient care (66%)

In this issue of *Arquivos Brasileiros de Cardiologia*, Bazan et al.[9] report that in a study performed in a tertiary hospital in the state of São Paulo, the mean TTR value of 52.2% among 203 patients with non-valvular AF. The authors considered this finding acceptable, associating it with cultural and socioeconomic factors. The manuscript contains valuable information but reveals the limitations of our public system in preventing thromboembolic phenomena in this population.

TTR values lower than 60% are indicative of poor anticoagulation quality. In the study by Bazan et al.[9] 63.5% of patients had TTR values below 60%, associating this population with higher rates of global mortality, major bleeding, stroke and systemic thromboembolism.[10] The average values estimated for Western Europe and Canada/United States countries are 63.2% and 64.1%.[10] Even for Latin America, the average value (55.2%)11 is higher than that reported by Bazan et al.[9]

On the other hand, the most relevant finding of this study, the association between INR instability in the anticoagulation adaptation phase with higher rates of adverse events, corroborated the lack of control of the global process because it corresponded to very low mean TTR values (mean of 46 .83%).

Therefore, it is concluded that to optimize success rates of anticoagulation with warfarin in our country, it is necessary to create multidisciplinary anticoagulation clinics composed of physicians, pharmacists, nurses, social workers and psychologists.

Anticoagulation clinics should operate through care protocols for handling warfarin by the multidisciplinary team and educational programs aimed at patients.

Finally, it is important to highlight that the goals for controlling the use of warfarin by our public health system must focus on the efficiency rates obtained by the best centers in the world, as we have done with numerous successful national programs.

Keywords

Atrial Fibrillation; Anticoagulants/therapeutic use; Stroke; Hemorrhage; Thromboembolism; Warfarin/adverse effects.

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Clinical Significance of Peptidase M20 Domain Containing 1 li Patients with Carotid Atherosclerosis

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Abstract

Background: **Atherosclerosis is the main cause for most cardiovascular diseases, and new biomarkers for this condition are always needed. Peptidase M20 domain containing 1 (PM20D1) is associated with both lipid metabolism and obesity. However, no study focuses on the role of PM20D1 in carotid atherosclerosis.**

Objective: **The present study aimed to investigate the role of PM20D1 in carotid atherosclerosis patients.**

Methods: **The present prospective observational study contained a total of 231 carotid atherosclerosis patients, who went to our department between July 2018 and December 2019. Blood samples and medical characteristics were also obtained from 231 healthy individuals with the same body mass index distribution of carotid atherosclerosis patients. Serum PM20D1 was determined using enzyme-linked immunosorbent assay. Clinical and demographic characteristics of all patients were collected, including age, sex, body mass index and medical history. Levels of C-reactive protein, tumor necrosis factor, homocysteine, as well as total cholesterol, triglyceride, high-density leptin cholesterol and low-density leptin cholesterol were recorded. Statistical analysis was conducted using the SPSS software, with $p<0.05$ as statistically different.**

Results: **Serum PM20D1 levels were markedly lower in carotid atherosclerosis patients when compared to the healthy control, which were significantly lower in severe carotid atherosclerosis patients and carotid atherosclerosis/stroke patients. Patients with unstable plaques showed markedly lower PM20D1 when compared to patients with stable plaques. No significant difference was found among carotid atherosclerosis patients with different body mass index. Patients with higher PM20D1 levels showed significantly lower expression of C-reactive protein, tumor necrosis factor, homocysteine, triglyceride, total cholesterol and low-density leptin cholesterol. PM20D1 was negatively correlated with C-reactive protein, tumor necrosis factor, homocysteine, total cholesterol and low-density leptin cholesterol in carotid atherosclerosis patients, and could be used as a biomarker for severe carotid atherosclerosis patients or carotid atherosclerosis patients with stroke. Sex, tumor necrosis factor, homocysteine and PM20D1 were risk factors for carotid atherosclerosis.**

Conclusion: **PM20D1 was decreased in carotid atherosclerosis patients and was associated with severity, plaque stability, and levels of C-reactive protein, tumor necrosis factor, homocysteine, triglyceride, total cholesterol and low-density leptin cholesterol in carotid atherosclerosis patients.**

Keywords: **Carotid Artery Diseases; Lipids; Body Mass Index.**

Introduction

As the main cause of most cardiovascular diseases, atherosclerosis (AS) can occur early in lifetime and remain asymptomatic for long periods before onset.[1,2] Among kinds of atherosclerosis, carotid atherosclerosis (CAS) is thought to be a predictor for ischemic stroke.[3] It is reported that carotid plaque is a risk factor for ischemic stroke, which is also associated with the cadmium, and increased carotid intima-media thickness and presence of carotid plaque are associated with increased risk of ischemic stroke in individuals with atrial fibrillation.[4,5] Many risk factors are reported to be associated with CAS, including dysfunction of lipid metabolism,[6] hypertension,[7] diabetes,[8] age,[9] smoking[10] etc. However, deeper insights are still needed for CAS onset and clinical outcomes.

Peptidase M20 domain containing 1 (PM20D1) is a newly identified secreted enzyme enriched in uncoupling protein 1 (UCP1+), versus UCP1- adipocytes.[11] A recent

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study found PM20D1 is associated with lipid metabolism and might be associated with obesity,[12] which are all risk factors for CAS. It was also found that PM20D1 could regulate lipidated amino acid uncouplers of mitochondria and increased PM20D1 augmented energy expenditure.[13] However, up to now, no study focuses on the role of PM20D1 in CAS.

The present research performed a prospective observational study in order to investigate the clinical significance of PM20D1 in CAS patients. This research might provide clinical evidence for the role of PM20D1 in CAS.

Methods and materials

Patients

The present prospective observational study enrolled a total of 231 CAS patients, who went to our department between July 2018 and December 2019. The inclusion criteria were: 1) all patients were diagnosed as CAS according to color Doppler ultrasound of neck blood vessels and aortic arch intracranial computed tomography angiography (CTA); 2) CAS patients with stroke were admitted within 72 hours after onset, and the diagnosis of stroke was confirmed by magnetic resonance imaging (MRI) and computed tomography (CT) scan; 3) patients agreed to participate in the observational research. The following patients were excluded: 1) patients with cerebral aneurysm, arteriovenous malformation, dissection, arteritis or moyamoya disease; 2) patients with cardiogenic cerebral embolism; 3) patients with other severe system diseases, including cancer and heart, renal or liver dysfunction. The severity of CAS was defined as: 1) mild/moderate CAS group, who showed thickening of the intima-media, with intima-media thickness (IMT) >1.0 mm, or plaque information with arterial stenosis <70% and without stroke; 2) severe CAS group, who showed one or more plaques with arterial stenosis ≥70% and without stroke; 3) CAS combined with stroke group, who showed CAS combined with large artery atherosclerotic ischemic stroke and cerebral vascular stenosis >50%. The plaques were divided into stable and unstable plaques as widely accepted in clinic: 1) IMT≥1.2 mm was considered as plaque; 2) the stable plaques are plaques with uniform strong echo or medium echo; 3) the unstable plaques are soft plaque or ulcerative plaque with mixed echo or low echo.[14] The measurement of IMT was conducted using a LOGIQ C9 Color Doppler ultrasound diagnostic instrument (General Electric, United States of America) with probe frequency of 7~14 MHz. The IMT of bilateral common carotid artery, proximal, distal and 1 cm from the bifurcation of common carotid artery were measured. All measurement was conducted at least three times and the mean value was considered as the final IMT value.

Additionally, patients were further divided into different body mass index (BMI) groups: the normal group, with BMI<24 kg/m^2; the overweight group, with 28 kg/m^2>BMI≥24 kg/m^2; and the obesity group, with BMI>28 kg/m^2.[15] Blood samples and medical characteristics were also obtained from 231 healthy individuals, who came to routine physical examination with the same BMI distribution of CAS patients. All patients signed the informed consent. The present study was approved by the ethical committee of the Fourth People's Hospital of Chengdu (CDH-2018-057).

Measurement of PM20D1

The blood samples of all cases were collected within 24 hours of admission or coming to outpatient. Briefly, 5 ml of blood was collected into tubes without any anticoagulant. After 1 hour, centrifugation was conducted at 2,000 g for 15 minutes, in room temperature, and the serum samples were obtained. The serum PM20D1 levels were measured by enzyme-linked immunosorbent assay (ELISA), using a PM20D1 kit (MYBioSource, cat. no. MBS280518), strictly according to the manufacturer's instruction.

Data collection and measurement

Clinical and demographic characteristics of all patients were collected, including age, sex, BMI and medical history. Routing whole blood test was performed using an automatic biochemical analyzer (Hitachi 7600, Hitachi Corporation, Japan), and the levels of C-reactive protein (CRP), tumor necrosis factor (TNF-□), homocysteine (Hcy), as well as total cholesterol (TC), triglyceride (TG), high-density leptin cholesterol (HDL-ch) and low-density leptin cholesterol (LDL-ch), were recorded.

Statistical analysis

Data distributed normally was expressed by mean ± standard deviation (SD), and non-normal distributed data was expressed as median (interquartile range). Categorical variables were shown as number (rates). The distribution of the data was analyzed by Kolmogorov-Smirnov method. For normally distributed data, comparison between two groups was conducted by unpaired t-test and one-way analysis of variance (ANOVA), followed by Tukey's post hoc test, which was used for comparison among three or more groups. For non-normal distributed data, Mann-Whitney test was used for comparison between two groups, and Kruskal-Wallis test was used for comparison among three or more groups, following with Dunn's post hoc test. Rates were analyzed using chi-squared test. Correlation among PM20D1, Hcy, lipid metabolism and inflammatory factors was analyzed using the Pearson's correlation. A receiver operating characteristic (ROC) curve was used for analysis of PM20D1 in CAS patients. Logistic regression was used for analysis of risk of CAS. $p<0.05$ was considered as statistically different. All calculation was performed using SPSS 25.0 (SPSS Inc., Chicago, United States of America) or GraphPad 6.0 (GraphPad Software, San Diego, California, United States of America).

Results

Basic clinical characteristics of all patients

This research included a total of 231 CAS patients, with 152 cases of mild/moderate CAS, 50 cases of severe CAS and 29 cases of CAS with stroke. The ratio of the sum of overweight and obesity patients was significantly higher in severe CAS patients when compared to the mild/moderate patients (Table 1). The ratio of unstable plaque was significantly higher in severe CAS and CAS/stroke patients. The levels of CRP, TNF-α and Hcy were markedly higher in severe CAS patients and CAS/stroke patients when compared to the mild/moderate patients. Only TG, TC and LDL-ch were found to be remarkably higher in severe CAS patients and CAS/stroke patients when compared to the mild/moderate cases. Besides, the healthy control showed significantly lower levels of CRP, TNF-α and Hcy, as well as TG, TC and LDL-ch than all CAS patients. No other significant difference was found.

PM20D1 was associated with severity and plaque stability of CAS patients

Then, the expression of serum PM20D1 in CAS patients was determined. It was found that serum PM20D1 levels were markedly lower in CAS patients when compared to the healthy control (Figure 1). Severe CAS patients and CAS/stroke patients showed significantly lower PM20D1 levels when compared to the mild/moderate patients. However, no significant difference was found between severe and CAS/stroke patients. Additionally, patients with unstable plaques showed markedly lower PM20D1 expression than patients with stable plaques.

Table 1 – Basic clinical characteristics of all patients

Variables	All CAS, n=231	Mild/moderate CAS, n=152	Severe CAS, n=50	CAS/stroke, n=29	Healthy, n=231	P1*	P2#
Age, y	57.85±9.04	58.17±9.35	58.32±8.90	55.37±7.37	58.36±8.97	0.543	0.289
Sex, female (%)	105 (45.45)	64 (42.11)	25 (50.00)	16 (55.17)	108 (46.75)	0.854	0.177
BMI, n (%)						0.968	0.176
<24 kg/m^2	98 (42.42)	65 (42.76)	15 (30.00)	8 (27.59)	102 (44.16)		
28 kg/m2>BMI≥24 kg/m^2	76 (32.90)	48 (31.58)	20 (40.00)	11 (37.93)	73 (31.60)		
>28 kg/m^2	57 (24.68)	39 (25.66)	15 (30.00)	10 (34.48)	56 (24.24)		
Complications, n (%)						-	0.993
Diabetes	62 (26.84)	39 (25.66)	15 (30.00)	8 (27.59)	-		0.790
Hypertension	114 (49.35)	75 (49.34)	24 (48.00)	15 (51.72)	-		0.868
History of coronary heart disease	41 (17.75)	27 (17.76)	9 (18.00)	5 (17.24)	-		0.990
History of stroke	12 (5.19)	7 (4.61)	3 (6.00)	2 (6.90)	-		0.804
Current smoker	129 (55.84)	87 (57.24)	24 (48.00)	18 (62.07)	97 (41.99)	0.090	0.126
Plaque, n (%)					-	-	<0.001
Stable	103 (44.59)	81 (53.29)	17 (34.00)	5 (17.24)	-		
Unstable	128 (55.41)	71 (46.71)	33 (66.00)	24 (82.76)	-		
CRP, mg/L	6.91 (0.52~34.87)	5.13 (0.52~9.99)	17.01 (2.92~34.87)	13.40 (3.01~33.64)	4.23 (0.57~10.01)	<0.001	<0.001
TNF-α, pg/ml	24.18±12.99	17.45±4.40	37.01±14.70	37.34±13.59	14.81±2.81	<0.001	<0.001
Hcy, μmol/L	12.28±3.22	10.78±2.34	15.08±2.72	15.33±2.61	7.46±1.45	<0.001	<0.001
TC, mmol/L	4.26±0.78	4.00±0.66	4.80±0.72	4.66±0.84	3.96±0.68	<0.001	<0.001
TG, mmol/L	1.48±0.51	1.37±0.54	1.65±0.40	1.77±0.36	1.28±0.45	<0.001	<0.001
LDL-ch, mmol/L	3.01±0.55	2.87±0.44	3.25±0.61	3.33±0.66	2.74±0.41	<0.001	<0.001
HDL-ch, mmol/L	1.15±0.08	1.15±0.07	1.16±0.08	1.15±0.09	1.16±0.08	0.473	0.735

**P1 comparison between all carotid atherosclerosis (CAS) and the healthy control. #P2 comparison among mild/moderate, severe and CAS/stroke patients. One-way analysis of variance followed by Tukey's post hoc test was used for normally distributed data. For non-normal distributed data, Kruskal-Wallis test was used for comparison among mild/moderate, severe and CAS/stroke patients, following with Dunn's post hoc test. Rates were analyzed using chi-squared test.*
BMI: body mass index; CRP: C-reactive protein; TNF-α: tumor necrosis factor; Hcy: homocysteine; TC: total cholesterol; TG: triglyceride; LDL-ch: low-density leptin cholesterol; HDL-ch: high-density leptin cholesterol.

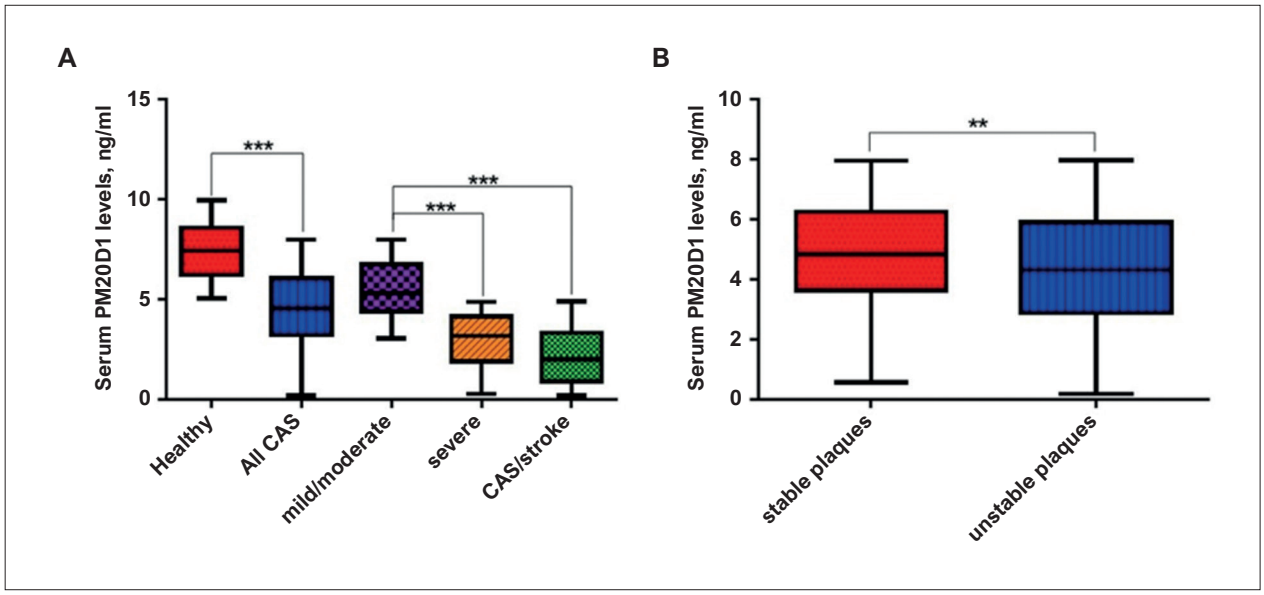

Figure 1 – *Serum levels of PM20D1 in carotid atherosclerosis (CAS) patients with different severity and plaque stability. ***p<0.001, **p<0.01.*

PM20D1 was not associated with carotid atherosclerosis patients with different body mass index

To further investigate the role of PM20D1 in CAS patients, we also evaluated the levels of PM20D1 in CAS patients with different BMI distribution. No significant difference was observed among patients with different BMI (Figure 2).

Correlation between PM20D1, lipid metabolism and inflammatory factors

Then, patients were divided into PM20D1 high expression group and low expression group, according to the mean level of PM20D1 (4.53 ng/ml). It was observed that patients with higher PM20D1 levels showed significantly lower expression of CRP, TNF-α, Hcy, TG, TC and LDL-ch (Table 2). Pearson's correlation was then conducted and results showed that PM20D1 was negatively correlated with CRP, TNF-α, Hcy, TC and LDL-ch in CAS patients (Table 3).

Diagnostic value of PM20D1 in carotid atherosclerosis

At last, a ROC curve was drawn in order to see the diagnostic value of PM20D1 for CAS, as well as severe CAS or CAS/stroke. It was found PM20D1 could be a potential diagnostic biomarker of CAS with cutoff value of 5.94 ng/ml, area under the ROC curve (AUC) 0.876, 95%CI (0.845~0.906), sensitivity 80.1% and specificity 73.6% (Figure 3). PM20D1 could also be used as a biomarker for severe CAS patients or CAS patients with stroke, with cutoff value of 3.99 ng/ml, AUC 0.917, 95%CI (0.883~0.951), sensitivity 81.6%, specificity 77.2%. Further binary logistic regression which included all factors of age, BMI, CRP, TNF-□, Hcy, TC, TG, LDL-ch, HDL-ch,PM20D1, as well as sex, diabetes, hypertension, history of coronary heart disease, history of stroke and current smoker, showed sex, TNF-α, Hcy and PM20D1 were risk factors for CAS (Table 4).

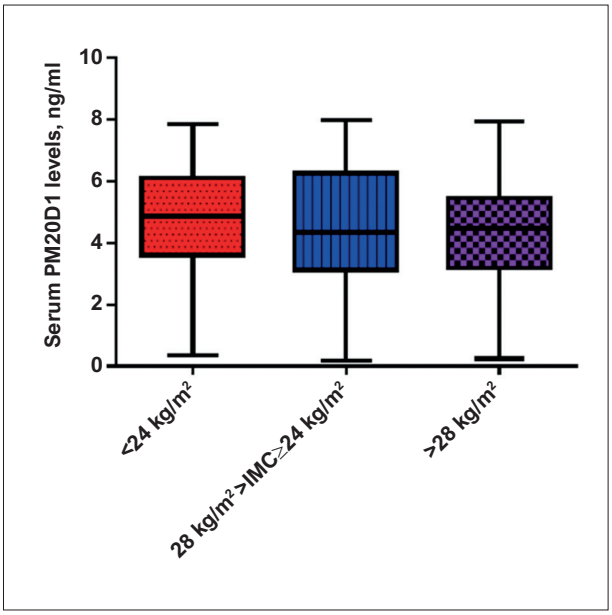

Figure 2 – *Serum levels of PM20D1 in carotid atherosclerosis (CAS) patients with different body mass index (BMI).*

Discussion

Early diagnosis and prediction of CAS can greatly improve the treatment efficacy and prognosis. Thus, biomarkers for diagnosis and prognosis of CAS are of great significance. In the present study, we demonstrated that PM20D1 was down-regulated in CAS patients and was associated with the severity and plaque condition of CAS patients. Besides, PM20D1 was negatively correlated with CRP, TNF-α, Hcy, TC and LDL-ch in CAS patients.

Lipid metabolism and obesity are both associated with development of CAS. It was found that levels of TG, TC and

Table 2 – Expression of lipid metabolism and inflammatory factors in patients with different PM20D1

Variables	PM20D1 high, n=117	PM20D1 low, n=114	p*
CRP, mg/L	5.27 (0.52~33.64)	15.16 (0.68~34.87)	<0.001
TNF-α, pg/ml	18.78±7.32	29.72±15.08	<0.001
Hcy, μmol/L	11.26±2.66	13.34±3.41	<0.001
TC, mmol/L	4.03±0.70	4.49±0.80	<0.001
TG, mmol/L	1.41±0.54	1.56±0.47	0.031
LDL-ch, mmol/L	2.90±0.48	3.12±0.59	0.003
HDL-ch, mmol/L	1.14±0.08	1.16±0.08	0.269

**Student's t-test was used for comparison among mild/moderate, severe and CAS/stroke patients for normally distributed data. For non-normal distributed data, Mann-Whitney test was used for comparison between two groups. Rates were analyzed using chi-squared test. CRP: C-reactive protein; TNF-α: tumor necrosis factor; Hcy: homocysteine; TC: total cholesterol; TG: triglyceride; LDL-ch: low-density leptin cholesterol; HDL-ch: high-density leptin cholesterol.*

Table 3 – Correlation between PM20D1, homocysteine (Hcy), lipid metabolism and inflammatory factors

Variables	Pearson's correlation	p value
CRP, mg/L	-0.514	<0.001
TNF-α, pg/ml	-0.585	<0.001
Hcy, μmol/L	-0.598	<0.001
TC, mmol/L	-0.254	<0.001
TG, mmol/L	-0.059	0.198
LDL-ch, mmol/L	-0.071	0.126
HDL-ch, mmol/L	0.022	0.622

CRP: C-reactive protein; TNF-α: tumor necrosis factor; Hcy: homocysteine; TC: total cholesterol; TG: triglyceride; LDL-ch: low-density leptin cholesterol; HDL-ch: high-density leptin cholesterol.

LDL-ch were significantly higher in patients with carotid artery plaque.[16] Another research found that treatment of atorvastatin or ezetimibe obviously decreased the levels of TC, TG and LDL-ch in CAS patients.[17] In a recent study, Pan *et al*. showed that, in low-income rural residents in China, LDL-ch and TC were risk factors for early-stage atherosclerosis and carotid plaque risk increased by 24% and 62% for each 1-mmol/L increase in TC and LDL-ch.[18] In our research, we also found that TG, TC and LDL-ch were highly expressed in CAS patients, especially in severe CAS cases, which was consistent with the aforementioned researches. Besides, we also observed that inflammatory factors such as CRP, TNF-α and expression of Hcy were elevated in CAS patients, which was also demonstrated in several researches.[19-22]

PM20D1 is a factor associated with both lipid metabolism and obesity. It was found that mice with increased circulating PM20D1 showed increased breathing and increased serum N-acyl amino acids, which improved glucose homeostasis and increased energy consumption, and thus might regulate

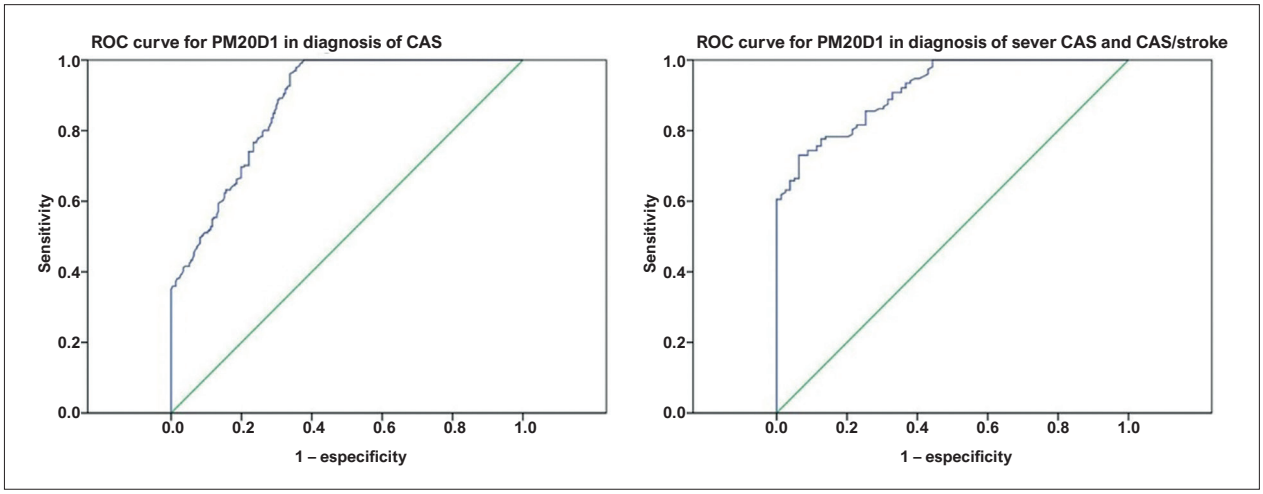

Figure 3 – *Receiver operating characteristic (ROC) curves for diagnostic value of PM20D1 of carotid atherosclerosis (CAS), severe CAS or CAS/stroke.*

Table 4 – Binary logistic regression for risk factors of carotid atherosclerosis

Variables	Wald	Odds ratio	95%CI	p
Age	0.011	1.003	0.935~1.078	0.914
Sex	4.210	0.208	1.073~21.401	0.040
BMI	0.524	1.057	0.909~1.231	0.469
Diabetes	<0.001	<0.001	0.000	0.995
Hypertension	<0.001	<0.001	0.000	0.993
History of coronary heart disease	<0.001	<0.001	0.000	0.995
History of stroke	<0.001	0.001	0.000	0.999
Current smoker	<0.001	0.844	0.232~3.075	0.798
CRP	0.004	1.008	0.777~1.310	0.947
TNF-α	11.820	0.664	0.526~0.839	0.001
Hcy	22.852	0.155	0.073~0.334	<0.001
TC	0.462	0.697	0.248~1.967	0.496
TG	1.403	0.411	0.095~1.787	0.236
LDL-ch	1.559	0.340	0.063~1.847	0.212
HDL-ch	1.216	0.008	1.797E-6~40.532	0.270
PM20D1	18.152	8.485	3.173~22.693	<0.001

BMI: body mass index; CRP: C-reactive protein; TNF-α: tumor necrosis factor; Hcy: homocysteine; TC: total cholesterol; TG: triglyceride; LDL-ch: low-density leptin cholesterol; HDL-ch: high-density leptin cholesterol.

obesity.[13] Benson et al. demonstrated that decreased PM20D1 was associated with the genetic relationship of obesity and neurodegenerative diseases in humans.[23] Li et al. found that inhibition of miR-324-5p increased the oxygen consumption of primary white and brown adipose tissue cells, increased fat consumption, and thus reduced the weight of mice by enhancing the levels of PM20D1.[24] Long et al. observed that, in PM20D1 deficiency mice, knockdown of PM20D1 decreased the N-acetil aspartato hydrolase/synthetase activity in serum and tissues, as well as a variety of metabolic and pain phenotypes, including insulin resistance, cold temperature changes and antinociceptive behavior, which are associated with obesity, diabetes and other diseases.[12] Thus, we can speculate that higher PM20D1 levels might be beneficial in the improvement of obesity and the reduction of lipid. Although there is no study demonstrating the role of PM20D1 in CAS, the down-regulation of PM20D1 in CAS patients in our study might be partly due to the dysfunction of lipid metabolism and obesity of CAS patients. Since CAS patients showed lower PM20D1 levels than healthy control who had the same BMI distribution, and CAS patients with different BMI showed no significant difference of PM20D1, this result indicated that BMI might not be associated with the level of PM20D1 in CAS patients. The negative correlation between PM20D1 and Hcy, TC and LDL-ch might be one of the reasons for the abnormal expression of PM20D1 in CAS patients. However, to substantiate all these speculations, more studies are needed in order to obtain further evidence.

The present study has some limitations. First, this is an observational study from a single center, with only 231 cases. Secondly, molecular mechanism for how PM20D1 influences CAS development is still unclear.

Conclusion

In conclusion, this observational study demonstrated that decreased PM20D1 was associated with the severity, plaque condition, and expression of CRP, TNF-α, Hcy, TG, TC and LDL-ch in CAS patients. This study might provide novel research target for PM20D1 in CAS.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual contente: Huang X, Wu L; Acquisition of data and Analysis and interpretation of the data: Huang X, He P; Statistical analysis: He P, Wu L; Writing of the manuscript: Huang X.

Potential Conflict of Interest

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

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Study Association

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

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Can PM20D1 be a New Kid on the Block in Cardiovascular Risk Stratification? Do Not Run before You Can Walk

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Short Editorial related to the article: Clinical Significance of Peptidase M20 Domain Containing 1 Ii Patients with Carotid Atherosclerosis

Cardiovascular diseases are the leading cause of death worldwide, representing around 30% of all deaths, particularly in developed countries, including cardiovascular and cerebral-vascular diseases.[1] Furthermore, in the analysis of the Global Burden of Diseases 2019 report, cardiovascular risk factors represent 75% of all cardiovascular burden, particularly hypertension, with an important impact on mortality.[1] This is also relevant in Portuguese-speaking countries.[2] Carotid intima-media thickness has long been recognized as a surrogate marker for coronary artery disease and has a relevant prognostic impact.[3] For that reason, it is a useful tool in cardiovascular risk stratification.

N-acyl amino acids (NAAA) are a family of cold-inducible circulating lipids that stimulate thermogenesis, and their biosynthesis in brown adipocytes is mediated by a secreted enzyme called Peptidase M20 domain containing 1 (PM20D1).[4] PM20D1 and NAAA activity regulation in blood plasma is still largely unknown.[4] However, what is already known is that PM20D1 circulates in tight association with both low- and high-density lipoproteins that are powerful co-activators of PM20D1 activity in vitro and NAAA biosynthesis in vivo.[4] Serum albumin is also a physiologic NAAA carrier that separates NAAA away from their sites of production, conferring resistance to hydrolytic degradation and establishing an equilibrium between thermogenic "free" versus inactive "bound" fractions.[4] It has been hypothesized that lipoprotein particles are probably the main extracellular sites of NAAA biosynthesis, and this supports the concept that a lipoprotein-albumin network regulates the activity of circulating thermogenic lipid family.[4]

Abnormalities in the PM20D1 gene have been associated with several diseases, particularly neurodegenerative diseases, such as Alzheimer's and Parkinson's disease.[5,6] There is also an association with polycystic ovarian syndrome.[7] In humans, Increased serum levels of PM20D1 and its catalytic products (NAAA) are also associated with obesity-related glucose dysregulation, insulin resistance and metabolic syndrome and can be potentially used as clinical biomarkers for diagnosing and monitoring these disorders.[8]

The paper published by Huang et al.[9] in the present issue of *Arquivos Brasileiros de Cardiologia* studied the role of PM20D1 in carotid atherosclerosis (CA). They prospectively studied 231 patients with established CA (assessed by carotid ultrasound) and compared them with the same number of healthy individuals. Some patients in the CA group were assessed in the context of acute stroke. Baseline clinical characteristics were well balanced between both groups. As expected, patients with moderate to severe CA (including those with stroke) had higher levels of inflammatory markers, more unstable carotid plaques and higher LDL cholesterol levels compared with mild to moderate severity and healthy individuals. Patients with CA had lower levels of PM20D1 compared to healthy individuals. Also, patients with unstable plaques and more severe CA had significantly lower levels. This biomarker is also negatively correlated with inflammatory markers but not lipid profiles. No difference was found according to body mass index. This biomarker showed good discriminative accuracy by ROC curve analysis for CA (cut-off 5.4 ng/mL) and severe CA (3.99 ng/mL). Unfortunately, they only report binary logistic regression data for the studied variables. For that reason, it is not possible to confirm with the available data whether this new biomarker is an independent predictor of outcome and if it has added prognostic value compared to the classical parameters. Also, the authors observed that patients with higher levels of PM20D1 had lower LDL cholesterol levels. However, contrary to the authors' report, no significant correlation was observed (correlation coefficient -0.071, p=0.126). The authors did not explain this finding; their relationship is now in question if we put it into context. For that reason, there are still important unanswered questions regarding the interaction between both players.

Overall, this study shed some initial light on the possible role of this pathway for CA. However, multiple questions remain unanswered, and it also lacks additional information on the clinical applicability of the method, particularly in daily practice, because this parameter is not yet ready for its clinical use.

Keywords

PM20D1; Cardiovascular Diseases; Neurodegenerative Diseases; Obesity; Diabetes Mellitus Type 2; Metabolic, Syndrome; Alzheimer Diseases; Insulin Resistance; Carotid Artery Diseases; Hypertension.

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Original Article

Systemic Immune-Inflammatory Index as a Determinant of Atherosclerotic Burden and High-Risk Patients with Acute Coronary Syndromes

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Abstract

Background: **Systemic immune-inflammatory index (SII), which is derived from neutrophil, platelet and lymphocyte counts, represents the homeostatic balance among inflammatory, immune and thrombotic status. The systemic immune-inflammatory index is superior to indices such as neutrophil-lymphocyte ratio in predicting prognosis in various malignancies, while it is shown to predict future cardiac events better than traditional risk factors after coronary intervention.**

Objectives: **Herein, we aimed to evaluate the relationship of the systemic immune-inflammatory index with atherosclerotic burden and in-hospital complications in acute coronary syndrome patients.**

Methods: **The clinical outcomes, such as extent of myocardial damage, atherosclerotic burden, bleeding, acute kidney injury, duration of hospital stay and in-hospital mortality, were evaluated in a retrospective cohort of 309 consecutive acute coronary syndrome patients. The systemic immune-inflammatory index was calculated as (Platelet X Neutrophil)/Lymphocyte count on admission. Study population was categorized into tertiles with regard to systemic immune-inflammatory index. A p value of <0.05 was considered statistically significant.**

Results: **The highest systemic immune-inflammatory index values were within ST elevation myocardial infarction patients (641.4 in unstable angina pectoris, 843.0 in non-ST elevation myocardial infarction patients and 996.0 in ST elevation myocardial infarction patients; p=0.004). Maximal troponin concentration (0.94 vs. 1.26 vs. 3; p<0.001), number of diseased vessels (1 vs. 2 vs. 2; p<0.001), the SYNTAX (synergy between percutaneous coronary intervention with taxus and coronary artery bypass grafting) score (9 vs. 14 vs. 17.5; p<0.001) and duration of hospital stay (2 vs. 2 vs. 3; p<0.001) also increased with increasing $SII_{tertile}$ (tertile1 vs. tertile 2 vs. tertile 3). Systemic immune-inflammatory index was an independent predictor of SYNTAX score (ß: 0.232 [0.001 to 0.003]; p<0.001), extent of myocardial damage (ß: 0.152 [0 to 0.001]; p=0.005) and duration of hospital stay (ß: 0.168 [0.0 to 0.001]; p=0.003).**

Conclusions: **This study has demonstrated that the systemic immune-inflammatory index, a simple hematological index, is a marker of atherosclerotic burden and longer hospital stay on well-known risk factors in high risk acute coronary syndrome patients.**

Keywords: **Inflammation; Acute Coronary Syndrome; Coronary Artery Disease.**

Introduction

Atherosclerosis is characterized by low grade chronic inflammation, which is interrupted by periods of acute exacerbations. These surges of inflammatory response accelerate the disease process and clinically manifest as acute coronary syndromes (ACS).[1,2] ACS is common in patients with coronary artery disease (CAD), resulting in high mortality and morbidity rates.[3] Accurate risk stratification in early disease course, therefore, is of paramount significance.

There are several inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor-α, and various interleukins, which are associated with poor outcome in the context of ACS.[4,5] Simple hematological indices, such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are also useful indicators of inflammation and promising prognostic factors in cardiovascular disease.[6,7]

In ACS, deranged activation of innate and adaptive immunity converges with platelet activation, resulting in thrombus formation. Systemic immune-inflammatory index (SII), which is derived from platelet, neutrophil and lymphocyte counts, combines all the main players of these

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pathophysiological pathways to represent the impaired balance. It was first described as a prognostic tool in hepatocellular carcinoma,[8] which was followed by other solid tumors, such as those for colorectal, esophageal, and cervical cancers.[9] SII was shown to predict survival better than other hematological indices, such as NLR or PLR in malignancies.[9] Recently, Yang et al.[10] have further demonstrated that SII predicts major cardiovascular events better than well-known cardiovascular risk factors in patients undergoing percutaneous coronary intervention (PCI).This study, therefore, aimed to explore the association of admission SII with atherosclerotic burden and early clinical outcomes in order to identify high-risk patients with ACS.

Methods

After obtaining approval from the local ethics committee (2019/28/02/12), we retrospectively evaluated ACS patients who presented to the emergency department and were treated with coronary angiography between January 2018 and January 2019. There were 520 consecutive patients diagnosed with ACS — namely, unstable angina pectoris (UAP), non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) — based on their electrocardiographic, clinical and laboratory characteristics.[11,12] Patients with high troponin concentrations due to a pathology other than ACS, with a known inflammatory/infectious disease, undergoing hemodialysis and with the diagnosis of myocardial infarction (MI) with normal coronary arteries, as well as those who did not undergo coronary angiography during the index hospitalization were not included in the study (Figure 1). From the hospital records of 334 eligible patients, demographic characteristics, such as age, gender and presence of cardiovascular risk factors, such as hypertension, hyperlipidemia and diabetes mellitus (DM), were recorded. Patients with previous coronary artery bypass grafting (CABG) were not included into the analyses, as the association of SII with the atherosclerotic burden could not be stratified in this specific population. Laboratory parameters on admission to the emergency unit, such as hemoglobin, urea and creatinine concentration, as well as neutrophil, platelet and lymphocyte counts, were determined. Clinical outcomes to be evaluated were identified as atherosclerotic burden, extent of myocardial damage, occurrence of bleeding, acute kidney injury, duration of hospital stay and in-hospital mortality.

To determine the atherosclerotic burden, coronary angiograms were evaluated by two cardiologists, blinded to the study groups, who assessed the number of diseased vessels and the synergy between percutaneous coronary intervention (PCI) with taxus and CABG (SYNTAX) scores. Any epicardial coronary artery with 50% or more stenosis was identified as a diseased vessel. SYNTAX score was calculated as previously described.[13] Maximum high sensitive troponin I (hs-cTnI) level represented the extent of myocardial damage. Bleeding was defined as a Hemoglobin (Hb) fall of 3 gr/dL or more during the hospital stay. Creatinine (Cr) levels during the hospital stay were obtained to calculate the increase from the baseline Cr level, in which an increase »0.3 mg/dL or 1.5 times baseline reflected the occurrence of acute kidney injury. SII was calculated as (platelet x neutrophil/lymphocyte), as described and studied previously.[8] The study population was stratified into three groups with regard to SII levels.

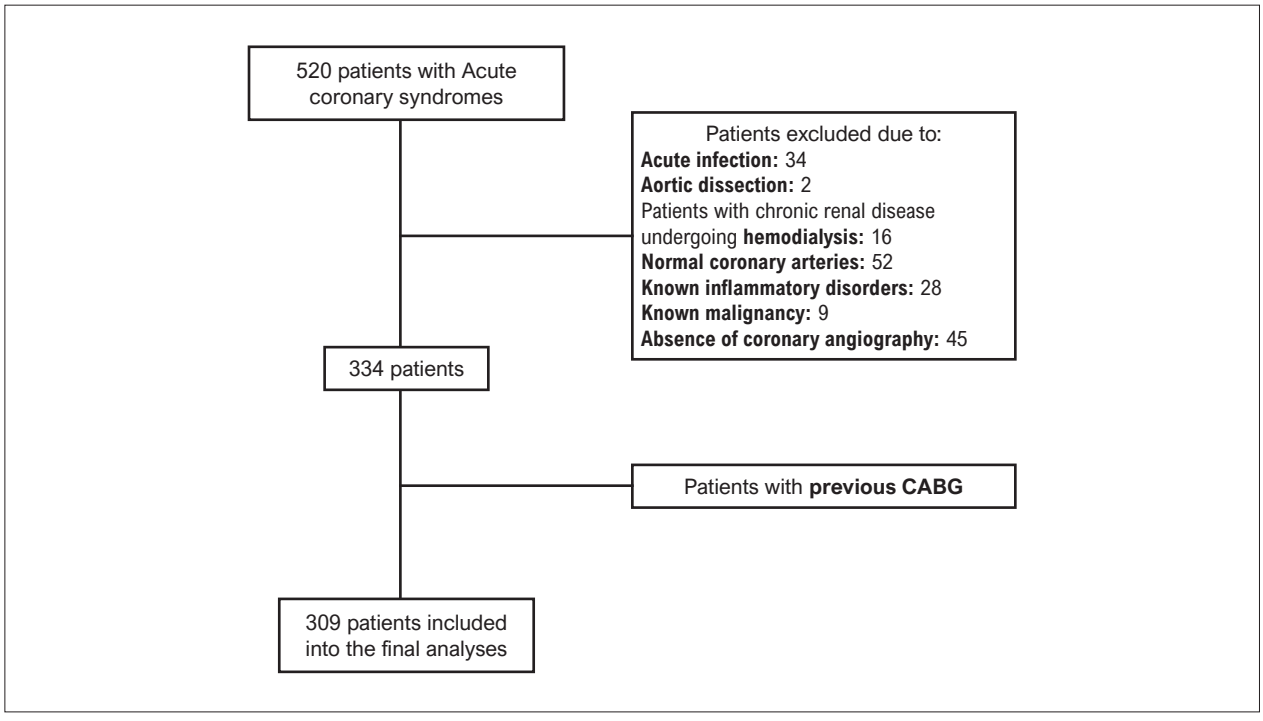

Figure 1 – *Flowchart for patient recruitment. CABG: coronary artery bypass grafting.*

Statistical analysis

Statistical analyses were carried out using IBM® SPSS® Statistics for Mac, Version 20 software (IBM Corp., Armonk, New York). The continuous variables were presented as mean ±standard deviation (SD) or median (interquartile range); the categorical variables were presented as number and percentages. The variables were tested for normality of distribution by Kolmogorov-Smirnov Test. SII tertiles were compared by the one-way analysis of variance (ANOVA) in normally distributed variables and Kruskal-Wallis test in variables without normal distribution. Dunn's test was used in the nonparametric pairwise comparisons if significant deviations were observed by Kruskal-Wallis test. Post hoc analysis in case of significant deviations showed by ANOVA was planned to be performed using Tukey's or Tamhane's test, depending on the homogeneity of variances. No post hoc analysis was performed for variables from which SII was driven. The categorical variables were compared by chi-squared. A p-value of 0.017 adjusted by the Bonferroni method was used in pairwise comparisons of categorical variables.

Correlation of hematological indices SII, NLR and PLR with SYNTAX score with respect to ACS type was tested with Spearman rank-order test. With setting each clinical outcome as the dependent variable, linear and logistic regression analyses were conducted, and the variables with a p value ≤0.2 in univariate comparisons were included into the multivariate model using the Stepwise method, in order to determine whether SII was a predictor of that specific clinical outcome. All necessary assumptions for the use of linear regression analysis were verified before results were interpreted. Results are presented with 95% confidence interval within [brackets]. Baseline variables such as age, gender, cardiovascular risk factors, creatinine, CRP and SII levels that are presented in Table 1 were included in the univariate analyses to determine possible predictors, but only the ones with a p value ≤0.2 were added to the multivariate model. A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the studied population and the comparison of these characteristics in relation to SII tertiles are presented in Table 1. There was no difference among study groups in terms of cardiovascular risk factors such as age, gender, diabetes mellitus, hypertension and hyperlipidemia. When the SII groups were compared with regard to presenting ACS type, patients with UAP were more likely to be in the lowest SII tertile, while patients with STEMI were more likely to have higher SII. Patients with UAP were more likely to be in the lowest SII tertile, while patients with STEMI were more likely to have higher SII values (Figure 2a). To uncover the association of clinical presentation and SII, type of presenting ACS was evaluated within the SII spectrum, which showed that SII significantly differed with regard to type of ACS. Pairwise comparisons revealed that SII gradually increased from UAP to STEMI, in which the difference between UAP and STEMI was statistically significant (Figure 2b). The hemoglobin concentration, urea, creatinine and CRP levels were comparable within SII subgroups.

Table 2 summarizes the clinical outcomes in SII groups. The burden and complexity of coronary artery disease were reflected by the number of diseased vessels and the SYNTAX score of each patient, both of which demonstrated significant deflection among the SII groups. There was significantly lower number of diseased vessels in the lowest SII tertile when compared to other SII groups (Figure 3a). Moreover, the SYNTAX score increased remarkably as the SII tertile increased (Figure 3b). Maximal troponin level, which was the marker of myocardial damage, increased with increasing SII tertile, in which the differences between Tertile 1 vs. Tertile 3 and between Tertile 2 vs. Tertile 3 were statistically significant (Figure 3c). Hospital stay was longer in patients with the highest SII when compared to other two SII groups (Figure 3d). There was no significant difference among SII groups in terms of bleeding, acute kidney injury or in-hospital mortality.

Correlations of hematological indices SII, NLR and PLR with SYNTAX score with respect to ACS type were evaluated (Table 3). In UAP patients, NLR and PLR were not correlated with SYNTAX score, while there was a positive correlation between SII and SYNTAX score. In NSTEMI patients, SII, NLR and PLR were positively correlated with SYNTAX score. Similarly, all three indices were positively correlated with SYNTAX score in STEMI patients.

Clinical outcomes tested by multivariate linear regression analyses were atherosclerotic burden represented by SYNTAX score, extent of myocardial damage (maximal troponin concentration) and duration of hospital stay. Linear regression revealed that SII (ß: 0.232 [0.001 to 0.003]; p<0.001), age (ß: 0.156 [0.019 to 0.165]; p=0.014) and DM (ß: 0.165 [0.935 to 4.42]; p=0.003) were significant predictors of SYNTAX score. The independent predictors of the extent of myocardial damage were SII (ß: 0.152 [0 to 0.001]; p=0.005); female gender (ß: -0.147 [-1.801 to -0.271]; p=0.008) and DM (ß: 0.142 [0.197 to 1.557]; p=0.012). Similarly, the independent predictors of duration of hospital stay were SII (ß: 0.168 [0.0 to 0.001]; p=0.003) and presence of diabetes mellitus (ß: 0.124 [0.095 to 1.74]; p=0.029).

Clinical outcomes tested by logistic regression analyses were bleeding and in-hospital mortality. Binary logistic regression indicated that an independent predictor of bleeding was baseline hemoglobin value (odds ratio (OR): 1.29 [1.09 to 1.52] p=0.002). For in-hospital mortality, only age (OR: 1.09 [1.035 to 1.155] p=0.001) and baseline creatinine (OR: 4.6 [1.137 to 18.787] p=0.032) were predictors. SII was not a predictor in neither of outcomes.

Discussion

In this retrospective cohort of ACS patients, we demonstrated that a simple hematological index derived from neutrophil, lymphocyte and platelet counts on admission can be utilized to extrapolate the atherosclerotic burden, the extent of myocardial damage and the duration of hospital

Table 1 – Baseline characteristics and comparison of baseline characteristics in relation to systemic immune-inflammatory index tertiles

Variable	Total n=309	SII Tertile 1 n=103	SII Tertile 2 n=103	SII Tertile 3 n=103	1 vs. 2 p value	2 vs. 3 p value	1 vs. 3 p value
Age, years	64.5±12.1	62.8±11.8	65.1±13.1	65.5±11.2	0.500	1.00	0.306
Female gender, n (%)	82 (26.5)	25 (24.3)	32 (31.1)	25 (24.3)	0.350	0.350	1.00
UAP, n (%)	53 (17.2)	27 (26.2)	17 (16.5)	9 (8.7)	0.125	0.141	0.002
NSTEMI, n (%)	113 (36.6)	36 (35)	46 (44.7)	31 (30.1)	0.200	0.043	0.552
STEMI, n (%)	143 (46.3)	40 (38.8)	40 (38.8)	63 (61.2)	1.00	0.002	0.002
Diabetes mellitus, n (%)	123 (39.8)	36 (35)	40 (38.8)	47 (45.6)	0.665	0.397	0.155
Hypertension, n(%)	117 (37.9)	43 (41.7)	33 (32)	41 (39.8)	0.194	0.309	0.887
Hyperlipidemia, n (%)	125 (40.5)	42 (40.8)	36 (35)	47 (45.6)	0.473	0.155	0.574
Hemoglobin, g/dL	13.5±1	13.8±1.8	13.2±1.8	13.3±1.8	0.047	1.00	0.075
White blood cells, 103/µL	9.9±2.7	9.1±2.7	9.5±2.3	11.4±2.5	0.571	<0.001	<0.001
Neutrophil count, 103/µL	6.8 (3.54)	5.1 (2.37)	6.7 (2.5)	8.8 (3.03)	<0.001	<0.001	<0.001
Lymphocyte count, 103/µL	1.84 (1.1)	2.3 (1.12)	1.8 (0.89)	1.3 (0.75)	<0.001	<0.001	<0.001
Monocyte count, 103/µL	0.63 (0.36)	0.7 (0.36)	0.6 (0.31)	0.6 (0.39)	0.163	0.893	0.341
Platelet count, 103/µL	238 (96)	207 (75.75)	241 (75.00)	278 (116.75)	0.001	<0.001	<0.001
C-reactive protein, mg/L	4.55 (8.63)	3.8 (8.1)	4.7 (8.1)	5.4 (10.8)	0.651	0.262	0.271
Urea, mg/dL	34 (15)	32 (13)	33.5 (15)	36 (17.1)	0.469	0.082	0.038
Creatinine, mg/dL	0.93 (0.32)	0.93 (0.28)	0.91 (0.33)	0.94 (0.38)	0.984	0.694	0.854
SII	835 (860.09)	462 (194.51)	833 (252.9)	2055 (935.7)	<0.001	<0.001	<0.001

**p values represent the pairwise comparisons of the systemic immune-inflammatory index tertiles of the three patient groups without post hoc analysis. Note that the level of significance for the p value according to the Bonferroni correction is 0.017 in this table. UAP: unstable angina pectoris; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; SII: systemic immune-inflammatory index.*

stay, independent of traditional cardiovascular risk factors and inflammatory markers such as CRP. Correlation of SII with SYNTAX score persisted in ACS patients irrespective of presence or absence of necrosis. This finding suggests that SII can potentially be used to identify high-risk individuals in ACS as early as on admission.

Mortality and morbidity in cardiovascular events are multifactorial, and results from a confluence of differing pathophysiological pathways in which inflammation plays a central role.[1] Although severe systemic inflammation is an established indicator of mortality in ACS, no single inflammatory biomarker could have been identified to guide the treatment of cardiovascular risk.[14] Even CRP, whose role in inflammation and atherosclerosis is well established, can only modestly predict cardiovascular events.[15] Several hematological indices, such as NLR or PLR, have been proposed to represent early inflammatory response in ACS and possess prognostic significance.[16] Nevertheless, inflammation is a continuous process and evidence revealed that a plethora of circulating cytokines

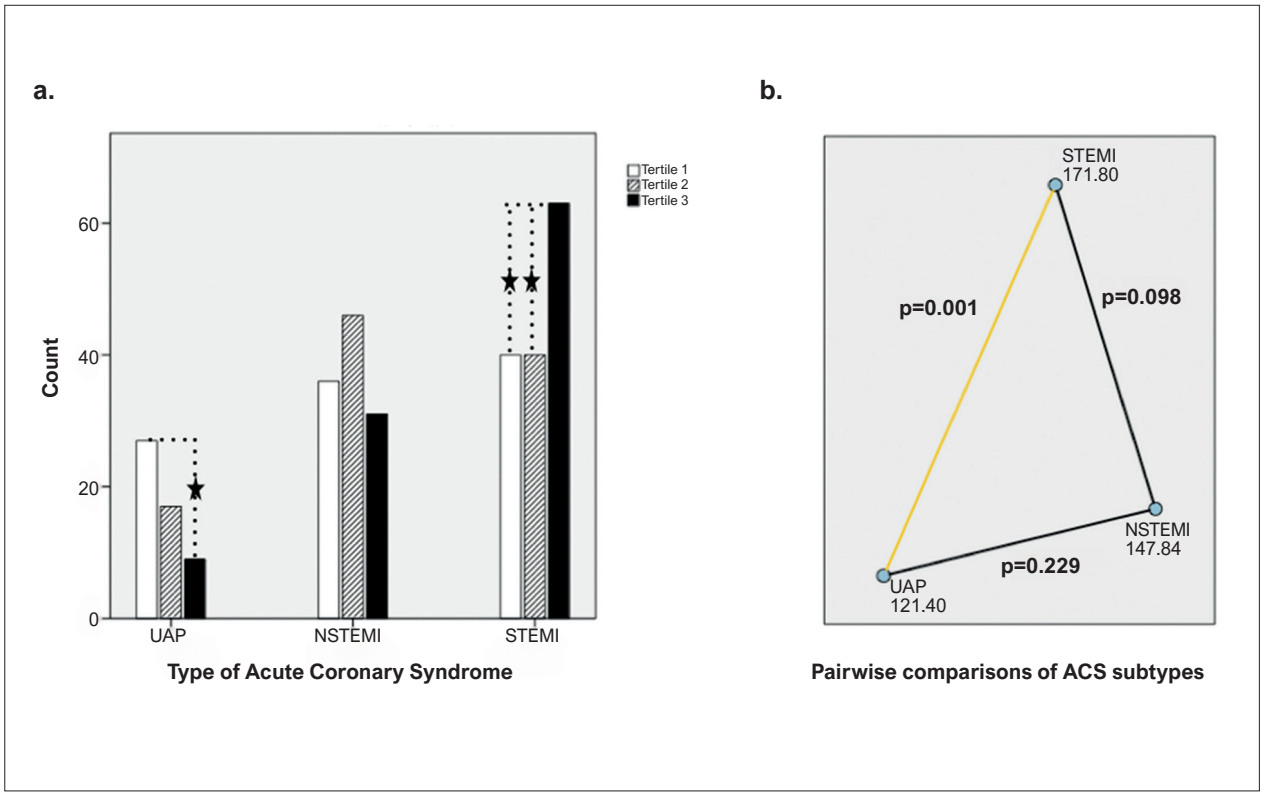

Figure 2 – *(a) Comparison of systemic immune-inflammatory index groups with regard to presenting acute coronary syndrome type; (b) Comparison of type of presenting acute coronary syndrome within the systemic immune-inflammatory index spectrum. UAP: unstable angina pectoris; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; ACS: acute coronary syndrome.*

Table 2 – Clinical outcomes in relation to systemic immune-inflammatory index tertiles

Outcome	SII Tertile 1 n=103	SII Tertile 2 n=103	SII Tertile 3 n=103	1 vs 2 p value	2 vs 3 p value	1 vs 3 p value
Number of diseased vessels	1 (1)	2 (2)	2 (2)	0.013	1.00	0.011
Atherosclerotic burden or SYNTAX Score	9 (11)	14 (11.5)	17.5 (11)	0.022	0.002	<0.001
Extent of myocardial damage or Maximal troponin, ng/L	0.94 (2.06)	1.26 (3.61)	3 (4.02)	0.434	0.002	<0.001
Hospital stay, days	2 (1)	2 (1)	3 (3)	0.709	<0.001	0.026
Bleeding, n(%)	27 (26.2)	22 (21.4)	32 (31.1)	0.257*	0.157*	0.538*
Acute kidney injury, n(%)	18 (17.5)	17 (16.5)	22 (21.4)	1.00*	0.477*	0.598*
In-hospital mortality, n(%)	5 (4.9)	8 (7.8)	9 (8.7)	0.568*	1.00*	0.407*

**Note that the level of significance for the p values according to the Bonferroni correction is 0.017 for categorical variables. CABG: coronary artery bypass grafting; SII: systemic immune-inflammatory index.*

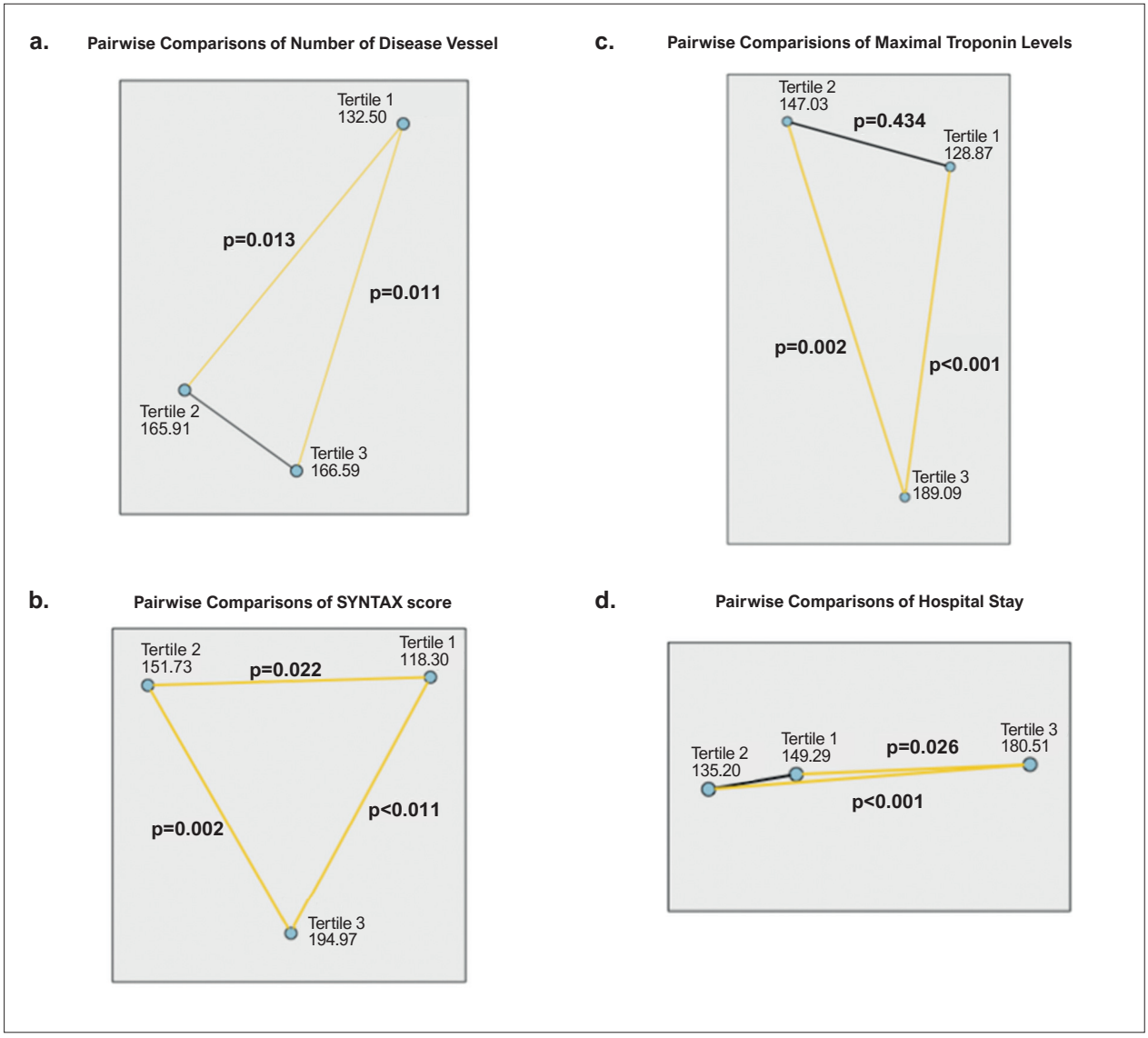

Figure 3 – *Pairwise comparison of systemic immune-inflammatory index tertiles with regard to (a) Number of diseased vessels; (b) SYNTAX score; (c) Maximal troponin levels; (d) Hospital stay. SYNTAX: synergy between percutaneous coronary intervention with taxus and coronary artery bypass grafting.*

subsides after an acute event with persisting high concentrations of some cytokines, such as interleukin-6 in the early post-MI period.[17]

Of white blood cell subtypes, neutrophils are the key elements of nonspecific first line defense. Neutrophil count is a well-defined prognostic factor in cardiovascular disease, particularly in patients with ACS.[18,19] Lymphocytes, on the other hand, are part of adaptive immunity, which alleviates inflammation through B_1, T-helper$_2$ and T-regulatory subtypes.[1,20] Lymphocyte count decreases secondary to acute stress hormones following myocardial infarction.[21] Clinical studies have also established the association of low lymphocyte count with increased in-hospital mortality.[21] A high NLR, thus, is associated with worse clinical outcomes, both in patients with ACS and in those with stable CAD undergoing percutaneous coronary intervention.[6,7] NLR was also shown to be associated with severity and complexity of CAD, as represented by SYNTAX score.[6]

On the basis of evidence that shows close leukocyte-platelet interaction in inflammation triggering thrombosis, Choi et al.[22] have combined NLR with mean platelet volume and showed that addition of a platelet related index predicts future cardiac events better, especially in patients with ACS. Çiçek et al.[7] have also shown that a combination of NLR and PLR increased the power of predicting poor short and long-term prognosis when compared to using them alone in patients undergoing primary PCI. In this study, we speculated that an index that combines NLR and PLR would better represent the inflammo-thrombotic status of patients in the peri-MI period.

Table 3 – Correlation of SYNTAX score with systemic immune-inflammatory index, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio with regard to type of presenting acute coronary syndrome.

		SII		NLR		PLR	
		r_s	p	r_s	p	r_s	p
UAP	SYNTAX	0.300	0.031	0.266	0.054	0.145	0.299
NSTEMI	SYNTAX	0.345	<0.001	0.236	0.011	0.183	0.045
STEMI	SYNTAX	0.471	<0.001	0.456	<0.001	0.387	<0.001

SII: systemic immune-inflammatory index; NLR: neutrophile-lymphocyte ratio; PLR: platelet-lymphocyte ratio; UAP: unstable angina pectoris; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction.

There is scarce data on the value of SII in cardiovascular diseases. Yang et al.[10] have evaluated the role of SII in patients undergoing PCI and showed that, on a follow-up of 54.6±35.1 months, SII predicted major cardiac events such as cardiovascular death, nonfatal MI and nonfatal stroke better than traditional cardiovascular risk factors. They simply suggested that inflammation quantified by SII accounted for the poor clinical outcomes. They did not, though, report the association of SII with complexity of CAD. For the first time in literature, we have demonstrated that the SII was independently associated with SYNTAX score, irrespective of CRP and other well-known cardiovascular risk factors. Our finding also explains the results of Yang et al.,[10] since patients with higher SII and SYNTAX scores are more prone to future cardiovascular events.

Herein, it was intriguing to find a positive correlation of SII with SYNTAX score in all ACS subtypes. Among three hematological indices, namely NLR, PLR and SII, only SII was correlated with SYNTAX score in UAP patients without severe myocardial necrosis. ACS studies showing the relation of NLR and PLR with atherosclerotic burden were mostly derived from patients with either non-ST MI or STEMI with severe myocardial necrosis and significantly elevated troponin concentrations.[23,24] Moreover, SII was profoundly influenced by the type of the presenting ACS; in which STEMI patients had remarkably higher SII indices and UAP patients had lower SII indices. These findings suggest that, contrary to simple perception that considers SII as the result of inflammatory surge around the time of ACS, SII reflects the intertwined baseline atherosclerotic process prone to complications.

SII was related to the extent of myocardial damage and this relationship was probably through the type of ACS, with higher SII values in STEMI patients. Our finding is in line with the previous studies which have shown that, in the absence of necrosis, correlation of white blood cell count (WBC) with mortality was diminished.[25,26] Nunez et al.[26] have found weaker association of WBC with non-STEMI when compared to STEMI, and speculated that the greater the extent of necrosis, the larger the WBC response. Our results suggest that SII, which integrates platelet count to the WBC counts, can define residual ongoing inflammation better than other hematological indices, even in the absence of necrosis.

In this study, SII was a predictor of duration of hospital stay in patients with ACS. Increasing SII values represent high-risk patients with high SYNTAX score and severe myocardial damage, which explains the reason of longer durations of hospital care. Herein, we did not demonstrate an association between SII and in-hospital mortality, which can be attributed to early treatment with primary percutaneous intervention and relatively short duration of hospital stay.

Study limitations

This study has several limitations regarding the retrospective nature of the study design and lack of follow-up data. Patient selection was elaborate as we have tried to exclude all patients with active infection or inflammatory condition, thus decreasing the number of subjects. Additionally, we did not include patients with CABG, since atherosclerotic burden could not be determined by neither number of diseased vessels nor SYNTAX score in patients with previous CABG. Another limitation of the current study was the fact that we could not include the baseline medication of the study population into the analyses.

Conclusions

Immune, inflammatory and thrombotic balance is of pivotal importance in the pathogenesis of ACS. Given the distinctive association of SII with SYNTAX score, extent of myocardial damage and duration of hospital stay, it can potentially be used to identify high risk patients through a readily available and inexpensive approach.

Author contributions

Conception and design of the research: Demet Ozkaramanli Gur, Muhammet Mucip Efe, Seref Alpsoy, Nurullah Uslu, Aliye Çelikkol, Ozcan Gur. Acquisition of data: Demet Ozkaramanli Gur, Muhammet Mucip Efe, Seref Alpsoy, Aydın Akyüz, Nurullah Uslu, Aliye Çelikkol. Analysis and interpretation of the data: Demet Ozkaramanli Gur, Muhammet Mucip Efe, Seref Alpsoy, Aydın Akyüz, Nurullah Uslu, Aliye Çelikkol, Ozcan Gur. Statistical analysis: Demet Ozkaramanli Gur, Muhammet Mucip Efe, Aydın Akyüz, Nurullah Uslu. Obtaining financing: Demet Ozkaramanli Gur. Writing of the manuscript: Demet Ozkaramanli Gur, Ozcan Gur. Critical revision of the manuscript for intellectual content: Demet Ozkaramanli Gur, Seref Alpsoy, Aydın Akyüz, Aliye Çelikkol, Ozcan Gur.

Potential Conflict of Interest

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

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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 Ethical Review Board of Namik Kemal University Faculty of Medicine under the protocol number 2019/28/02/12. 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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Are There Alternative Ways to Estimate Atherosclerotic Inflammatory Activity in Patients with Acute Coronary Syndrome?

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Short Editorial related to the article: Systemic Immune-Inflammatory Index as a Determinant of Atherosclerotic Burden and High-Risk Patients with Acute Coronary Syndromes

The theme of inflammation in the atherosclerotic process has been the subject of numerous researches for years. Atherosclerosis is an inflammatory disease since the accumulation of leukocytes in the subendothelium is one of the first processes in plaque formation. Subsequently, other inflammatory cells (monocytes, macrophages, dendritic cells, lymphocytes and mast cells) participate continuously from forming the "fatty groove" until the occurrence of the acute coronary event.[1-3]

The orchestrated action of all the pro-inflammatory signals in the plaque increases inflammation and directly affects the structural elements that support its mechanical stability. Various pro-inflammatory messengers are released by immune and vascular endothelial cells, activating cytokines, chemokines, bioactive lipid compounds and adhesion molecules that maintain and accelerate inflammation and the local development of atherosclerotic lesions.[4,5]

C-reactive protein (CRP) has been the most used in clinical practice among all inflammatory markers related to atherosclerosis. CRP levels can often provide useful information for diagnosing, treating and monitoring patients with atherosclerosis and confirming the patient's responses to various stimulating factors. Some studies indicate that CRP binds to LDL and is present in atherosclerotic plaques. CRP is not normally present in the healthy vessel wall but becomes detectable in the early stages of atherogenesis and accumulates during the progression of atherosclerosis. CRP is considered a predictor of future cardiovascular events, and in the general population, CRP levels can independently predict the risk of cardiovascular mortality.[4]

In addition to CRP, other classical markers were studied and are directly related to the atherosclerotic process. Among them interleukin-6, interleukin-1, adhesion molecules (P-selectin, L-selectin, ICAM-1, VCAM-1 and PECAM-1) and metalloproteinases (MMPs) stand out.[4,6,7] Currently, the role of dead cells in apoptosis, antibodies against phospholipids, heat shock proteins, plaque infections (*Chlamydia pneumoniae*. *Porphyromonas gingivalis, Aggregatibacter actinoomycetemcomitans, Helicobacter pylori and Cytomegalovirus*) is being discussed.[6]

Despite the enormous amount of data in the literature, most studies only explore chronic atherosclerotic disease. In patients with acute coronary syndromes, information is scarce. In the presented study, the authors evaluated the systemic immunoinflammatory index (SII) as a prognostic marker in acute conditions. This index, represented by the relationship between platelets x neutrophils/lymphocyte count, was applied in 309 patients and correlated with atherosclerotic burden and in-hospital complications. Neutrophils are classically related to acute inflammatory processes, and their significant increase possibly elevates SII in more severe cases. In fact, higher SII was observed in patients with longer hospital stays, with higher Syntax scores, higher troponin values and acute coronary syndrome with ST-elevation. Therefore, it is an easily reproducible index that can alert to greater inflammatory activity in the current acute atherosclerotic process, reflecting severity.[8]

Although the inflammatory activity of atherosclerosis is well described, anti-inflammatory therapies capable of targeting inflammation are still lacking in the physician's arsenal. Most clinical trials of 'anti-inflammatory' were negative, although CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) using canakinumab proved that blocking the interleukin-1β pathway can reduce cardiovascular events.[9] Newer targets are needed, and genetics can help solve this problem.[1]

Keywords

Atheroclerosis/prevention and control; Plaque, Atherosclerotic/drug therapy; Inflammation/blood; Inflammation/drug therapy; Acute Coronary Syndrome; Anti-Inflammatory Agents/therapeutic use.

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The Predictive Value of CHA2DS2-VASc Score on Residual Syntax Score in Patients With ST Segment Elevation Myocardial Infarction

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Abstract

Background: The CHA_2DS_2-VASc score is associated with adverse clinical outcomes in patients with cardiovascular disease. The residual Syntax score (rSS) is a scoring tool which has prognostic value in patients with ST segment elevation myocardial infarction (STEMI).

Objectives: Our aim in this study is to investigate the predictive value of the CHA_2DS_2-VASc score on rSS in STEMI patients.

Methods: A total of 688 consecutive patients with STEMI undergoing percutaneous coronary intervention were evaluated. Baseline demographic and clinical variables besides the CHA_2DS_2-VASc score were assessed. The patients were divided into two groups; patients with rSS of 8 or below as group 1 (509 patients) and more than 8 as group 2 (179 patients). A p-value < 0.05 was considered statistically significant.

Results: The CHA_2DS_2-VASc score was higher in group 2 [1 (0-2); 1 (1-3), p<0.001] compared to group 1. The incidence of hypertension [151 (29.7%); 73 (40.8%), p=0.006], patients ≥75 years [18 (3.5%); 21 (11.7%), p<0.001], diabetes mellitus [85 (16.7%); 50 (27.9%), p=0.001] and vascular disease [12 (2.4%); 11 (6.1%), p=0.029] were higher in group 2. In multivariate logistic regression analysis, the CHA_2DS_2-VASc score (OR=1.355; 95%CI=1.171-1.568; p<0.001), age ≥75 years [OR=3.218; 95%CI=1.645-6.295; p=0.001] and diabetes mellitus [OR=1.670; 95%CI=1.091-2.557; p=0.018] were independent predictors of high rSS. The receiver-operating characteristic curve analysis demonstrated that the CHA_2DS_2-VASc score had good predictive value for high rSS with a cut-off value of 1.5 (area under curve (AUC): 0.611, 95% confidence interval (CI):0.562-0.659, p<0.001).

Conclusions: The CHA_2DS_2-VASc score has a predictive value on rSS in patients with STEMI. The CHA_2DS_2-VASc score was also an independent predictor of higher rSS.

Keywords: ST Elevation Myocardial Infarction. Percutaneous Coronary Intervention. Atrial Fibrillation.

Introduction

ST segment elevation myocardial infarction (STEMI) is still the leading cause of increased morbidity and mortality rates in cardiovascular diseases.[1] Thus, prognostic determinants of adverse cardiovascular events in this population are studied in several randomized trials and clinic registries. Coronary artery disease severity is related with higher coronary atherosclerotic burden results in poorer prognosis in coronary artery disease, especially in STEMI patients.[2]

The residual Syntax score (rSS) is a scoring system which reflects obstructive coronary atherosclerosis after performing percutaneous coronary intervention (PCI) to culprit lesion. It was demonstrated that increased rSS (>8) had a prognostic value on myocardial infarction (MI) and 1- year mortality in high-risk acute coronary syndrome patients.[2]

Coronary artery disease can appear together with several comorbidities. Age, gender, hypertension, diabetes mellitus are some of these risk factors that are related with the progression of coronary atherosclerosis.[3] Most patients with coronary artery disease had at least one risk factor of coronary artery disease and also a combination of these risk factors resulting in increased coronary atherosclerotic burden.[4,5] The CHA_2DS_2-VASc score is firstly described to determine atherothrombotic activity in atrial fibrillation.[6] In previous studies, it was revealed that the CHA_2DS_2-VASc score was associated with adverse clinical outcomes in patients with cardiovascular disease. The CHA_2DS_2-VASc score was found to be related with coronary artery disease severity[7] and all-cause mortality in STEMI patients.[8] However, to the best of our knowledge, the relationship between the CHA_2DS_2-VASc score and rSS has not been studied yet. Our aim in this study is to investigate the predictive value of the CHA_2DS_2-VASc score on rSS in STEMI patients.

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Methods

Six hundred eighty-eight (688) consecutive patients with ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) from 2017 to 2020 were included in our retrospective observational study. The inclusion criteria are as follows: (a) typical chest pain for more than 20 minutes, (b) ST-segment elevation in at least two contagious leads, and (c) treatment with primary PCI. Patients who were treated with medical therapy alone or underwent coronary artery bypass grafting were excluded from the study. Additionally, patients with history of coronary revascularization with percutaneous or surgical therapy were also excluded from the study. The study was approved by the local ethics committee at Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital in May 2020 (no:2020/28).

The demographic and clinical parameters were recorded from the hospital database. Biochemical analyses including complete blood count, serum creatinine, glucose, cholesterol and electrolytes levels were assessed. The clinical parameters in the CHA_2DS_2-VASc score were evaluated. Congestive heart failure was defined as signs or symptoms of heart failure or objective evidence of reduced ejection fraction (<%40). Hypertension was defined as resting blood pressure >140/90 mmHg on at least two occasions, or treatment with antihypertensive medications. Diabetes mellitus was defined as at least 8 hours fasting plasma glucose level >125 mg/dl, or the previous use of oral anti-diabetic agent and/or insulin therapy. Vascular disease was defined as history of previous myocardial infarction (MI) or peripheral arterial disease or aortic plaque. Additionally, the STEMI index was not included in this scoring system.

Coronary angiography and PCI were performed through femoral or radial access immediately for each patient. Two independent, experienced cardiologists evaluated the coronary angiographic images individually to calculate coronary artery disease severity. The residual Syntax score (rSS) was defined based on the residual coronary artery obstruction after performing the percutaneous coronary intervention (PCI) for culprit lesion. Firstly, coronary arteries were defined as 16 separate segments. Each segment was evaluated and the segment that had at least 50% of luminal stenosis and a 1.5mm diameter was assessed. Additionally, some determinant factors were evaluated, such as a pre-specified corresponding weighing factor of each segment, calcification and lesion length. The Syntax score calculator (www.syntaxscore.com) was used to obtain rSS for each patient. Then, patients were divided into two groups according to their rSS values; the patients with a score of 8 or below as the low-rSS group (group 1) and more than 8 as the high-rSS group (group 2).

Statistical analysis

The statistical analysis was made by using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, New York, USA). Pearson chi-square, continuity-corrected chi-square and Fisher exact tests were performed for categorical variables, where appropriate. The fitness to normal distribution was analyzed with the Kolmogorov-Simirnov test. "mean±standard deviation" was used for variables with normal distribution, "median (25^{th}-75^{th} percentiles)" for variables without normal distribution and "n (%)" for categorical variables.

The analyses were done with an independent sample t-test for comparing quantitative variables with normal distribution, while the Mann Whitney u test was used for comparing the means between groups without normal distribution.

The Spearman analysis was used to evaluate the correlation between the CHA_2DS_2-VASc score and rSS. Univariate and multivariate logistic regression analyses were used to evaluate independent predictors of high residual Syntax score (rSS).

A Receiver Operating Characteristic (ROC) curve analysis was conducted to determine the optimal CHA_2DS_2-VASc score value to indicate high rSS in terms of both sensitivity and specificity. A p-value < 0.05 was considered statistically significant.

Results

A total of 688 consecutive patients with ST segment elevation myocardial infarction (STEMI) who undergone primary percutaneous coronary intervention (PCI) were evaluated in this study. Of these 688 patients, 509 patients had low rSS (group 1) and 179 had high rSS (group 2). Baseline demographic and clinical variables of the entire study group were demonstrated in table 1. There were no differences in terms of gender, smoking status, history of chronic obstructive pulmonary disease, ejection fraction, creatinine, leukocyte, thrombocyte, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride levels between the two groups.

The mean age of group 2 was higher than in group 1. The incidence of hyperlipidemia was lower in group 1. While the hemoglobin level was lower in group 2, the glucose level was higher in group 2. The incidence of the culprit vessel as left anterior descending artery was higher in group 1, while the incidence of right coronary artery as a culprit vessel was higher in group 2. The median value of the CHA_2DS_2-VASc score was higher in patients with high rSS compared to patients with low rSS.

The comparison of variables into the CHA_2DS_2-VASc scoring system between groups was demonstrated in table 2. There were no differences in the incidence of congestive heart failure, history of stroke/transient ischemic attack or thromboembolism, age (65-74 years) and sex category between groups. The incidence of hypertension, patients ≥75 years, diabetes mellitus and vascular disease was higher in group 2 compared to group 1. Additionally, the number of patients with a CHA_2DS_2-VASc score of 0 was higher in group 1, while the number of patients with a CHA_2DS_2-VASc score of 4 and 5 was higher in group 2 (Table 3).

The logistic regression analysis was conducted and significant variables which were found in the univariate analysis were put into the multiple logistic regression analysis

Table 1 – Baseline demographic and clinical variables of patients

	Low rSS group (n= 509)	High rSS group (n= 179)	p
Age (years)	54±11	59±11	**<0.001**
Gender (female), n (%)	88 (17.3)	40 (22.3)	0.135
Smoking, n (%)	245 (48.1)	76 (42.5)	0.190
Hyperlipidemia, n (%)	49 (9.6)	28 (15.6)	**0.028**
COPD, n (%)	14 (2.8)	11 (6.1)	0.064
Ejection fraction (%)	50 (40-55)	45 (40-55)	0.154
Creatinine (mg/dl)	0.85 (0.74-1.0)	0.85 (0.72-1.05)	0.809
Hemoglobin (g/dl)	14.8 (13.4-15.8)	14.3 (13.0-15.3)	**0.009**
Leukocyte × 103/mm^3	11.9 (9.61-14.07)	12.3 (9.6-15.2)	0.178
Thrombocyte × 103/mm^3	261 (224-317)	264 (224-320)	0.849
Glucose (mg/dl)	132 (109-181)	155 (121-230)	**<0.001**
Total cholesterol (mg/dl)	198.5±42.3	200±45.4	0.689
LDL cholesterol (mg/dl)	120±37	122±39	0.615
HDL cholesterol (mg/dl)	40 (33.5-46)	41 (35-48)	0.068
Triglyceride (mg/dl)	181 (118-258)	160 (111-235)	0.139
Culprit lesion, n (%)			
LAD	274 (53.8)	64 (35.8) *	**<0.001**
CXA	79 (15.5)	36 (20.1)	
RCA	156 (30.6)	79 (44.1) †	
CHA_2DS_2-VASc score	1 (0-2)	1 (1-3)	**<0.001**

**: lower than the low rSS group, †: higher than the low rSS group. COPD: chronic obstructive pulmonary disease; CXA: circumflex artery; HDL: high density lipoprotein; LAD: left anterior descending; LDL: low density lipoprotein; RCA: right coronary artery; rSS: residual Syntax score.*

Table 2 – Comparison of variables into the CHA_2DS_2-VASc scoring system between patients with low and high rSS

	Low rSS group (n= 509)	High rSS group (n= 179)	p
Congestive heart failure/LV dysfunction, n (%)	150 (29.5)	60 (33.5)	0.312
Hypertension, n (%)	151 (29.7)	73 (40.8)	**0.006**
Age ≥75 years, n (%)	18 (3.5)	21 (11.7)	**<0.001**
Diabetes mellitus, n (%)	85 (16.7)	50 (27.9)	**0.001**
History of stroke/TIA or thromboembolism, n (%)	1 (0.2)	0 (0)	0.740
Vascular disease, n (%)	12 (2.4)	11 (6.1)	**0.029**
Age 65-74 years, n (%)	76 (14.9)	33 (18.4)	0.162
Sex category (female), n (%)	88 (17.3)	40 (22.3)	0.135

LV: left ventricle; rSS: residual Syntax score; TIA: transient ischemic attack.

to predict the independent risk factor of high residual Syntax score (rSS). In the multivariate logistic regression analysis, the CHA_2DS_2-VASc score and RCA as a culprit lesion were found to be independent predictors of high rSS (Table 4). Additionally, in the multivariate logistic regression analysis for variables into the CHA_2DS_2-VASc score, advanced age ≥75 years and diabetes mellitus were also independent predictors of high rSS (Table 5).

The Receiver Operating Characteristic (ROC) curve analysis was conducted to determine the optimal CHA_2DS_2-VASc score cut-off value to indicate high rSS. The highest combined sensitivity and specificity values crossed the curve at 1.5 (sensitivity 49.2% and specificity 67.6%). The area under the curve (AUC) was 0.611 (95% CI:0.562-0.659, p<0.001).

The ROC curve analysis was also conducted in male and female genders, separately. In the male population, the optimal

Table 3 – Comparison of groups in terms of the number of patients for each CHA_2DS_2-VASc score

	Low rSS group (n= 509)	High rSS group (n= 179)	p
CHA_2DS_2-VASc score: 0, n (%)	195 (38.3)	44 (24.6)	**0.001**
CHA_2DS_2-VASc score: 1, n (%)	149 (29.3)	47 (26.3)	0.442
CHA_2DS_2-VASc score: 2, n (%)	97 (19.1)	42 (23.5)	0.207
CHA_2DS_2-VASc score: 3, n (%)	43 (8.4)	20 (11.2)	0.349
CHA_2DS_2-VASc score: 4, n (%)	18 (3.5)	17 (9.5)	**0.003**
CHA_2DS_2-VASc score: 5, n (%)	6 (1.2)	7 (3.9)	**0.029**
CHA_2DS_2-VASc score: 6, n (%)	1 (0.2)	2 (1.1)	0.167

rSS: residual Syntax score.

Table 4 – Univariate and multivariate logistic regression analyses providing information about independent predictors of high rSS

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI (Lower-Upper)	p	Odds ratio	95% CI (Lower-Upper)	p
Hyperlipidemia	1.741	1.056-2.868	0.030	1.605	0.956-2.696	0.074
COPD	2.315	1.031-5.198	0.042	1.522	0.637-3.638	0.344
Hemoglobin	0.892	0.815-0.977	0.014	0.977	0.883-1.081	0.658
CHA_2DS_2-VASc score	1.374	1.210-1.560	<0.001	1.355	1.171-1.568	**<0.001**
Culprit lesion RCA	1.788	1.260-2.537	0.001	1.963	1.360-2.831	**<0.001**

COPD: chronic obstructive pulmonary disease; RCA: right coronary artery.

Table 5 – Univariate and multivariate logistic regression analyses for CHA_2DS_2-VASc score variables to detect independent predictors of high rSS

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI (Lower-Upper)	p	Odds ratio	95% CI (Lower-Upper)	p
CHF/LV dysfunction	1.207	0.838-1.737	0.312			
Hypertension	1.633	1.146-2.325	0.007	1.296	0.888-1.892	0.179
Age ≥75 years	3.626	1.884-6.977	<0.001	3.218	1.645-6.295	**0.001**
Diabetes mellitus	1.933	1.295-2.887	0.001	1.670	1.091-2.557	**0.018**
Stroke/TIA	0.000	0.000	1.000			
Vascular disease	2.712	1.175-6.260	0.019	2.059	0.858-4.942	0.106
Age 65-74 years	1.288	0.821-2.019	0.270			
Sex (female)	1.377	0.905-2.095	0.136			

CHF: Congestive heart failure; LV: left ventricle; TIA: transient ischemic attack.

CHA_2DS_2-VASc score cut-off value was 1.5 (sensitivity of 36.7% and specificity of 77.0%) with the AUC of 0.592 (95% CI:0.536-0.647, p=0.001). In the female population, the optimal CHA_2DS_2-VASc score cut-off value was 3.5 (sensitivity of 47.5% and specificity of 78.4%) with the AUC of 0.653 (95% CI:0.550-0.756, p=0.006).

We also demonstrated that the CHA_2DS_2-VASc score was correlated with both baseline and residual Syntax scores. The Spearman's correlation analysis revealed that there was a positive correlation between the CHA_2DS_2-VASc score and the residual Syntax score (rSS) (r:0.203, p<0.001) (Figure 1). Also, there was a positive correlation between the CHA_2DS_2-VASc score and the residual Syntax score (rSS) (r:0.234, p<0.001). Additionally, patients with a baseline low Syntax score had a lower CHA_2DS_2-VASc score [1 (0-2), 1 (0-3); p<0.001] compared to patients with a baseline intermediate or high Syntax score.

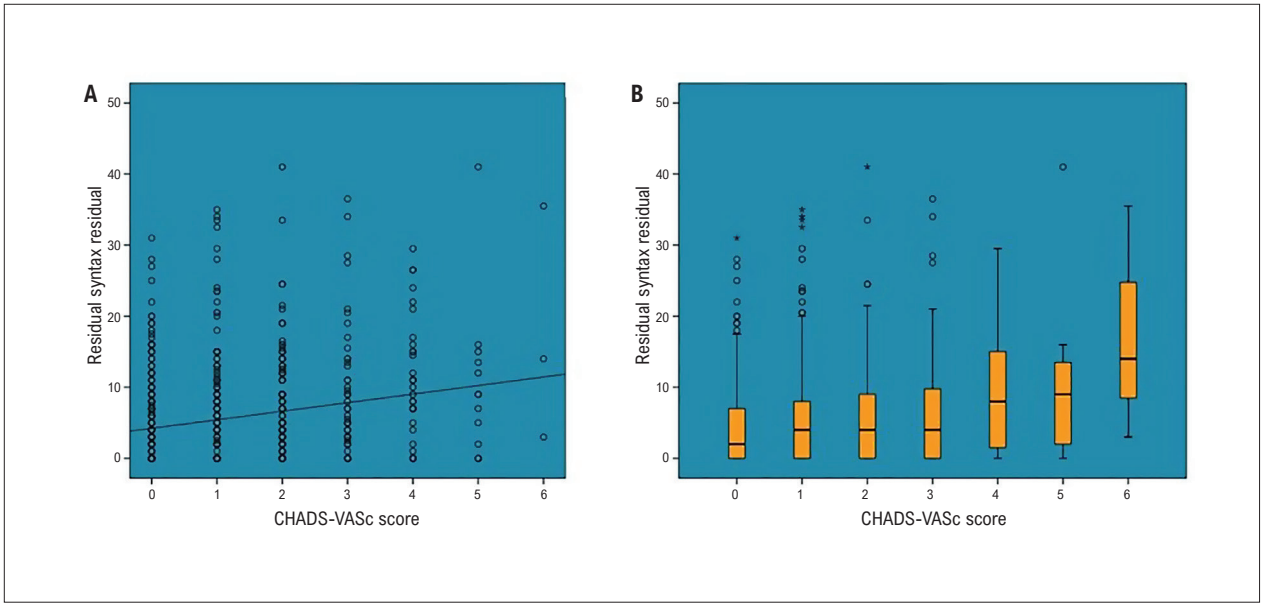

Figure 1 – *A) Correlation between CHA_2DS_2-VASc score and residual Syntax score. B) Residual Syntax score value for each CHA_2DS_2-VASc score.*

Discussion

In our study, to the best of our knowledge, the association of the CHA_2DS_2-VASc score and rSS was demonstrated for the first time in STEMI patients. An increased CHA_2DS_2-VASc score, especially advanced age ≥75 and diabetes mellitus were found to be independent predictors of high rSS. Additionally, the CHA_2DS_2-VASc score was correlated with rSS.

Coronary artery disease is a progressive disease and still an important reason of the increased morbidity and mortality rates in worldwide.[1] Several risk factors of coronary artery disease are well described. Age, diabetes mellitus, hypertension and gender are some of these risk factors that demonstrate the presence and extent of coronary atherosclerosis, and they are accepted as major risk factors for the development of cardiovascular disease.[3] That is why some scoring tolls are described to determine cardiovascular risk and prognosis.

The CHA_2DS_2-VASc score is one of the most important scoring systems to predict adverse clinical outcomes in patients with cardiovascular disease. It was firstly used in patients with atrial fibrillation to estimate the risk of thromboembolism.[6] It was demonstrated that the risk of development of thromboembolism increases with a higher CHA_2DS_2-VASc score.[6] It was also revealed that this score was a useful predictor of subsequent adverse clinical events in patients with acute coronary syndrome.[9] The CHA_2DS_2-VASc score ≥2 was found to be related with composite endpoint of myocardial infarction, stroke and death in 3183 patients with acute coronary syndrome.[9] In a study by Nof et al., each 1-U increment in the CHA_2DS_2-VASc score was associated with a significant increase of 33% in mortality risk in 1820 patients with reduced ejection fraction heart failure.[10] Additionally, the CHA_2DS_2-VASc score predicts all-cause mortality in patients with ST segment elevation myocardial infarction (STEMI).[8]

In light of the foregoing data, increased thrombogenic activity and thrombotic burden may be the reason for adverse cardiovascular outcomes in patients with a high CHA_2DS_2-VASc score. These results can be explained by variables of the CHA_2DS_2-VASc score which are associated with a higher atherothrombotic process, such as advanced age, hypertension, diabetes mellitus and heart failure. In a study by Scudiero et al., 1729 consecutive patients with acute coronary syndrome undergoing percutaneous treatment were evaluated in a prospective study and the CHA_2DS_2-VASc score was found to be related with high platelet reactivity.[11] Ipek et al. also showed that the CHA_2DS_2-VASc score is associated with no-reflow phenomena in STEMI patients who underwent primary percutaneous coronary intervention (PCI).[12] As a result, the CHA_2DS_2-VASc score is a good tool to predict increased atherothrombosis.

It is well known that the extent and severity of coronary artery disease is associated with the mentioned atherothrombotic status. It means higher atherosclerotic activity results in increased coronary atherosclerotic burden. Supporting this, in previous studies, the relationship between the CHA_2DS_2-VASc score and coronary artery disease severity was revealed.

In a study by Cetin et al., 407 consecutive patients who underwent diagnostic coronary angiography were evaluated, and the CHA_2DS_2-VASc score was significantly correlated with a number of diseased vessels and associated with coronary artery disease severity.[7] A total of 252 consecutive patients with non-ST segment elevation myocardial infarction (non-STEMI) were evaluated by Tasolar et al., and the CHA_2DS_2-VASc score was related with a higher Syntax score.[13]

However, to the best of our knowledge, the association between the CHA_2DS_2-VASc score and residual coronary

artery disease severity after performing percutaneous coronary intervention (PCI) has not been studied yet.

Approximately 40-65% of multivessel coronary artery disease is detected in acute coronary syndrome patients, and it is also a predictor of poorer prognosis.[14,15] The residual Syntax score (rSS) is a grading system to determine the complexity and severity of coronary atherosclerosis after performing PCI for culprit lesion. It was firstly used and described through a post hoc analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial.[2] High rSS (>8) was a strong independent predictor of unplanned revascularization, myocardial infarction (MI), cardiac and 1-year mortality in 2686 patients with moderate-high risk acute coronary syndrome undergoing PCI.[2] Supporting this, Loutfi et al. showed that lower rSS (a score of 8 or below) is associated with the reduction in 1 year of major adverse cardiac and cerebrovascular events (MACCE), death, MI, cerebrovascular accident and repeated revascularization in STEMI patients.[16]

An unexpected result of the substudy group of the COURAGE trial (clinical outcomes utilizing revascularization and aggressive drug evaluation) revealed that the extent and severity of the anatomic obstruction of coronary arteries had a more predictive value on MI and death compared to the degree of ischemia.[17] It reflects the prognostic value of coronary atherosclerotic burden on adverse clinical outcomes. Thus, the importance of the residual coronary artery disease severity is revealed.

To the best of our knowledge, we also demonstrated the association of the CHA_2DS_2-VASc score and residual Syntax score (rSS) for the first time in STEMI patients who underwent primary PCI. It may be the reason for increased adverse cardiovascular outcomes in ST segment elevation myocardial infarction (STEMI) patients with a higher CHA_2DS_2-VASc score. However, large scaled studies are needed for future investigations, especially focused on clinical events.

Study limitations

A relatively small sample size was the major limitation of our study. Lack of data about clinical outcomes and prognosis was the other major limitation. Some risk factors can be modified with lifestyle changes and medical therapy. However, this study was inadequate to demonstrate the effect of modified factors on clinical results due to the retrospective design of the study.

Conclusion

The CHA_2DS_2-VASc score has a predictive value on rSS in patients with STEMI. The CHA_2DS_2-VASc score was also an independent predictor of higher rSS. Additionally, this score was positively correlated with coronary atherosclerotic burden.

Author Contributions

Conception and design of the research: Kalkan AK, Kahramann S, Avci Y, Turkyilmaz AB, Erturk M; Acquisition of data: Kalkan AK, Kahramann S, Bulut U, Gulmez R, Erturk M; Analysis and interpretation of the data: Kalkan AK, Kahramann S, Avci Y, Gulmez R, Turkyilmaz AB, Erturk M; Statistical analysis: Kahramann S, Bulut U, Gulmez R; Obtaining financing: Erturk M; Writing of the manuscript: Kalkan AK, Kahramann S, Avci Y, Erturk M; Critical revision of the manuscript for intellectual content: Kalkan AK, Kahramann S, Bulut U, Turkyilmaz AB, Erturk M.

Potential Conflict of Interest

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

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

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Atherosclerotic Burden is the Highway to Cardiovascular Events

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Short Editorial related to the article: The Predictive Value of CHA2DS2-VASc Score on Residual Syntax Score in Patients With ST Segment Elevation Myocardial Infarction

Atherosclerotic cardiovascular disease is still a major cause of morbidity and mortality worldwide, and its risk factors have already been identified. Dyslipidemia, high blood pressure, cigarette smoking, diabetes and adiposity are frequently present, mostly in combination, in patients with coronary artery disease (CAD).[1,2] Identifying patients at risk for developing CAD and presenting acute coronary syndromes is of great value, and many scores were created with this aim, such as the Framingham risk score, the ASSIGN score and the QRISK^{R}2 risk score.

CHA_2DS_2VASc score, which comprises congestive heart failure (C), hypertension (H), age ≥ 75 (A_2), diabetes (D), stroke or transient ischemic attack (S_2), vascular disease (V), age 65-74 years (A) and male gender (Sc), was originally developed to predict stroke risk in patients with atrial fibrillation. Recently, the CHA_2DS_2VASc score was also associated with major adverse events in patients with ST-segment elevation myocardial infarction (STEMI)[3] non-ST elevation acute coronary syndromes[4,5] and in patients with chronic stable ischemic disease.[6] Moreover, Tasolar et al.[4] and Chua et al.[5] demonstrated its association with coronary artery disease severity.

Residual syntax score (rSS) was designed to quantify the incompleteness of revascularization after percutaneous coronary intervention (PCI), calculating the remaining SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score, a quantitative angiographic measure of anatomic severity and complexity after a PCI. A high rSS was associated with a poor 30-day and 1-year prognosis.[7]

In this issue of *Arquivos Brasileiros de Cardiologia*, Kalkan et al.[8] demonstrated for the first time the association between CHA_2DS_2VASc score and rSS in 688 patients who underwent primary PCI after STEMI.[8] Although it seems obvious to find a relationship between a score that includes some of the main risk factors for atherosclerosis (CHA_2DS_2VASc) and the atherosclerotic burden itself (rSS), it brings our attention to the relevant and contemporary discussion about the importance of the severity of atherosclerosis. Possibly, the atherosclerotic burden is the mechanism behind the association of CHA_2DS_2VASc score and cardiovascular events found in many previous studies[3,5,6]

International guidelines suggest the documentation of ischemia before elective invasive procedures to treat coronary artery disease, either by exercise electrocardiogram testing, stress echocardiography, single-photon emission computed tomography or cardiac magnetic resonance. Moreover, invasive functional testing, such as fractional flow reserve, is recommended before revascularization if non-invasive ischemia is not demonstrated.[9] Controversially, the superiority of anatomic assessments over ischemia testing has been repeatedly demonstrated in different scenarios. In a randomized trial of 3283 patients, Singh et al.[10] showed that computed tomography (CT) angiography had a stronger association with 5-year coronary heart disease, death, or non-fatal myocardial infarction (MI) than exercise electrocardiogram.[10] Similarly, Hoffmann et al.[11] demonstrated in a randomized trial of 9102 patients that CT angiography had a greater discriminatory ability than functional testing in predicting cardiovascular events[11]. In a sub-analysis of the COURAGE trial, anatomic burden assessed by coronary angiography was a consistent predictor of death, MI and non-ST segment elevation acute coronary syndromes, whereas ischemic burden was not.[12] A recent sub-analysis of the ISCHEMIA trial revealed that CAD severity, evaluated by CT angiography, was a highly significant predictor of all-cause mortality, cardiovascular death and MI, both spontaneous and periprocedural; again, ischemia severity was not associated with adverse events.[13]

The rationale behind anatomic tests being superior to ischemia testing is simple. Spontaneous MI occurs when either an obstructive or non-obstructive plaque ruptures; functional tests identify only obstructive plaques, whereas angiography, invasive or CT, identifies big and small plaques, which can erode or rupture, causing MI and possibly death. Consequently, if you have more plaques, you have a bigger chance of instability in one of those and a higher risk of cardiovascular events. One theoretical benefit of coronary artery bypass graft over PCI relies on the idea that the graft bypasses long segments of proximal coronary plaques, and the patient would be protected from MI if any of those ruptures, whereas the stents protect only the stented segment.[14]

In conclusion, Kalkan et al.[8] demonstrated that patients with higher CHA_2DS_2VASc score have higher rSS, which means higher CAD severity. Based on recent evidence, those patients might consequently be at higher risk of plaque rupture and cardiovascular events, such as MI or death, and therefore would benefit from more aggressive plaque stabilizing therapies. By predicting atherosclerotic burden, the CHA_2DS_2VASc score might be another tool for risk prediction in patients with CAD.

Keywords

Atherosclerosis; Coronary Artery Disease; Atrial Fibrillation; Myocardial Infarction; Percutaneous Coronary Intervention

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Assessment of the Relationship Between the Adropin Levels and the Coronary Collateral Circulation in Patients with Chronic Coronary Syndrome

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Abstract

Background: **Coronary collateral circulation (CCC) provides an alternative blood flow to myocardial tissue exposed to ischemia and helps to preserve myocardial functions. Endothelial-derived nitric-oxide (NO) production and vascular endothelial growth factor (VEGF) have been suggested as the most important factors in the development of CCC. Adropin is a peptide hormone responsible for energy hemostasis, and is known for its positive effects on the endothelium through NO and VEGF.**

Objective: **The aim of this study is to investigate the association between adropin and the presence of CCC in patients with chronic coronary syndrome (CCS).**

Methods: **A total of 102 patients with CCS, who had complete occlusion of at least one major epicardial coronary artery, were included in the study and were divided into two groups: the group of patients (n:50) with poor CCC (Rentrop 0-1) and the group of patients (n:52) with good CCC (Rentrop 2-3). The level of significance adopted in the statistical analysis was 5%.**

Results: **Mean adropine levels were found as 210.83±17.76 pg/mL and 268.25±28.94 pg/mL in the poor and good CCC groups, respectively (p<0.001). Adropin levels proved to be positively correlated with neutrophil-to-lymphocyte ratios (r:0.17, p:0.04) and the rentrop scores (r:0.76, p<0.001), and negatively correlated with age (r:-0.23, p:0.01) and Gensini scores (r:-0.19, p:0.02). Adropin level is a strong independent predictor of good CCC development (OR:1.12, 95% CI:(1.06–1.18), p<0.001).**

Conclusion: **This study suggests that adropin levels may be a possible factor associated with the presence of CCC in CCS patients.**

Keywords: **Acute Coronary Syndrome; Atherosclerosis; Peptides; Adropin; Coronary Artery Diseases; Coronary Collateral Circulation; Diagnostic Imaging; Coronary Angiography.**

Introduction

Coronary artery disease (CAD) is a disease characterized by narrowing or occlusion of the coronary arteries, usually due to atherosclerosis. It is the leading cause of death in men and women worldwide, and its incidence increases with age.[1] In chronic coronary syndrome (CCS), symptoms may vary over time due to such factors as myocardial oxygen consumption, emotional stress, or temperature changes. CCS is also associated with the stability or quiescence of the atherosclerotic plaque.[1]

Adropin is a peptide hormone containing seventy-six amino acids and is encoded by the "energy homeostasis-associated gene (ENHO)". The term "adropin" was derived from the Latin words of "aduro" and "pinquis", and refers to an agent that promotes burning of fats.[2] The effects of adropin in heart diseases have been suggested by various mechanisms, but its effects on endothelial functions have been accepted as its main mechanism. Adropin increases the expression of eNOS, which is primarily responsible for NO production. In parallel, adropin deficiency has been associated with a decrease in NO bioavailability in the endothelium.[3] Furthermore, adropin has been reported to inhibit platelet aggregation,[4] smooth muscle proliferation[5] endothelial adhesion of leukocytes and monocytes,[6] and LDL oxidation.[7] Endothelial dysfunction characterized by endothelial NO deficiency is an independent predictor of the onset of CAD. Adropin is known to be effective on NO metabolism. Concordantly, its positive effects on endothelial functions have been shown,[8] and low adropin levels have been associated with endothelial dysfunction.[8,9] Additionally, Cardiac Syndrome X patients with endothelial dysfunction were shown to have lower adropin levels when compared to healthy individuals.[10]

Adropin activates the vascular endothelial growth factor receptor-2 (VEGFR-2) and phosphatidyl inositol-3-phosphate

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kinase pathways in the vessel wall endothelium, and contributes to the nitric oxide (NO) secretion by increasing the endothelial nitric oxide synthase (eNOS) activity. It has been reported in the literature that adropin indirectly led to vasodilation in the vessel wall, and that injection of synthetic adropin into a tissue, in which ischemia has developed, led to the healing of tissue through reperfusion.[8]

It has also been shown in the literature that the imbalance between myocardial oxygen supply and oxygen demand resulting from coronary artery stenosis or coronary artery occlusion increases the development of coronary collateral circulation (CCC). The formation of CCC occurs in the form of either "angiogenesis", which occurs de novo through the budding of new capillaries from the existing blood vessels, or "arteriogenesis", which occurs as a result of the growth and maturation of anastomosis channels that exist between the existing arteries since birth.[11]

Current technology does not allow the non-invasive measurement of CCC in humans. Thus, the easiest way to evaluate CCC is through the visual evaluation of the collateral arteries using coronary angiography, which can be done in a semi-quantitative method, as described by Rentrop et al.[12]

There are many studies available in the literature on the factors that affect the CCC. Nevertheless, there is no study in which the effect of adropin levels on the CCC has been addressed, despite the fact that there are a number of studies conducted in previous years which demonstrated the protective role of adropin on endothelial structure and function. In view of that mentioned above, for the first time, in this study, adropin is investigated as to whether it can be a possible factor associated with the presence of CCC from the pathophysiological standpoint in individuals with CCS.

Methods

This study included, prospectively, 102 patients, who underwent CA due to CCS between March 2017 and March 2020 at Niğde Ömer Halisdemir University Hospital (Single-center). The patients were divided into two groups: the group of patients with poor CCC (Rentrop 0-1)(n:50) and the group of patients with good CCC (Rentrop 2-3)(n:52) based on the Rentrop scores.

Patients with CCS, who had complete occlusion of at least one major epicardial coronary artery on the coronary angiography, were included in the study, whereas patients who presented an acute coronary syndrome in the last 6 months, previous coronary artery bypass (CABG) operation, moderate to severe heart valve disease, acute/chronic kidney failure, eGFR (estimated glomerular filtration rate) levels of <30 ml/min, liver failure, any known malignancy, heart failure symptoms [NYHA (New York Heart Association) class 3 or 4], moderate/severe chronic obstructive pulmonary disease, any acute/chronic infective disease, and acute/chronic rheumatological or inflammatory disease, were excluded from the study.

Patients, whose blood pressure levels were found to be >140/90 mm/Hg as a result of repetitive measurements or who were found to have been using any antihypertensive medication, were considered to be hypertension patients, whereas patients, whose fasting plasma glucose levels were found to be > 126 mg/dL as a result of repetitive measurements or who were found to have been using any antidiabetic medication, were considered to be diabetes mellitus patients.

Blood samples were collected venously after at least 10 hours of fasting, and were then quickly centrifuged at 1000 g and 4°C for 10 minutes. The resultant blood serums were stored at -80°C for biochemical analysis. Serum adropin concentrations were studied twice, using a commercially available ELISA kit (Fankew, Shanghai Kexing Trading Co., Ltd, China). The inter-assay and intra-assay coefficients of variation were found to be below 9% and 10%, respectively.

All patients underwent a transthoracic echocardiography by the same cardiologist, and their left ventricular ejection fractions (LVEF) were calculated using the Simpson's method.

Body mass index (BMI) (kg/m^2) values of the patients were calculated by dividing their body weights by the squares of their heights.

Angiographic evaluations

Angiographic images were evaluated by two experienced cardiologists using the Picture Archiving and Communication Systems. Two cardiologists made a joint decision in the case of borderline lesions.

Gensini scores were calculated based on the degree of angiographic stenosis. Accordingly, 1 point was assigned for 0-25% stenosis, 2 points were assigned for 25-50% stenosis, 4 points were assigned for 50-75% stenosis, 8 points were assigned for 75-90% stenosis, 16 points were assigned for 90-99% stenosis, and 32 points were assigned for 100% lesion (complete occlusion). These scores were then multiplied by the coefficient defined for each main coronary artery and each segment points [left main coronary artery:5, proximal segment of the left anterior descending artery (LAD):2.5, middle segment of LAD:1.5, apical segment of LAD:1, first diagonal branch:1, second diagonal branch:0.5, proximal segment of the circumflex artery (Cx) in the presence of right coronary artery (RCA) dominance:2.5, distal segment of the Cx artery:1, the obtuse marginal branch:1, posterolateral branch:0.5, RCA proximal segment:1, RCA middle segment:1, RCA distal segment:1, and posterior descending artery:1].[13]

Rentrop classification is made based on the coronary angiography. Accordingly, cases with no collateral flow from the coronary artery with a blood flow, to the completely occluded coronary artery were assessed as grade 0, cases that filled in the lateral branches of the occluded artery but that did no fill in the epicardial segment were assessed as grade 1; cases with partial filling in the epicardial segment were assessed as grade 2; and cases with complete collateral filling of the epicardial vessel were assessed as grade 3.[12]

Statistical analysis

SPSS 23.0 (Statistical Package for the Social Sciences Version 23.0) software package was used to conduct the statistical analyses. Kolmogorov-Smirnov test was used to assess the distribution pattern of the research data. Normally distributed numerical variables were expressed in terms of mean± standard deviation (SD), whereas non-normally

distributed numerical variables were expressed in terms of median and interquartile range (IQR). Categorical variables were summarized as numbers and percentages, and compared between the groups using the Chi-square test. 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. A value of $p<0.05$ was accepted as statistically significant. Univariate and multivariate logistic regression analyses were performed to identify the dependent predictors of good CCC. The Spearman correlation test was performed to define the correlation between adropin level and other parameters. Receiver operating characteristic (ROC) curve was used to reveal the sensitivity, specificity, and the optimal cut-off value of adropin level that can be used to predict good CCC.

Results

A total of 102 patients, of whom 50 presented poor CCC and 52 presented good CCC, were included in the study. No significant differences were found between the patient groups with poor or good CCC in terms of gender, age, BMI, smoking status, diabetes mellitus (DM), hypertension, arterial blood pressure levels, heart rates, LVEF, and medications used (Table 1).

The laboratory characteristics of the groups are shown in Table 2. Mean adropine levels were found to be significantly different, in 210.83±17.76 pg/mL and 268.25±28.94 pg/mL in the poor and good CCC groups, respectively. The two groups did not differ significantly in any of the other laboratory parameters.

Coronary angiographic characteristics of the patient groups are shown in Table 3. No significant difference was found between the groups according to the location of the occluded coronary arteries. Mean Gensini scores of the poor and good CCC groups were found to be significantly different, in 104.3±18.9 and 95.3±14.4, respectively. There was also no difference between the groups in terms of left main coronary artery disease, multivessel disease, and bifurcation lesions.

No significant correlation was found between the adropine levels and the BMI values, heart rates, high-sensitive C-reactive protein levels, hemoglobin A1c (glycated hemoglobin) levels, smoking status, presence of DM, presence of hypertension, total cholesterol, HDL, triglyceride and LDL levels. A significant and moderately positive correlation was observed between the adropin levels and the neutrophil-to-lymphocyte ratios (NLR), whereas a significant and strongly positive correlation was observed between the adropin levels and the Rentrop scores. By contrast, a significant and moderately negative correlation was observed between the adropin levels and the age and Gensini scores (Table 4) (Figure 1).

ROC curve analysis was performed to assess the role of adropin level in predicting good CCC (Figure 2). The ROC analysis revealed that a cut-off value of 276.25 pg/mL in terms of adropin level predicted good CCC with 91% sensitivity and 96% specificity (ROC area=952, $p<0.001$).

As shown in Table 2, adropin levels were higher in the good CCC group, hence logistic analyses were performed in order to determine whether or not adropin levels can be used as an independent predictor of developing good CCC. The results of the univariate logistic regression analysis indicated that adropin levels were a strong independent predictor of developing good CCC. Gensini score, multivessel disease, LAD occlusion, and RCA occlusion were found to be independent predictors of developing good CCC as well. In addition, the results of the multivariate logistic regression analysis, which was adjusted

Table 1 – Clinical characteristics of the study population

	Poor CCC (n:50)	Good CCC (n:52)	p-value
Male, n(%)	35(70)	38(73)	0.80
Age, years, mean (SD)	60.47(8.06)	59.04(8.96)	0.47
BMI, mean (SD), kg/m^2	24.28(1.61)	24.12(1.62)	0.67
Current smoker, n (%)	15(30)	26(50)	0.11
DM, n (%)	15(30)	16(31)	0.94
Hypertension, n (%)	10(20)	13(25)	0.79
Systolic blood pressure, mean (SD), mm Hg	122.77(10.32)	125.87(11.24)	0.22
Diastolic blood pressure, mean (SD), mm Hg	74.37(8.50)	74.65(8.63)	0.88
Heart rate, mean (SD), beat/min	76.93(13.95)	76.69(13.61)	0.94
LVEF, (%), mean (SD)	55.80(8.18)	53.77(8.12)	0.28
Statins usage, n (%)	10(20)	11(21.1)	0.78
β-Blocker usage, n (%)	11(22.2)	13(25)	0.88
Nitrate usage, n (%)	3(6)	3(5.7)	0.93
Angiotensin converting enzyme inhibitor usage, n (%)	9(18)	8(15.3)	0.74
Angiotensin receptor blocker usage, n (%)	11(22.2)	7(13.5)	0.22
Calcium channel blocker usage, n (%)	10(20)	7(13.5)	0.53

CCC: coronary collateral circulation; SD: standard deviation; BMI: body mass index; DM: diabetes mellitus; LVEF: left ventricular ejection fraction.

Table 2 – Laboratory characteristics of the study population

	Poor CCC (n:50)	Good CCC (n:52)	p-value
Adropin level, mean (SD), pg/mL	210.83(17.76)	268.25(28.94)	<0.001
High-sensitive C-reactive protein, median (IQR), mg/L	3.55(0.93)	3.40(0.93)	0.68
Fasting glucose, mean (SD), mg/dl	117.03(33.83)	123.80(44.09)	0.48
Hemoglobin A1c, mean (SD), %	6.40(1.19)	6.39(1.02)	0.97
Total cholesterol, mean (SD), mmol/L	187.90(25.30)	194.23(28.34)	0.31
HDL, mean SD), mmol/L	43.73(5.57)	44.33(6.17)	0.67
Triglyceride, median (IQR), mmol/L	154.00(50.85)	163.50(47.20)	0.73
LDL, mean (SD), mmol/L	108.50(28.20)	110.92(29.60)	0.72
Creatinine, mean (SD), mg/dl	1.14(0.15)	1.13(0.16)	0.71
Hemoglobin, mean (SD), g/L	14.56(0.94)	14.25(1.09)	0.19
Red cell distribution width, mean (SD), %	12.79(1.01)	12.61(1.14)	0.47
White blood cell, mean (SD), x 10^9/L	8.34(1.65)	8.36(1.44)	0.95
Neutrophil, mean (SD), x 10^9/L	6.31(1.94)	6.21(1.44)	0.78
Lymphocyte, mean (SD), x 10^9/L	1.75(0.44)	1.70(0.43)	0.57
NLR, mean (SD), %	3.92(1.64)	3.89(1.56)	0.76
Platelet, mean (SD), x 10^9/L	241.90(41.35)	225.04(39.80)	0.07

CCC: coronary collateral circulation; SD: standard deviation; NLR: neutrophil-to-lymphocyte ratios.

Table 3 – Coronary angiographic findings of the study population

	Poor CCC (n:50)	Good CCC (n:52)	p-value
LAD occlusion, n(%)	15(30)	12(23.1)	0.51
Cx occlusion, n(%)	15(30)	16(30.8)	0.93
RCA occlusion, n(%)	18(36)	24(46.2)	0.44
Gensini score, mean (SD)	104.3(18.9)	95.3(14.4)	0.007
Left main coronary artery disease, n(%)	3(6)	2(3.8)	0.08
Multivessel disease, n(%)	23(46)	21(40.4)	0.65
Bifurcation lesions, n(%)	10(20)	8(15.4)	0.14
Rentrop Score 0, n(%)	18(36)		
Rentrop Score 1, n(%)	32(64)		
Rentrop Score 2, n(%)		31(59.6)	
Rentrop Score 3, n(%)		21(40.4)	

CCC: coronary collateral circulation; LAD: left anterior descending artery; Cx: circumflex artery; RCA: right coronary artery.

for possible confounding factors, such as age, BMI, heart rate, total cholesterol, and low-density lipoprotein (LDL), revealed that not only the adropine level, but also the gensini score, multivessel disease, LAD occlusion, and RCA occlusion were independent predictors of developing good CCC (Table 5).

Discussion

This is the first study in which the relationship between the adropin levels and CCC was investigated in patients diagnosed with CCS. The main finding of the study was that the adropine levels were lower in the poor CCC group than in the good CCC group. Additionally, a positive correlation was found between the adropin levels and the NLR values and Rentrop scores, whereas a negative correlation was found between the adropin levels and the age and gensini scores. Furthermore, logistic regression and ROC analyses indicated that adropin was an independent predictor of developing good CCC. Apart from the adropin level, other factors such as Gensini score, presence of multivessel disease, LAD occlusion, and RCA occlusion have been shown to be predictive of developing good CCC as well.

CCC occurs when the coronary vessels narrow down for 70% or more.[14] The resultant collateral vessels are between

Table 4 – Correlation between adropin level and other variables of the study population

	r	p-value
Age	-0.23	0.01
BMI	-0.10	0.55
Heart rate	0.12	0.43
High-sensitive C-reactive protein	0.04	0.84
Hemoglobin A1c	0.69	0.56
Current smoker	0.33	0.16
DM	0.06	0.85
Hypertension	0.09	0.51
Total cholesterol	0.10	0.81
HDL	-0.14	0.45
Triglyceride	0.25	0.34
LDL	0.09	0.76
NLR	0.17	0.04
Gensini score	-0.19	0.02
Rentrop score	0.76	<0.001

BMI: body mass index; DM: diabetes mellitus; NLR: neutrophil-to-lymphocyte ratios.

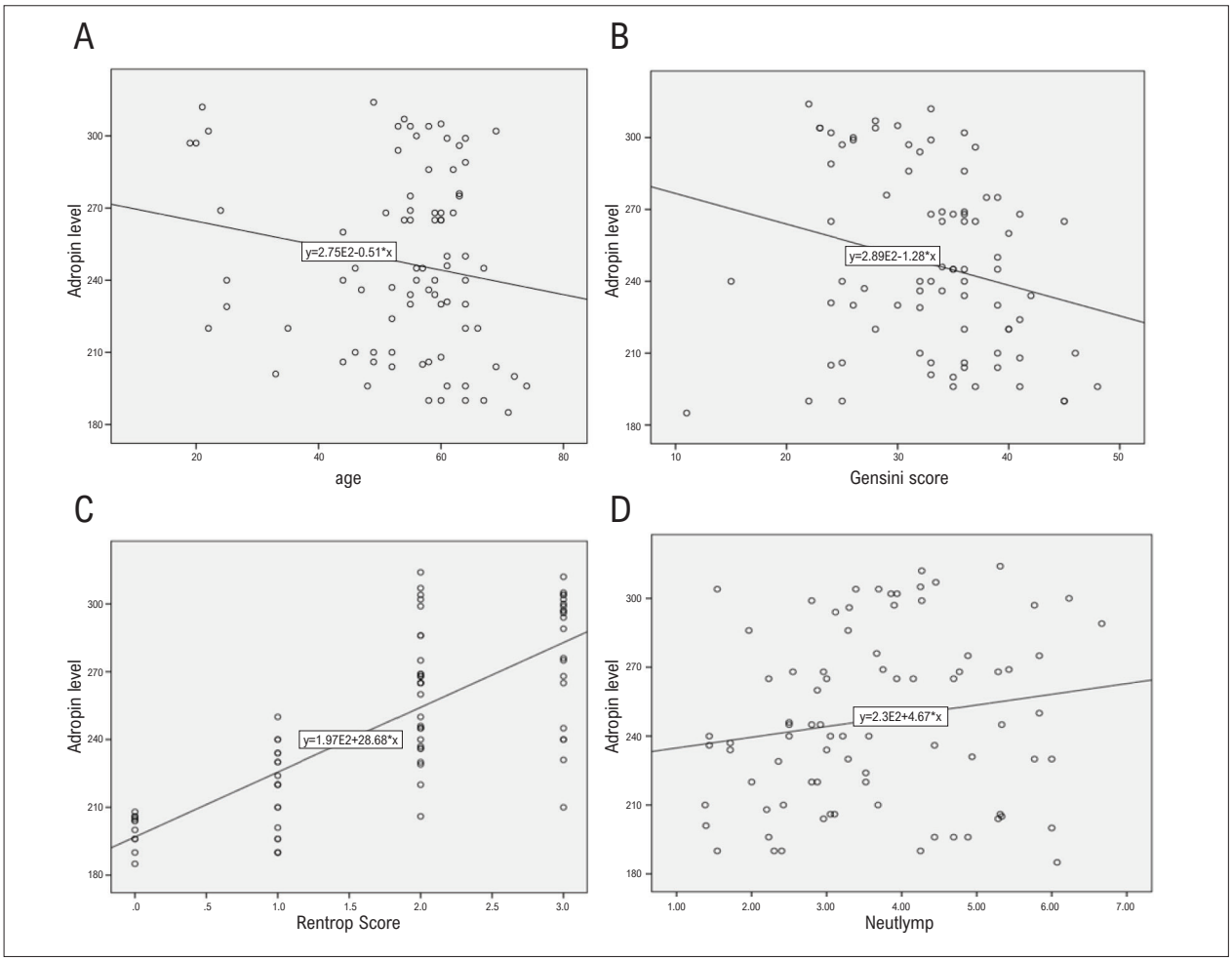

Figure 1 – *Dispersion graphs showing the relationship between adropin level and a) Age (r: -0.23, p: 0.01); b) Gensini score (r: -0.19, p: 0.02); c) Rentrop score (r: 0.76, p: <0.001); d) NLR (r: 0.17, p: 0.04).*

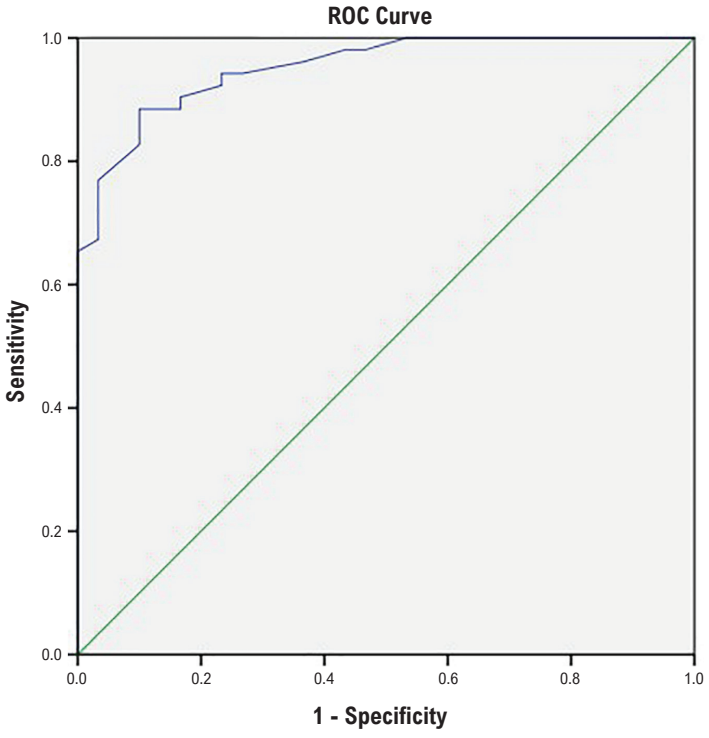

Figure 2 – *Receiver–operating characteristic (ROC) analysis for adropin level to predict good coronary collateral circulation.*

20-200 μm in size and are thin-walled. The denseness of the collateral vessels formed varies from species to species, and it is moderate in humans.[15] These vessels are the alternative blood supply pathway of the ischemic myocardium. CCC vessels are normally closed and non-functional. However, when the pressure difference occurs as a result of coronary stenosis, the rudimentary vessels rapidly open up.[14]

Coronary collateral arteries help maintain myocardial functions by providing an alternative blood flow to myocardial tissue left ischemic by occlusive CAD. It is usually ischemia that gives rise to an excess of collateral arteries, yet even those without CAD have an excess of collateral arteries, as the existing CCC may render insufficient during exercise even though it provides the blood needed by the myocardium while at rest. Several independent clinical and angiographic variables have been associated with the CCC grade in the literature. In patients with CAD, the time of occlusion,[16] the location of the lesion, the severity of coronary stenosis, and the duration of angina[17] affect the degree of CCC; while in healthy individuals, hypertension and resting heart rate[18] affect the degree of CCC.

The clinical importance of CCCs is that they protect the myocardial functions,[19] limit the infarct size[20] and positively affect ventricular remodeling,[21] particularly during the acute myocardial infarction. Additionally, it has been also reported in the literature that CCCs partially reduced the incidence of concomitant cardiogenic shock.[22]

Recently, it has been suggested that the most important factors in the development of CCC are the production of endothelium-derived NO and VEGF. It is known that NO and VEGF increase angiogenesis, especially in coronary collateral vessels, and contribute to the maturation of collateral arteries.[23] Adropin has been shown to increase VEGFR-2 in endothelial cells, and as a result, it has also been shown to increase the expression of eNOS mRNA and eNOS protein, via Akt (Ak strain transforming), that is protein kinase B, and ERK½ (extracellular signal-regulated protein kinase ½) as well.[8] Thus, it is obvious that coronary collaterals will mature further through VEGFR-2. As a matter of fact, in this clinical study, a positive and significant correlation was observed between the Rentrop scores, which indicate the coronary collaterals, and the adropin levels, substantiating the findings of the above-mentioned cellular study.

A relationship has been shown between CAD and low adropin levels; and SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery), Gensini and Friesinger scores and serum adropin levels were shown to be negatively correlated in the patient group with type 2 DM.[24] It has been suggested that low serum adropin levels are an independent predictor of coronary atherosclerosis[24] and the patency of saphenous vein grafts after CABG operation.[25] In comparison, in this study, similar to the findings of other studies mentioned above, a moderately negative correlation

Table 5 – Univariate and multivariate logistic regression analysis showing independent predictors of good CCC

	Univariate		Multivariate*	
	p-value	OR (95% CI)	p-value	OR(95% CI)
Adropin level	<0.001	1.12(1.06-1.18)	<0.001	1.13(1.06-1.19)
Age	0.48	1.01(0.97-1.04)	0.54	1.01(0.97-1.05)
BMI	0.38	1.24(0.76-2.02)	0.45	1.23(0.74-2.01)
Heart rate	0.43	1.03(0.98-1.05)	0.51	1.04(1.01-1.07)
High-sensitive C-reactive protein	0.19	0.58(0.26-1.30)	0.41	0.61(0.30-1.42)
Hemoglobin A1c	0.96	0.98(0.51-1.90)	0.34	1.01(0.56-1.96)
Current smoker	0.12	1.86(0.89-3.89)	0.48	1.35(0.55-3.32)
DM	0.81	1.09(0.55-2.14)	0.87	1.06(0.51-2.25)
Hypertension	0.89	0.96(0.48-1.90)	0.80	0.91(0.43-1.93)
Total cholesterol	0.09	1.42(1.10-1.83)	0.10	1.44(1.09-1.90)
HDL	0.48	1.56(0.46-5.32)	0.85	1.05(0.27-4.20)
Triglyceride	0.10	1.23(0.96-1.58)	0.27	1.19(0.88-1.60)
LDL	0.77	0.99(0.97-1.02)	0.23	1.01(0.98-1.03)
NLR	0.23	0.66(0.44-1.10)	0.31	0.74(0.51-1.33)
Gensini score	<0.001	1.02(1.01-1.03)	<0.001	1.01(1.00-1.02)
Multivessel disease	<0.001	2.63(1.68-4.14)	<0.001	2.45(1.53-3.93)
LAD occlusion	<0.001	4.59(2.13-9.90)	<0.001	4.73(2.08-10.70)
Cx occlusion	0.09	2.21(1.07–4.34)	0.11	2.41(1.12-4.41)
RCA occlusion	0.01	2.31(1.17-4.53)	0.03	2.17(1.03-4.56)

**Adjusted for age, heart rate, BMI, total cholesterol and LDL. In this statistical analysis, adropin levels, as well as age, BMI, total cholesterol, HDL, triglyceride, LDL, multivessel disease, and gensini score are continuous values, others are binary variables. BMI: body mass index; DM: diabetes mellitus; NLR: neutrophil-to-lymphocyte ratios; LAD: left anterior descending artery; Cx: circumflex artery; RCA: right coronary artery.*

was found between the Gensini scores and the adropin levels. Nevertheless, in this study, patients with type 2 DM comprised 30.5% (30% in the poor CCC group, 31% in the good CCC group) of the study group. In addition, the patients, who underwent CABG, were not included in this study.

Several studies have suggested that there is an inverse relationship between aging and adropin levels, and that this decrease in adropin levels may be one of the minor factors that trigger CAD, which is known to increase with age.[9,24] It was also shown in another study that the effect of adropin-induced eNOS-mediated vasodilation decreases with age.[26] In comparison, in this study, similar to the findings of other studies mentioned above, a significant moderate correlation was observed between adropin levels and age in the negative direction.

There is no doubt that the NLR is associated with inflammation and that the inflammation plays a role in CAD. To give an example, in a study conducted with chronic CCS patients, mean NLR was found as 5.0±5.1 in the group with atherosclerosis progression, and as 3.2±3.0 in the group without progression, and this finding was attributed to the correlation between the atherosclerosis progression and increased NLR.[27] In addition to the associated classical risk factors, NLR has been shown to be associated with the prevalence of CAD and the complexity of the lesions as well.[28] In another controlled study, high NLR values proved to be a good predictor of Gensini scores in the group of patients with CCS. NLR values above 2.04 were found to have effectively predicted the presence of CAD.[29] In fact, it has been shown in another study that NLR values even predicted the chronic total occlusions of patients.[30] A correlation was reported between good CCC development and NLR in the group of patients with concomitant chronic total occlusion.[31] In comparison, in this study, contrary to the respective findings reported in the literature, NLR was not found to have differed between the poor and good CCC groups, yet it was found to have correlated with adropin levels. It is thought that this discrepancy between the said result of this study and the respective results reported in the literature might be due to the low number of patients included in this study.

Limitations to the study

There were several limitations to this study. First, the number of patients included in this study was limited, and secondly, there was no control group comprising individuals with normal coronary arteries. Hence, it would be beneficial to replicate the study with a larger study group and with the addition of a control group. Additionally, the development of

CCC is a long process, thus a single measurement of adropin levels may not give a clear idea about lifelong development of CCC. Another limitation was that Rentrop classification, a visual method used in the evaluation of CCC, was used, and intravascular ultrasonography was not used. CCC examined in the Rentrop classification are affected by the patient's blood pressure, the contrast injection strength of the operator, and the filming time. Lastly, despite the fact that a correlation was found between the adropin levels and the CCC, the underlying mechanisms are not clear, thus large-scale studies are needed to verify the effect of adropin on the development of CCC.

Conclusion

In conclusion, the findings of this study suggest that adropin levels correlate with the presence and amount of CCC in CCS patients.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis, Obtaining financing; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Akkaya H, Güntürk EE, Akkaya F, Karabıyık U, Güntürk İ, Yılma S.

Potential Conflict of Interest

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

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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 Niğde Ömer Halisdemir under the protocol number 2017/08. 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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Another Player in Increasing Collateral Circulation in the Heart – Another Potential Therapeutic Target in Cardiovascular Medicine?

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Short editorial related to the article: Assessment of the Relationship Between the Adropin Levels and the Coronary Collateral Circulation in Patients with Chronic Coronary Syndrome

Richard Lower of Amsterdam first called attention to channels connecting the right and left coronary arteries in 1669.[1] The Swiss anatomist Albrecht von Haller demonstrated these anastomoses by dissecting the coronary arteries. So, for centuries now, the presence of a well-developed collateral network providing blood supply to an underperfused myocardium has gained significant interest in physiology and physiopathology, and later, in therapeutics. Many questions kept scientists working restlessly to unravel the key players favoring the development of collateral vessels in the heart.[2]

The coronary collateral circulation is a preformed network of immature anastomoses which connect the territory supplied by one epicardial coronary artery with that supplied by another. In 1959, Pitt et al.[1] studied the prevalence of interarterial coronary anastomoses in seventy-five hearts obtained from an autopsy. Of the 15 normal hearts, only one (6%) was found to have such anastomoses. In those cases with occlusive coronary artery disease, myocardium fibrosis, or infarction, anastomoses were found in 75% to 100% of the cases. It was clear, from the beginning, that the presence of sustained periods of tissue ischemia was a pre-requisite to incite de establishment of collateral circulation.

On the other hand, many patients with angina or objective evidence of myocardial ischemia failed to develop such a network of vessels. Patients responded differently in their capacity for collateralization in the presence of ischemia.[3] A quest began to comprehend why...

The formation of blood vessels in the mature cardiovascular system occurs through three distinct dynamic processes: vasculogenesis, angiogenesis, and arteriogenesis. These systems are influenced by various factors, including signaling and transcriptional control, soluble mediators and their receptors, biomechanical forces, and hypoxia.[2]

For instance, the relationship between the systemic immune-inflammation index (SII) and coronary collateral circulation (CCC) in patients with stable CAD and chronic total occlusion (CTO) was studied by Adali et al.[4] They found that a high SII level was significantly related to poor coronary collateral circulation. Therefore, a simple index based on a few laboratory tests could be very informative in clinical practice as a predictor of a patient´s capability of collateral formation.

Now, another potential player in coronary collateral development emerges from the work of Akkaya et al.[5] published in this issue of the ABC.[5] They sought to determine the association between adropin levels with the presence of collateral circulation in patients with chronic coronary syndrome. They found a 27% increase in the mean adropin levels in patients with good compared to patients with poor coronary collateral circulation. As the authors correctly noted, developing a good network of collaterals demands time, and a single snapshot of this process must be understood as reflecting that particular moment. If we allow enough time to elapse, perhaps the picture will be different.

As research progresses, novel angiogenic factors are reported with increased frequency, exposing the complexity of the vascular growth in ischemic conditions. At some point, scientists felt confident they could recapitulate the natural process of vascular growth through hyperexpression of specific angiogenic factors in the new field of gene therapy.[6] Unfortunately, randomized clinical trials with this approach did not succeed as expected, and the early enthusiasm was replaced by disappointment.

The work of Akkaya et al.[5] adds to the growing literature exploring the role of adropin, a peptide hormone secreted primarily by the liver, in clinical conditions as diverse as diabetic cardiomyopathy, obstructive sleep apnea, or inflammatory bowel disease.[7] Because adropin emerged as an essential regulatory component of the vascular endothelium by affecting endothelial NO synthesis, we may foresee that it is a matter of time when adropin will be considered a therapeutic target in cardiovascular medicine.

If one needs another example of the importance of keeping an open dialog between basic and clinical science, the paper by Akkaya et al.[5] offers just that.

Keywords

Collateral Circulation; Neovascularization, Physiologc; Adropin; Myocardial, Ischemia; Coronary Artery Disease.

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Predictive Ability of Cardiopulmonary Exercise Test Parameters in Heart Failure Patients with Cardiac Resynchronization Therapy

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Abstract

Background: **There is evidence suggesting that a peak oxygen uptake (pVO_2) cut-off of 10ml/kg/min provides a more precise risk stratification in cardiac resynchronization therapy (CRT) patients.**

Objective: **To compare the prognostic power of several cardiopulmonary exercise testing (CPET) parameters in this population and assess the discriminative ability of the guideline-recommended pVO_2 cut-off values.**

Methods: **Prospective evaluation of consecutive heart failure (HF) patients with left ventricular ejection fraction ≤40%. The primary endpoint was a composite of cardiac death and urgent heart transplantation (HT) in the first 24 follow-up months, and was analysed by several CPET parameters for the highest area under the curve (AUC) in the CRT group. A survival analysis was performed to evaluate the risk stratification provided by several different cut-offs. p values <0.05 were considered significant.**

Results: **A total of 450 HF patients, of which 114 had a CRT device. These patients had a higher baseline risk profile, but there was no difference regarding the primary outcome (13.2% vs 11.6%, p =0.660). End-tidal carbon dioxide pressure at anaerobic threshold ($P_{ET}CO_{2AT}$) had the highest AUC value, which was significantly higher than that of pVO_2 in the CRT group (0.951 vs 0.778, p =0.046). The currently recommended pVO_2 cut-off provided accurate risk stratification in this setting (p <0.001), and the suggested cut-off value of 10 ml/min/kg did not improve risk discrimination in device patients (p =0.772).**

Conclusion: **$P_{ET}CO_{2AT}$ may outperform pVO_2's prognostic power for adverse events in CRT patients. The current guideline-recommended pVO2 cut-off can precisely risk-stratify this population.**

Keywords: **Heart Failure; Cardiac Resynchronization Therapy/methods; Exercise Test/methods; Oxygen Consumption; Heart Transplantation.**

Introduction

The cardiopulmonary exercise test (CPET) is a powerful predictor of mortality in heart failure patients with reduced ejection fraction (HFrEF) and is used to guide patient referral for advanced therapies, such heart transplantation (HT) and mechanical circulatory support (MCS).[1-3]

Peak oxygen uptake (pVO_2) and the VE/VCO_2 slope are CPET-derived variables most commonly used as risk assessment tools; however, several other CPET variables have been shown to predict HF events and, some of them, can improve clinical stratification of HF patients when used together with the aforementioned variables (i.e., exercise oscillatory ventilation, end-tidal carbon dioxide variation during exercise testing, HR recovery, systolic blood pressure and the ECG response to exercise).

Cardiac resynchronization therapy (CRT) has emerged as a major therapeutic option in the management of HFrEF patients and, in selected patients, has shown to improve symptomatic burden and quality of life, as well to have a prognostic benefit regarding morbidity and mortality.[4-8] A growing number of patients referred to HT already have a CRT device, either with or without defibrillator (CRT-D and CRT-P, respectively). Survival in HFrEF patients has improved significantly in recent years and some authors suggest the need for re-evaluation of the listing criteria for HT and prognostic thresholds of peak oxygen uptake (pVO_2) and VE/VCO2 slope.[9,10]

The *2016 International Society for Heart Lung Transplantation (ISHLT) listing criteria for heart transplantation* defined pVO_2 as a major criterion for listing patients for HT and that the presence of CRT device does not alter the recommended cut-off value of pVO_2.[11] This recommendation was based on a sub-analysis of the COMPANION trial which showed that CRT did not alter

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the predictability of pVO_2 on adverse HFrEF events.[12,13] Conversely, Goda et al.[14] showed that a cut-off value of 10 ml/kg/min rather than the traditional cut-off value of 14 ml/kg/min may be more useful for risk stratification in patients with CRT.[14] Several other CPET variables were proven to be robust predictors of a worse clinical outcome in HFrEF populations, such as the VE/VCO_2 slope, the O_2 uptake efficiency slope (OUES) and the Cardiorespiratory Optimal Point (COP)[15,16].

The present study seeks to evaluate the predictive ability of the guideline recommended cut-off values in patients with CRT, to compare the prognostic power of several exercise parameters to that of pVO_2 in this population and to compare their performance between patients with and without a CRT device.

Methods

Ethics

The investigation conforms to the principles outlined in the Declaration of Helsinki. The local institutional ethics committee approved the study protocol. All patients provided informed consent.

Study Sample

Single centre analysis of 450 consecutive HF patients referred to our institution from 2009 to 2018 with left ventricular ejection fraction (LVEF) ≤40% and New York Heart Association (NYHA) class II or III, who were submitted to CPET. All patients were referred for evaluation by the HF team with possible indication for HT or MCS.

Study Protocol

Patient follow-up included initial evaluation within a period of one month in each patient with: clinical data including aetiology of HF (ischemic vs non-ischemic), implanted cardiac devices (CIED), medication, comorbidities, NYHA class; laboratorial data; electrocardiographic data; echocardiographic data; CPET data; Heart Failure Survival Score (HFSS).

Patients were excluded if one of the following: age <18 years; planned percutaneous coronary revascularization or cardiac surgery; exercise-limiting comorbidities (cerebrovascular disease, musculoskeletal impairment, or severe peripheral vascular disease); previous HT.

Patients who underwent CRT implantation performed CPET and transthoracic echocardiogram at least 6 months after the procedure.

Patients with elective HT during the follow-up period (patients who had indication for HT and a heart become available in the first two year of follow-up) were censured from the analysis at the time of HT.

Cardiopulmonary exercise testing

A maximal symptom-limited treadmill CPET, defined by peak respiratory exchange rate (RER) >1.05, was performed using the modified Bruce protocol (GE Marquette Series 2000 treadmill). Gas analysis was preceded by calibration of the equipment. Minute ventilation, oxygen uptake and carbon dioxide production were acquired breath-by-breath, using a SensorMedics Vmax 229 gas analyser.

The pVO_2 was defined as the highest 30-second average achieved during exercise and was normalized for body mass. The anaerobic threshold was determined by combining the standard methods (V-slope preferentially and ventilatory equivalents). The VE/VCO_2 slope was calculated by least squares linear regression, using data acquired throughout the whole exercise. COP was measured as the minimum value of the ventilatory equivalent for oxygen (VE/VO_2 minimum). Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) was reported before exercise ($P_{ET}CO_{2AR}$), at anaerobic threshold ($P_{ET}CO_{2AT}$) and at peak exercise in mmHg units, and the increase during exercise until the anaerobic threshold is achieved ($P_{ET}CO_{2DIF}$) was also calculated. Peak oxygen pulse (PP) was calculated by dividing derived pVO_2 by the maximum heart rate (HR) during exercise and was expressed in millilitres per beat. Circulatory power was calculated as the product of pVO_2 and peak systolic blood pressure and the ventilatory power was calculated by dividing peak systolic blood pressure (BP) by the VE/VCO_2 slope. Several composite parameters of CPET were also automatically calculated.

Follow-up and endpoint

All patients were followed-up for 24 months from the date of completion of the aforementioned complementary exams.

The primary endpoint was a composite of cardiac death and urgent HT occurring during an unplanned hospitalisation with dependency of inotropes for worsening HF. Data was obtained from the outpatient clinic visits (i.e., both unplanned visits for HF - clinical deterioration requiring iv diuretics - or planned visits for HF medication up-titration, diuretic therapy or routine clinical evaluation by the HF team) and was complemented with a standardised telephone interview to all patients at 24 months of follow-up.

Statistical analysis

All analyses compare patients with and without a CRT device (CRT and noCRT, respectively). Data was analysed using the software Statistical Package for the Social Science for Windows, version 24.0 (SPSS Inc, Chicago IL).

Baseline characteristics were summarised as frequencies (percentages) for categorical variables, as means and standard deviations for continuous variables when normality was verified and as median and interquartile range when normality was not verified by the Kolmogorov-Smirnov test. The Student's t-test for independent samples or the Mann-Whitney test (when normality was not confirmed) were used for all comparisons. Chi-Square test or Fisher exact test were used to compare categorical variables.

Multivariate analysis for the prediction of the primary endpoint during two-years follow-up was performed using

Cox regression, by including all statistically significant variables in the univariate analysis, in the total cohort and in each group.

The predictive power of several CPET parameters regarding the primary outcome in each group was analysed with Receiver Operating Characteristics (ROC) curve and area under the curve (AUC). Cut-off values for variables were determined from ROC curves so that the sum of sensitivity and specificity was maximised. Hanley and McNeil test was used to compare two correlated ROC curves.[17]

Event-free survival was determined using the Kaplan-Meier method and compared with log-rank analysis in order to evaluate the risk discriminative ability provided by the guideline-recommended cut-off values of pVO_2 ($pVO_2 \leq$ 12 ml/kg/min or ≤ 14 ml/kg/min without beta-blocker - BB) and VE/VCO_2 slope[11] and the suggested cut-off value of 10ml/kg/min.[14] Statistical differences with a p value <0.05 were considered significant.

Results

Overview of CRT and noCRT groups

A total of 450 patients were enrolled in the study, of which 25.3% (n = 114) had a CRT device, mostly a CRT-D (98.2%). The overall population had a mean age of 56.2 years, with 78.7% being male and a mean LVEF of 28.6%. All CRT patients with atrial fibrillation underwent AV node ablation during the implantation procedure and the percentage of biventricular pacing was 96%. CPET was performed on average 8 months after CRT implantation. The baseline characteristics of both groups are presented in Table 1.

Primary endpoint

The primary endpoint occurred in 54 (12.0%) patients as represented in Table 2, with 37 patients experiencing cardiac death and 16 patients undergoing urgent HT. A similar proportion of patients met the primary endpoint in both groups, which also applied to its individual components. Survival analysis revealed a similar event-free survival between groups during the follow-up period (Figure 1).

Relationship between CPET prognostic parameters and primary outcome

Both in patients with CRT and in the total cohort, pVO_2, VE/VCO_2 slope and $P_{ET}CO_{2AT}$ were independent predictors of the primary endpoint – Table 3.

In the CRT group, $P_{ET}CO_{2AT}$ had the highest AUC value followed by $P_{ET}CO_{2DIF}$ and VE/VCO_2 slope – Table 4. COP presented the lowest predictive power in this group. The Hanley & McNeil test revealed that $P_{ET}CO_{2AT}$ was the only variable presenting a significantly higher predictive power than that of pVO_2 – Table 5.

In the noCRT group, OUES and $P_{ET}CO_{2DIF}$ presented the highest AUC values, both higher than the one of pVO_2 and VE/VCO_2 slope, but no statistically significant difference was found.

$P_{ET}CO_{2AR}$ and $P_{ET}CO_{2AT}$ were the only parameters revealing a better performance in patients with CRT than in patients without device – Table 4. A $P_{ET}CO_{2AT}$ of 33mmHg had a sensitivity of 90% and a specificity of 78% for the primary outcome in the CRT group and below this value, patients had a significantly lower 24 months survival free of events, not only in the total cohort, but also in the two study groups – Figure 2.

Cut-off value for HT selection

In the overall cohort, as well as in each group, patients with a pVO_2 > 12ml/kg/min (or > 14ml/kg/min if under BB)[11] had a better prognosis in comparison to $pVO_2 \leq$ 10ml/kg/min and 10 < $pVO_2 \leq$ 12ml/kg/min strata, whereas a cut-off of 10ml/kg/min did not provide a proper risk stratification – Figure 3. A VE/VCO_2 slope cut-off of 35 significantly discriminated the risk for HF events in all cohorts – Figure 3.

For the traditional pVO_2 cut-off for HT selection, the PPV for the primary outcome was 98.4% in the CRT group and 93.3% in the no CRT group (Table 5), with a NPV of 27.5% and 27.2%, respectively. A pVO_2 cut-off of 10 ml/kg/min revealed a lower PPV in both groups, despite a similar NPV, with no significant differences between groups – Table 6.

In the CRT group, $P_{ET}CO_{2AT} \leq$ 33 mmHg had slightly higher PPV and NPV values than the recommended pVO_2 cut-off.

Discussion

Previous trial have shown that the addition of CRT to optimal medical therapy or defibrillator therapy significantly reduces mortality among patients with HFrEF[4,7] and improves exercise capacity, leading to an increase in pVO_2 and a reduction of VE/VCO_2 slope, thereby safely delaying HT.[18,19] It has been recognized the need to review HT selection cut-offs due to the improvement in HF therapies.[9,10] Based on the survival benefit conferred by CRT, and its effect on pVO_2, it is unclear whether this is still a valid tool for HT selection. A work from 2011 suggested that the HFSS outperformed pVO_2 in risk stratification in the presence of a CIED and that a pVO_2 cut-off of 10 ml/kg/min would be more suitable.[14] Our analysis tried to address this unmet need in contemporary cardiology.

There were crucial baseline differences between groups, as patients in CRT group were significantly older, more symptomatic, had a lower LVEF, higher mean natriuretic peptides levels, higher prevalence of AF and CKD, and a poorer exercise performance – lower baseline pVO_2 and higher VE/VCO_2 slope. However, this did not translate into a worse prognosis, as a similar proportion of patients met the primary endpoint in both groups (12.0% vs 13.2%, p = 0.660), with no significant difference in event-free survival (p = 0.856).

As expected, pVO_2 presented an acceptable prognostic power, irrespective of the presence of a CRT device (p = 0.531). The VE/VCO_2 slope has been suggested to be

Table 1 – Baseline Characteristics of CRT and no CRT groups

	Overall n 450	CRT n 114	no CRT n 336	p value
		CLINICAL DATA – CHARACTERISTICS		
Age	56.2 ± 12.5	62.3 ± 11.5	54.2 ± 12.2	**< 0.001**
Male (%)	354 (78.7%)	85 (74.6%)	269 (80.1%)	0.216
BMI (kg/m_2)	27.2 ± 4.3	27.2 ± 4.1	27.1 ± 4.4	0.829
Ischemic aetiology (%)	211 (46.9%)	42 (36.8%)	169 (50.6%)	**0.011**
ACEi/ARB/ARNI (%)	423 (94.0%)	104 (96.3%)	319 (96.1%)	1.000
BB (%)	388 (86.2%)	93 (85.3%)	295 (88.9%)	0.325
MRA (%)	340 (75.6%)	93 (84.5%)	247 (74.2%)	**0.026**
Diabetes (%)	98 (21.8%)	23 (22.3%)	75 (23.4%)	0.817
CKD (%)	140 (31.1%)	48 (46.6%)	92 (32.1%)	**0.008**
AF (%)	112 (24.9%)	43 (38.1%)	69 (20.6%)	**< 0.001**
ICD (%)	271 (60.2%)	112 (98.2%)	159 (47.3%)	**< 0.001**
NYHA Functional Class	2.2 ± 0.6	2.5 ± 0.5	2.1 ± 0.6	**0.001**
HFSS*	8.5 ± 1.0	8.14 ± 0.86	8.65 ± 1.04	**< 0.001**
		LABORATORIAL DATA		
Creatinine (mg/dL)	1.4 ± 0.7	1.6 ± 0.4	1.0 ± 0.3	**0.041**
Sodium (mEq/L)	137.9 ± 3.1	137.5 ± 3.4	138.5 ± 2.9	0.138
NT-proBNP (pg/ml)	2224.2 ± 2764.0	2769.7 ± 2575.4	2034.3 ± 2808.1	**0.045**
		ECHOCARDIOGRAPHIC DATA		
LVEDD (mm/m^2)*	35.5 ± 5.9	37.9 ± 5.5	34.7 ± 5.9	**0.032**
LVEF (%)	28.6 ± 6.9	26.2 ± 7.2	29.6 ± 6.6	**< 0.001**
MR III-IV (%)	65 (14.7%)	16 (14.0%)	49 (14.5%)	0.935
		CPET DATA		
CPET duration (min)	9.6 ± 4.4	7.4 ± 4.1	10.3 ± 4.3	**< 0.001**
Peak RER	1.07 ± 0.11	1.05 ± 0.11	1.08 ± 0.10	0.139
pVO_2 (ml/kg/min)	17.9 ± 6.1	15.2 ± 5.1	18.8 ± 6.1	**< 0.001**
VE/VCO_2 slope	33.8 ± 9.5	35.8 ± 10.9	33.2 ± 8.9	**0.026**
OUES	2.1 ± 1.8	2.2 ± 2.2	2.0 ± 1.6	0.645
pVO_2 (ml/kg/min) at AT	13.1 ± 4.5	10.3 ± 3.4	13.8 ± 4.5	**0.001**
O_2 Pulse (mL/kg/beat)	0.14 ± 0.06	0.12 ± 0.04	0.14 ± 0.07	**0.028**
Circulatory Power (mmHg.ml.kg-1 min-1)	2786.9 ± 1578.8	2262.3 ± 965.4	2963 ± 1702.4	**< 0.001**
Ventilatory Power (mmHg)	4.8 ± 1.7	4.4 ± 1.7	4.9 ± 1.7	**0.020**
Cardiorespiratory Optimal Point	29.6 ± 7.4	30.7 ± 7.5	29.3 ± 7.4	0.274
$P_{ET}CO_2$ at rest (mmHg)	33.4 ± 4.7	32.9 ± 4.8	33.6 ± 4.7	0.241
$P_{ET}CO_{2AT}$ (mmHg)	36.7 ± 5.9	35.3 ± 5.9	37.1 ± 5.9	**0.010**
$P_{ET}CO_{2DIF}$ (mmHg)	3.3 ± 3.7	2.3 ± 3.2	3.6 ± 3.8	**0.004**

*Values are mean ± standard deviation or median (interquartile range);p values are calculated by Student´s T-test for independent samples or Mann-Whitney U test as appropriate; chi square test or Fisher exact test were used to compare categorical variables. *Variables with normal distribution. AT: anaerobic threshold; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; AF: Atrial fibrillation; BB: Beta-blockers; BMI: body mass index; CPET: cardiopulmonary exercise test; CKD: chronic kidney disease; HFSS: Heart Failure Survival Score; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; MRA: mineralocorticoid receptor antagonists; MR: Mitral regurgitation; NYHA: New York Heart Association; OUES: oxygen uptake efficiency slope; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; $P_{ET}CO_{2AT}$: $P_{ET}CO_2$ at AT; $P_{ET}CO_{2DIF}$: $P_{ET}CO_2$ increase until the AT is achieved; pVO_2: peak oxygen uptake; RER: respiratory exchange ratio; CRT: cardiac resynchronization therapy.*

Table 2 – Adverse events at 24 months follow-up

Adverse events at 24 months follow-up	Overal n (%)	CRT Group n (%)	No CRT n (%)	p value
Combined primary endpoint	54 (12.0%)	15 (13.2%)	39 (11.6%)	0.660
Total mortality	38 (8.4%)	11 (9.6%)	27 (8.0%)	0.592
Cardiac mortality	37 (8.2%)	11 (9.6%)	26 (7.7%)	0.521
Sudden cardiac death	14 (3.1%)	3 (2.6%)	11 (3.3%)	0.977
Death for worsening HF	23 (5.1%)	8 (7.0%)	15 (4.5%)	0.285
Urgent HT	16 (3.6%)	4 (3.5%)	12 (3.6%)	0.991

CRT: cardiac resynchronization therapy; HF: heart failure; HT: heart transplantation.

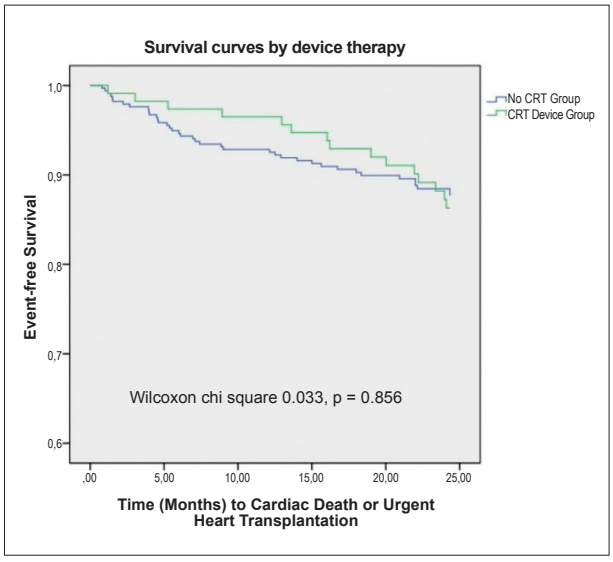

Figure 1 – *Survival curves by cardiac resynchronization therapy. CRT: cardiac resynchronization therapy.*

more accurate than the current listing criteria for HT.[20] There was no difference between groups regarding its predictive power (p = 0.159), and its predictive ability, despite being numerically higher than that of pVO_2, this difference did not reach statistical significance in any group.

$P_{ET}CO_2$ correlates with cardiac output in HF patients and can reflect disease severity, having a prognostic value independent of that of pVO_2.[21-24] A $P_{ET}CO_{2AR} < 33.0$ mmHg or an increase < 3 mmHg during exercise test were associated with a worse prognosis.[3] In CRT patients, $P_{ET}CO_{2AR}$, $P_{ET}CO_{2AT}$ and $P_{ET}CO_{2DIF}$ presented higher AUC values than pVO_2, but this difference only reached statistical significance for $P_{ET}CO_{2AT}$ (p = 0.046). Patients with a $P_{ET}CO_{2AT} \leq 33.0$ mmHg had a significantly lower 24-months survival free of events, not only in the CRT arm, but also in the overall cohort and in the no CRT group (p < 0.001).

A pVO_2 cut-off value of 10 ml/kg/min did not improve risk stratification in the CRT group, since it has a markedly lower NPV than the traditional cut-offs. There was no discrimination between the high-risk ($pVO_2 \leq 10$ ml/min/kg) and the medium risk strata ($10 < pVO_2 \leq 12$ ml/min/kg) regarding event-free survival during the first 24 months of follow-up in neither of the groups. The low-risk strata ($pVO_2 \geq 12$ ml/min/kg) had a significantly better prognosis than the remainder strata, in both groups. The recommended cut-off value for VE/VCO_2 provided accurate 2 years-risk discrimination in the CRT group (72.6% vs 96.6%, p = 0.001).

Despite CRT patients having a higher risk baseline profile in our study, this did not translate into a higher rate of events during follow-up. The current cut-off of pVO_2 for HT selection can stratify these high-risk patients more precisely than the suggested pVO_2 cut-off of 10ml/kg/min,[14] irrespective of the presence of a CRT device.

The low PPV and the high NPV of the analysed variables suggest that in the studied population all these parameters, when used individually, are best suited to identify patients who do not need HT.

Our results suggest that advanced HF therapies can be safely withheld in HF patients, with $pVO_2 > 12$ ml/kg/min (or 14 ml/kg/min in the absence of beta-blocker), irrespective of the presence of CRT device, as the event-rate in these population is low. Patients below this cut-off should be managed accordingly, and their timely referral for HT or MCS should be considered. The low PPV of the recommended cut-offs suggests that pVO_2 alone is insufficient to guide referral and other prognostic factors must be taken into account, such as, NYHA functional class, INTERMACS profile, LVEF, HFSS, recurrent planned and unplanned hospitalizations for HF or ventricular arrhythmias, persistent congestion/need for escalating diuretic doses or combining it with other CPET variables, such as $P_{ET}CO_{2AT}$. The surprisingly low PPV might be explained by the fact that a significant proportion of our cohort performed a submaximal CPET, a setting on which pVO_2 may lose discriminative power.

$P_{ET}CO_{2AT}$ may increase the prognostic value of CPET in HFrEF, irrespective of the presence of a CRT device, and eventually refine the predictive ability of the current CPET parameters used for HT referral decision.

Table 3 – CPET Predictors of adverse events at 24 months follow-up

Total Cohort	Univariate, OR (CI 95%)	p value	Multivariate analysis, OR (CI 95%)	p value
pVO_2 (ml/kg/min)	0.851 (0.799-0.906)	<0.001	0.867 (0.812-0.921)	0.004
VE/VCO_2 slope	1.092 (1.061-1.124)	0.005	1.104 (1.020-1.196)	0.015
Cardiorespiratory Optimal Point	1.128 (1.050-1.212)	0.010		0.250
OUES	0.357 (0.179-0.713)	<0.001		0.284
Circulatory Power (mmHg.ml.kg-1 min-1)	0.996 (0.994-0.999)	0.040		0.540
Ventilatory Power (mmHg)	0.471(0.367-0.605)	0.017		0.287
Peak O_2 Pulse (mL/kg/beat)	0.769 (0.573-1.031)	0.079		0.357
$P_{ET}CO_2$ at rest (mmHg)	0.871 (0.814-0.931)	0.012		0.135
$P_{ET}CO_{2AT}$ (mmHg)	0.814 (0.763-0.868)	<0.001	0.713 (0.577-0.880)	0.002
$P_{ET}CO_{2DIF}$ (mmHg)	0.734 (0.660-0.815)	<0.001		0.110
CRT Group	**Univariate, OR (CI 95%)**	**p value**	**Multivariate analysis, OR (CI 95%)**	**p value**
pVO_2 (ml/kg/min)	0.794 (0.688-0.916)	0.002	0.821 (0.647-0.905)	0.005
VE/VCO_2 slope	1.162 (1.077-1.253)	<0.001	1.109 (1.053-1.165)	0.008
Cardiorespiratory Optimal Point	1.101 (0.982-1.235)	0.090		0.319
OUES	0.974 (0.702-1.353)	0.470		0.657
Circulatory Power (mmHg.ml.kg-1 min-1)	0.997 (0.998-0.999)	0.047		0.470
Ventilatory Power (mmHg)	0.313 (0.157-0.624)	0.001		0.314
Peak O_2 Pulse (mL/kg/beat)	0.751 (0.371-1.063)	0.097		0.490
$P_{ET}CO_2$ at rest (mmHg)	0.779 (0.668-0.910)	0.002		0.197
$P_{ET}CO_{2AT}$ (mmHg)	0.564 (0.413-0.771)	<0.001	0.527 (0.309-0.898)	0.001
$P_{ET}CO_{2DIF}$ (mmHg)	0.595 (0.451-0.786)	<0.001		0.097
No CRT Group				
pVO_2 (ml/kg/min)	0.860 (0.801-0.924)	<0.001	0.819 (0.668-0.930)	0.007
VE/VCO_2 slope	1.075 (1.040-1.110)	<0.001	1.109 (1.015-1.210)	0.012
Cardiorespiratory Optimal Point	1.143 (1.040-1.257)	0.005		0.154
OUES	0.088 (0.030-0.253)	<0.001		0.454
Circulatory Power (mmHg.ml.kg-1 min-1)	0.095 (0.091-0.097)	0.039		0.564
Ventilatory Power (mmHg)	0.513 (0.391-0.674)	<0.001		0.309
Peak O_2 Pulse (mL/kg/beat)	0.783 (0.453-1.021)	0.070		0.410
$P_{ET}CO_2$ at rest (mmHg)	0.900 (0.834-0.972)	0.007		0.229
$P_{ET}CO_{2AT}$ (mmHg)	0.849 (0.794-0.907)	0.001		0.080
$P_{ET}CO_{2DIF}$ (mmHg)	0.765 (0.682-0.858)	<0.001	0.689 (0.532-0.893)	0.005

CI: confidence interval; CPET: cardiopulmonary exercise test; OR: Odds-ratio; NS: not significant (> 0.05); OUES: oxygen uptake efficiency slope; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; $P_{ET}CO_{2AT}$: $P_{ET}CO_2$ at anaerobic threshold; $P_{ET}CO_{2DIF}$: $P_{ET}CO_2$ increase until the anaerobic threshold is achieved; pVO_2: peak oxygen uptake. CRT: cardiac resynchronization therapy.

Table 4 – AUC analysis for the Primary Endpoint

Characteristics	CRT Group		No CRT Group		Hanley and McNeil for ROC curve comparison between groups (p value)
	AUC	CI 95%	AUC	CI 95%	
pVO_2 (ml/kg/min)	0.778	0.683-0.873	0.723	0.643-0.804	0.531
VE/VCO_2 slope	0.868	0.782-0.954	0.757	0.693-0.822	0.159
Cardiorespiratory Optimal Point	0.668	0.355-0.980	0.739	0.487-0.991	0.699
OUES	0.775	0.591-0.960	0.800	0.710-0.890	0.808
Circulatory Power (mmHg.ml.kg-1 min-1)	0.777	0.679-0.876	0.743	0.668-0.819	0.697
Ventilatory Power (mmHg)	0.830	0.729-0.930	0.759	0.687-0.830	0.398
Peak O_2 Pulse (mL/kg/beat)	0.659	0.486-0.831	0.716	0.642-0.761	0.546
$P_{ET}CO_2$ at rest (mmHg)	0.797	0.518-0.713	0.615	0.518-0.713	**0.042**
$P_{ET}CO_{2AT}$ (mmHg)	0.951	0.900-0.980	0.741	0.662-0.8220	**0.002**
$P_{ET}CO_{2DIF}$ (mmHg)	0.889	0.819-0.960	0.776	0.712-0.841	0.121

AUC: Area under the curve; CI: confidence interval; OUES: oxygen uptake efficiency slope; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; $P_{ET}CO_{2AT}$: $P_{ET}CO_2$ at anaerobic threshold; $P_{ET}CO_{2DIF}$: $P_{ET}CO_2$ increase until the anaerobic threshold is achieved; pVO_2: peak oxygen uptake; ROC: receiver operating curve. CRT: cardiac resynchronization therapy.

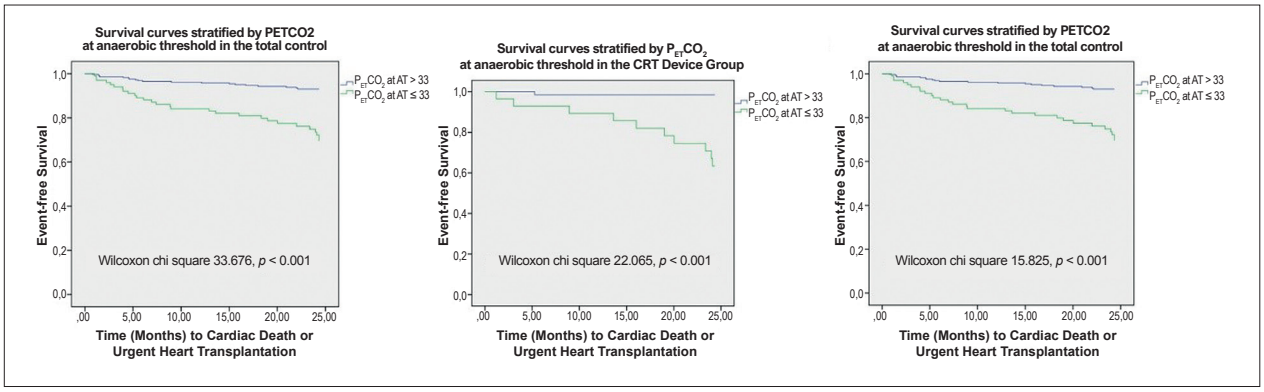

Figure 2 – *Survival curves according to a $P_{ET}CO_{2AT}$ cut-off of 33mmHg in the general cohort, CRT group and no CRT group.*

Study limitations

This was a single-centre experience, and therefore, the results can reflect our local practice and might not be applicable to other HF Centres.

Secondly, despite a high number of patients were receiving guideline-approved neurohormonal blockade therapies, several patients were included in this analysis before the advent of angiotensin receptor-neprilysin inhibitors – ARNI (<10% of patients under ARNI). So, it is unclear if our results can be extrapolated to the sacubitril-valsartan era, as this drug has shown to have an impact on exercise capacity.The vast majority of the patients in the CRT cohort had a CRT-D device (98.4%), so it is unknown whether $P_{ET}CO_{2AT}$ and other CPET variables would retain their predictive ability in patients with CRT-P devices. As patients in the CRT arm had a theoretical higher risk baseline clinical profile, it would be expected that in the absence of a defibrillator, a higher proportion of these patients would meet the primary endpoint, due to higher rates of arrhythmic death. Fourth, there are no data regarding CRT response and it would be useful to compare these variables' performance between clinical/ echocardiographic responder and non-responders.Furthermore, pVO_2 and other CPET variables may lose some of their prognostic value in a submaximal setting.[25] However, our total cohort presented a mean RER of 1.07 and the CRT group of 1.05, meaning that a substantial proportion of patients performed submaximal exercise, which may have an influence on each parameter's performance.

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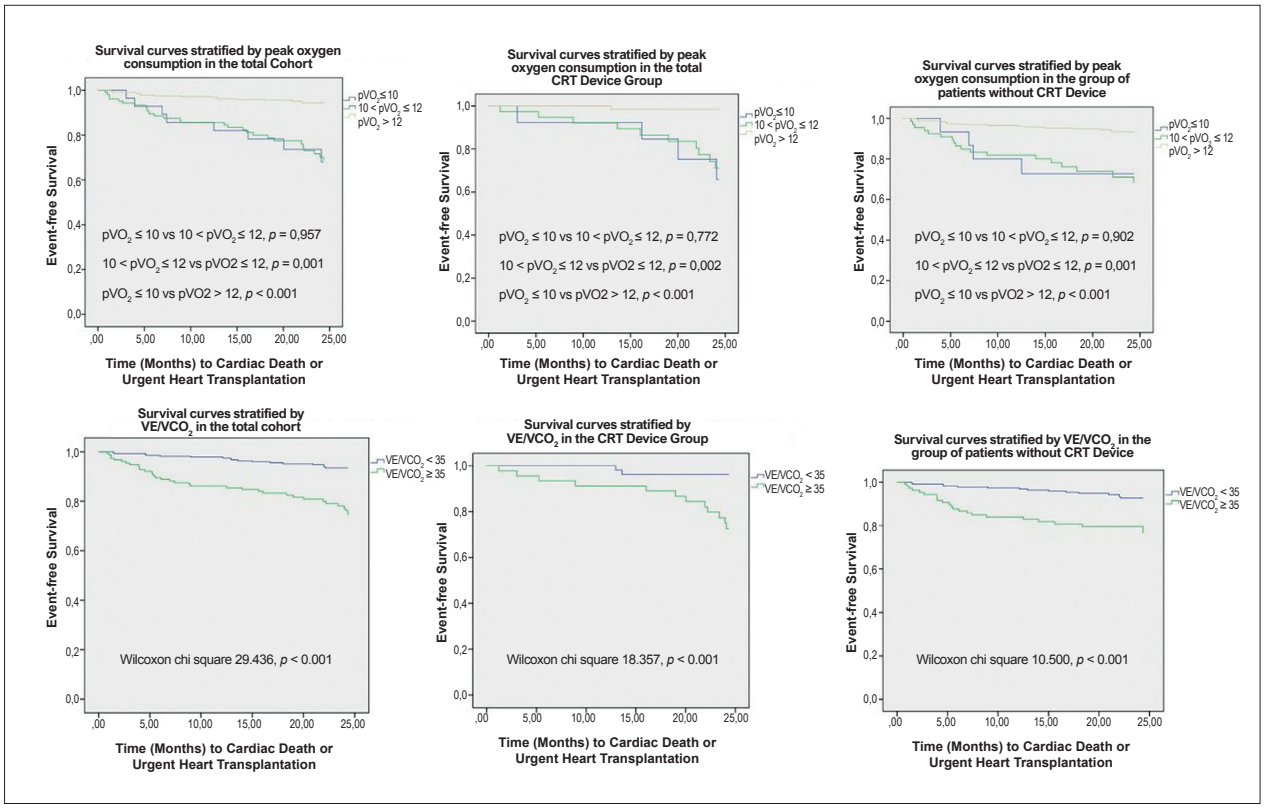

Figure 3 – *Survival curves stratified by pVO2 and VE/VCO2 for the total cohort, CRT group and no CRT group. CRT: cardiac resynchronization therapy.*

Table 5 – Hanley and McNeil for ROC curve comparison between each variable and pVO_2 (p value

Characteristics	CRT Group	No CRT Group
VE/VCO_2 slope	0.353	0.613
Cardiorespiratory Optimal Point	0.487	0.900
OUES	0.979	0.261
Circulatory Power (mmHg.ml.kg-1 min-1)	0.992	0.766
Ventilatory Power (mmHg)	0.607	0.592
Peak O_2 Pulse (mL/kg/beat)	0.277	0.918
$P_{ET}CO_2$ at rest (mmHg)	0.855	0.123
$P_{ET}CO_{2AT}$ (mmHg)	**0.046**	0.794
$P_{ET}CO_{2DIF}$ (mmHg)	0.213	0.431

AUC: Area under the curve; OUES: oxygen uptake efficiency slope; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; $P_{ET}CO_{2AT}$: $P_{ET}CO_2$ at anaerobic threshold; $P_{ET}CO_{2DIF}$: $P_{ET}CO_2$ increase until the anaerobic threshold is achieved; pVO_2: peak oxygen uptake; CRT: cardiac resynchronization therapy.

Table 6 – PPV and NPV of several variables' cut-offs for the primary endpoint

Characteristics	CRT Group		No CRT Group	
	NPV	PPV	NPV	PPV
$pVO_2 \leq 10$ ml/kg/min	89.0%	30.8%	89.1%	26.7%
$pVO_2 \leq 12$ ml/kg/min[1]	98.4%	27.5%	93.3%	27.2%
VE/VCO_2 slope ≥ 35	96.4%	26.1%	93.1%	21.7%
$P_{ET}CO_{2AT} \leq 33$ mmHg	98.4%	35.7%	91.9%	27.4%

[1] $pVO_2 \leq 12$ ml/kg/min ou ≤ 14 ml/kg/min without beta-blocker
NPV: Negative predictive value; $P_{ET}CO_{2AT}$: partial pressure of end-tidal carbon dioxide at anaerobic threshold; pVO_2: peak oxygen uptake; PPV: Positive predictive value; CRT: cardiac resynchronization therapy.

Conclusions

The performance of risk stratification tools in HF patients referred for HT was defined before the widespread use of CRT devices and there is limited data regarding their prognostic accuracy in these patients. Our findings suggest that the recommended pVO_2 and VE/VCO_2 cut-off values retain their discriminative ability in this setting; however, $P_{ET}CO_{2AT}$ may provide a higher predictive ability for adverse events in a 24-months follow-up in CRT patients. This parameter was an independent prognostic predictor in CRT patients and had a better performance in this population than in patients without a CRT. Further studies are required to assess the reproducibility of our data and if $P_{ET}CO_{2AT}$ can improve risk stratification when combined with pVO_2.

Author Contributions

Conception and design of the research: Reis JF, Gonçalves AV, Moreira RI, Rio P, Soares RM; Acquisition of data: Reis JF, Gonçalves AV, Brás PG; Analysis and interpretation of the data: Reis JF, Brás PG, Soares RM; Statistical analysis: Reis JF, Brás PG; Obtaining financing and Writing of the manuscript: Reis JF; Critical revision of the manuscript for intellectual content: Reis JF, Gonçalves AV, Moreira RI, Rio P, Timóteo AT, Soares RM, Ferreira RC.

Potential Conflict of Interest

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

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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 Centro Hospitalar Central de Lisboa under the protocol number 1232. 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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Measurement of PETCO2 at Anaerobic Threshold: A Best Prognostic Marker in Patients with Cardiac Resynchronization Therapy?

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Short Editorial related to the article: Predictive Ability of Cardiopulmonary Exercise Test Parameters in Heart Failure Patients with Cardiac Resynchronization Therapy

The cardiopulmonary exercise test (CPET) is a consolidated tool in the functional and prognostic assessment of patients with heart failure[1] with reduced ejection fraction (HFrRF), being a cornerstone in the evaluation for the indication of advanced therapies in HFrEF.[1,2] Cardiac resynchronization therapy (CRT), in addition to reducing mortality, can improve cardiorespiratory fitness, leading to an increase in peak oxygen consumption (VO_2 peak) and a reduction in the slope of the respiratory equivalent CO2 ratio (VE / VCO2 slope).[3-5] In recent years, with the evolution of treatments, general mortality and the risk of the sudden death of patients with HFpEF have been reduced.[6,7] In this context, reviewing the prognosis and the values associated with a higher risk among the CPET variables in patients undergoing CRT becomes important.

The measurement of end-tidal carbon dioxide pressure (PETCO2) during CPET, both at rest,[8] and at the first ventilatory threshold or anaerobic threshold ($P_{ET}CO2_{LA}$),[9] has a well-established prognostic value in heart failure.[8,9] The increase of dead space ventilation, caused by the impairment of the ventilation/perfusion (V/Q) ratio, for example, in patients with left ventricular dysfunction, leads to a reduction in alveolar CO2 and, consequently, in $P_{ET}CO_2$. It is expected that there will be an increase in its measurement up to the anaerobic threshold, which is correlated with an increase in cardiac output.

In this issue of *Arquivos Brasileiros de Cardiologia*, Reis et al.[10] present an interesting analysis of the prognostic role of CPET in a cohort of 450 patients, 114 of whom underwent CRT.[10] The patients were followed up for 2 years, and the evaluated outcome was cardiovascular mortality and the need for urgent transplantation. The classic evaluation studies for heart transplantation[9,11] involving CPET do not include patients with CRT, which makes it important to question how the behavior of prognostic variables would be in this context.[9,11] Knowledge of this scenario is scarce, and some evidence suggests a less important role of peak VO_2 in these patients in the selection for heart transplantation.[12]

In the study by Reis et al.,[10] VO_2 peak, VE/VCO2 slope, $_{PET}CO2$ and $P_{ET}CO2_{LA}$ were able to predict outcomes in patients with HF and CRT in uni- and multivariable analyses.[10] However, in the ROC curve analysis, $P_{ET}CO2_{LA}$ apparently showed superior accuracy for predicting events. Interestingly, the optimal cut-off point was 33 mmHg, lower than the 36 mmHg in previous studies that evaluated this variable.[8,13] On the other hand, the cut-off points for peak VO_2 (12 ml/kg/min) and VE/VCO2 slope (35) were similar to values previously described in the literature16, with no difference in patients with and without CRT.[14] It is important to emphasize that, in this observational study, there was no difference in the incidence of major cardiovascular events between patients with and without CRT.

A possible limitation of the study, already mentioned by the authors, is the presence of submaximal tests in a reasonable number of patients, which reduces the discriminatory power of peak VO^2 for predicting events. However, the evidence provided, in addition to consolidating the prognostic role of CPET in these patients, calls attention to the importance of routinely measuring $P_{ET}CO2_{LA}$ in these cases. This variable has excellent prognostic power and can add information to traditional CPET measurements. Its measurement has an excellent relationship with the increase in cardiac output on exertion, and an altered response (absence of increase up to the AT) characterizes a greater loss in the increase in output during exercise.

Studies with larger sample sizes, preferably multicenter, evaluating the prognostic power of $P_{ET}CO2_{LA}$ in patients with HF and comparing it to other prognostic measures are welcome. The replication of results in different populations strengthens the evidence found and expands the external validity of the findings.

Keywords

Ergoespyrometry/methods; Stroke Volume; Cardiac Resynchronization Therapy/methods; Heart Failure; Cardiac Output, High; Prognosis.

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Aortic Intima Media Thickness is Increased and Closely Related to Elevated Oxidative Stress Increases in Beta Thalassemia Minor

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Abstract

Background: **Abdominal aortic intima media thickness (A-IMT) may be an early marker of subclinical atherosclerosis and an objective indicator of increased oxidative stress in beta-thalassemia minor patients.**

Objective: **To evaluate whether aortic and carotid IMTs change with oxidative stress and to assess the relationship between these parameters in beta-thalassemia minor patients.**

Methods: **The study included 80 patients diagnosed with beta-thalassemia minor, and 50 healthy individuals with similar age and gender. After routine procedures, blood samples were collected from the study groups for thiol-disulfide hemostasis and ischemia-modified albumin (IMA). C-IMT measurements were performed in four different regions (right and left internal and external carotid artery) by ultrasonography. In addition, A-IMT measurement was performed by abdominal ultrasonography. Statistically significant p value was set as <0.05 for all comparisons.**

Results: **In beta-thalassemia minor patients, native thiol, total thiol and native thiol / total thiol ratio were lower, and the IMA, disulfide / native thiol ratio and disulfide / total thiol ratios were higher than in healthy control group. A-IMT measurement was significantly higher in beta-thalassemia minor group than controls (1.46±0.37 vs 1.23±0.22 and p<0.001). When the parameters associated with A-IMT in univariate analysis were evaluated by multivariate linear regression analysis, A-IMT was positively related, and native thiol and total thiol levels were negatively and closely related to IMA (p<0.01).**

Conclusion: **We demonstrated, for the first time, that oxidative stress status increased with increased A-IMT, while C-IMT remained unchanged in beta-thalassemia minor patients.**

Keywords: **Beta-Thalassemia; Carotid Intima-Media Thickness; Oxidative Stress.**

Introduction

Thalassemia is a genetic disease that occurs due to a decrease or absence of one or more globulin chains that make up the hemoglobin tetramer. Thalassemia is inherited in an autosomal recessive pattern.[1] There are production defects in various polypeptide chains (alpha, beta, gamma or delta), which differ clinically and biochemically. Beta-thalassemia minor is a carrier form of beta thalassemia with heterozygous genotype and mild anemia.[1] It is common in the Middle East and central Asia countries and Mediterranean countries like Turkey.[2]

Endothelial damage is an important part of the atherosclerotic process. In beta-thalassemia patients, it is known that an increase in iron accumulation due to increased hemolysis, transfusion and intestinal absorption, leads to a decrease in endothelial nitric oxide (NO) bioavailability, and consequently to endothelial dysfunction.[3] The resulting oxygen radicals are bound and neutralized by thiols. Free disulfide bonds appear as a result of the reaction and turn into thiol again, leading to a thiol-disulfide homeostasis. Impaired balance causes endothelial dysfunction and atherosclerosis to begin.

It has been shown that the carotid intima media thickness (C-IMT) measurement, which is an objective indicator of both oxidative stress[4,5] and subclinical atherosclerosis, is increased in patients with thalassemia major.[6-8] The relationship of increased oxidative stress with increased C-IMT is clear in many diseases, including the beta-thalassemia major.[9,10]

However, there are not many studies in the literature evaluating C-IMT or oxidative stress in beta-thalassemia minor patients. Only one study reported that both C-IMT value and oxidative stress levels were increased in a limited number of beta-thalassemia minor patients.[11,12] It has been supported that IMT measurement can be predictive of cardiovascular events caused by atherosclerosis and useful

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in detecting subclinical atherosclerosis.[13-17] Atherosclerosis is a disease that begins in childhood and primarily increases abdominal aortic IMT (A-IMT). Many diseases have an early A-IMT involvement without affecting the C-IMT.[18,19] In this study, we investigated and the relationship between A-IMT, C-IMT and oxidative stress markers, and whether these parameters are changed in beta-thalassemia minor patients.

Methods

Our study was a single-center case-control study. The study was approved by the Ethics Committee of the Faculty of Medicine of the Cukurova University (April 13, 2018, meeting number: 76, decision number: 88). Consent of patients wishing to participate in the study was obtained.

Study population

Individuals who were referred to the Department of Internal Medicine of Adana Health Practice and Research Center / University of Health Sciences, Adana, Turkey, between 01.01.2016 and 02.03.2018 for various reasons and who were asked for hemoglobin electrophoresis were considered eligible. The study included 80 patients older than 18 years of age, who were diagnosed with beta-thalassemia minor by hemoglobin electrophoresis, who did not have a systemic disease and gave verbal and written consent. Then, 50 healthy individuals, similar in age and gender, were included as controls. Individuals under the age of 18, pregnant women, smokers and alcohol users, those with any systemic disease (diabetes mellitus, hypertension, heart failure, cerebrovascular accident, metabolic syndrome, kidney failure, liver failure, malignancy, autoimmune diseases), patients with acute or chronic infection, and those who did not give verbal and written consent were not included in the study. Anamnesis and physical examinations of all individuals were performed. Age, gender, height, body weight, and blood levels of urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, high-sensitive C-reactive protein, triglyceride, low-density lipoprotein cholesterol, thyroid stimulating hormone and complete blood count were recorded. Body mass index (BMI) was calculated using the standard formula "weight (kg) / height (m^2)". No additional tests were requested from the patients. Individuals who underwent hemoglobin electrophoresis with the high-performance liquid chromatography (HPLC) method and had HbA2 ≥3.5 and HbF value between 2-10% were considered as beta thalassemia carriers. Complete blood count was evaluated using the SYSMEX XE-2100i (Japan) device, by the fluorescence flow cytometry method. Glucose value was measured by the hexokinase method, cholesterol values were measured by the enzymatic colorimetric method, and creatinine values were determined by the Jaffe method, all using the Roche C-501 (Japan) device.

Thiol-disulfide homeostasis and ischemia-modified albumin measurement

For evaluation of thiol-disulfide homeostasis, blood samples were collected into yellow top gel tubes, which were centrifuged for 10 minutes at 2000 rpm; the serum was separated and stored at -80 degrees. Later, these samples were sent to the Department of Biochemistry, Ankara Health Practice and Research Center, University of Health Sciences – and maintained in cold chain until analysis by Prof Dr Özcan Erel. Index 1 was obtained by dividing disulfide (D) by native thiol (NT) (D /NT); index 2 was obtained by dividing D by total thiol (TT) (D / TT), index 3 was obtained by dividing NT by TT (NT / TT). Measurements were made with a Cobas C501 automatic analyzer (Roche-Hitachi, Mannheim, Germany). Albumin Cobalt Binding Test was used for IMA measurement in serum and spectrophotometric measurement was performed. For this test, 50μl 0.1% cobalt chloride was added to 200μl patient serum, and the sample was incubated for 10 minutes to allow the binding of albumin with to cobalt. Then, 50μL 1.5 mg / mL dithiothreitol (DTT) was added to measure the cobalt that was not bound to albumin. Free cobalt was dyed with DTT to form a colored complex, and this complex was measured spectrophotometrically at a wavelength of 470 nm. The measured free cobalt was determined as the IMA value. The costs of the kits were covered by Prof Dr Özcan Erel, and no additional costs were incurred for our hospital or the Social Security Institution.

B-mode ultrasonography of carotid arteries and abdominal aorta[13]

The abdominal aorta and left and right carotid (common and internal) arteries were examined with a high-resolution ultrasound Doppler system (Philips EPIQ 7) equipped with high resolution linear (12 MHz) and convex (5 MHz) transducers (Philips Health Care, Bothell, WA, USA). All arteries were studied in both longitudinal and transversal sections. All arteries were scanned longitudinally to visualize IMT in the posterior or distal arterial wall. All measurements were made on frozen images. The two best quality images from each subject were chosen for analysis. IMT was defined as the distance from the front edge of the first echogenic line to the anterior margin of the second line. The first line represents the intima-lumen interface, and the second line represents the collagen-containing top layer of the adventitia. Vascular IMT was measured using ultrasonic calipers by two independent and blinded observers. The IMT values were defined as the average of six measurements (Figure 1).

Subjects were examined at supine position. Patients' head were turned 45° to the right so that the carotid artery could be scanned. IMT that measured within 10-20 mm proximal (for common carotid arteries) and distal (for internal carotid arteries) to bifurcation on two-dimensional ultrasound images were accepted as CC-IMT and IC-IMT, respectively. A-IMT was measured from the renal artery bifurcation to the iliac artery bifurcation. The IMT measured from the posterior wall of the abdominal artery was considered as the A-IMT (Figure 2).

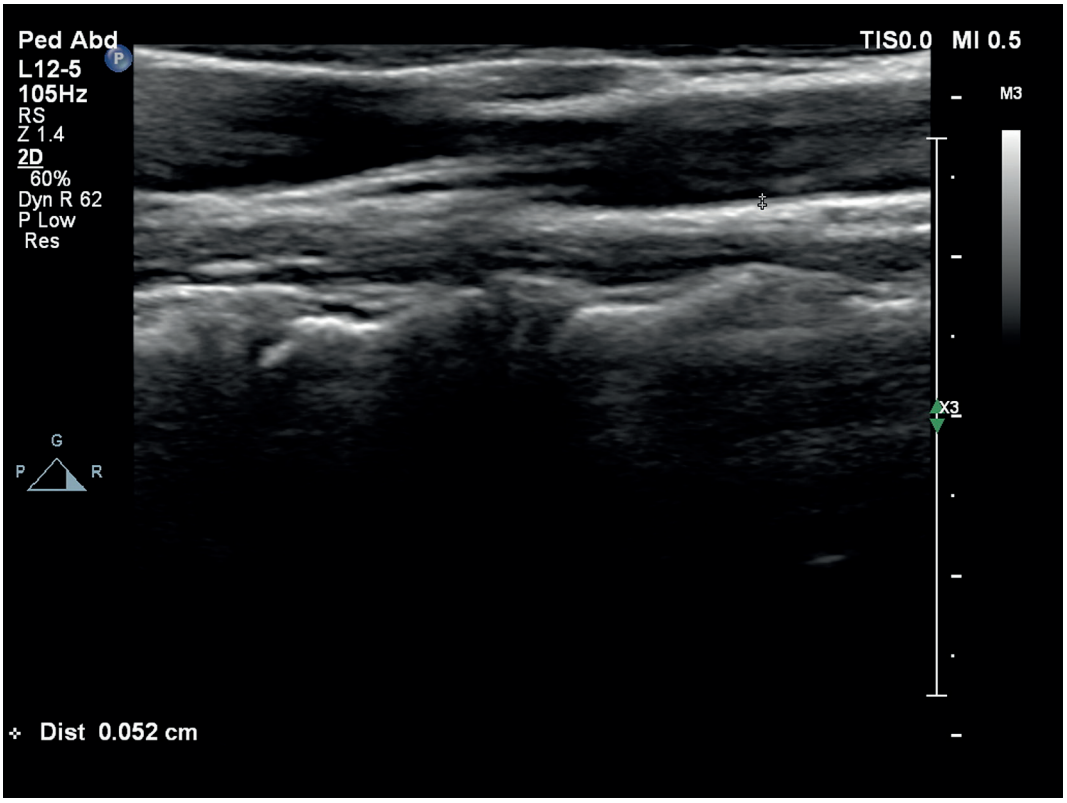

Figure 1 – *Common carotid intima-media thickness (CC-IMT) measurement by B-mode ultrasound in a patient with beta thalassemia minor (normal CC-IMT: 0.57 mm).*

Statistical analysis

All analyzes were performed using SPSS 22.0 (SPSS for Windows 22.0, Chicago, IL, USA). Categorical data were shown as numbers and percentages and compared with the chi-square test. Continuous variables were expressed as mean ± standard deviation or median and interquartile range, as appropriate. The normal distribution of continuous variables was analyzed by the Shapiro-Wilk test. Normally distributed continuous variables were compared with independent samples t test and variables that did not show normal distribution were compared with Mann Whitney U test. The kappa coefficient was used to evaluate the interobserver and intraobserver variability of all electrocardiographic and echocardiographic measurements. Pearson's correlation was used to examine the relationship between continuous variables. All variables associated with A-IMT, identified in the univariate analysis, were evaluated by multivariate linear regression analysis. The normally distributed parameters met the necessary assumptions. Significant variables at a $p < 0.1$ level in the univariate correlation analysis were included in the analysis. Statistically significant p value was set as <0.05 for all comparisons.

Results

The study data were compared between beta thalassemia minor patients and healthy controls. Cohen kappa were above 90% for all electrocardiographic and echocardiographic measurements – inter-observer and intra-observer variability for electrocardiogram (ECG): 96% and 98%, echocardiography: 97% and 98%, respectively). IMT measurements were successfully taken from all patients included in the study. All demographic and clinical data were found to be similar between the groups, except for heart rate, that was higher in beta-thalassemia minor patients. All biochemical parameters of the two groups were similar except for blood count parameters. Red blood cell count, hemoglobin, hematocrit and mean corpuscular volume were lower in beta thalassemia minor patients, and red blood cell distribution width was higher (Table 1). NT, TT and NT/TT ratio were lower in the beta-thalassemia minor patients, and IMA, and the D/NT and D/TT ratios were higher than the healthy control group, serum D level was not different between the two groups (Table 2). While A-IMT value was significantly higher in beta thalassemia minor patients, all C-IMT values were not different compared to healthy controls. A-IMT negatively correlated with the TT level. Linear regression analysis was performed with parameters significantly related to A-IMT measurement (Table 3). Table 4 shows the correlation

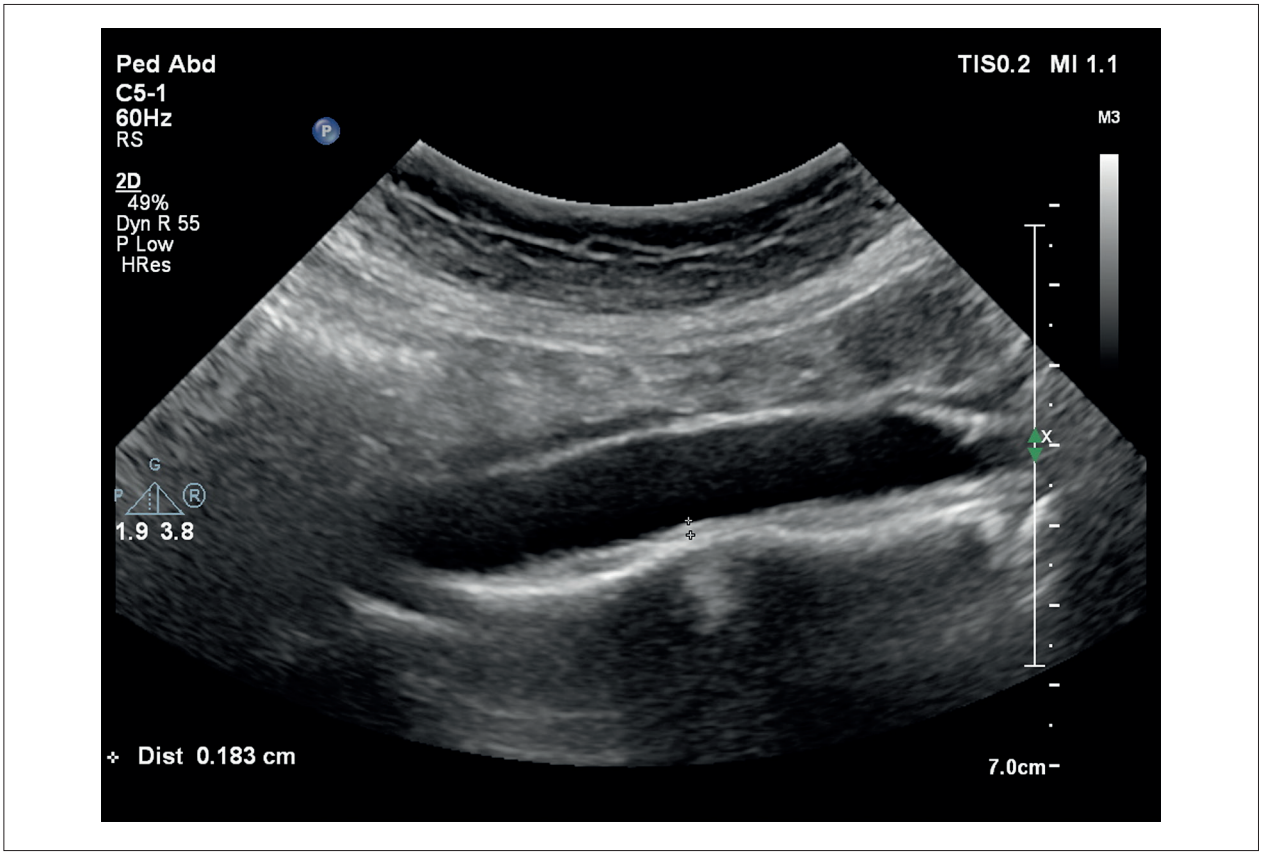

Figure 2 – *Abdominal aortic intima-media thickness (A-IMT) measurement by B-mode ultrasound showing increased A-IMT (1.83 mm) in a patient with beta thalassemia minor.*

of A-IMT measurements with the clinical and laboratory parameters. A-IMT positively correlated with the systolic and diastolic blood pressures, NT, D and IMA levels, and the D/NT and D/TT ratios. In linear regression analyses, A-IMT was found to be independently associated with the IMA, and NT and TT levels. The strongest relationship was found between A-IMT and IMA (Figure 3).

Discussion

Our study gave a lot of new information to the literature about beta thalassemia minor. The first and the main finding was that A-IMT but not C-IMT values were increased in individuals with beta-thalassemia minor. This is the first study to evaluate and to demonstrate the increase in A-IMT in these patients. We also evaluated the thiol-disulfide balance and IMA levels for oxidative stress status and showed that it was increased in beta-thalassemia minor patients. In addition, increased A-IMT was positively correlated with IMA, one of the oxidative stress parameters, and negatively and closely related to TT and NT. Although the relationship between increased oxidative stress and increased IMT is known for many diseases other than beta-thalassemia minor, this is the first time that this association was shown in this group of individuals.

Oxidative stress is caused by the unbalance between the production of reactive oxygen species and the antioxidant system. One of the antioxidant mechanisms is the thiol-disulfide balance; the evaluation of this balance is critical for elucidating the effects of oxidative stress on the pathogenesis of diseases and evaluating responses to antioxidant treatments.[20] Studies have shown that an abnormal thiol-disulfide balance is involved in the pathogenesis of various diseases such as diabetes mellitus, cardiovascular diseases, malignancies, rheumatoid arthritis, Parkinson's disease, celiac disease and other inflammatory bowel diseases, Alzheimer's disease and multiple sclerosis.[21-24] In our study, the dynamic thiol-disulfide balance was compared between beta-thalassemia minor individuals and healthy control group. In addition, the relationship between IMA and C-IMT, previously shown in beta-thalassemia major patients, was evaluated in beta-thalassemia minor individuals. Also, this is the first and only study to evaluate both IMA levels and thiol /D homeostasis in individuals with beta-thalassemia minor. While IMA levels, D/NT, and D/TT ratios were significantly higher in beta-thalassemia minor patients than the control group, NT and TT levels, and NT/ TT ratio were significantly lower than the control group. This may be explained by the presence of excess free alpha globin chains due to β-globin chain deficiency, leading to formation of superoxide

Table 1 – Comparison of demographic and laboratory findings between beta thalassemia minor and healthy controls

	Beta thalassemia minor n=80	Healthy control group n=50	p
Age (years)	38.5 ± 13.9	38.4 ± 13.9	0.957
Female gender n (%)	53 (%66.2)	33 (%66)	0.977
Systolic blood pressure (mmHg)	116 ± 6.0	117 ± 6.8	0.399
Diastolic blood pressure (mmHg)	73.2 ± 3.6	74.3 ± 5.4	0.182
Heart rate (pulse/minute)	81.4 ± 11.3	67.3 ± 3.6	**<0.001**
Body mass index (kg/m^2)	28.0 ± 2.5	27.4 ± 1.6	0.154
Urea (mg/dL)	23.4 ± 5.40	23.2 ± 5.3	0.800
Creatinine (mg/dL)	0.56 ± 0.16	0.55 ± 0.16	0.867
Glucose (mg/dL)	93.5 ±9.86	92.8 ± 10.5	0.677
Aspartate aminotransferase (u/L)	19 (12.8 – 21.7)	19.5 (12.4 – 21.7)	0.961
Alanine aminotransferase (u/L)	16.6 (12.1 – 19.1)	16.6 (12.1 – 19.1)	0.940
Triglyceride (mg/dL)	94 (82 – 167)	102 (82 – 171)	0.858
Low density lipoprotein cholesterol (mg/dL)	114 ± 27	115 ± 27	0.852
Thyroid stimulating hormone (uIU/dL)	1.74 ± 0.88	1.67 ± 0.92	0.679
High sensitive C reactive protein (mg/dL)	0.60 (0.30 – 0.90)	0.55 (0.30 – 0.90)	0.799
White Blood Cell Count (x10^6/µl)	7.54 ± 1.48	7.57 ± 1.51	0.903
Red Blood Cell Count (x10^6/µl)	5.51 ± 0.86	4.55 ± 0.41	< 0.001
Hemoglobin (g/dL)	11.6 ± 1.45	12.8 ± 1.22	< 0.001
Hematocrit (%)	35.8 ± 4.82	38.6 ± 3.75	< 0.001
Mean Corpuscular Volume (fL)	65.2 ± 8.1	84.8 ± 7.1	< 0.001
Red Blood Cell Distribution Width	16.8 ± 2.9	13.3 ± 1.5	< 0.001
Thrombocyte Count (x10^3/µl)	249 ± 69	249 ± 71	0.990

Table 2 – Comparison of oxidative stress parameters between beta thalassemia minor and healthy controls

	Beta thalassemia minor n=80	Healthy control group n=50	p
Native thiol (µmoL)	337 ± 52	384 ± 38	<0.001
Total thiol (µmoL)	350 ± 42	417 ± 35	<0.001
Disulfide (µmoL)	18.2 ± 7.40	16.6 ± 3.72	0.106
Disulfide / Native thiol ratio	6.08 ± 2.73	5.16 ± 1.23	0.010
Disulfide / total thiol ratio	5.32 ± 2.06	4.64 ± 1.21	0.020
Native thiol / total thiol ratio	89 ± 4.13	91 ± 2.25	0.026
Ischemia modified Albumin (absorbance unit)	0.70 ± 0.14	0.59 ± 0.06	<0.001

and hydroxyl radicals and initiation of oxidative chain reactions.[25] Epidemiological studies and clinical trials have shown that C-IMT, determined by high-resolution B-mode ultrasonography, positively correlates with traditional cardiovascular risk factors, and can provide increased risk information. Ultrasonography for C-IMT evaluation is recommended by traditional guidelines on cardiovascular risk classification as a non-invasive screening method for subclinical atherosclerosis.[14-17] In autopsy studies, the first atherosclerotic lesion was shown to start from the dorsal surface of the distal abdominal aorta.[26] Although the abdominal aorta is an artery prone to atherosclerosis, A-IMT has not been as extensively investigated as C-IMT. Studies have found a positive correlation between A-IMT

Table 3 – Comparison of carotid and abdominal aortic intima-media thickness between beta thalassemia minor patients and healthy controls

	Beta thalassemia minor n=80	Healthy control group n=50	p
Aortic IMT(mm)	1.46 ± 0.37	1.23 ± 0.22	<0.001
Right common carotid IMT (mm)	0.57 ± 0.11	0.56 ± 0.11	0.943
Right internal carotid IMT (mm)	0.56 ± 0.13	0.56 ± 0.12	0.941
Left common carotid IMT (mm)	0.59 ± 0.12	0.58 ± 0.12	0.948
Left internal carotid IMT (mm)	0.56 ± 0.11	0.56 ± 0.10	0.940

IMT: intima-media thickness.

Table 4 – Correlation between blood pressure values and oxidative stress parameters with aortic intima-media thickness (A-IMT) in patients with beta-thalassemia minor

	Correlation Analysis		Regression Analysis	
	p	R	p	β
Systolic Blood Pressure (mmHg)	**<0.001**	0.701	0.127	0.113
Diastolic Blood Pressure (mmHg)	**<0.001**	0.720	0.127	0.089
Native thiol levels (µmoL)	**<0.001**	– 0.435	**0.002**	– 0.173
Total thiol levels (µmoL)	**<0.001**	– 0.721	**<0.001**	– 0.296
Disulfide levels (µmoL)	**<0.001**	0.609	0.223	0.118
Disulfide / Native thiol ratio	**<0.001**	0.621	0.455	0.021
Disulfide / total thiol ratio	**<0.001**	0.645	0.372	0.026
Native thiol / total thiol ratio	**<0.001**	– 0.670	0.787	– 0.270
Ischemia Modified Albumin levels (absorbance unit)	**<0.001**	0.784	**<0.001**	0.491

$R^2_{adjusted} = 0.666$.

and systolic blood pressure, heart rate, creatinine, thyroid stimulating hormone, insulin-like growth factor-1 and growth hormone levels. Examination of abdominal aortic atherosclerosis has the potential to provide important information for cardiovascular risk assessment. Current ultrasound devices and high-resolution probes allow clear visualization of the abdominal aorta and measurement of the A-IMT.[18,19,27-29] It has been clearly shown that C-IMT measurement is increased in patients with beta-thalassemia major.[6-8] However, as far as we know, IMT evaluation in beta-thalassemia minor patients was performed in a limited number of patients in only one study,[11] which reported that this group had increased C-IMT.[11] The most important reason for this may be that in beta-thalassemia minor patients, the risk of initiating a subclinical atherosclerotic process is lower than in beta-thalassemia major patients, and current clinical features are not at a level to increase IMT. In our study, C-IMT measurements were made from four different regions – right and left internal and external carotid artery, and it was found that IMT values were not different between beta-thalassemia minor and control groups. In the study by Gullu et al.,[11] IMT measurement was taken from the right common carotid artery only, and the number of beta thalassemia minor patients included in the study was half as our study.[11] Therefore, our results may be more meaningful than those of the previous report. However, to elucidate the relationship between the pathophysiology of beta-thalassemia minor and C-IMT, further studies are required. It is known that A-IMT is an earlier indicator of atherosclerotic diseases and risk factors for many diseases than C-IMT.[18,19,27-29] In the literature, there is no study evaluating A-IMT in beta-thalassemia patients. In our study, A-IMT was found to be significantly greater in beta-thalassemia minor patients than in healthy controls. In recent studies on A-IMT as an early indicator of atherosclerosis, A-IMT increase without a C-IMT increase was found in patients with myocardial infarction, hyperparathyroidism, and diabetes mellitus in accordance with our study.[18,19,30]

Paraoxonase-1 and oxidative status have been shown to be increased in beta-thalassemia major patients, contributing to the development of coronary artery disease and atherosclerotic plaque formation.[31]

In another study, it was shown that oxidative stress increases with decreased paraoxonase-1 activity in beta-

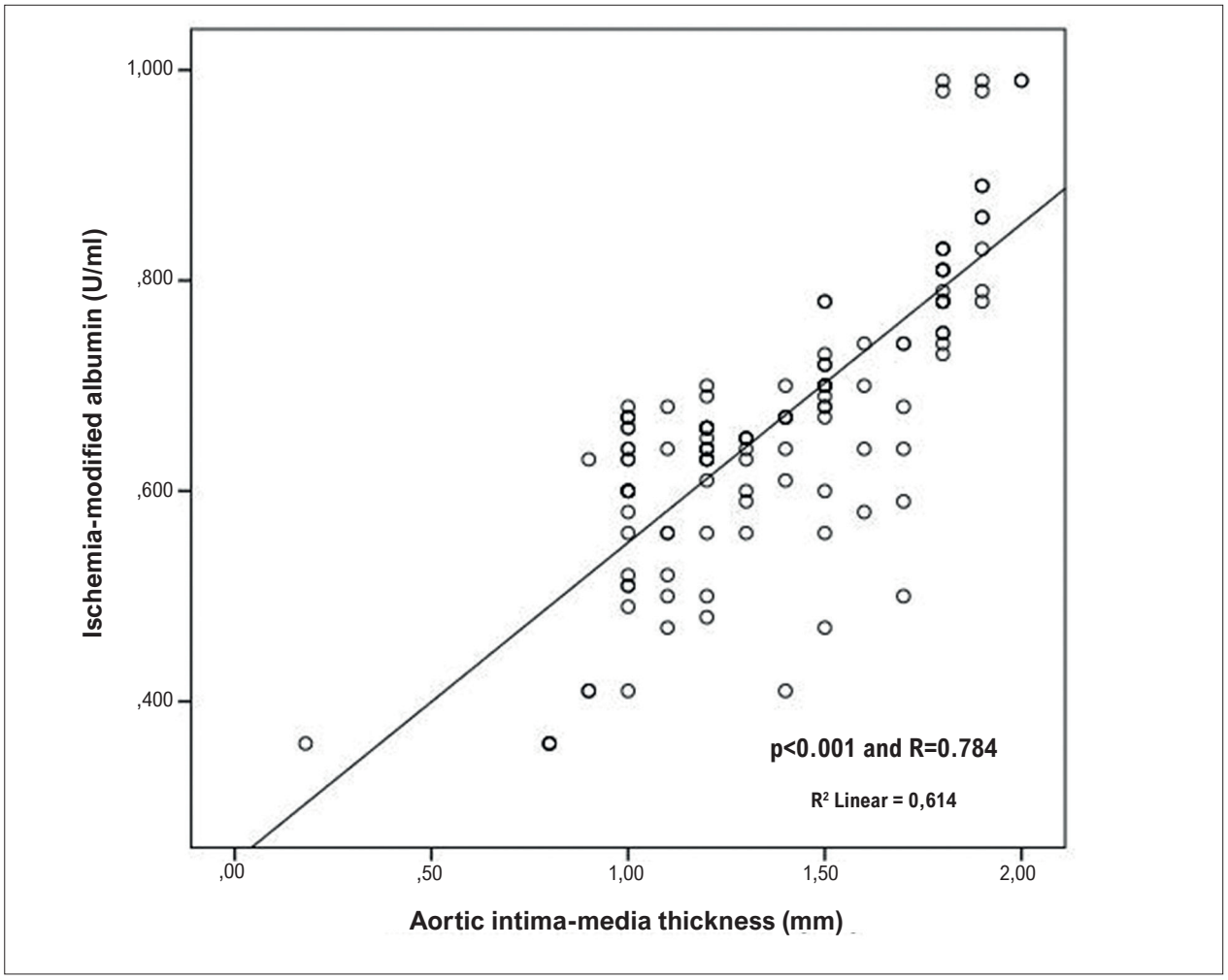

Figure 3 – *Significant correlation between aortic intima-media thickness and ischemia modified albumin levels.*

thalassemia minor patients.[12] In addition, the prevalence of metabolic syndrome is relatively high in individuals with beta-thalassemia minor, which is also in accordance with our study, considering the contribution of metabolic syndrome to atherosclerosis.[32] Another study also showed that individuals with beta-thalassemia minor are at twice the risk of diabetes and insulin resistance compared to the individuals without the disease.[33]

In our study, beta-thalassemia minor patients had increased oxidative stress, with impaired thiol-disulfide hemostasis and increased IMA; and all these oxidative stress parameters were closely related to A-IMT. This finding proved that oxidative stress was associated with increased IMT in beta-thalassemia minor patients as well as in beta-thalassemia major patients.[10]

Limitations

The most important limitation of our study is that it was a single-center, cross-sectional study with a limited number of patients. Another limitation is that beta thalassemia major and intermedia patients were not taken as study groups, since both C-IMT and oxidative stress were clearly increased in them. If included, these parameters could be compared with the beta thalassemia minor group. Another important limitation of our study was that we did not perform analysis of genetic mutation or of proatherogenic biochemical phenotype of patients with beta thalassemia minor. The frequency of proatherogenic biochemical phenotype has been shown to be increased in beta thalassemia minor patients compared to the general population.[34] In our study, the analysis of the proatherogenic biochemical phenotype and genetic mutation would provide more meaningful results. Also, IMT measurement was performed by a radiologist with previous experience on IMT, who has many publications and 10 years of experience on ultrasonography. However, since all measurements were made by the same specialist, the inter-observer variability was not assessed.

Conclusion

In the present study, we found that A-IMT, which can be evaluated non-invasively and reliably with abdominal ultrasound, was increased in patients with beta thalassemia minor. In addition, the levels of NT and TT were decreased and IMA levels were increased; the antioxidant mechanism and the prooxidant-antioxidant balance were deteriorated in favor of prooxidants. Similarly to the relationship between increased oxidative stress and elevated C-IMT reported in the literature, in our study, A-IMT was found to be closely related to increased oxidative stress. Also, the assessment of A-IMT may be a promising tool in the detection of subclinical atherosclerosis and in the evaluation of the oxidative stress status. Further studies with a long-term follow-up of beta thalassemia minor patients are warranted.

Author Contributions

Conception and design of the research: Cansu Tumer, Hilmi Erdem Sumbul; Acquisition of data: Muhammed Zubeyir Aslan, Ayse Selcan Koc, Ozcan Erel, Salim Neselioglu, Erdinc Gulumsek, Begum Seyda Avci; Analysis and interpretation of the data: Akkan Avci; Statistical analysis: Erdinc Gulumsek, Begum Seyda Avci; Writing of the manuscript: Cansu Tumer, Akkan Avci, Hilmi Erdem Sumbul; Critical revision of the manuscript for intellectual content: Tayyibe Saler, Mevlüt Koc.

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 Cukurova University under the protocol number 88. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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The Association of TWEAK with Coronary Artery Calcification in Patients with Chronic Kidney Disease

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Abstract

Background: The soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) is a member of the TNF superfamily that plays a critical role in proliferation and inflammation in the arterial circulation.

Objectives: This prospective study aimed to show the relationship between the sTWEAK levels and coronary artery calcification (CAC) in patients with chronic kidney disease (CKD).

Methods: This prospective study included 139 consecutive patients undergoing computed coronary angiography for any reason except for acute coronary syndromes from August 2020 to February 2021. A total of 12 patients were excluded from the study due to exclusion criteria. Patients were divided into two groups with regard to having a CAC score of less than 400 (n=84) and 400 or more (n=43). Significance was assumed at a 2-sided p<0.05.

Results: As the CAC score increased, sTWEAK levels presented a statistically significant decrease, and a strong relationship between sTWEAK levels and the CAC score (r: -0.779, p<0.001) was observed. The ROC analysis revealed that the optimal cut-off level of sTWEAK for predicting the CAC score of 400 was 761 pg/mL with a sensitivity of 71% and a specificity of 73% (AUC: 0.78; 95% CI:0.70-0.85; p < 0.001)

Conclusions: Even though the large-scale studies showed a positive correlation between eGFR and the sTWEAK levels, some studies found the increased sTWEAK levels to be associated with mortality and the severity of the coronary artery system in patients with CKD. Our results support our hypothesis that the sTWEAK level shows coronary calcification rather than other types of atherosclerotic plaques.

Keywords: Cardiovascular Diseases; Renal Insufficiency,Chronic; Vascular Stiffness; Atherosclerosis; Coronary Artery Disease.

Introduction

The association of atherosclerosis with chronic kidney disease (CKD) is well-established, and the patients with CKD are associated with a more than 8-fold atherosclerosis-related death rate than in the general population.[1,2] The pathophysiology of atherosclerosis includes lipid abnormalities, endothelial dysfunction, aging, and inflammation.[3] The role of inflammation and immunity in the pathophysiology of atherosclerosis has been demonstrated in recent decades.[3-5] The soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) is a member of the TNF superfamily that plays a critical role in proliferation and inflammation.[6-8] The sTWEAK has been studied in patients with CKD, and it has been shown that its' level declines as the estimated glomerular filtration rate (eGFR) decreases.[9, 10] Even though the decreased sTWEAK level was found in atherosclerosis, another study found the association of increased sTWEAK level with severity of coronary arteries.[11]

In CKD, the abnormal metabolism of minerals and bones results in the accumulation of arterial calcification.[12] On account of the controversial results, this prospective study aimed to show the relationship between the sTWEAK level and coronary artery calcification (CAC) in patients with CKD under conservative treatment.

Methods

Study participants

This prospective study included 139 consecutive patients undergoing computed coronary angiography (CCA) for any reason from August 2020 to February 2021. All patients enrolled in the study were diagnosed with CKD, who had an estimated glomerular filtration rate (eGFR) below 60 for ≥ 3 months or an eGFR above 60 with albuminuria (urine albumin/creatinine ratio ≥ 30 mg/g).[13] The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[14] A total of 57 patients (41%) had category 2 CKD; 45 (32%), category 3a CKD; 33 (24%), category 3b CKD; and 4 (0.2%), category 4. The studied population had no history of atherosclerosis

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(coronary artery disease, ischemic stroke, peripheral artery disease, and thoracic/abdominal aneurysm). The exclusion criteria included: (i) any previous cardiovascular disease, (ii) previous organ transplantation, (iii) presence of more than a mild valvular disease, (iv) presence of systolic or heart failure, (v) presence of diastolic dysfunction other than grade 1 diastolic dysfunction and left ventricular hypertrophy, (vi) presence of epicardial coronary artery stenosis, (vii) patients on hemodialysis, and (viii) patients with acute coronary syndromes. A total of 12 patients were excluded from the study before the CCA, as they presented peripheral artery disease (n=4), showed severe aortic stenosis (n=1), and were taking medication for the chronic coronary syndrome (n=7) (Figure 1). A total of 127 patients were divided into two groups based on having coronary artery calcium (CAC) scores of less than 400 (n=84) and 400 or more (n=43). This study was approved by the local Clinical Studies Ethics Committee (No: 2021/0005). Informed consent was obtained from all patients enrolled in this study.

Demographic and clinical data

All patients completed the health and medication history questionnaires, including the clinical history of coronary artery disease (CAD), peripheral artery disease (PAD), Diabetes Mellitus (DM), hypertension (HTN), and medication use. Before CTA, all patients underwent transthoracic echocardiography, carotid duplex ultrasound, and lower extremity arterial Doppler ultrasound to exclude subclinical atherosclerosis. An echocardiogram was performed using a Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway), and left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method.[15]

Blood values were obtained from venous blood samples upon hospital admission. The complete blood count was measured by using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland, Inc., Galway, Ireland). Biochemical measurements were performed by using Siemens Healthcare Diagnostic Products kits and calibrators (Marburg, Germany). The blood samples for plasma sTWEAK levels were obtained before the CTA and were determined using ELISA kits (Bender MedSystems, Vienna, Austria).

Definitions

The Agatston score is one of the most frequently used scoring systems to assess coronary artery calcification. In general, the CAC score is divided into five groups as: 0, no coronary calcification; 1-100, mild coronary calcification; >100 to 399, moderate calcification; 400 to 999, severe calcification; and ≥1,000, extensive calcification.[16,17] We divided the study population into two groups as patients with severe to extensive CAC (n=43) and patients without any CAC or mild to moderate CAC (n=84).

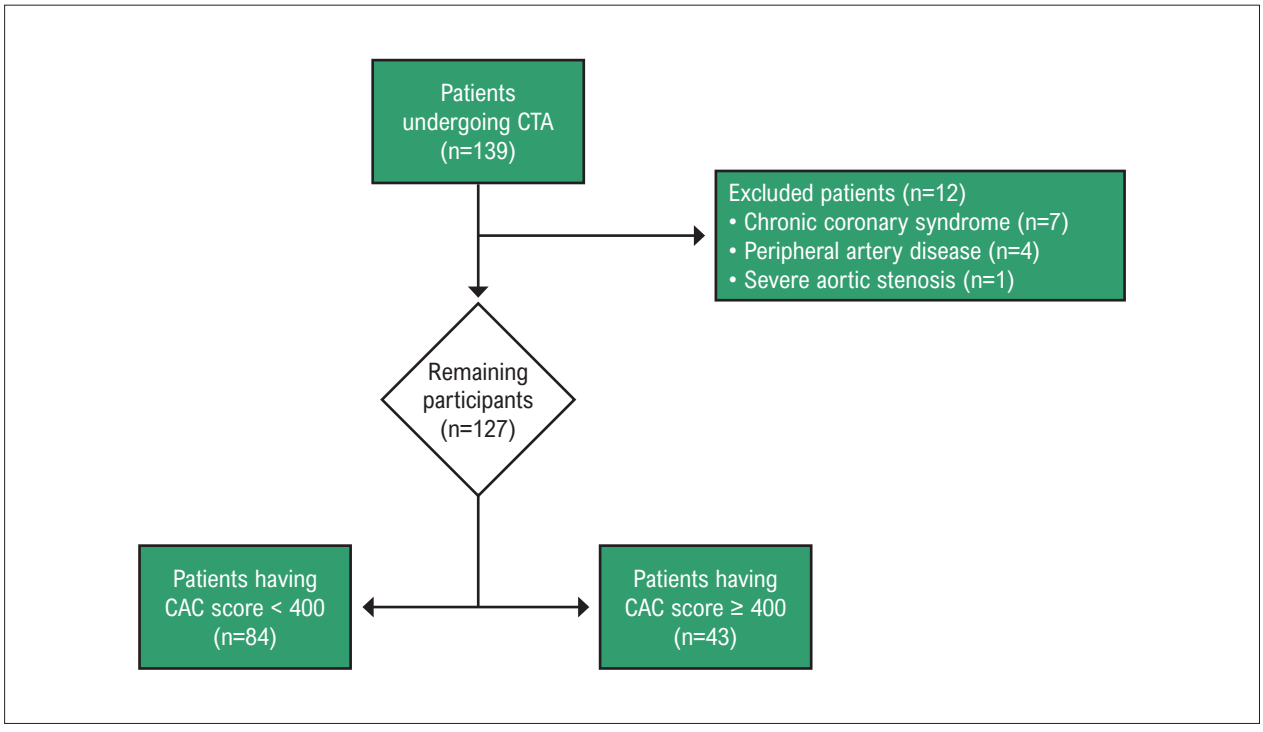

Figure 1 – *The flowchart illustrating the exclusion of participants for the final study sample.*

Statistical analyses

All statistical tests were conducted using the Statistical Package for the Social Sciences 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze the normality of the data. Continuous variables with normal distribution were described using mean ± standard deviation (SD); and continuous variables without normal distribution were described using median and interquartile range. The categorical data are expressed as frequency (%). The Chi-square test was used to assess differences in categorical variables between groups. The relationships among parameters without normal distribution were assessed using Spearman's correlation analysis. The Student's t-test or Mann Whitney U test was used to compare unpaired samples as needed. Univariate and multivariate logistic regression analysis were used to identify independent variables of CAD and CAC. After performing univariate analysis, significantly obtained variables were selected into the multivariate logistic regression analyses with the stepwise method. The results of univariate and multivariate regression analyses were presented as odds ratio with 95%. For the laboratory parameter of sTWEAK receiver operating characteristic (ROC) curves were obtained, and the optimal values with the greatest total sensitivity and specificity in the prediction of coronary calcium score (≥400) were selected. Significance was assumed at a 2-sided $p<0.05$.

Results

A total of 127 patients (mean age 59.9± 9.4 years; men 39%) undergoing CTA enrolled in the study, and the baseline characteristics and laboratory parameters are shown in Table 1. The patients enrolled in the study were diagnosed with CKD stages 3-5, and the mean eGFR, creatinine, blood urea nitrogen levels were 39.9±13.1 mL/dk/1.73 m2, 1.8±0.2 mg/dL, 43.5±8.4 mg/dL, respectively. The mean Agatston CAC score was 90 (0-1605), and 43 patients had a score of >400, which represents severe to extensive CAC (Table 1).

The relationship between sTWEAK levels and the CAC score was evaluated by Spearman correlation analysis. As the CAC score increased, sTWEAK levels decreased significantly, and there was a good relationship between sTWEAK levels and the CAC score, which is shown in Figure 2 (r: -0.615, $p<0.001$).

The participants were divided into two groups as patients with a CAC score of <400 (n=84) and patients with a CAC score of ≥400 (n=43). There were no statistically significant differences between the groups concerning age, gender, BMI, HTN, DM, and smoking status, as shown in Table 2. The laboratory parameters, such as fasting glucose, Hgb, platelet WBC, creatinine, eGFR, uric acid, sodium, potassium, TC, LDL, HDL, Tg, showed no statistically significant differences (Table 2).

The sTWEAK level was significantly lower in the group with a CAC score of ≥400 than the group with a CAC score of <400 (Table 2). The relationship between sTWEAK levels and the CAC score in patients with lower CAC scores (<400) was evaluated by Spearman correlation analysis. As the CAC score increased, sTWEAK levels decreased significantly, and there was a moderate relationship between sTWEAK levels and the CAC score, which is shown in Figure 3 (r: -0.385, $p<0.001$). The relationship between sTWEAK levels and the CAC score in patients with higher CAC scores (≥400) was evaluated by Spearman correlation analysis. As the CAC score increased, sTWEAK levels decreased significantly, and there was a strong relationship between sTWEAK levels and the CAC score, which is shown in Figure 4 (r: -0.779, $p<0.001$). We evaluated the specificity and sensitivity of the sTWEAK levels by Receiver Operating Characteristic (ROC) analysis to predict the presence of the CAC score of 400. The ROC analysis revealed that the optimal cut-off level of sTWEAK for predicting the CAC score of 400 was 761 pg/mL, with a sensitivity of 71% and specificity of 73% (AUC: 0.78; 95% CI:0.70-0.85; $p < 0.001$) (Figure 5).

The parameters affecting the development of CAC were evaluated by univariate and multivariate analysis. The probable predictors of CAD, such as age, gender, HTN, DM, CKD, smoking, BMI, CRP, LDL, and sTWEAK were evaluated in the univariate analysis. In the multivariate analysis, age, smoking, LDL, and sTWEAK were associated with the CAC score of 400 (Age OR:1.033, p: 0.003; smoking OR: 4.638, p: 0.003; LDL OR:1.016, p: 0.005; sTWEAK OR: 0.345, $p<0.001$) (Table 3).

Discussion

The patients with the CAC score of 400 have a high risk for adverse cardiac events (>2% per year), and one-third of those patients have abnormal myocardial perfusion imaging.[18,19] In our study, the study population was divided into two groups regarding their CAC scores. As the score of CAC increased, the sTWEAK decreased in a statistically significant manner, especially in patients with a score of 400 (r: -779, $p<0.001$, strong correlation) (Figure 2-4). The lower sTWEAK levels remained an independent predictor of a high CAC score in the multivariate analysis (Table 2).

The atherosclerotic plaque consists of proinflammatory mediators, cytokines, and chemokines.[20,21] The cytokines can destabilize the plaque and increase the risk of thrombotic events.[22-24] The sTWEAK is one of the inflammatory messengers that contributes to atherosclerotic plaque formation, and the high level of sTWEAK was found to be associated with the severity of coronary arteries in patients with the chronic coronary syndrome.[11] Several animal studies supported these findings, which showed the relationship between the sTWEAK and prothrombic activities.[6,7,25]

Furthermore, anti-TWEAK treatment was found to reduce atherosclerotic plaque progression and inflammation in animal models.[6,25]

Table 1 – Clinical and laboratory characteristics of patients with chronic kidney disease

	n=127
Age, years	59.9 ± 9.4
Gender (male, %)	49 (39%)
BMI, kg/m^2	29.0 ± 3.7
HTN, n(%)	87 (68%)
DM, n(%)	53 (42%)
Smoking, n(%)	35 (27%)
Systolic blood pressure, mmHg	134.2±22.7
Diastolic blood pressure, mmHg	77.4±11.8
Fasting blood glucose, mg/dL	119.4±47.1
Hemoglobin, g/dL	13.8±1.6
PLT, cells/μL	237.7±65.2
WBC, cells/μL	7.5±1.8
Creatinine, mg/dL	1.8±0.2
eGFR, ml/dk/1.73 m^2	39.9±13.1
BUN, mg/dL	43.5±8.4
Uric acid, mg/dL	7.4±1.2
Sodium, mmol/L	139.6±2.3
Potassium, mmol/L	4.3±0.4
Calcium, mmol/L	9.4±0.4
AST, U/L	22.4±9.3
ALT, U/L	23.8±11.2
CRP, mg/dL	0.3 (0.1-9.2)
Albumine, g/dL	4.3±0.4
TC, mg/dL	207.3±45.8
LDL, mg/dL	126.7±42.5
HDL, mg/dL	48.7±12.0
Tg, mg/dL	161.3±77.5
sTWEAK , pg/mL	845.0±418.0
CAC score	90 (0-1605)
CAC score <400, n(%)	84 (66%)
CAC score ≥400, n(%)	43 (34%)

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index; CAC: coronary artery calcification; CRP: C-reactive protein; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; HTN: hypertension; LDL: low-density lipoprotein; Plt: platelet; TC: total cholesterol; TG: triglyceride; sTWEAK: soluble tumor necrosis factor-like weak inducer of apoptosis; WBC: white blood cell. [a]Continuous variables are presented as mean (SD); categorical variables presented as frequency (%).

The inverse relationship was shown in atherosclerosis in carotid arteries in patients on hemodialysis.[26] This association was also found in carotid atherosclerosis in patients with HIV infection.[27] In several studies, the gradual reduction in the level of sTWEAK was observed as eGFR declined.[9,28,29] Even though it was hypothesized that the increased level of sTWEAK might reflect healthy vessels, the increased sTWEAK level in patients on hemodialysis was found to be a predictor of mortality.[30] It is still controversial whether the high or low sTWEAK level is associated with atherosclerosis. Several studies found that the sTWEAK level was lower in CKD patients with atherosclerosis and observed a continuous decrease in the sTWEAK level after a 2-year follow-up.[10,28,31] The opposite results were found in another study, which showed that an increase in the sTWEAK level was associated with a high Gensini score.[11]

Atherosclerotic plaques usually develop calcifications. The member of the TNF family, such as the Receptor activator of NF-κB ligand (RANKL), is known to promote calcium formation in atherosclerotic plaques.[3] The patients with CKD have more severe calcified coronary plaques than those without CKD.[31-33] As the eGFR declines, especially at below 60 mL/min/1.73 m2, the capacity of elimination of phosphorus falls. It ends up reducing 1,25 dihydroxy-vitamin D levels, which causes relative hypocalcemia. This hypocalcemia can trigger the release of parathyroid hormone, causing the accumulation of calcium in the vascular system.[12]. Sastre C et al.[6] found that sTWEAK might decrease the burden of calcification of the plaque; this may explain the inconsistency of the studies in terms of the sTWEAK levels in patients with atherosclerosis. The study found a positive correlation with the severity of coronary arteries, including the mild to moderate CKD patients, and the investigators assessed the conventional invasive coronary angiograms.[11] They did not use the CTA, which is excellent to show calcifications of the coronary arteries. The present study analyzed a homogenous group of CKD patients with and without coronary calcifications. Our results support that the sTWEAK level shows coronary calcification rather than atherosclerosis.

Limitations

This study has potential limitations. First, our population was limited to patients with CKD. Hence, our results cannot be generalized to all patients with atherosclerosis. Second, the number of study patients was relatively small; therefore, further larger-scale studies are needed to confirm these findings. Third, the study was carried out in a single tertiary university hospital. Hence, there was a possibility of selection bias, although great attention was paid to include all consecutive patients undergoing CTA to avoid selection bias. Furthermore, interobserver bias could be high in the Agatston score, which was used to calculate the burden of calcification.

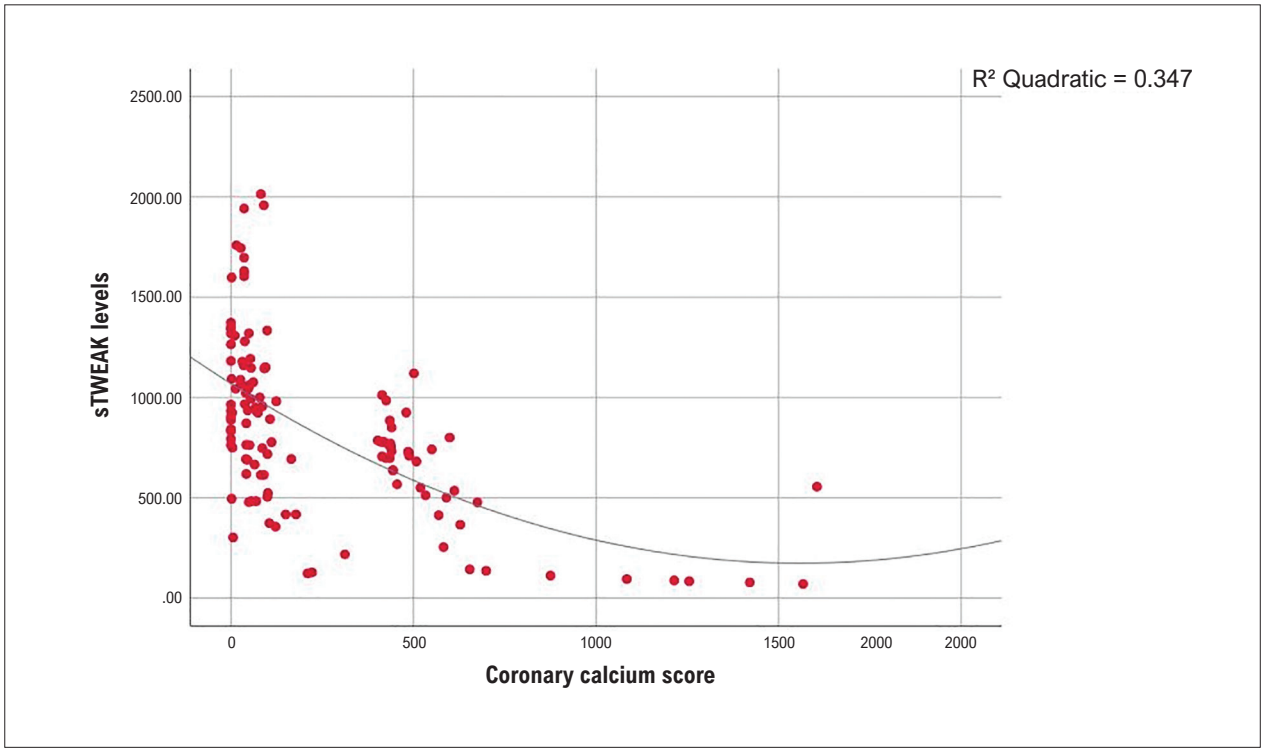

Figure 2 – *The correlation analysis of sTWEAK and the coronary artery calcification score (r:-0.615, p<0.001, good correlation).*

Conclusions

Even though the large-scale studies showed a positive correlation between eGFR and the sTWEAK levels, some studies found the increased sTWEAK levels to be associated with mortality and the severity of the coronary artery system in patients with CKD. Our results support our hypothesis that the sTWEAK level shows coronary calcification rather than other types of atherosclerotic plaques.

Author contributions

Conception and design of the research and Acquisition of data Tatlisu MA, Atici A, Ozcan FB, Çelik M, Kirac E, Baycan OF; Analysis and interpretation of the data: Tatlisu MA, Atici A, Ozcan FB, Çelik M, Kirac E, Baycan OF, Caliskan M; Statistical analysis: Atici A, Caliskan M; Obtaining financing: Tatlisu MA, Caliskan M; Writing of the manuscript: Tatlisu MA; Critical revision of the manuscript for intellectual content: Tatlisu MA.

Potential Conflict of Interest

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

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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 Goztepe Research and Training Hospital under the protocol number 2021/0005. 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.

Table 2 – Clinical and laboratory characteristics of patients divided into two groups with regard to coronary artery calcification score[a]

	CCS≥400 (n=43)	CCS<400 (n=84)	p
Age, years	61.7 ± 8.8	59.0 ± 9.6	0.126
Gender (male%)	19(44%)	30(35%)	0.353
BMI, kg/m^2	29.8 ± 3.8	28.6± 3.6	0.098
HT, n(%)	33(78%)	54(65%)	0.121
DM, n(%)	22(52%)	31(37%)	0.108
Smoking, n(%)	15(36%)	20(25%)	0.198
Systolic blood pressure, mmHg	137.5±20.7	132.4±23.6	0.241
Diastolic blood pressure, mmHg	80.0±11.5	76.0±11.7	0.073
Fasting blood glucose, mg/dL	122.8±62.9	117.5±24.5	0.601
Hemoglobin, g/dL	13.6±1.4	13.9±1.7	0.336
PLT, cells/μL	235.5±68.1	239.0±63.9	0.797
WBC, cells/μL	7.4±1.8	7.5±1.9	0.687
Creatinine, mg/dL	1.8±0.2	1.9±0.1	0.887
Stages of CKD			
Stage 2	18	36	0.914
Stage 3a	15	27	0.756
Stage 3b	10	18	0.814
Stage 4	1	2	0.984
eGFR, ml/dk/1.73 m^2	39.8±13.6	40.2±12.9	0.890
BUN, mg/dL	36.4±9.3	32.0±7.4	0.009
Uric acid, mg/dL	7.5±1.1	7.3±1.3	0.274
Sodium, mmol/L	139.5±2.2	139.6±2.3	0.825
Potassium, mmol/L	4.2±0.5	4.3±0.3	0.115
Calcium, mmol/L	9.3±0.3	9.4±0.4	0.066
AST, U/L	22.2±8.1	22.6±11.3	0.875
ALT, U/L	23.5±11.1	24.0±10.0	0.898
CRP, mg/dL	0.3 (0.1-9.2)	0.2 (0.1-2.0)	0.009
Albumine, g/dL	4.1±0.5	4.4±0.2	0.005
TC, mg/dL	215.8±41.6	202.9±47.5	0.132
LDL, mg/dL	135.2±40.0	122.4±43.4	0.108
HDL, mg/dL	49.6±13.3	48.3±11.3	0.550
Tg, mg/dL	158.4±59.1	162.8±85.7	0.758
sTWEAK, pg/mL	586.2±286.6	977.5±413.8	<0.001
CAC score	488 (402-1605)	45 (0-312)	<0.001

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index; CAC: coronary artery calcification; CRP: C-reactive protein; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; HTN: hypertension; LDL: low-density lipoprotein; PLT: platelet; sTWEAK: soluble tumor necrosis factor-like weak inducer of apoptosis; TC: total cholesterol; TG: triglyceride; WBC: white blood cell. aContinuous variables are presented as mean (SD); categorical variables presented as frequency (%).

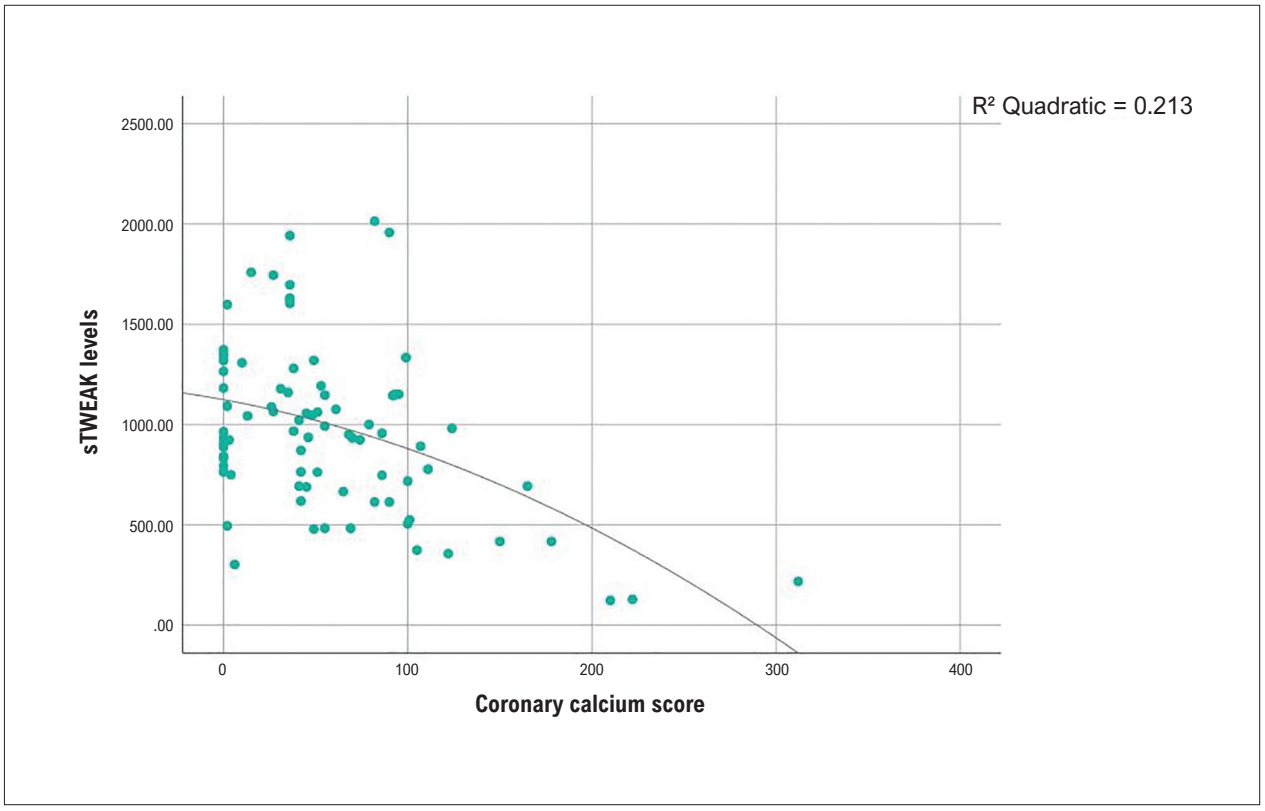

Figure 3 – *The correlation analysis of sTWEAK and the coronary artery calcification score of less than 400 (r:-0.385, p<0.001, moderate correlation).*

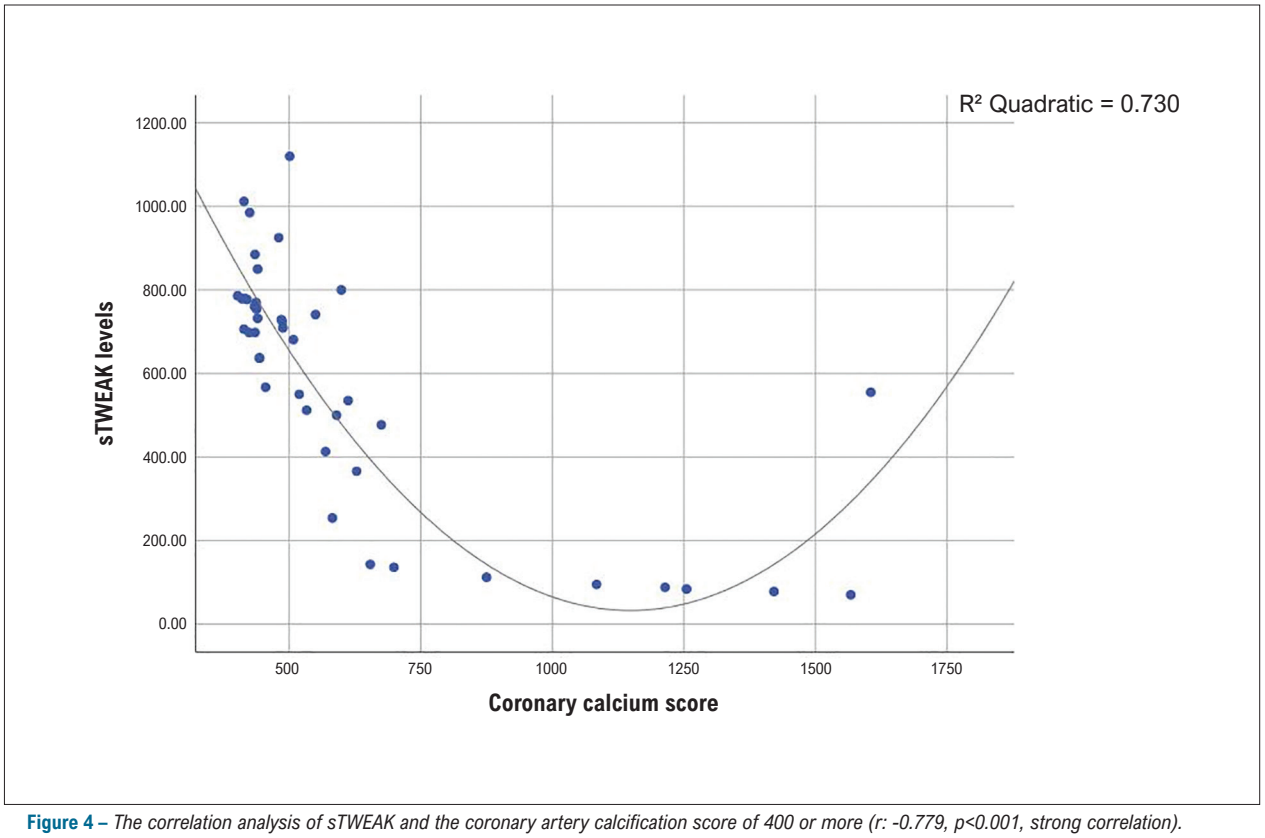

Figure 4 – *The correlation analysis of sTWEAK and the coronary artery calcification score of 400 or more (r: -0.779, p<0.001, strong correlation).*

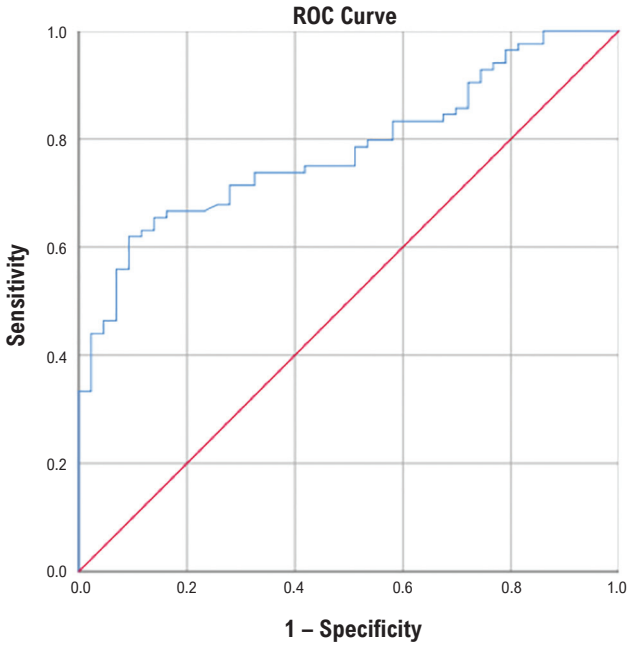

Figure 5 – *The ROC analysis revealed that the optimal cut-off value of the sTWEAK to predict the CAC score of ≥ 400 was 761 pg/mL with a sensitivity of 71% and specificity of 73% (AUC=0.78; 95% CI:0.70-0.85; p<0.001).*

Table 3 – Univariate predictors and multivariate model for the coronary artery calcification score of ≥400

Variable	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Age	1.049	1.009-1.091	0.016	1.033	1.016-1.058	0.003
Gender	0.567	0.276-1.166	0.123			
HTN	1.093	0.492-2.265	0.877			
DM	0.591	0.289-1.209	0.150			
CKD	1.105	0.151-8.105	0.922			
Smoking	4.552	1.898-10.915	0.001	4.638	1.965-11.236	0.003
BMI	0.969	0.881-1.066	0.513			
CRP	2.490	0.802-7.731	0.314			
LDL	1.017	1.007-1.027	0.001	1.016	1.005-1.028	0.005
sTWEAK	0.314	0.172-0.507	<0.001	0.345	0.201-0.581	<0.001

BMI: body mass index; CKD: chonic kidney disease; CRP: C-reactive protein; DM: diabetes mellitus; HTN: hypertension; LDL: low-density lipoprotein; sTWEAK: soluble tumor necrosis factor-like weak inducer of apoptosis.

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Should We "Tweak" Our Approach to Coronary Artery Disease?

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Short Editorial related to the article: The Association of TWEAK with Coronary Artery Calcification in Patients with Chronic Kidney Disease

Despite our great advances in medical technology, Cardiovascular Disease remains the leading cause of death worldwide. Coronary Artery Disease (CAD) is one of the hallmarks.[1]

It is believed that the first correlation between coronary flow and angina pectoris was made by William Heberden in 1768, but its anatomical remarks were only described by 1829, when Jean Lobstein introduced the term Arteriosclerosis, reporting an abnormal formation in arterial walls.[2] Later, in 1856, Rudolph Virchow suggested an arterial wall injury mechanism that could explain those findings from a cellular pathology compound.[3] However, it was only until the 20th century, in the late 70´s, that the consortium of endothelial damage-wall shear stress-smooth muscle proliferation-thrombogenesis was first elucidated in the "Response to Injury Hypothesis" by Ross et al..[4]

Modern cardiology has evolved exponentially since those first discoveries, offering state-of-the-art technology to treat the full range of Acute Coronary Syndromes.[5,6] Our better comprehension of this disease's complex molecular dynamics is fundamental to improving an early diagnosis and further, preventing its disastrous outcomes.[7]

21st-century medicine offers a great armamentarium of molecular diagnoses for several diseases, but CAD is somewhat lacking behind.[8]

It is widely known that inflammation plays a major role in atherogenesis;[9] thus, several biomarkers have been studied in this context, such as C-reactive Protein, Interleukin (IL)6, Tumor Necrosis Factor (TNF) alfa, among others.[10–12] One of these tools' mean issues is the lack of specificity or its right association with net mortality.

In this issue, Tatlisu et al.[13] contemplate using soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK), a known player in proliferation and inflammation,[14] to elucidate coronary artery calcification.

In a prospective study, 139 consecutive patients with Chronic Kidney Disease (CKD) were included with further computed coronary angiography (CCA) for coronary artery calcium (CAC) score analysis. Blood samples were collected to analyze sTWEAK, where they sought the relationship with the CAC score. They found that as the CAC score increased, sTWEAK levels decreased significantly. Furthermore, they concluded that low sTWEAK levels were a predictor of high CAC scores in their studied population.

It is quite early to start adopting these new biomarkers as a standard for CAD diagnosis in our clinical practice; however, these kinds of efforts drive us to an enhanced view of the complex dynamic of CAD, walking us to the near future of precision medicine, when we could finally have a tweak to the disease itself.

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Keywords

Coronary Artery Disease; Atherosclerosis; Cardiovascular Diseases/mortality; Biomarkers; Biomedical, Technology/trends

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Predictors of Hospital Mortality Based on Primary Angioplasty Treatment: A Multicenter Case-Control Study

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Abstract

Background: **Identification of high-risk patients undergoing primary angioplasty (PCI) is essential.**

Objective: **Identify factors related to the causes of death in PCI patients.**

Methods: **This work consisted of a multicenter case-control study using a Brazilian registry of cardiovascular interventions as the data source. The association between each variable and death was assessed using a binary logistic regression model, p <0.05 was considered significant.**

Results: **A total of 26,990 records were analyzed, of which 18,834 (69.8%) were male patients, with a median age of 61 (±17) years. In the multivariate analysis, the main variables related to the causes of death with their respective odds ratios and 95%confidence intervals (CI) were advanced age, 70-79 years (2.46; 1.64-3.79) and ≥ 80 years (3.69; 2.38-5.81), p<0.001; the classification of Killip II (2.71; 1.92-3.83), Killip III (8.14; 5.67-11.64), and Killip IV (19.83; 14.85-26.69), p<0.001; accentuated global dysfunction (3.63; 2,39-5.68), p<0.001; and the occurrence of infarction after intervention (5.01; 2.57-9.46), p<0.001. The main protective factor was the post-intervention thrombolysis in myocardial infarction (TIMI) III flow (0.18; 0.13-0.24), p<0.001, followed by TIMI II (0.59; 0.41 -0.86), p=0.005, and male (0.79; 0.64-0.98), p = 0.032; dyslipidemia (0.69; 0.59-0.85), p<0.001; and number of lesions treated (0.86; 0.9-0.94), p<0.001.**

Conclusion: **The predictors of mortality in patients undergoing PCI were Killip's classification, reinfarction, advanced age, severe left ventricular dysfunction, female gender, and post-intervention TIMI 0 / I flow.**

Keywords: **Acute Myocardial Infarction; Database; Myocardial Reperfusion; Percutaneous Coronary Intervention; Mortality.**

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in Brazil. Cardiac conditions account for 8.3% of all hospitalizations and 18.6% of all hospital expense reimbursements in the Brazilian public health system. Ischemic heart disease is the leading CVD cause of death.[1]

Access to treatment restoring coronary flow is essential in reducing mortality from ST-Elevation Myocardial Infarction (STEMI). Studies have shown a significant reduction in early mortality using aspirin with fibrinolytic medications.[2-4]

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Another treatment method, primary percutaneous coronary intervention angioplasty (PCI), consists of the mechanical opening of the artery related to STEMI. It is the preferred treatment strategy if performed by an experienced team up to ninety minutes after admission.[5-7] Compared to chemical fibrinolysis, PCI is considered the most effective treatment, and can reduce mortality rates, nonfatal infarction recurrence, and stroke.[8]

Identifying high-risk patients is essential for prognostic information and aids in the medical decision-making process. Knowing these variables can help select patients with a higher rate of events for future studies, adjust population baseline characteristics in epidemiological studies, and generate hypotheses for further studies.[9,10]

Several publications present models for risk stratification, but little data refer to the Brazilian population.[11-16] In 1991, the National Cardiovascular Intervention Center (CENIC) was created, an official database of the Brazilian Society of Hemodynamics and Interventional Cardiology (SBHCI). This database contains information that comes

from the spontaneous contribution of its members and has been used in other key publications in the literature.[17-19]

The present study aims to identify the risk factors for death in Brazilian patients undergoing PCI.

Methods

This study used a secondary data source (CENIC) in a multicenter case-control study. Patients were divided into two groups: those who survived the procedure (controls) and those who died (for any reason). Data were collected during the hospitalization period.

Population

Records of patients undergoing primary PCI were selected from January 2004 to December 2018. The exclusion criteria involved patients younger than 18 years of age or an unknown age, missing data on hospital mortality, and previous use or unknown use of thrombolytics.

This study also excluded patients submitted to procedures unapproved for primary angioplasty, according to the Brazilian Society of Cardiology Guidelines,[7] including cases that used rotational, directional atherectomy; cutting balloon; and excimer laser devices. Altogether, 109 records reported at least one of these techniques.

From 29,003 original records, 26,990 were included in the analysis. The flowchart with the study population, exclusion criteria, and distribution of cases and controls is shown in Figure 1.

Definitions

Patients with clinical and electrocardiographic criteria compatible with the diagnosis of STEMI, selected for a primary angioplasty strategy, were included. The diagnosis was confirmed by angiography in all cases. The decision to include patients in the registry was at the discretion of the interventional cardiologist.

Analysis regarding the angiographic variables, including ventricular function, was visually estimated by the examiners. The definitions followed the SBHCI Guidelines for Percutaneous Coronary Intervention and Adjunct Diagnostic Methods in Interventional Cardiology.[20]

The choice of vascular access, use of adjuvant medications, and procedure techniques were chosen by the examiners.

Coreware managed the CENIC registry, performed the research data extraction, and maintained participants and hospitals of origin confidential (www.coreware.com.br).

The variables were selected based on previous publications.[10-16]

Statistical analysis

Qualitative variables were presented as frequencies and quantitative variables as medians (interquartile range). Quantitative variables were subjected to the Kolmogorov-Smirnov normality test. The comparison of mortality rates between genders was evaluated using the chi-square test. The association between each predictor variable and death outcome was assessed using a simple logistic regression model. The univariate analysis was performed with all variables shown in Table 1. These variables were selected based on previous studies. Variables with $p<0.20$ in the univariate analysis were included in a multivariate binary logistic regression model. The final model was obtained using the stepwise strategy, and the quality of the adjustment was assessed using the Hosmer-Lemeshow test. The missing data were not considered in the statistical analysis.

Results were presented as odds ratios (OR) with the respective 95% confidence intervals (95% CI). The analyses were performed using the free R program, version 4.0.0, and $p<0.05$ was considered significant.

Ethical aspects

The research was approved by the Research Ethics Committee of Faculdade de Ciências Médicas de Minas Gerais, logged under protocol number: 3.502.883. The need for free and informed consent forms was waived. All procedures in this study were in accordance with resolution 466/2012.

Results

A total of 26,990 records were analyzed, from all Brazilian regions; the distribution of cases is shown in Figure 2. Most of the records, 1,883 (69.8%) were male, with a median age of 61 (±17) years, and the most frequent risk factor was systemic arterial hypertension, reported by 19,045 (70.6%) participants.

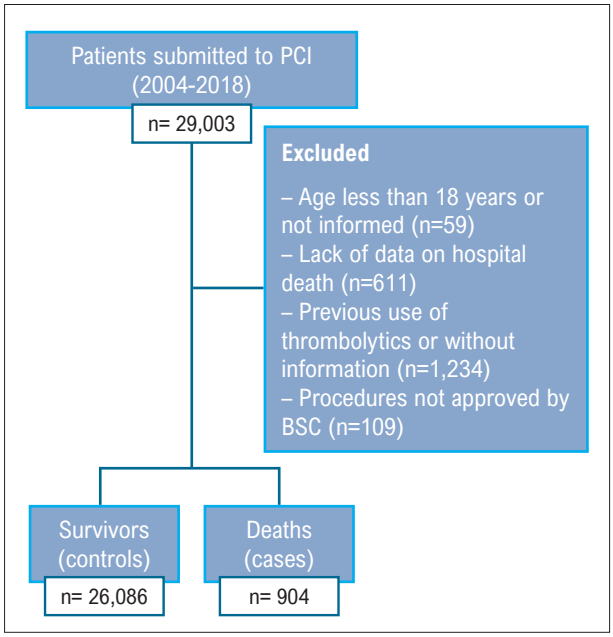

Figure 1 – *Population, exclusion criteria, and distribution of cases and controls. BSC: Brazilian Society of Cardiology; PCI: primary angioplasty.*

Table 1 – Sample characteristics and association with the outcome of death

Features	All sample (n = 26,990)	No (n = 26,086)	Yes (n = 904)	p-value	OR (95% CI)
Gender					
F	8.156 (30.2%)	7.764 (29.8%)	392 (43.4%)	-	-
M	18.834 (69.8%)	18.322 (70.2%)	512 (56.6%)	<0.001	0.55 (0.48; 0.63)
Age					
19 to 49 years	4.472 (16.6%)	4.400 (16.9%)	72 (8.0%)	-	-
50 to 59 years	7.886 (29.2%)	7.734 (29.6%)	152 (16.8%)	0.204	1.20 (0.91; 1.60)
60 to 69 years	7.395 (27.4%)	7.166 (27.5%)	229 (25.3%)	<0.001	1.95 (1.50; 2.57)
70 to 79 years	4.968 (18.4%)	4.714 (18.1%)	254 (28.1%)	<0.001	3.29 (2.54; 4.32)
≥ 80 years	2.269 (8.4%)	2.072 (7.9%)	197 (21.8%)	<0.001	5.81 (4.44; 7.69)
Killip* (n = 26,989)					
I	20.560 (76.2%)	20.359 (78.0%)	201 (22.2%)	-	-
II	3.560 (13.2%)	3.452 (13.2%)	108 (11.9%)	<0.001	3.17 (2.49; 4.01)
III	1.079 (4.0%)	969 (3.7%)	110 (12.2%)	<0.001	11.50 (9.01; 14.60)
IV	1.790 (6.6%)	1.305 (5.0%)	485 (53.7%)	<0.001	37.64 (31.69; 44.86)
Lesion location* (n = 27,179)					
Proximal LAD	7.266 (26.9%)	6.951 (26.6%)	315 (34.8%)	-	-
Middle / distal right coronary and branches	6.451 (23.9%)	6.326 (24.3%)	125 (13.8%)	<0.001	0.44 (0.35; 0.54)
Middle / distal LAD and branches	5.515 (20.4%)	5.379 (20.6%)	136 (15.0%)	<0.001	0.56 (0.45; 0.68)
Proximal right coronary	3.696 (13.7%)	3.561 (13.7%)	135 (14.9%)	0.089	0.84 (0.68; 1.03)
Distal circumflex / branches	1.989 (7.4%)	1.949 (7.5%)	40 (4.4%)	<0.001	0.45 (0.32; 0.62)
Proximal circumflex	1.486 (5.5%)	1.423 (5.5%)	63 (7.0%)	0.869	0.98 (0.73; 1.28)
Grafts	370 (1.4%)	345 (1.3%)	25 (2.8%)	0.029	1.60 (1.02; 2.39)
Left main	217 (0.8%)	152 (0.6%)	65 (7.2%)	<0.001	9.44 (6.87; 12.83)
Disease extent* (n = 26,751)					
Single arterial	12.699 (47.5%)	12.484 (48.3%)	215 (24.0%)	-	-
Biarterial	7.889 (29.5%)	7.610 (29.4%)	279 (31.1%)	<0.001	2.13 (1.78; 2.55)
Multiarterial + LMCA	36 (0.1%)	29 (0.1%)	7 (0.8%)	<0.001	14.02 (5.60; 30.59)
Left main	44 (0.2%)	29 (0.1%)	15 (1.7%)	<0.001	30.03 (15.48; 55.99)
Triarterial	6.083 (22.7%)	5.702 (22.1%)	381 (42.5%)	<0.001	3.88 (3.28; 4.61)
Door-to-balloon time[1]* (minutes) (n = 25,837)	70.00 (75.00)	70.00 (75.00)	80.00 (66.80)	0.010	1.0006 (1.0001; 1.001)
Previous CABG surgery	803 (3.0%)	759 (2.9%)	44 (4.9%)	<0.001	1.71 (1.23; 2.30)
Previous angioplasty	3.143 (11.6%)	3.044 (11.7%)	99 (11.0%)	0.508	0.93 (0.75; 1.14)
Previous AMI* (n = 26,957)	2.948 (10.9%)	2.808 (10.8%)	140 (15.5%)	<0.001	1.52 (1.26; 1.82)
Diabetes Mellitus	5.270 (19.5%)	5.021 (19.2%)	249 (27.5%)	<0.001	1.59 (1.37; 1.85)
Insulin-dependent	753 (2.8%)	697 (2.7%)	56 (6.2%)	<0.001	2.41 (1.80; 3.16)
Hypertension	19.045 (70.6%)	18.406 (70.6%)	639 (70.7%)	0.934	1.006 (0.87; 1.17)

ARF	43 (0.2%)	25 (0.1%)	18 (2.0%)	<0.001	21.18 (11.35; 38.75)
Smoking	9.521 (35.3%)	9.273 (35.5%)	248 (27.4%)	<0.001	0.69 (0.59; 0.79)
Dyslipidemia	13.221 (49.0%)	12.825 (49.2%)	396 (43.8%)	0.002	0.81 (0.70; 0.92)
Family history	6.364 (23.6%)	6.208 (23.8%)	156 (17.3%)	<0.001	0.67 (0.56; 0.79)
TIMI Pre					
0	18.160 (67.3%)	17.472 (67.0%)	688 (76.1%)	-	-
1	1.576 (5.8%)	1.513 (5.8%)	63 (7.0%)	0.678	1.06 (0.81; 1.36)
2	2.435 (9.0%)	2.371 (9.1%)	64 (7.1%)	0.004	0.69 (0.52; 0.88)
3	4.819 (17.9%)	4.730 (18.1%)	89 (9.8%)	<0.001	0.48 (0.38; 0.59)
TIMI Post* (n = 26,975)					
0	1.175 (4.4%)	955 (3.7%)	220 (24.4%)	-	-
1	322 (1.2%)	257 (1.0%)	65 (7.2%)	0.554	1.10 (0.80; 1.49)
2	1.289 (4.8%)	1.146 (4.4%)	143 (15.9%)	<0.001	0.54 (0.43; 0.68)
3	24.189 (89.7%)	23.715 (91.0%)	474 (52.5%)	<0.001	0.09 (0.07; 0.10)
Diameter of vessel[1]* (n = 19,931)	3.00 (0.75)	3.00 (0.75)	3.00 (0.75)	<0.001	0.63 (0.52; 0.76)
LV function* (n = 16,880)					
Normal	3.169 (18.8%)	3.139 (19.2%)	30 (6.0%)	-	-
Mild global dysfunction	6.167 (36.5%)	6.123 (37.4%)	44 (8.8%)	0.230	0.75 (0.47; 1.21)
Moderate global dysfunction	5.230 (31.0%)	5.130 (31.3%)	100 (20.0%)	<0.001	2.04 (1.37; 3.13)
Marked global dysfunction	2.314 (13.7%)	1.989 (12.1%)	325 (65.1%)	<0.001	17.10 (11.92; 25.47)
Minor vascular complications	87 (0.3%)	82 (0.3%)	5 (0.6%)	0.219	1.76 (0.62; 3.94)
Major vascular complications	31 (0.1%)	25 (0.1%)	6 (0.7%)	<0.001	6.97 (2.58; 15.94)
Hemorrhagic stroke	16 (0.1%)	12 (<0.1%)	4 (0.4%)	<0.001	9.66 (2.70; 27.78)
Ischemic stroke	17 (0.1%)	11 (<0.1%)	6 (0.7%)	<0.001	15.84 (5.45; 41.72)
Access site* (n = 25,032)					
Femoral	19.278 (77.0%)	18.690 (76.7%)	588 (86.6%)	-	
Brachial - dissection	299 (1.2%)	291 (1.2%)	8 (1.2%)	0.709	0.87 (0.39; 1.66)
Brachial - puncture	165 (0.7%)	162 (0.7%)	3 (0.4%)	0.364	0.59 (0.15; 1.55)
Radial	5.290 (21.1%)	5.210 (21.4%)	80 (11.8%)	<0.001	0.49 (0.38; 0.61)
Abxicimab* (n = 25,107)	830 (3.3%)	800 (3.3%)	30 (4.4%)	0.103	1.36 (0.92; 1.94)
Tirofiban* (n = 25,107)	3.199 (12.7%)	3.067 (12.6%)	132 (19.4%)	<0.001	1.68 (1.38; 2.03)
AAS* (n = 25,107)	22.475 (89.5%)	21.873 (89.5%)	602 (88.5%)	0.394	0.90 (0.71; 1.15)
Calcification	5.448 (20.2%)	5.176 (19.8%)	272 (30.1%)	<0.001	1.74 (1.50; 2.01)
Intracoronary thrombus	16.812 (62.3%)	16.197 (62.1%)	615 (68.0%)	<0.001	1.30 (1.13; 1.50)
Reinfarction	130 (0.5%)	98 (0.4%)	32 (3.5%)	<0.001	9.73 (6.40; 14.42)
Obstructions treated[1]	1.00 (1.00)	1.00 (1.00)	1.00 (0.00)	<0.001	0.84 (0.79; 0.89)

**variables that presented missings, n valid is in parentheses. [1]Data presented as median (interquartile range). The p-values refer to the simple binary logistic model. LAD: left anterior descending artery; LMCA: left main coronary artery; CABG: coronary artery bypass graft; SAH: systemic arterial hypertension; ARF: acute renal failure; LV: left ventricle; ASA: acetylsalicylic acid. Source: The author, 2021.*

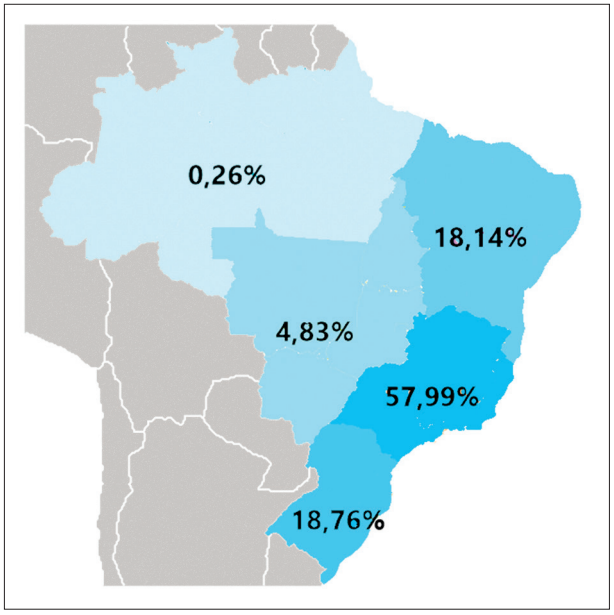

Figure 2 – *Distribution of cases by region.*

Most of the patients, 20,560 (76.2%), presented a Killip class I classification, while 12,699 (47.5%) presented a predominance of disease affecting a single vessel and 6,167 (36.5%) presented mild ventricular dysfunction.

The total number of deaths was 904 patients, and the overall mortality rate was 3.3%. The mortality rate was lower in males than in females (2.7% and 4.8%, respectively, p<0.001).

Table 1 shows all sample characteristics, their association with death outcomes, and the results of the OR association test with a 95%CI, with respective p-values obtained by adjusting univariate logistic models. In this univariate analysis, the variables with p<0.20 used in the multiple models were gender, age, Killip classification, location of lesions, extent of coronary disease, door-to-balloon time, personal history of coronary bypass surgery, report of infarction, diabetes, smoking, dyslipidemia, systemic arterial hypertension, family history of early coronary disease, classification of TIMI flow before and after the intervention, vessel diameter, the development of major vascular complications, renal failure and ischemic hemorrhagic stroke, reinfarction, vascular access, the average number of obstructions treated and the presence of calcification, and thrombus.

Table 2 shows the factors related to the death outcomes, OR association test with a 95% CI, and p-values obtained by adjusting the multivariate binary logistic regression model.

Table 2 – Variables that correlated significantly and independently with in-hospital death

Feature	OR	CI 95% OR	p-value
Intercept	0.021	(0.011; 0.039)	<0.001
Gender M	0.789	(0.635; 0.981)	0.032
Age (ref. <50)			
50 to 59	1.625	(1.059; 2.540)	0.029
60 to 69	2.004	(1.336; 3.076)	0.001
70 to 79	2.462	(1.635; 3.789)	<0.001
≥ 80	3.688	(2.384; 5.812)	<0.001
Killip (ref. I)			
II	2.718	(1.919; 3.827)	<0.001
III	8.139	(5.672; 11.637)	<0.001
IV	19.833	(14.851; 26.688)	<0.001
Dyslipidemia	0.689	(0.558; 0.850)	<0.001
TIMI Post (ref. 0)			
1	1.303	(0.774; 2.162)	0.313
2	0.593	(0.409; 0.857)	0.005
3	0.176	(0.133; 0.235)	<0.001
LV function (ref. Normal)			
Mild global dysfunction	0.799	(0.491; 1.322)	0.373
Moderate global dysfunction	1.206	(0.782; 1.914)	0.410
Marked global dysfunction	3.625	(2.393; 5.675)	<0.001
Infarction after intervention	5.006	(2.568; 9.460)	<0.001
Number of lesions treated	0.859	(0.785; 0.938)	<0.001

Hosmer-Lemeshow, p-value 0.683. LV: left ventricle. Source: The author, 2021.

Discussion

The main mortality indicators in patients submitted to primary PCI found in the present study, in addition to age and female gender, were related to the impact of infarction on ventricular function, such as the Killip classification and the presence of marked LV global dysfunction analyzed by angiography. On the other hand, the presence of TIMI II/III flow after the intervention reflected the success of the treatment, which seeks precisely to maintain ventricular function and prevent other cardiovascular complications. The occurrence of reinfarction was rare, but it proved to be an independent indicator of mortality in these patients.

Mortality rates in patients undergoing PCI vary from 2.3% to 11.9%, according to different sources.[15,21-24] The present study's database identified a 3.4% death rate. This finding may be related to underreporting and the lower risk of the sample. Table 3 shows the comparison between variables correlated to the death outcome in our study with others published in the literature. [11-14,25,26]

The present study found that the only indicator of the CENIC study that differs from the other risk models presented in Table 3 was the female sex. However, this finding has already been reported by other publications.[27,28]

Some authors report the more significant presence of atypical symptoms in females who delay their treatment,

Table 3 – Comparison of variables related to death outcomes

	CENIC (n=26,990)	DynTIMI (n=20,506)	PAMI (n=3,252)	CADILLAC (n=2,082)	GRACE (n=11,389)	Zwolle (n=1,791)	ALPHA (n=1,255)
Time	**Hospital**	**One year**	**Six months**	**One year**	**Six months**	**30 days**	**30 days**
Age	+	+	+	+	+	+	+
Female	+						
Arterial Hypotension		+			+		+
Heart Rate		+	+		+		+
Killip classification	+	+	+	+	+		
Diabetes mellitus			+				
Hypertension							
Angina pectoris							
Previous AMI or BBB		+	+			+	
Weight		+				+	
Ischemia time		+					
Flow (final TIMI from 0 to 2)	+			+		+	
LVEF				+			
Marked LV Dysfunction	+						
Anemia				+			
Three vessel disease				+		+	
ST-segment deviation					+		
Creatinine / ARF		+		+	+		
Cardiac arrest					+		+
Myocardial injury markers					+		
Infarction recurrence	+	+					
Stroke		+					
Arrhythmia		+					
HF / Shock		+				+	
Major bleeding		+					
Femoral access							+

*CENIC: National Cardiovascular Intervention Center; dynTIMI: dynamic Thrombolysis In Myocardial Infarction; PAMI: Primary Angioplasty in Myocardial Infarction; CADILLAC: Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; GRACE: Global Registry of Acute Coronary Events; ALPHA: (*Age, Life support, Pressure, Heart rate, Access site*); SAH: systemic arterial hypertension; AMI: acute myocardial infarction; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; LV: left ventricle; SBP: systolic blood pressure; ARF: acute renal failure; HF: heart failure. Source: The author, 2021.*

the so-called Yentl syndrome. Angioplasty can also be more challenging, leading to a lower success rate.[29] Total ischemia time, other bleeding complications outside the access site, and weight were missing from our database, which could partly explain this worse outcome in women.

The Killip and Kimball classification was the variable that proved to be the best prognostic indicator, a fact corroborated by other studies.[10,12,13] In the Grace registry, the chance of death increased nearly three-fold with each increase in the Killip classification, 3.30 (3.00-3.60), p <0.001. The present study's series showed 1,790 cases (6.6% of the total) with Killip class IV (cardiogenic shock), similar to the incidence described in the literature (5 to 10%).[30]

Ventricular failure is the leading cause of death in these patients, and the only effective treatment is early reperfusion. The use of ventricular assist devices, such as

the intra-aortic balloon, has conflicting results.[31] Other devices have been tested and even used in clinical practice, but no conclusive studies have been published in the literature.[32]

The purpose of the intervention is to obtain the final TIMI III flow. This result was strongly related to reducing the chances of death (OR 0.18; CI 0.13-0.23, p <0.001). Other studies also corroborate this finding.[33] Other indicators that reflect the microcirculation injury, such as the resolution of the elevation of the ST segment and the quantification of the myocardial blush, was able to improve our model.[34]

According to published data in the literature, the reinfarction rate in patients treated with primary angioplasty is lower than in those receiving fibrinolysis as a reperfusion strategy.[35] In our sample, the rate was 0.5%. This finding is compatible with randomized studies, comparing PCI with fibrinolysis.[8] Although reinfarction incidence was relatively low, the chance of death was about five-fold higher in patients who experienced this event.

The present study identified an inverse correlation between the number of lesions treated and the chance of death. Previous studies suggest that the revascularization of vessels other than those directly related to AMI does not seem to significantly interfere with the chances of death and reinfarction.[36] We speculate that the most likely reason would be a selection bias, where lower-risk patients would have eventually been selected for additional interventional treatment. However, the hypothesis that selective intervention in high-risk obstructions may have improved the results is impossible to rule out.

Another unexpected finding was the potential protective effect of dyslipidemia. In the TIMI study, the use of lipid-lowering drugs was also associated with a better evolution.[10] The explanation for this discovery, known as the "lipid paradox," is not entirely known. It is assumed that patients who report dyslipidemia are more likely to take medications and care for their health. On the other hand, the finding of low levels of low-density lipoprotein (LDL) may lead to a lower prescription of statins.[37,38]

Several trials, including a meta-analysis of randomized studies[39] and a risk model,[25] have demonstrated the impact of radial access in reducing mortality. Our model did not corroborate these findings, which can possibly be explained by the study's sample characteristics. Cases with a previous use of fibrinolytic medications were excluded, and a low rate of glycoprotein IIb / IIIa inhibitors was found. Moreover, our study's operators likely selected the access site based on patients' clinical characteristics and operator procedural expertise, thus leading to better results.

Among the risk models presented in Table 3, ours was the only one that showed an association with the female gender as a risk factor for mortality in patients treated for PCI. This finding reinforces the need for a faster, more accurate diagnosis and adoption of different treatment strategies in females. Another interesting result was the pseudo "protective" effect of dyslipidemia. As discussed, this finding strongly suggests that patients without dyslipidemia should receive statins in the same recommended doses, regardless of the cholesterol levels indicated in the guidelines.

Measures to attenuate reperfusion injury can further decrease the mortality rate, since, as demonstrated, in addition to the TIMI III flow, ventricular function was an important marker of good prognosis. Finally, new antiplatelet agents, combined with new intervention materials and techniques, can reduce stent thrombosis and decrease mortality.

Study limitations

The present study does have some limitations. It is an observational, non-randomized study, which assessed the association between death and clinical, angiographic variables, complications, and non-causality. Additionally, the variables were collected from a secondary source, resulting from spontaneous contributions; therefore, it was impossible to properly judge the data. Finally, the study lacked uniformity in definitions of some variables related to AMI. It was observed that the CENIC record was rich in angiographic variables and relatively poor in clinical variables, precisely because it was conceived by interventionists.

A low rate of hospital mortality was also observed, which suggests underreporting, a situation commonly found in nonmandatory records and not linked to reimbursement, which may have generated inclusion bias.

Another limitation was the presence of missing data. In Table 1, the variables with n different from the sample are marked with an asterisk. Low data loss was observed in most variables. The variable of ventricular function by angiography presented a high level of *missing*. However, ventriculography has been less and less used in clinical practice, and the present study better reflects the "real world". Another variable with significant loss was the diameter of the vessel, which may have occurred due to measurement difficulty related to the fact that the vessel was occluded in most cases.

Conclusion

The predictors of mortality in patients undergoing primary PCI cataloged in the CENIC registry were: Killip classification, reinfarction, advanced age, severe systolic dysfunction of the left ventricle, female gender, and postintervention TIMI 0 / I flow. This identification of the worst prognosis elements can be useful in stratifying and caring for coronary patients.

Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Castro PPN, Moura I, Pena JLB; Acquisition of data: Castro PPN, Castro MAN, Nascimento GA; Statistical analysis: Moura I; Writing of the manuscript: Castro PPN; Critical revision of the manuscript for intellectual content: Moura I, Pena JLB.

Potential Conflict of Interest

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

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Study Association

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*Supplemental Materials

For additional information, please click here.

ST-Elevation Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention: The Importance of Local Data

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Short Editorial related to the article: Predictors of Hospital Mortality Based on Primary Angioplasty Treatment: A Multicenter Case-Control Study

Castro et al.[1] should be commended for providing the scientific community with a useful publication analyzing predictors of all-cause mortality in patients with ST-elevation acute myocardial infarction (STEMI) who are submitted to primary percutaneous coronary intervention (PPCI).

PPCI is the preferred method of reperfusion for patients with STEMI presenting within 12 hours of evolution from onset of symptoms.[2] To the best of my knowledge, the most recent meta-analysis comparing fibrinolytic therapy with PPCI found odds ratios of 0.73 ($p = 0.002$), 0.38 ($p < 0.001$), 0.38 ($p < 0.001$), and 1.03 ($p = 0.86$) for all-cause death, reinfarction, stroke, and major bleeding, respectively. However, absence of widespread availability of catheterization laboratories and logistical problems, mainly related to transportation, limit the access of patients with STEMI to this form of treatment.[3] This is highlighted in the present publication, where only 0.26% of the analyzed population was from the vast North Region of Brazil, whereas the majority (58%) was from the Southeast Region. Maybe more importantly, the utilization of reperfusion therapies (fibrinolytics or PPCI) in general is far from ideal in Brazil, and important regional differences have been observed.[4,5] Importantly, the previously cited meta-analysis by Fazel et al.[3] found odds ratios of 0.79, 0.53, 0.70, and 1.19 for all-cause deaths, reinfarction, stroke, and major bleeding, respectively, when comparing the pharmacoinvasive approach with fibrinolytic treatment, which can be an option for issues related to access to PPCI.

The comparison between the paper by Castro et al.[1] and the literature summarized in Table 3 must be interpreted carefully. First, the Brazilian paper analyzed only the in-hospital phase, while the others analyzed follow-ups ranging from 30 days to 1 year. Second, not all studies were related to patients submitted to PPCI. For example, the "DynTIMI"[6] was derived from the ExTRACT study, which tested the role of enoxaparin versus non-fractioned heparin in patients with STEMI, and the GRACE[7] was an international registry with a broad population of patients with acute coronary syndromes (with or without ST-elevation). It is noteworthy that all the studies included in Table 3 developed risk scores to facilitate understanding and to increase the utilization of the results in daily practice, which was not the case of the publication by Castro et al.[1] The authors missed an excellent opportunity to develop a risk score based on a Brazilian population, as did some previous publications from Brazil.[8]

In a somewhat simplistic manner, Castro et al.[1] stated that the only risk factor from the National Registry of Cardiovascular Interventions (CENIC, acronym in Portuguese) not in agreement with the other publications was female sex. The role of female sex as a prognostic risk factor in STEMI has been a matter of discussion for decades, with some studies, such as the present one, concluding that female sex is an independent risk factor for worse prognosis and others concluding that it is not.[9] The best explanation was, perhaps, the one provided in the classical publication by Vacarinno et al.[10] many years ago, namely, that there is an interaction between sex, age, and mortality in myocardial infarction with younger women, but not older women, having higher rates of in-hospital deaths than men of the same age;[10] however, a more recent publication suggested that other interactions may be important as well.[11] In a more detailed analysis, we can note that there are many other differences between the Brazilian study and the others. For example, the CADILLAC risk score included 7 variables, including anemia and renal insufficiency,[12] and the ALPHA score had only 5 variables, including heart rate, need for life support, and arterial access, reaching an impressive c-statistic of 0.88 for all-cause mortality at 30 days.[13]

In summary, the study by Castro et al.[1] contributes to a better understanding of the epidemiology of STEMI in Brazil, with a robust number of approximately 27,000 patients analyzed. Its main limitation is likely a potential inclusion bias, since the contribution of the investigators was spontaneous, and, maybe more importantly, an opportunity to develop and validate a Brazilian score for patients with STEMI submitted to PPCI was missed.

Keywords

ST Elevation Myocardial Infarction; Percutaneous Coronary Intervention; Myocardial Reperfusion; Fibrinolityc Therapy; Epidemiology; Mortality

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Percutaneous Closure of Ductus Arteriosus in Preterm Babies: The Initial Brazilian Experience

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Abstract

Background: **The presence of patent ductus arteriosus can be as high as 50% in preterm babies. Hemodynamically significant patent ductus arteriosus is a common cause of delayed weaning of respiratory support and an important risk factor of necrotizing enterocolitis, intraventricular hemorrhage, and bronchopulmonary dysplasia in this population.**

Objective: **The aim of this study is to describe an initial experience of percutaneous closure of the ductus arteriosus in preterm infants weighing less than 2 kg.**

Methods: **This was a prospective study, comprised of 14 consecutive patients submitted to percutaneous closure of ductus arteriosus between March 2020 and February 2021 in 6 institutions in Brazil.**

Results: **Mean gestational age was 28.45±3.14 weeks, mean age at the procedure was 38.85±17.35 days and mean weight was 1.41 ±0.41 kg; 79% of the patients were under mechanical ventilation, and 79% had been submitted, on average, to a 1.5 cycle of non-steroidal anti-inflammatory drugs. Most patients were weaned off of mechanical ventilation in a mean of 12.6 ±7.24 days after the procedure. Success rate was 100%. No procedure-related mortality was observed.**

Conclusion: **This study concluded that percutaneous closure of ductus arteriosus in premature babies below 2 kg has satisfactory results and a low complication rate in this study sample.**

Keywords: **Heart Defects, Congenital; Ductus Arteriosus; Catheterization; Infant; Premature; Neonatology.**

Introduction

The incidence of patent *ductus arteriosus* (PCA) may reach 50% in premature patients. When hemodynamically significant, it can be responsible for extended mechanical ventilation time, in addition to being an important risk factor for necrotizing enterocolitis, intraventricular hemorrhage, and bronchopulmonary dysplasia in this population.[1-5] Some patients benefit from PCA closure in this period of life, with an important progression in ventilatory weaning and improvement of the overall outcome. Historically, the gold standard treatment has been medicinal therapy with non-steroidal anti-inflammatory drugs, even with success rates around 60% and associated with significant adverse effects.[6] Surgical ligation is an alternative for patients who do not have the conditions for an enteral diet or after failure of the medicinal therapy. However, up to 45% of

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the patients develop hemodynamic instability shortly after the surgical procedure.[7-10] Until 2010, only a few isolated cases of percutaneous closure of ductus arteriosus in preterm babies had been reported in the literature. The arrival of the Amplatzer Duct Occluder II Additional Sizes (ADO II AS) (Abbot Structural Heart, Plymouth, MN) device revolutionized PCA treatment in preterm patients weighing less than 2kg. More recently, the Piccolo[tm] (Abbot Structural Heart, Plymouth, MN) device was designed specifically for that population and approved by FDA. The purpose of this study is to describe the initial experience of the percutaneous closure of ductus arteriosus in premature infants weighing less than 2 kg.

Methods

This is a prospective study about the percutaneous treatment of ductus arteriosus in newborn premature infants with ≤ 2 kg of weight, conducted with new devices dedicated to that population. The procedures were conducted in six centers with distinct operators in the period from March 2020 to February 2021. All agreed to participate in this study. Patients were selected based on specific criteria of each center involved in the study. However, all patients whose enteral nutrition was not contraindicated had received oral treatment for ductus arteriosus closure with an unsuccessful application of at least one cycle of non-steroidal anti-inflammatory drugs before recommending the percutaneous procedure. Furthermore, the need for refractory extended mechanical ventilation, associated with the presence of patent ductus arteriosus with signs of volumetric overload and an increase of the left atria, was the main indication for the use of non-steroidal anti-inflammatory drugs and, subsequently, percutaneous closure of ductus arteriosus should the clinical treatment fail.

Collected data: demographic data: gestational age, birth weight, gender, age (in days), and weight (in g) at the moment of the procedure; clinical data: use of mechanical ventilation and vasoactive drugs, associated comorbidities, use of previous drugs for ductus arteriosus closure (ibuprofen, paracetamol and others) and procedure data: vascular access route, device type and size, use of contrast, technical difficulties reported and related complications, such as: pulmonary artery or aorta stenosis, among others. Post-procedure data and evolution, such as the presence of residual shunt, mechanical ventilation and vasoactive drugs weaning, and cardiac function were also recorded.

Statistical Analysis: The quantitative variables were described through mean and standard deviation, as there was no normality violation, assessed through the Kolmogorov-Smirnov Test at the significance level of 5%. The categorical variables were described through absolute (n) and relative (%) frequencies. The SPSS software, version 21 was used.

This study was approved by the Ethics Committee on Research of the Cardiology Institute of RS and follows resolution 466/2012. All patients' legal guardians signed the free and informed consent form.

Description of device and technique

All procedures were conducted in the catheterization laboratory or surgery room, using the C-arm of the respective services, requiring the transportation of the newborn to that sector. The procedure was conducted under general anesthesia. Care with temperature maintenance was taken, with minor variations among the centers and, in general, involving the use of heated mattress or blankets, temperature monitoring with rectal or esophageal thermometer, and/or extra heating by covering the ends and cephalic pole. To reduce the procedure time, blood loss, and delivery of unnecessary fluids, invasive blood pressure measurements were not performed routinely. Puncture of the femoral vein was performed with a 21G needle or a 22G jelco and guided by vascular ultrasonography. A 4F radial introducer was then inserted. A JR curve or vertebral (Cordis or Terumo) catheter (4F) guided by a 0.014″ flexible guide of moderate support was, then, placed through the right chambers and the ductus arteriosus in the descending aorta (Figure 1A). For placing the prothesis delivery system (4Fr TorqVue, Abbot Structural Heart), different supporting techniques can be used, namely: the use of microcatheter on a 0.014″ guide previously placed in the descending aorta (Figure 1B), replacing the 0.014″ guide with a 0.035″ teflonized guide placed in the descending aorta, use of the 0.014″ guide placed in the contralateral femoral artery and pressed externally, or use of two 0.014″ parallel guides to increase the support. To preserve the renal functions of such premature babies, the use of contrast was limited to small manual injections, only when necessary, in order to clarify uncertainties regarding the procedure in some cases (Figure 2). All procedures were guided by transthoracic echocardiography to measure the ductus arteriosus and to place and release the device (Figure 3A and B).

The Amplatzer ADO IIAS and Piccolo (Abbot Structural Heart, Plymouth, MN) devices, both developed for the occlusion of ductus arteriosus in small children, the latter being specific for premature newborn infants weighing more than 700g and commercially available in Brazil from mid-2020, were used in all procedures. Both present similar features regarding structure, as they consist of compact nitinol mesh to minimize the residual shunt immediately after the implant, symmetrical design composed of two articulated discs, and a central belt corresponding to the dimensions of the low-profile device with lengths of 2, 4, and 6 mm, in addition to the delivery system and cable, also flexible to facilitate placing and release (Figure 4A and 4B). The devices were selected to be at least 1 mm larger than the ductus arteriosus in diameter and with a shorter length than the ductus arteriosus to prevent pulmonary artery or aorta stenosis. As previously mentioned, prothesis placing and release were guided by echocardiography, in addition to fluoroscopy, observing the presence of residual shunt or stenosis in the left branch of the pulmonary artery or aorta caused by the device. If present, the device may be replaced before its full release. After the procedure, the patients are transported in a heated incubator back to the neonatal ICU.

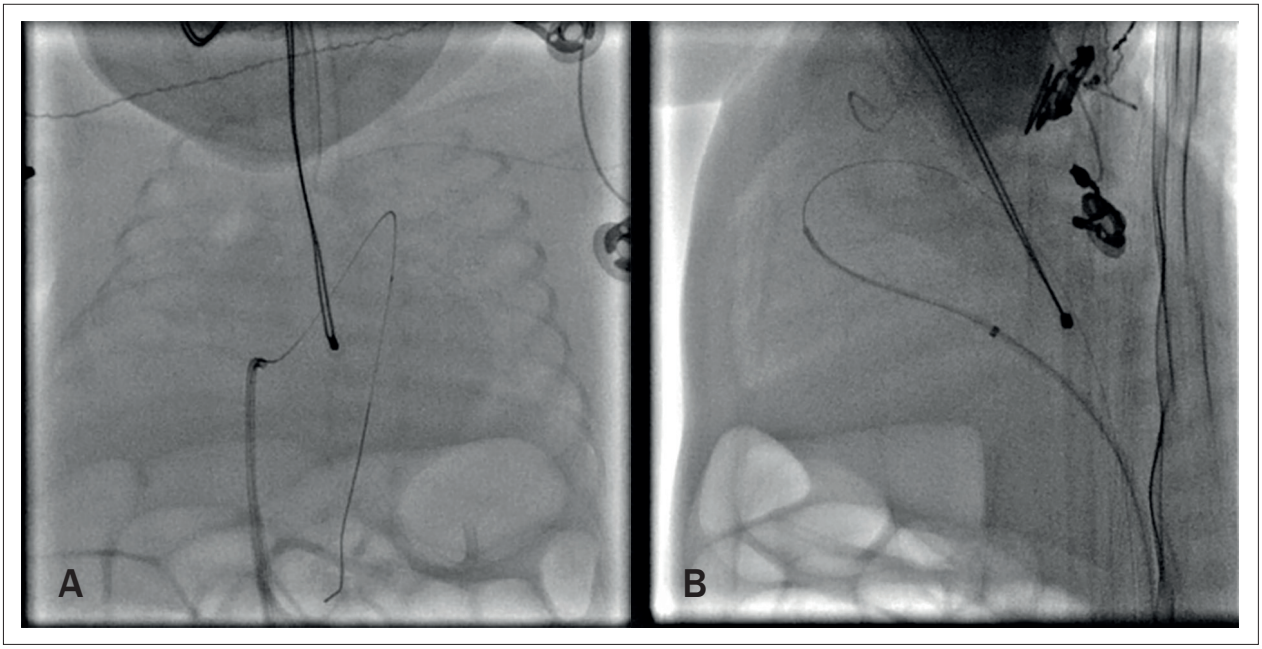

Figure 1 – *A) 0.014" guide crossing the ductus arteriosus inserted through a catheter placed in the right ventricle. B) Microcatheter on 0.014" guide crossing the ductus arteriosus and serving as support to access the delivery system of the device.*

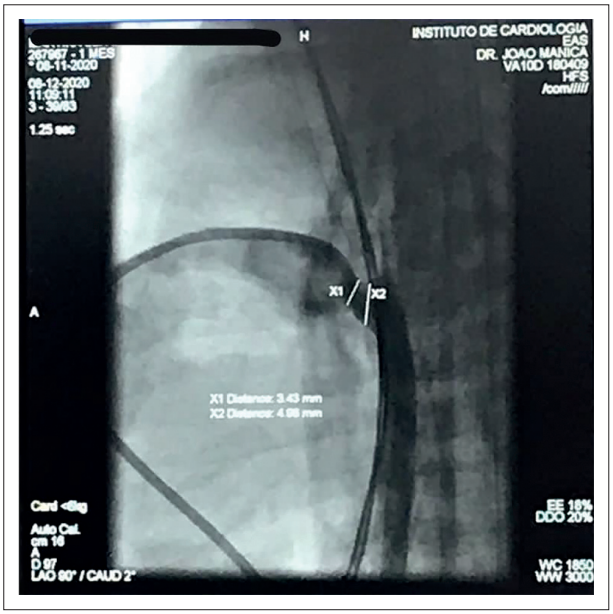

Figure 2 – *Injection of contrast in a 90° position through the release system.*

Results

From March 2020 to February 2021, percutaneous closure of ductus arteriosus in premature infants weighing less than 2 kg was performed in 14 patients by 8 different operators in Brazil. Demographic data are described in Table 1. The average age of the patients at the moment of the procedure was 38.85 ± 17.35 days and the average weight during the procedure was 1.41 ± 0.41Kg. Four patients weighed < 1 kg at the moment of the procedure. Most of the patients needed mechanical ventilation during the procedure (11/14) and at least 6 patients had bronchopulmonary dysplasia diagnosis. Three patients had received no previous cycle of ibuprofen, one due to acute kidney injury and anuria, one due to duodenal atresia, and one due to a tracheoesophageal fistula. The recommendation of the closure of ductus arteriosus was defined by the neonatology team of each institution. Data on the procedure are described in Table 2. The average diameter of ductus arteriosus was around 3.0 0.67 mm, and the average length was 6.9 ± 2.12 mm. No patient was submitted to puncture in the artery. Heparinization after venipuncture was not performed routinely and depends on the operator's choice. The most used device was 0402 ADO II AS or Piccolo (Abbot Structural Heart, Plymouth, MN) in 7 cases, followed by 0502 ADO II AS or Piccolo (Abbot Structural Heart, Plymouth, MN) in 5 patients. In one patient, the ADO II AS 0504 device (Abbot Structural Heart, Plymouth, MN) was implemented, while in another one, the ADO II AS 0406 device (Abbot Structural Heart, Plymouth, MN) was implanted, both longer than the others. One patient needed pulmonary valvuloplasty during the procedure due to pulmonary valve stenosis. Two patients presented a drop in systemic saturation related to tricuspid insufficiency during the procedure. No patient presented significant tricuspid regurgitation after the procedure. The success rate of the procedure was 100%. Two patients presented residual shunt immediately after the procedure, however, in 100% of the cases there was no residual shunt in 7 days. The three patients depending on nasal oxygen catheter discontinued the use in an average of three days after the procedure. Amongst the patients using oxygen catheter, one of them had the closure of ductus arteriosus recommended due to overt cardiac failure, with a weight lower than the birth weight after

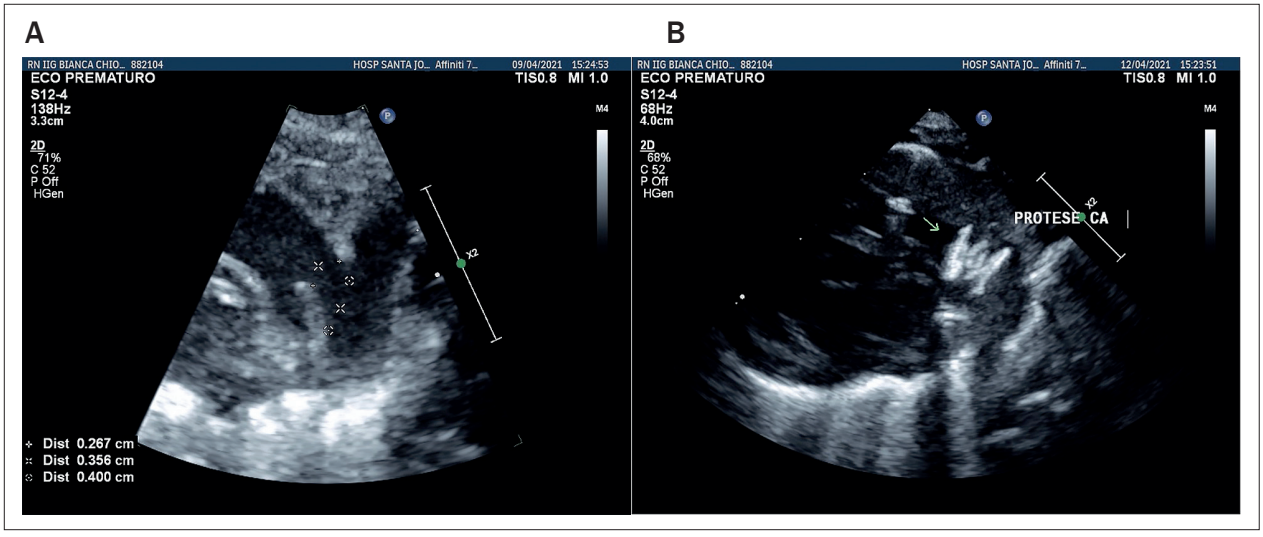

Figure 3 – *A) Echocardiogram performed during the procedure, with measures of the diameters in the aortic and pulmonary ends and ductus length. B) Echocardiogram performed immediately after the release of the device so as to dismiss residual injury such as left pulmonary artery or aorta stenosis.*

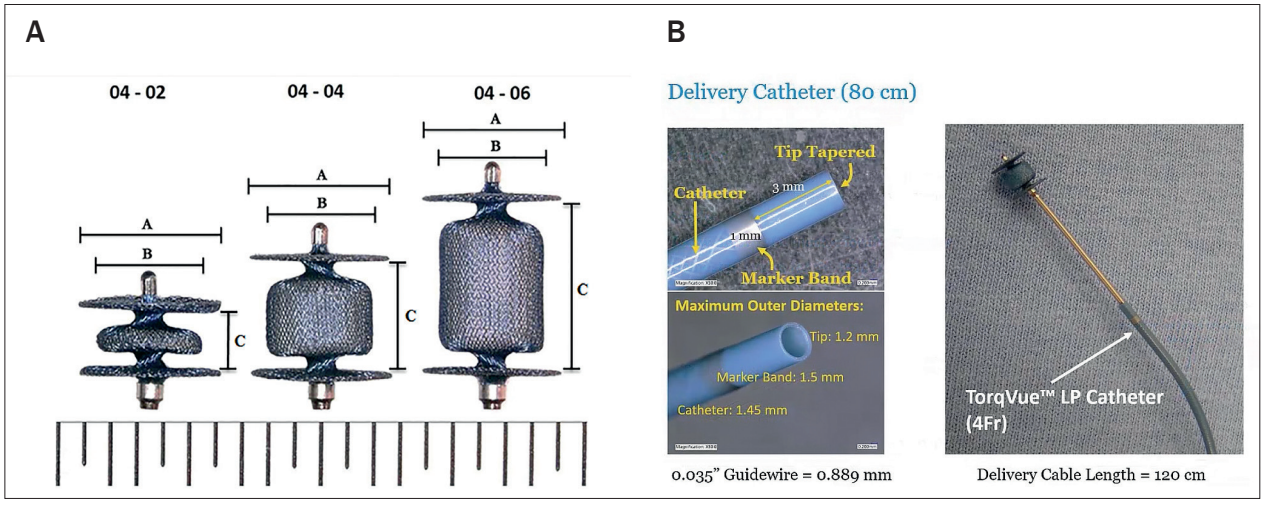

Figure 4 – *A) TorqueVue 4F delivery system and device. B) 4 mm diameter Piccolo™ device in different lengths 2, 4, and 6 mm.*

55 days of life, with use of a nasogastric tube and a clinical picture of important malnutrition. This patient experienced an immediate improvement, returning to oral administration immediately after extubation and discharge after 48 hours in an excellent clinical condition. From the 11 patients in mechanical ventilation, nine patients were extubated within an average of 13.6 ± 7.4 days after the procedure. No complications related to vascular access were reported. Three deaths were reported among the patients in the study, none related to the procedure. One patient improved the renal function, experiencing a return of diuresis two days after the procedure, with an improvement in ventilatory parameters but not evolving to extubation due to a broad intraventricular communication and Edwards syndrome diagnosed 13 days after the procedure. That patient evolved to death by sepsis not related to the procedure after 22 days. Another patient with associated genetic syndrome, bronchopulmonary dysplasia, and severe pulmonary artery hypertension had also not achieved the clinical conditions for extubation and evolved to death 30 days after the procedure due to sepsis. The other patient was extubated 23 days after the procedure, experienced great evolution, and 57 days after the procedure, weighing approximately 2 kg, became infected with SARS-CoV-2 (COVID-19), evolving again to mechanical ventilation and extubation 10 days later. That patient, 80 days after the procedure, weighing around 2300g, using O_2 through nasal catheter at 0.5 L/min due to bronchopulmonary dysplasia, presented sudden mesenteric ischemia, was submitted to urgent surgery, and evolved to death. In this case, it is not possible to dismiss post-COVID-19 thrombosis.

Both patients who needed vasoactive drugs discontinued the use 24 hours after the procedure. No hemodynamic

Table 1 – Demographic data

GA (weeks)	BW	Age (days)	Weight (Kg)	MV*	VAD†	NSAID cycles‡	Comorbidities
28.6	0.58	62	0.965	Yes	No	1	BDP§, HIC//
29.2	1.01	15	0.92	Yes	Yes	No	AKI¶ in anuria, Genetic syndrome[1], wide IVC#
26.6	0.82	41	1.15	Yes	No	2	BPD, ICH, exposed B24
32	1.55	33	1.85	Yes	No	2	Suspected dandy-walker
26	0.85	45	1.55	Yes	No	3	BPD
27	0.7	28	1.2	Yes	No	2	
26	0.9	32	1.5	Yes	No	2	**PVS[2]
25	0.8	45	1.2	Yes	Yes	2	BPD
35	2	55	1.95	No	No	1	
35	1.2	58	2.0	No	No	1	
28	0.8	45	1.45	Yes	Yes	1	BPD, severe PH††, Genetic syndrome
27	0.98	7	0.98	Yes	No	No	duodenal atresia
26	0.58	63	2.0	No	No	2	BPD
27	0.78	15	0.96	Yes	Yes	No	tracheoesophageal fistula, gastrostomy
28.46	0.97	38.86	1.41	79%	28%	1.55	

*GA: gestational age; BW: birth weight; *MV: mechanical ventilation; †VAD: vasoactive drug; ‡NSAID: non-steroidal Anti-inflammatory drug; §BPD: bronchopulmonary dysplasia; //ICH: intracranial hemorrhage; ¶AKI: acute kidney injury; #IVC: interventricular communication; **PVS: pulmonary valve stenosis; ††PH: pulmonary hypertension. [1] Diagnosis of Edwards Syndrome 13 days after the procedure. [2] Pulmonary valvuloplasty performed in the same procedure.*

instability was reported after the procedure. No major complications were reported during or after the procedure. Two patients were diagnosed with mild stenosis in the left pulmonary artery related to the device, with no clinical significance.

Discussion

Premature infant patients have an increased incidence of patent ductus arteriosus due to several factors, including greater sensitivity of prostaglandin receptors and greater exposure to hypoxia and tissue acidosis. Historically, closure of ductus arteriosus in premature infants is performed through the administration of non-steroidal anti-inflammatory drugs or by open surgery, approaches that are limited and not exempt from complications. The first description of percutaneous occlusion of ductus arteriosus in premature infants occurred in 2005 in a patient weighing 1400 grams, who was subjected to closure using "Flipper" coil.[11] In 2007, Roberts P et al.[12] described the percutaneous closure of ductus arteriosus in 10 well-selected patients weighing between 1660 and 2600 grams, once again using "Flipper" coils.[12] Controlled release coils were not developed for the closure of large ductus arteriosus, and often 2 or 3 devices are required to occlude a 3- or 4-mm ductus arteriosus. Francis et al.[13] described percutaneous closure of ductus arteriosus in premature infant patients with an average weight of 1100 g using a specific technique of the simultaneous implant of 2 or 3 coils.[13] However, only 10% of the patients of this institution had favorable anatomy for closure with coils, showing the limitation of that technique in this population. The characteristic and uniform shape of the premature infant's ductus arteriosus also does not favor closure with traditional devices like ADO I (Abbot Structural Heart, Plymouth, MN) or ADO II (Abbot Structural Heart, Plymouth, MN) due to the size of the discs that determine obstruction to aortic and/or pulmonary flows.[14-16] The arrival of the ADO II AS (Abbot Structural Heart, Plymouth, MN) device, with discs only 1 mm larger than the center, allowed safe intravenous percutaneous closure for patients under 3 kg, without the complications previously described with larger devices.[17] The first study with patients under 1 kg displayed promising results with percutaneous closure, with no hemodynamic instability when crossing the tricuspid valve, with a guide and low-profile delivery system and without complications.[18] In 2020, a large French study with 102 patients, 21 of whom under 1 kg, confirmed the excellent results of this technique and showed that most patients in that population of premature infants benefited from devices with only 2 mm of length.[19] Finally, in a study designed for the approval of the device by FDA, 100 premature infant patients were subjected to percutaneous closure with the Piccolo ™ (Abbot Structural Heart, Plymouth, MN) device, specifically developed for percutaneous closure of ductus arteriosus in premature infants, once again with encouraging results, with no residual shunt in 6 months and

Table 2 – Procedure data

ductus arteriosus < diameter (mm)	ductus arteriosus > diameter (mm)	Length	Device	Success	Immediate residual shunt	7-day residual shunt	Major complications	Mild LPA obstruction	Extubation (days)
2	3	5	ADOII AS 0402	Yes	Discreto	No	No	No	7
2.3	3.5	6	ADOII AS 0402	Yes	No	No	No	Yes	No
2	4	4.8	ADOII AS 0402	Yes	No	No	No	No	12
2.5	5.6	6.5	ADOII AS 0402	Yes	No	No	No	No	5
3.5	4.5	5.5	ADOII AS 0504	Yes	No	No	No	No	25
2	3.2	6	ADOII AS 0402	Yes	No	No	No	No	15
3	5	8	ADOII AS 0402	Yes	No	No	No	No	7
3.5	4	12	ADOII AS 0406	Yes	Yes	No	No	Yes	23
3.5	5	10	PICCOLO 0402	Yes	No	No	No	No	
3	4	7	ADOII AS 0502	Yes	No	No	No	No	
3.5	3.8	6	ADOII AS 0502	Yes	No	No	No	No	No
3.8	3.8	4	PICCOLO 0502	Yes	No	No	No	No	7
3.9	4.2	8	ADOII AS 0502	Yes	No	No	No	No	
3.5	3.5	9	PICCOLO 0502	Yes	No	No	No	No	22
3.00	4.08	6.99		100%	14%	0%	0%	14%	13.6

LPA: left pulmonary artery.

without cases of significant aortic or pulmonary obstruction related to the procedure.[20] The Brazilian experience meets literature. It involves 14 cases of patients under 2 kg, with a device occlusion rate of 100% in 48 hours and with no major complications. Only two patients presented non-significant stenosis in the left pulmonary branch, which were not clinically significant. One of these patients, in the beginning of the experience, with long ductus arteriosus (12 mm), was subjected to closure with a 6-mm device, and it is believed that the length of that device is related to the stenosis of the left pulmonary artery. All patients since then have received 2-mm-long devices, except for 1 patient who received a 4-mm-long device. No patient needed blood transfusion due to important bleeding, and all of them evolved favorably from a ventilatory point of view with weaning in an average of 13.6 ± 7.4 days after the procedure. No death related to the procedure was reported, however, three patients did not survive at the end of the study due to other causes, showing that this is a severe population with high mortality rates.

In recent decades, an extensive debate has taken place with the purpose of assessing the benefits of the closure of ductus arteriosus in premature infant patients. The use of non-steroidal anti-inflammatory drugs is still the first therapeutic option today, but it is associated with a greater incidence of renal injury, necrotizing enterocolitis, in addition to low effectiveness. By contrast, patients submitted to surgical closure have an increased risk of low cardiac output, systemic hypoperfusion, and brain damage after the surgery, in addition to being associated with a greater incidence of bronchopulmonary dysplasia and retinopathy of prematurity in long-term follow-up.[21-23] Countless studies faced difficulties to prove the benefits of treating the ductus arteriosus of premature infants with non-steroidal anti-inflammatory drugs or surgery, resulting in an important decrease in recommendations in neonatology centers in the United States and around the world.[24] This change of approach may have contributed to the worst outcome of such patients, as shown recently by a study comparing two samples from different periods in a large neonatology center in the United States.[25] Comparing surgical closure with percutaneous closure in premature infant patients, a faster improvement in the respiratory pattern of patients submitted to percutaneous approach was noted, in addition to a lower rate of complications associated with the procedure.[26] In that context, the arrival of a low-risk therapy is essential to prevent the development of damages related to extended low output which some premature infant patients suffer from, and that are clearly associated with the development of necrotizing enterocolitis, bronchopulmonary dysplasia, and intraventricular hemorrhage. Currently, percutaneous closure of ductus arteriosus in premature infant patients over 700 grams is a safe procedure, with high effectiveness and exceptionally low complication rates, and it has been proven to be associated with the improvement of the prognosis for well-selected patients. Most of the patients in this study experienced improvement in ventilatory parameters after the closure of ductus arteriosus. One doubt remains regarding the best moment for the procedure. The high morbidity rate of the clinical treatment with non-steroidal anti-inflammatory drugs may cause, in the near future, the percutaneous closure of ductus arteriosus to be

the first choice for well-selected premature infant patients with hemodynamic repercussion, left chamber overload, and the risk of prematurity complications associated with ductus arteriosus.

Limitations

The main limitation of this study was the lack of standardization of the recommendation for the closure of ductus arteriosus among the participating centers. Recommendation of closure of ductus arteriosus in premature infant patients has been extensively discussed in recent decades, and still no consensus has been reached among neonatologists regarding the criteria for use of non-steroidal anti-inflammatory drugs, surgery, or even percutaneous closure. This context makes it much more difficult to standardize the recommendation criteria among the different centers in a continental country such as Brazil. Studies such as this, even with a limited number of patients, are extremely important to show the safety of the procedure and the immediate results. Novel studies detailing the indications of the procedure are warranted to define the patients who benefit the most from this technique. Long-term evolution studies must be conducted as well, for an adequate follow-up of the patients, given that it is a new strategy in the management of such patients.

Conclusion

According to the sample presented, percutaneous closure of ductus arteriosus in premature infant patients under 2 kg is associated with the improvement of ventilatory parameters in most of the patients included in this study. Furthermore, it is an effective and extremely safe procedure, with an exceptionally low rate of minor complications. The population that benefits the most from this procedure consists of severe patients with high morbimortality. The development of a safe and effective procedure may mean an advance in the treatment of patent ductus arteriosus in premature infant patients.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Manica JLL; Acquisition of data: Manica JLL, Neves JR, Arrieta R, Abujamra P, Giuliano LC, Coimbra G, Teixeirense PT, Costa RN, Cristóvão SAB, Pedra C; Critical revision of the manuscript for intellectual content: Manica JLL, Neves JR, Arrieta R, Abujamra P, Rossi Filho RI, Giuliano LC, Coimbra G, Teixeirense PT, Rossi JHA, Costa RN, Cristóvão SAB, Pedra C.

Potential Conflict of Interest

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

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Study Association

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Let's Keep Pushing the Envelope

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Short Editorial related to the article: Percutaneous Closure of Ductus Arteriosus in Preterm Babies: The Initial Brazilian Experience

The Ductus Arteriosus (PDA) was the first congenital heart disease to be treated surgically in 1938[1] and recently returned to the spotlight of the pediatric cardiology scenario due to the possibility of percutaneous treatment in a very vulnerable population, premature newborns and with low weight. In fact, the topic Arterial Canal and prematurity never went off the radar of Neonatologists and Pediatric Cardiologists, because treatment has always been a challenge and numerous randomized studies have been done to answer questions about the best way to treat and the impact on survival.

Prematurity is one of the world's greatest public health challenges and has increased incidence worldwide. Recent data show that the incidence of prematurity worldwide was 10.6 per 100 live births. Unfortunately, Brazil is among the 10 countries with the highest incidence of premature births (11.2 per 100 births).[2]

The incidence of the PDA is inversely proportional to gestational age: the more premature (< 24 weeks) and the lower the weight, the higher the incidence and complications. There is a long debate and vast literature about it and it is known that there is an association between the PDA and multiple morbidities, including intracranial hemorrhage, necrotizing enterocolitis, retinopathy and pulmonary bronchodysplasia. Once the neonatologist and the pediatric cardiologist understand the appropriate and necessary time, whenever possible they try to close with non-steroids anti-inflammatory (NSAIDS) as the first option. Unfortunately, the success of the treatment is still relatively low, around 70%, that is, there is a large portion of premature infants who need other strategies for closure, until then done surgically.[3]

This initial Brazilian experience is of great importance yet because it has passed two major tests: technical feasibility and low risk of complications. There was 100% success of the procedure, without major complications (only 2 patients with mild stenosis of the left branch of the pulmonary artery). It is important to contextualize, using the world experience for a better understanding and future strategy. Sathanandam et al.[4] reviewed all cases published using the device Amplatzer Piccolo Occluder: a total group of 327 patients, were successful in 97%, 8 cases of embolism, 4 cases with Aortic Arch obstruction, 4 cases of obstruction of the left pulmonary art, Tricuspid insufficiency in 4 and 2 deaths related to the procedure. Hypothetically, if we include this initial Brazilian experience, there will be a positive contribution to these outcomes. Another positive factor was the impact on the short outcome of patients (79% of patients were able to leave the ventilation of the disease, which is one of the most important and determining factors of the clinical repercussion of the PDA.

By the nature and design of this study, Manica et al.[5] objective was only to describe the experience, using several centers in the country, which implies the no uniformity of the patients selection, different operators, the lack of follow-up of a single protocol and other possible factors that would compromise the analysisof the results. The interesting point, which on the one hand is one of the limitation of this study, on the other hand make these results even more relevant. I would mention as an example the age at the time of the procedure was 38 days +- 17 days, which contributes to a more prolonged exposure to the hemodynamic effects of a significant left-right shunt. The world's trend is to intervein earlier once the clinical indication is made.

The debate will continue about the indication, the ideal time to approach the PDA in premature infants. The direction of this debate has changed. The evolution of the technology (appropriate devices) as safe (or even with less risk) than surgical treatment. However, we need to walk further and longer, maybe at a faster pace. There are also other fronts to be explored, such as the possibility of the bedside procedure guided by the echocardiogram.

The next steps certainly include an alignment with neonatologists and move on to robust, well-designed, prospective, randomized studies comparing the results and outcomes with other forms of treatment, such as the pharmacological. Only in this way can we concretely and permanently aggregate the option of percutaneous treatment for PDA in premature newborns/infants.

The expression "Let's keep pushing the envelope" can be applied in several situations in pediatric cardiology. We must innovate, extend our boundaries, and overcome barriers. In a slightly different version the interventional cardiology deals with very similar situations than pediatric cardiac surgery: the paradigm shift always requires someone or a group to push the envelope. The difference is that the industry/ technology needs to offer resources for this process to move forward, but making the resources accessible through the public health system, in a socioeconomic context of countries as Brazil.

Keywords

Heart Defexts, Congenital/complications; Ductus Arteriosus Patent/abnormalities; Epidemiology; Diagnostic Techniques, Cardiovascular/trends

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Review Article

Critical Analysis and Limitations of the Diagnosis of Heart Failure with Preserved Ejection Fraction (HFpEF)

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Abstract

With the increase in the population's life expectancy and the higher frequency of risk factors such as obesity, hypertension and diabetes, an increase in the prevalence of heart failure with preserved ejection fraction (HFpEF) is expected. However, to date, the diagnosis and treatment of patients with HFpEF remain challenging. The syndromic diagnosis of HFpEF includes several etiologies and diseases with specific treatments but has points in common regarding the clinical presentation, laboratory evaluation related to biomarkers, such as BNP and NT-ProBNP, and echocardiographic evaluation of cardiac remodeling and left ventricular diastolic filling pressures. Extensive randomized clinical trials involving the treatment of this condition have failed to demonstrate benefits to the patient, making it necessary to reflect on the diagnosis, mechanisms of morbidity, mortality and reversibility in this syndrome. In this review, the current concepts, controversies and challenges, especially regarding diagnosis, will be addressed, critically analyzing the *European Heart Failure Association* score for the diagnosis of HFpEF.

Introduction

It is estimated that in the general population over 60 years of age, approximately 5% of the patients are diagnosed with heart failure with preserved ejection fraction (HFpEF), and the prevalence rate varies between 3.8 and 7.4% among the studies, considering the different methodologies used for the diagnosis.[1] With the increase in the population's life expectancy and the higher frequency of risk factors such as obesity, hypertension and diabetes, an increase in the prevalence of HFpEF is expected.[2-4]

However, until now, the diagnosis and treatment of patients with HFpEF remain challenging. The syndromic diagnosis of HFpEF includes several etiologies and diseases with specific treatments but has points in common regarding the clinical presentation, laboratory evaluation related to biomarkers, such as BNP and NT-ProBNP, and echocardiographic evaluation of cardiac remodeling and left ventricular diastolic filling pressures.[1] In contrast to heart failure with reduced ejection fraction (HFrEF), no treatment has yet convincingly shown a reduction in morbidity or mortality in HFpEF, making it necessary to reflect on the diagnosis, mechanisms of morbidity, mortality and reversibility in this syndrome.[5]

In this review, the current concepts, controversies and challenges will be addressed, especially regarding the diagnosis, critically analyzing the *European Heart Failure Association* score for the diagnosis of HFpEF.[1]

European Heart Failure Association score for the diagnosis of HFpEF

In 2019, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) published a new statement on the diagnosis of HFpEF, including the role of clinical comorbidities and a system based on a score with updated values of echocardiographic criteria, biomarker measurement, and the role of stress tests (Table 1).[6-8]

The initial evaluation should take into account the anamnesis, while addressing the risk factors and comorbidities and the presence of symptoms and signs on the physical examination of heart failure that suggest the diagnosis of HFpEF, according to the diagram below (Table 1). In this initial phase, blood tests should be performed, including natriuretic peptides (NPs), as well as an electrocardiogram, exercise tests, 6-minute walk tests or cardiopulmonary tests, in addition to echocardiographic evaluations.[1]

The electrocardiogram (ECG) may show signs of left ventricular hypertrophy (Sokolow-Lyon Index ≥ 3.5 mV)

Keywords

Heart Failure/physiopathology; Diagnostic,Imaging; Echocardiography/methods; Natriuretic Peptides

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Table 1 – Algorithm for the diagnosis of HFpEF, *Heart Failure Association* (HFA) of the *European Society of Cardiology* (ESC)

P	Initial workup	• Symptoms and/or signs of HF
	Step 1 (P): Prestest Assessment	• Comorbidities / Risk factors
		• ECG
		• Standard echocardiography
		• Natriuretic peptides
		• Ergometry / 6 min walking test or cardiopulmonary exercise testing
E	Diagnostic workup	• Comprehensive echocardiography
	Step 2 (E): echocardiographic and natriuretic peptide score	• Natriuretic peptides, if not measured in step 1
F1	Advaced workup	• Diastolic stress test: exercise stress echocardiography
	Step 3 (F1): functional testing in case of uncertainty	• Invasive hemodynamic measurements
F2	Etiological workup	• Cardiovascularmagnetic resonance
	Step 4 (F2): final etiology	• Cardiac or non-cardiac biopsies
		• Scintigraphy / CT / PET
		• Genetic testing
		• Specific laboratory tests

HF: heart failure; ECG: electrocardiogram; CT: computed tomography; PET: positron emission tomography. Adapted from Pieske B et al.[1]

and/or left atrial overload, but its main indication is to detect the presence of atrial fibrillation (AF), which is highly predictive of underlying HFpEF.[9,10]

The rationale for the use of the score is based on the fact that no noninvasive criterion alone is sufficient for the diagnosis of HFpEF and, therefore, an integrated evaluation of clinical information, measurements of serum levels of natriuretic peptide and evaluation of cardiac structure and function by echocardiography is suggested.[10] It is important to remember that the cutoff values may vary according to age, gender, body weight, renal function and the presence of atrial fibrillation. Thus, minor and major criteria are recommended according to the degree of change in the presence of the modifying factors described above.[1]

Natriuretic peptide levels in patients with AF rhythm may be up to three times higher than in patients in sinus rhythm; therefore, the cutoff values are different for these two patient populations.[11,12] To date, definitive cutoff values for the diagnosis of HFpEF in patients with sinus rhythm or AF have yet to be established.[1] The suggested values for the diagnosis of HFpEF are described in Table 2.

Echocardiographic evaluation

Echocardiography is the cardiac imaging method of choice in the evaluation of patients with signs and symptoms of HF. The echocardiogram allows cardiac functional and anatomical evaluation by measuring the diameters and volumes of the cardiac cavities, estimating the left ventricular mass, and analyzing systolic function by the ejection fraction, in addition to global longitudinal and segmental myocardial function. It is the noninvasive method of choice for the analysis of diastolic function, left ventricular filling pressures and pulmonary artery pressures.[1]

Morphological criteria

Measurements of Left Atrial Volume index (LAVI)

LAVI is related to LV filling pressures and other diastolic function indices, being the most accurate measure of chronic LA remodeling when compared to LA diameter and area.[13,14]

In patients without atrial fibrillation (AF) or heart valve disease, LAVI > 34 ml/m^2 is an independent predictor of death, heart failure (HF), atrial fibrillation and ischemic stroke.[15,16] In patients with HFpEF and permanent AF, the LAVI was 35% higher than that of patients with HFpEF in sinus rhythm.[11] Patients with permanent AF may have higher LAVI even in the absence of diastolic dysfunction. Thus, different LAVI cutoff values are recommended for the diagnosis of HFpEF in patients with sinus rhythm and AF (Figures 1 and 2).[15,16]

Myocardial thickness measurement and left ventricular mass estimation

In the HFA score, the left ventricular thickness at the end of diastole of the septal and posterior walls are considered morphological criteria for the diagnosis of HFpEF.[1] These measurements should be obtained preferentially in 2D mode or 2D-guided M mode according to the formula recommended by the American Society of Echocardiography.[17,18]

The left ventricular myocardial mass index (LVMI) is defined as the left ventricular mass indexed by the body surface area.

Hypertrophy is defined as an increase in LVMI according to the following reference values: ≥ 95 g/m² in women and ≥ 115 g/m² in men. [17,18] It is also important to consider the calculation of the left ventricular relative wall thickness (RWT).[17,18] The analysis of LVMI and RWT allows the categorization of hypertrophy into concentric (increase in LVMI and RWT >0.42) and eccentric (increase in LVMI and RWT <0.42) or concentric remodeling (normal LVMI and RWT >0.42).[17,18]

Remodeling patterns or concentric hypertrophy can be seen in patients with HFpEF. The absence of left ventricular hypertrophy, however, does not exclude the diagnosis of HFpEF.[1] Thus, for the diagnosis of HFpEF, the criteria described in Figures 1 and 2 are considered.

Functional criteria

Measurements of LV Global Longitudinal Systolic Strain (GLS)

The measurement of LV global longitudinal myocardial deformation or strain (GLS) by speckle tracking is independent of the ultrasound insonation angle, conferring an advantage over the strain evaluated by Doppler, being considered the technique of choice.[19]

It is important to consider that equipment by different manufacturers can show variations between GLS values acquired from the same patient. An absolute value of GLS <16% can be considered abnormal and a minor criterion for the diagnosis of HFpEF (see Figure 2).[1] Low values of GLS are predictors of hospitalization for HF, cardiovascular death or cardiorespiratory arrest, showing good correlation with LV stiffness and biomarkers.[19-20]

Measurements on conventional doppler

On conventional Doppler, E-wave measurements are obtained by Pulsed Doppler analysis of the mitral valve to calculate the E/e´ ratio and the tricuspid regurgitation (TR) jet peak velocity is obtained by continuous Doppler. These measurements are important for estimating the increase in filling pressures and, consequently, for the diagnosis of HFpEF.[1,19,20]

CLINICAL HISTORY + PHYSICAL EXAMINATION = EVALUATION OF PRE-TEST PROBABILITY

Risk factors and findings consistent with HFpEF in a symptomatic patient
Age > 70 years
Overweight/obesity
Metabolic syndrome/DM
Systemic arterial hypertension
Atrial fibrillation
EKG abnormalities (other than AF)
BNP ≥ 35pg/ml or NT-pro BNP ≥ 125 pg/ml)

Typical symptoms	More specific signs
Shortness of breath	High jugular venous pressure
Orthopnea	Hepato jugular reflux
Fatigue/tiredness	Third cardiac sound
Exercise intolerance	Left deviation of apical ictus
Less typical symptoms	Less specific signs
Nocturnal cough	Pulmonary rales
Weight gain	Tachycardia
Abdominal pain	Hepatomegaly and ascites
Loss of appetite/ weight loss	Peripherical edema
Nocturia and oliguria	

EVALUATION OF CARDIAC BIOMARKERS AND MORPHOLOGICAL AND FUNCTIONAL ECHOCARDIOGRAPHIC PARAMETERS

Echocardiographic and natriuretic peptide heart failure with preserved ejection fraction workup and scoring system (diagnostic workup)

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major Criteria	e´ septal < 7cm/s or e´ lateral < 10 cm/s or E/e´ ratio ≥ 15 or TR velocity > 2,8 m/s (PSAP > 35 mmHg)	LAVI > 34 ml/m² ou LVMI ≥ 149/122 g/m² (M/F) e RWT > 0,42	NT-pró BNP > 220 pg/ml or BNP > 80 pg/ml	NT-pró BNP > 660 pg/nl or BNP > 240 pg/nl
* Minor Criteria	E/e´ ratio 9-14 or GLS < 16%	LAVI 29-34 ml/m² or LVMI > 115/95 g/m² (M/F) ou RWT > 0,42 or LV wall thicknes ≥ 12 mm	NT-pró BNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-pró BNP 365-660 pg/nl or BNP 105-240 pg/nl
Major Criteria: 2 points		≥ 5 points: HFpEF		
Minor Criteria: 1 point		2-4 pontos: Diastolic stress test or Invasive Haemodynamic measurements		

Figure 1 – *Clinical evaluation flowchart integrating risk factors, physical examination, evaluation of biomarkers and echocardiographic analysis. AF: atrial fibrillation;DM: diabetes mellitur; TR: tricuspid regurgitation; LAVI: left atrial volume index; LVMI: left ventricular mass index; RWT: left ventricular relative wall thickness; BNP: B-type natriuretic peptide; GLS: global longitudinal strain; PASP: pulmonary artery systolic pressure; HFpEF: heart failure with preserved ejection fraction. * Minor criterion should not be counted within the same domain.*

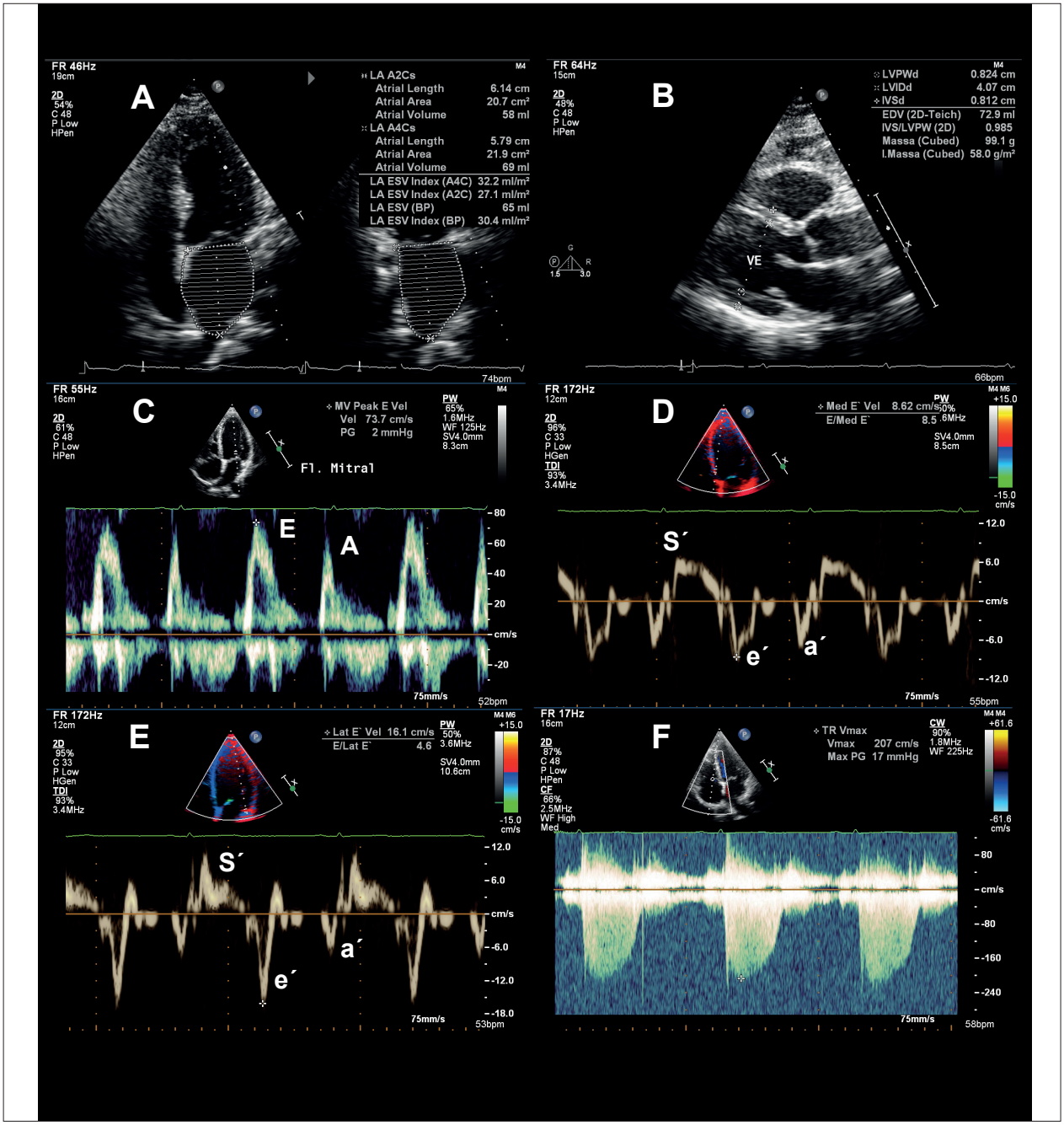

Figure 2 – *Morphological (A and B) and functional (C to F) echocardiographic criteria for the diagnostic algorithm application in patients with suspected HFpEF. The morphological criteria included the measurement of the left atrial volume index (A) and the calculation of the myocardial mass index and relative wall thickness (B). The functional criteria include the E/e´ ratio calculated from the measurement of the E wave on mitral Doppler (C) (v = 73.7 cm/s) and e´ wave septal (D) (v = 8.6 cm/s) and lateral (E) (v = 16.1 cm/s) velocities on tissue Doppler, in addition to the tricuspid regurgitation jet peak velocity (v = 2.07 cm/s) to measure the pulmonary artery systolic pressure (F). v: velocity.*

High levels of pulmonary artery systolic pressure (PASP) and right ventricular function reduction are important predictors of mortality in patients with HFpEF. TR jet peak velocity values >2.8 m/s are indirect markers of diastolic dysfunction and are associated with the HFpEF diagnosis.[21-24]

Tissue doppler measurements

The measurements of early diastolic peak velocities (e´ waves) in the septal and lateral walls by pulsed tissue Doppler constitute a key parameter in patients with HFpEF.[1,25] All measurements should represent the mean of three or more consecutive cardiac cycles, and preferably,

the measurements of the e´ wave of the septal and lateral velocities should be performed, especially for the calculation of the E/e´ ratio.[25]

The major determinant of the early diastolic velocity of the mitral annulus is LV relaxation. The e´ wave reflects the LV relaxation and is influenced by preload.[26,27] The e´ wave velocity decreases with age; therefore, reference values are recommended according to the age range to calculate the score for the HFpEF diagnosis (Figures 1 and 2).[28]

The average E/e´ ratio of the septal and lateral walls reflects the capillary pressure in the absence of pulmonary stenosis and correlates with left ventricular stiffness and the presence of fibrosis, in addition to being less dependent on age and aging than the e' wave.[1,25,29,30] This measure also has diagnostic value during physical effort, being little influenced by volumetric changes but influenced by the left ventricular hypertrophy severity.[1,31-33]

Diagnostic evaluation by echocardiographic and natriuretic peptide score

The score includes functional, morphological and biomarker-related domains, with each major criterion assigning 2 points and each minor criterion assigning 1 point to the score (Table 2). It is important to remember that not all parameters of each domain can be analyzed. A total score ≥ 5 points is considered diagnostic for HFpEF, while scores ≤ 1 point indicate a very unlikely diagnosis and make the investigation of differential diagnoses mandatory.[1] Patients with intermediate scores require an additional complementary assessment (Step 3), as follows. In a structured manner, in practice, steps 1 and 2 can be summarized in the flowchart of Table 2.

Figures 3 and 4 illustrate examples of the score application in real cases.

In the real-life case of Figure 3, it is important to note that although the patient meets the minor morphological criterion of relative wall thickness >0.42, as she has already received a score within the morphological domain for a major criterion (2 points) due to the dilation of the indexed volume, the minor criterion is not counted within the same domain.

This case is also illustrative because it shows the limitation of the suggested measurements in real cases. In this patient, it was not possible to measure the pulmonary artery systolic pressure due to the absence of tricuspid regurgitation, which is not uncommon in daily practice.

In addition, this patient had limitations in performing the test under exertion due to obesity and degenerative joint abnormalities and did not continue the etiological investigation suggested by the HFA protocol.

It is important to consider that in patients diagnosed with mitral stenosis, the E wave may not reflect diastolic function, as in patients with significant tricuspid regurgitation, in which the tricuspid regurgitation velocity may be reduced due to the equalization between RV and RA, underestimating the measurement of PASP.[25]

Step 3 (F1): Advanced Evaluation - Functional Test in case of uncertainties

In patients with intermediate diagnostic scores, the performance of complementary evaluation with echocardiography under physical exertion is indicated because many patients only exhibit symptoms on exertion. Thus, symptoms compatible with HFpEF can be confirmed by hemodynamic abnormalities, such as reduced cardiac output, reduced systolic volume and increased LV filling pressures at rest or during physical exertion.[1,34]

The stress echocardiography may disclose systolic and diastolic dysfunction during exercise testing. The parameters most frequently used for this analysis when HFpEF is suspected are the E/e´ ratio and the TR jet peak velocity. It is advisable to perform the test at rest and throughout the exertion or immediately after the peak of the exertion. However, to date, there are no universally accepted protocols, and the tests are performed according to the availability and experience of each service.[1,34]

The E/e´ ratio and the TR jet peak velocity should be acquired at baseline and at each stage, including the peak of exertion, and during the submaximal stage or during the first two minutes of the recovery phase.[34]

The stress echocardiogram should be considered abnormal if the E/e´ ratio obtained at peak effort is ≥ 15, with or without an increase in the TR peak velocity to a value >3.4 m/s. An isolated increase in the TR peak velocity should not be considered for the diagnosis of HFpEF, as this change may be caused merely by a normal hyperdynamic response to exercise (with increased pulmonary flow) in the absence of LV diastolic dysfunction. An E/e´ ratio during exertion ≥ 15 adds 2 points to the HFA score. An E/e´ ratio ≥ 15 and TR peak velocity >3.4 m/s add 3 points to the score from Step 2 (E). The association of the combined score from Step 2 (E) and Step 3 (F1) ≥ 5 confirms, then, the diagnosis of HFpEF.[1,34]

However, some limitations may occur: the E/e´ ratio might not be analyzed in approximately 10% of patients during submaximal effort (20 W), the TR peak velocity was measurable in only 50% of patients, and approximately 20% of the patients could be considered false positive cases.[31] In addition, in our country, the availability of services that perform echocardiography under physical exertion is very scarce, even in cities with large cardiology referral services. As shown in Figure 4, some patients are not capable of performing the test under physical exertion, either due to symptomatic limitations or functional limitations, such as the coexistence of orthopedic, joint, vascular or neurological diseases.[34]

Finally, the data obtained from the stress echocardiography are not sufficient to replace invasive hemodynamic measures. When the score remains <5 points or if the stress echocardiogram cannot be performed, the invasive evaluation is recommended in case of doubt.[1] The last European Association of Cardiovascular Imaging (EACVI) guideline[25] recommends invasive hemodynamic evaluation under stress; however, this test is very rarely used and only in specific patients in the Brazilian

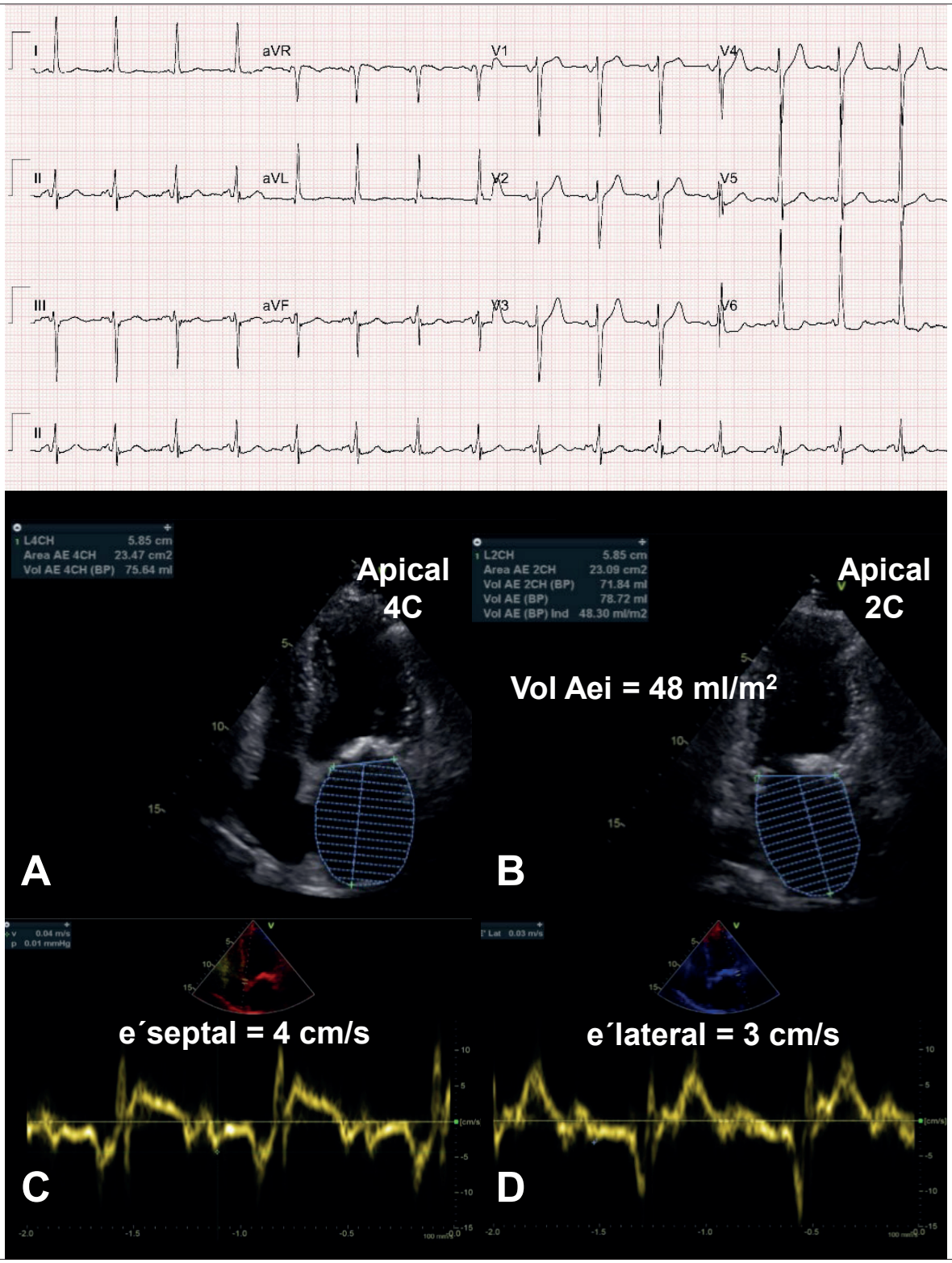

Figure 3 – *Illustrative example of the diagnostic score application in a patient with suspected HFpEF. A 64-year-old female patient had a history of metabolic syndrome (obesity grade III – Body Mass Index: 35.6, systemic arterial hypertension and diabetes mellitus) and complaints of dyspnea on minimal effort (FC III NYHA). The ECG (above) showed signs of left ventricular hypertrophy according to the Sokolow-Lyon criteria. The TTE displays an interventricular septum and posterior wall thickness of 12 mm and LVMI: 105 g/m² (1 point). The left atrial volume index estimated at the apical 4C (top left) and apical 2C (top right) views was 48 mL/m² (2 points). Tissue Doppler shows e' wave septal velocity = 4 cm/s (bottom left) and lateral e´ wave velocity = 3 cm/s (bottom right) (2 points). Thus, by applying the score for the diagnosis of HFpEF, the patient attained 5 points and, therefore, the HFpEF diagnosis was confirmed.*

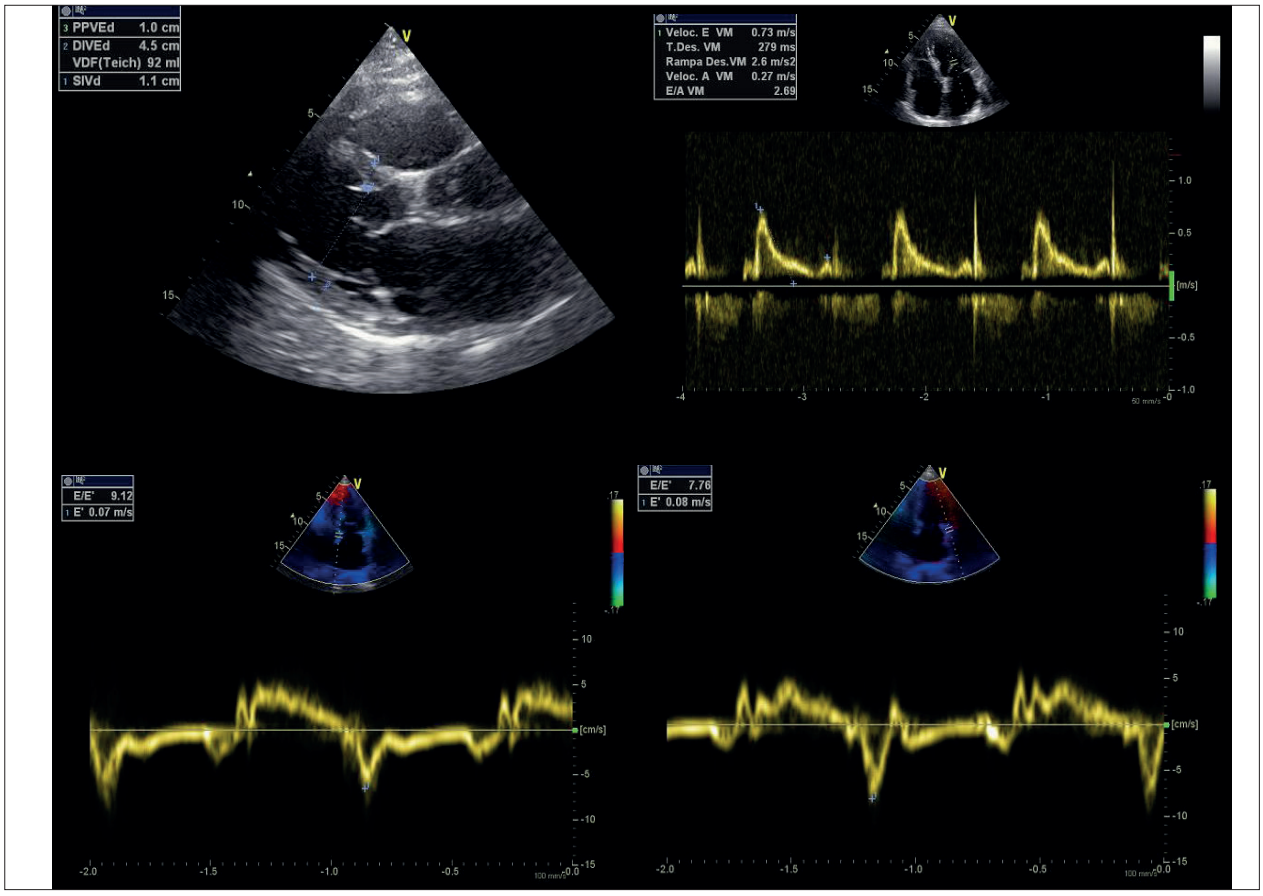

Figure 4 – *A 78-year-old patient with obesity, systemic arterial hypertension, type 2 diabetes mellitus, paroxysmal atrial fibrillation, in NYHA FC II. On the TTE, LA = 50 mm, LAVI = 38 mL/m² (2 points), LV mass index: 89 g/m², LV relative wall thickness = 0.47, non-analyzable PASP and E/e´ ratio = 8.8. BNP = 367 pg/mL (2 points). After applying the score for the diagnosis of HFpEF, the patient attained 4 points and, therefore, had an inconclusive diagnosis of HFpEF.*

population. In clinical practice, the invasive evaluation can be performed to confirm the elevation of LV filling pressures at rest (LV end-diastolic pressure ≥ 16 mmHg), confirming the HFpEF diagnosis.[1] An invasive evaluation should also be considered for the exclusion of coronary disease or in specific populations.[35]

Step 4 (F2): Etiology F final

The majority of HFpEF cases are related to risk factors and comorbidities; however, the possibility of a specific underlying etiology should always be considered, such as hypertrophic cardiomyopathy, myocarditis, autoimmune diseases, infiltrative cardiomyopathies, deposit diseases and endomyocardial fibrosis.[36-38] Once the diagnosis of HFpEF syndrome is made, the investigation of each specific etiology should be guided by clinical suspicion and conducted in a targeted manner, depending on the presumptive diagnosis. The diagnosis of specific etiologies is essential, because these findings can be translated into specific therapies. It is also important to consider that etiologies unrelated to the myocardium may present a clinical picture similar to that of HFpEF, such as constrictive pericarditis, primary valve diseases and high output heart failure.[1]

Limitations, perspectives and final considerations:

HFpEF is a clinical syndrome with multiple contributing factors, etiologies and distinct pathophysiological mechanisms; hence, it is impossible to create a single algorithm capable of diagnosing such a diverse group of diseases.[39] In addition, the results of the tests may be limited in this group of patients at different stages of the disease and with heterogeneous etiologies.[1]

The HFA score does not assign a score to the clinical risk factors and signs and symptoms on physical examination as proposed by American authors.[10] It is important to consider these factors because, individually, the other parameters dissociated from the clinical condition and physical examination lose diagnostic accuracy. Moreover, clinical conditions other than HF, for example, may lead to elevated serum levels of biomarkers, such as chronic kidney and lung diseases and infectious processes, limiting their application in the context of patients with suspected HF, since the occurrence of these diseases in this group of patients is not uncommon.[40]

Currently, distinct phenotypes have also been recognized in the clinical presentation of patients with HFpEF, such

as the characterization of left atrial function, pulmonary pressures and right ventricular function.[41] In this context, other echocardiographic parameters may be incorporated into the score in the near future, increasing the diagnostic sensitivity and detailing the pathophysiology of HFpEF.

Variables such as left atrial strain indices are increasingly important in the evaluation of diastolic function and left ventricular filling pressures. The development of software dedicated to the evaluation of LA strain has allowed a more accurate evaluation of left atrial function and the analysis of left atrial stiffness, a parameter that shows a logarithmic correlation with LV filling pressures and better accuracy in predicting values >15 mmHg of the LV end-diastolic pressure in relation to the E/e´ ratio.[42-44] In addition, other parameters, such as right ventricular deformation (global or free wall), also have a promising role in the diagnosis of HFpEF.[45-46]

In the near future, it will probably be possible to perform a noninvasive morphological analysis of cardiac chamber volumes integrated with hemodynamic parameters such as systolic volume, cardiac output and LV filling pressures in association with new markers of systolic and diastolic function, adding diagnostic and prognostic value to the significance of LVEF in the characterization of HF.[47-49]

The use of modern imaging methods in an integrated manner can provide the abovementioned data in addition to dynamic analyses on arterial and endothelial function and myocardial perfusion, which can be coupled with the demographic data, including classic risk factors and new biomarkers, with data on proteomics, metabolomics and genetics. This information may be processed by artificial intelligence and may be useful to define the pathophysiology and diagnosis, in addition to therapeutic guidance and outcome prediction.[47-49]

Thus, despite the development of updated scores for the diagnosis of HFpEF in the light of new knowledge, especially in relation to echocardiographic techniques and biomarker values, refinements and incorporation of more clinical and echocardiographic indices are still needed, which will allow not only the syndromic diagnosis but also recommendations on the final etiology of patients with HFpEF.

Author contributions

Conception and design of the research: Hotta VT, Vieira MLC; Acquisition of data and Analysis and interpretation of the data: Hotta VT; Writing of the manuscript: Hotta VT, Rassi DC, Pena JLB, Vieira MLC; Critical revision of the manuscript for intellectual content: Hotta VT, Rassi DC, Pena JLB, Vieira MLC, Rodrigues ACT, Fernandes F, Cardoso J, Ramires F, Mady C.

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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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COVID-19 Myocarditis Mimicking ST-Segment Elevation Myocardial Infarction

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Introduction

The new SARS-CoV-2, that causes the coronavirus disease 2019 (COVID-19) has proven to be a virus that affect not only the respiratory system, but to cause several systemic manifestations, including cardiovascular ones.[1,2] Patients with previous cardiovascular disease who develop myocardial injury usually have worse outcomes,[2,3] such as acute coronary syndrome (ACS)[4,5] and myocarditis.[6-8] Myocarditis is mostly asymptomatic but can manifest with angina, cardiac failure, and arrythmias.[9-12]

The clinical diagnosis of myocarditis without the aid of complementary exams is usually difficult to be made. A meta-analysis with 2,866 with myocardial infarction without obstructive coronary artery disease (MINOCA) who underwent cardiac magnetic resonance (CMR) showed a prevalence of myocarditis of 34.5%.[11] In COVID-19, a study carried out in Germany reported that 60% of recently recovered patients had signs of myocardial inflammation at CMR.[13]

Case report

Male patient, 43 years old, without comorbidities, admitted to a primary care emergency. The patient complained of typical angina in the form of retrosternal pain radiating to the left arm, for five days, triggered by exertion and relieved with rest, lasting a few minutes, associated with functional class II dyspnea. On admission day, the patient had strong, debilitating pain of the same pattern during exertion, with no improvement with resting. The pain had started about one hour before admission. The patient reported a flu-like illness two days before the first episode of pain, temperature of 37.7ºC. His wife had a flu-like illness initiated ten days before and had received a diagnosis of COVID-19.

Keywords

Myocarditis, Acute Coronary Syndrome, COVID-19, Magnetic Resonance Imaging

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On physical examination, the patient was conscious, fully oriented, eupneic, with peripheral oxygen saturation of 98% on room air, afebrile, heart rate of 80 bpm, blood pressure of 120x90mmHg, normal cardiac and pulmonary auscultations, normal abdominal examination, and no signs of congestion.

Twelve-lead electrocardiogram (ECG) (Figure 1) showed sinus rhythm with 2-mm inferior wall (D2, D3 and aVF) and anterolateral ST-segment elevation (V4-V6). The patient received dual antiplatelet therapy with acetylsalicylic acid (ASA) and clopidogrel, and enoxaparin for anticoagulation, and antithrombotic therapy with alteplase two hours after pain onset. The patient had partial improvement, but the ST-segment elevation was maintained.

Approximately eight hours after thrombolysis, the patient was transferred to a tertiary hospital. The patient underwent catheterization, which revealed no coronary atheroma or thrombosis, and normal ventriculography. The first high-sensitivity troponin was >25,000 ng/L (VR <58 ng/L) and CK-MB mass of 96 ng/mL (VR <4.4 ng/mL). Chest X-ray revealed little opacity of lung bases. Due to suspected COVID-19, a rapid antigen test was performed, with a negative result, in addition to two RT-PCR tests for SARS-CoV-2 (oropharyngeal swab) on separate days, with negative results.

The patient underwent echocardiography, which showed preserved ejection fraction (65%), with no segmental wall motion abnormalities. Chest computed tomography (Figure 2) revealed bilateral ground-glass opacities, predominantly in lung basis, compatible with viral pneumonia, including COVID-19. The extent of pulmonary involvement was estimated as 25-50%.

Considering that the patient had ST-elevation ACS and absence of coronary lesions or segmental systolic dysfunction, on the fourth day of hospitalization, CMR was performed (Figure 3). Non-ischemic delayed myocardial enhancement was detected, in the mid and basal segments of the lower lateral wall, and in the apical segment of the lateral and inferior walls, mild myocardial edema, suggestive of acute myocarditis. Quantitative analysis with parametric (T1 and T2) mapping was not performed.

The patient had a good clinical course, without complications, and was discharged on the sixth day of hospitalization for outpatient follow-up. The CMR result was reviewed, and it was decided to discontinue dual antiplatelet therapy and to continue atorvastatin. ECG did not show the typical pattern of infarction, evidenced by the maintenance of sinus rhythm with ST elevation in V4-V6 and D2, and change in repolarization in D3 and AVF.

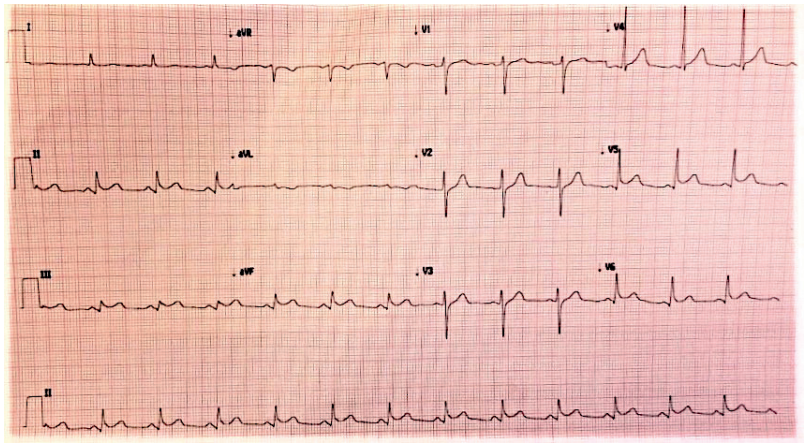

Figure 1 – *Electrocardiogram on admission, showing inferior and lateral wall ST-segment elevation.*

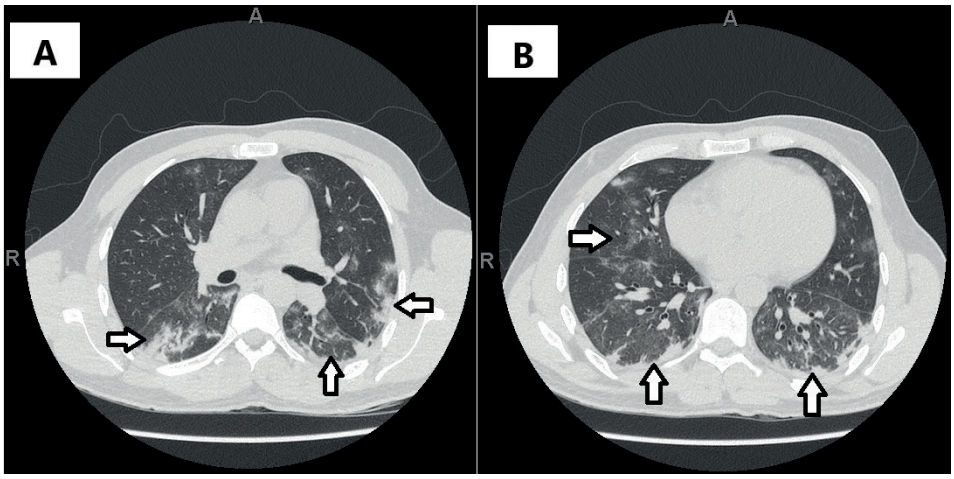

Figure 2 – *Chest computed tomography showing bilateral ground-glass opacities, predominantly in lung basis, compatible with COVID-19. Involvement of right and left lower lobes, and the lower portion of the right upper lobe (A); areas of ground-glass opacities and peripheral confluent consolidation in lower lobes (B).*

The patient had a positive SARS-CoV-2 antibody test on day of discharge (874 units of bound antibodies/mL, VR ≥ 33.8/mL – WHO standards). The patient had not been vaccinated against COVID-19.

Discussion

Because of its heterogenous presentation, the diagnosis of myocarditis remains a challenge.[12] The same occurs in patients with ACS and a presumed diagnosis of infarction but with no coronary changes that explain it.[14] Several studies with CMR have shown that most of these patients have in fact myocarditis.[14,15]

In the United Kingdom, 79 patients admitted for ACS with elevation of troponin levels and no injury at angiography were submitted to CMR. Of these patients, 81% were diagnosed with myocarditis, with myocardial edema in 58% and compatible enhancement in 92%.[15] In another English study 60 patients were submitted to CMR within three months of the episode of chest pain, with increased troponin and no obstructive lesions at catheterization. A diagnosis was established in 65% of cases, and 50% of patients had myocarditis. Of these patients, 40% had elevation of ST segment and 31% received thrombolytic treatment.[14] Although the improvement of pain with thrombolytic agents is not well explained, a cause-effect relationship is not implied. The patient had already experienced chest pain with spontaneous resolution for days before the worst pain episode, and no typical temporal pattern of infarction was seen on ECG.

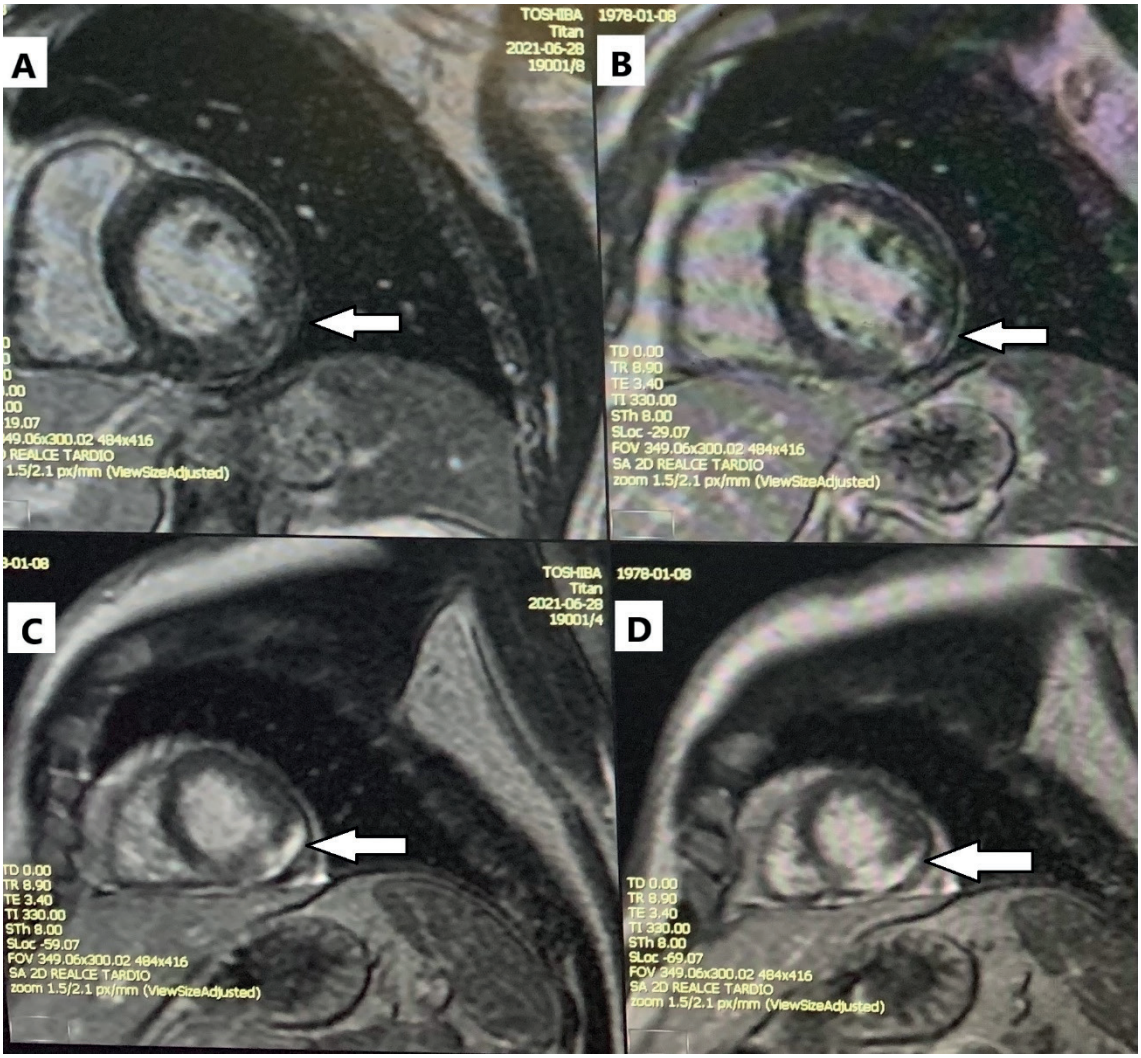

Figure 3 – *Cardiac magnetic resonance showing late gadolinium enhancement of non-ischemic pattern, predominantly in mid-myocardium and subendocardium, compatible with myocarditis. Delayed myocardial enhancement in the basal (A) and mid (B) segments of the lower lateral, apical segment of the lateral and inferior walls (C), apical segment of the inferior wall (D). Areas affected are indicated by white arrows.*

Endomyocardial biopsy is still the gold standard for the diagnosis of myocarditis.[9,12,16] Nevertheless, due to its invasive nature, potential complications, low availability and diagnostic limitations, the procedure is not performed routinely, especially in non-severe cases, as in this reported case. CMR has already been well established as a non-invasive alternative for this purpose.[9,12,14-16] This method combines safety, anatomical assessment, consistency between observers, and quantitative accuracy, providing diagnostic information in many diseases.[16]

The European Society of Cardiology (ESC) suggests clinical criteria and reference results for non-invasive complementary tests (e.g., ECG, troponin, echocardiogram and CMR) for the diagnosis of myocarditis, making the endomyocardial biopsy not necessarily mandatory.[12] The Lake Louise criteria are the diagnostic CMR imaging criteria for myocarditis and involve: 1- measurement of myocardial signal intensity in T2 compatible with edema; 2- early gadolinium enhancement in T1; and 3- late gadolinium enhancement in T1.[12,16] The pattern of injury after an ischemic insult is characterized by transmural progression, including the subendocardium. The non-ischemic pattern varies from non-transmural, mainly mid-myocardial and subendocardial, multifocal, until transmural, which may make differentiation difficult.[12-16]

The presentation of COVID-19 with ACS has been documented,[4,5] and associated with a poor prognosis. In a Brazilian study, hospital mortality rate was 23.7%; 12.5% of 152 patients did not have obstructive lesions.[5] In a small Italian study, 40% of ACS patients did not have obstructive coronary disease, with a mortality of 40% in a mean follow-up period of two weeks. Of these patients, 85% did not

Table 1 – Temporal progression of laboratory test results during hospitalization

	First day	Second day	Fourth day	Sixth day	RV*
Troponin, ng/L	> 25000	10128	4565	2330	< 58
CK-MB, ng/mL		96	9.2	0.61	< 4.4
Creatinine, mg/dL		0.83	0.98	0.77	0.7 - 1.3
Urea, mg/dL		25	41	25	15 - 39
Sodium, mmol/L	137	136	139	140	136 - 145
Potassium, mmol/L	3.5	4.0	4.0	4.6	3.5 - 5.0
Magnesium, mg/dL	2.5	2.3	2.1	2.1	1.8 - 2.4
C-reactive protein, mg/L		35.3	9.7	4.6	< 5
Hemoglobin, g/dL		12.3	10.3	11.3	13.5 - 17.5
Hematocrit, %		37	31	34	39 - 50
Leukocytes, U/mm³		10800	9360	10200	3500 - 10500
Platelets, U/mm³		818000	699000	612000	150000 - 450000
Total cholesterol, mg/dL				205	< 190
HDL cholesterol, mg/dL				23	> 40
LDL cholesterol, mg/dL				104	< 130
Triglycerides, mg/dL				388	< 150
Glycated hemoglobin, %				5.0	< 5.7

**RV: reference value HDL: high-density lipoprotein; LDL: low-density lipoprotein.*

have respiratory symptoms or positive test for COVID-19 at the time of catheterization, with ST elevation ACS the first clinical manifestation of COVID-19.[4]

Myocardial injury is strongly correlated with a worse prognosis of COVID-19, including fatal outcomes.[1-3,17] The incidence of myocarditis caused by SARS-CoV-2 is still unknown, despite several cases reported.[1,6,7,13,17,18]

We report a case of a COVID-19 patient who developed with ST elevation ACS, underwent thrombolysis with catheterization, with no obstructive lesions and no echocardiographic changes, and a final diagnosis of myocarditis determined by CMR. The long-term consequences are also unknown, reinforcing the need for follow-up studies.[7,17]

The diagnosis of myocarditis is not obvious in the case of angina with electrocardiographic changes and elevation of troponin, requiring the exclusion of coronary disease by catheterization, to fulfill the current criteria of MINOCA.[11,19] Once the diagnosis could not be established, it is recommended to continue with the etiologic investigation, preferably with CMR.[19] There is no consensus on the best moment or how early CMR should be performed, but it is known that the test is feasible as soon as the patient is clinically stable. This report addresses several clinical conditions involved in the diagnostic challenge of myocarditis, reinforcing the role of CMR in this case, of a COVID-19 patient with no history of coronary disease, who developed ST elevation ACS.

Author Contributions

Conception and design of the research: Conceição AM, Pereira CAC; Acquisition of data: Conceição AM, Rahal MJ; Analysis and interpretation of the data: Pereira CAC, Rahal MJ, Ishikawa WY, Rochitte CE; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Conceição AM, Pereira CAC, Rahal MJ, Ishikawa WY, Rochitte CE.

Potential Conflict of Interest

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

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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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Tetralogy of Fallot Associated with Aberrant Right Subclavian Artery. Clinical Implications

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Abstract

Since the first description of Tetralogy of Fallot (ToF) in 1671 by Niels Stensen and in 1888 by Étienne-Louis Arthur Fallot, numerous papers have reported on this anomaly, along with its variants and concomitant cardiovascular anomalies. Aberrant right subclavian artery (ARSA) is the most common anomaly of the aortic arch. Different from the left aberrant subclavian artery, occurrence of ARSA in ToF-patients has only casuistically been reported so far. The present study reports on two ToF-patients with ARSA. It is important to note that knowledge of the coexistence of both anomalies has highly practical points during surgical or endovascular corrections of congenital heart defects (including ToF).

Introduction

Anomalies of the aortic arch may be isolated or may be associated with other congenital heart defects (CHD). A detailed assessment of the aortic arch (including its laterality and branching pattern) is crucial during the diagnostic exams of CHD, as it may influence the surgical incision or cardiopulmonary bypass.[1] An aberrant subclavian artery (ASA) or arteria lusoria is a common aortic arch anomaly. This may originate from the left-sided aortic arch (LAA) or from the right-sided aortic arch (RAA). An aberrant right subclavian artery (ARSA) is the most common LAA-anomaly (prevalence 0.5%-2%). More than 20 aortic arch configurations have been described. Recently a new classification of ASA has been proposed, which distinguished four main types of ASA (based on the aortic arch laterality and the presence of common carotid trunk).[2] Next, tetralogy of Fallot (ToF) is not rarely accompanied by RAA (up to 37% in a study by Khan et al.[3] An aberrant left subclavian artery (ALSA) branching-off from RAA may also be associated with ToF (21.4% in our previous cardiac computed tomography (cCT) study on ALSA-cohort.[4]

Keywords

Heart Defects Congênital; Tetralogy of Fallot; Aorta, Thoracic; Esophageal, Obstruction; Subclavian, Artery

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Different from ALSA, the occurrence of ARSA (from LAA) in ToF-patients has, to date, been reported only casuistically. Oswal et al.,[5] identified 8 ARSA patients among 257 ToF patients.[5] De Luca et al.,[6] reported one ARSA patient with ToF identified among 3,334 patients (prevalence of ARSA and ToF - 0.03%),[6] Finally, Nakajima et al.,[7] identified seven ASA patients among 233 ToF patients. However, no details were given whether these ASA originated from LAA or RAA.[7] The present study reports on two adult patients who underwent surgical corrections of ToF in their childhood and were admitted for further assessment. Imaging modalities in both of the children revealed the presence of ARSA originating from LAA.

Patient 1

A twenty-six-year-old female patient underwent complete ToF correction at the age of three and remained in functional class II, according to New York Heart Association (NYHA). Transthoracic echocardiography (TTE) revealed a heavily calcified pulmonary homograft with a pressure gradient of 72/56 mmHg (Fig.1A), moderate pulmonary regurgitation (PR), and a hypertrophied wall (12mm) of the right ventricle (RV). Otherwise, the systolic function of both ventricles was preserved. Performed cCT revealed LAA (Figure 1B) with ARSA (Figures 1C, D). Due to calcification of the homograft, the patient was not qualified for percutaneous treatment of the stenotic homograft and was treated conservatively. TTE performed 10 years later showed no increase in the homograft's pressure gradient. Repeated cardiopulmonary exercise testing (CPET) showed a decreased respiratory oxygen uptake: 15.3ml/kg/min (43% of the predicted value) after 2 years, and 16.9ml/min/kg (36% of the predicted value) 10 years later.

Patient 2

A twenty-year-old male patient underwent a Blalock-Taussig shunt at one year of age, with complete ToF correction at the age of 3 years. However, he required a re-operation nine months later for a significant residual left-to-right shunt through the congenital ventricular septal defect and replacement of the unicuspid pulmonary homograft with a bicuspid pulmonary homograft. He remained in NYHA class II. His most current TTE revealed significant PR in the homograft (Fig.2A, B), together with an enlarged RV-inflow tract (54mm) with borderline RV systolic function (RV S' 9cm/s). Systolic function of the non-dilated left ventricle was preserved. Both cCT and cardiac magnetic resonance revealed LAA (Figure 2C)

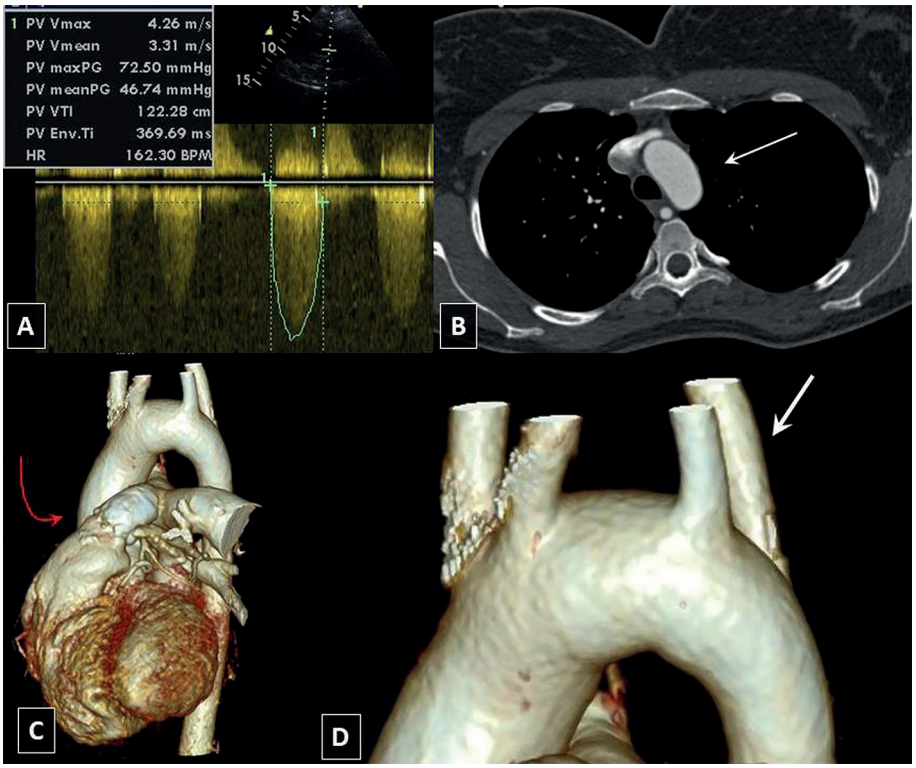

Figure 1 – *Patient 1 A) Transthoracic echocardiography, parasternal short axis view. Significant pressure gradient across the pulmonary homograft; B) Cardiac computed tomography, axial plane. White arrow indicates left-sided aortic arch; C) Cardiac computed tomography. Visible calcifications of the pulmonary homograft at the level of the pulmonary valve (red arrow); D) Magnification of panel "B" with a focus on the right aberrant subclavian artery (white arrow) branching-off from the left-sided aortic arch.*

with ARSA (Figures 2D, E). Due to unfavorable anatomy of the RV-outflow tract, the patient was not a candidate for the percutaneous treatment of the PR and was offered a surgical approach.

Neither Kommerell's diverticulum nor the esophageal compression was visible in the cCT of these patients.

Our report adds to the very limited literature of ARSA among ToF patients and has highly practical points. Firstly, the presence of ARSA may lead to a misdiagnosis of the aortic arch branches, especially during emergency palliative surgeries before detailed imaging evaluation of the aortic arch branching has been performed. Idhrees et al.,[8] reported on a ToF patient with ARSA, in whom the right common carotid artery (RCCA) was misidentified as the subclavian artery. As a consequence, Blalock-Taussig shunt was performed using RCCA. This resulted in a loss of blood flow from RCCA to the brain and hypoxic seizures.[8] Secondly, ARSA may cause tracheobronchial compression (in approximately 10%). Multiple case reports of subclavian-esophageal fistulae in the setting of ARSA (and subsequent massive upper digestive tract bleeding) have been previously reported, especially after tracheal or esophageal manipulation following cardiac surgeries.[9] Finally, heart cannulation via the right radial artery and subsequent ARSA may be challenging. Thus, the knowledge of aortic arch branching is crucial for Blalock-Taussig shunt surgery of ToF patients (although rarely performed nowadays) or other cyanotic CHD, as well as matters for any cardiac or extra-cardiac operations requiring tracheal/esophageal manipulation.

Author Contributions

Conception and design of the research and Writing of the manuscript: Michałowski M, Tyczynski P; Acquisition of data: Tyczynski P, Lipczynska M, Wójcik A, Michałowska I; Critical revision of the manuscript for intellectual content: Hoffman P, Witkowski A, Michałowska I.

Potential Conflict of Interest

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

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Study Association

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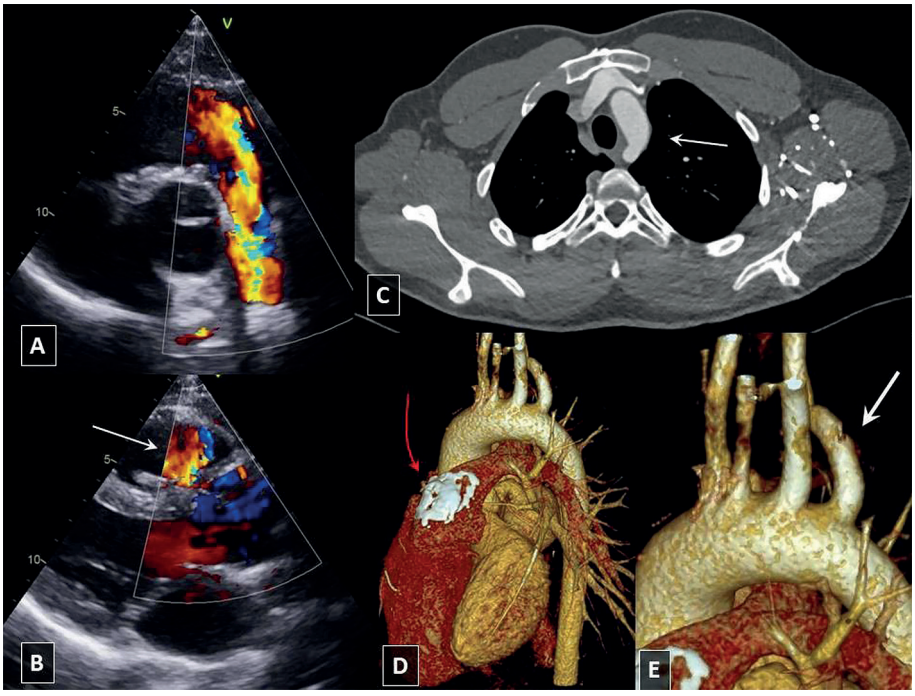

Figure 2 – *Patient 2 A) Transthoracic echocardiography, parasternal short axis view. Significant regurgitation across the pulmonary homograft; B) Transthoracic echocardiography, parasternal long axis view. Jet of the significant pulmonary regurgitation visible in the right ventricle outflow tract (white arrow); C) Cardiac computed tomography, axial plane. White arrow indicates left-sided aortic arch; D) Cardiac computed tomography. Visible calcifications of the pulmonary homograft at the level of the pulmonary valve (red arrow). E) Magnification of panel "D" with a focus on the right aberrant subclavian artery (white arrow) branching-off from the left-sided aortic arch.*

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Non-Atherosclerotic Coronary and Vascular Disease Case Report: Searching for a Rare Clinical Entity

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Introduction

Here we report a challenging case of a rare systemic condition – immunoglobulin G4-related disease (IgG4-RD) – that presented with a rare cardiovascular manifestation. Aortitis due to IgG4-RD is well-documented in the literature, but rarely has it been related to the involvement of the coronary arterial tree.[1] We documented IgG4-RD with diffuse coronary periarteritis, presenting as acute heart failure in this particular case. Despite the initial severity, multidisciplinary teamwork was the key to expeditious diagnosis and initiating tailored life-saving treatment targeting systemic inflammation and autoimmune organ involvement.

Case presentation

A 56-year-old Caucasian woman presented to the emergency department with atypical chest pain, dyspnea, tiredness, and occasional abdominal pain bursts during the previous week. In addition, intermittent proximal lower limb myalgia, cervical hot flashes, xerostomy and xerophthalmia were reported. The patient was afebrile, normotensive with sinus tachycardia (113 beats/min) and tachypnea. The physical examination was remarkable for S3 gallop and signs of pulmonary congestion (no peripheral edema). Past medical history was notable for allergic rhinitis, emaciation (40 Kg, 151 cm) and continued tobacco use (27 pack-year). Five years before, the patient had persistent lower limb cramps for 5 months, with an unremarkable arterial Doppler ultrasound study, treated with non-steroidal therapy.

Diagnostic workup at the emergency revealed slightly elevated high sensitivity troponin T levels (73 ng/mL), increased levels of N-terminal pro–B-type natriuretic peptide (NT- proBNP) (3485 pg/mL) as well as a slight elevation of creatine kinase. Electrocardiography showed ventricular extrasystoles and non-specific repolarization abnormalities. Transthoracic echocardiography (TTE) was remarkable for severe left ventricular (LV) systolic dysfunction (LV ejection fraction [LVEF] <30%) with global hypokinesia, restrictive filling pattern and moderate aortic valve regurgitation (Video 1).

In order to exclude coronary artery disease and investigate persistent abdominal pain, a thoracoabdominal computed tomographic (CT) angiography was performed. While no coronary artery calcium was observed, diffuse coronary artery fibrolipidic infiltration was documented, in addition to proximal left anterior descendent (LAD) aneurysm and distal LAD suboclusion. Dilatation of the ascending aorta (42 mm) with concentric homogeneous low-density wall thickening and an abdominal aorta aneurysm (47mm) with mural thrombus was identified (Figure 1). Coronary angiography confirmed Angio CT (diffuse intermediate disease with thin distal bed) results, not amenable revascularization.

Cardiac magnetic resonance (CMR) diagnosed LV dysfunction with severe dilatation (LVEF 21%; LV end-diastolic volume index: 229mL/m^2) and diffuse subendocardial late gadolinium enhancement. T2-weighed sequences showed no myocardial edema, albeit a hyperintense signal at the aortic root wall level (Video 2; Figure 2).

Given the diffuse polivascular disease and as a non-atherosclerotic etiology was highly suspected, an extensive diagnostic workup was performed. Infectious and immunologic disease investigation panels (syphilis, cytomegalovirus, hepatitis B and C virus, Epstein Barr virus, complement, cryoglobulins, anti-nuclear, SCL70, Jo1; anti-GBM, ECA and lupus antibodies) were all within normal range, except for a high erythrocyte sedimentation rate (ESR) and polyclonal hypergammaglobulinemia. Notably, serum levels of IgG4 were increased (1100 mg/L: reference value < 291 mg/L).

An additional imaging study with Positron Emission Tomography (PET) - CT depicted intense tracer activity over the proximal ascending and infra-renal aorta (Figure 3A).

Regarding the previous history of allergic rhinitis, a nasal mucosal biopsy was performed: it found a dense lymphocytic infiltrate and a slight increase in lamina propria plasma cells (CD138+), many of these positive for IgG4+ (an IgG4+/IgG+ ratio of 0-40% and an indeterminate number of IgG4+ cells/HPF) (Figure 4). Given all the

Keywords

Coronary Artery Disease; Immunoglobulin G4-Related Disease; Aortitis; Multimodal Imaging/methods; Inflammation; Heart Failure; Ventricular Dysfunction, Left; Diagnostic,Imaging/methods

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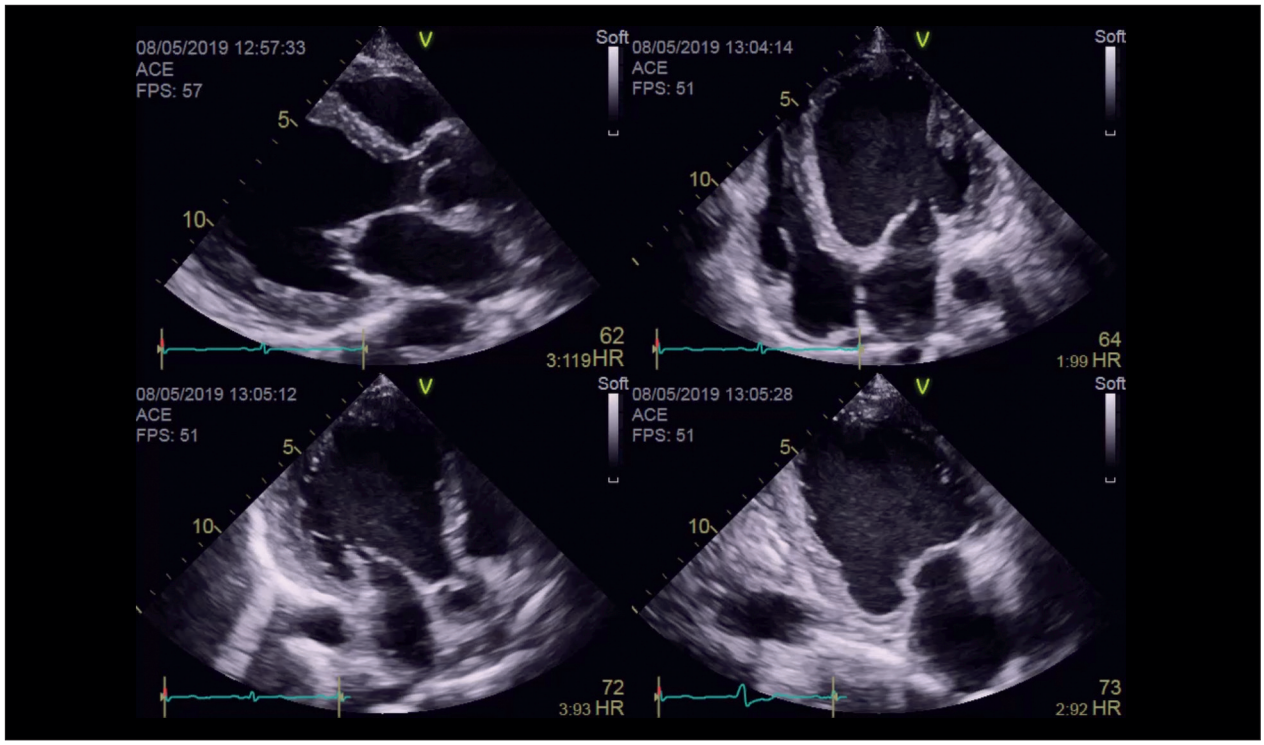


Video 1 – *Transthoracic echocardiogram at initial evaluation: severe LV dilation (219ml/m²) with depressed LV function (LVEF 25% SBP; Global longitudinal strain -8.1%) due to diffuse and global hypokinesia.*
Link: http://abccardiol.org/supplementary-material/2022/11903/2021-0722_CC_video-1.mp4

above, the diagnosis of IgG4-RD was suspected when we considered the EULAR criteria (Table 1).[1]

Accordingly, the patient was started on high-dose corticosteroid therapy (1000 mg of methylprednisolone in the first 3 days, followed by 1mg/kg/day for 2 months with slow tapering afterward) added to 6 cycles of cyclophosphamide infusion and methotrexate subcutaneous administration. Heart failure disease-modifying drugs were initiated, and the patient was referred to our cardiac rehabilitation center. Repeated angio-CT at discharge (15 days after the start of targeted treatment) showed a significant reduction in aortic wall thickening (10 to 5 mm) (Figure 1B).

At one year follow-up, there was an improvement in functional capacity, as assessed by NYHA class and peak V02 value (13.8 to 19.9 ml/kg/min), a reduction in NT-proBNP levels (5260 to 2052 pg/mL) and signs of reverse cardiac remodeling (namely LVEF improvement from 30 to 40%). Moreover, there was a progressive decline in inflammatory disease markers towards normal values (IgG4 1100 to 83 mg/dl, ESR 42 to 10 mm/h) and complete resolution of abnormal metabolic activity at PET CT reassessment (Figure 3B).

Discussion

IgG4-RD is a multi-organ immune-mediated fibroinflammatory condition characterized by diffuse tissue infiltration of IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis, and increased serum IgG4.[1,2] This case describes an anecdotally reported and complex presentation with aortitis and concomitant coronary arteritis. Chronic arteritis is a typical presentation of IgG4-RD involving the large and, less frequently, medium-sized arteries.[3,4] Coronary artery disease is seldom reported, and to the best of our knowledge, this is the only case report in which acute heart failure was the trigger for the initial investigation.[5,6]

The authors state that the non-atherosclerotic origin, in this case, was suspected due to the absence of coronary calcium (calcium score 0)- demonstrating the high negative predictive value for classic calcified/atherosclerotic disease; the presence of diffuse disease on coronary angiography with only intermediate lesions and very distal LAD suboclusion does not explain the diffuse kinetic changes on echocardiography and CMR. Also, against an atherosclerotic origin, there is diffuse subendocardial LGE at CMR rather than segmental. Furthermore, the flowery clinical history of this case is better explained by a multisystemic disease, despite a typically non-atherosclerotic etiology.

Multimodality imaging coupled with the inflammatory signature was essential for this diagnostic and therapeutic challenge. Cardiovascular imaging techniques, namely TTE, angio-CT, PET-CT and CMR, were successfully used for disease detection, symptom assessment, and monitoring. While ESR and polyclonal hypergammaglobulinemia raised the suspicion of a possible vasculitis, the aortic wall thickening and non-atherosclerotic coronary artery disease were

Research Letter

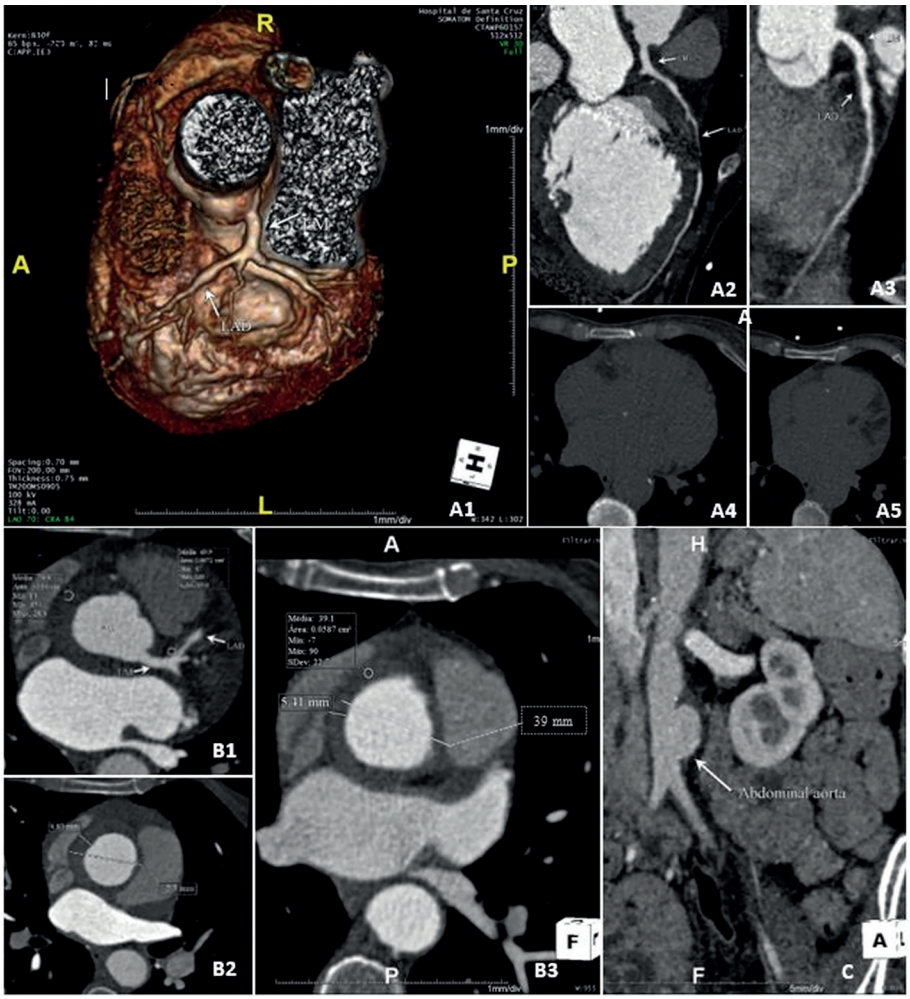
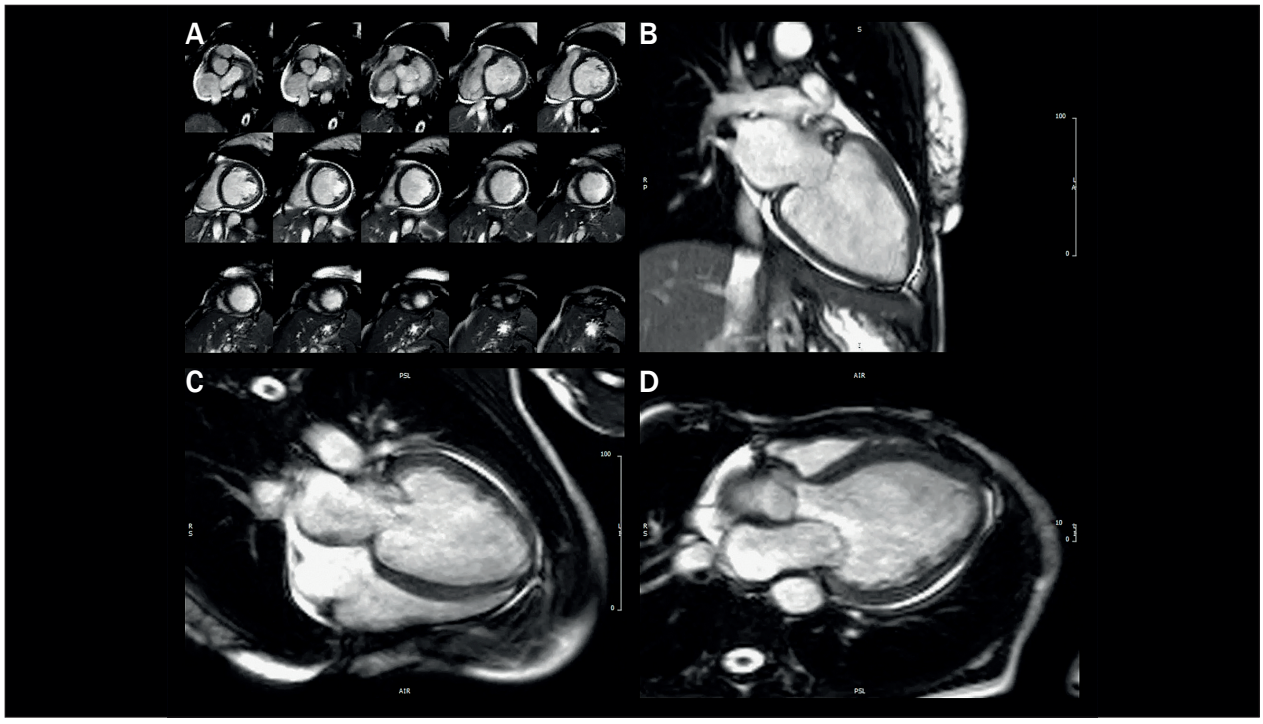


Figure 1 – *Cardiac angio-CT Panel A: Diffuse coronary artery fibrolipidic infiltration, in addition to proximal left anterior descendent (LAD) aneurysm (Panel A1 and A2) and distal bed LAD suboclusion (panel A3). Coronary artery wall infiltration density is similar to aortic wall density (panel B1). Panel A4 and A5 showed no coronary artery calcium. Panel B: Panel B1 and B2 - initial evaluation: 10mm homogeneous low-density (~70 Hounsfield unit [HU]) aortic wall thickening, with no increased density after contrast dye injection. Panel B3 - 15 days after starting targeted treatment: reduction in thickening of the parietal wall (10mm to 5 mm), in aortic root maximum diameter (43mm to 39mm) and the density of the parietal wall before the contrast injection (to 40 HU). Panel C: Abdominal angio-CT showed abdominal aorta aneurysm (47mm) with mural thrombus before treatment.*

paramount in guiding the investigation toward an etiology different than classical atherosclerosis. PET-CT confirmed the active periarterial and coronary artery inflammation. Moreover, it provided clues for clinical correlation, namely abdominal pain bursts, proximal lower limb myalgia and cervical hot flashes (as noted by diffuse whole body enhanced metabolic/inflammatory activity). According to a large retrospective study, PET-CT imaging may be the only imaging modality useful for assessing treatment response during follow-up;[7,8] nonetheless, we also repeated Angio-CT demonstrating a significant improvement of aortitis. Due to its capability to perform functional evaluation and tissue characterization, CMR allows simultaneous assessment of disease activity and specific repercussions on LV function when coronary arteritis is present.

A multidisciplinary team (Cardiology, Rheumatology, Nuclear Medicine and Pathology) was of utmost importance in investigating the multitude of organ involvement and key to achieving the diagnosis of IgG4-RD. After ruling out the most frequent diagnosis, the multidisciplinary team, based on all clinical and laboratory findings, decides to assume the IgG4 - related disease. Although the biopsy was not fully pathogenic, it was performed in a site not actively affected at this moment (but in the previous medical history); we chose not to perform an aortic or myocardial biopsy in the acute and unstable phase, potentially greater risks. Although we did not have a confirming diagnosis of gland involvement, the rheumatology, essential in this case, considers the involvement of salivary glands and xerophthalmia to be quite typical. Even though the



Video 2 – *Cardiac magnetic resonance: A) SSFP Short Axis Cine; B) SSFP 2 chamber view; C) SSFP 4 chamber view; D) SSFP Long axis view. Left ventricular systolic dysfunction with severe LV dilatation.*
Links: A) http://abccardiol.org/supplementary-material/2022/11903/2021-0722_CC_video-2A.mp4
B) http://abccardiol.org/supplementary-material/2022/11903/2021-0722_CC_video-2B.mp4
C) http://abccardiol.org/supplementary-material/2022/11903/2021-0722_CC_video-2C.mp4
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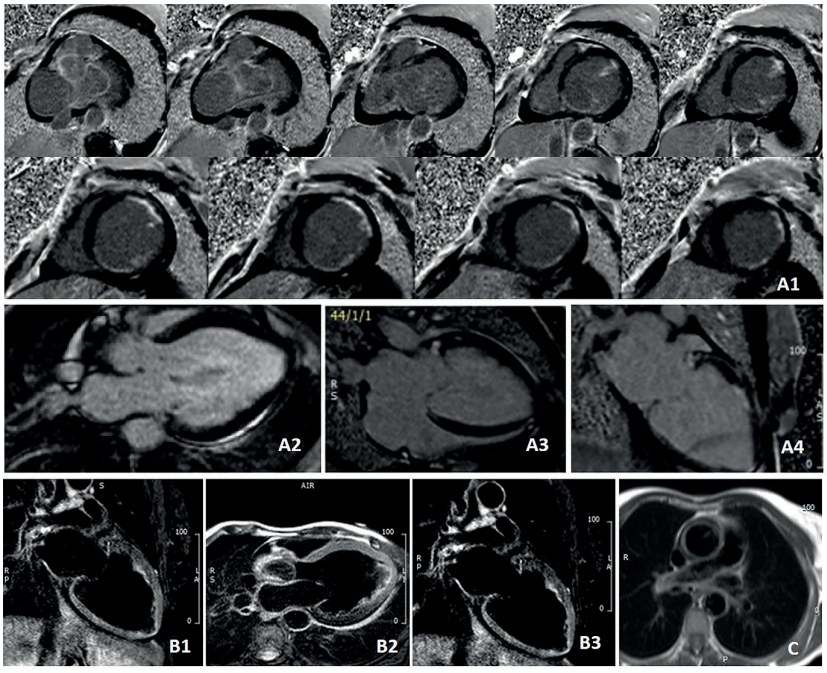

Figure 2 – *Cardiac magnetic resonance: A) Late gadolinium enhancement dark blood sequence, showing diffuse non-transmural late enhancement, confirming subendocardial ischemic scar across multiple artery territories; B) T2-W sequence revealed the absence of myocardial edema (confirmed with normal T2 mapping) with aortic wall edema, appreciated as a hyperintense signal (arrowhead); C) T2-STIR sequence supporting the aortic wall thickening.*

Research Letter

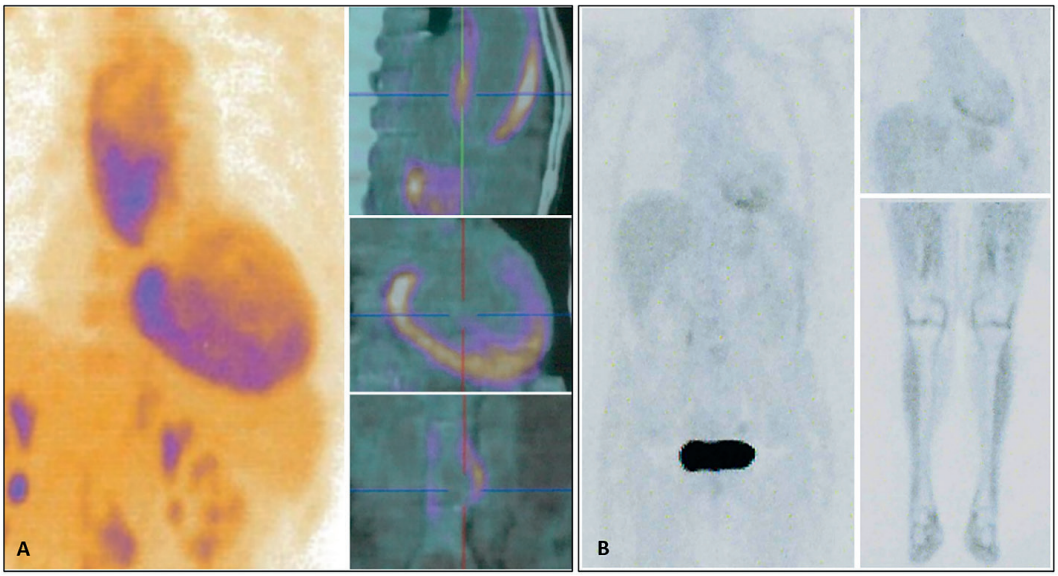

Figure 3 – *Panel A – PET-CT (Fluorodeoxyglucose) with high metabolic activity across ascending and infrarrenal aorta (*). Slight diffuse activity in the myocardium (arrowhead). This imaging study was also notable for the abnormal metabolism across the carotids and lower limb arterial axis (possibly explaining the heat neck sensation and myalgias). Panel B – Whole body PET-CT (Fluorodeoxyglucose) after one-year treatment: complete resolution with normal metabolic activity across myocardium, ascending and infra-renal aorta, carotids, and lower limb axis.*

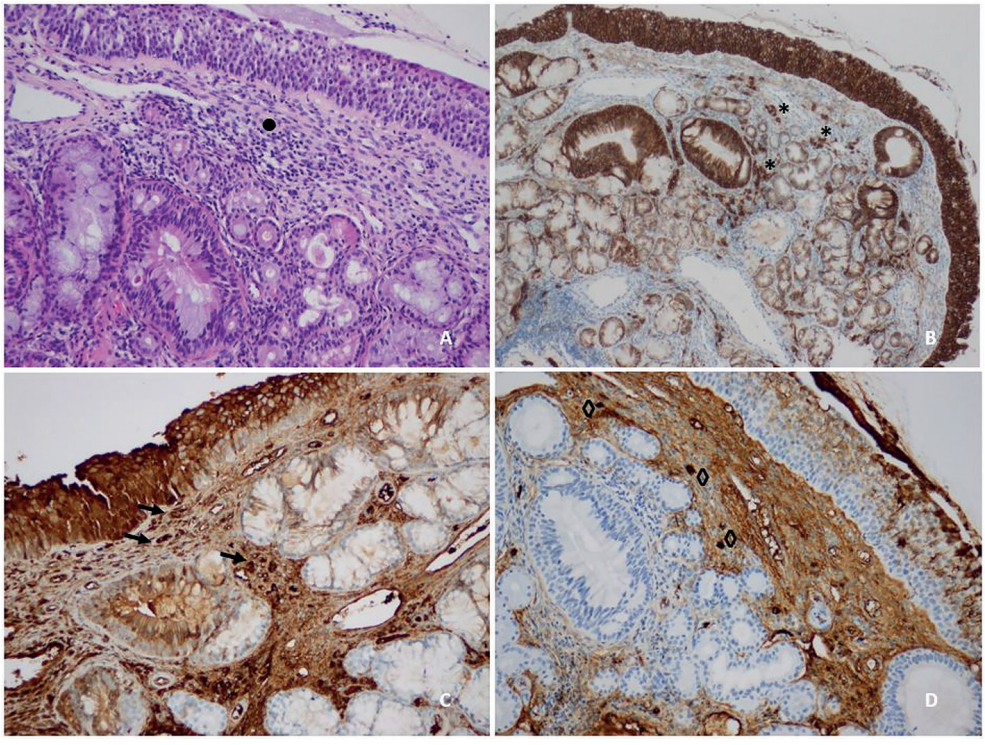

Figure 4 – *Nasal mucosa biopsy: Panel A- HE x20: diffuse and dense lymphoplasmacytic infiltrate (•); Panel B- CD138 x20: plasmacytic population (*); Panel C- IgG x40: infiltrate of IgG cells (arrowhead); Panel D- IgG4 x40, revealing the supobupolation of IgG4 cells (◊). The biopsy was mostly uninformative and lacked a dense lymphocytic infiltrate, highlighting the heterogeneous organ involvement characteristic of IgG4-RD. Nevertheless, there was a slight increase in lamina propria plasma cells (CD138+); many were positive for IgG and even with such a sparse inflammatory infiltrate, an IgG4+/IgG+ ratio of 23.1% was calculated. This fits the criteria EULAR: IgG4+/IgG+ ratio of 0-40% and an indeterminate number of IgG4+ cells/HPF.*

Table 1 – EULAR criteria for IgG4- Related disease

Entry Criteria	
Characteristic* clinical or radiologic involvement of a typical organ (e.g., pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges, or thyroid gland OR Pathologic evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain etiology in one of these same organs.	
Inclusion Criteria	**Points**
Histopathology	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
Immunostaining	
- IgG4+: IgG+ ratio is 0–40% or indeterminate, and the number of IgG4+ cells/HPF is 0–9.	0
- IgG4+: IgG+ ratio is ≥41%, and the number of IgG4+ cells/HPF is 0–9 or indeterminate;	+7
- IgG4+: IgG+ ratio is 0–40%, and the number of IgG4+ cells/HPF is ≥10 or indeterminate.**	+7
- IgG4+: IgG+ ratio is 41–70%, and the number of IgG4+ cells/HPF is ≥10	+14
- IgG4+: IgG+ ratio is ≥71%, and the number of IgG4+ cells/ HPF is 10–50.	+14
- IgG4+: IgG+ ratio is ≥71%, and the number of IgG4+cells/ HPF is ≥51.	+16
Serum IgG4 concentration	
Normal or not checked	0
> Normal but <2x upper limit of normal	+4
2–5x upper limit of normal	+6
>5x upper limit of normal	+11
Bilateral lacrimal, parotid, sublingual, and submandibular glands	
No set of glands involved	0
One set of glands involved	+6
Two or more sets of glands involved	+14
Chest	
Not checked, or neither of the items listed is present	0
Peribronchovascular and septal thickening	+4
Paravertebral band-like soft tissue in the thorax	+10
Pancreas and biliary tree	
Not checked, or none of the items listed is present	0
Diffuse pancreas enlargement (loss of lobulations)	+8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+11
Pancreas (either of the above) and biliary tree involvement	+19
Kidney	
Not checked, or none of the items listed is present	0
Hypocomplementemia	+6
Renal pelvis thickening/soft tissue	+8
Bilateral renal cortex low-density areas	+1
Retroperitoneum	
Not checked, or neither of the items listed is present	0
Diffuse thickening of the abdominal aortic wall	+4
Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	+8

*If the entry criteria are met, the case meets the classification criteria for IgG4-RD, and the total points of inclusion criteria are ≥20. Of note, only the highest-weighted item in each domain is scored. * Refers to enlargement or tumor-like mass in an affected organ except in the following: 1) the bile ducts, where narrowing tends to occur; 2) the aorta, where wall thickening or aneurysmal dilatation is typical; and 3) the lungs, where thickening of the bronchovascular bundles is common. ** "Indeterminate" refers to a situation in which the pathologist cannot clearly quantify the number of positively staining cells within an infiltrate yet can still ascertain that the number of cells is at least 10/high-power field (HPF). For many reasons, most often about the quality of the immunostaining, pathologists are sometimes unable to count the number of IgG4+ plasma cells with precision, yet, even so, can be confident in grouping cases into the appropriate immunostaining result category.*

criteria might not be fulfilled, the fact that the patient presented a good response to the IgG4-RD targeted therapy corroborates this hypothesis.

Neuro-hormonal blockade with disease-modifying agents is essential to improve survival in patients with Heart Failure and reduce LVEF. According to the International Consensus on the treatment of IgG4-RD, glucocorticoids are the first-line agents for induction of remission,[9] even in the advanced fibrotic stages.[10] IgG4-related cardiovascular lesions usually require higher doses of corticosteroids,[11,12] often improving the inflammatory lesions on CT or PET imaging.[7] This case was further complicated by the mineralocorticoid-like effect derived from corticosteroids, which can facilitate Heart Failure decompensation. Although observational data may support this approach, initial treatment with combination immunosuppressors remains controversial.[13] Cyclophosphamide has been shown to have good long-term outcomes and lower relapse rates.[14] Likewise, rituximab has also been suggested to have beneficial effects in IGG4-RD, yet severely reduced LVEF and Heart Failure symptoms and latent tuberculosis, contra-indicated its use in our case. Unlike the previously published case involving coronary arteries,[5] in the multidisciplinary discussion, we consider that aspirin had no role in this type of artery involvement and increased the bleeding risk due to ongoing steroid treatment.

We reported a challenging case of IgG4-RD presenting with acute heart failure consequent to coronary arteritis and aortitis, with successful conservative management, rather than invasive coronary bypass graft surgery as an initial strategy.[6] Besides being remarkable for its rare presentation, this case highlights the role of multimodality imaging and multidisciplinary workup as key players in correctly establishing a diagnosis and facilitating a tailored treatment plan.

Author contributions

Conception and design of the research and analysis and interpretation of the data: Mendes GJAS, Mesquita AE, Ramos S, Trabulo M; acquisition of data: Mendes GJAS, Mesquita AE, Trabulo M; writing of the manuscript: Mendes GJAS, Mesquita AE, Rocha B; critical revision of the manuscript for intellectual content: Mendes GJAS, Mesquita AE, Rocha B, Ramos S, Trabulo M.

Potential Conflict of Interest

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

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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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Guidelines, Position Statements, and Standardizations: Documents to Assist Medical Practice

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Medical practice, which must be shared, is based on two pillars, the intellectual one, which cannot being standardized because it depends on the cognitive capacity of the professional when making decisions, and the technical one, which depends on training, improvement, and updates and which can, therefore, be regulated by clinical practice guidelines (CPG). CPG are important tools, especially in an area as complex and rapidly changing as cardiology, and they have the following objectives: to improve the quality of care based on the best available evidence and to reduce the disparity of medical conduct for the same type of clinical situation.[1,2]

It is worth underscoring that adherence to CPG varies greatly and that some physicians are concerned that these instruments represent rigid or simplified practice of medicine.[3] Therefore, the proper implementation of CPG is of great interest to national organizations, professional societies, healthcare providers, policymakers, the judicialization of Medicine, patients, and the general public. Given the importance of the topic, several tools have been developed to evaluate the credibility of existing guidelines,[4] as well as step-by-step guidance on how to produce practical and reliable documents.[5]

Since 1992, the Brazilian Society of Cardiology (SBC) has systematically published guidelines on the most relevant topics in the specialty.[6] Nonetheless, a lack of discernment has been registered in relation to three important concepts,[7] in this effort, on the part of the departments that compose the SBC: a) guideline is the term that should be reserved for documents that formally summarize evidence in the areas of disease diagnosis and therapy; b) position statement (or clinical guidance) should be used for official publications that provide expert advice on challenges in patient management; and c) standardization (or communication), in turn, should be used for manuscripts that inform laboratory methodology and definitions of clinical outcomes.

It is imperative for the documents published by the SBC to be presented with appropriate titles and foundations in order to avoid confusion on the part of the reader in differentiating these terms and consequent lack of interest in reading them.

Therefore, the main objective of this publication is to establish, in a simplified and objective manner, the meaning of these terms, aiming to standardize the publication of guidelines, communications, and position statements by the SBC.

Clinical practice guidelines

CPG are made up of systematically developed statements, and they are designed to support decision-making processes in patient care, under specific conditions.[8] Unlike documents that provides guidance, guidelines address a topic where there is moderate to high quality evidence, generally from randomized trials with a satisfactory number of participants, to make the most appropriate clinical practice possible.

In drafting them, a process is used to summarize the evidence and provide a standardized method to express the classes of recommendations with their respective levels of evidence. For a guideline to be reliable, it is advisable to observe the following criteria: a) be based on systematic reviews of the literature; b) be developed by a multidisciplinary and experienced panel of experts; c) consider the values and preferences of patients, as well as their subgroups; d) be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest; e) provide a clear explanation of the relationships between alternative care options and clinical outcomes, and f) be updated when important new evidence warrants changes to recommendations.[9]

Guidelines can improve clinical outcomes; nevertheless, adherence to them varies.[10] They rarely address medical

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Practice Guideline; Guideline; Cardiovascular Diseases

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practice where evidence is scarce. Therefore, it is necessary to use innovative strategies to facilitate the dissemination of these documents. It is worth underscoring that CPG are not recipe books, given that most of them have limitations in their availability and applicability in the context of the level of evidence of the recommendations, as only a small percentage is based on randomized clinical trials.[11] Consequently, it is necessary to frequently update these guidelines in order to incorporate more robust evidence that eventually emerges.

Positioning documents

These documents aim to address a determined diagnostic, therapeutic, or laboratory topic of recognized clinical interest, for which evidence of substantial quality, notably evidence from randomized clinical trials either does not exist or is unlikely to be produced. These documents are complementary to the guidelines, and they are prepared by a team of professionals with established experience on the topic.

As an example, we may cite the use of direct anticoagulants in pregnant patients.[11] In general, the guidance contained in these documents continues to be anchored in the best available evidence; nonetheless, they frequently incorporate the personal opinion of experts.

Standardization documents

These documents differ from those listed above, insofar as they address topics primarily aimed at standardizing clinical and laboratory practices and research methodologies. We may cite, as an example, the report of the Subcommittee on Control of Anticoagulation of the International Society of Thrombosis and Haemostasis to measure the anticoagulant activity of factor Xa inhibitors.[12] It is, therefore, a useful tool that is available to departments of the SBC.

In conclusion, the movement toward evidence-based healthcare has been rapidly gaining ground in recent years, driven by clinicians, policymakers, and managers who are concerned about the quality, consistency, and costs of healthcare.

Accordingly, these documents, based on standardized best practices, provided that they are written in a practical and objective manner, are able to promote improvements in the quality and consistency of healthcare. Guaranteeing the applicability and implementation of these recommendations will depend on the extent to which patients accept them, the availability of procedures, the experience required in the specific context, and their impact when put into practice.[13]

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Conception and design of the research and Analysis and interpretation of the data: Sousa AC, Markman-Filho B; Acquisition of data and Writing of the manuscript: Sousa AC; Critical revision of the manuscript for intellectual content: Sousa AC, Corrêa-Filho H, Nascimento B, Issa AC, Vieira MLC, Markman-Filho B.

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Transesophageal Two- and Three-Dimensional Echocardiographic Assessment of Spontaneous Left Atrial Dissection

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A 41-year-old woman was admitted to the emergency room with an onset of acute dyspnea, jugular ingurgitation, and with the first heart sound diminished, followed by a grade III/IV holosystolic murmur that was better heard at the apex and edema of the lower limbs.

The vital signs were heart rate 91 bpm, respiratory rate 21 rpm, blood pressure 110/60 mmHg, and oxygen saturation 91%. The chest x-ray showed cardiomegaly with a cardiothoracic index of 0.62 and pulmonary venocapillary hypertension.

Transthoracic 2D echocardiography showed a cyst-like, lesion occupying a thin-walled space in the left atrium (Figure 1, Panels A, B), moderate mitral regurgitation, ventricular systolic function of 68%, and left pleural effusion (Figure 1, Panels C, D). A transoesophageal technique (TEE) at 60° (Figure 1, Panel E) and 90° (Figure 1, Panel F) was performed for better characterization, which confirmed the presence of heterogeneous cyst-like mass of the left atrium, involving the posterior mitral and occupying approximately 60% of the left atrial chamber (Video 1). Color Doppler revealed a blood flow to this pseudo-cavity (Figure 1, Panel G). The 3D TEE, from the surgeon's view, clearly showed a pseudo-cavity inside the left atrium appearing and disappearing in relation to the cardiac cycle (Figure 2, Panel A) and comprising the postero-medial segment of the mitral annulus (Figure 2, Panel B), (Video 2).

Medical treatment for acute heart failure was initiated with poor response and progression to cardiogenic shock. The patient was taken immediately to the operating room.

An emergency approach was executed according to the echocardiographic findings. A pericardiotomy was performed, an approach to the left atrium was initiated, in which the posterior fibrotic and retracted leaflet was observed with a perforation in P2 and P3 and evidence of a dissection hole in the annulus and posterior wall of the atrium.

Management of damage control and life support was initiated with poor response and, unfortunately, the patient died during surgery.

Spontaneous left atrial dissection is an extremely rare disease and must be suspected as an uncommon cause of acute heart failure. Its true incidence, pathophysiology, clinical course, and management is poorly understood.[1,2] TEE, especially the 3D method, is the diagnostic modality of choice for this entity, before the era of TEE, the diagnosis was based on gross intraoperative findings or incidental autopsy findings.[2,3]

Author Contributions

Conception and design of the research: Armenta-Moren JI, Berarducci J, Espinola-Zavaleta N; Acquisition of data: Armenta-Moreno JI, Garcia-Cardenas AM, Armendariz-Ferrari JC, Espinola-Zavaleta N; Analysis and interpretation of the data: Garcia-Cardenas AM, Armendariz-Ferrari JC, Luna-Alvarez-Amezquita JA; Statistical analysis: Bermudez-Gonzalez JL; Obtaining financing: Straface JI; Writing of the manuscript: Armenta-Moreno JI, Berarducci J, Armendariz-Ferrari JC; Critical revision of the manuscript for intellectual content: Berarducci J, Garcia-Cardenas AM, Armendariz-Ferrari JC, Bermudez-Gonzalez JL, Straface JI, Luna-Alvarez-Amezquita JA, Espinola-Zavaleta N.

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Keywords

Heart Failure/physiopathology; Atrial Function, Left/physiology; Diagnostic, Imaging/methods; Echocardiography Three-Dimensional/methods; Shock, Cardiogenic

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Image

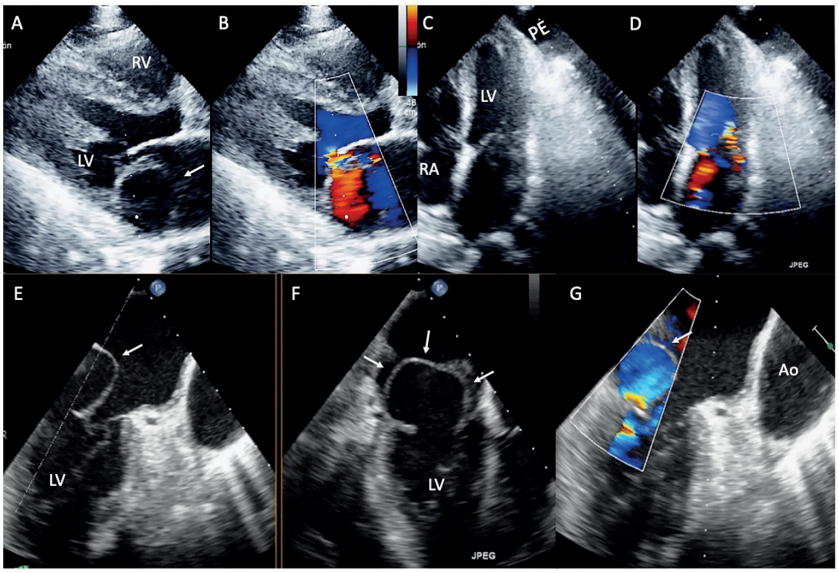

Figure 1 – *Transthoracic 2D Doppler echocardiography in the parasternal long axis view showing a cyst-like thin-walled atrium (A) and moderate mitral regurgitation (B). In the apical chamber a left pleural effusion (C) and also a moderate mitral regurgitation (D) were visualized. Transoesophageal 2D images at 60º and 90º (E-F) confirmed the presence of a heterogeneous cyst-like mass (white arrows) in the left atrium involving the posterior mitral annulus. The color Doppler revealed a blood flow to this cavity (G). LV: left ventricle; LA: left atrium; RA: right atrium; RV: right ventricle; Ao: aorta; PE: pleural effusion.*

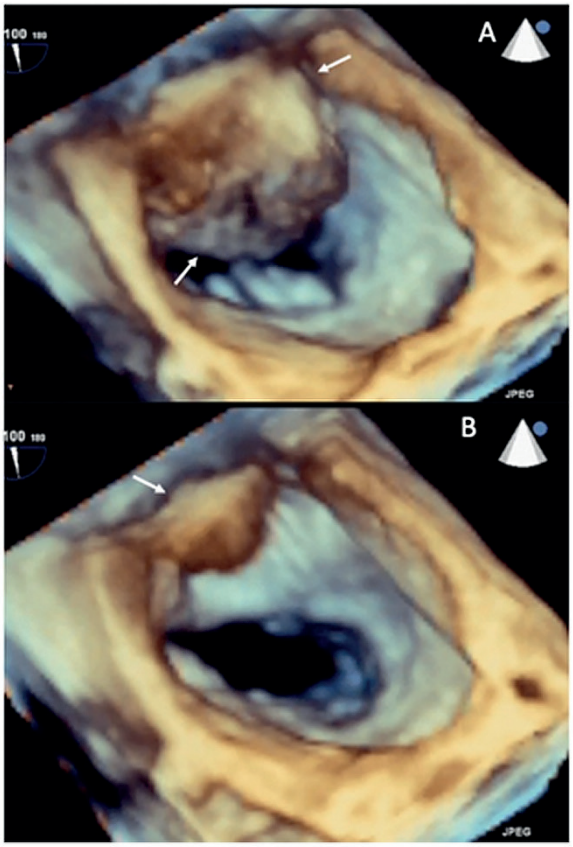

Figure 2 – *Transoesophageal 3D echocardiography in the surgeon view with a pseudo-cavity inside the left atrium appearing and disappearing (white arrows) in relation to the cardiac cycle (A) and comprising the postero-medial segment of the mitral annulus (white arrows), (B).*

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*Supplemental Materials

See the Supplemental Video 1, please click here.

See the Supplemental Video 2, please click here.

Impact of Active Helicobacter pylori Infection-related Metabolic Syndrome on Systemic Arterial Hypertension

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To the Editor,

In their meta-analysis, Huang et al.[1] concluded that *Helicobacter pylori* infection (*H. pylori* infection) is positively associated with systemic arterial hypertension, particularly by introducing the diagnostic 13C-urea breath test, signifying current *H. pylori* infection.

In this regard, systemic arterial hypertension is one of the most significant parameters of the metabolic syndrome (MetS), and its pathogenesis may mostly comprise of a noxious interplay between vascular, renal, neural, and hormonal mechanisms, of which augmented activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) predominate.[2] Augmented activity of SNS is a usual feature of resistant systemic arterial hypertension, accompanied by increased release of norepinephrine, signifying a neurogenic element that contributes to the development of systemic arterial hypertension; and overactivation of SNS is associated with morbidity and mortality of MetS-related cardiovascular disorders.[3] Moreover, RAAS dysregulation, including the systemic and brain RAAS, has been documented as one of the chief causes of several types of systemic arterial hypertension; and RAAS overactivation also contributes to MetS-associated obesity and cardiovascular morbidity and mortality.[4]

Likewise, *H. pylori* infection is also associated with MetS-related systemic pathologies, especially cardio-cerebrovascular and neurodegenerative diseases, the endpoints of MetS.[5-8] Specifically, *H. pylori* infection seems to contribute to insulin resistance (IR), the chief underlying mechanism responsible for MetS,[9] which also plays n critical role in the pathogenesis and progression of systemic arterial hypertension-triggered target organ injuries.[10] MetS contributes to an increased risk of developing atherosclerosis,[11] and in this respect, invasion of *H. pylori* into atheroma has been detected by introducing polymerase chain reaction (PCR).[12] Direct *H. pylori* colonization in the arterial walls has been observed. *H. pylori* is associated with arterial stiffness, an early marker of systemic atherosclerosis correlated with systemic arterial hypertension and an independent predictor of cardiovascular complications and all-cause mortality. Thus, *H. pylori* have been associated with MetS-related atherosclerosis via a diversity of involved mechanisms, thereby potentially triggering systemic arterial hypertension. *H. pylori* infection might independently be involved in atherosclerosis and arterial hypertension through mechanisms distinct from the conventional causes of atherosclerosis, including the three non-conventional coronary artery disease risk factors homocysteine, fibrinogen and lipoprotein(a).[6,13,14]

Besides, MetS-related dyslipidemia is linked with systemic arterial hypertension[15] and in this regard, chronic *H. pylori* infection can trigger abnormal lipid metabolism of the host, including, beyond the mentioned lipoprotein(a), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC),[16] also mentioned by the authors;[1] *H. pylori*-related lower HDL-C appears to promote dyslipidemia.[17] In contrast, *H. pylori* eradication significantly decreases the levels of TC, TG, LDL-C and fibrinogen, an independent risk factor for cardiovascular disease,[6] whereas increases HDL-C concentrations.[18,19] Moreover, beyond dyslipidemia and systemic arterial hypertension, *H. pylori* eradication also improves other MetS-related parameters, including body mass index (BMI),[20] IR,[21] and total oxidant status.[22] Therefore, eradication *of H. pylori* infection reduces the occurrence of MetS-related dyslipidemia and other parameters including systemic arterial hypertension,[23,24] thereby potentially preventing the occurrence of MetS-related cardiovascular disease accompanied by arterial hypertension.

Recent data indicate that MetS-related sarcopenia, *H. pylori* infection, dyslipidemia, systemic arterial hypertension, diabetes mellitus, smoking, alcohol consumption, and diet (salty and/or spicy diets) are linked with precancerous gastric mucosa lesions, including gastric atrophy, intestinal metaplasia, and dysplasia.[25] In this respect, interesting recent evidence also indicates that bariatric patients with *H. pylori* infection display baseline significantly high rates of the mentioned gastric

Keywords

Helicobacter pylori; Hypertension; Metabolic Syndrome; Atherosclerosis; Dyslipidemias.

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pre-malignant lesions, including gastric atrophy and intestinal metaplasia accompanied with IR and arterial hypertension.[26]

Finally, nonalcoholic fatty liver disease (NAFLD), recently renamed as metabolic dysfunction-associated fatty liver disease (MAFLD), is the hepatic component of MetS also associated with *H. pylori* infection, which appears to contribute to its development and progression;[27] NAFLD/MAFLD is associated with an about 1.6-fold augmented risk of developing systemic arterial hypertension; and MetS- related characteristics including high BMI, dyslipidemia, and type 2 diabetes mellitus in the setting of *H. pylori* infection exhibit a greater tendency for the development of NAFLD/MAFLD. In this regard, recent data indicate that *H. pylori* infection is connected with IR and augmented intestinal permeability, which could contribute to the development of NAFLD/MAFLD;[28] and active *H. pylori* infection is independently positively associated with the severity of nonalcoholic steatohepatitis and fibrosis, findings suggesting probable clinical implications.[27] Among patients with NAFLD/MAFLD, the prevalence of arterial hypertension varies from 40-70%, and relative studies have shown that NAFLD/MAFLD is strongly related to the augmented risk of systemic arterial prehypertension and hypertension.[29] In contrast, beyond the reduction of the mentioned systemic arterial hypertension, *H. pylori* eradication particularly increases HDL-C and reduces LDL-C,[30] thus restoring the cardioprotective activity of the HDL-C/LDL-C ratio and diminishing the cardiovascular risk linked to MAFLD.[30]

Viewing the aforementioned data, *H. pylori* infection seems to display pleiotropic effects beyond the gastrointestinal tract and rising evidence associates it with MetS, including systemic arterial hypertension. Further research is warranted, however, to clarify the potential impact of *H. pylori* related MetS on systemic arterial hypertension, which represents a serious public health problem with high global incidence and prevalence that continues to increase and may contribute to global high morbidity and mortality. Identifying *H. pylori* and MetS-related NAFLD/MAFLD and other relative disorders – as important risk factors for systemic arterial hypertension – may be helpful for improving the risk prediction, identifying primary preventive strategies, and selecting a therapeutic program for systemic arterial hypertension.

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