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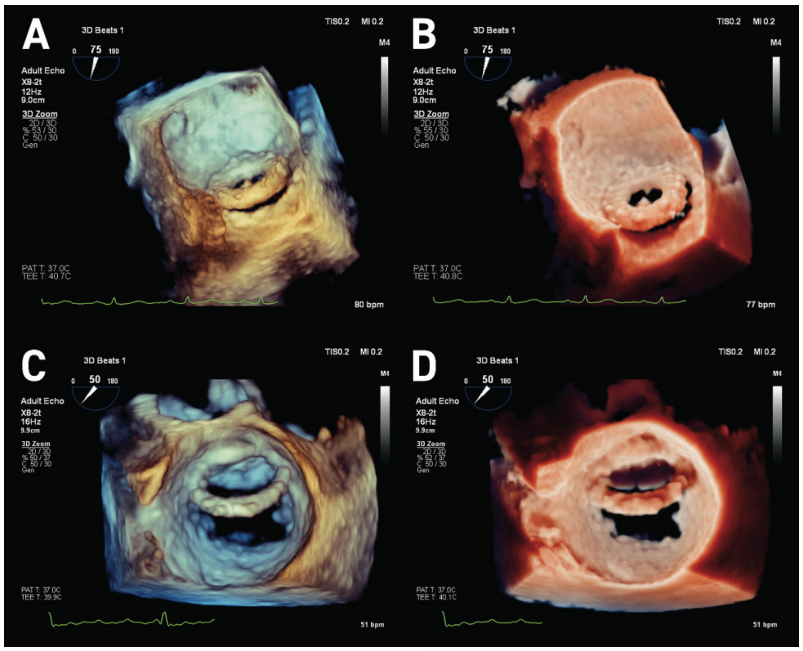

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Diagnostic Role of NT-proBNP in Patients with Cardiac Amyloidosis Involvement: A Meta-Analysis

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Abstract

Background: **Amyloidosis is defined as a disorder characterized by the deposition of extracellular protein material of amyloid in tissues.**

Objectives: **N-terminal pro-B-type natriuretic peptide (NT-proBNP) is used to predict the cardiac amyloidosis (CA), but its diagnostic effect on CA involvement remains unclear, especially in terms of specificity and sensitivity.**

Methods: **A search for literature was conducted in the Pubmed, Embase, and Cochrane library databases, and QUADAS 2 was used for quality assessment. Midas command in Stata 12.0 was used to analyze the subject indicators. Cochran's Q and I^2 were to test for heterogeneity, and the significant heterogeneity was set at $p < 0.05$ and/or $I^2 > 50\%$. Spearman correlation analysis was used to evaluate the threshold effect, and the publication bias was assessed using the asymmetry test. The statistical significance was set at $p < 0.05$.**

Results: **As results, 10 sets of data from 7 studies were included for analysis, showing high methodological quality and minimal confounding bias. The sensitivity and specificity of NT-proBNP in the diagnosis of cardiac involvement for patients with amyloidosis were 0.93 and 0.84, respectively. ROC curves also suggested a high diagnostic validity of NT-proBNP with an AUC of 0.95. A Fagan's nomogram plot showed probabilities for NT-proBNP positive and negative in developing CA involvement were 90% and 8%, respectively. The Deek's funnel plot suggested no significant publication bias across included studies, and the results were stable and reliable.**

Conclusions: **NT-proBNP plays the positive role in the early diagnosis of CA involvement with high sensitivity and specificity.**

Keywords: **Amyloidosis; Diagnosis; Network Meta-Analysis.**

Introduction

Amyloidosis is defined as a disorder characterized by the deposition of extracellular protein material of amyloid in tissues, and it is pathologically caused from cleavage, denaturation or excessive production of abnormal protein.[1,2] The heart is the main affected organ of different fibrous types of amyloidosis.[2] Cardiac amyloidosis (CA) is an invasive cardiomyopathy caused by amyloidosis, and may give rise to heart failure and conductive disease.[3] The prevalence of CA involvement in the general population ranges from 5%-74%, and the wide differences in research variability are associated with population selection criteria and diagnostic strategies.[4] Protein misfolds and deposits of amyloid immunoglobulin light chain protein (AL) and amyloid transthyretin (TTR) proteins, which may be induced by the mutation of TTR gene, are the main causes of CA involvement.[5] Phenotypic heterogeneity and delays in diagnosis caused by comorbidities contribute to the poor prognosis of cardiac involvement for patients with amyloidosis.[6] Many cases of CA involvement are usually confirmed in the disease course of late with limited treatment options.[7] Therefore, increasing the understanding of CA involvement and developing amyloidosis-related biomarkers for early diagnosis will effectively improve the clinical outcome of patients.

B-type natriuretic peptide (BNP) is a type of hormone secreted by myocyte cells, and may function in maintaining fluid homeostasis through the action of sodium, diuresis, and vasodilation.[8] N-terminal pro-BNP (NT-proBNP) is cleaved to proBNP, which is secreted by cardiomyocytes.[8] NT-proBNP is considered to be directly regulated by light chain and can be used as a biomarker for AL amyloidosis after analysis and validation.[9] However, one relevant study pointed out that NT-proBNP may be a sensitive but non-specific biomarker for the assessment of CA.[10] Palladimi et al. also illustrated that the severity of cardiac dysfunction in patients with CA could be assessed by NT-proBNP cardiac biomarkers and cardiac troponins (cTn), and their evaluations were highly sensitive.[11] Other incertitudes regarding the role of NT-proBNP in predicting CA involvement stem mainly from the limitations of sample

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size.[12] In light of the above research controversies, studies with a relevantly larger size are warranted in order to explore the independent role and diagnostic specificity of NT-proBNP to predict the CA involvement.

Therefore, this meta-analysis was conducted to obtain a larger sample size by integrating data from previous studies and to evaluate the diagnostic value of NT-proBNP for CA involvement from various aspects, including sensitivity, specificity, likelihood ratios, among others. Our study provides a diagnostic marker for cardiac involvement in patients with amyloidosis, which may help patients to receive more accurate early diagnosis and treatment.

Methods

Literature retrieval strategy

A search for literature was conducted in the Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/) and Cochrane library (https://www.cochranelibrary.com/) databases with the deadline date of January 28, 2021, and the key words included: 1) Amyloidosis OR amyloidoses; 2) cardiomyopathy OR (cardiac involvement) OR (heart involvement) OR (myocardial dysfunction); 3) NT-proBNP OR (N-terminal prohormone of brain natriuretic peptide) OR (N-Terminal Pro-B-Type Natriuretic Peptide). These three groups of key words were combined with "AND". Moreover, subject words and free words were combined in the search, and the retrieval strategies varied according to the characteristics of three databases. The detailed retrieval process and related results were shown in Supplemental Table 1-3. Furthermore, the paper version of literatures was manually retrieved, and the references of the included literatures and relevant reviews were also screened according to the inclusion criteria.

Publication selection

The inclusion criteria were as follows: 1) subjects with AL amyloidosis or TTR-related amyloidosis; 2) subjects with left/right ventricular dysfunction, heart failure, and other cardiac dysfunction diagnosed by cardiac magnetic resonance imaging or biopsy; 3) provided diagnostic results of NT-proBNP-caused cardiac injury including true positive (TP), false positive (FP), true negative (TN) and false negative (FN), or can be extrapolated according to data from the literature. Non-treatise literatures, such as reviews, letters, comments, among others, were excluded from this study.

Data acquisition and quality evaluation

The two investigators independently logged the data according to a standardized form designed in advance. The acquired information included the name of the first author, publication year, study area, sample size; age and sex of subjects; data of TP, FP, TN and FN; and criteria for heart damage. After data extraction, discussion was conducted to solve the inconsistency. QUADAS 2 was applied to assess the quality of research methods used in each included study.[13]

Statistical analysis

Midas command (bivariate mixed-effect model) in Stata12.0 version 12 SE (Stata Corporation, TX, USA) was applied for statistical analysis on indexes of subjects including summary receiver operating characteristic (SROC) curve, sensitivity, specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), diagnostic odds ratio (DOR), and 95% confidence intervals (CI). The value of DOR ranged from 0 to infinite, and the larger value indicated the greater discriminatory ability of diagnostic methods.[14] The SROC curve was established based on sensitivity and specificity, and the closer the area under the curve (AUC) to 1, the higher the diagnostic validity.[15] Cochran's Q and I^2 tests were used to evaluate the heterogeneity,[16] and $p > 0.05$ and/or $I^2 > 50\%$ indicated significant heterogeneity between studies. Spearman correlation analysis was used to assess the threshold effect, and $p < 0.05$ indicated a significant threshold effect.[17] Deek's funnel plot was used to evaluate whether there was significant publication bias between studies,[18] while Fagan's nomogram was used to evaluate the clinical utility of NT-proBNP.[19] Sensitivity analysis was performed using a graph model to evaluate whether or not it contained possible misspecifications, goodness of fit, identify outlying, and possibly influential data points.[20]

Results

Literature screening

The process and results of literature retrieval were shown in Figure 1. We obtained 450, 146, and 29 articles from Embase, PubMed and Cochrane library databases, respectively. A total of 494 articles were screened after having eliminated duplicates. Among these, 483 articles were removed after reading the titles and abstracts. After reading the full paper, 4 articles were further eliminated. Furthermore, the manual search failed to screen the publications that met the requirements. Finally, 7 articles[12,21-26] were included in this analysis.

Features of included literatures

A total of 7 articles were incorporated in this study. Among these, the study of Nicol et al.[25] contained two sets of data, the study of Palladini et al.[26] contained three sets of data, and the other five studies contained one set of data each. Therefore, a total of 10 sets of data were included for further analysis. These seven studies, published from 2003 to 2020, involving 810 subjects in total (including 490 patients with CA involvement and 320 controls), were conducted in the Netherlands, Germany, France, Italy, among other countries. Moreover, the levels of NT-proBNP were all detected by immunoassay in the included studies. Among these, 4 studies focused on AL amyloidosis, 2 studies included TTR amyloidosis, while the other study incorporated both AL and TTR amyloidosis. Meanwhile, amyloidosis was confirmed by biopsy in 6 studies, not including Damy et al.,[21] who did not report a diagnostic strategy. Characteristics of these 7 studies, including the

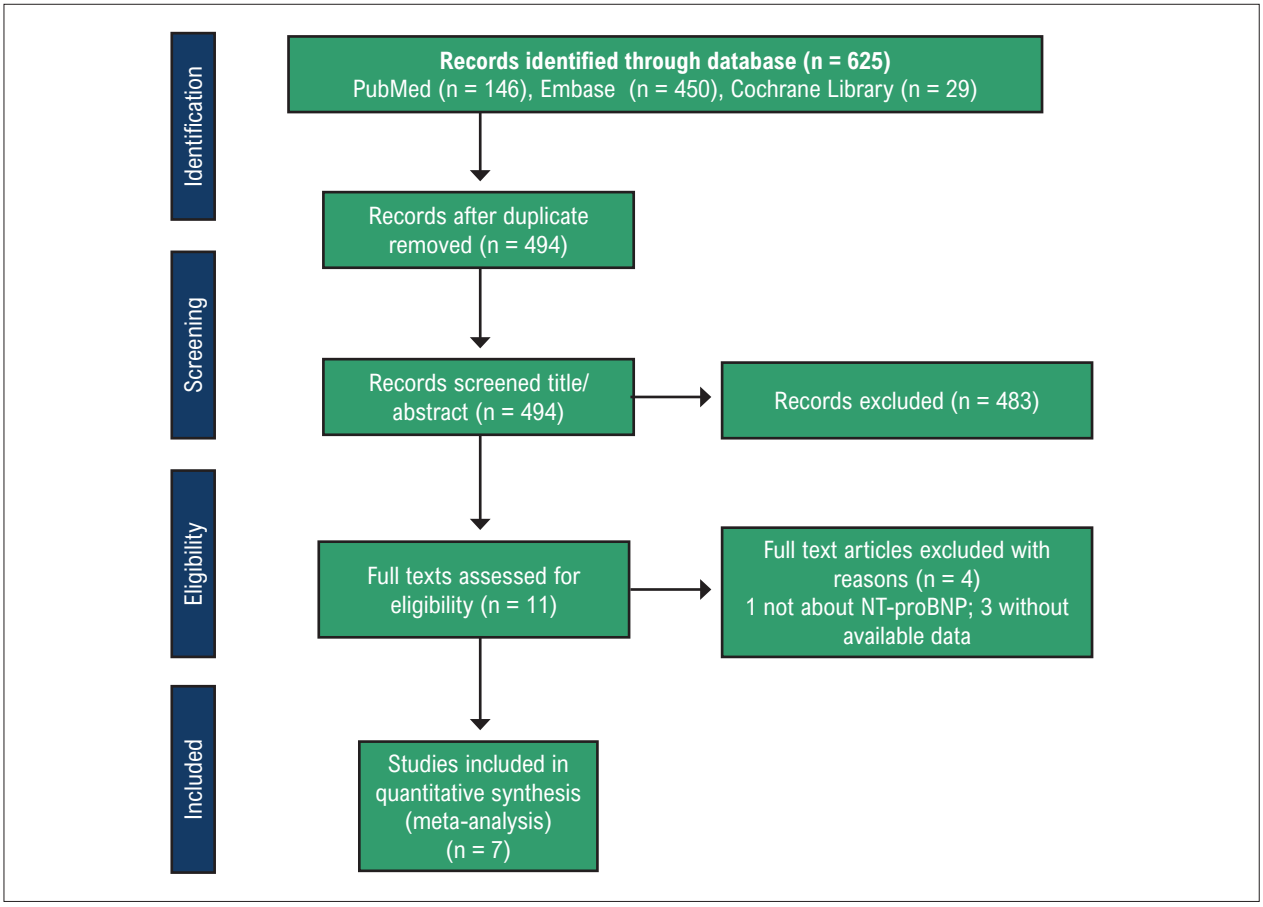

Figure 1 – *The process and results of literature retrieval.*

criteria of cardiac involvement and diagnostic thresholds were organized in Table 1. Among the 7 included studies, 5[12,21-23,25] generated differential analysis on age of subjects, and 4 studies[12,21-23] compared the difference in gender between cases and controls. In these studies, Damy et al.[21] found significant differences in the gender and age of the study subjects ($p < 0.05$); samples included by Klaassen et al. were significantly different in age ($p < 0.05$); and other comparisons at $p \geq 0.05$ were considered age- and/or gender-matched. Other three studies from Nicol[25] and Palladini et al.[24,26] did not compare differences in age and/or sex. We then used QUADAS 2 for the quality assessment of publications, and results showed a low risk of bias and a high quality of methodology of involved studies (Supplemental Figure 1).

Diagnostic value of NT-proBNP

A total of 7 articles (10 sets of population data) reported the results of NT-proBNP levels in the diagnosis of heart damage in patients with amyloidosis, and Spearman correlation analysis suggested a $p = 1.00$ as the result which indicated no significant threshold effect. A bivariate mixed effect model was then established to investigate the diagnostic value of NT-proBNP in heart damage based on different indicators, and Cochran's and I^2 tests were applied for analysis on heterogeneity among studies. The results (Figure 2) showed that the estimated sensitivity and specificity were 0.93 and 0.84, respectively. No significant heterogeneity was found in sensitivity ($p = 0.67$, $I^2 = 0.0\%$); however, a significant heterogeneity was identified in specificity ($p = 0.01$, $I^2 = 58.86\%$) across studies. In Figure 3, the combined value of PLR was 5.77, with a significant heterogeneity between studies ($p = 0.01$, $I^2 = 34.74\%$), while that for NLR was 0.80 with no significant heterogeneity ($p = 0.79$, $I^2 = 0.0\%$). Figure 4A showed these data sets were significantly heterogeneous in DOR ($p < 0.01$, $I^2 = 84.77\%$) with a combined estimate of 69.53. The AUC of SROC was 0.95, and these studies were not significantly distributed in a curvilinear shape (Figure 4B), suggesting a great diagnostic validity of NT-proBNP in heart damage.

Clinical utility of NT-proBNP

We further performed a Fagan's nomogram to evaluate the clinical utility of NT-proBNP, as shown in Figure 5, and the Fagan nomogram plot presented the pre-test probability, PLR, NLR, and post-test probability of NT-proBNP in the diagnosis of heart injury. The results

Table 1 – Characteristics of 7 included studies in this meta-analysis

Study	Area	Proof of amyloidosis	Type of amyloidosis	Criterion of cardiac involvement	N	Case/ Control			Cut-off, pg/ml	TP	FP	FN	TN
						n	Age, years	Male, n (%)					
CappelliF,[12] 2014	Italy	Biopsy	AL	RVD	76	23/53	70.7±9.2/ 68.9±10.1	9 (39.1)/ 24 (45.3)	≥2977	20	8	3	45
Damy, T[21] 2013	France	NR	TTR	LVD	36	26/10	65(56-74)/ 40 (33-56) *	20 (76.9)/ 3 (30.0) *	≥82	24	1	2	9
Klaassen, SHC[22] 2017	The Netherlands	Biopsy	TTR	Structural myocardial wall abnormalities and/ or conduction disturbances	77	39/38	59.3±10.9/ 46.1±13.0 *	25 (64.1)/ 18 (47.4)	≥125	36	13	3	25
Lehrke, S[23] 2009	Germany	Biopsy	AL or TTR	Positive heart biopsy and/or LVH	34	25/9	55.5±11.0/ 59.8±7.8	10 (40.0)/ 6 (66.7)	≥1736.5	23	3	2	6
Nicol, M[25] 2020	France	Biopsy	AL	CMR and endomyocardial biopsy	114	82/32	66 (58-73)/ 68 (60-76)	NR	≥850	75	8	7	24
					73	48/25	NR	NR	≥850	44	1	4	24
Palladini, G[24] 2003	Italy	Biopsy	AL	Clinical symptoms of heart failure, LVH	152	90/62	61 (34-78) #	NR	≥152	84	6	6	56
Palladini, G[26] 2012	Italy	Biopsy	AL	Left ventricular wall thickness >12 mm	109	62/47	62 (29-83) #	63 (58) #	≥332	62	5	0	42
					77	54/23	64 (35-85) #	34 (44) #	≥543	50	2	4	21
					62	41/21	65 (38-82) #	33 (53) #	≥2642	38	6	3	15

*AL: amyloid light chain; TT: hereditary transthyretin-related; CMR: cardiac magnetic resonance imaging; RVD: Right ventricular dysfunction; LVD: Left ventricular dysfunction; LVH: left ventricular hypertrophy; NR: not reported; TP: true positive; FP: false positive; FN: false negative; TN: true negative. #, data of total sample. Statistical significances of all studies except Palladini et al.[24,26] were set at $p < 0.05$, and * indicates the statistical difference.*

suggested that the pre-test probability of patients with heart damage was 60.5%, while the post-test probability was 90% and 8% for positive and negative patients, respectively. That means after the diagnosis of NT-proBNP, the probability of developing heart damage in populations with NT-proBNP positive was 90%, while the possibility for NT-proBNP negative populations was only 8%.

Sensitivity analysis and publication bias test

A graph model was then conducted for sensitivity analysis. The results suggested a great residual-based goodness-of-fit of the model (Figure 6A), which basically conformed to the bivariate normality assumption (Figure 6B). This study also found that each independent study had no significant effect on the combined results of the model, and no outlier was identified (Figure 6C-D). Finally, a Deek's funnel plot was created to test the publication bias, and results in Figure 7 suggested no significant publication bias with a $p = 0.31$ in the asymmetry test. These findings proposed stable and reliable combined results in this meta-analysis.

Discussion

Diagnosis of cardiac involvement for patients with amyloidosis is often delayed by the diversity of its clinical manifestations, thereby resulting in a poor prognosis.[5] It is reported that once AL amyloidosis presents symptoms of congestive heart failure, untreated patients have a median survival of less than 6 months.[2] Therefore, it is essential to develop a CA involvement-related biomarker to improve the efficiency of early diagnosis. NT-proBNP has been used as a potential biomarker to assess the severity of cardiac involvement in AL amyloidosis,[27] but the independent role in CA involvement and its diagnostic specificity have not been fully investigated. Hence, this meta-analysis was performed based on 7 articles, and evaluated the influence of NT-proBNP on the diagnosis of CA involvement. Our results suggested that NT-proBNP had significant diagnostic values for heart damage in patients with amyloidosis, with a sensitivity of 0.93, a specificity of 0.84, a PLR of 5.77, a NLR of 0.08 and a DOR of 69.53. The AUC of SROC curve was also close to 1 (0.95), thus demonstrating a great diagnostic validity of NT-proBNP.

It is reported that the local destruction of cardiomyocytes will lead to elevated levels of NT-proBNP, and the increasing NT-proBNP level could be considered as a predictor of cardiac involvement before the onset of heart failure.[7] Banypersad et al. also found a correlation between heart disease and NT-proBNP in 100 patients with AL amyloidosis scanned by nuclear magnetic resonance imaging.[28] Furthermore, 1-year mortality of 125 patients with AL amyloidosis can be predicted through the risk stratification analysis on NT-proBNP and cTn.[29] As for the potential regulation mechanism of NT-proBNP expression on amyloid in cardiomyocytes, Shi et al.

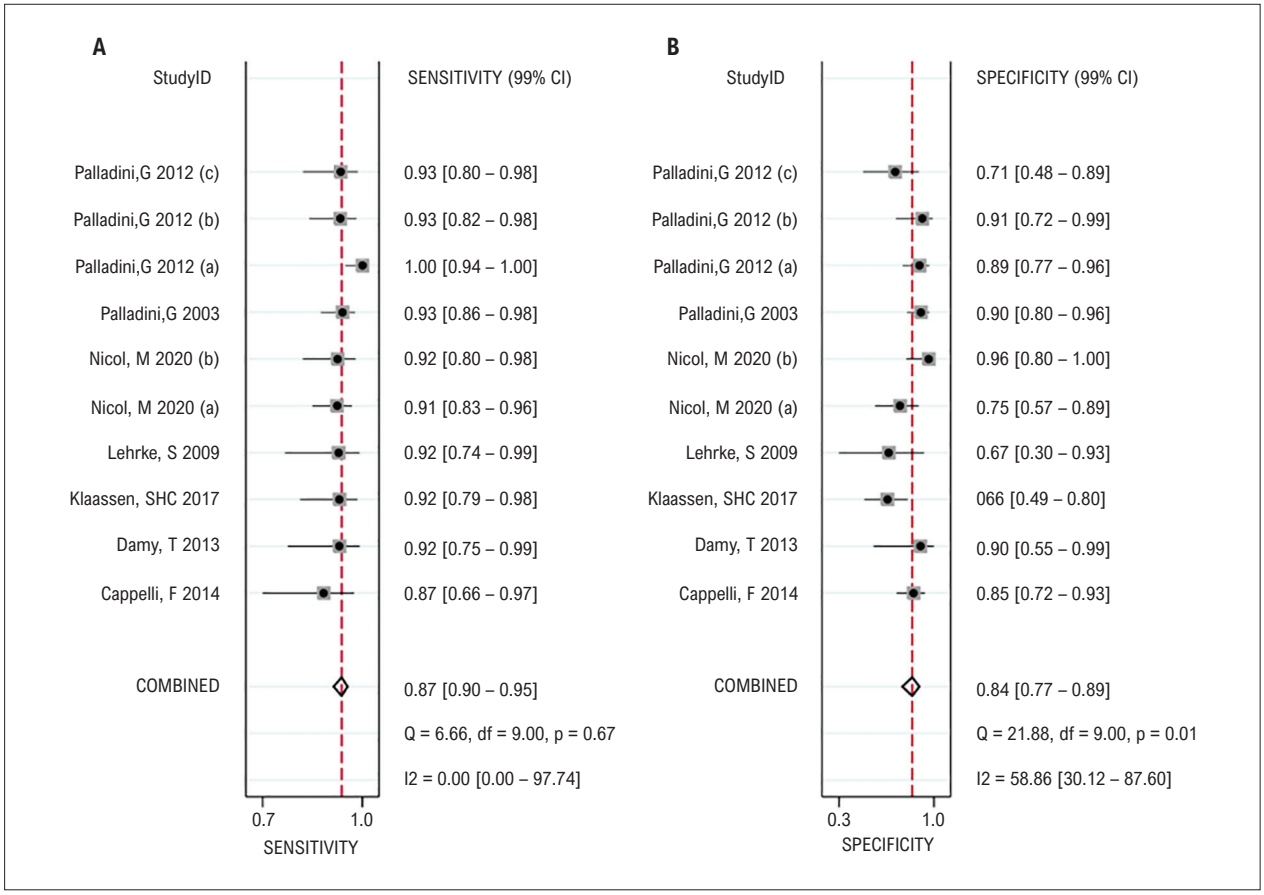

Figure 2 – *Forest plots of estimates of sensitivity (A) and specificity (B) in the diagnosis of NT-proBNP to heart damage from 10 sets of data.*

proposed that light chain proteins isolated from amyloid cardiomyopathy tissues may induce p38 mitogen activated protein kinase (MAPK) signal, thereby contributing to the oxidative stress and death of cardiomyocytes.[30] Moreover, for AL amyloidosis, MAPK signal could mediate BNP transcription, and their interaction may support the cardiotoxic effect of light chain proteins.[31] Combined with the above findings, it can be speculated that the expression of NT-proBNP could be directly regulated by the MAPK signal transduction pathway induced by light chain proteins in cardiomyocytes, and the increased expression level of NT-proBNP can predict the attack of heart failure.

A variety of studies have focused on the influence of NT-proBNP on cardiac involvement, including heart failure, cardiomyopathy, and myocardial infarction. A related meta-analysis reported that the combined sensitivity and specificity of NT-proBNP level in differentiating heart failure associated effusion was 94%, with a PLR of 15.2 and a NLR of 0.06.[32] The increasing level of NT-proBNP also shows a strong ability to predict the prognosis of cardiomyopathy.[33] Additionally, by comparing to revised cardiac risk index, the high-sensitivity biomarker NT-proBNP can improve the prediction of myocardial infarction after major non-cardiac surgery.[34] These findings supported our conclusions, but Januzzzi et al. further proposed that the level of NT-proBNP was correlated with the severity of heart failure symptoms, and the sensitivity and specificity of heart failure varied between different age groups.[35] In this study, no direct relationship was observed between age and NT-proBNP levels, and we were unable to confirm the importance of age in the CA involvement diagnosed by NT-proBNP. Additionally, studies also found that female subjects have higher levels of NT-proBNP than age-matched male subjects.[36] Therefore, a stratified analysis will be conducted at a future moment to explore the differences of NT-proBNP markers based on analytical performance, so as to provide more accurate diagnostic information for patients with CA involvement at different clinical stratification.

The virtue of this study included that the incorporated study was highly qualified in methodology, and the confounding bias was minimal. Furthermore, there was no significant publication bias in this study, and the influence analysis also suggested that the combined results were not affected by each independent study. More importantly, the combined results of all indicators were relatively consistent, suggesting that NT-proBNP had

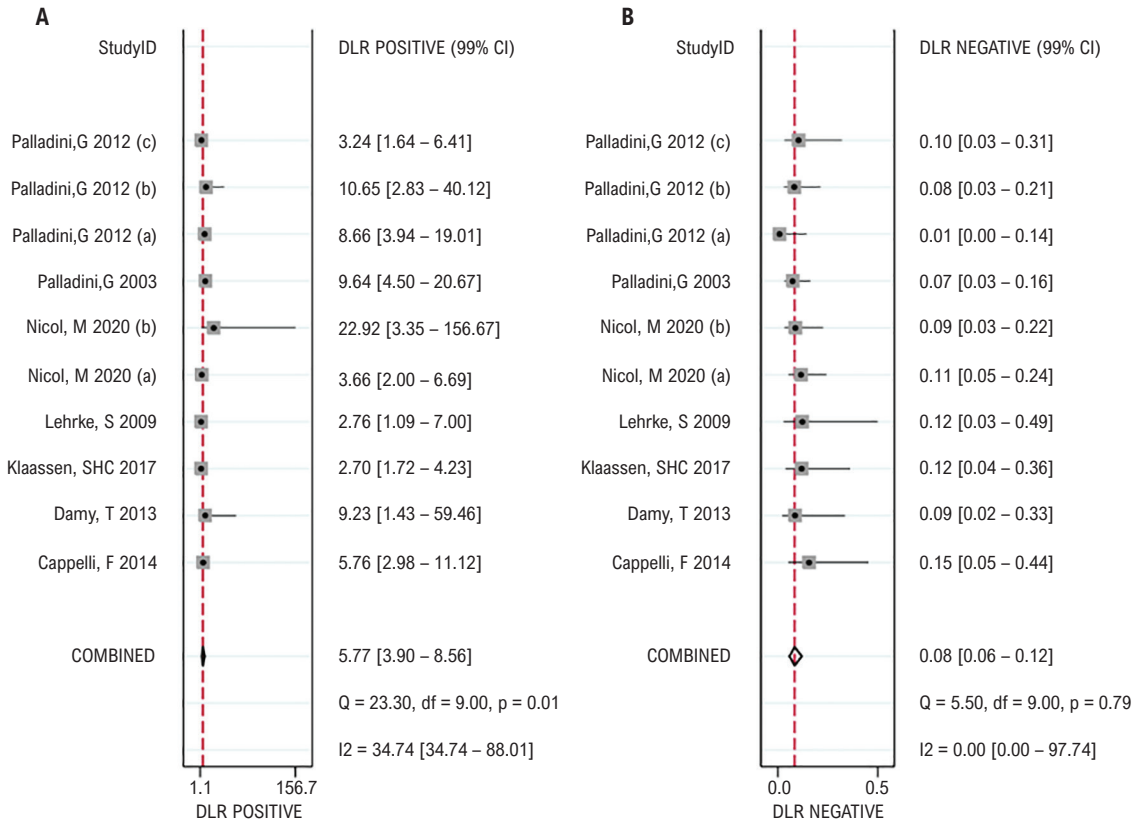

Figure 3 – *Forest plots of estimates of PLR (A) and NLR (B) in the diagnosis of NT-proBNP to heart damage from 10 sets of data.*

a high application value in the diagnosis of heart damage in patients with amyloidosis, and the results were stable and reliable. Although our results suggested high sensitivity and specificity of NT-proBNP in the diagnosis of CA involvement, the significant heterogeneity in specificity, PLR and DOR between included studies was one of the limitations. Meanwhile, there were also differences in diagnostic criteria, types of amyloidosis and criteria for determining cardiac damage among the subjects. However, due to limited simple size of included literatures, it is difficult to explore the source of heterogeneity through quantitative methods, such as meta-regression. Secondly, all included studies were carried out based on the population of Europe with a poor generalization of results. High-quality studies are still needed in Asia, Africa, and other regions to validate the performance of results.

Conclusion

In conclusion, this study suggested that NT-proBNP played a positive role in the early diagnosis of cardiac involvement in patients with amyloidosis. Large-scaled studies in other regions and races are needed to verify the extrapolation of the results.

Author Contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Zhang Y; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual contente: Chaolu H.

Potential Conflict of Interest

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

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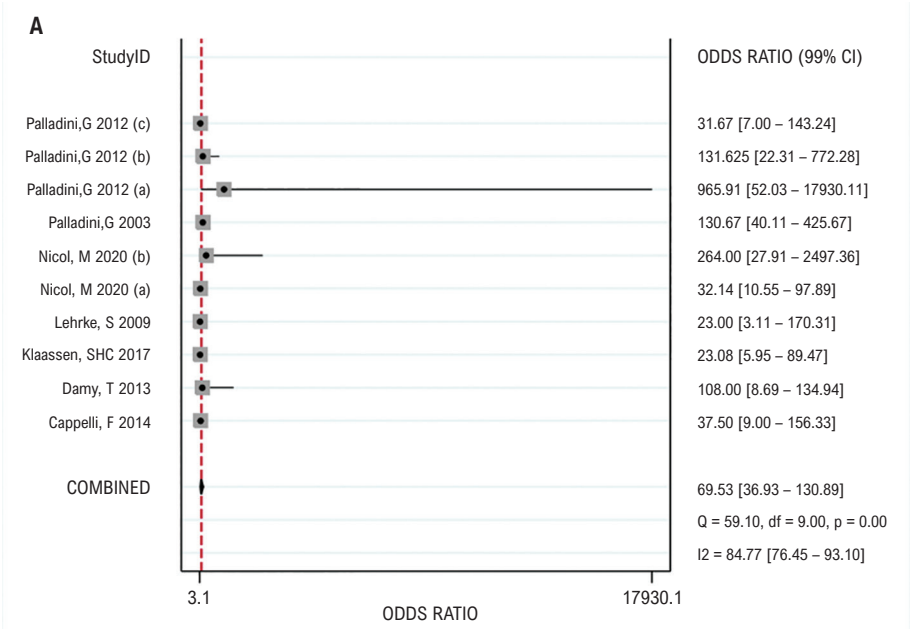
Study Association

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.



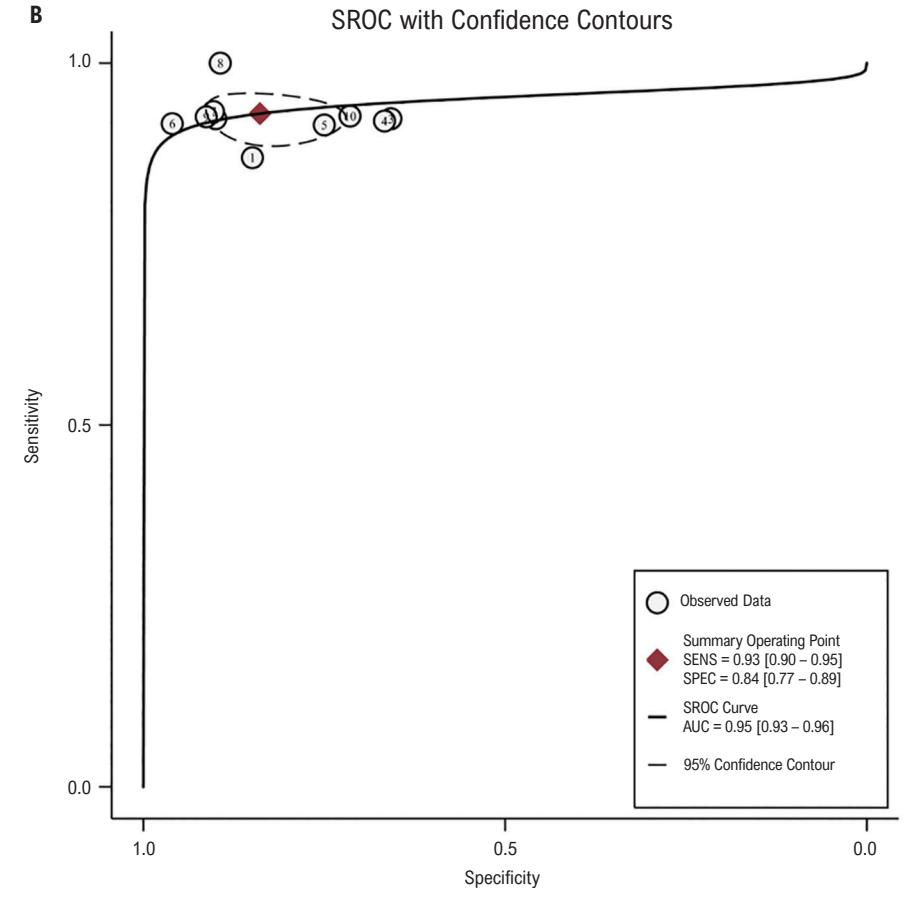


Figure 4 – *Diagnostic validity of NT-proBNP to heart damage. A) Forest plots of estimates of DOR from 10 sets of data. B) SROC curve showed the diagnostic validity of NT-proBNP in heart damage with an AUC of 0.95.*

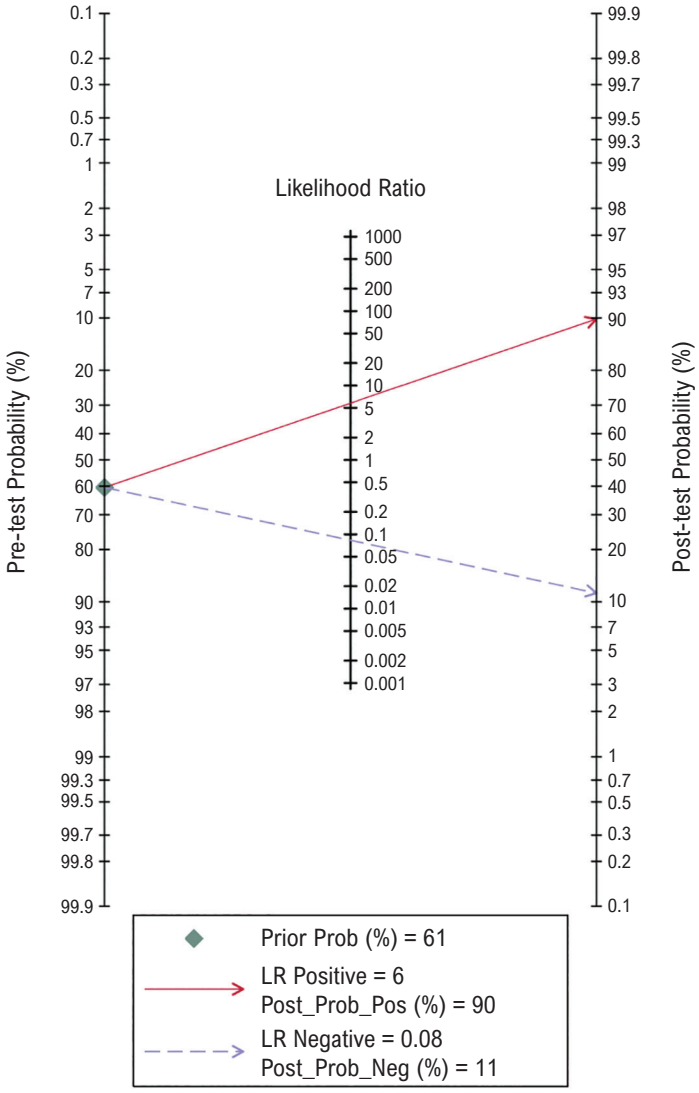


Figure 5 – *The clinical utility of NT-proBNP. The Fagan nomogram plot showed the pre-test probability, PLR, NLR, and post-test probability of NT-proBNP for the diagnosis of heart injury.*

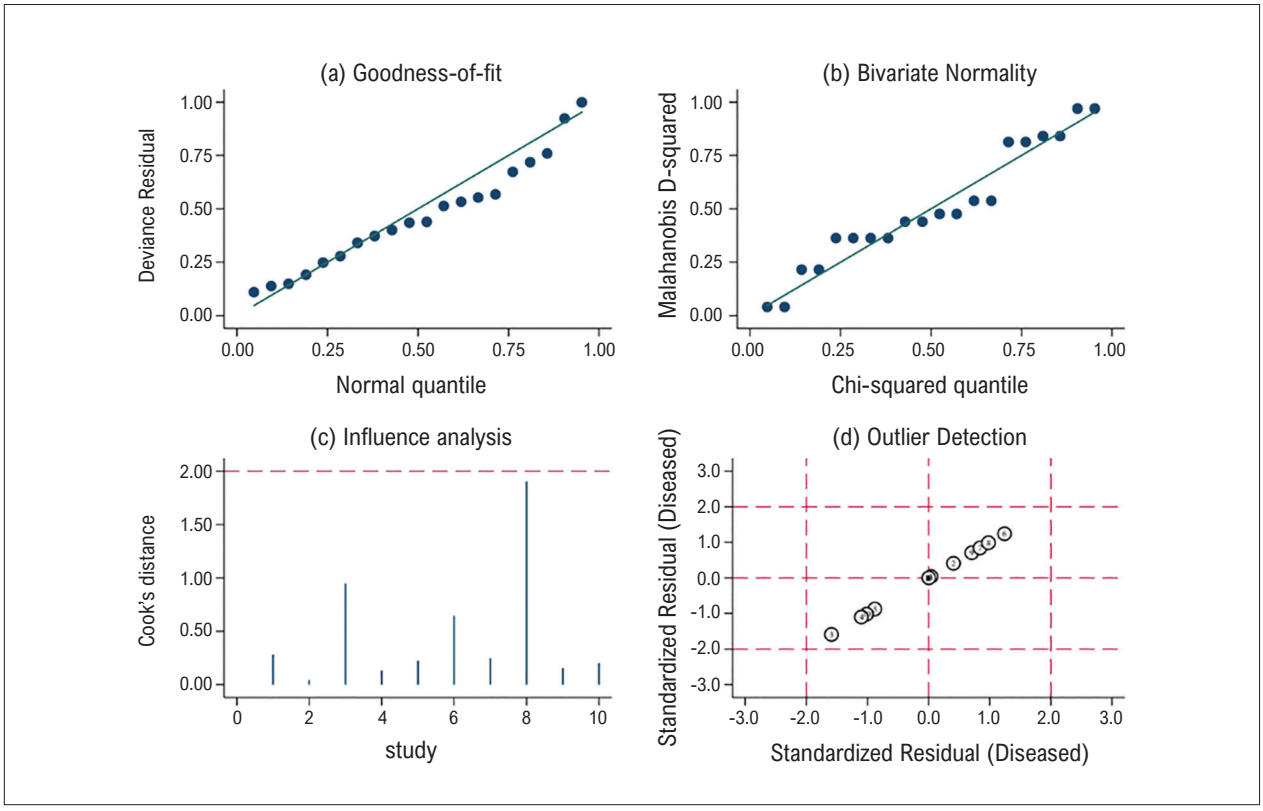


Figure 6 – *Sensitivity analysis in a graph model. A-B) showed the goodness-of-fit and bivariate normality of the model. C) Influence analysis of independent study on the combined results. D) Outlier detection of independent study.*

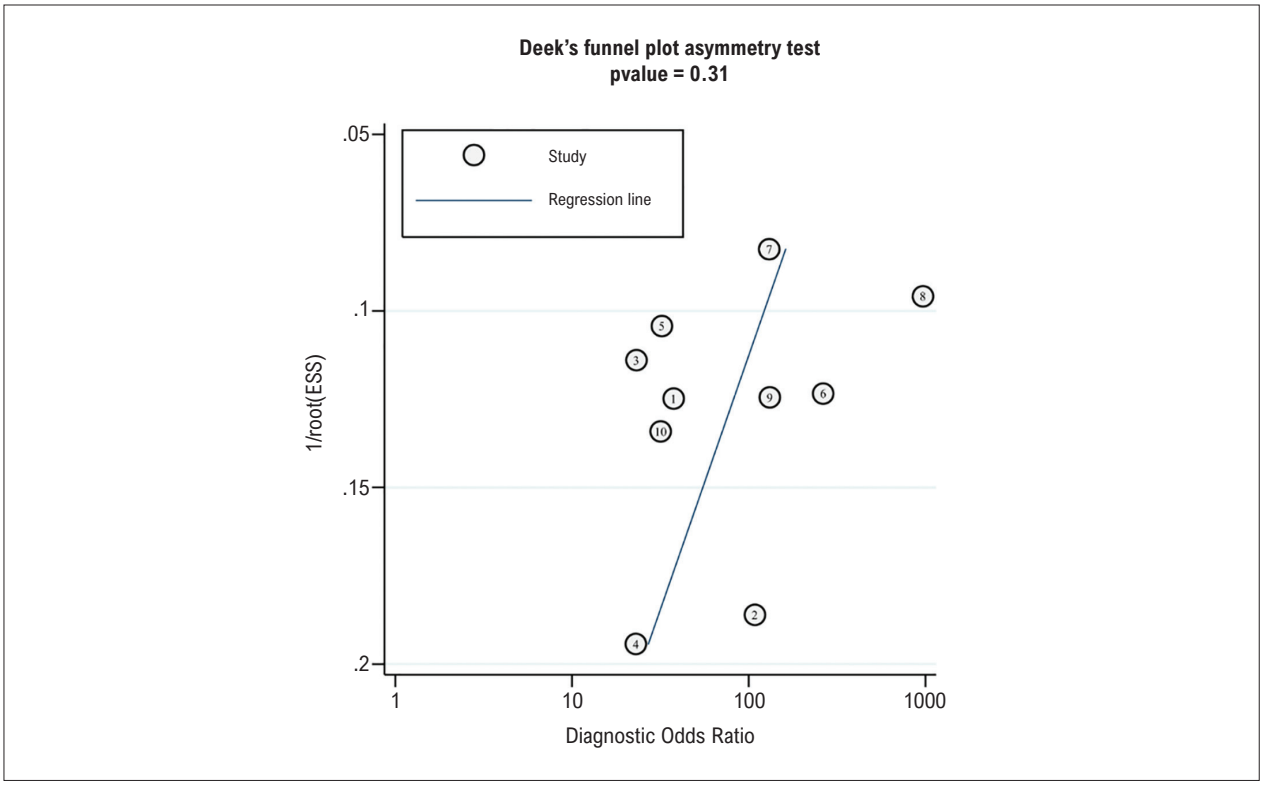


Figure 7 – *Publication bias test. Deek's funnel plot showed the publication bias in the asymmetry test.*

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*Supplemental Materials

See the Supplemental Figure, please click here.

See the Supplemental Tables, please click here.

Utility of Biomarkers in Suspected Cardiac Amyloidosis: Opportunity for More Frequent and Early Diagnosis

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Short Editorial rellated to the article: Diagnostic Role of NT-proBNP in Patients with Cardiac Amyloidosis Involvement: A Meta-Analysis

The meta-analysis entitled "Diagnostic Role of NT-proBNP in Patients with Cardiac Amyloidosis Involvement: A Meta-Analysis" brings us an important review of the usefulness of NT-proBNP measurement in patients with cardiac involvement by amyloidosis. The demonstration of good sensitivity and specificity of this biomarker reinforces its usefulness in the diagnosis of cardiac amyloidosis (CA).[1]

Cardiac amyloidosis has been increasingly diagnosed, especially in patients with the heart failure phenotype of preserved ejection fraction.[2] Just over half of the patients with symptoms of heart failure have preserved ejection fraction, especially elderly individuals. This finding is usually considered only as age-related diastolic dysfunction and associated comorbidities. However, this factor should be one of the warning signs for diagnosing CA, especially when associated with high levels of biomarkers.[3] A great variability in the frequency of diagnosis of CA in the general population has been described, ranging from 5 to 74% between the various studies.[1] This variability may be related to factors such as low clinical suspicion or difficulties accessing complementary exams necessary for diagnosing cardiac involvement in amyloidosis. The diagnostic flowchart in patients with suspected cardiac involvement by amyloidosis is mainly based on imaging tests.[4-6] These tests can be expensive, such as myocardial scintigraphy, strain echocardiography and cardiac magnetic resonance, and, often, they are only available at cardiology referral centers, making the diagnosis of CA more difficult and delayed.[3] In addition, it is important to note that the late diagnosis of these patients can directly influence the prognosis by delaying the start of treatment, leading to a median of 6 months of survival after the development of symptoms in the AL form of amyloidosis for example.[4]

Therefore, especially in less developed centers, CA is still underdiagnosed, configuring a serious public health problem. With this, the use of non-invasive, easily accessible and low-cost exams can be important. In this scenario, the measurement of biomarkers such as NT pro-BNP, troponin or others can be useful not only in the initial evaluation but also in the prognostic evaluation of patients with suspected cardiac amyloidosis. NT pro-BNP has been used for several years in the diagnosis, clinical follow-up and prognosis of patients with other etiologies of heart failure.[7,8] Studies with NT-proBNP in CA have shown good diagnostic accuracy, including being part of the evaluation for the prognostic staging of the disease.[9,10] In addition to diagnostic and prognostic evaluation, biomarkers can also be used to assess the therapeutic efficacy of these patients, especially in hematologic patients under chemotherapy, where they may be cardiotoxic.[4]

It is important to point out that cardiac amyloidosis is an increasingly frequent disease due to the aging of the population. However, this disease is still underdiagnosed, especially in less developed centers or where high-cost tests are not easily accessible to the population that uses public services. Therefore, it is necessary to organize diagnostic flowcharts that are more accessible to most of the population, and the measurement of biomarkers such as NT-proBNP is very useful in this scenario.

Keywords

Amyloidosis, Cardiac; Biomarkers; NT-proBNP;Stroke Volume; Heart Failure; Ventricular Dysfunction; Diagnostic, Imaging/methods

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Original Article

Comparison of Novel Martin/Hopkins and Sampson Equations for Calculation of Low-Density Lipoprotein Cholesterol in Diabetic Patients

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Abstract

Background: The accurate determination of low-density lipoprotein cholesterol (LDL-C) is important to reach guideline-recommended LDL-C concentrations and to reduce adverse cardiovascular outcomes in diabetic patients. The commonly used Friedewald equation (LDL-Cf), gives inaccurate results in diabetic patients due to accompanying diabetic dyslipidemia. Recently two new equations – Martin/Hopkins (LDL-Cmh) and Sampson (LDL-Cs) – were developed to improve the accuracy of LDL-C estimation, but data are insufficient to suggest the superiority of one equation over the other one.

Objective: The present study compared the accuracy and clinical usefulness of novel Martin/Hopkins and Sampson equations in diabetic patients.

Methods: This study included 402 patients with diabetes. Patients' cardiovascular risk and LDL-C targets were calculated per European guidelines. Calculated LDL-Cmh, LDL-Cs, and LDL-Cf concentrations were compared with direct LDL-C concentration (LDL-Cd) to test agreement between these equations and LDL-Cd. A p-value <0.05 was accepted as statistically significant.

Results: Both LDL-Cmh and LDL-Cs had a better agreement with LDL-Cd as compared to LDL-Cf, but no statistical differences were found among novel equations for agreement with LDL-Cd (Cronbach's alpha 0.955 for both, p=1). Likewise, LDL-Cmh and LDL-Cs showed a similar degree of agreement with LDL-Cd in determining whether a patient was in a guideline-recommended LDL-C target (96.3% for LDL-Cmh and 96.0% for LDL-Cs), which were marginally better than LDL-Cf (94.6%). In patients with a triglyceride concentration >400 mg/dl, agreement with LDL-Cd was poor, regardless of the method used.

Conclusion: Martin/Hopkins and Sampson's equations show a similar accuracy for calculating LDL-C concentrations in patients with diabetes, and both equations were marginally better than the Friedewald equation.

Keywords: Metabolic Diseases; Atherosclerosis, Dyslipidemias; Coronary Artery Disease; Diabetes Mellitus; Lipoproteins, LDL; Cholesterol, LDL.

Introduction

There is a well-known relationship between low-density lipoprotein cholesterol (LDL-C) and atherosclerotic coronary artery disease (CAD).[1] Patients with diabetes are not only more likely to have CAD but are also more prone to dyslipidemias, including elevated triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), and increased concentrations of small, dense LDL-C particles.[2-4] There is strong evidence suggesting improved cardiovascular outcomes with cholesterol-lowering treatment in Diabetes Mellitus (DM) patients with dyslipidemias, and although the relationship between LDL-C and CAD is less certain in patients with DM, available international guidelines recommend using LDL-C as the primary target for management decisions.[5-8] Thus, accurate measurement of LDL-C is of paramount importance in patients with DM.

The gold standard for measuring LDL-C is β-quantification, but this technique is technically demanding and resource-intensive, so it is not routinely employed in practice.[9] While direct LDL-C (LDL-Cd) assays are now commercially available, these are not widely adopted, and many laboratories still report calculated LDL-C concentrations

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instead.[10] Friedewald equation (LDL-Cf), which is the most common method employed in practice, is unreliable when triglyceride concentration exceeds 150 mg/dl and LDL-C is below 70 mg/dl.[11-12] This is a particular concern for patients with DM, as hypertriglyceridemia is a common component of diabetic dyslipidemia. Recently, Martin/Hopkins (LDL-Cmh) and Sampson (LDL-Cs) equations were developed to provide a better estimate of LDL-C concentration, especially when TG is elevated.[13-14] However, few studies have provided a head-to-head comparison of these two equations, and there are no data in patients with DM.[15-17]

The present study aimed to compare LDL-Cmh, LDL-Cs, and LDL-Cf equations with LDL-Cd to understand which equation had a better agreement with LDL-Cd in diabetic patients and to what degree these novel equations could change clinical decision-making as compared to LDL-Cf.

Materials and Methods

Patient selection

For the present investigation, cardiology outpatient records were reviewed retrospectively for the years 2019 and 2020. Patients who were 18 years of age or older and had diabetes at the time of admission were included in the study. Patients with incomplete records were excluded. No other inclusion or exclusion criteria were used. Diabetes was defined as having one of the following: i) being on antidiabetic treatment with a previous diagnosis of diabetes or ii) a hemoglobin A1c% concentration equal to or greater than 6.5%. Patients' demographic, clinical, and laboratory data were retrospectively collected from an institutional electronic database. Glomerular filtration rate was calculated using Modified Diet in Renal Disease – Glomerular Filtration Rate equation, and patients with a glomerular filtration rate <60 ml/min/1.73 m^2 were accepted as having chronic renal disease. Patients were classified into intermediate, high, and very-high cardiovascular risk according to the 2019 European guidelines on the management of dyslipidemias.[7] LDL-C targets for each individual patient were determined using the same guidelines. The study was conducted according to the principles of the 1975 Declaration of Helsinki and its subsequent revisions, and ethical approval was obtained from a local ethics committee.

Measurement of direct LDL-C and calculation of estimated LDL-C

Blood samples were collected using standard methods, and samples were sent to the laboratory within 30 minutes after collection. LDL-Cd was measured by a colorimetric method using the Abbott Architect Plus ci8200 integrated analysis system (Abbott Labs, Chicago, IL, USA) and Archem LDL-Cd test reagents (Archem Health Ind, Turkey). Other blood chemistry analyses, including lipid parameters, were carried out using standard methods, and the same blood sample was used for all analyses. LDL-Cf was calculated as:

Eq1. LDL-C = TC - HDL-C - (TG/5)

as previously described. To calculate LDL-Cs, the second equation reported in the work of Sampson et al. was used,[13] which is as follows:

Eq2. (TC / 0.948) - (HDL-C / 0.971) - (TG / 8.56) + [(TG * Non-HDL-C / 2140) - (TG2 / 16100)] - 9.44

LDL-Cmh needs different VLDL: TG "factors" for calculation and a single mathematical equation could not be used to derive LDL-Cmh.[14] Instead, LDL-Cmh was calculated using spreadsheets provided by a supported and maintained website by Johns Hopkins University School of Medicine.[18]

Statistical analyses

Continuous variables were given as mean ± standard deviation, while categorical variables were presented as percentages. For continuous variables, distribution patterns were analyzed with the Shapiro-Wilk test and visual inspection of the histograms. Correlation analyses were conducted by applying the Pearson test, and correlation coefficients were provided to give an overall measure of strength of relationship between different methods. Bland-Altman plots were drawn to visually assess the agreement between LDL-Cd and calculated LDL-C concentrations. Similarly, Cronbach's alpha and intraclass correlation coefficients were calculated for a quantitative assessment of the agreement. Cronbach's alpha values were compared using Feldt's method.[19] Correct classification for being within the guideline-recommended LDL-C target, as well as reclassification rates relative to LDL-Cd was given as percentages. Kappa coefficients for the agreement were calculated for each pair. Patients were stratified per TG concentrations (TG<150 mg/dl, TG 150-400 mg/dl, and TG>400 mg/dl) and separate subgroup analyses were done for each stratum. Finally, patients on anticholesterolemic medications were analyzed to understand the agreement between LDL-Cd and calculated LDL-C concentrations in terms of reaching the target LDL-C concentration. A p-value <0.05 was accepted as statistically significant for all comparisons. Statistical analyses were performed with Jamovi (The jamovi project (2020). Jamovi (Version 1.2) for Windows, retrieved from (https://www.jamovi.org) and SPSS 25.0 (IBM Corp, Armonk, NY, USA) statistical packages.

Results

The demographic and clinical characteristics of the study group were presented in Table 1. More than four-fifths of the study cohort had either high or very high risk, while only a quarter of the patients were on at least one anticholesterolemic drug. Mean LDL-C calculated with all three equations were lower than LDL-Cd, while the largest difference was between LDL-Cd and LDL-Cf.

Correlation and agreement between LDL-Cd and calculated LDL-C

All three equations presented a strong correlation with LDL-Cd, but LDL-Cf showed the lowest value (r=0.915) compared

to LDL-Cmh (r=0.932) and LDL-Cs (r=0.929) (Figure 1). Data on the agreement between LDL-Cd and calculated LDL-C concentrations were presented in Table 2. LDL-Cmh and LDL-Cs had a virtually similar agreement with LDL-Cd, while both equations had a significantly better agreement compared to LDL-Cf (p<0.001 for both). On Bland-Altman plots, the number of cases that exceeded upper and lower limits of agreement was 12 (2.98%) for LDL-Cmh, 15 (3.73%) for LDL-Cs, and 16 (3.98%) for LDL-Cf (Figure 2).

Concordance and reclassification

Data on agreement with LDL-Cd for "being in LDL-C target", as well as reclassification rates, were provided in Table 3. Concordances were similar for LDL-Cmh and LDL-Cs, and 3.7% - 3.9% of cases can be reclassified with LDL-Cd, respectively. Reclassification rates were lower with both equations as compared to LDL-Cf, as LDL-Cd reclassified 5.5% of the cases that were proved to be within or out of LDL-C target with LDL-Cf.

Agreement and reclassification per TG strata

In patients with a TG <400 mg/dl, all three equations had a good agreement with LDL-Cd, but the agreement was slightly better with both LDL-Cmh and LDL-Cs as compared with LDL-Cf (Supplementary Tables 1 and 2). The agreement was somewhat better with LDL-Cmh in patients within the TG <150 mg/dl strata and with LDL-Cs in patients with a TG 150-400 mg/dl, but the differences were minimal. Reclassification rates were also similar, although concordance with LDL-Cd was somewhat better with LDL-Cmh than LDL-Cs in patients with a TG 150-400 mg/dl. To note, the reclassification rate was similar with LDL-Cf when compared to novel equations in those with a TG <150 mg/dl, but not in those with a TG >150 mg/dl.

Concordance between LDL-Cd and novel equations was poor in those with a TG concentration above 400 mg/dl. Agreement for "being in target" was somewhat better for LDL-Cs as compared to LDL-Cmh, though the difference was rather trivial (Supplementary Table 2).

Patients on anticholesterolemic treatment

Similar to the whole study cohort, the performance of LDL-Cmh and LDL-Cs were similar in the subgroup of patients on anticholesterolemic drugs. To note, both equations had a small but significantly better agreement with LDL-Cd as compared to LDL-Cf, and reclassification rates were somewhat lower when either LDL-Cmh or LDL-Cs were used instead of LDL-Cf (Supplementary Tables 3 and 4).

Patients with an LDL-C <70 mg/dl

In the present study, 20 patients (4.9%) presented an LDL-Cd <70 mg/dl, while 33 (8.2%), 28 (7.0%), and 44 (10.9%) presented an LDL-C <70 mg/dl when Sampson, Martin/Hopkins, and Friedewald equations were used. The number of patients incorrectly classified as having an LDL-C were 15 (3.7%), 12 (3.0%), and 26 (6.4%) when LDL-Cs, LDL-Cmh, and LDL-Cf were used, respectively. Supplemental Table 5 summarizes reclassification rates with LDL-Cd for patients with a calculated LDL-C below 70 mg/dl. Reclassification rates were comparable for LDL-Cmh and LDL-Cs, but proportionally more patients with a LDL-Cf <70 mg/dl can be reclassified with LDL-Cd as compared to patients with LDL-Cmh or LDL-Cs <70 mg/dl.

Table 1 – Demographic. clinical. and laboratory characteristics of the study sample

Characteristic	Value
Age (years)	56 ± 13
Gender (female)	189 (47.0%)
Body mass index (kg/m^2)	29.4 ± 4.4
Systolic blood pressure (mmHg)	134.0 ± 17.5
Diastolic blood pressure (mmHg)	80.5 ± 10.1
Smoking (%)	118 (29.4%)
Coronary artery disease (%)	83 (20.6%)
Chronic kidney disease (%)	10 (2.7%)
Oral antidiabetic (%)	372 (92.5%)
Insulin (%)	58 (14.4%)
Antihypercholesterolemic drugs (%)	111 (27.6%)
Fasting glucose (mg/dl)	140.0 ± 54.1
Hemoglobin A1c (%) (n=336)	7.0 ± 1.7
Creatinine (mg/dl)	0.88 ± 0.24
GFR (ml/min/m^2)	90.4 ± 38.1
Total cholesterol (mg/dl)	199.0 ± 45.3
Triglycerides (mg/dl)	163 (108 – 223)
HDL-cholesterol (mg/dl)	45.3 ± 10.6
Direct LDL-cholesterol (mg/dl)	125.0 ± 35.0
SCORE risk strata	
Intermediate risk	75 (18.7%)
High risk	212 (52.7%)
Very high risk	115 (28.6%)
Martin/Hopkins LDL-cholesterol	120.0 ± 38.4
Sampson LDL-cholesterol	123.0 ± 38.1
Friedewald LDL-cholesterol	24.5 (7.6)

GFR: Glomerular Filtration Rate; HDL: High-density lipoprotein; LDL: low-density lipoprotein; OAD: Oral antidiabetic; SCORE: Systematic coronary risk evaluation.

Discussion

The present study compared calculated LDL-C concentrations with LDL-Cd in diabetic patients, with a particular focus on comparing LDL-Cmh and LDL-Cs to understand which novel equation would be the most clinically useful. The main takeaways from the present study are: i) both LDL-Cmh and LDL-Cs had a strong relationship and a good agreement with LDL-Cd, and there are no major differences between equations in terms of reclassification; ii) both equations were better than LDL-Cf - especially in patients with a TG>150 mg/dl; however, the benefits of using either

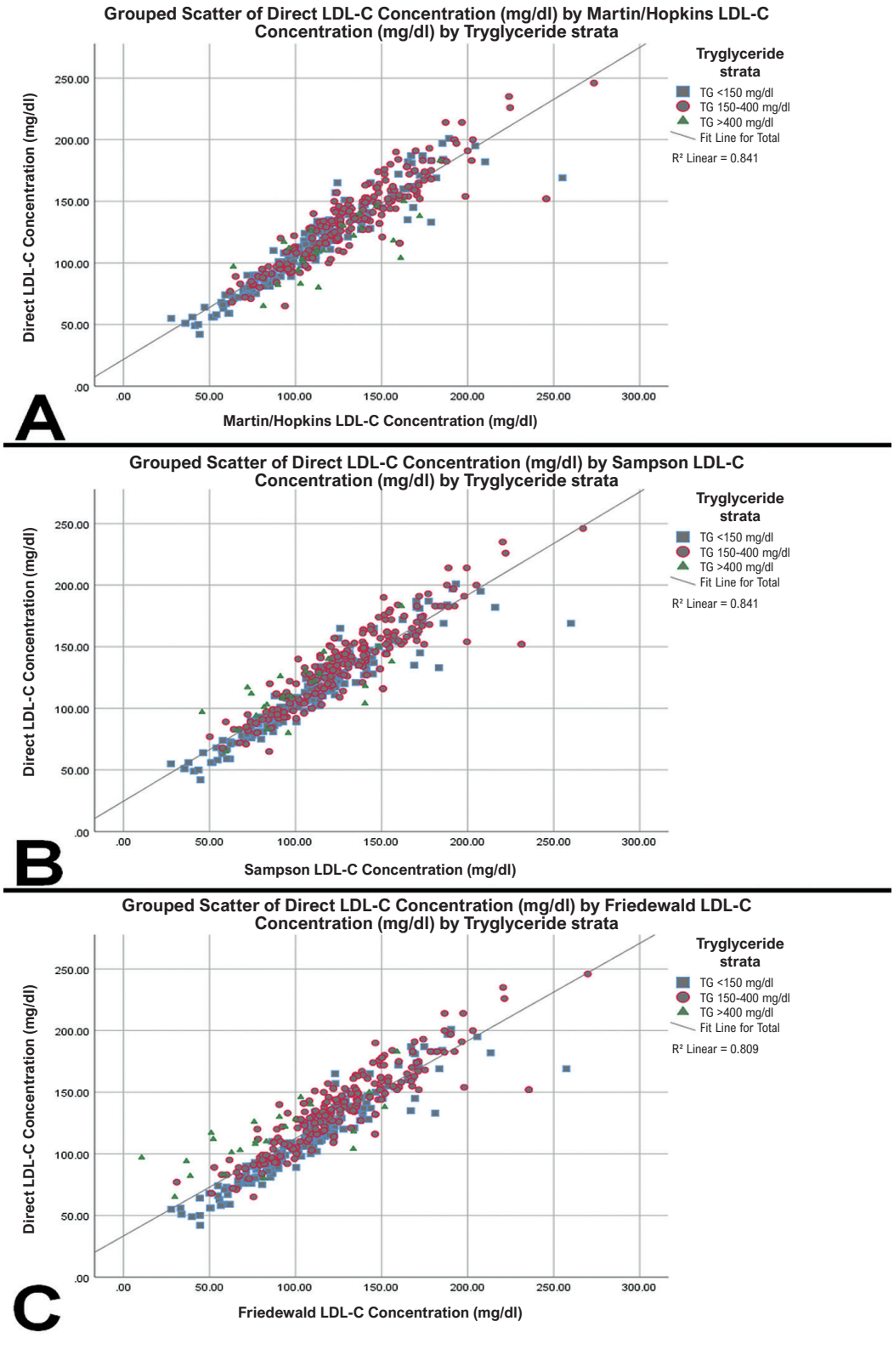

Figure 1 – *Scatter plots showing the correlation of direct LDL-cholesterol concentrations with LDL-cholesterol concentrations calculated with (A) Martin/Hopkins equation, (B) Sampson equation, and (C) Friedewald equation. Plots were color-coded to reflect LDL-cholesterol concentrations at different triglyceride concentrations.*

Table 2 – Agreement between direct LDL-cholesterol concentration and calculated LDL-cholesterol concentrations

Method	Cronbach's alpha				ICC	
	alpha	p (vs. Martin)	p (vs. Sampson)	p (vs. Friedewald)	Coefficient	95% CI
Martin/Hopkins	0.955	-	1	<0.001	0.912	0.893 - 0.928
Sampson	0.955	1	-	<0.001	0.905	0.870 - 0.929
Friedewald	0.943	<0.001	<0.001	-	0.867	0.754 - 0.918

CI: Confidence Interval; ICC: intraclass correlation coefficient.

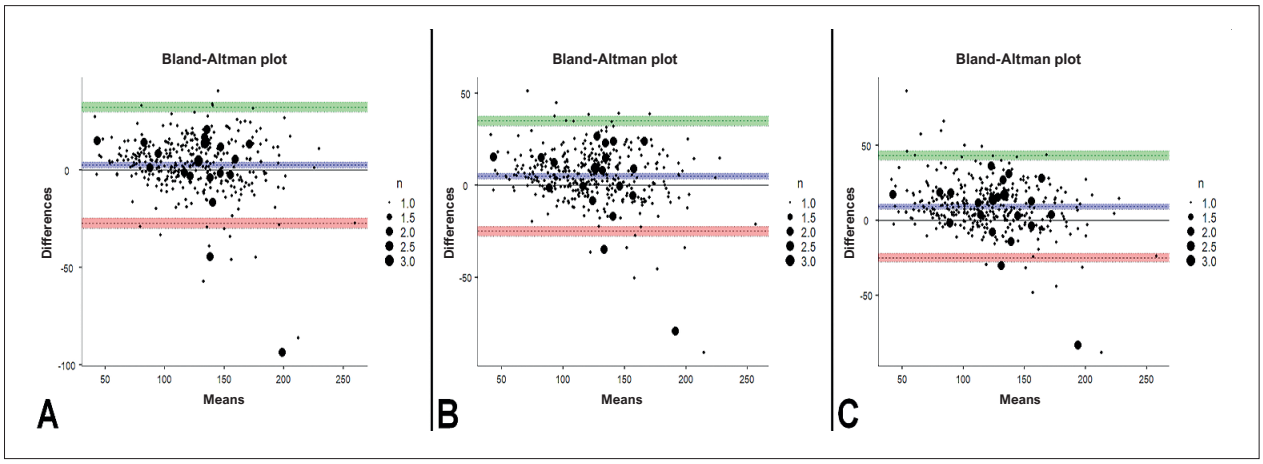

Figure 2 – *Bland-Altman plots showing the agreement between direct LDL-cholesterol concentrations with LDL-choleserol concentrations calculated with (A) Martin/Hopkins equation, (B) Sampson equation, and (C) Friedewald equation. Colored regions at the upper and lower parts of the plots show 95% confidence intervals (CI) of upper and lower agreement limits.*

equation were marginal; iii) LDL-Cmh had a near-excellent concordance with LDL-Cd in those with a TG concentration between 150-400 mg/dl, with only 1.5% of the patients being misclassified when LDL-Cmh was used, iv) all equations performed poorly when TG concentration exceeded 400 mg/dl, with less than 90% of the patients being classified correctly even with the best-performing LDL-Cs equation; and v) agreement between LDL-Cd and calculated LDL-C was poor in those with a calculated LDL-C below 70 mg/dl, with more than a quarter of the patients being reclassified with LDL-Cd, regardless of the equation used. Nevertheless, in this latter subgroup, LDL-Cs and LDL-Cmh performed better than LDL-Cf.

With the possible exception of younger patients with a short exposure to hyperglycemia, diabetic patients are at high risk for myocardial infarction and coronary mortality.[20] As dyslipidemia is also common in these patients, multiple lines of evidence suggest that diabetic patients benefit from intensive LDL-C lowering with lifestyle modifications and antihypercholesterolemic drugs.[3,21,22] However, an accurate calculation of LDL-C is more problematic in diabetic patients, given that elevated TGs are common in diabetic patients and high TG concentrations cause an inaccurate estimation of LDL-C. This is especially true for calculations done with the Friedewald equation, which gives inadequate LDL-C estimates when TG concentrations are above 150 mg/dl.[11] Martin/Hopkins equations give more robust LDL-C estimates and are less sensitive to changes in TG, as long as TG concentrations are below 400 mg/dl.[14] More recently, Sampson et al. defined a new equation, and their initial findings suggest that this equation gives correct LDL-C estimates as long as TG concentrations are below 800 mg/dl.[13] However, to what extent were these initial findings applicable for diabetic patients, or whether these new equations could have any impact on patient management, were less certain. A recent study that included 1,828 Japanese patients with diabetes has found that Martin/Hopkins equations have a better agreement with LDL-Cd and as compared to LDL-Cf, especially when TG was above 150 mg/dl.[23] However, this study used Japanese guidelines to determine whether patients were within guideline-recommended targets, and as Japanese guidelines were not widely used outside Japan, the applicability of their results for other populations was uncertain.[23] While our results are largely confirmatory of this previous work, the present findings also indicate that the concordance between calculated LDL-C and LDL-Cd is above 90% regardless of the equation used; therefore, the clinical benefits of using novel Martin/Hopkins or Sampson equations over Friedewald equation is much less apparent than initially claimed. However, given that both equations allow correct classification of a significantly higher proportion of cases with virtually no additional costs (perhaps with the exception of incorporating more complex equations to the existing automation systems), using either equation could be advisable in diabetic patients.

Table 3 – Agreement between direct LDL-cholesterol method and other methods for reaching guideline-recommended LDL-cholesterol target

Method	Concordance	Underestimation	Overestimation	Kappa	p-value
Martin/Hopkins	387 (96.3%)	12 (3.0%)	3 (0.7%)	0.774	<0.001
Sampson	386 (96.0%)	14 (3.4%)	2 (0.5%)	0.768	<0.001
Friedewald	380 (94.6%)	20 (5.0%)	2 (0.5%)	0.703	<0.001

Concordance means both methods agree whether a patient was within or out of the LDL-cholesterol target. Underestimation means that the method in question classified cases as within the specified LDL-cholesterol target, although these cases did not reach specific LDL-cholesterol target per direct LDL-cholesterol methods. Overestimation means that the method in question was classified as out of the specified LDL-cholesterol target while direct LDL-cholesterol method suggested otherwise.

Since both Martin/Hopkins and Sampson equations were defined in the last ten years, studies directly comparing these equations with each other are scarce. Two studies that compared Martin/Hopkins and Sampson equations with the Friedewald equation have found that their ability to reclassify cases was roughly similar.[15,16] However, these studies did not compare the accuracy of these equations against a benchmark method. More recently, Cwiklinska et al.[17] used both β-quantification and a direct LDL-assay to compare Martin/Hopkins and Sampson equations, and they reported that both methods were more accurate than the Friedewald equation.[17] While this study did not provide a head-to-head comparison between two novel equations, their numbers indicate that the number of cases exceeding the total error goal of 12% was smaller with Martin/Hopkins equations (134 vs. 157 cases).[17] Nonetheless, this study did not report the possible clinical importance of these findings, and their findings were not specific to patients with diabetes. Our results indicate that both equations had a very similar agreement with LDL-Cd and the clinical decision-making should be similar in the vast majority of patients regardless of which equation was used. Taking this into account, in the subgroup of patients with a TG 150-400 mg/dl, LDL-Cmh had a near-perfect agreement with LDL-Cd, thus making it preferable for diabetic patients in this TG strata.

Estimating LDL-C becomes even more difficult when TG concentrations exceed 400 mg/dl, not only because very-low-density lipoprotein concentrations are underestimated, but also because LDL-C is suppressed by increasing TGs beyond this point.[13] Neither the Friedewald nor the Martin/Hopkins equations gave a reliable estimate of LDL-C beyond that cut-off value.[10,24] The Sampson equation enabled a better estimation of LDL-C for patients with hypertriglyceridemia for TG concentrations up to 800 mg/dl, and in the original study, the misclassification rate was comparable to the misclassification rate of LDL-Cf equation for those with a TG <400 mg/dl.[13] A promising new equation, which was not included in this analysis, was also recently introduced for patients with chronic kidney disease, in whom hypertriglyceridemia is also common.[25] This latter equation appears to be as accurate as LDL-Cmh in this patient subset, but it was not validated beyond those with kidney disease.[26] Indeed, present findings were not suggestive of the superiority of one novel equation to another. Our results have indicated that while LDL-Cs had the best agreement with LDL-Cd, misclassification rates were unacceptable, as more than 10% of the cases were misclassified regardless of the equation used. Indeed, only one extra patient could be correctly classified when LDL-Cs were used instead of LDL-Cmh (Supplementary Table 2). Therefore, using LDL-Cd or an alternative method, such as non-HDL-C cholesterol or apolipoprotein B concentrations, should be preferred over estimated LDL-Cd in these patients, until a more reliable equation is available.

Finally, it has been suggested that LDL-Cf performs poorly in patients with an LDL-C <70 mg/dl due to its "fixed factor", and this can be improved with novel equations.[13,14] Our findings indicate that LDL-Cf misclassifies up to one-third of the diabetic patients with a LDL-Cf less than 70 mg/dl, and this figure can be lowered by applying novel equations, but up to one quarter of these patients are still misclassified as being within treatment targets even when using these equations, with no major difference between LDL-Cs and LDL-Cmh. Although this finding supports the use of novel equations rather than LDL-Cf in this subgroup, they nonetheless suggest that none of the available equations have adequate reliability for diabetic patients with an LDL-C below 70 mg/dl.

Study Limitations

Direct enzymatic LDL-C assays have been criticized for a lack of reliability and standardization, and β-quantification remains as the gold standard method for quantifying LDL-C.[10] However, next-generation assays are much more reliable and are endorsed by relevant international guidelines, and enzymatic LDL-C assays have already served as the reference method in several studies.[7,23,27,28] β-quantification is too labor intensive to be used in routine practice, and even β-quantification of LDL-C is not devoid of errors, as it can include cholesterol from other lipoproteins.[13] The study population was rather small (402 cases), and the number of cases with a TG >400 mg/dl was only 24, a condition that might have affected the reliability of the subgroup analysis in this stratum.

Conclusions

In diabetic patients, Martin/Hopkins and Sampson's equations have similar reliability to estimate LDL-C, with no obvious advantage of preferring one equation over another. However, both equations were superior to the Friedewald equation in terms of agreement with LDL-Cd, and both

had lower reclassification rates when compared to LDL-Cf, especially in patients with TG>150 mg/dl. Since the difference between the two equations was trivial, either equation could be preferred over the Friedewald equation in diabetic patients. In the small subset of patients with a TG concentration above 400 mg/dl, none of the equations had adequate accuracy and as such, direct measurement of LDL-C should be considered in these patients.

Author contributions

Conception and design of the research, writing of the manuscript and critical revision of the manuscript for intellectual content: Abdulrahman Naser, Khagani Isgandarov, Tolga Sinan Güvenç, Rengin Çetin Güvenç, Müslüm Şahin. Acquisition of data: Abdulrahman Naser, Khagani Isgandarov, Rengin Çetin Güvenç. Analysis and interpretation of the data: Abdulrahman Naser, Tolga Sinan Güvenç, Rengin Çetin Güvenç, Müslüm Şahin. Statistical analysis: Tolga Sinan Güvenç.

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 Istinye University Ethics Office on Human Research under the protocol number (2017-KAEK-120) / 2/2020.G-080. Desion number: 2/2020.K-057.

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*Supplemental Materials

For additional information, please click here.

Friedewald, Martin/Hopkins, or Sampson/NIH: Which is the Best Method to Estimate LDL-Cholesterol?

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Short Editorial related to the article: Comparison of Novel Martin/Hopkins and Sampson Equations for Calculation of Low-Density Lipoprotein Cholesterol in Diabetic Patients

Atherosclerotic cardiovascular disease (ASCVD) is the main cause of death in Brazil and most of the world.[1] Reduction in low-density lipoprotein cholesterol (LDL-c) is the first lipid goal to prevent ASCVD. The decision on the initiation or intensification of LDL-c lowering drug therapy is based on the risk of events and the LDL-c level,[2] so an accurate determination of LDL-c is highly desirable.

The gold standard method to determine the plasma concentration of LDL-c is β-quantification, an expensive, time-consuming procedure based on ultracentrifugation and precipitation. Direct methods that use proprietary chemicals instead of ultracentrifugation are also time-consuming and costly. Moreover, they lack standardization, and the accuracy is not always good.[3]

For several decades, LDL-c has been estimated by a formula proposed by Friedewald in the 1970s.[4] LDL-c is given by subtracting HDL-cholesterol (HDL-c) and VLDL-cholesterol (VLDL-c) from total cholesterol, and VLDL-c is estimated by dividing triglycerides (TG) by a fixed factor of 5. The problem is that the fraction of TG that estimates VLDL-c is not constant. When the TG level is high, or the LDL-c concentration is low, the Friedewald formula overestimates VLDL-c and, consequently, underestimates LDL-c. When the TG level is ≥400 mg/dL, the accuracy of the Friedewald formula is unacceptably low.[3] LDL-c underestimation may prevent appropriate treatment and exacerbate low achievement of LDL-c targets, a relevant issue in the fight against ASCVD.[5,6]

Other methods to calculate LDL-c more accurately have been proposed, and the most successful so far is the Martin/Hopkins formula. This method estimates VLDL-c by dividing TG by an adjustable factor according to TG and non-HDL-c levels.[7] This equation is especially indicated when the LDL-c is <70 mg/dL, the TG are between 175 and 400 mg/dL, or in nonfasting conditions, when the Friedewald formula has more limitations.[3,8]

Keywords

Cholesterol-LDL; Hypercholesterolemia; Laboratory Tests/methods; Hyperlipidemias

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In 2020, another equation was proposed by Sampson et al. using samples from the National Institutes of Health. VLDL-c was estimated by multiple least squares regression. The authors state that the method has similar or greater accuracy than other approaches and is useful for calculating LDL-c in conditions of high TG levels up to 800 mg/dL.[9]

In this context, Naser et al.[10] report in the *Arquivos Brasileiros de Cardiologia* a study comparing LDL-c calculated by the aforementioned methods with LDL-c directly measured in 402 patients with diabetes mellitus. They conclude that the Martin/Hopkins and Sampson/NIH equations have a similar agreement with measured LDL-c, slightly better than that observed with the Friedewald formula. However, all the equations showed poor performance when the TG concentration was >400 mg/dL.[10] Although the comparator used in this study (direct method) is subject to criticism, as pointed out above, the work contributes to the knowledge while assessing the relative accuracy of the Sampson/NIH method. In this sense, evidence from two large databases using directly measured LDL-c as the comparator favored the Martin/Hopkins approach,[11,12] whereas a smaller study found that the Sampson/NIH formula had higher concordance with LDL-c estimated using VLDL-c measured by ultracentrifugation in individuals with familial combined hyperlipidemia.[13]

Two recent studies published by Sajja et al.[14,15] from Johns Hopkins University have raised concerns about the Sampson/NIH method. In one of them, the authors showed that an extended version of the Martin/Hopkins equation had better accuracy than the Friedewald and Sampson/NIH formulas in individuals with TG levels of 400 to 799 mg/dL. However, LDL-c underestimation was common at low levels with all the methods, especially Friedewald and Sampson/NIH. Importantly, a nonfasting state did not change the performance of the Martin/Hopkins method but reduced the accuracy of the Sampson/NIH formula.[14] In another work, the authors demonstrated clinically meaningful differences in LDL-c calculated by different formulas in patients with ASCVD. LDL-c was usually higher with the Martin/Hopkins equation, suggesting a higher rate of LDL-c underestimation with the Friedewald and Sampson/NIH methods.[15]

What could be practical recommendations regarding LDL-c estimation? At low LDL-c levels or high TG concentrations, the clinician should remember that the calculated LDL-c may be underestimated, particularly if the Friedewald formula was used. Accordingly, current guidelines have recommended the Martin/Hopkins method when the LDL-c is <70 mg/dL or the TG level is

175-400 mg/dL.[3] While the newer Sampson/NIH equation has performed consistently better than the Friedewald formula, accuracy comparable to that of the Martin/Hopkins method has been questioned, and its routine use should wait for more validation data.

When the TG level is >400 mg/dL, LDL-c is better determined by a direct method. Measurement of apolipoprotein B and calculation of non-HDL-c level are also useful to refine risk stratification and help clinical decisions.[3]

Estimating LDL-c by equations is an evolving issue. Newer methods have surpassed the old Friedewald formula. At low LDL-c levels or high TG concentrations (especially ≥400 mg/dL), caution is advised in calculating LDL-c due to the chance of underestimation and undertreatment.

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Cardiometabolic Risk in Children and Adolescents: The Paradox between Body Mass Index and Cardiorespiratory Fitness

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Abstract

Background: Cardiometabolic risk has been shown to be inversely associated with cardiorespiratory fitness (CRF) and positively associated with body mass index (BMI).

Objective: Our objective was to analyze the association of cardiometabolic risk factors with combined BMI and CRF in schoolchildren from a city in southern Brazil.

Methods: Cross-sectional study with a sample of 1252 schoolchildren aged seven to 17 years. Total cholesterol (TC), HDL-c, LDL-c, triglycerides (TG), systolic (SBP) and diastolic blood pressure (DBP) were evaluated. CRF and BMI were grouped into one variable and the schoolchildren were classified as eutrophic/fit, eutrophic/unfit, overweight-obese/fit, and overweight-obese/unfit. Crude and adjusted analyzes were performed using Poisson Regression and an alpha of 0.05 was adopted.

Results: Overweight-obese and fit schoolchildren showed a prevalence ratio (PR) of 1.50 (1.04 – 2.16) for altered TG, 3.05 (2.05 – 4.54) for elevated SBP, and 2.70 (1.87 – 3.88) for elevated DBP. Overweight-obese and unfit schoolchildren showed a PR for high TC of 1.24 (1.11 – 1.39) and 1.51(1.11 – 2.04) for low HDL levels. In addition, they had a risk of 2.07 (1.60 – 2.69) for altered TG, 3.36 (2.31 – 4.60) for elevated SBP and 2.42 (1.76 – 3.32) for altered DBP.

Conclusion: BMI played a central role in the association with risk and CRF was shown to attenuate the association between risk factors and obesity. Overweight-obese children and adolescents had a higher cardiometabolic risk, but the effect size was larger among the unfit.

Keywords: Students; Child; Adolescent; Obesity; Cardiorespiratory Fitness; Risk Factors.

Introduction

Body mass index (BMI) and cardiorespiratory fitness (CRF) have been independently and oppositely associated with a higher occurrence of cardiometabolic risk in children and adolescents.[1–3] However, the joint relationship of these variables with risk is still unclear, but evidence indicates that CRF could attenuate the association between overweight and cardiometabolic risk factors.[4]

In this regard, evidence suggests that subjects with overweight and obesity but good levels of cardiorespiratory fitness have a more favorable cardiometabolic profile than subjects with excess adiposity but low levels of CRF.[1,5] There is also evidence that higher levels of CRF are related to lower mortality risk among groups with similar BMI[6] and that satisfactory levels of CRF in childhood may mitigate cardiometabolic risks related to overweight and obesity in adulthood.[7]

The paradox of obese individuals but with good levels of CRF who do not have significant risk for cardiometabolic factors has already been evidenced in adults.[8,9] In children and adolescents, this paradox is still inconsistent.[9,10] Given these premises, the objective of the present study is to analyze the association of cardiometabolic risk factors with BMI and CRF combined in schoolchildren from a city in southern Brazil. Our hypothesis is that overweight and obese schoolchildren with good cardiorespiratory fitness will present a lower risk than schoolchildren with similar BMI but low levels of fitness.

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Method

Cross-sectional study based on data from the research "School Health – Phase II", approved by the local Ethics Committee for Research with Human Beings, protocol 3044/11. To participate in the research, children and adolescents needed to present the Informed Consent Form (ICF) signed by their guardians.

The inclusion criteria established for the study were: belonging to the age group of 7 to 17 years old; not having any contraindication for biological sample collection (blood), not having any limitation for physical fitness tests. The schoolchildren who did not fill out the research instruments correctly did not collect blood or did not perform physical fitness tests were excluded from the study.

Data collection was carried out in 2011 and 2012 at the university campus, on a day and time previously scheduled by the researchers with the school. Sample calculation was performed for Poisson regression, using the G * Power 3.1 program (Heinrich-Heine-Universität - Düsseldorf, Germany), considering a test power (1 - β) = 0.95, significance level α = 0.05, and an effect size of 0.30.

The selection of the subjects that made up the sample occurred randomly, with the selected schools stratified by urban and rural areas. The urban area was stratified by center and periphery (south, north, east, and west) and the rural area by south, north, east, and west regions. After applying the exclusion criteria, the sample for the present study consists of 1252 schoolchildren belonging to 19 schools in the city of Santa Cruz do Sul (RS, Brazil). Figure 1 presents the flowchart with the sample selection process.

Weight and height measurements were taken in the early morning, with the subject fasting and wearing light clothes and barefoot. From these measurements, BMI was calculated using the formula BMI = weight / height^2 (kg/m^2) and classified according to the CDC/ NCHS percentile curves,[11] according to sex and age, considering underweight (<p5), eutrophic (≥p5 and <p85), overweight (p≥85 and <p95), and obesity (≥p95).

Cardiorespiratory fitness was assessed using the 9-minute running and walking test performed on an athletics track, according to the protocol and cutoff points for sex and age of the Brazil Sport Project (PROESP-BR) manual.[12] The manual recommends that the students run/walk the longest distance

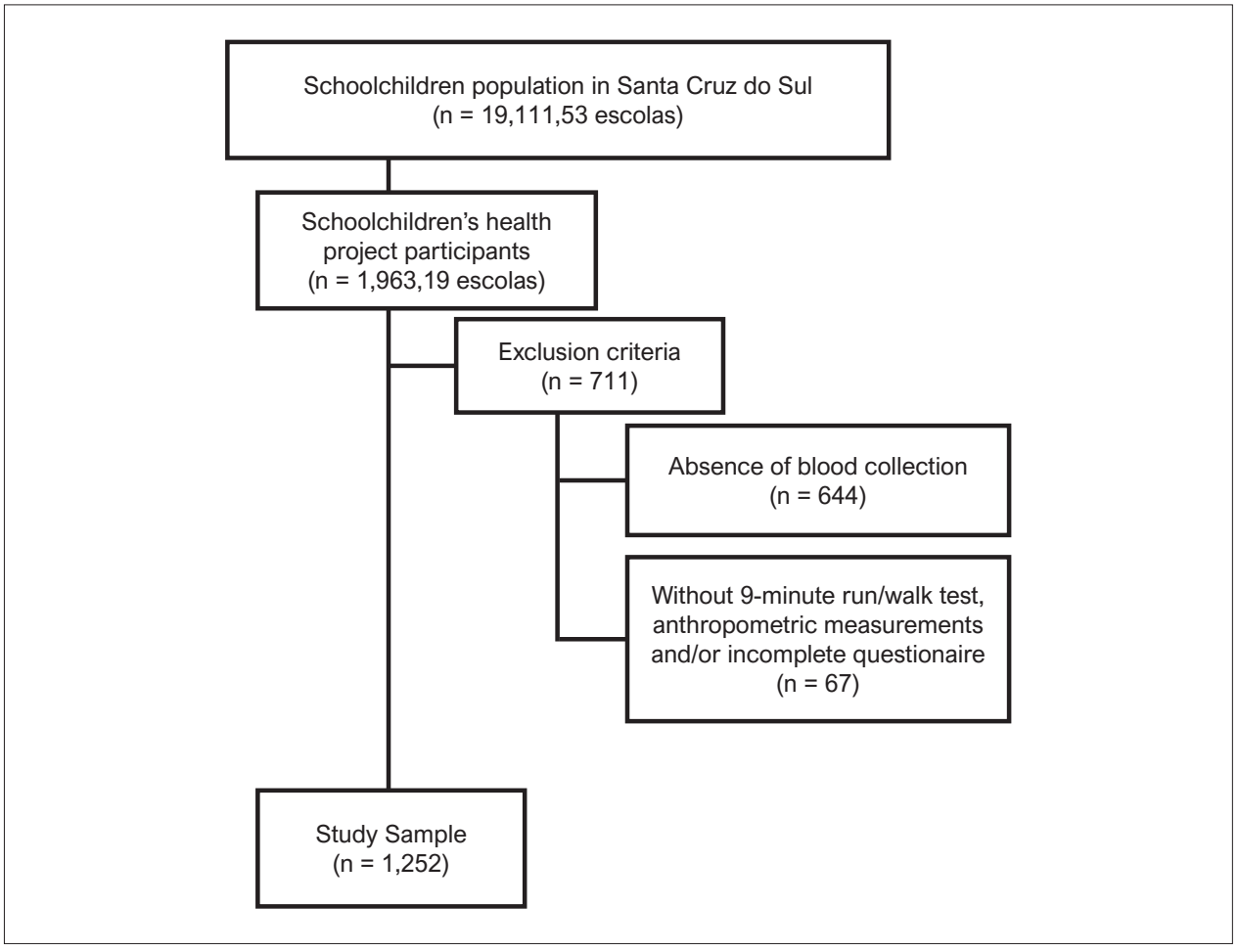

Figure 1 – *Sample selection flowchart.*

possible for nine minutes, no breaks over the period. In the end, the distance covered by the students (in meters) was classified considering the critical values proposed by the manual for age and sex.

A combined variable was generated from the BMI and CRF categories, used as exposure in the present study. This variable was classified into four categories: (1) eutrophic/fit: schoolchildren with low weight and eutrophic and classified as fit in the CRF evaluation; (2) Eutrophic/unfit: schoolchildren with low weight and eutrophic and classified as unfit in the CRF evaluation; (3) overweight - obese/fit: schoolchildren classified with overweight or obesity and as fit; (4) overweight – obese/unfit: schoolchildren classified with overweight or obesity and unfit.

The outcomes evaluated were cardiometabolic risk factors: total cholesterol (TC), HDL-cholesterol (HDL-c), LDL-cholesterol (LDL-c), triglycerides (TG), systolic (SBP) and diastolic blood pressure (DBP). Biochemical variables were assessed by blood sampling from the brachial vein after a 12-hour fast. The analyses of TC, TG, and HDL-c were performed in serum sample, in automated equipment Miura One (I.S.E, Rome, Italy), using commercial kits DiaSys (Diagnostic Systems, Germany). For LDL-c determination, the calculation LDL = TC - HDL-c - (Triglycerides/5) according to the Friedewald, Levy and Fredrickson formula was used.[13] The serum lipid levels of the students were classified according to the cut-off points of the National Heart Lung and Blood Institute.[14]

Blood pressure was measured based on the auscultatory method, using a sphygmomanometer for brachial perimeter and a stethoscope placed on the left arm. The student was seated, resting for at least 5 minutes. The classification of SBP and DBP was performed according to the VI Brazilian Guidelines on Hypertension.[15]

The variables sex, age, housing area, type of school, economic class, and physical activity were collected through a questionnaire and used as control variables in this study. Based on the ages reported, the sample was classified into two age groups: (1) children: from 7 to 12 years and (2) adolescents: from 13 to 17 years

The schoolchildren's economic class was classified based on the ABEP criterion.[16] From this classification, the economic classes were grouped into upper – classes A1, A2, B1 and B2; (2) middle – classes C1 and C2, and (3) lower – classes D and E. The practice of physical activity (PA) was investigated based on the question "Do you currently practice any sport/physical activity? The students were instructed to report only physical activities performed in leisure, not counting activities performed in physical education classes, commuting, work or domestic. The students were classified as (1) active: students who practice some sport or physical activity and (2) inactive: students who reported not practicing any activity.

Statistical analysis

Statistical analyses were performed using SPSS v.23.0 software (IBM SPSS Statistics for Windows, IBM Corp., NY, USA). First, descriptive analyses of simple and relative frequencies of the sample were performed regarding the characteristics of sex, age group, economic class, type of school, housing area, practice of PA, and cardiometabolic risk factors (TC, HDL-c, LDL-c, TG, SBP, and DBP), according to the categories of the BMI/CRF variable. Pearson's chi-square test was used for these comparisons. The age of the sample was described using mean and standard deviation.

Poisson regression with robust estimation was used to calculate the crude and adjusted prevalence ratios (PR) and their respective confidence intervals (95%CI) of cardiometabolic risk factors according to the independent variable BMI/CRF. For the adjusted analyses, the variables sex, age, economic class, type of school, housing area, and PA practice were tested for each outcome, and a $p \leq 0.20$ was adopted to define the variable entry in the model. For all final fitted models, the significance level obtained was <0.001. For all analyses, the alpha adopted was 5%.

Results

A total of 1,252 students were included in the study. The mean age was 11.88 ± 3.02 years, most of them are male, teenagers and live in the urban area of the city (Table 1).The physical inactivity rate of the sample is 36.5%. The rate of overweight and obesity is 29.0% and 50.8% had low levels of cardiorespiratory fitness (data not shown). The highest prevalences of schoolchildren with overweight/obesity and low CRF were found among adolescents, girls, and urban area residents.

Regarding the assessed risk factors, the highest prevalence are observed for high levels of TC and LDL-c. For all risk factors except LDL-c and DBP, the highest prevalence's were observed among students with overweight or obesity and low cardiorespiratory fitness (Table 2).

Table 3 shows the crude and adjusted prevalence ratios for cardiometabolic risk factors according to BMI and CRF, using eutrophic/ fit students as reference. Overweight and obese schoolchildren had a higher prevalence of increased triglyceride rates and elevated systolic blood pressure levels, and this prevalence was higher among the unfit. The prevalence of altered TG rates was 50% higher among overweight-obese/ fit schoolchildren and 107% among overweight-obese/unfit students. Schoolchildren classified with overweight/fit and overweight/unfit had a two-fold higher a prevalence of high SBP. Overweight and obese students were also at higher risk for high DBP, both fit and unfit. In addition, only students with overweight and low physical fitness were at risk for altered TC and HDL-c, with a risk of 24% for high cholesterol and 51% for low HDL-c.

Discussion

Our findings show that overweight and obese schoolchildren had a higher cardiometabolic risk when compared to eutrophic schoolchildren with good levels of physical fitness. Eutrophic students and those with low physical fitness did not present higher risk prevalence. However, in overweight schoolchildren, although the

Table 1 – Characteristics of the sample according to BMI and CRF of schoolchildren aged 7 to 17 years in the municipality of Santa Cruz do Sul (RS - Brazil), 2011-2012 (n = 1,252)

	Eutrophic/ fit n (%)	Eutrophic/ unfit n (%)	Overweight-obese/ fit n (%)	Overweight-obese/ unfit n (%)	Total n (%)	p*
Sex						< 0.001
Male	229 (47.2)	77 (58.8)	150 (37.1)	111 (47.8)	567 (45.3)	
Female	256 (52.8)	54 (41.2)	254 (62.9)	121 (52.2)	685 (54.7)	
Age range						< 0.001
Child	140 (28.9)	54 (41.2)	63 (15.6)	85 (36.6)	342 (27.3)	
Adolescent	345 (71.1)	77 (58.8)	341 (84.4)	147 (63.4)	910 (72.7)	
Housing area						0.004
Urban	255 (52.6)	73 (55.7)	253 (62.6)	149 (64.2)	730 (58.3)	
Rural	230 (47.4)	58 (44.3)	151 (37.4)	83 (35.8)	522 (41.7)	
Economic Class						0.480
Upper (A – B)	255 (52.6)	69 (52.7)	226 (55.9)	129 (55.6)	679 (54.2)	
Middle (C)	217 (44.7)	55 (42.0)	170 (42.1)	95 (40.9)	537 (42.9)	
Lower (D – E)	13 (2.7)	7 (5.3)	8 (2.0)	8 (3.4)	36 (2.9)	
School type						0.683
Public	453 (93.4)	121 (92.4)	380 (94.1)	221 (95.3)	1175 (93.8)	
Private	32 (6.6)	10 (7.6)	24 (5.9)	11 (4.7)	77 (6.2)	
Physical activity						0.004
Active	335 (69.1)	87 (66.4)	239 (59.2)	134 (57.8)	795 (63.5)	
Inactive	150 (30.9)	44 (33.6)	165 (40.8)	98 (42.2)	457 (36.5)	

**Chi squared test*

risk for elevated TG and blood pressure levels was demonstrated in fit schoolchildren, the effect size was greater among unfit schoolchildren. In addition, only overweight/unfit schoolchildren were at risk for elevated TC and low HDL-c levels.

In our study, CRF does not seem to be independently associated with the the occurrence of risk factors among the evaluated schoolchildren. Although some studies have pointed out an association between lower CRF and higher cardiometabolic risk,[2,3] the results show that among eutrophic and unfit students there is no association with risk factors. On the other hand, in overweight, fit and unfit schoolchildren, there is an increase in risk prevalence, proposing a central role of BMI in these associations. These findings are confirmed in a similar study that used combined BMI and CRF and showed that the eutrophic and fit group had the lowest score for metabolic syndrome, while the overweight and unfit group had the highest.[5]

Our findings showed that schoolchildren with low fitness combined with overweight and obesity had higher prevalence of risk for almost all variables, except for LDL-c and DBP. Other studies also showed a more favorable lipid profile in children and adolescents with lower BMI and good fitness.[17–20] It has been shown that eutrophic children and adolescents with low CRF did not have more favorable blood pressure levels and lipid profile than eutrophic children and adolescents with good CRF[20] and that thinner but less fit children and adolescents have a more favorable cardiometabolic profile than their heavier peers with good cardiorespiratory fitness.[19]

Although the relationship between low fitness and risk has not been demonstrated in eutrophic individuals, in overweight/obese individuals the results indicate that there is an increase in risk, and indicating that CRF may mitigate this relationship. A study of European adolescents found that CRF can partially mediate about 10% of this relationship, demonstrating that overweight-related risk can be partially mitigated by improving CRF levels.[4]

Other studies have also shown that good levels of CRF showed a beneficial role in risk compensation in overweight schoolchildren, suggesting that moderate to high levels of CRF may mitigate the detrimental consequences attributed to excess adiposity.[5,18] Furthermore, some evidence has shown that although CRF has an inverse association with risk factors, after adjustment for BMI, the associations are attenuated or are no longer significant, proving that BMI has an important influence on the relationship between CRF and risk factors.[21–24]

Table 2 – Cardiometabolic risk factors according to BMI and CRF of schoolchildren aged 7 to 17 years in the municipality of Santa Cruz do Sul (RS - Brazil), 2011-2012 (n= 1,252)

	Eutrophic/ fit n (%)	Eutrophic/ unfit n (%)	Overweigh-obese/ fit n (%)	Overweight-obese/ unfit n (%)	Total n (%)	p*
Cholesterol						< 0.001
Normal	214 (44.1)	51 (38.9)	176 (43.6)	66 (28.4)	507 (40.5)	
Altered	271 (55.9)	80 (61.1)	228 (56.4)	166 (71.6)	745 (59.5)	
HDL-c						0.021
Normal	404 (83.3)	107 (81.7)	347 (85.9)	177 (76.3)	1035 (82.7)	
Altered	81 (16.7)	24 (18.3)	57 (14.1)	55 (23.7)	217 (17.3)	
LDL-c						0.025
Normal	272 (56.1)	68 (51.9)	256 (63.4)	124 (53.4)	720 (57.5)	
Altered	213 (43.9)	63 (48.1)	148 (36.6)	108 (46.6)	532 (42.5)	
Triglycer-ides						< 0.001
Normal	403 (83.1)	99 (75.6)	335 (82.9)	149 (64.2)	986 (78.8)	
Altered	82 (16.9)	32 (24.4)	69 (17.1)	83 (35.8)	266 (21.2)	
SBP						< 0.001
Normal	441 (90.9)	104 (79.4)	354 (87.6)	178 (76.7)	1077 (86.0)	
Altered	44 (9.1)	27 (20.6)	50 (12.4)	54 (23.3)	175 (14.0)	
DBP						< 0.001
Normal	428 (88.2)	99 (75.6)	348 (86.1)	178 (76.7)	1053 (84.1)	
Altered	57 (11.8)	32 (24.4)	56 (13.9)	54 (23.3)	199 (15.9)	

*HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. *Chi-squared test.*

Our work has some strong points to consider, such as the sample size, representative of the schoolchildren population in Santa Cruz do Sul, a medium-sized municipality in the south of Brazil. Different from most investigations, carried out in large urban centers. We highlight the joint evaluation of BMI and CRF as an exposure variable, still little explored, and the several risk factors evaluated as outcome.

As a limitation, it is important to consider the possible influence of unmeasured factors, especially sexual maturation, genetic factors, diet, and other lifestyle factors such as sedentary time, since cardiometabolic risk is a multifactorial issue. The use of BMI in adiposity assessment and the assessment of CRF levels through indirect estimates by runway test have limitations, although they are widely used, especially in population assessments.

We highlight the worrying prevalence's found in our study for physical inactivity, overweight and obesity, physical unfitness, and cardiometabolic risk factors. Our results are important from a clinical and public health perspective because they demonstrate that although BMI plays a central role in the relationship with risk factors, adequate levels of cardiorespiratory fitness can mitigate risk in overweight and obese schoolchildren, and therefore improving fitness levels may be an important strategy independent of weight loss.

In this sense, is worrying about the indications that, although the levels of CRF have remained stable in the last decade in the pediatric population, more than 80% of these children had low levels of fitness.[25] It is essential to encourage this population to comply with the recommendations for physical activity, given the important relationship that recommended levels of PA have with better rates of CRF.[2]

The relevance of investing in strategies that promote improvements in fitness in the young population is reinforced by evidence indicating that good levels of CRF during childhood result in a healthier cardiometabolic profile in adulthood[7] and that unfit individuals have twice the risk of mortality, regardless of BMI, when compared to fit and eutrophic individuals.[26]

Conclusion

Cardiometabolic risk in overweight and obese schoolchildren can be partially mitigated, although not eliminated, by satisfactory levels of cardiorespiratory fitness. Low levels of CRF in eutrophic schoolchildren do not appear to be directly related to risk. Our results contribute to existing evidence suggesting a protective role of CRF, mitigating the deleterious effects of obesity on cardiometabolic health.

Table 3 – Crude and adjusted prevalence ratios of cardiometabolic risk factors according to BMI and CRF of schoolchildren aged 7 to 17 years in the municipality of Santa Cruz do Sul (RS - Brazil), 2011-2012 (n = 1,252)

	Eutrophic// unfit PR (IC95%)	Overweight-obese/ fit PR (IC95%)	Overweight-obese/ unfit PR (IC95%)	p*
Cholesterol				
Normal	1	1	1	
Altered crude	1.01 (0.90 – 1.14)	1.09 (093 – 1.28)	1.28 (1.14 – 1.43)	< 0.001
Altered adjusted†	0.99 (0.88 – 1.11)	1.09 (0.93 – 1.28)	1.24 (1.11 – 1.39)	< 0.001
HDL-c				
Normal	1	1	1	
Altered crude	0.85 (0.62 – 1.15)	1.10 (0.73 – 1.66)	1.42 (1.05 – 1.93)	0.019
Altered adjusted‡	0.81 (0.60 – 1.11)	1.19 (0.78 – 1.80)	1.51 (1.11 – 2.04)	0.003
LDL-c				
Normal	1	1	1	
Altered crude	0.83 (0.71 – 0.98)	1.10 (0.89 – 1.34)	1.06 (0.89 – 1.26)	0.030
Altered adjusted§	0.85 (0.73 – 1.00)	1.17 (0.96 – 1.43)	1.14 (0.97 – 1.33)	0.005
Triglycerides				
Normal	1	1	1	
Altered crude	1.01 (0.76 – 1.35)	1.45 (1.01 – 2.07)	2.12 (1.63 – 2.75)	< 0.001
Altered adjusted//	0.98 (0.74 – 1.32)	1.50 (1.04 – 2.16)	2.07 (1.60 – 2.69)	< 0.001
SBP				
Normal	1	1	1	
Altered crude	1.36 (0.93 – 2.00)	2.27 (1.47 – 3.52)	2.57 (1.78 – 3.70)	< 0.001
Altered adjusted¶	1.19 (0.82 – 1.72)	3.05 (2.05 – 4.54)	3.26 (2.31 – 4.60)	< 0.001
DBP				
Normal	1	1	1	
Altered crude	1.02 (0.98 – 1.06)	1.11 (1.04 – 1.19)	1.10 (1.05 – 1.16)	< 0.001
Altered adjusted#	1.04 (0.75 – 1.46)	2.70 (1.87 – 3.88)	2.42 (1.76 – 3.32)	< 0.001

*HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. *Poisson regression. Adjusted: †Sex, age range and housing area. ‡Continuous age, housing area and school type. §Sex, age range, economic class, housing area, physical activity and school type. //Sex, age range, physical activity and school type. ¶Sex, continuous age and physical activity. #Sex, continuous age, physical activity and school type.*

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Author Contributions

Conception and design of the research: Tornquist L, Tornquist D, Franke SIR, Renner JDP, Reuter CP; Acquisition of data and Writing of the manuscript: Tornquist L, Tornquist D, Schneiders LB, Franke SIR, Renner JDP, Reuter CP; Analysis and interpretation of the data: Tornquist L, Tornquist D, Schneiders LB; Statistical analysis: Tornquist L, Tornquist D, Franke SIR,; Obtaining financing: Franke SIR, Renner JDP, Reuter CP; Critical revision of the manuscript for intellectual contente: Tornquist L, Franke SIR, Renner JDP, Reuter CP.

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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The Influence of Obesity and Physical Activity on Cardiovascular Risk

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Short Editorial related to the article: Cardiometabolic Risk in Children and Adolescents: The Paradox between Body Mass Index and Cardiorespiratory Fitness

Atherosclerotic cardiovascular disease (ACVD) is common in the general population, affecting most adults over 60 years of age. The disease includes four main areas: (1) Coronary heart disease, (2) Cerebrovascular disease, (3) Peripheral arterial disease, and (4) Aortic atherosclerosis with aneurysms.[1] The conditions traditionally associated with the installation of ACVD (the so-called "risk factors") are dyslipidemia, diabetes mellitus, arterial hypertension, smoking, obesity, sedentary lifestyle and a family history of ACVD.[2] Atherosclerotic vascular changes may begin in childhood, setting the stage for cardiovascular events in adulthood.[3] Tornquist et al.[4] present in this issue of Arquivos Brasileiros de Cardiologia some aspects of obesity and cardiorespiratory fitness in relation to cardiometabolic risk in children.

Obesity is a public health problem that has expanded worldwide. According to a report by the World Health Organization in 2016, obesity has tripled since 1980.[5] The prevalence of obesity and overweight also increased among young people, from 16% in 1980 to 23% in 2013.[5]

Obesity has long been associated with an increased risk of ACVD. There are several physiological and metabolic changes associated with obesity that may contribute to increased risk: (1) Insulin resistance and hyperinsulinemia; (2) Abnormalities in lipid metabolism; (3) Arterial hypertension; (4) Left ventricular remodeling; (5) Sleep disorders; (6) Increased systemic inflammation; (7) Activation of the sympathetic nervous system, and, (8) Endothelial dysfunction.[6]

Obesity has been associated with total mortality in several studies, as well as with Coronary Heart Disease, Heart Failure, Atrial Fibrillation and Sudden Death.[6]

Autopsy studies of children show that obesity is positively correlated with atherosclerotic changes in the aorta and coronary arteries during childhood.[7] Also, a large prospective Danish study, with 276,835 children born between 1930 and 1976, evaluated the Body Mass Index of children and observed a positive linear relationship with the number of ischemic coronary events in adulthood.[8]

Thus, there is much evidence that associates obesity with ACVD since childhood. On the other hand, weight reduction greatly improves obesity-related risk factors: it lowers blood pressure, reduces the incidence of diabetes, improves the lipid profile, decreases insulin resistance, improves endothelial function, and reduces protein C-reactive concentration.[9]

A sedentary lifestyle has been recognized as an independent risk factor for ACVD. The increase in physical activity is related to health gains, a better quality of life and longer life expectancy.[2] Physical activity involves occupational, domestic and leisure activities.[10]

Improvement in physical capacity and quality of life would be sufficient reasons for adhering to physical exercises, but several other beneficial effects are related to physical practice. It contributes to weight control, improves lipid profile, lowers blood pressure, helps treat and prevent diabetes mellitus, and reduces inflammation (expressed by C-reactive protein). Exercise also influences lifestyle, reducing the possibility of smoking, reducing stress and appetite.[11]

The benefits of routine exercise are extremely valuable. They are repeated in different age groups, from young people to the elderly,[12] and are confirmed for children and young people in the study by Tornquist.[4]

Keywords

Cardiovascular Diseases; Obesity; Risk Factors; Sedentarism, Peripheral Artery Disease; Diabetes. Dyslipidemias; Life Style.

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Clinical Implementation of Different Strategies for Exercise-Based Rehabilitation in Kidney and Liver Transplant Recipients: A Pilot Study

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Abstract

Background: Cardiovascular disease is among the leading causes of death in solid organ transplant recipients with a functional graft. Although these patients could theoretically benefit from exercise-based rehabilitation (EBR) programs, their implementation is a challenge.

Objective: We present our initial experience on different delivery modes of a pilot EBR program in kidney and liver transplant recipients.

Methods: Thirty-two kidney or liver transplant recipients were invited for a 6-month EBR program delivered at the hospital gym, community gym or at home, according to the patient's preference. The significance level adopted was 5%.

Results: Ten patients (31%) did not complete their program. Among the 22 who did, 7 trained at the hospital gym, 7 at the community gym, and 8 at home. The overall effect was an 11.4% increase in maximum METs (Hedges' effect size g = 0.39). The hospital gym group had an increase in METs of 25.5% (g= 0.58, medium effect size) versus 10% (g= 0.25), and 6.5% (g= 0.20) for the community gym and home groups, respectively. There was a beneficial effect on systolic and diastolic blood pressures, greater for the hospital gym (g= 0.51 and 0.40) and community gym (g= 0.60 and 1.15) groups than for the patients training at home (g= 0.07 and 0.10). No significant adverse event was reported during the follow-up.

Conclusion: EBR programs in kidney and liver transplant recipients should be encouraged, even if they are delivered outside a hospital gym, since they are safe with positive effects on exercise capacity and cardiovascular risk factors.

Keywords: Exercise; Exercise Movement Techniques; Physical Conditioning Human; Kidney/transplantation; Liver/transplantation; Exercise Therapy.

Introduction

Short-term survival among solid-organ transplant recipients (SOTRs) has significantly improved due to decreased mortality from infections and acute graft rejections.[1] Although liver and kidney transplant recipients have a lower cardiovascular (CV) risk than their counterparts on transplant waiting lists,[2,3] their mortality risk is still higher than the general population.[4,5] In fact, cardiovascular diseases are the most common causes of death in patients with a functional graft and are responsible for 30% of early graft loss after kidney transplantation.[4,6] Certain pre-transplantation risk factors, including diabetes, hypertension, dyslipidemia, and obesity, contribute to this high CV risk.[6,7] There are also post-transplantation factors which contribute to this CV risk, such as a new onset of diabetes,[8] development of a metabolic syndrome[9] and sedentary lifestyle.[10] Most of the SOTRs do not achieve the guideline-recommended levels of physical activity in their daily routine[11,12] suggesting that patients could benefit from more guidance and tailored social and professional support[13,14] to improve their daily physical activity.

Since exercise-based rehabilitation programs (EBR) improve cardiovascular risk factors in the general population,[6,15] they are expected to have a beneficial impact on solid organ transplant recipients. While the effects of these programs are well known in cardiac and lung transplant recipients (due to direct effects of exercise on cardiac and pulmonary function),[16-19] their benefits and safety are more uncertain for other SOTRs patients.[17,18,20,21] Costs, logistics, and insurance coverage are also significant barriers[22] which limit the rapid and widespread implementation of these EBR programs for this

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specific population. We believe that tailored delivery strategies and out-center programs could be helpful to overcome these challenges and enroll patients that would not participate in centre-based programs, especially in unexpected situations such as the COVID-19 pandemic.[23,24]

Therefore, we present our initial experience on the cardiovascular effects of different delivery modes of a pilot EBR program in kidney and liver transplant recipients.

Methods

In 2016, we conducted at our institution a randomized pilot study on the impact of resistance training on factors involved in the development of new-onset diabetes after renal transplantation.[20] We learned from this study that almost 55% of our patients declined the invitation to join because they were unable to come to our center as often as required by this program (3 times a week). Our team decided to design a new EBR program for kidney and liver transplant patients which can be delivered at the hospital gym as well as in a community gym or at home, depending on the patient's preference. We present here our initial experience with the first 32 patients engaged within this new Combined EBR program. This retrospective analysis was approved by the CRCHUM Ethical Committee on Human Research, which complies with the Declaration of Helsinki (REC 2017-6733).

The EBR Program

In our institution, SOTRs (18 years and older) are invited to join the EBR program after transplantation as part of their care trajectory, usually 6 months after renal transplantation and 9 months after liver transplantation. All kidney and liver-recipient patients that participated in our program between 2016 to 2018 were included in our analysis. Pre-participation assessment (physical exam and stress test) was performed at the hospital by a cardiologist and a kinesiologist. In the absence of cardiovascular contraindication, each patient participated in a 6-month EBR, tailored according to its current condition and whether or not they preferred to train outside the hospital context. A discussion between the patient and the kinesiologist on the pros and cons was made at that time. The exercise prescription followed the ACSM and CAN-Restore recommendations,[25,26] combining aerobic, resistance and flexibility exercises: 1) aerobic training: 3-5 times a week, targeting 50-80% VO_2max (5-6 Borg), starting with 20 min/section and increasing progressively up to 60 min; 2) resistance training: 2-3 times a week, 1-3 series of 10 to 15 repetitions of 5-6 exercises (total of 20 to 30 min), using multi-joints exercises including the major muscle groups according to patient's abilities (the full list of the prescribed exercises is available in supplemental material – Table 1); and 3) flexibility exercises 2-3 times a week, 2-3 exercises/positions according to patient symptom limitation (i.e., pain). The prescription table is available in the supplemental material – Table 2.

For patients who decided to train at our hospital gym, exercise sessions were performed under the supervision of a kinesiologist 3 days/week. For patients training at a community gym or at home, there was an initial visit at the hospital during which the patients received a table of prescription describing the training program and is taught how to perform each exercise, depending on which devices they have access to (i.e. elastics, free weights and/or bodyweight), and how to control the intensity during exercise sessions (i.e. familiarization with a perceived exertion scale). If patients were exercising at the community gym this

Table 1 – Clinical characteristics according to the intervention group

	Hospital gym (n=7)	Community gym (n=7)	Home-based (n=8)	Total (n=22)
Age	58.0±6.9	53.7±12	60.4±8.0	57.5±9.2
Gender (M/F)	5/2	3/4	6/2	14/8
Transplant time (months)	126±97	103±71	113±93	114±84
Range transplant time (min-max)	253 (5 - 258)	198 (8 - 206)	242 (12 – 254)	253 (5 - 258)
Transplant (n)				
Kidney	2	6	7	15
Liver	3	1	0	4
Kidney+Pancreas	2	0	1	3
Diabetes	2	5	3	10
Hypertension	4	5	6	15
Medication use				
Beta-blocker	2	6	3	11
Immunossupressors	4	4	7	15

*Values are presented as mean ± SD or numbers of patients (percentages); GLM: generalized linear model; * group difference (CHUM vs HOME): p=0.017.*

Table 2 – Clinical characteristics according to the intervention group

	Hospital gym (n=7)		Community gym (n=7)		Home-based (n=8)		TOTAL (n=22)		Interaction GLM
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Weight (Kg)	81.3±18.9	81.3±20.4	91.4±14.7	85.3±15.1	82.9±12.0	80.3±13.9	85.1±15.2	82.1±16.2	0.87
BMI (m/kg^2)	28.6±5.8	28.6±6.4	32.1±4.8	30.1±2.5	30.1±4.7	29.1±4.6	30.2±5.1	29.2±4.7	0.86
Waist circumference (cm)	100.4±15.5	98.9±16.1	111.8±11.7	105.0±8.6	105.7±8.4	105.0±9.2	105.7±12.7	102.6±12.2	0.78
Exercise test									
METs max	5.5±2.3	6.9±2.2	6.0±2.0	6.6±2.4	6.1±1.7	6.5±2.0	5.8±1.9	6.6±2.1	0.76
METs predicted (%)	75±28	96±31	81±34	87±37	91±35	96±40	82±32	93±35	0.76
VO_2max calculated (ml.kg.min^{-1})	19.2±7.9	24.1±7.8	21.1±7.0	23±8.3	21.2±6.0	22.8±7.1	20.5±6.7	23.3±7.4	0.76
Exercise time (min)	7:47±3:51	8:11±3:21	6:00±1:31	7:00±1:37	7:37±2:36	7:30±2:55	7:09±2:47	7:33±2:39	0.86
HR max (bpm)	133±18	131±35	131±33	130±35	131±26	130±25	132±25	130±30	0.99
HR predicted (%)	82±12	80±23	78±20	77±19	80±14	81±17	80±15	79±18	0.98
SBP pre-test	131±15	122±18	138±20	127±14	125±16	124±9	131±17	124±10	0.55
DBP pre-test*	74±8	71±6	81±6	73±7	76±8	75±10	77±8	73±7	0.36
SBP max (Hgmm)	172±23	157±26	178±17	171±24	163±25	168±29	170±22	165±26	0.47
DBP max (Hgmm)	76±11	75±6	77±5	71±14	78±12	75±8	77±10	74±10	0.78
Blood analysis									
Hb (g/L)	123±11	125±4	133±12	125±18	136±21	135±19	131±16	129±16	0.69
Sodium (mmol/L)*	139±3	138±4	141±3	141±2	141±2	142±2	140±3	140±3	0.86
Potassium (mmol/L)	4.2±0.7	4.3±0.8	4.1±0.3	4.3±0.4	4.4±0.3	4.2±2.2	4.2±0.4	4.2±0.5	0.48
Creatinine (µmol/L)	131±35	123±38	96±24	218±308	132±104	132±112	121±71	158±187	0.40
Total cholesterol (mmol/L)	4.6±1.6	4.6±1.2	4.0±1.0	4.0±1.0	4.5±0.8	4.3±0.7	4.3±0.5	4.2±0.9	0.95
Triglycerides (mmol/L)	1.5±0.8	1.5±1.1	1.9±0.6	2.6±1.8	2.1±1.4	1.6±0.9	1.9±1.0	1.9±1.3	0.41
Glucose (mmol/L)	7.5±4.0	6.2±1.3	6.4±1.0	7.7±3.3	6.1±1.2	5.3±1.4	6.6±2.2	6.4±2.4	0.27

*Values are presented as mean ± SD or numbers of patients (percentages); GLM: generalized linear model; * group difference (CHUM vs HOME): p=0.017 BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; MET: metabolic equivalent.*

document was shared with a local trainer. If the patients were training at home, they kept this document for themselves. During the days when no training was scheduled, all the patients were asked to keep themselves active by walking at least 30 minutes per day at an intensity of 2-3/10 on the Borg scale.

Follow-up consultations by phone were performed every four weeks for patients who decided to exercise outside the hospital context in order to maintain motivation and to capture program compliance. For patients who completed the program, a second cardiovascular assessment was performed at six months.

Abstracted data from medical records

The following parameters were extracted from the medical records of the patients who completed the program:

- Clinical characteristics: demographics, transplanted organ, date of transplantation and reason for transplantation;

- Cardiovascular assessment at baseline and six months: clinical data (weight (Health O Meter , model 500 KL) height, waist circumference, blood pressure, heart rate (GE Case T2100)); and biological data (i.e. electrolytes, Hb, lipid profile and glycemia);

- Exercise capacity assessment: results were extracted from the reports of the stress test performed on a treadmill (treadmill and ECG: GE Case T2100). The maximum metabolic equivalent (MET) was determined as the last completed stage on the Cornell protocol. HR max was determined as the maximum heart rate achieved at the peak of the test;

- Patient self-reported or kinesiologist-reported adherence to the training program.

Data analysis

Results were expressed as means and standard deviation (SD), or as the number of cases and proportions (%), total and according to groups (hospital gym, community gym or home-based). The entire dataset was screened for outliers to ensure group representativeness. Hedges' g effect size was calculated for main outcomes:[27] effect sizes between 0.2 and 0.49 are considered small effect; between 0.50 and 0.79 moderate; and higher than 0.8 high effect.

Distribution normality was analyzed using descriptive statistics (mean, standard deviation, median and range), as well as visual inspections. Generalized Linear Models (GLM) were used to compare groups and time (visit 1 vs. visit 2) due to small sample sizes. A paired t-test was used to compare pre- and post-values for the whole group (n=22). Sample size calculations were not performed since we analyzed the entire cohort of patients, and we are presenting the results in a pilot analysis fashion. Statistical significance was set at an alpha level of .05, and all analyses were performed using SPSS version 24 (Chicago, IL, USA).

Results

From the first 32 transplant recipients who agreed to participate in this EBR program, 10 (hospital gym n=1; community gym n= 4; and home-based n=5) did not complete their program (for details, see flowchart – Figure 1): eight due to lack of interest or motivation, one due to distance to go to the centre for final assessment, and one due to a change in his medical condition with the need of a second transplantation. The retention rate was 69%. Among the 22 patients who completed the EBR program, 7 trained at the hospital gym, 7 at a community gym and 8 at home. Table 1 describes the clinical characteristics of those 22 patients. GLM did not show any differences for group factor, visit (pre and post) or interaction factors.

When the pre-post results were analyzed as one single group (n=22), we found significance for the diastolic blood pressure (T-test - p= 0.037) and borderline significance for METs max (T-test - p = 0.072). Figures 2 and 3 describe delta-value individual patient data for METs (Figure 2), systolic (Figure 3A) and diastolic blood pressure (Figure 3B).

Exercise test parameters are shown in Table 2. Overall METs max was increased by 11.4% (Hedges' g= 0.39). For those training at the hospital gym, METs max increased by 25.5% (Hedges' g= 0.58), whereas METs max increased by 10% (Hedges' g= 0.25) for patients training at a community gym, and 6.5% (Hedges' g= 0.20) for those in home-based training. Figure 1 presents individual delta analyses for METs.

Considering all groups together, systolic blood pressure decreased by 5.4% (Hedges' g= 0.49), and diastolic blood pressure decreased by 5.2% (Hedges' g= 0.52). Hedges'

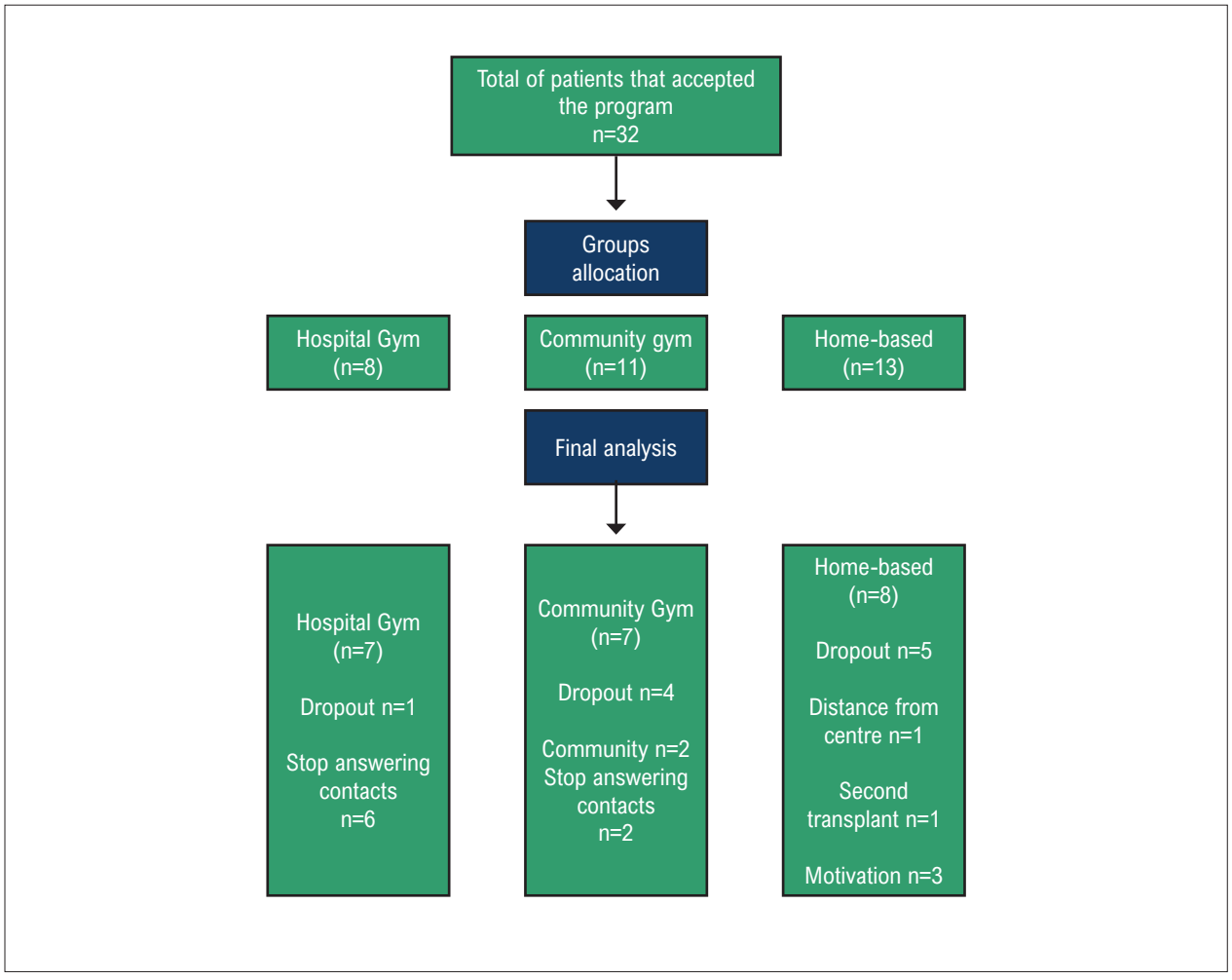

Figure 1 – *Flowchart of the study.*

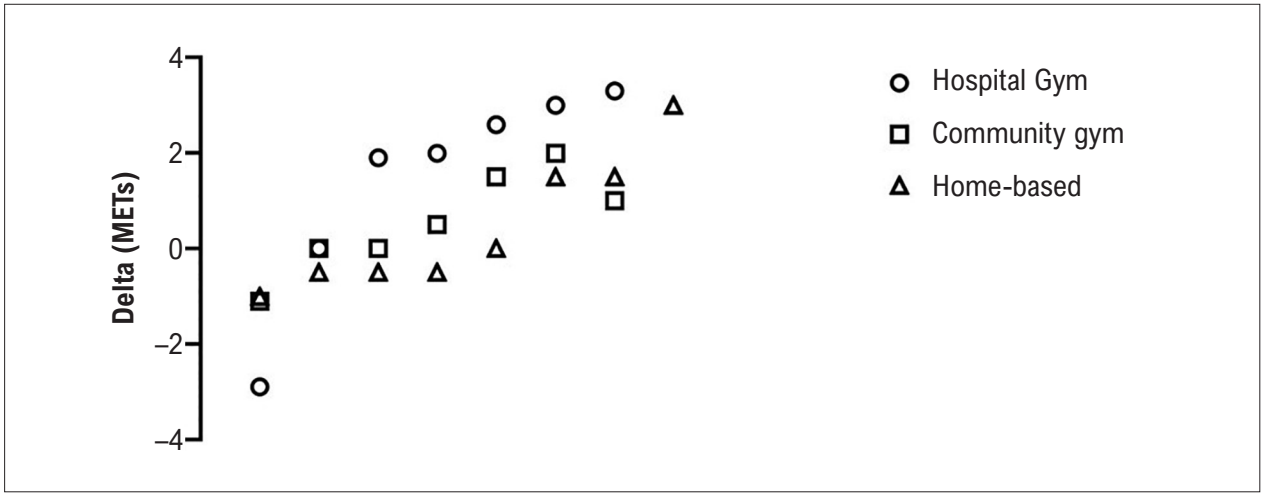

Figure 2 – *Individual patients' changes (deltas) in maximal METs according to exercise training group. MET: metabolic equivalent.*

Figure 3A

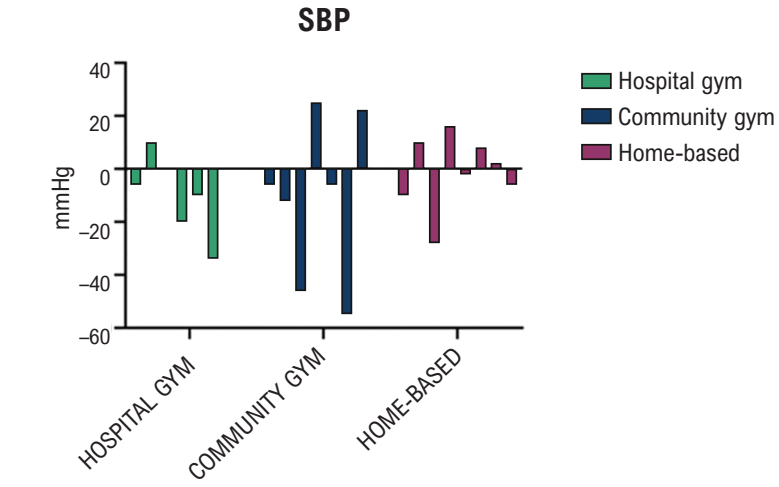

Figure 3B

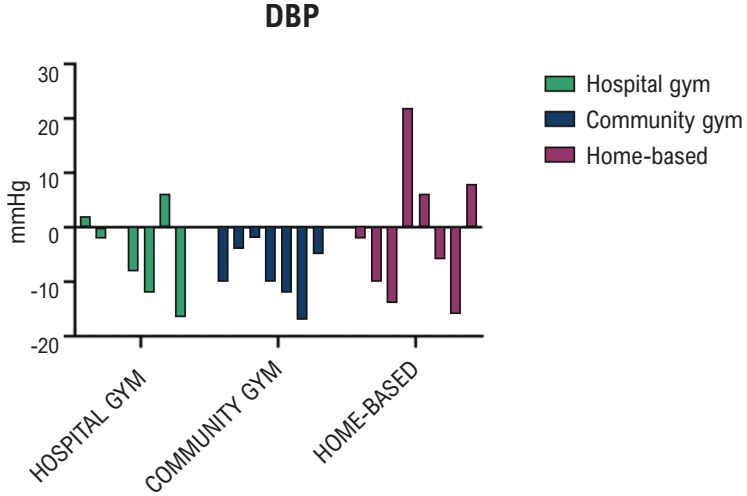

Figure 3 – *Individual patients' changes (deltas) in SBP (A) and DBP (B) according to exercise training group. SBP: systolic blood pressure; DBP: diastolic blood pressure.*

effect-sizes for systolic and diastolic blood pressures were g= 0.51 and 0.40 for those training at our hospital gym; g= 0.60 and 1.15 for those training at a community gym; and g= 0.07 and 0.10 for those training at home.

No related adverse event was reported during the follow-up of these patients. The kinesiologists in charge of these patients did not observe any differences between groups in terms of compliance and adherence to exercise prescription.

Discussion

An EBR program in kidney and liver transplant recipients appears to be safe and has benefits on exercise capacity and cardiovascular risk factors, regardless of how the program is delivered. However, the magnitude of these benefits seems to be greater in patients training at the hospital gym compared to the other ones (though this may reflect patient self-selection bias as well).

The Canadian Association for Cardiovascular Prevention and Rehabilitation recommends, as a Quality Indicator of rehabilitation programs, that functional capacity should increase by a half MET through the end of intervention.[28,29] This was attained by 61% of our patients (hospital-based n=6, community-based n=4, and home-based n=3). Moreover, 77% of our patients were able to maintain their exercise capacity over the course of the 6-months. We observed similar benefits on systolic and diastolic blood pressures, although our kidney transplant recipients were theoretically at a higher risk of developing post-transplant hypertension.[30]

The literature about exercise training in SOTRs is scarce, and previous reviews of the literature[31] and a meta-analysis of randomized controlled trials[17] showed no effect on exercise capacity for kidney[32] (only one study) or liver recipients[33,34] (only two studies). However, previous trials have been designed as fully supervised programs.[21]

Compliance with any kind of treatment has a direct effect on its efficacy.[35-37] There will not be high compliance to an EBR program if the patient does not express a strong motivation to begin with. In the specific context of SOTRs, patient preferences have to be taken into consideration, especially regarding how the program is going to be delivered. Despite that, 31% of our SOTRs did not complete their program, especially among those training in a community gym or at home. This suggests that follow-up by regular phone calls is not sufficient to keep our patients motivated and engaged. Considering the exponential development of user-friendly web platforms and apps for SOTR patients,[38] the next step is to build up features that help monitor exercise programs - we believe these technologies could be the missing piece for these programs delivered outside the hospital context.

Limitations

The results presented here are from a real-life setting retrospective analysis, not a randomized controlled trial, therefore some flexibilization of the scientific rigor is observed. We did not rigorously assess the specific factors influencing the patient's choice of the type of EBR or discontinuation of the program. The effect of EBR on quality of life of these patients was not prospectively measured, and our compliance assessment is limited to patient and kinesiologist self-reports. Our small sample size underpowered our analysis and did not allow us to prove that our findings using Hedges' effect size method were not likely to be due to chance. Regardless, most of our patients were able to at least maintain exercise capacity over the course of the 6-months. Moreover, this is the first study that investigated the effect of an EBR program that is focused on phase 3 rehabilitation (i.e. not after surgery), where patients are already stable and some decline (not improvement) in physical function is expected. Still, the fact that we are the first to demonstrate the positive effects of out-of-center training in SOTR is also encouraging.

Conclusion

EBR programs in kidney and liver transplant recipients are feasible and seem to provide positive results on exercise capacity and classic cardiovascular risk factors. They should be encouraged, even if they are delivered outside a hospital context, as safety seems to be similar to a hospital setting. However, programs delivered in a community gym or at home should be associated with a reinforced telemonitoring of each patient to ensure proper compliance and reduce the risk of demotivation and disengagement.

Author Contributions

Conception and design of the research: Ribeiro PAB, Tournoux F; Acquisition of data: Ribeiro PAB, Gradassi M, Martin SA, Leenknegt J, Baudet M; Analysis and interpretation of the data: Ribeiro PAB, Martin SA, Baudet M, Räkel A, Tournoux F; Statistical analysis: Ribeiro PAB; Writing of the manuscript: Ribeiro PAB, Gradassi M, Räkel A, Tournoux F; Critical revision of the manuscript for intellectual content: Ribeiro PAB, Gradassi M, Martin SA, Leenknegt J, Baudet M, Le V, Pomey MP, Räkel A, Tournoux F.

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.

Exercise-Based Rehabilitation for Pre- and Post-Solid Organ Transplant Patients

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Short Editorial related to the article: Clinical Implementation of Different Strategies for Exercise-Based Rehabilitation in Kidney and Liver Transplant Recipients: A Pilot Study

In the last decades, numerous advances in solid organ transplantation (SOT) have resulted in greater patient survival, resulting in a considerable increase in the number of transplants performed in the world.[1,2] SOT is a life-saving intervention in patients with heart disease, pulmonary, renal or hepatic. Although the recipients improve both in functional capacity and quality of life (QoL), these are still not equivalent to the same levels of healthy individuals.[3]

The long waiting period, caused by the lack of organ donors, often makes patients unprepared for the transplant physically and mentally. In addition to the classic cardiovascular risk factors, we still have the patient's lack of adherence to the programs, knowledge deficits about the rules of conduct after transplantation, non-acceptance of the new organ, fear of rejection, lack of a physical exercise routine, strategies for coping and occupational health issues and social rights.[4,5]

Rehabilitation is an essential part of contemporary care for patients before and after transplantation. The aim is to improve graft survival and reduce deaths from infection/rejection. Rehabilitation programs have prophylactic and therapeutic objectives, meeting the recommendations of maintaining improvements in QOL, reducing morbidity from cardiovascular diseases and improving long-term survival in transplant recipients.[6] Therefore, greater attention should be given to postoperative interventions surgical procedures that help in the individualized management of these patients and that can result in a better prognosis.[7]

Physical training should be highlighted among non-pharmacological post-surgical interventions, as it is associated with significant improvement in exercise tolerance and functional capacity, reduced disability and decreased cardiovascular morbidity and mortality. This has also been shown to be beneficial in several groups of chronic diseases that can lead to SOT. It is known that there is a limitation in the ability to perform physical exercises in pre-SOT individuals, and most studies have focused on candidates for heart and lung transplantation.[8] However, people with chronic kidney or liver disease also demonstrate limitations in pre-transplant exercise capacity, often due to secondary consequences of disuse, such as muscle weakness, rather than as a consequence of their primary disease process.[9] In these individuals, peak oxygen consumption limitation seems to be related to peripheral muscle dysfunction and not to central factors, such as cardiovascular or respiratory limitations.[10]

Despite the evidence showing the potential benefits of physical exercise for both pre and post-SOT patients, there is a great lack of places that offer this care globally. This worsened after the COVID-19 event that further restricted access to rehabilitation centers. A large proportion of TOS recipients engage in low levels of physical exercise and face barriers to being physically active.

The study by Ribeiro et al.[11] suggests a strategy where, after pre-participation assessment, in the absence of cardiovascular contraindication and according to the patient's preference, he can choose to perform his exercise program at the hospital gym, at the gym community or at home. This model allows more people to engage in an exercise program, receive guidance from a qualified professional, and have periodic face-to-face or teleconsultation consultations.[12] The results found by the authors reinforce the importance of the supervised program but emphasize that any type of treatment will be effective as long as the patient proposes to perform it.[11] In addition to the limitations described by the authors, the fact that, in the same study, recipients of different organs were approached have a pathophysiological inheritance that can directly influence rehabilitation outcomes.

Larger, well-controlled studies of physical exercise that specifically include transplant candidates are still needed to propose specific guidelines on exercise dose and program duration to achieve the best benefits.[13] Future studies on this topic should also focus on the effects of exercise during the waiting list period, preparing the patient for the transplant event and early post-transplant clinical outcomes.

For the world population, access to rehabilitation centers is still very limited, especially in places with a low structure and health resources and a low socioeconomic and cultural level. Our challenge is knowing how to use the knowledge of academia and scientists in conducting well-designed studies which can propose safe strategies, guidance and practice of PRBE in patients pre and post-SOT of great scope.

Keywords

Organ Transplantation/rehabilitation; Transplantation Immunology; Physical Activity; Kidney Transplantation; Liver Transplantation.

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Correlation among Waist Circumference and Central Measures of Blood Pressure

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Abstract

Background: Arterial stiffness is a strong predictor of cardiovascular disease (CVD). Body fat measures such as waist circumference (WC) have been associated with CVD in adulthood.

Objectives: The objective of this study was to evaluate the association of arterial stiffness, measured by applanation tonometry-Sphygmocor, with WC.

Methods: Observational study with 240 participants who make routine consultations at the outpatient clinic of a university hospital. Participants were interviewed and had central blood pressure measurements (CBPM), anthropometric parameters, abdominal fat and visceral fat measured. Paired and unpaired t and chi-square tests were used. A significance level of 5% was adopted.

Results: Of the 240 participants, 51.82% were male with a mean age of 59.71(±14.81) years and a mean WC of 99.87 (11.54) cm. Mean CBPM values were: Central arterial pressure (CAP) = 130.23 (91-223) mmHg, pulse wave velocity (PWV) = 9.8 (5.28-19.6)m/s and Augmentation Index [Amplification Index (AI)] = 29.45 (-14-60). PWV and CAP were highly correlated with WC with p<0.001 and p=0.02, respectively; however, the same positive correlation was not found between WC and AI (p=0.06).

Conclusion: The present study showed a positive association between WC and arterial stiffness, through the femoral carotid pulse wave velocity (cf-PWV) and AI, being stronger with cf-PWV, suggesting the evaluation of the effect of WC in vascular health as a method of aid in the early treatment of CVD and in the prevention of clinical outcomes.

Keywords: Cardiovascular Diseases; Atherosclerosis; Blood Pressure; Vascular Stiffness, Waist Circumference, Pulse Wave Analysis, Outcome Assessment, Health Care.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in Brazil and in the world, determining an increase in morbidity and disability adjusted for years of life.[1] Its increasingly high prevalence has been a reflection of the aging and illness of the population, even after optimizing public prevention policies.[1]

The presence of classic risk factors (hypertension, dyslipidemia, obesity, physical inactivity, smoking, diabetes and family history) increases the pre-test probability of CVD – with emphasis on coronary artery disease (CAD) – and guides primary and secondary prevention.[2]

Obesity is associated with an increased incidence of heart failure (HF), myocardial infarction (MI), stroke and death.[3,4] Studies of overweight and obese patients with CVD suggest an "obesity paradox", whereby high body mass index (BMI) may be associated with lower mortality and cardiovascular events.[5,6]

On the other hand, the body mass index (BMI) is unable to differentiate lean mass from fat[7] and the use of other measures of adiposity, such as waist circumference (WC), has been proposed to be a good predictor of abdominal fat and cardiovascular risk.[8,9]

Part of the atherosclerotic process is related to increased arterial stiffness, whose main biomarker is pulse wave velocity (PWV).[10,11] Arterial stiffness is an important independent predictor of cardiovascular mortality in diverse patient populations, including hypertensive patients.[12-14]

Consistent with the central role of arterial stiffness in cardiovascular function, arterial stiffness measurements may represent a promising biomarker in the prevention of cardiovascular outcomes, as they predict cardiovascular risk.[15]

Based on the current knowledge of the significance of arterial stiffness measures in the prognosis of cardiovascular diseases, the present study aims to analyze the association of WC with the central hemodynamic profile, making it possible to correlate the early identification of patients

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who are exposed to greater cardiovascular risk, to implement lifestyle changes and treatments that can prevent complications and progression of cardiovascular disease. We conducted the present study with the aim of evaluating the association between WC values and central blood pressure measurements (CBPM) - PWV, Augmentation Index (AI) and Central Blood Pressure (CBP).

Methods

Study design and participants

This is a cross-sectional observational study. Eligible participants were those seen at the outpatient clinic of a university hospital, comprising a reference laboratory for vascular aging, where arterial stiffness is assessed by applanation tonometry with pulse wave velocity measurements (SphygmoCor®). This is an instrument that provides measurement of carotid-femoral pulse wave velocity (fc-PWV) in the femoral and carotid arteries by applanation tonometry. The system, validated and used for decades, is currently considered the gold standard non-invasive method for the acquisition of central hemodynamic measurements.[16]

Participants aged over 18 years were adopted as inclusion criteria. The exclusion criteria used were: absence of adequate techniques to verify peripheral BP,[17] peripheral BP measurements not performed on digital, calibrated and validated devices; participation in other research protocols for less than one year according to ANVISA – Brazil regulations; chronic diseases in terminal stages; previous cardiovascular disease, including coronary artery disease (MI, angina, previous bypass surgery, or angioplasty) or stroke (ischemic stroke or TIA) for <6 months. The exclusion criteria for previous CVD presented were defined based on information obtained from the participants through direct interviews or evidence through complementary exams.

In the aforementioned outpatient unit, an average of 40 patients are seen per day, with an average of 200 patients per week, with central blood pressure measurements (CBPM) being performed in the indicated patients. The selection of participants was through an invitation to participate to those who met the inclusion and exclusion criteria, and acceptance by the patient. The sample size was 247 participants, according to the convenience of the field.

Collected data

Data collection was performed at the time of routine patient care at the outpatient clinic in June and October 2019. Information such as gender, age and associated comorbidities was collected, evaluated by self-reference and through chronic use medications. Smokers were defined as those who consumed at least one cigarette a day.[18]

Weight (in kg) and height (in m) were also collected by calculating the body mass index (Quetelet's formula);[19] and waist circumference (in cm). All measurements were taken with individuals in the standing position using standards created for population health studies.[19,20]

The investigation of cardiac and vascular damage of the target organ was performed through Doppler echocardiography and carotid Doppler, using a TOSHIBA Xsario model device. The following parameters were analyzed: measurements of the interventricular septum and the posterior wall of the left ventricle, left ventricular mass index and left atrial volume, on Doppler echocardiography, and measurement of intima media thickness and presence of carotid plaques, on carotid Doppler

Microalbuminuria was defined as albumin excretion in the urine between 30 and 300 mg / 24 hours[21] performed by means of a 24-hour urine collection or in the presence of the exam with less than 6 months of completion.

cf-PWV was measured with the CvMS Sphygmocor device (version 9 of the software, AtCor Medical) by applanation tonometry (PWVton) sequentially in the carotid and femoral arteries, blocked by an electrocardiogram signal recorded simultaneously.[22]

CAP measurement was performed by applanation tonometry, in a SphygmoCor® device, calibrated and clinically validated by the European Society of Hypertension (ESH) and the European Society Cardiology (ESC).[23] The instrument consists of a tonometer (portable pressure sensor or transducer) coupled to a computer with dedicated software for data collection and analysis. When used in the radial artery, SphygmoCor® also obtains measurements related to central systolic (CSBP) and diastolic (CDBP) blood pressure, pulse pressure amplification (PPA), central pulse pressure (CPP) and Augmentation Index (AIx) by transfer function. When used on the carotid and femoral arteries, the system also calculates PWV.

Sample size

Sample calculation was performed to estimate prevalence in a finite population of 1250 individuals, prevalence of systolic and central diastolic hypertension of 13.7%[24], tolerable absolute error of 5%, and confidence coefficient of 97.5%, totaling a sample of 200 patients. 20% was added to guarantee losses due to deficiencies in the adequate completion of the questionnaire.

At the end of the collection, data from 247 participants were obtained and 7 were excluded, of which 5 due to lack of data on WC and the other two due to more than 30% of the questionnaire being incomplete, ending up with a sample of 240 patients.

Statistical analysis

Categorical data are presented in absolute (n) and relative (%) frequencies. Numerical variables are presented as mean and standard deviation of the mean or median and interquartile range (25th-75th percentile). To verify the normality of data distribution, the Shapiro Wilk test was used. For comparison between groups, the Mann Whitney U test or the Kruskal Wallis test or the unpaired t-Student test or one-way ANOVA was used. For the analysis of correlation between variables, the Spearman or Pearson correlation coefficient was calculated.

Linear and logistic regression analysis was also performed, having as outcomes the cardiological exams and the determining variable WC classified as altered and normal; the other variables were used as adjustments to determine the confounding potential. The analyses were performed using STATA version 14.p and for all tests a significance level of 5% was considered.

Ethical aspects

The research project was evaluated and approved by the Research Ethics Committee of the Hospital das Clínicas, Universidade Federal de Goiás (UFG), opinion number: 3,907,884, with the signature of the Free and Informed Consent Form (ICF) by all participants.

Results

A total of 240 patients who attend at the outpatient clinic of a university hospital participated in the study; however, it was not possible to collect some information from all patients. The sample consisted mostly of males, middle-aged, overweight and mean WC above the upper normal limit for females.[17] There was a high prevalence of smokers[25] and more than a quarter of the population studied had CVD (Table 1). The CBPM showed a mean PWV close to the upper limit of normality for target organ damage (PWV > 10m/s)[17,23] and a CAP above the upper limit of normality for the studied population[17] (Table 1).

In females, who were overweight, smokers and ex-smokers, dyslipidemia, diabetes mellitus and heart damage, there was a higher frequency of altered WC. The medians of age, weight and BMI are higher in individuals with altered WC than in those with eutrophic WC (Table 1).

Lower AIx values and higher PWV values were observed in males. There were also higher PWV and CAP in patients with vascular damage, but no difference in these parameters was found in relation to smoking (Table 2).

There was an inverse and significant correlation between AIx and Weight, BMI and WC. There was also a direct and significant correlation between: PWV and age and WC; between CAP and age and WC; and between AIx and age (Table 3).

In the crude association analysis, there was a direct association between altered WC and PSBP. When using an age- and sex-adjusted model, there was an inverse association between altered WC and AIx. In another model adjusted for age, sex, smoking, nutritional status and comorbidities, altered WC was not associated with any of the parameters evaluated. Finally, in the model adjusted for determinant variables, the altered WC was only determinant for PSBP (Table 4).

Discussion

Excess abdominal obesity is associated with a variety of metabolic abnormalities and CVD.[8,26] WC measurement is used as a surrogate indicator of visceral obesity to predict morbidity and mortality at the population level,[27-29] in addition to being a low-cost and easy-to-use biomarker.[30]

Arterial stiffness is also related to CVD and atherosclerosis[31] and has been a strong independent predictor of coronary events and cardiovascular mortality in several groups of patients.[12,32] In this study, we examined the relationships between arterial stiffness measured by PWV and a specific cardiovascular risk factor: WC of 240 participants.

Univariate associations were therefore significant between WC and all components of CBPM, with the exception of AIx. The strongest correlation was observed between WC and fc-PWV ($p<0.001$), which is not surprising, considering that it is currently the gold standard method for assessing arterial stiffness.[33]

In our study, waist circumference was a significant determinant of arterial stiffness through fc-PWV. The association between increased body fat and high arterial stiffness was also found in other observational, cross-sectional and longitudinal studies, in agreement with our findings.[34-36] Other mechanisms, such as those involving adipokines and endothelial regulation, may also explain this association,[35] as well as the hypothesis of a negative impact on the health of large arteries caused by abdominal adiposity.[37]

Choi et al.[38] showed no significant correlation between WC and PWV in their study,[38] which can be explained by the fact that WC cannot distinguish between visceral and subcutaneous fat.[39]

Previous cross-sectional work demonstrates that the increase in abdominal obesity was associated with the decrease in AIx. This finding may have been due to a decrease in the transmural aortic pressure gradient and consequent reduction in the point of operational stiffness of the aorta or to subclinical left ventricular dysfunction that manifests as a lower degree of pressure increase for any given magnitude of reflection.[40,41]

Our study also showed no correlation between WC and AIx, but with a borderline p ($p=0.06$), suggesting that a likely larger sample could show a different result. When adjusted for age, there was also an inverse association between WC and AIx.

Shiva et al., however, who evaluated changes in AIx over a period of approximately 3 years, found that increasing waist circumference over time was associated with an increase in AIx. The direct prospective relationship between abdominal obesity and AIx suggests a progressive vascular dysfunction caused by obesity, resulting in a late increase in systolic pressure.[42]

Our study revealed that increasing WC had a positive association ($p=0.002$) with increasing CAP. A representative cohort of 2742 adults in Taiwan presented a multivariate analysis, which revealed that higher WC was independently associated with high CAP.[43] The same association was also found in adolescents in the city of Salvador, Brazil.[44] Previous studies showed results similar to ours,[24,45] suggesting the benefit of measuring CAP as a better approach in the pathogenesis of cardiovascular diseases.

Our results must be interpreted within the context of the potential limitations of the study. First, most participants in our study had at least one CV risk factor among hypertension,

Table 1 – Characterization of the sample and relationship with the waist circumference classification of patients treated at the outpatient clinic of a university hospital[17]

	Total sample n=240	Waist Circumference		p-value
		Normal 34(14,17%)	Altered 206(85,83%)	
Age, years, median [IQR] , n=240	60,25 [51,50-70,00]	54,00 [38,00-64,00]	63,00 [53,00-71,00]	0,004[1]
Gender, n(%), n=240				0,001[3]
Female	115(47,92)	7(20,59)	108(52,43)	
Male	125(52,08)	27(79,41)	98(47,57)	
Weight, kg, median [IQR] , n=237	75,10 [67,00;84,00]	64,80 [55,80-76,70]	75,75 [69,55-85,10]	<0,001[1]
Body mass index, kg/m², median [IQR] , n=238	27,98 [25,40-31,86]	22,94 [21,47-25,40]	28,62 [26,23-32,46]	<0,001[1]
Nutritional Status, n(%), n=238				<0,001[3]
Eutrophic	72(30,25)	24(72,73)	48(23,41)	
Overweight	166(69,75)	9(27,27)	157(76,59)	
Waist circumference, cm, mean (SD) , n=240	99,95(11,59)	84,52(7,83)	102,49(10,04)	<0,001[2]
Smoking habit, n(%), n=240				0,023[4]
Non smoker	166(69,17)	24(70,59)	142(68,93)	
Smoker	37(15,42)	9(26,47)	28(13,59)	
Ex smoker	37(15,42)	1(2,94)	36(17,48)	
Chronic diseases, n(%), n=240				
Arterial hypertension	213(88,75)	28(82,35)	185(89,81)	0,203[3]
Dyslipidemia	179(74,58)	19(55,88)	160(77,67)	0,007[3]
Brain stroke	46(19,17)	5(14,71)	41(19,90)	0,639[4]
Diabetes Mellitus	95(39,58)	6(17,65)	89(43,20)	0,005[3]
Microalbuminuria, n(%), n=212	81(38,21)	7(26,92)	74(39,78)	0,282[4]
PSBP, mmHg, median [IQR], n=240	140,00 [128,00-154,00]	132,00 [122,00-154,00]	140,00 [129,00-154,00]	0,068[1]
PDBP,mmHg, median [IQR], n=240	77,50 [70,00-86,00]	77,50 [70-84]	77,50 [70,00-87,00]	0,464[1]
PWV, m/s, median [IQR], n=239	9,30 [7,90-11,30]	8,91 [7,28-10,32]	9,41 [8,00-11,40]	0,151[1]
PAC,mmHg, median [IQR], n=240	128,00 [116,00-141,00]	124,00 [110,00-138,00]	129,00 [117,00-141,00]	0,106[1]
AIx, %, mean (SD), n=240	29,55(12,46)	28,93(15,29)	29,65(11,96)	0,756[2]
Heart damage, n(%), n=183	98(53,55)	7(31,82)	91(56,52)	0,029[3]
Vascular damage, n(%), n=112	87(77,68)	9(69,23)	78(78,79)	0,482[4]

IQR: interquartile range; SD: standard deviation; n: absolute frequency; % relative frequency; CRP: C-reactive protein; PSBP: peripheral systolic blood pressure; PDBP: peripheral diastolic blood pressure; CSBP: central systolic blood pressure; AIx: Augmentation index; PWS: pulse wave speed. [1] - Mann-Whitney; [2] - Student's t-test for independent samples; [3] - Chi-square test; 4 – Fisher's exact test, all with 5% significance.

dyslipidemia, diabetes, overweight, or cardiovascular comorbidities. Although these factors have been properly accounted for, our data may not be representative of an entire population.

Finally, it is estimated that the presence of a more expressive sample volume can improve the statistical power of the work and reinforce the benefits of the results presented.

Conclusion

This study demonstrated a positive correlation between WC and arterial stiffness measured by fc-PWV and CAP, suggesting the evaluation of the effect of WC on vascular health as a method of aid in the early treatment of CVD and in the prevention of clinical outcomes. Therefore, future studies to determine the relationship between abdominal obesity

Table 2 – Differences in CBPM between sex, carotid Doppler and smoking habit

Variables	PWV		CAP		AIx	
	Median [IQ]	p-value	Median [IQ]	p-value	Mean (DP)	p-value
Gender		<0,001[1]		0,526[1]		0,010[3]
Female	8,88 [7,68-10,10]		127,00 [114,00-140,00]		31,70(12,01)	
Male	10,10 [8,30-12,15]		129,00 [117,00-141,00]		27,58(12,58)	
Altered Carotid Doppler		0,004[1]		0,037[1]		0,072[3]
No	8,90 [7,70;10,20]		127,00 [114,00;135,00]		26,32(13,66)	
Yes	10,36 [9,20-12,10]		133,00 [119,00-148,00]		30,93(10,38)	
Smoking Habit		0,219[2]		0,682[2]		0,437[4]
Non smoker	9,21 [7,84-11,36]		128,50 [116,00-146,00]		30,20(12,61)	
Smoker	9,11 [7,93-10,61]		128,00 [112,00-138,00]		27,45(9,94)	
Ex Smoker	10,10 [8,70-11,50]		126,00 [116,00-136,00]		28,73(13,97)	

n: absolute frequency of individuals; IQR: Interquartile-range; SD: standard deviation of the mean; PWV: Pulse wave velocity; CAP: Central arterial pressure; AIx: Augmentation index; p-value obtained by [1]Mann-Whitney test, or [2]Kruskal-Wallis test; [3] Student t-test; 4 – Oneway ANOVA test, all with 5% level of significance.

Table 3 – Correlation between WC and CBPM

Variables	Correlation rho correlation coefficient (p-value)		
	PWV[1]	CAP[1]	AIx[2]
Age (years)	0,54 (<0,001)	0,20 (0,002)	0,33 (<0,001)
Weight (kg)	0,09 (0,192)	0,03 (0,671)	-0,31 (<0,001)
BMI (kg/m²)	0,11 (0,095)	0,11 (0,080)	-0,17 (0,009)
WC (cm)	0,33 (<0,001)	0,15 (0,020)	-0,10 (0,131)

CBPM: Central Blood Pressure Measurements; PWV: Pulse wave velocity; CAP: Central arterial pressure; AIx: Augmentation index; BMI: Body Mass Index; WC: Waist Circumference;. [1] Spearman's correlation test or Pearson's [2], with 5% significance level.

and the risk of arterial stiffness may consider WC to estimate more accurately. Our study provides information that requires confirmation by a large-scale randomized clinical trial because the effects of observational studies may be overestimated.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript: Guimarães Filho GC; Critical revision of the manuscript for intellectual contente: Guimarães Filho GC, Silva LT, Castro e Silva RM.

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.

Table 4 – Association between Waist Circumference and Cardiological Exams

	Model 1			Model 2			Model 3			Model 4		
	Coef.	$CI_{95\%}$	p	Coef.	$CI_{95\%}$	p	Coef.	$CI_{95\%}$	p	Coef.	$CI_{95\%}$	p
PSBP*	0,02	0,00;0,05	0,042	0,02	-0,00;0,05	0,074	0,01	-0,02;0,04	0,495	0,03	0,00;0,06	0,030
PDBP*	0,01	-0,01;0,04	0,270	0,02	0,00;0,05	0,046	0,01	-0,02;0,03	0,594	0,00	-0,03;0,03	0,812
PWV*	0,03	-0,01;0,07	0,120	0,00	-0,03;0,04	0,792	-0,00	-0,04;0,04	0,867	-0,01	-0,05;0,03	0,705
CAP*	0,02	-0,00;0,04	0,084	0,01	-0,01;0,04	0,321	0,00	-0,03;0,03	0,905	0,02	-0,01;0,05	0,180
AIx	0,72	-3,83;5,27	0,756	-4,47	-8,90-0,04	0,048	-2,87	-7,91;2,14	0,259	2,65	-2,31;7,62	0,294
Heart damage	1,02	0,07;1,97	0,034	0,87	-0,21;1,96	0,115	0,09	-1,14;1,33	0,882	-0,08	-1,51;1,36	0,916
Altered ABPM	-0,50	-1,71;0,70	0,415	-0,24	-1,49;1,01	0,706	-0,93	-2,42;0,55	0,218	-1,55	-3,13;0,03	0,054
Vascular damage	0,50	-0,77;1,77	0,440	1,18	-0,32;2,69	0,124	0,30	-1,50;2,10	0,743	1,08	-0,87;3,03	0,279

*Coef.: Coefficient of linear or logistic regression; 95%CI: 95% confidence interval; PWV: Pulse wave velocity; CAP: Central arterial pressure; AIx: Augmentation index; ABPM: Ambulatory blood pressure monitoring. ¹ -Linear regression analysis ² - Logistic regression analysis, using as determining variable waist circumference classified as normal vs altered and dependent variables on the cardiological exams. * Used variable on the logarithmic scale due to the absence of normality. Model 1 – crude; Model 2 - adjusted for age and sex; Model 3 – adjusted for age, sex, smoking habit, nutritional status and comorbidities; Model 4 – adjusted by variables with p<0.20 in the binary analysis.*

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Waist Circumference: A Parameter of Vascular Health

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Short Editorial related to the article: Correlation among Waist Circumference and Central Measures of Blood Pressure

Obesity plays a central role in chronic noncommunicable diseases due to its high prevalence and strong correlation with risk factors like hypertension, dyslipidemia, diabetes mellitus, and morbidity and mortality. In particular, abdominal obesity has been renowned as an emerging risk factor for an inflammatory and prothrombotic state, which is associated with an increased prevalence of hypertension and increased risk of cardiovascular (CV) events. These data are of utmost importance in the scenario of increasing prevalence of obesity not only in adults, but also among children and adolescents.[1,2] Results of a study conducted in Rio de Janeiro[2] showed an unfavorable relationship of elevated blood pressure (BP) and excess weight in adolescents with increased BP levels and anthropometric and metabolic variables in young adults.

Over the last years, the understanding of the CV continuum has grown, and CV disease has been seen in the context of vascular damage. In this sense, endothelial dysfunction, which results in atherosclerotic disease and its complications, involves the tunica media of large arteries, affected by an accelerated aging of the vessel, resulting in early arterial stiffness and arteriosclerosis, which in turn contributes to CV morbidity and mortality.[3-5]

Pulse wave velocity (PWV) is the most studied non-invasive parameter of arterial stiffness with renowned clinical application. A meta-analysis[6] showed that, for every increase of 1m/s in PWV, there was an increase by 14% in overall cardiovascular events, 15% in CV mortality and 15% in overall mortality. Therefore, arterial stiffness is a strong predictor of CV events and overall mortality, and the main international guidelines have recommended the measurement of PWV for CV risk stratification.[1,3,4]

The article by Guimarães et al.[7] showed a positive relationship of waist circumference (WC) and PWV with augmentation index (AIx). The authors suggested that WC, measured in a simple and cheap way, may be associated with vascular damage, and hence play a role in the assessment of CV risk and contribute to the early treatment and prevention of CV disease.

Studies[8-13] on the association between arterial stiffness, BP and anthropometric and metabolic variables have yielded varied results; it is believed that the combined action of CV risk factors is the main determinant of vascular damage.[5]

In the elderly, a study[8] reported significant associations between PWV, age, BP, WC, fat body mass, and leptin. However, the logistic regression revealed that only elevated leptin and low adiponectin were predictors of arterial stiffness. Another study[9] demonstrated that the greater the muscle mass, the lower the arterial stiffness in long-lived adults, with no statistical relationship between PWV and body composition. On the other hand, another study[10] showed an association of PWV with WC, waist-hip ratio, and visceral fat area, but not with body mass index (BMI); in the multivariate analysis, only waist-hip ratio and visceral fat area were associated with PWV.

In young adults, a Swedish study[11] did not find an association between carotid intima-media thickness and body composition. However, arterial distensibility had the strongest associations with body composition measurements in both women and men. Analysis of the Rio de Janeiro study[12] revealed a significant positive correlation of PWV with BP, BMI, and low-density lipoprotein (LDL)-cholesterol, and a negative correlation with high-density lipoprotein (LDL)-cholesterol and adiponectin in young adults. Nevertheless, in the multiple regression analysis, only male sex and BP had a significant correlation with PWV. A study[13] with obese children showed that arterial structure and elasticity are negatively affected by excess weight and BP levels.

Therefore, the article under discussion[7] makes important contributions to the understanding of determinants of vascular damage and the role of traditional and emerging risk factors, including simple anthropometric variables like WC. The authors present key information for the potential use of this measure as a therapeutic target and as a biomarker of improvement of the arterial wall structure and effective CV risk reduction.

Keywords

Cardiovascular Diseases/complications; Blood Pressure; Atherosclerosis; Vascular Stiffness; Dyslipidemias; Waist Circumference; Pulse Wave Analysis; Outcome Assessment (Health Care)

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Abnormal Echocardiographic Findings in Hospitalized Patients with Covid-19: A Systematic Review and Meta-analysis

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Abstract

Background: **Coronavirus disease 2019 (Covid-19) can lead to severe respiratory distress and acute cardiac injury, but it is unclear how often it can cause cardiac dysfunction.**

Objective: **In this systematic review, we aimed to summarize the main echocardiographic findings in patients with Covid-19.**

Methods: **We systematically searched in PUBMED, EMBASE, LILACS and Cochrane databases, in addition MedRxiv and Scielo preprints from inception to July 21st, 2021. Studies reporting echocardiographic data in patients with Covid-19 were included. Demographic characteristics, previous cardiovascular disease (CVD), and echocardiographic findings were extracted. We performed a meta-analysis of proportions to estimate the main echocardiographic findings. The level of significance was $p < 0.05$.**

Results: **From 11,233 studies, 38 fulfilled inclusion criteria and were included in the meta-analysis. The estimated proportions of left ventricular (LV) systolic dysfunction were 25% (95%CI: 19, 31; I^2 93%), abnormal global longitudinal strain 34% (95% CI 23, 45; I^2 90%), righ ventricular (RV) systolic dysfunction 17% (95%CI 13, 21; I^2 90%), pericardial effusion 17% (95%CI: 9, 26; I^2 97%), and pulmonary hypertension 23% (95%CI: 15, 33, I2 96%). LV systolic dysfunction was directly associated with study-specific prevalence of previous abnormal echocardiogram ($p<0.001$). The proportion of patients in mechanical ventilation, indicating severity of disease, did not explain the heterogeneity in the proportions of LV dysfunction ($p=0.37$).**

Conclusion: **Among hospitalized patients with Covid-19, LV dysfunction has been reported in one quarter, with smaller proportions of right ventricular dysfunction, pericardial effusion and pulmonary hypertension. However, there was a higher proportion of LV dysfunction among studies reporting the presence of prior heart disease, which suggests that cardiac dysfunction was mostly pre-existing.**

Keywords: **Echocardiography; Covid-19; Ventricular Function, Left.**

Introduction

Coronavirus disease 2019 (Covid-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may result in severe respiratory distress and acute cardiac injury. Elevated troponin blood levels and imaging showing abnormal cardiac function have been associated with worse prognosis in patients with acute Covid-19.[1] The worse prognosis may result from a combination of disease-related factors, such as virulence and inflammatory response, and patient-related factors, such as pre-existent cardiovascular risk factors and established cardiovascular disease (CVD). For this reason, it has been recommended to assess cardiac function using transthoracic echocardiography (TTE) to guide the management of patients with new or worsening cardiovascular symptoms, hemodynamic instability, and increased biomarkers levels.[2]

At the beginning of the pandemic, there have been anecdotal reports of new-onset heart failure (HF) and fulminant myocarditis in patients with Covid-19.[3,4] Studies using cardiovascular magnetic resonance have shown that evidence of myocardial inflammation in elite athletes who had recently recovered from Covid-19 was common, but with uncertain clinical significance.[5] Nevertheless, more recent reports have shown that myocarditis is far less common (less than 2%) than earlier suggested, even among patients with

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elevated circulating troponin levels.[6,7] It is also unclear how often Covid-19 affects cardiac function, either due to direct myocardial injury or through increasing pulmonary resistance when the lungs are severely damaged. Echocardiographic studies have shown varied findings of left and right ventricular dysfunction; for instance, left ventricular (LV) systolic dysfunction has been found in less than 10% of patients in some studies and almost 40% in others.[8,9] Large-scale studies showing accurate estimates of the incidence of major cardiac dysfunction, its clinical significance, and associated risk factors are lacking. Because of the risk of contamination of healthcare workers, the use of echocardiography should be based on critical consideration of the benefits for the patient.[10] Therefore, we aimed to summarize the main echocardiographic findings of patients with Covid-19 through a systematic review and meta-analysis.

Methods

Study design and eligibility criteria

We performed a systematic review, study selection and meta-analysis of proportions according with the PRISMA statement for meta-analysis.[11] We included all studies with at least 10 participants describing echocardiogram findings in hospitalized patients with Covid-19, published in English, Portuguese, and Spanish languages, from inception to July 21, 2021. Studies that did not report any echocardiogram findings were excluded. We also excluded unpublished abstracts, studies lacking baseline clinical information of participants or insufficient echocardiographic data to obtain the number of participants with abnormal cardiac function or structure.

Information sources and search

We systematically searched in PUBMED, EMBASE, LILACS and Cochrane (CENTRAL) databases. We also searched articles in the repository of unpublished (preprints) manuscripts in MedRxiv (https://www.medrxiv.org/) and Scielo preprint databases. Our search used the terms "Covid-19", "SARS CoV 2", "Coronavirus infection", "Heart Diseases" and "Echocardiography" as descriptors (Medical Subject Headings – MeSH) or supplementary concept, and synonyms as free text in title and abstract to increase sensitivity. The full search strategy was displayed in the supplemental material (Supplemental table 3).

Study selection and data extraction

We merged the search results from each database using the EndNote software and removed duplicated studies. Four authors (EB, GR, PO, AP) independently examined titles and abstracts to remove irrelevant reports. Then, the full texts of potentially relevant reports were examined and the studies that fulfilled the eligibility criteria were selected. Different reports from the same study were linked and the study with the largest sample size was selected. Discrepancies were resolved by consensus. References of review articles were examined for additional studies, and those considered eligible were further incorporated into the meta-analysis.

The following data were extracted from the studies: authors' names, month of publication, previous abnormal echocardiogram of patients, sample size of patients undergoing echocardiogram, and the number of individuals with LV systolic dysfunction, right ventricular (RV) systolic dysfunction, pulmonary hypertension, and pericardial effusion. The study-specific definitions for each echocardiographic abnormality were detailed in the supplemental table 2. When LV systolic dysfunction was not clearly defined by the authors, we adopted a LV ejection fraction (LVEF) below 50%. Abnormal global longitudinal strain (GLS) was defined as below 18%. Similarly, RV dysfunction was determined by study specific definition; otherwise, it was defined as tricuspid annular plane systolic excursion (TAPSE) below 17 mm and/or tissue Doppler of the free lateral wall of the right ventricle (S') below 9.5 cm/s. Pulmonary hypertension was defined by tricuspid regurgitation velocity above 2.8 m/s, pulmonary acceleration time below 100 ms and/or pulmonary artery systolic pressure (PASP) above 35 mmHg (Supplemental Table 2). Only two studies defined pulmonary hypertension by different cut off values of PASP: one above 40mmHg,[12] and one above 45mmHg.[13] The number of patients with LV or RV dysfunction was estimated using the mean LVEF and the respective standard deviation (or 95% confidence interval) as previously recommended for data extraction in systematic reviews.[14]

Population characteristics, including mean age, proportion of men, prevalence of obesity, hypertension, diabetes, previous coronary heart disease and heart failure were also extracted. All data were entered in a table using Excel software.

Hypothesized sources of heterogeneity

Since patient characteristics varied among the studies, we expected a significant heterogeneity across them. We decided to evaluate severity of disease using the proportion of individuals under mechanical ventilation and history of previous CVD (either HF or coronary heart disease). We used I^2 statistics to identify heterogeneity and meta-regression using these characteristics as potential modifiers of abnormal echocardiographic findings.

Quality assessment

We used a previously reported tool for evaluating methodological quality of observational studies, adapted for case reports and case series.[14] For each study, the reviewers answered the following questions to evaluate whether they fulfilled the quality criteria:

– Selection: Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?

– Exposure ascertainment: Was the exposure adequately ascertained?

– Alternative cause ruled out: Were other alternative causes that may explain the observation ruled out?

– Enough follow-up: The echocardiography was performed in the most critical moment during the patient hospitalization?

– Sufficient detail: Is the case described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences to their own practice?

Funnel plots were used to assess for publication bias, as case reports of abnormal cardiac findings might be more likely to be published. Funnel plots were constructing by plotting sample size against log odds ratio of each outcome, as previously proposed to assess publication bias in meta-analysis of non-comparative proportion studies.[15]

Statistical analysis

We performed a meta-analysis of proportions to estimate the proportion of LV systolic dysfunction, RV systolic dysfunction, pulmonary hypertension and pericardial effusion among patients with acute Covid-19. To assess whether previous CVD and severity of disease influenced the proportion of abnormal echo findings, we performed a meta-regression using the prevalence of CVD and the proportion of participants under mechanical ventilation in each study. The level of significance was $p < 0.05$.

Due to expected variability in the selected studies, we performed a random-effects meta-analysis with Freeman-Tukey double arc-sine transformation to account for any violation of the assumption of normality in this variable. Heterogeneity was assessed with the I^2 statistic. The meta-analysis was performed using Stata (*StataCorp*. College Station, Texas) version 15.0.

Results

Search Results

The initial search yielded 11,233 titles, and the final number after exclusion of duplicates was 7,550 (Figure 1). From these, 318 were potentially relevant studies and the respective full texts were assessed for eligibility. Finally, 38 studies met the eligibility criteria and were included in the meta-analysis (Table 1*)*.

Echocardiographic findings in Covid-19 patients

Overall, we found that the proportion of LV systolic dysfunction was 25% (95%CI: 19, 31; I^2 93%; Figure 2), but heterogeneity was high across the studies. This heterogeneity was neither explained by study-specific prevalence of previous CVD (Figure 2, p for interaction = 0.16), nor by the study-specific proportion of patients under mechanical ventilation (Supplemental figure 1, p for interaction = 0.37). Among the studies that reported echocardiographic data before SARS-CoV2 infection, we found a direct relationship between previous abnormal echocardiogram and proportions of LV dysfunction (Supplemental Figure 3, p for interaction < 0.001).

RV systolic dysfunction was present in 17% (95%CI 13, 21; I^2 90%; Figure 3) of patients with Covid-19. However, despite the high heterogeneity, previous CVD (p=0.53), pulmonary hypertension (p=0.96), or mechanical ventilation (p=0.65) do not explain the variation in proportion of RV dysfunction across the studies (Figure 3, Supplemental Figures 2 and 4).

Pulmonary hypertension was found in 23% (95%CI: 15, 33, I2 96%; Figure 4) and pericardial effusion was found in 17% (95%CI: 9, 26; I^2 97%; Figure 5) of patients with Covid-19. Abnormal regional LV wall motion were reported in 23% (95% CI 12, 38; I^2 96%; Figure 6) in Covid-19 patients. GLS was abnormal in 34% (95% CI 23, 45; I^2 90%) of patients with Covid-19 *(*Figure 7*)*.

Publication bias

We evaluated potential publication bias of studies reporting LV systolic dysfunction, RV systolic dysfunction, pericardial effusion, and pulmonary hypertension. Visual analysis of the funnel plot suggests publication bias of studies reporting RV systolic dysfunction, with a higher likelihood of small studies reporting a higher proportion of the outcome *(*Supplemental Figure 5*)*.

Discussion

In this systematic review of echocardiographic findings in patients with Covid-19, we found that the estimated proportions of LV systolic dysfunction was 25%, RV systolic dysfunction was 17%, pulmonary hypertension was 23% and pericardial effusion was 17%. GLS, which is more sensitive to detect subclinical LV dysfunction, was abnormal in 34% of patients with Covid-19. Despite the method, the findings of LV systolic dysfunction varied considerably, with lower proportions in studies reporting proportionally fewer individuals with previous abnormal echocardiogram.

The echocardiographic findings in patients with Covid-19 have been very heterogeneous. The prevalence of LV systolic dysfunction, RV dysfunction and RV dilation have ranged from 5.4[8] to 37.4%,[9] 3.6[8] to 33%,[16] and 0[17] to 46.9%,[18] respectively. While most studies have pointed out RV dysfunction and/or dilation as the most frequent echocardiographic changes,[19-22] others have found LV systolic dysfunction to be more prevalent.[8,9] The contradictory results about the prevalence and consequences of echocardiographic changes among patients with Covid-19 may be explained by several factors. Relatively small samples, referral bias, different TTE protocols, inaccurate definitions of echocardiographic abnormalities, and differences of population characteristics, such as the proportion of patients on mechanical ventilation and/or with previous CVD, might have led to the wide-ranging conclusions about cardiac manifestations of Covid-19. In the search for sources of heterogeneity, some interesting points should be mentioned in our study. When we separated the studies by the proportion of patients under mechanical ventilation (as an indicator of disease severity), the proportions of LV and RV dysfunction did not change. When we analyzed a population composed of healthier individuals (the lowest tertile of prior CVD prevalence), the proportion of patients with LV dysfunction tended to be lower, but this difference was not statistically significant. On the other hand, it is conceivable that high proportions of abnormal echocardiographic findings at the beginning of the pandemic reflect previous LV dysfunction, as we found higher proportion of LV dysfunction in studies reporting proportionally more individuals with previous abnormal echocardiogram. An analysis from the

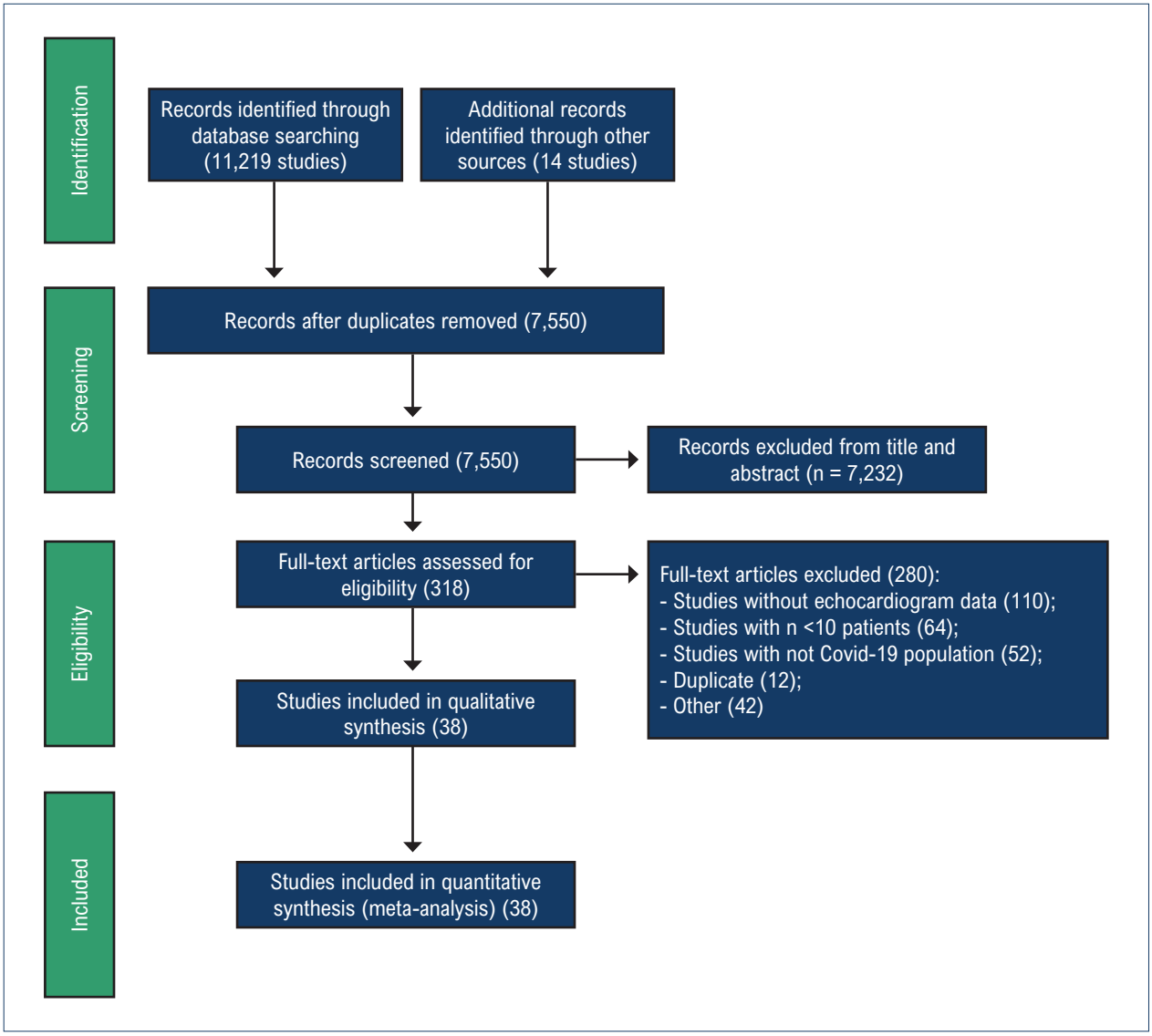

Figure 1 – *Flow-chart of study selection for the meta-analysis.*

Brazilian Echocardiographic Registry showed that patients with Covid-19 without previous CVD were less likely to have LV systolic dysfunction than those with previous CVD (13 vs 34%, p <0.001).[23]

The study by Dweck et al.[9] was the first (and the largest) to show that echocardiographic abnormalities were very common in hospitalized Covid-19 patients. Using an online survey which collected data from 1,216 patients (26% with pre-existing CVD) of 69 countries, they found that more than half of the patients (55%) had an abnormal TTE. Subjects with abnormal echocardiographic findings were older, and had a higher prevalence of pre-existing CVD, HF or valvular heart disease. Any degree of LV systolic dysfunction was diagnosed in 37.4% of subjects and biventricular impairment in 14.3%. On the other hand, only 3% had evidence of a new myocardial infarction, 3% of myocarditis and 2% of findings suggestive of Takotsubo syndrome. The study was limited by selection bias, which might have led to the overestimation of cardiac findings.

In order to mitigate referral bias, Szekely et al.[19] systematically performed TTE in 100 consecutive patients hospitalized for Covid-19, 43% of which had prior CVD. They found that the most frequent abnormality was RV dysfunction/dilation (39%) while only a minority of patients (10%) presented LV systolic dysfunction.[19] In addition, Covid-19 patients with myocardial injury or worse clinical condition did not have any significant difference in LV systolic function but had worse RV function when compared to patients without myocardial injury or better clinical condition. The higher prevalence of RV dysfunction and small proportion of LV dysfunction have been similarly found in other smaller studies.[20,21,24] Although most studies of this meta-analysis have not clearly identified the presence of pre-existing echocardiographic changes, it is possible that in a small proportion of patients, LV systolic dysfunction reflects a Covid-19-related "de novo" LV impairment, particularly

Table 1 – Characteristics of studies included in the meta-analysis

First author (Month Year)	Country	Population characteristics	Sample with echo	Mean age	Men, %	Obesity, %	Hypertension, %	Diabetes, %	Previous CVD, %	Previous HF, %	Previous Abnormal Echo, %	Mechanical ventilation, %
Deng (Mar2020)[8]	China	hospitalized patients with Covid-19	112	65	51	37	32	17	13	4	4	25
Li (Apr2020)[16]	China	Covid-19 patients with echocardiogram	120	61	48	18	40	12	9	0	0	13
Bangalore (Apr2020)[29]	USA	Covid-19 patients with electrocardiogram	17	63	83	NR	61	33	17	NR	50	67
Rath (May2020)[18]	Germany	hospitalized patients with Covid-19	98	68	63	20	70	24	23	NR	NR	40
Ge (May2020)[30]	China	Covid-19 patients in the ICU	51	70	73	NR	43	31	31	8	NR	41
Evrard (May2020)[31]	France	Covid-19 patients in mechanical ventilation	18	70	67	NR	61	22	NR	NR	NR	100
Szekely (May2020)[19]	Israel	hospitalized patients with Covid-19	100	66.1	63	29	57	29	16	7	2	10
Stefanini (Jun2020)[32]	Italy	Covid-19 patients with STEMI	28	68	71	4	71	32	21	NR	NR	0
Dweck (Jun2020)[9]	69 countries	Presumed Covid-19 patients with echocardiogram	1216	62	69	NR	37	19	20	9	NR	0
Vasudev (Jun2020)[33]	USA	Covid-19 patients with echocardiogram	45	61.4	51	NR	64	56	27	24	9	NR
Lazzeri (Jul2020)[13]	Italy	hospitalized patients with Covid-19	28	61	79	61	89	39	29	NR	NR	86
Rodríguez-Santamarta (Jul2020)[34]	Spain	Covid-19 patients in the ICU	37	67.6	92	NR	NR	NR	5	0	NR	NR
van den Heuvel (Jul2020)[17]	Netherlands	hospitalized patients with Covid-19	51	63	80	0	41	18	22	0	18	33
Stöbe (Aug2020)[35]	Germany	Covid-19 patients with echocardiogram	18	64	78	NR	72	28	11	NR	NR	78
Giustino (Aug2020)[36]	USA	hospitalized patients with Covid-19	118	66	100	NR	NR	NR	NR	NR	NR	NR
Krishnamoorthy (Aug2020)[37]	EUA	Covid-19 patients with echocardiogram	12	57	42	42	58	33	17	NR	NR	42
Schott (Aug2020)[38]	USA	Covid-19 patients with echocardiogram	66	60	58	86	58	35	NR	11	6	35
Sud (Aug2020)[22]	USA	Covid-19 patients with echocardiogram	24	64.5	54	NR	NR	NR	NR	8	8	42

Duerr (Sep2020)[39]	Germany	hospitalized patients with Covid-19	19	69	47	NR	63	26	37	NR	NR	NR
Kunal (Oct2020)[40]	India	symptomatic Covid-19 patients	28	51	65	NR	38	32	13	1	NR	23
Lassen (Oct2020)[26]	Denmark	Covid-19 patients with echocardiogram	214	69	55	18	57	24	16	10	NR	0
Jain (Oct2020)[20]	USA	Covid-19 patients with echocardiogram	77	61	7	5	6	4	2	2	NR	5
Lairez (Oct2020)[41]	France	hospitalized patients with Covid-19	31	57	87	23	48	32	NR	NR	NR	68
Weckbach (Nov2020)[42]	Germany	Covid-19 and myocardial injury	18	70	89	NR	78	39	39	6	NR	50
Argulian (Nov2020)[43]	USA	hospitalized patients with Covid-19	105	66	61	NR	NR	NR	NR	NR	NR	28
Gonzales (Dec2020)[44]	Portugal	Covid-19 patients in the ICU	30	61	NR	53	73	30	NR	NR	NR	23
Ferrante (Dec2020)[45]	Italy	Covid-19 patients with chest-CT	21	67	71	NR	54	21	15	NR	NR	20
Bagate (Dec2020)[12]	France	Covid-19 patients in the ICU	67	61	82	31	54	36	NR	10	NR	99
Shmueli (Jan2021)[46]	USA	Covid-19 patients with echocardiogram	60	66.2	65	17	47	27	17	13	NR	32
Moody (Jan2021)[47]	United Kingdom	Covid-19 patients with echocardiogram	164	61	78	NR	41	32	13	NR	NR	73
Pishgahi (Feb2021)[48]	Iran	Covid-19 patients with echocardiogram	680	55	63	NR	44	25	16	NR	NR	NR
Morin (Mar2021)[49]	USA	Covid-19 patients with echocardiogram	396	67	48	NR	58	31	NR	NR	NR	21
Norderfeldt (Mar2021)[50]	Sweden	Covid-19 patients in the ICU	67	58	94	NR	NR	NR	NR	NR	NR	100
Li (Mar2021)[51]	China	hospitalized patients with Covid-19	157	62	50	15	45	15	17	3	NR	24
Liaqat (Mar2021)[52]	Pakistan	hospitalized patients with Covid-19	181	44	59	5	17	17	NR	NR	NR	28
Mercedes (Apr2021)[53]	Dominican Republic	Covid-19 pregnant patients	15	29	0	33	0	NR	0	0	NR	0
Karagodin (May2021)[54]	10 countries	hospitalized patients with Covid-19	870	60	56	NR	43	20	14	7	NR	27
Barberato (Jul2021)[23]	Brazil	hospitalized patients with Covid-19	223	61.4	59	27	52	35	13	7	NR	NR

All studies adopted a 5% level of statistical significance for hypothesis testing. ICU: intensive care unit; NR: not reported.

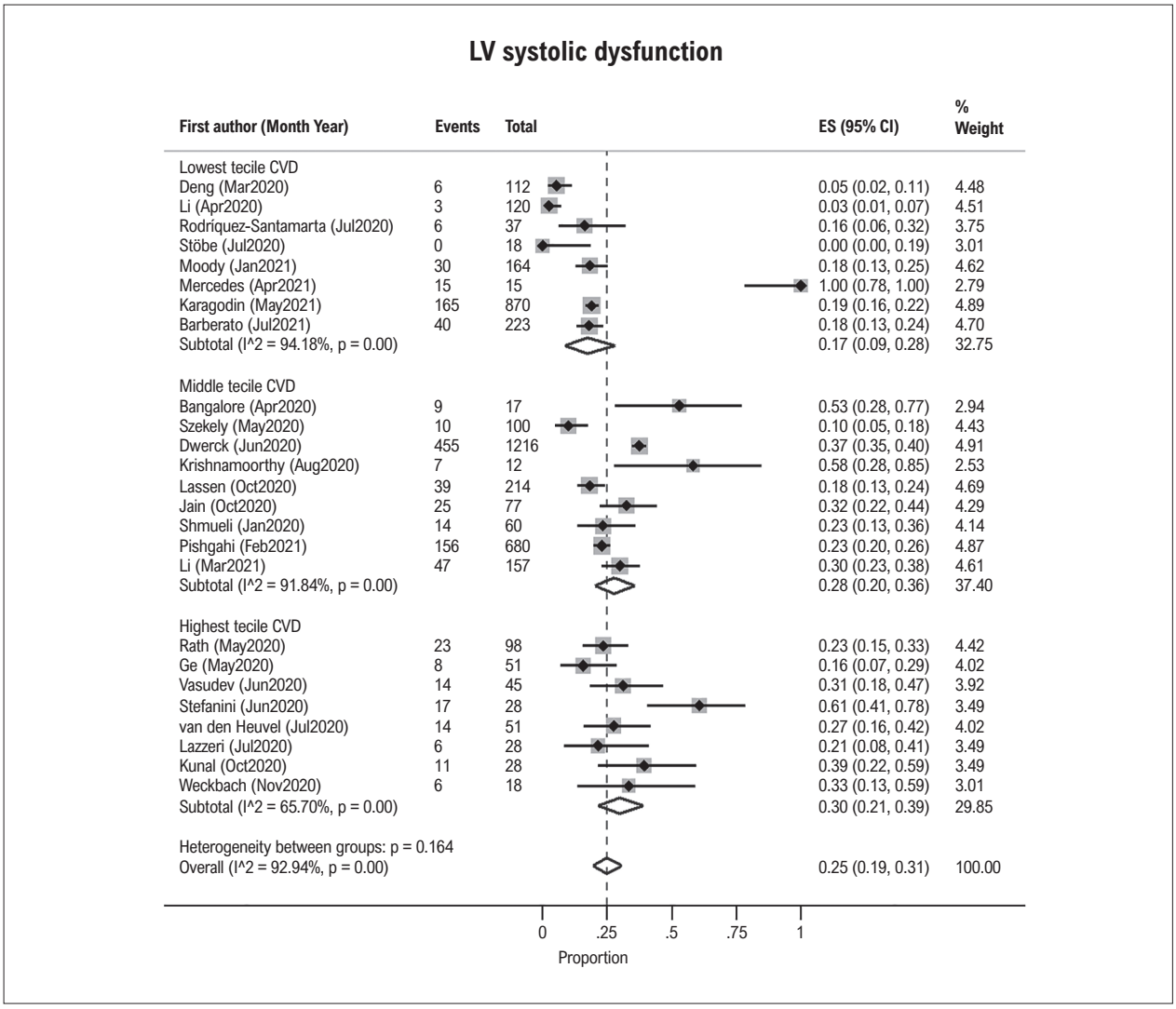

Figure 2 – *Proportion of left ventricular dysfunction in patients with Covid-19 across the studies according to the prevalence of cardiovascular diseases. CVD: cardiovascular diseases. LV: left ventricular. * Studies were divided according to the percentage of patients with CVD: Lowest tercile (less than 15%), Middle tercile (15 to 21%) and the highest tercile (>21%).*

in those without previous CVD. Moreover, echocardiographic abnormalities might denote the presence of pre-existing stable cardiac disease that has worsened because of the SARS-CoV-2 infection. Therefore, it appears that the prevalence of cardiac dysfunction is lower than that suggested at the beginning of the pandemic. Data regarding the use of echocardiography on hospitalized Covid-19 patients, retrieved from studies with variable designs, sample sizes, and severity scores, have shown that normal echocardiographic findings were reported in about 50% of subjects, with LVEF usually less affected.[25] Indeed, it has been recently shown that persistent LV dysfunction is uncommon after Covid-19: in patients who had elevated troponin blood levels, cardiovascular magnetic resonance two months after infection revealed LV systolic dysfunction in only 11% of patients, although one-third had findings suggestive of myocarditis.[6]

Since the major efforts of the scientific community aim to prevent the severe health consequences of the Covid-19 pandemic, it has been challenging to balance the use of echocardiography to provide high-quality medical care without an increase in the risk of cross-infection between healthcare professionals and patients. On the other hand, it is important to emphasize that the presence of cardiac dysfunction is independently associated with worse prognosis in patients with severe Covid-19.[26,27] Echocardiographic parameters that identify myocardial damage earlier and more accurately than the traditional ones, such as two-dimensional LV or RV GLS, have been less used in the context of Covid-19 due to the recommendations for using focused protocols, which reduces the exposure of health care professionals to infection. Our meta-analysis showed that studies that assessed LV systolic function with GLS detected a higher proportion of patients with LV dysfunction compared to those that used LVEF. A recently published meta-analysis showed that lower LV and RV GLS were independently associated with poor outcome in Covid-19.[28]

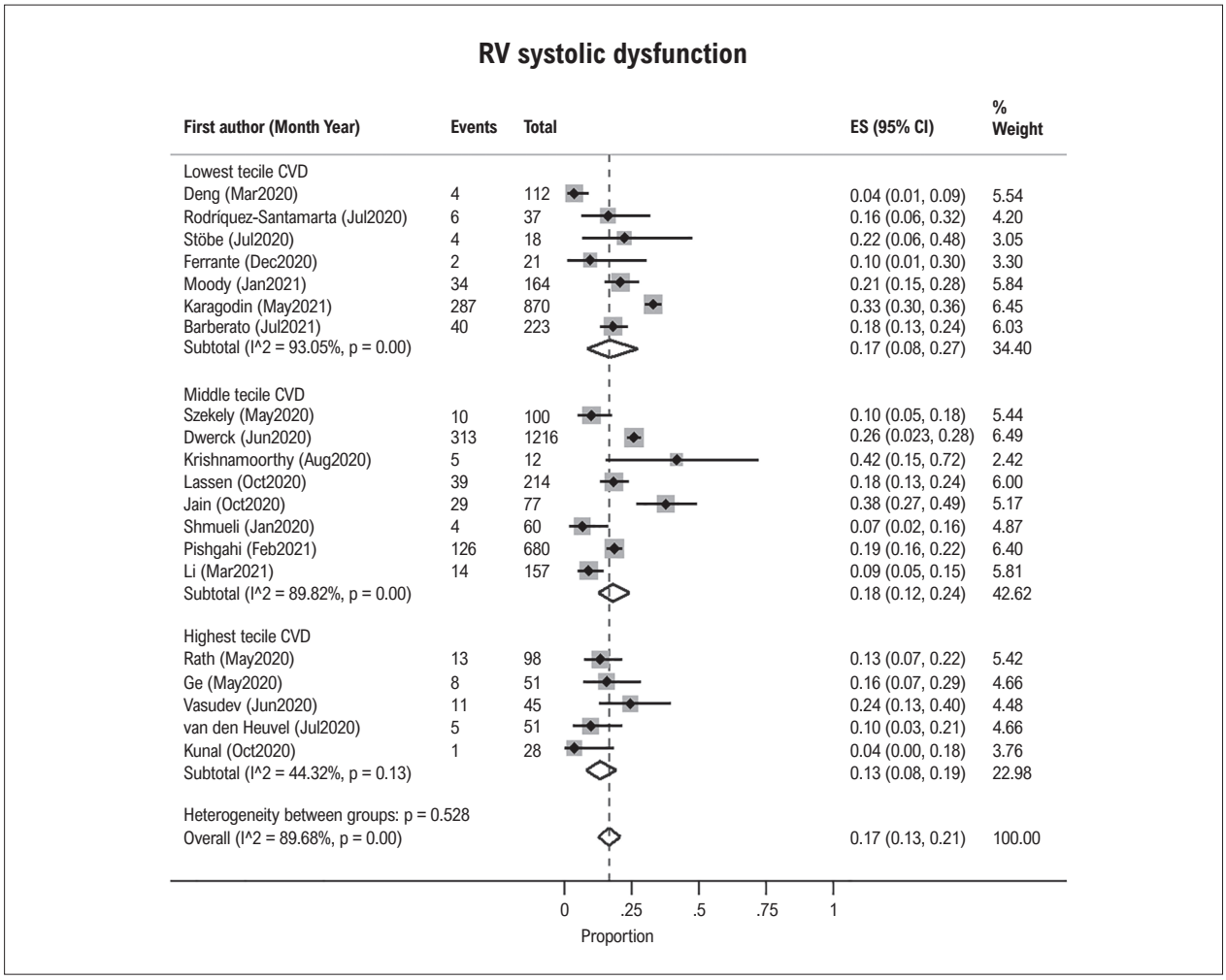

Figure 3 – *Proportion of right ventricular dysfunction in patients with Covid-19 across the studies according to the prevalence of cardiovascular diseases. CVD: cardiovascular diseases; RV: right ventricular. * Studies were divided according to the percentage of patients with CVD: Lowest tercile (less than 15), Middle tercile (15 to 21%) and Highest tercile (>21%).*

Our study has limitations that deserve attention. Most studies are subject to referral bias because echocardiograms were performed at the discretion of the attending physician, which may have overestimated the occurrence of abnormal echocardiographic findings. Most studies had a retrospective design, except for one prospective study in which TTE was performed in consecutive patients hospitalized for Covid-19, regardless of clinical indication.[19] Moreover, population characteristics and presentation of Covid-19 varied across studies, resulting in considerable heterogeneity. Although we explored a few sources of heterogeneity, heterogeneity remained high within subgroups. Echocardiogram-related technical aspects, leading to potential misclassification bias, and different definitions of cardiac abnormalities may be additional sources of heterogeneity. For instance, bedside evaluation of RV function and pulmonary hypertension may be limited in critical ill patients. Also, most studies did not report the presence of prior cardiac abnormalities nor whether the echocardiographic findings were new. Finally, because of language restriction in our search, possible exclusion of relevant papers that were not published in Portuguese, English or Spanish may not be excluded.

Conclusion

In hospitalized patients with Covid-19, abnormal echocardiographic findings indicating LV dysfunction have been reported in one of four patients. Lower prevalence of RV dysfunction and pericardial effusion was detected, although LV systolic dysfunction may be related to prior heart disease. Indeed, we found a direct association between previous abnormal echocardiogram and the proportions of LV dysfunction in the subgroup of studies that reported previous echocardiogram, which provide insights that help plan echocardiographic studies in Covid-19.

Author contributions

Conception and design of the research: Silvio Henrique Barberato, Eduardo G. Bruneto, Odilson Silvestre, Miguel M. Fernandes Silva; Acquisition of data and Writing of the manuscript: Silvio Henrique Barberato, Eduardo G. Bruneto, Gabriel S. Reis, Paula Rauen Franco de Oliveira, Alexandre F. Possamai, Miguel M. Fernandes Silva; Analysis and

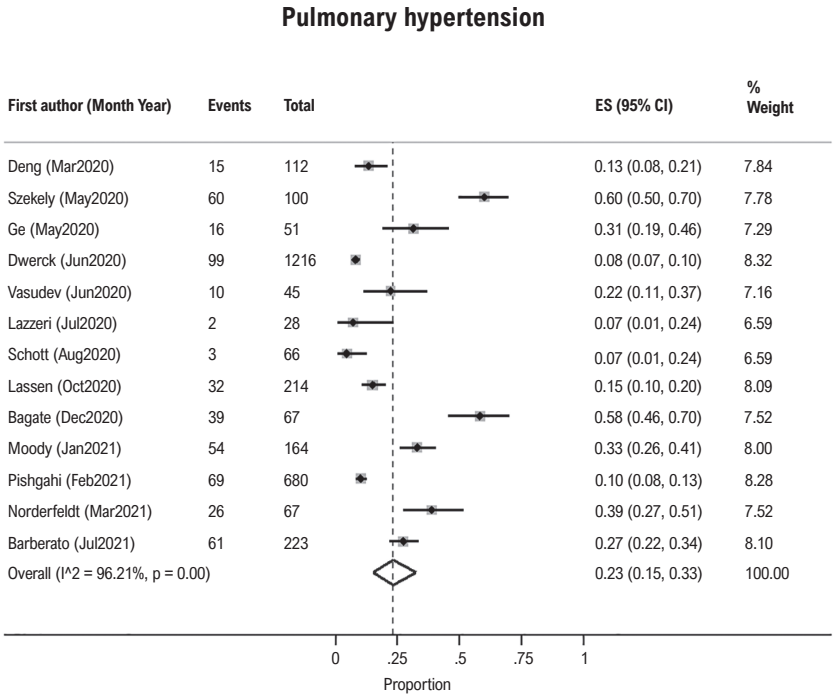

Figure 4 – *Proportion of pulmonary hypertension in patients with Covid-19.*

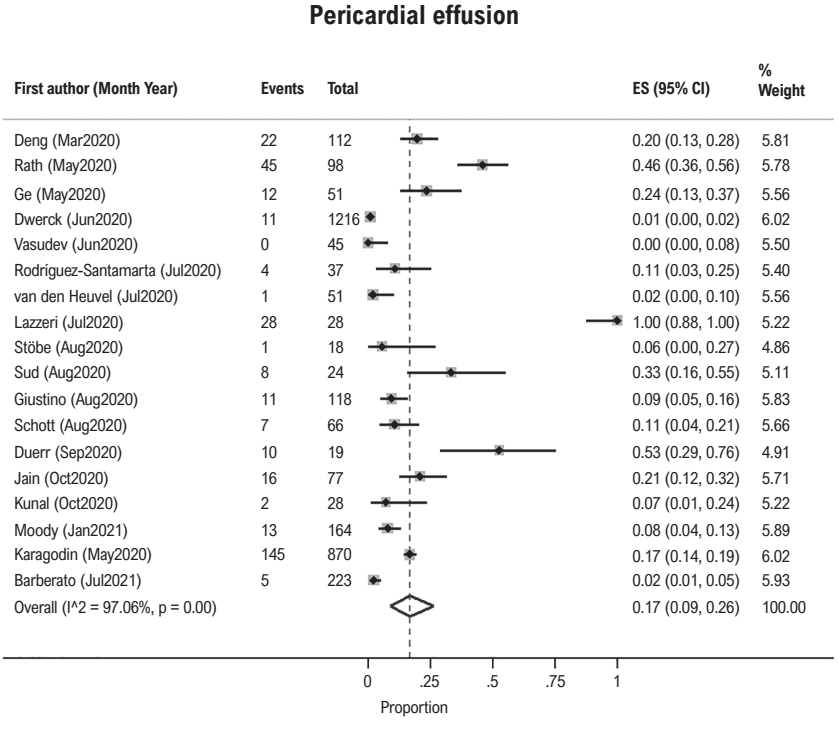

Figure 5 – *Proportion of pericardial effusion in patients with Covid-19.*

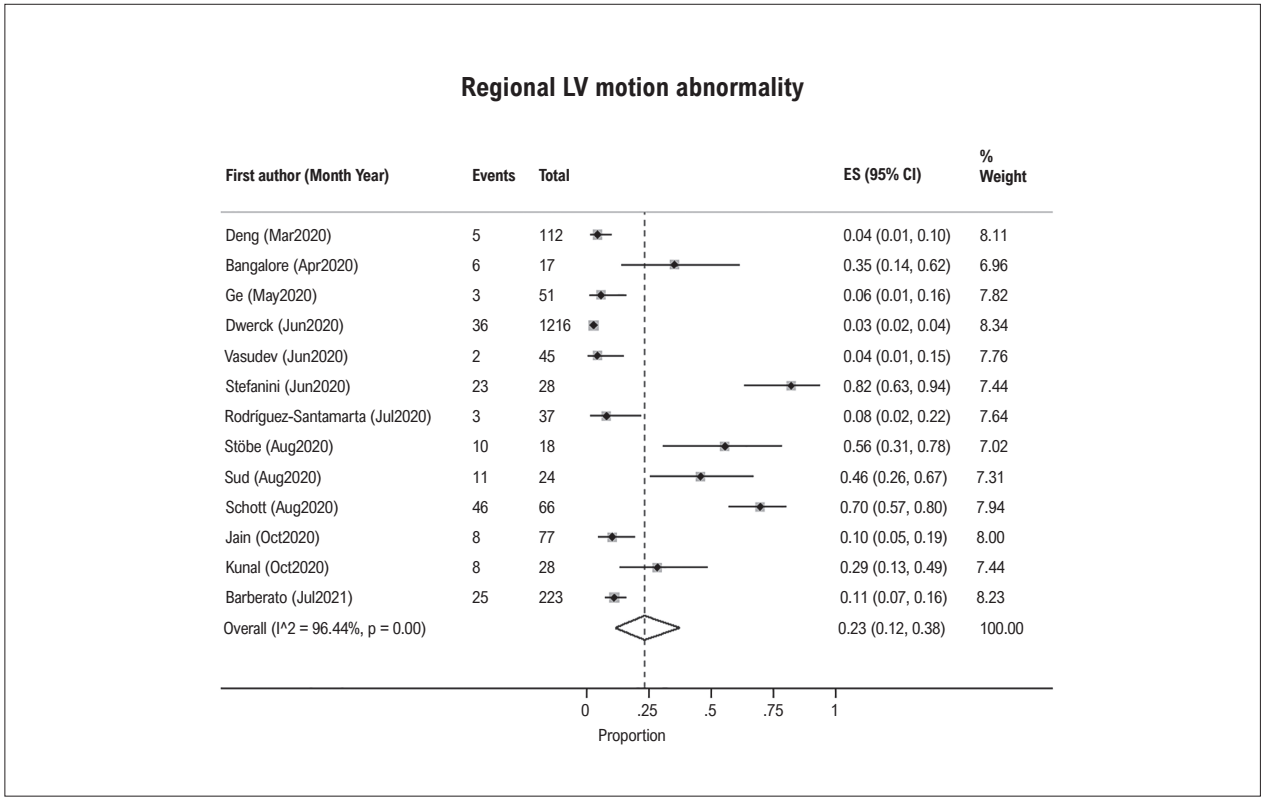

Figure 6 – *Proportion of regional LV motion abnormality in patients with Covid-19. LV: left ventricular.*

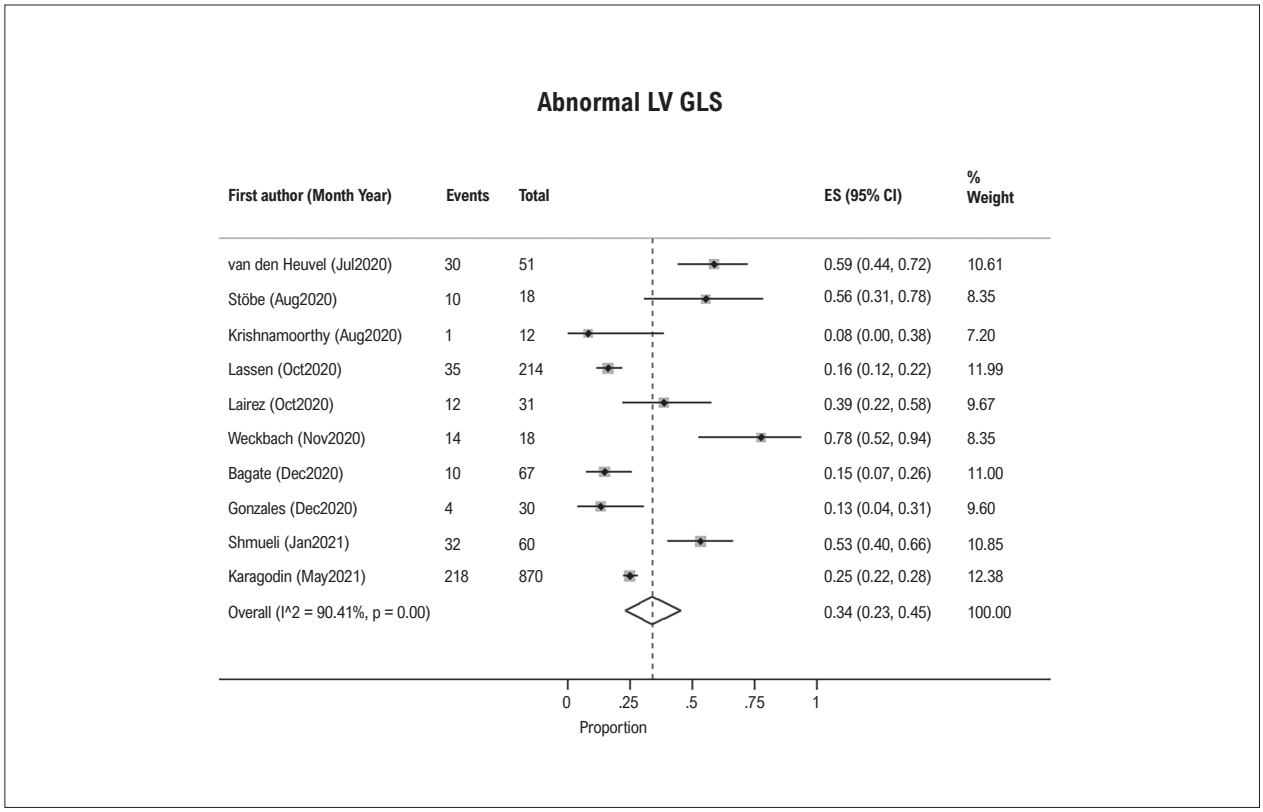

Figure 7 – *Proportion of Abnormal LV global longitudinal strain in patients with Covid-19. LV: left ventricular; GLS: global longitudinal strain.*

interpretation of the data: Silvio Henrique Barberato, Eduardo G. Bruneto, Gabriel S. Reis, Paula Rauen Franco de Oliveira, Alexandre F. Possamai, Odilson Silvestre, Miguel M. Fernandes Silva; Statistical analysis: Silvio Henrique Barberato, Eduardo G. Bruneto, Miguel M. Fernandes Silva; Critical revision of the manuscript for intellectual content: Silvio Henrique Barberato, Odilson Silvestre, Miguel M. Fernandes Silva.

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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*Supplemental Materials

For additional information, please click here.

Systematic Reviews and Meta-Analyses: Lighthouses in the Data Storm from the COVID-19 Pandemic

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Short Editorial related to the article: Abnormal Echocardiographic Findings in Hospitalized Patients with COVID-19: A Systematic Review and Meta-analysis

Since recognizing the COVID-19 pandemic as a public health emergency, the global scientific community has driven efforts to understand the infection by the new coronavirus SARS-CoV-2. The World Health Organization soon proclaimed the need to fast-track research to reduce mortality and avoid crisis escalation.[1] As a result, we now observe an extraordinary amount of data on COVID-19 obtained in a short time. Indeed, a search in the Pubmed database promptly reveals more than 164,000 papers on the disease in less than two and a half years, an unprecedented phenomenon in the medical literature. Putting this into perspective, this profusion of publications is numerically greater than papers identified by the term "myocardial infarction" in the last four decades.

Although this outstanding scientific advance has been crucial to fighting the pandemic, at the same time, it went along with a data storm with marked adverse effects. Health professionals had challenges searching, interpreting, and summarizing this dizzying volume of evidence. Conflicting results, typical of the twisted paths of science, were frequent causes of confusion and disagreement.[2] In this setting, systematic reviews and meta-analyses can serve as lighthouses, guiding us to safer routes. They offer organized and integrated assessment of multiple data sources, thus allowing more robust estimates and reliable answers to clinical practice dilemmas.

For this purpose, Barberato et al.[3] present in this edition of *Arquivos Brasileiros de Cardiologia* a systematic review and meta-analysis on abnormal echocardiographic findings in hospitalized patients with COVID-19.[3] From 6,427 publications initially selected (already excluding duplicates), the authors identified 38 original articles that met the selection criteria, all published until June 2021. Noteworthy, left ventricular (LV) systolic dysfunction was found in a quarter of cases by conventional echocardiography and in up to a third of patients by the speckle tracking method. On the other hand, right ventricular (RV) dysfunction was less prevalent, present in 17% of individuals, while pulmonary hypertension and pericardial effusion were described in 23% and 17% of cases, respectively.

Cardiac involvement in patients with COVID-19 has been a concern since the pandemic's beginning.[4,5] Recent evidence shows that direct myocardial injury by the virus is less relevant than indirect lesions from systemic inflammation and hypercoagulability in these patients.[6,7] Despite understanding these pathogenic mechanisms, the prevalence of myocardial involvement in COVID-19 remains debatable. Diagnosis of myocardial injury based exclusively on the elevation of serum biomarkers, such as troponin, may overestimate the number of cases.[8,9] On the other hand, complementary methods such as cardiac magnetic resonance and endomyocardial biopsy are not always available to confirm cardiac damage.

Although the systematic review and meta-analysis by Barberato et al.[3] certainly contribute to phenotyping the cardiac abnormalities in hospitalized patients with COVID-19, the findings raise other questions. For instance, would the cardiac damage correspond to pre-existing abnormalities or be a consequence of the SARS-CoV-2 infection? To answer this question, the authors reported a direct association between previous echocardiographic abnormalities and higher proportions of LV systolic dysfunction. However, it is essential to note that only 8 of the 38 studies (9% of all polled patients) described prior echocardiograms.

In addition, the meta-analysis' findings underline other extremely relevant aspects. The heterogeneity of the studies was quite high, apparently not explained by the prevalence of pre-existing cardiovascular diseases or the proportion of patients on mechanical ventilation. This warning lack of homogeneity could be explained by other factors, emphasizing small sample sizes, differences between the echocardiographic protocols, and demographic and clinical singularities among the study populations.[10] Furthermore, the graphical analysis strongly suggests the presence of publication bias in studies documenting RV systolic dysfunction, with a tendency for smaller sample size investigations to report a more significant proportion of this finding.

Finally, today we are faced with a quite different scenario from the one evaluated by the studies until the middle of last year: expansion of vaccine coverage, the appearance of viral variants, recognition of COVID-19 prolonged symptoms, and increased cardiovascular risk after the acute infection.[11-13] Therefore, new questions

Keywords

COVID-19; Pandemics; Coronavirus; Severe Acute Respiratory Syndrome; Systematic Reviews; Meta-Analysis

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emerged, especially regarding the prevalence of heart injury in milder conditions, the cardiac involvement's role in long-term COVID-19, and the predictive value of the myocardial damage related to the infection.[14]

During the data storm from the COVID-19 pandemic, the study by Barberato et al.[3] fulfills its aim of guiding us towards more reliable conclusions. Furthermore, and equally relevant, it highlights the shortcomings and pitfalls of a rushing science. Further ahead, we now have the challenge of phenotyping the cardiac involvement in a new and already announced clinical and epidemiological scenario.

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Early Outcomes of the Norwood Procedure in a Reference Center in Brazil

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Abstract

Background: **Only two papers have addressed the early outcomes of patients with hypoplastic left heart syndrome (HLHS) undergoing the Norwood operation, in Brazil.**

Objectives: **We evaluated patients with HLHS undergoing the first-stage Norwood operation in order to identify the predictive factors for early (within the first 30 days after surgery) and intermediate (from early survival up to the Glenn procedure) mortality.**

Methods: **Patients with HLHS undergoing the stage I Norwood procedure from January 2016 through April 2019, in our service, were enrolled. Demographic, anatomical, and surgical data were analyzed. Endpoints were early mortality (within the first 30 days after surgery), intermediate mortality (from early survival up to the Glenn procedure) and the need for postoperative ECMO support. Univariate and multivariate analyses were performed, and odds ratios, with 95% confidence intervals, were calculated. A p-value <0.05 was considered statistically significant.**

Results: **A total of 80 patients with HLHS underwent the stage I Norwood procedure. The 30-day survival rate was 91.3% and the intermediate survival rate 81.3%. Fourteen patients (17.5%) required ECMO support. Lower weight (p=0.033), aortic stenosis (vs aortic atresia; p=0.036), and the need for postoperative ECMO support (p=0.009) were independent predictive factors for 30-day mortality. Mitral valve stenosis (vs mitral valve atresia; p=0.041) was an independent predictive factor for intermediate mortality.**

Conclusion: **The present study includes the largest Brazilian cohort of patients with HLHS undergoing the stage I Norwood procedure in the recent era. Our survival rates were comparable to the highest survival rates reported globally. Low body weight, aortic valve stenosis, and the need for postoperative ECMO support were independent predictors for 30-day mortality. Mitral valve stenosis was the only independent predictive factor for intermediate mortality.**

Keywords: **Hypoplastic Left Heart Syndrome; Norwood Procedures; Extracorporeal Membrane Oxygenation; Mortality.**

Introduction

Hypoplastic left heart syndrome (HLHS) is a complex congenital heart defect that results in an underdeveloped heart with a hypoplastic left ventricle, stenotic or atretic mitral and aortic valves, and hypoplasia of the ascending aorta and aortic arch. The disease is associated with a high mortality rate and currently treated with a three-stage surgical palliation strategy. At the first stage, a neoaorta is reconstructed and either a systemic-to-pulmonary shunt or right ventricle to pulmonary artery conduit created. During the second stage, a partial cavopulmonary connection is constructed (Glenn procedure) and, at the third stage, a total cavopulmonary connection is completed (Fontan-Kreutzer procedure).

The HLHS is nearly always fatal without surgical palliation. However, since Norwood first described his technique for the palliative reconstruction of HLHS,[1] survival rates have progressively increased.[2] The early survival rate is currently lower than for other congenital heart defects, which require neonatal surgical intervention.[3] Notably, higher mortality occurs in the interstage period between the Norwood and Glenn procedures, reaching close to 25%.[4–6] Many different factors may contribute to the survival rates, including body weight and age at surgery, size and function of the valves and heart chambers, native aorta size, and variables intrinsic to the surgical procedure (time under cardiopulmonary bypass [CPB], shunt size, and shunt banding in order to manage excessive pulmonary flow rate). The identification of such risk factors could contribute to the improvement in the

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general treatment concepts, surgical technique, and ancillary therapeutic measures, in order to improve the survival rates.

Few reports have addressed the early outcomes of patients with HLHS undergoing Norwood operation in Brazil.[7,8] These reports came from previous eras and describe patient cohorts accumulated over long time periods. Here, we aim to evaluate the early (first 30 postoperative days) and intermediate (interstice between the early survival and the Glenn shunt procedure) survival of patients with HLHS undergoing the Norwood-Sano operation during a strict period of time (40 months) in the era of extracorporeal membrane oxygenation (ECMO) support and other medical advances, in a reference center in Brazil. The aim of the study was to identify predictive factors for early and intermediate post-operative mortalities, as well as for post-operative ECMO support.

Methods

The current study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[9] A retrospective cohort including all successive patients, private or public, diagnosed with HLHS (International Classification of Diseases, 10th revision, code q23.4) and undergoing the Norwood procedure by our group at *Hospital Beneficência Portuguesa de São Paulo,* between January 2016 and April 2019, was evaluated. Exclusion criteria included syndromic patients, infants with severe cerebral hemorrhage or infarction, or those with severe complications (e.g ECMO support) during the preoperative period.

The independent variables evaluated in this study were demographic (age, weight, and sex), anatomical (type and size of atrial septal defect, presence of aortic and/or mitral atresia, ascending aorta diameter, and size of the patent ductus arteriosus), and surgical (shunt diameter, Gore-Tex tube banding, and CPB, cross-clamp, and cardiac arrest times). The two main objectives were to determine the early (30-day post-operative) and the intermediate (from 30-day post-operative throughout the Glenn procedure) survival rates. We also investigated the need for ECMO support.

All clinical and surgical data on this patient cohort were retrieved from the institutional database. The study was approved by the Research Ethics Committee of the institution.

Preoperative management

Private patients came from all parts of Brazil and all of them had previous fetal diagnosis. The delivery was done in our service and the patient immediately transferred to our cardiac intensive care unit (CICU). Usually, a C-section is scheduled at 38 or 39 gestational weeks; however, normal labor may also occur according to the family's desire. A mean of 50 deliveries per year take place in our service (two HLHS births/month). Patients referred from public services were usually diagnosed after birth and were admitted as soon as possible.

In the CICU, an umbilical venous catheter is inserted and low-dose prostaglandin E_1 (PGE_1 0.005-0.01mcg/kg/min) is initiated to maintain ductal patency with low risk of apnea. If there is no need for immediate atrial septum manipulation, surgery occurs at 3-5 days of life. The technique of preference is the Norwood-Sano surgery, as detailed ahead. Cardiac output is monitored using clinical and laboratorial measures (urine output, peripheral perfusion, blood pressure, NIRS, arterial blood gas, lactate and central venous saturation). The clinically unstable infants may receive milrinone, low dose epinephrine and hypoxic gas mixture by adding nitrogen to lower FiO_2 to 17%, in order to treat low cardiac output syndrome. Infants with apnea secondary to PGE_1 or persistent unstable hemodynamics secondary to pulmonary overcirculation usually benefit from endotracheal intubation and controlled ventilation before surgery.

Operative technique

We entered the chest via median sternotomy and harvested a piece of pericardium, which was treated with glutaraldehyde 0.6% for 30 minutes. The ascending aorta, aortic arch, ductus arteriosus, and proximal descending aorta were exposed. Cardiopulmonary bypass was established by cannulation of the ductus arteriosus and the right atrial appendage. The arterial cannula was advanced through the ductus arteriosus into the descending aorta and a tourniquet tightened around the ductus and the cannula, which allows for part of the operation to be performed without circulatory arrest. While the patient was being cooled, the arterial ductus was divided near the pulmonary artery and its proximal stump sutured. The pulmonary artery was then divided close to its bifurcation, thus disconnecting the distal pulmonary artery and its pulmonary branches from the main pulmonary artery. The pulmonary artery distal stump opening was reduced with a small transverse plication, by placing one or two interrupted 7.0 Prolene sutures at its anterior and posterior wall edges. Next, a polytetrafluoroethylene (PTFE) conduit (usually 5 mm) was beveled to match the size of the resulting opening in the pulmonary artery and sutured directly to its distal stump, completing the distal pulmonary artery preparation. As the esophageal temperature was gradually reduced to 18ºC, we cross-clamped the native hypoplastic ascending aorta distally. Then, we made a small longitudinal anterolateral aortic incision near the clamped site to introduce an olive tip bendable needle toward the coronary artery. This special instrument, whose size would meet the ascending aorta diameter, serves to infuse the Del Nido cardioplegia solution into the proximal aorta. Sometimes, it is necessary to tighten the ascending aorta around the needle by pinching the aorta with a forceps to prevent cardioplegia wasting. Alternatively, a tourniquet can be placed around the aorta to gently tighten the aorta around the cardioplegia needle. Next, we extend that initial aortic incision longitudinally to near the coronary artery. The proximal portion of the ascending aorta was anastomosed on the lateral surface of the pulmonary artery trunk with 7.0 Prolene continuous suture, starting the neoaorta reconstruction. Only at this point, the CPB was interrupted, and the arterial cannula removed from the distal part of the ductus arteriosus. The remaining ductal tissue was completely excised, and the resulting opening extended proximally towards the aortic arch and ascending aorta, as well as distally. A 0.6% glutaraldehyde-treated autologous pericardial graft was used to enlarge the ascending aorta, aortic arch, and descending aorta, which was anastomosed to the pulmonary

trunk, completing the neoaorta. No tests for leakings spots on the long anastomotic line were done. The arterial cannula was again placed in the pulmonary trunk (neoaorta). Aorta deairing was accomplished by slowly flushing the arterial line while keeping tourniquets applied to the aortic arch branches, as well as a small opening in the proximal neoaorta anterior suture line. The CPB was restarted, but rewarming was not yet initiated. The CPB was interrupted again for 2-3 minutes for an enlarged atrial septal defect or tricuspid annuloplasty when necessary. The atrial septal enlargement was performed through an atriotomy below the venous cannula purse string.

To complete the pulmonary circulation, a small incision is made in the RV outflow tract and a 5mm RV hole is punched out. Then, the PTFE conduit that was already anastomosed to the pulmonary arteries is now connected to that hole. For that anastomosis, we use a 6.0 Prolene running suture technique that trespasses all the myocardial layers. We usually don't bevel the proximal side of the PTFE conduit. No surgical glue is routinely applied. In general, the heartbeat returns spontaneously as CPB is restarted and rewarming is initiated. The thorax was kept open using a latex membrane sutured to the skin edges. A sterile plastic adhesive was applied over the membrane and surrounding skin for better wound insulation. The delayed sternal closure was usually performed within 24 to 48 hours; once circulatory stability was ac hieved.

Norwood-Sano is used in the vast majority of cases, primarily to prevent reduction of coronary flow during diastole, thus facilitating postoperative management. This strategy was based on the results published previously by our group, showing lower mortality in patients undergoing Norwood-Sano.[7]

We used the same technique even for very small aortas but, in these cases, we enlarged the native aorta until closer to the coronary artery ostial plane, adjusting the anastomosis with a small incision performed in the proximal PA stump. In some < 2.5Kg patients (n=2, 2.5%), the Norwood operation was postponed, and surgical selective banding of both pulmonary arteries was otherwise performed, while the prostaglandin infusion was maintained. These patients were submitted to the Norwood operation when they reached a targeted weight short of 3 kg. No patient was denied operation and offered just clinical supportive care instead.

In patients with body weight between 2.5 and 2.7 kg, we used a 4-mm RV-PA conduit. In the post-operative period, all patients with unstable hemodynamics associated with excessive pulmonary flow were managed by banding the RV-PA conduit with a 5-0 Monocryl absorbable suture tied at the surgeon's discretion. When the chest was closed, removal of the prolene suture band was considered, but we almost always ended up leaving it alone. In patients suspected of high pulmonary vascular resistance due to either late referral for surgical treatment or restrictive atrial septal defect, we preferred to perform the classic Norwood procedure with a 3.5 or 4.0-mm modified Blalock-Taussig shunt.

Postoperative management

All patients were transferred to CICU with the chest left open. The chest was usually closed 24-48h postoperatively, provided that hemodynamic stability had already been achieved. Inotropic and vasoactive support was regularly achieved with milrinone and adrenaline and, if possible, associated with continuous infusion of Amplictyl (chlorpromazine). We used a peritoneal dialysis (PD) catheter in most children, even those with adequate urine output. PD was usually initiated in the first postoperative days with isotonic and/or hypertonic dialysate to manage fluid overload. We used ECMO support on patients who evolved to refractory low cardiac output syndrome (low urinary output, hypotension, high lactate and/or high inotropic requirements), persistent hypoxemia, arrhythmias, cardiac arrest, or failure to wean from cardiopulmonary bypass (CPB). Most patients were placed on ECMO support in the ICU, before the sternum was closed. In just two patients (14.3%), ECMO was started in the OR in order to wean them from CPB. Arrhythmia was responsible for ECMO initiation in just one patient (7%). ECMO assistance was always performed through central cannulation and the chest incision was kept open until clinical stabilization allowed for ECMO decannulation.

Due to the frequent distant referencing, we adopted a common policy of keeping all patients in this cohort hospitalized until they recovered from the second surgical stage.

Statistical analysis

Qualitative data were described as frequencies with percentages, and quantitative data as medians with interquartile ranges. All data were treated as non-parametric due to the size of the sample. To evaluate associations between qualitative data, we performed Fisher's exact test. To compare quantitative data among survivors and non-survivors, we used Mann–Whitney U test. A Kaplan-Meier survival analysis was performed, and the log-rank test was used to determine significant differences in survival between strata. Logistic regression was performed to identify the univariate and multivariate predictors of mortality. Variables with $p<0.25$ in the univariate analysis were included in the multivariate analysis and the backward conditional stepwise method used to define the final model. Results are presented as odds ratios with 95% confidence intervals and p-values. A p-value <0.05 was considered statistically significant. Data were analyzed and plotted using IBM SPSS Statistics for Windows (Version 25.0; IBM Corp, Armonk, NY) and GraphPad Prism (Version 6.01; GraphPad Software, Inc., La Jolla, United States).

Results

A total of 80 patients with HLHS underwent the Norwood procedure (stage I) between January 2016 and April 2019. The stage I Norwood procedure was performed in 80 (private, n=79, 98.7%; public, n=1, 1.3%) patients. A Norwood-Sano procedure was performed in 78 (97,5%) patients, and a classic Norwood, in 2 (2.5%). The whole cohort early survival rate was 91.3% (n=73), while the intermediate survival rate was 81.3% (n=65).

Demographics

Fifty-one patients (63.8%) were male, the median age at surgery was 3.0 (1.0-147.0) days, and the mean weight was

3080 (2765-3360) grams. The stratified data for survivors (73 patients) and non-survivors (7 patients), as well as the comparisons between the groups, are described in Table 1. Briefly, 30 postoperative day non-survivors presented with a lower weight at the time of surgery (p=0.0257). No differences were found for the other demographic characteristics.

Anatomy

Anatomical characteristics were described with regard to the size of the atrial septal defect, the anatomy of the mitral and aortic valves, and the size of the ascending aorta and patent ductus arteriosus. For patients with a single atrial septal defect (ASD), the median size of the defect was 3.55 (2.65-4.73) mm. For patients presenting multiple atrial septal defects, the total estimated ASD area was 10.8 (6.1-18.1) mm^2. The mitral valve was normal in 1.3% (n=1) of the patients, stenotic in 53.7% (n=43), atretic in 43.7% (n=35), and one case had a single atrioventricular valve. The aortic valve was normal in 2.5% of patients (n=2), stenotic in 30% (n=24), and atretic in 67.5% (n=54). The ascending aorta size was 2.7 (2.0-4.3) mm and the size of the patent ductus arteriosus was 5.8 (5.00-6.5) mm. Anatomy variables from the survivor and the non-survivor patient groups were similar (Table 2). We found no significant differences regarding the patients' anatomy.

Operative data

The shunt diameter in the two patients who underwent the classic Norwood operation was 3.5 mm. In those who were submitted to the Norwood-Sano operation, a 4.0 mm (n=21; 27%) or a 5.0 mm graft (n=57; 73%) was selected. In 25 (32.4%) patients, shunt banding was employed. The median CPB, cross-clamp and circulatory arrest times were respectively 188 (170-214) min, 76 (70-80) min, and 48 (45-53) min. No significant difference was found between the surviving and non-surviving patient groups (Table 3).

Early and intermediate mortality, and ECMO support

Within the first 30 postoperative days, 7 patients (8.7%) died, resulting in an early survival rate of 91.3% (Figure 1A). Also, during these first 30 days, 14 patients (17.5%) required ECMO support. Among the survivors, only 13.7% received ECMO, compared to 57.1% of non-survivors (p=0.0039). The stratified survival curves for patients requiring or not requiring ECMO are illustrated in Figure 1B. The comparison of the survival curves indicates a worse outcome for those requiring circulatory support (Log-rank test, p=0.0020).

The intermediate survival rate was 81.3% once 8 additional patients died between the postoperative day 30 and the Glenn procedure (Figure 2A). ECMO was employed in 33,3% (n=3) of the 8 non-survivors, in contrast to 13,8% (n=9) of those who received the Glenn operation. Fig. 2B shows that the ECMO supported patients had a worse outcome as compared to those not requiring ECMO (Log-rank test, p=0.0088).

Irreversible neurological injury occurred in 4 children (28%) submitted to ECMO treatment. Dialysis was necessary in 85% (n=68) of the cases. All survivors recovered renal function. Post-operative aortic coarctation demanded reintervention in 6 (7.5%) patients (percutaneous stent placement, n=4; surgical enlargement simultaneous with the Glenn procedure, n= 2).

Predictors of ECMO assistance, 30-day operative mortality, and intermediate mortality

Table 4 through 6 explore the potential predictors for ECMO assistance, early and intermediate mortality, respectively. Shunt size and bandage could not be analyzed due to missing data. By univariate analysis, CPB time was the only predictive factor for ECMO assistance, as no other variable reached the p< 0.250 threshold (Table 4). For this reason, a multivariate analysis could not be carried out, and no variable could be confirmed as an independent ECMO predictor.

In regard to 30-day postoperative mortality (Table 5), body weight, mitral and aortic valve anatomy, CPB time, and ECMO assistance were considered predictive factors by the univariate analysis. However, by multivariate analysis, the mitral valve anatomy and the CPB time did not hold as independent predictors, in contrast to body weight, the aortic valve anatomy and the need for ECMO support, which were confirmed as independent risk factors. The greater the weight, the lower the risk (OR 0.997 per gram; 95% CI 0.995- 1.000; p=0.033). Aortic valve atresia was a protective factor as compared to stenosis (OR 0.090; 95% CI 0.009-0.857; p=0.036), and the need for post-operative ECMO was an important independent risk factor for mortality (OR 20.975; 95% CI 2.116-207.886; p=0.009). Shunt size and Sano tube banding could not be analyzed by uni/multivariate logistic regression due to missing data.

By univariate analysis, mitral and aortic valve anatomy, CPB time, and ECMO support were predictive factors for intermediate mortality (Table 6). In the multivariate analysis, however, the mitral valve anatomy came up as the only predictor for mortality. Valvar stenosis led to a worse prognosis as compared to valve atresia (OR 0.242; 95% CCI 0.062-0.942; p=0.041).

Table 1 – Demographic characteristics

Sex (males)	Survivors	Nonsurvivors (30-day)	p-value
	46/73 (63.0%)	5/7 (71.4%)	1.000
Weight (g)	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
	3115 (2820-3440)	2740 (2500-2990)	0.0257
Age (days)	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
	3.0 (1.0-147.0)	3.0 (2.0-5.0)	0.1893

Table 2 – Anatomical characteristics

ASD			
Area (mm²)	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
Total estimated ASD area	10.95 (5.93-18.10)	8.7 (7.10-20.40)	0.7714
Heart valves (LEFT)			
Mitral valve	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
normal	1/72 (1.4%)	0/7 (0.0%)	
stenosis	37/72 (51.4%)	6/7 (85.7%)	0.2187
atresia	34/72 (47.2%)	1/7 (14.3%)	
Aortic valve	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
normal	2/73 (2.7%)	0/7 (0.0%)	
stenosis	20/73 (27.4%)	4/7 (57.1%)	0.2508
atresia	51/73 (69.9%)	3/7 (42.9%)	
Subgroups	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
MS/AS	17/73 (23.3%)	4/7 (57.1%)	
MS/AA	19/73 (26.0%)	2/7 (28.6%)	
MA/AS	2/73 (2.7%)	0/7 (0.0%)	0.3267
MA/AA	32/73 (43.8%)	1/7 (14.3%)	
other	3/73 (4.1%)	0/7 (0.0%)	
Aorta			
Ascending aorta	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
size (mm)	2.80 (2.00-4.30)	2.00 (2.00-6.20)	0.6612
patent ductus arteriosus	Survivors	Nonsurvivors (30-day)	p-value
size (mm)	5.75 (5.00-6.50)	6.70 (4.50-7.30)	0.5569

NA: not applicable. ASD: atrial septal defect.

Table 3 – Surgery

Shunt diameter (mm)	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
3.5	1/41 (2.4%)	0/3 (0.0%)	
4.0	11/41 (26.8%)	1/3 (33.3%)	0.9403
5.0	29/41 (70.7%)	2/3 (66.7%)	
Banding	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
patients undergoing shunt banding	11/32 (34.4%)	0/2 (0%)	0.3134
Surgery times	**Survivors**	**Nonsurvivors (30-day)**	**p-value**
CPB (min)	185 (170-210)	205 (180-240)	0.2202
Cross-clamp (min)	76 (70-80)	77 (59-82)	0.7057

Obs.: There were missing data for the variables "shunt size" and "shunt banding" for 36 and 44 patients respectively. For this reason, we did not use these variables in uni or multivariate analysis. CPB: cardiopulmonary bypass.

Discussion

Since the establishment of the classic Norwood or the Norwood-Sano procedures as the standard surgical management for the treatment of patients with HLHS, there has been a progressive worldwide improvement in the survival rate. The present study included 80 consecutive patients operated on from 2016 who were extracted from our group series of more than 500 patients to represent current early outcomes in the era of ECMO support. Our 8.7% early mortality rate for patients undergoing the Norwood/Norwood-Sano procedures is among the lowest reported.[10,11] Others have reported a 30-day postoperative mortality of 15.2%.[12] Interim mortality (from after hospital discharge following the Norwood procedure through the Glenn

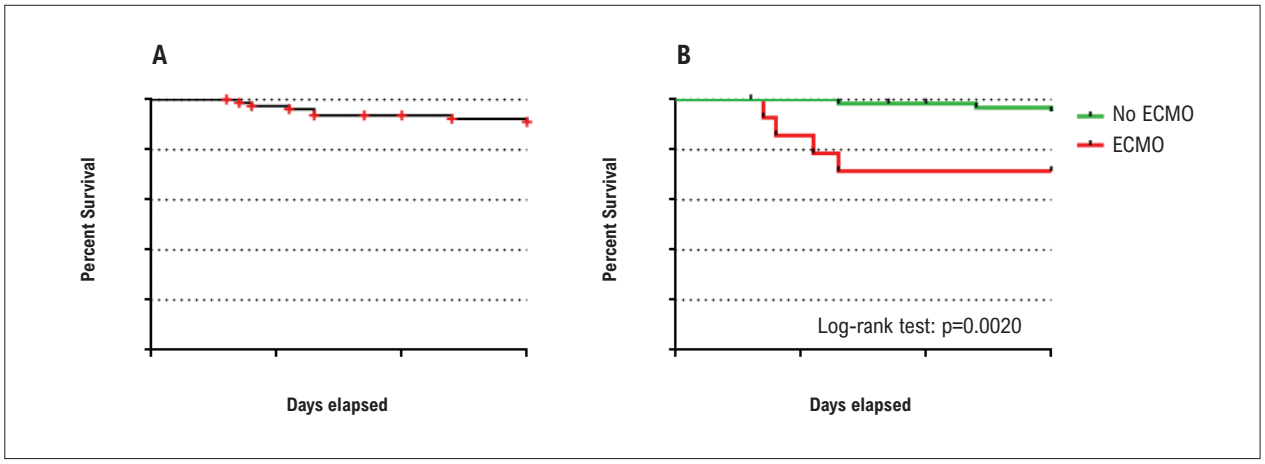

Figure 1 – *Early (up to 30 post-operative days) survival rates following the stage I Norwood procedure. A) Whole cohort (n=80). B) Comparison between ECMO (n=14) vs no ECMO (n=66) patients. ECMO: extracorporeal membrane oxygenation.*

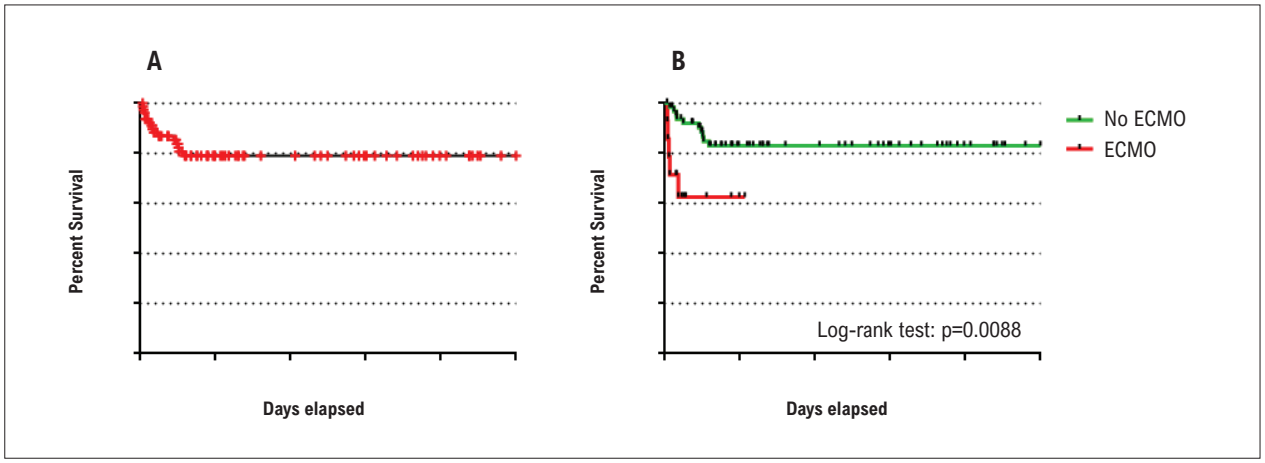

Figure 2 – *Intermediate survival rates (from 30 post-operative days through the Glenn procedure). A) Whole cohort (n=73). B) Comparison between ECMO (n=9) vs no ECMO (n=64) patients. ECMO: extracorporeal membrane oxygenation.*

Table 4 – ECMO assistance predictors according to univariate and multivariate logistic regression

	univariate		multivariate	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Demographics				
Sex (for male)	1.524 (0.432-5.383)	0.513	-	-
Weight (per g)	1.000 (0.998-1.001)	0.515	-	-
Age (per day)	0.860 (0.606-1.220)	0.397	-	-
Anatomy				
Total estimated ASD area (per mm^2)	0.982 (0.944-1.021)	0.354	-	-
Mitral valve (atresia vs. stenosis)	0.905 (0.282-2.909)	0.867	-	-
Aortic valve (atresia vs. stenosis)	1.791 (0.451-7.112)	0.408	-	-
Asc Ao size (per mm)	0.907 (0.635-1.295)	0.590	-	-
Surgery				
CPB (per min)	1.006 (0.996-1.016)	0.248	1.006 (0.996-1.016)	0.248
Cross-clamp (per min)	0.997 (0.944-1.054)	0.922	-	-

ASD: atrial septal defect; CPB: cardiopulmonary bypass.

Table 5 – 30-day mortality predictors according to univariate and multivariate logistic regression

	univariate		multivariate	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Demographics				
Sex (for males)	1.467 (0.266-8.091)	0.660	-	-
Weight (per g)	0.998 (0.996-1.000)	0.056	0.997 (0.995-1.000)	0.033
Age (per day)	0.734 (0.382-1.413)	0.355	-	-
Anatomy				
total estimated ASD area (per mm^2)	1.010 (0.983-1.037)	0.465	-	-
mitral valve (atresia vs. stenosis)	0.181 (0.021-1.585)	0.123	0.491 (0.024-10.089)	0.645
aortic valve (atresia vs. stenosis)	0.294 (0.060-1.433)	0.130	0.090 (0.009-0.857)	0.036
Asc Ao size (per mm)	0.981 (0.620-1.552)	0.935	-	-
Surgery				
CPB (per min)	1.010 (0.999-1.021)	0.089	1.018 (0.992-1.044)	0.173
Cross-clamp (per min)	0.952 (0.874-1.037)	0.260	-	-
ECMO	8.400 (1.631-43.256)	0.011	20.975 (2.116-207.886)	0.009

ASD: atrial septal defect; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation.

Table 6 – Intermediate mortality predictors according to univariate and multivariate logistic regression

	univariate		multivariate	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Demographics				
Sex (for males)	1.719 (0.493-5.991)	0.395	-	-
Weight (per g)	1.000 (0.998-1.001)	0.511	-	-
Age (per day)	1.008 (0.986-1.031)	0.457	-	-
Anatomy				
Total estimated ASD area (per mm^2)	1.010 (0.989-1.031)	0.354	-	-
Mitral valve (atresia vs. stenosis)	0.242 (0.062-0.942)	0.041	0.242 (0.062-0.942)	0.041
Aortic valve (atresia vs. stenosis)	0.422 (0.133-1.343)	0.144	0.357 (0.059-2.174)	0.264
Asc Ao size (per mm)	1.003 (0.723-1.392)	0.984	-	-
Surgery				
CPB (per min)	1.008 (0.998-1.018)	0.131	1.017 (0.998-1.037)	0.080
Cross-clamp (per min)	0.992 (0.936-1.051)	0.785	-	-
ECMO	3.111 (0.862-11.231)	0.083	3.011 (0.623-14.542)	0.170

ASD: atrial septal defect; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation.

operation) varies from 5-28%.[13–19] According to the Society of Thoracic Surgeons' (STS's) Congenital Heart Surgery Database,[20] overall mortality is 22%, while the mortality for patients with any complication (27%) is much higher ($p<0.0001$) as compared to patients who did not suffer a complication (7%).

In the present study, low body weight was found as an independent predictor for early mortality following the stage I Norwood operation, in accordance with what has been described by several previous studies.[12,16,21,22]

The aortic and mitral valve anatomy have also been recognized as predictors of early mortality in previous studies.[23–29] The presence of aortic and/or mitral atresia is usually associated with higher mortality rates, particularly when mitral stenosis is accompanied by aortic atresia,[23,24,29] or is associated with a restrictive ASD.[25] In the present investigation, both the aortic valve anatomy and the need for ECMO assistance showed up as independent risk factors for early mortality. Curiously, in our study, aortic valve atresia, as compared to aortic valve stenosis, was a protective factor

against mortality, and the same was true concerning the mitral valve anatomy.

Furthermore, we detected the need for ECMO support as an important independent risk factor for early mortality. Indeed, ECMO supported patients had a >20-times mortality risk than patients who did not need mechanical circulatory support. Unfortunately, we could not isolate any independent predictive factor for ECMO assistance, although previous studies reported birth weight <2.5 kg and longer CPB time as independently associated with the need for ECMO after the Norwood operation.[30]

In the present study, mitral valve atresia and prolonged CPB times turned up as predictors for early mortality by univariate analysis, but they were not confirmed as independent predictors for early mortality by multivariate analysis. When intermediate mortality was examined, only the mitral valve anatomy came out as an independent risk factor, mitral valve stenosis correlating with a worse prognosis as compared to valve atresia. Prolonged CPB times have not been reported as a mortality predictor in the Norwood procedure,[14,16,18] although some studies have reported borderline p- values.

Two other important mortality predictors of the stage I Norwood operation are the center and surgeon surgical volumes. Both these variables have been significantly associated with outcomes following the Norwood procedure according to the STS's Congenital Heart Surgery Database.[31] The STS reported that centers operating on more than 20 cases per year and surgeons operating on more than 10 cases per year presented lower mortality rates. The present study confirms the same holds true outside North America, as the low mortality rates herein reported derived from both high center and surgeon caseloads.

Limitations

We recognize that our study has some limitations. The retrospective analyses made it impossible to avoid data missing, as clinical information recording was being transitioned from manual to digital over the study period. Outcomes might have been negatively affected once ECMO indication was more conservative and sometimes delayed early in the series, when an in-house ECMO team was not yet available. Accordingly, the interstice between ECMO indication and ECMO support initiation was much reduced later in the series.

Conclusion

The present study reports a large Brazilian cohort of patients with HLHS undergoing the Norwood procedure in the recent era. We had a 30-day survival rate of 91.3%, which is comparable to the highest survival rates reported worldwide and an intermediate survival rate of 81.3%. Low body weight, aortic stenosis (as compared to aortic atresia), and the need for ECMO support were independent predictors of 30-day mortality, whereas mitral and aortic valve anatomy, CPB time, and ECMO support were predictive factors for intermediate mortality. No independent risk factor for ECMO support could be evidenced. Future studies targeting the interstage mortality, as well as the mortality of other procedures involved in the palliative reconstruction of HLHS, may provide additional evidence for the long-term survival rate and add other potential predictive factors for mortality.

Author Contributions

Conception and design of the research: Bezerra RF, Pacheco JT, Franchi SM, Castro RM; Acquisition of data: Pacheco JT, Fittaroni RB, Castro RM, Silva LF; Analysis and interpretation of the data: Pacheco JT, Franchi SM, Silva LF, Silva JP; Statistical analysis: Pacheco JT, Silva JP; Writing of the manuscript: Bezerra RF, Pacheco JT, Franchi SM, Fittaroni RB, Silva LF, Silva JP; Critical revision of the manuscript for intellectual contente: Bezerra RF, Franchi SM, Baumgratz JF, Silva LF, Silva JP.

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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The First Stage Norwood Operation, in Brazil – The Bar Was Raised

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Short Editorial related to the article: Early Outcomes of the Norwood Procedure in a Reference Center in Brazil

Outcomes of the first stage Norwood operation in Brazil have been scarcely reported. Countrywide dismal results, contrasting to those from the developed world, possibly explain this finding.

Contrariwise to this scenario, in this issue of *The Braz J Cardiol*, da Silva´s group presents their single-center experience comprising the largest series of the first-stage Norwood operation with adjuvant postoperative extracorporeal membrane oxygenation (ECMO) support in our country. Their 30-day 91.3% survival, an outstanding surgical result, is on par with those from just a few international elite institutions where ECMO is also available.[1]

The Rubicon was crossed! Hats off to the authors!

Considering that hypoplastic left heart syndrome (HLHS) is the most prevalent and one of the most challenging forms of a single ventricle, the aforementioned report will resonate in the Brazilian pediatric cardiology community and its referral surgical centers, the Brazilian Universal Health System (SUS), the private medical health sector and the general public.

I enjoyed the paper very much. It entails a retrospective evaluation of 80 pts. (private, n=79; public, n=1) operated on from 2016 through 2019. During the period, ECMO assistance was provided to their base hospital, one of the country´s largest cardiovascular surgery referral centers. The report is meticulous and the data are properly analyzed.

It is noteworthy that the authors acknowledge the fact that the patient series benefitted from the surgical group expertise that was accumulated and refined over a long time, encompassing more than 500 cases. In other words, we are looking at the very tip of da Silva´s iceberg-size experience.[1]

A proactive treatment protocol including scheduled, on-site, maternal admission, and cesarean-section delivery was adopted. Immediate low-dose prostaglandin infusion was started and the operation was carried out 3 – 5 days later, as recommended by international guidelines.[2]

The surgical protocol included an open chest policy and a Sano shunt technique. Of note, the shunt was banded with a 5-O absorbable ligature whenever it was deemed necessary to counteract excessive pulmonary flow with concurrent hemodynamic instability. Peritoneal dialysis was implemented in most babies.

ECMO support was instituted postoperatively in 14 patients (17,5%). Among the 73 survivors, 13.7% (10 pts.) required ECMO, as compared to 57.1% (4 pts.) of the 7 non-survivors.

Eight additional pts. died in the interstage period towards the Glenn operation, resulting in an 81.3% interstage survival rate. This result is also comparable to those from major international reference centers, where a competitive home monitoring surveillance policy coexists.[3] However, one cannot argue that the author´s interstage survival speaks for itself and should be seen as a savvy policy by teams operating on patients coming from remote places.

Although the authors did not comment on this, I wish to highlight that, were ECMO not available, the 30-day mortality rate for the whole cohort (80 pts.) would have probably reached 21.25%, yet a very satisfactory result, comparable to those from international leading centers with handy access to ECMO.

This hypothetical result is worth mentioning though. Although the paper adds strong evidence for postoperative ECMO support as a lifesaving resource, one must not downplay the authors' previous long and large experience with the first stage Norwood operation, nor the fact that it took place in one of the nation´s best cardiology centers.

The reader should thus perceive da Silva´s group's pathway to success as resulting from the association of surgical skill, perseverance, teamwork, fitting treatment protocol, and private institutional provision of ECMO runs. Quite a recipe!

Properly considered, the ECMO results presented by the authors provide timely leverage to the Brazilian Society of Cardiovascular Surgery and other related Societies, in their sustained efforts trying to incorporate ECMO into the SUS armamentarium.

The fact is that, in the present era of constrained resource allocation, quality control policies, and surgical results surveillance by health care regulators, the SUS lags behind many other South American countries' national health administration agencies concerning ECMO backup.

As the bar for the first-stage Norwood operation, in this nation, is now raised, I envision that the SUS regional reference centers caring for HLHS babies be granted ECMO equipment to pursue outcome improvements under equipoise with the private sector.

Of course, the country´s continental size, the regional disparities, and the present economical, geopolitical,

Keywords

Heart Defects,Congenital; Hypoplastic Left Heart Syndrome/surgery; Extracorporeal Membrane Oxygenation; Norwood Procedures/surgery

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and worldwide health distress require pondered consideration. Accordingly, guidelines for SUS ECMO provision should benefit from an "ad hoc" committee with the wise participation of the aforementioned professional Societies.

That happening, and respecting other possible management strategies, I foresee trained and staffed SUS pediatric cardiovascular surgery affiliated institutions, from many Brazilian states, renewing efforts aiming for better outcomes with the Norwood operation, as well.

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(-)-Carvone Modulates Intracellular Calcium Signaling with Antiarrhythmic Action in Rat Hearts

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Abstract

Background: **(-)-Carvone is a monoterpene found in essential oils with antioxidant and anti-inflammatory activity.**

Objective: **The aim of this paper was to analyze the antiarrhythmic property of (-)-carvone in the rat heart and its effects on the intracellular Ca^{2+} signaling.**

Methods: **The effects of (-)-carvone were evaluated on the ventricular (0.5 mM) and atrial contractility (0.01 – 4 mM) and on electrocardiogram (0.5 mM). Fractional shortening, L-type calcium current ($I_{Ca,L}$) and Ca^{2+} signaling were measured in the isolated cardiomyocyte (0.5 mM). Antiarrhythmic effect was evaluated in arrhythmia model induced by calcium overload (0.5 mM) (n = 5). P < 0.05 was used as the significance level.**

Results: **In the atrium, (-)-carvone evoked negative inotropism that was concentration-dependent (EC50 0.44 ± 0.11 mM) and decreased the positive inotropism evoked by $CaCl_2$ (0.1 to 8.0 mM) or BAY K8644 (5 to 500 nM), an agonist of L-type Ca^{2+} channel. In isolated heart, (-)-carvone (0.5 mM) promoted reduction of ventricular contractility (73%) and heart rate (46%), increased PRi (30.7%, time from the onset of the P wave until the R wave) and QTc (9.2%, a measure of the depolarization and repolarization of the ventricles) without changing the QRS complex duration. (-)-Carvone decreased the fractional shortening (61%), $I_{Ca,L}$ (79%) and Ca^{2+} intracellular transient (38%). Furthermore, (-)-carvone showed antiarrhythmic action, verified by decrease of the arrhythmia score (85%) and occurrence of ventricular fibrillation.**

Conclusion: **(-)-Carvone decreases Ca^{2+} entry through L-type Ca^{2+} channels, reducing the cardiac contractility and intracellular Ca^{2+}, and, therefore, presenting promising antiarrhythmic activity in the rat hearts.**

Keywords: **Arrhythmias, Cardiac; Monoterpenes; Rats.**

Introduction

Arrhythmias are considered a serious public health problem and are an important cause of morbidity and mortality in the world.[1] Among the main cardiac arrhythmias, ventricular premature beats (VPB), sustained ventricular tachycardia and fibrillation are common in patients with ischemic and nonischemic cardiomyopathy.[1] However, treatments with antiarrhythmic drugs often cause pro-arrhythmic adverse responses or no improvement in the quality of life of people affected by arrhythmias.[2]

Since 1970, when Vaughan-Williams classified the antiarrhythmic drugs based on their pharmacological mechanisms to block specific ion channels or receptors, researchers have invested a great deal of time and effort to discover new therapies with a lower risk of adverse effects for the patient.[3–5]

Among the new therapies, compounds of natural origin have demonstrated their capacity to inhibit ventricular cardiac arrhythmias generating interest in the scientific community. Terpenes have been shown to be the main compounds with proven antiarrhythmic activity.[6–9] Among these terpenes, one of particular interest is carvone (*p*-mentha-6,8-dien-2-one) because of its already established properties. Carvone is a monoterpene ketone known for its antioxidant, antimicrobial and antifungal activity.[10,11] It has also been reported to have a blocking effect on voltage-gated sodium channels in neurons, leading to an anticonvulsant effect.[12,13] Furthermore, carvone has also shown an antispasmodic effect through voltage-dependent calcium channel inhibition, and synergistic anticancer action with doxorubicin on the MCF 7 cell line while decreasing its cardiotoxicity.[14] As has already been described in the literature, carvone blocks sodium and calcium channels, and drugs of this class have antiarrhythmic and cardioprotective properties. Therefore, we decided to study

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the effects or carvone on the cellular calcium handling and its possible antiarrhythmic action in rat hearts.[9]

Although there are several studies about (-)-carvone in the scientific literature, there are, to the best of our knowledge, no explanations or hypotheses on the mechanism of action of this monoterpene in the cardiac muscle. Therefore, our objective was to assess the possible cardiac effects of (-)-carvone, and to provide a better scientific understanding of its action in cardiac tissue that might serve as basis for the development of new drugs of natural origin for the treatment of arrhythmias.

Material and Methods

Animals

The experiments were performed using male Wistar rats (250-300 g) obtained from the animal care facility of the Federal University of Sergipe (UFS). In each experimental procedure, five animals were used.[15] This research was approved by the Ethics Committee on Animal Research of the UFS (protocol 61/16, February 20th 2017). Animal handling was in compliance with the Principles of Laboratory Animal Care (NIH publication 86-23, revised 1985; http://oacu.od.nih.gov/regs/index.htm).

Evaluation of inotropic effect of (-)-carvone

The inotropic effect of (-)-carvone was evaluated in the left atrium of rat hearts immersed in an organ bath containing Krebs-Henseleit solution comprising (in mM): NaCl 120, KCl 5.4, $MgCl_2$ 1.2, $NaHCO_3$ 27, $CaCl_2$ 1.25, Glucose 10, NaH_2PO_4 2.0 (pH 7.4). The atrium was maintained at 29° ± 0.1°C, oxygenated (95% O_2 and 5% CO_2), stretched to 5 mN and submitted to field stimulation (1 Hz, 100 V, 0.5 ms) (Stimulator SD9 GRASS). Atrial force was recorded using an isometric force transducer (GRASS FT03), and the signals digitalized (DATAQ DI710, WINDAQ PRO Acquisition). The concentration-response curves of (-)-carvone (0.001 to 4.0 mM) and nifedipine (0.03 to 100 μM, Ca^{2+} channel blocker) were obtained to determine contractile response and calculate the EC_{50}. Dimethyl sulfoxide (DMSO) at 0.5% was used as the diluent for (-)-carvone.

Effects of (-)-carvone on Ca^{2+} influx in the atrial myocardium

To analyze the effect of (-)-carvone on the Ca^{2+} influx, the concentration-response curves of $CaCl_2$ (0.1 to 8.0 mM) and (±)-Bay K8644 (5 to 500 nM) in the left atrium in the control and after pre-incubation with (-)-carvone (1 mM) for 15 min were obtained. The results were expressed as percentages of the maximum atrial contractile response to $CaCl_2$ in the control. In both protocols, the initial concentration of $CaCl_2$ in the K-H solution was 0.5 mM.[7,16]

Effects of (-)-carvone on the electrocardiographic profile and left ventricular developed pressure (LVDP)

After intraperitoneal administration of heparin in rats (1000 IU) for 15 minutes, the hearts were removed and mounted on a constant-flow (10 mL/min) aortic perfusion system. The heart was perfused with previously filtered K-H solution (0.45 μm), oxygenated (95% O_2 + 5% CO_2) and maintained at 34 ± 0.1°C (Haake F3). To record the electrocardiogram (ECG), three electrodes (Ag/AgCl/NaCl 1 M) were placed on the heart to sense electrical signals. The signals were amplified and digitalized (PowerLab 4/35 ADInstrument, USA). LVDP was measured using a water-filled balloon (15 cm/Hg) introduced into the cavity of the left ventricle. This device was coupled to a pressure transducer (MLT0699/A). The signals were amplified (Bridge Amp FE221 ADInstrument, USA) and sent to an AD converter (PowerLab 4/35 26 ADInstrument, USA). The system was calibrated using a column of mercury. Contractile parameters (LVDP, time to peak and relaxation time) were evaluated in 30 consecutive beats using LabChart 8.0 Pro Software (ADInstruments, USA) in control situation and after 5, 10 and 15 minutes from the start of carvone perfusion (0.5 mM). The ECG measured the PR interval (PRi - the period that extends from the beginning of the P wave until the R wave), QRS complex duration (QRS - the period that extends from the Q wave until the S wave), and the QT interval (QTi - the period that extends from the beginning of the Q until the end of the T wave). QTi was converted to QTc using the Bazett's formula normalized for rodents (QTc-B = QTi/*RR*/*f*), f is the average duration of RR interval in control (f = 271 ms).

Effects of (-)-carvone on the fractional shortening

Left and right ventricular cardiomyocytes were isolated from rats according to the protocol of Shioya (2007),[17] with some modifications. Shortening fraction was assessed by measuring the change in cell length using an inverted microscope coupled to an edge detection system (Ionoptix, USA). The cardiomyocytes were placed in an experimental chamber (room temperature) containing Tyrode solution (in mM: NaCl 150, KCl 5.4, $MgCl_2$ 0.5, HEPES 10, Glucose 10, $CaCl_2$ 1.8, pH 7.4). The cardiomyocytes were visualized using a camera (Ionoptix Myocam at 240 Hz) coupled to a microscope and an image detection program (Ionoptix Ionwizard 6.3) was used. Cells were submitted to an electrical field (1 Hz, 100 V, 4 ms) using a pair of platinum electrodes. The longitudinal changes in the borders of the cardiomyocytes were captured by the edge detection system and the generated data were stored and analyzed. The fractional shortening was evaluated in control cells and after incubation with 0.5 mM (-)-carvone.

Effects of (-)-carvone on the L-type calcium current ($I_{Ca,L}$)

Whole-cell voltage-clamp recordings were obtained using an EPC 10.2 (HEK Elektronik, Germany). In whole-cell configuration, 3-5 min was waited to establishment of an ionic equilibrium between the pipette solution and intracellular environment. The recording electrodes had tip resistances of 2-3 MΩ. Ventricular cardiomyocytes with series resistance above 8 MΩ were discarded. The composition of internal solution was (in mM): 120 CsCl, 20 TEACl, 5 NaCl, 10 HEPES and 10 EGTA, 1 $MgCl_2$ (pH was set to 7.2 using CsOH) and external solution was (in mM): 150 TEACl, 0.5 $MgCl_2$, 1.8 $CaCl_2$, 10 HEPES and 11 glucose (pH 7.4 set using TEAOH). To evaluate the acute effects of 0.3 and 0.5 mM (-)-carvone

on $I_{Ca,L}$, a time course of $I_{Ca,L}$ peak current was recorded in absence and after exposure to a given concentration of (-)-carvone. Pre-pulses from a holding potential of −80 mV to −40 mV for 50 ms was applied to inactivate any remnant Na^+ or T-type Ca^{2+} channels. Then, a test pulse to 0 mV was applied during 300 ms to measure $I_{Ca,L}$.

Effects of (-)-carvone on the intracellular global Ca^{2+} transient

Left and right ventricular cardiomyocytes were loaded with 10 M of FLUO4-AM (Molecular Probes, Eugene, OR, USA) diluted in DMSO for 30 min. To remove the excess dye the cells were washed with Tyrode solution (1.8 mM Ca^{2+}). A confocal system (LSM 510 Meta, Zeiss GmbH, Jena, Germany) with a 63x oil immersion objective was used for confocal fluorescence imaging. FLUO4-AM was excited at 488 nm (Argon laser) and the emission intensity was measured at 510 nm. Cardiomyocytes were scanned with a 512-pixel line that was positioned along the longitudinal axis of the cell, every 1.54 ms. Digital image processing was performed using IDL programming language (Research Systems, Boulder, CO, USA).[9] The intracellular Ca^{2+} levels were reported as F/F_0, where F_0 is the resting fluorescence. Intracellular global Ca^{2+} transient was recorded in the control and after three minutes of incubation with 0.5 mM (-)-carvone in room temperature.

Effects antiarrhythmic of (-)-carvone

Ex vivo arrhythmia was determined in isolated hearts as previously described.[18] Initially, the hearts were perfused with K-H solution containing 1.25 mM of calcium (control group). After 20 min, the hearts were perfused with K-H solution containing 3.3 mM of calcium (high calcium group) or with high calcium + 0.5 mM (-)-carvone during 15 min (high calcium group + carvone). The ECG was monitored for 15 min to evaluate the occurrence of arrhythmias. The arrhythmias observed were VPB, ventricular tachycardia (VT) and ventricular fibrillation (VF). The 15 minutes of the experiment was divided into three-minute intervals and the arrhythmia scores were added at the end as described by Curtis and Walker (1988).[9,19] Episodes of VPB < 10 events/3 min were classifed as score 0 and > 10 events/3 min scored 1; 1-5 episodes of VT < 40 s were 2 and > 5 episodes of VT or 1 episode of VF with duration < 40 s were scored 3; 2 - 5 episodes of VT or VF with duration < 80 s were scored 4; > 5 episodes of VF, VT and/or VF with duration < 160 s was scored as 5; VT and/or VF with duration < 300 s was scored as 6 and > 300 s scored as 5.

Statistical analysis

All results are shown as the means ± standard deviation of mean (S.D). GraphPad Prism v.5.0 (GraphPad Software, CA, USA) was used for the statistical analyses. Data were tested for normality using the Shapiro-Wilk test. Mean values were compared using the one-way analysis of variance (ANOVA) followed by Tukey's post hoc test or unpaired t-test. $P < 0.05$ was used as the significance level.

Results

(-)-Carvone (0.003 to 4 mM) decreased the atrial force in a concentration-dependent manner. Figure 1A shows tracing of curves of isolated atrial contraction in the control situation and with 0.3, 2 and 4 mM of (-)-carvone and washout. As can be seen, 4 mM of (-)-carvone decreased myocardial contractility by approximately 96% and the reversibility after washout was of approximately 65%. Figure 1B shows a concentration-response curve of the negative inotropic effect of (-)-carvone that presented EC_{50} of 0.44 ± 0.11 mM (n = 5). Nifedipine, used as positive control, presented EC_{50} values of 0.0034 ± 0.0011 mM (n = 5). DMSO at 0.5%, used as a diluent, had no effect on atrial force (data not shown).

As (-)-carvone evoked a negative inotropic effect, we decided to investigate the involvement of calcium channel in its action mechanism. The results revealed that (-)-carvone (1 mM), shifted the concentration-response curve of $CaCl_2$ to the right, increasing the EC_{50} of $CaCl_2$ from 1.46 ± 0.14 mM (control) to 3.17 ± 0.22 mM ($CaCl_2$ + carvone) (Fig. 1C, n = 5, $p < 0.05$). Interestingly, (-)-carvone impaired the positive inotropism induced by (±)-BAY K8644, an agonist of the L-type calcium channel (Figure 1D).

In the isolated hearts, 0.5 mM (-)-carvone also induced reduction in LVDP, as can be seen in the representative traces shown in Figure 2A (n = 5). A 73% reduction in LVDP was observed after 15 minutes of heart perfusion with 0.5 mM of (-)-carvone (Figure 2B). (-)-Carvone did not change the time to peak (Figure 2C) but it did significantly reduce the relaxation time (24%) after 15 min of (-)-carvone perfusion (Figure 2D).

Figure 3A shows representative ECG tracings in the control situation, after 15 min perfusion with 0.5 mM of (-)-carvone and washout. As can be seen, (-)-carvone decreased heart rate (n = 5, Figure 3B) and increased PRi and QTi (n = 5, Figures 3C and D), without changing the duration of QRS complex (Figure 3E).

Figure 4A shows representative records of the cellular contractility in the control situation (top panel) and after perfusion with 0.5 mM of (-)-carvone (bottom panel), showing the reduction in fractional shortening in cardiomyocytes. The average results showed reduction of the fractional shortening after incubation with (-)-carvone (n = 5, Figure 4B). Furthermore, (-)-carvone decreased both time to peak and time to 50% relaxation (Figures 4C and D).

Considering the major role of L-type Ca^{2+} channels in the control of the cardiac contraction, we used whole-cell patch-clamp to test whether (-)-carvone affects $I_{Ca,L}$ in ventricular cardiomyocytes. Figure 5A shows $I_{Ca,L}$ recordings of 300-ms depolarizing steps from −40 to 0 mV in the control situation and with 0.5 mM (-)-carvone. Figure 5B ilustrates the time course of $I_{Ca,L}$ showing reduction of $I_{Ca,L}$ after (-)-carvone incubation. The average decrease of peak $I_{Ca,L}$ induced by (-)-carvone was 79% (n = 4, 10 cells, Fig. 5C). The effect of 0.3 mM of (-)-carvone on the $I_{Ca,L}$ was also evaluated, and a 43% reduction in the $I_{Ca,L}$ was observed (data not shown). We concluded that (-)-carvone inhibits L-type Ca^{2+} channels and that this effect may contribute to its negative inotropic effect evidenced in atrial and ventricle tissues.

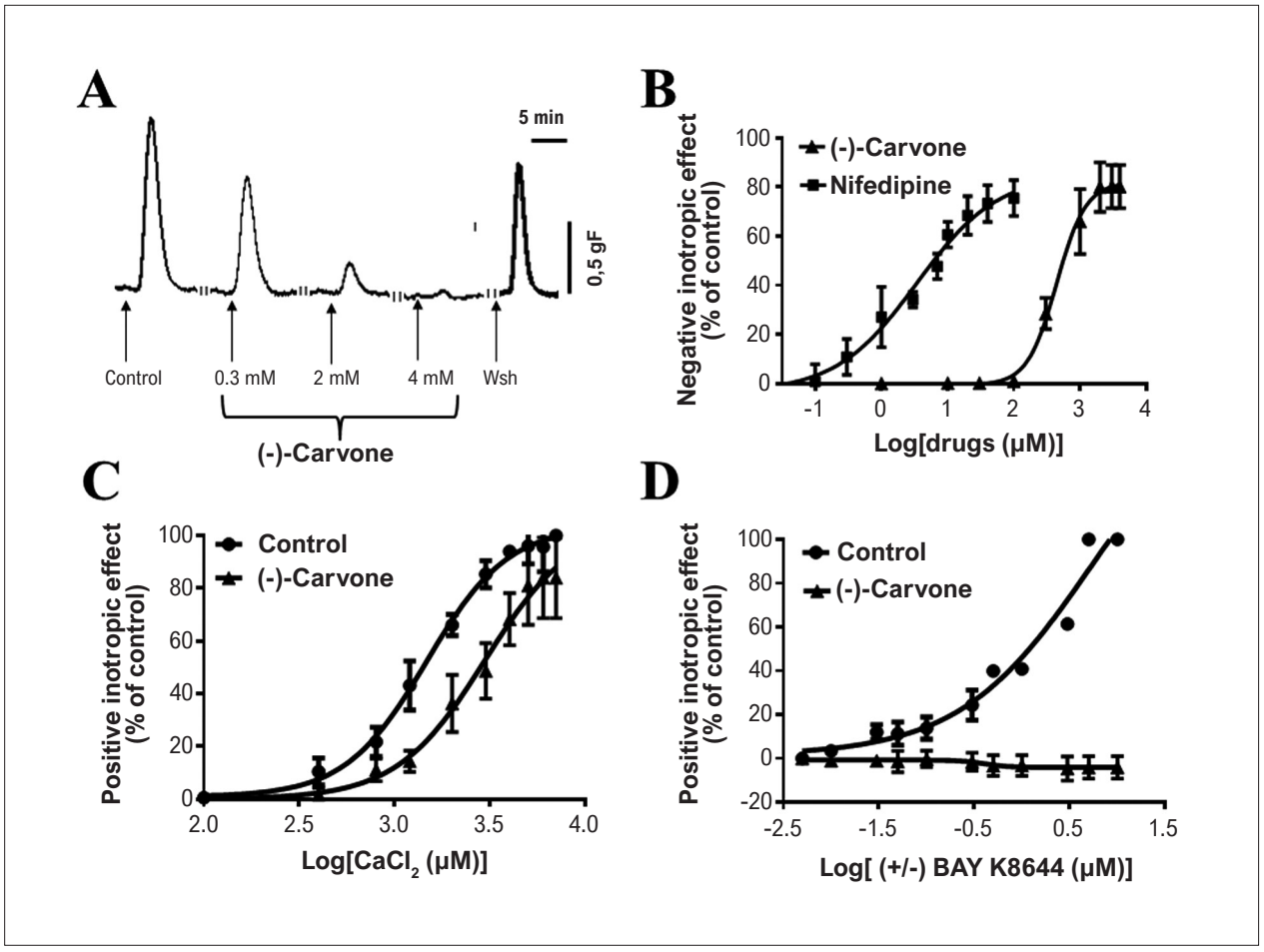

Figure 1 – *(-)-Carvone exhibited negative inotropic effect and decreased the calcium influx in the rat left atrium. (A) Experimental tracing of isolated atrial contraction in the control, after incubation with (-)-carvone (0.3, 2 and 4 mM) and washout (Wsh); (B) Concentration-response curves of negative inotropism of (-)-carvone and nifedipine (calcium channel blocker), (C) and (D) Concentration-response curves of $CaCl_2$ and (±)-BAY K8644 in the absence and presence of 1 mM of (-)-carvone, respectively (n = 5).*

In view of these results, we sought to evaluate the intracellular calcium transient in ventricular cardiomyocyte loaded with FUO4-AM. Figure 5D (left) shows the images obtained using confocal microscopy of the intracellular calcium transient in the control and after pre-incubation with 0.5 mM of (-)-carvone. It was noted that the fluorescence of calcium, shown in green, was reduced with (-)-carvone. Figure 5D (right) shows representative tracings of the intracellular calcium transient in the control and with (-)-carvone. Figure 5E shows calcium fluorescence as the F/F_0 ratio, which was reduced after incubation with (-)-carvone (n = 5). (-)-Carvone pretreatment of cardiomyocytes accelerated the time to 50% decay (Figure 5G), whereas the time to peak Ca^{2+} transient (Fig. 5F) remained unchanged.

Since calcium channel blocking drugs present antiarrhythmic effects, we decided to investigate whether (-)-carvone could present this property. The antiarrhythmic effect of (-)-carvone was evaluated in an arrhythmia model induced by calcium overload. Three types of arrhythmias were observed in hearts perfused with high calcium: VPB, VT, e VF (Figure 6A). As can be seen in Figure 6B, (-)-carvone significantly decreased the arrhythmia score (n = 5). In addition, our results showed that in hearts subjected to high calcium with simultaneous perfusion of (-)-carvone the severity of arrhythmias was lower, as the occurrence of VF decreased from 34% (high calcium) to 8%. Furthermore, the hearts perfused with (-)-carvone had mostly VPB (52%), considered an arrhythmia of lesser severity.

Discussion

Our results showed the ability of monoterpene (-)-carvone to reduce the atrial force of rat hearts in a concentration-dependent manner that was partially reversible after washing. (-)-Carvone showed low potency when compared to nifedipine, a classic L-type Ca^{2+} channel blocker. It is known that contractile force is dependent on free cytoplasmic Ca^{2+} concentration and that Ca^{2+} influx through L-type Ca^{2+} channels is essential to trigger the calcium-induced calcium release from the sarcoplasmic reticulum (SR).[20] This mechanism is very important because it regulates myocardial force.

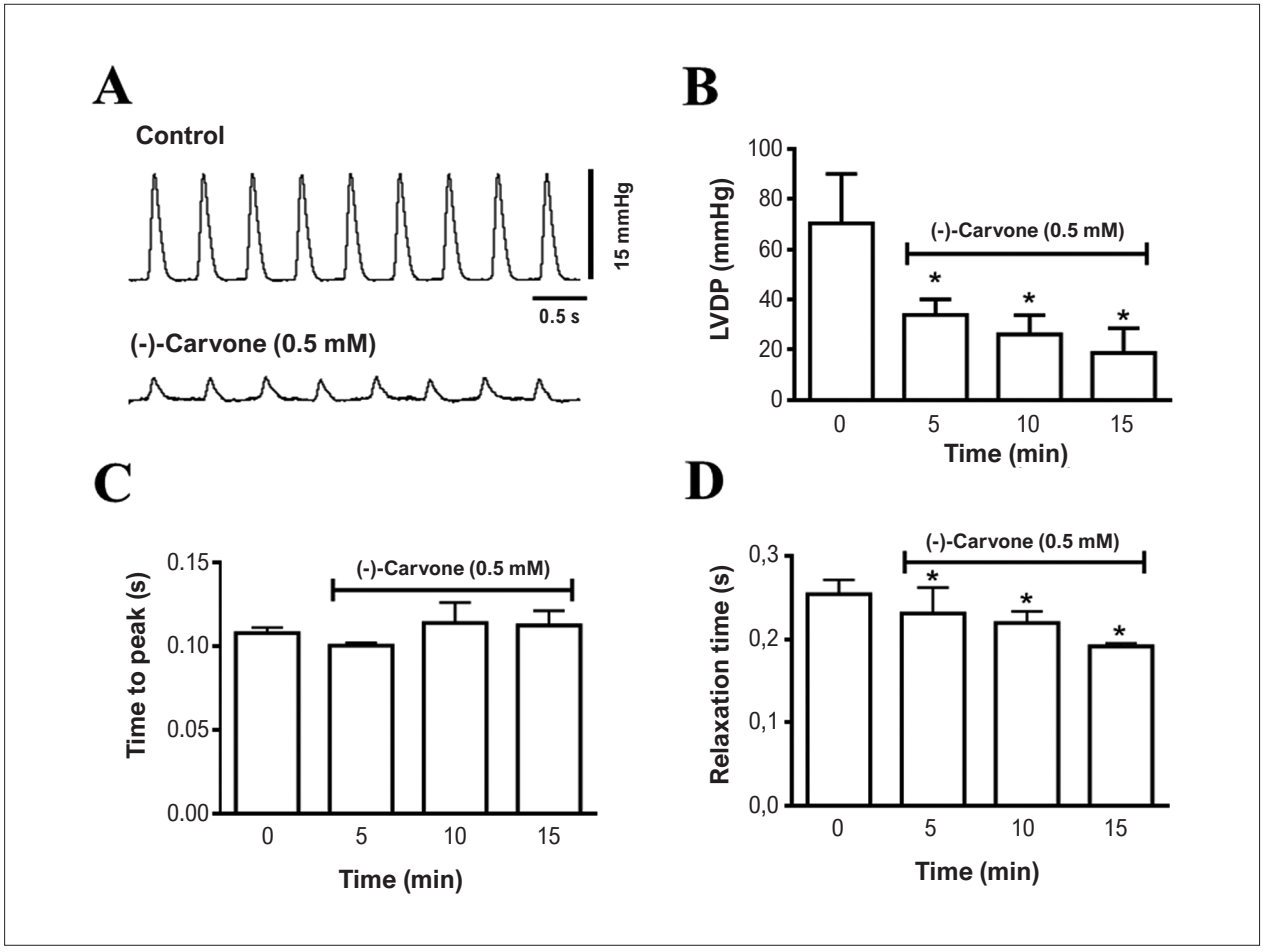

Figure 2 – *Effects of (-)-carvone on the cardiac contractility in the isolated rat heart. (A) Records of left ventricle developed pressure (LVDP) in the control (top panel) and with 0.5 mM (-)-carvone (bottom panel); (B) LVDP; (C) time to peak; and (D) relaxation time (n = 5, *p < 0.05).*

Thus, we decided to investigate whether there was a correlation between atrial force reduction and a decrease in Ca^{2+} entry in the action mechanism of (-)-carvone. Our results showed that (-)-carvone reduced Ca^{2+} influx in the atria by impairing the positive inotropic response to both Ca^{2+} and (-)-Bay K 8644, an agonist of L-type Ca^{2+} channels. The blockade of Ca^{2+} channel promoted by (-)-carvone was probably responsible for the decreased atrial force observed in our experiments. In smooth muscles, carvone presents antispasmodic effect; it reduced the contraction induced by high K^+ and was almost 100 times more potent than verapamil, a calcium channel blocker.[13]

The ability of terpenes to block the Ca^{2+} channel has been observed both in smooth muscle and cardiac muscle.[21] Monoterpenes can modulate the function of voltage-dependent and ligand-dependent ion channels.[22,23] Therefore, they are useful in preventing cardiovascular diseases such as arrhythmia and hypertension. With respect to the cardiovascular system, several studies have reported that monoterpenes such as rotundifolone,[24] terpineol,[25] timol,[23] and carvacrol[23] act as blockers of calcium channel. It has also been shown that in isolated cardiomyocyte, R(+)-pulegone,[16] geraniol,[6] nerol,[7] farnesol [9] and (-)-menthol[26] blocked the L-type Ca^{2+} channel.

Blockage of Ca^{2+} channels can induce important electrophysiological changes, such as a decrease in electrical conduction in the heart and heart rate. Therefore, we investigated whether (-)-carvone could induce physiological changes in the heart. Experiments using isolated hearts were performed to simultaneously record LVDP and ECG profiles. (-)-Carvone promoted a decrease in LVDP, which corroborates our findings in the isolated left atrium, as discussed earlier, and also induced a reduction in heart rate. As is known, heart rate is usually controlled by the heart's primary pacemaker, the sinus node. Sinus node cells display the property of automaticity as a result of gradual depolarization during electrical diastole (slow diastolic depolarization). The slow diastolic depolarization and the phase of depolarization of the pacemaker action potential are essential processes for the formation of the electrical impulse of the sinus node. These phenomena are linked to Ca^{2+} influx by the sarcolemma; a decreased influx can induce electromechanical decoupling of the myocardium and bradycardia.[27] The ionic current that

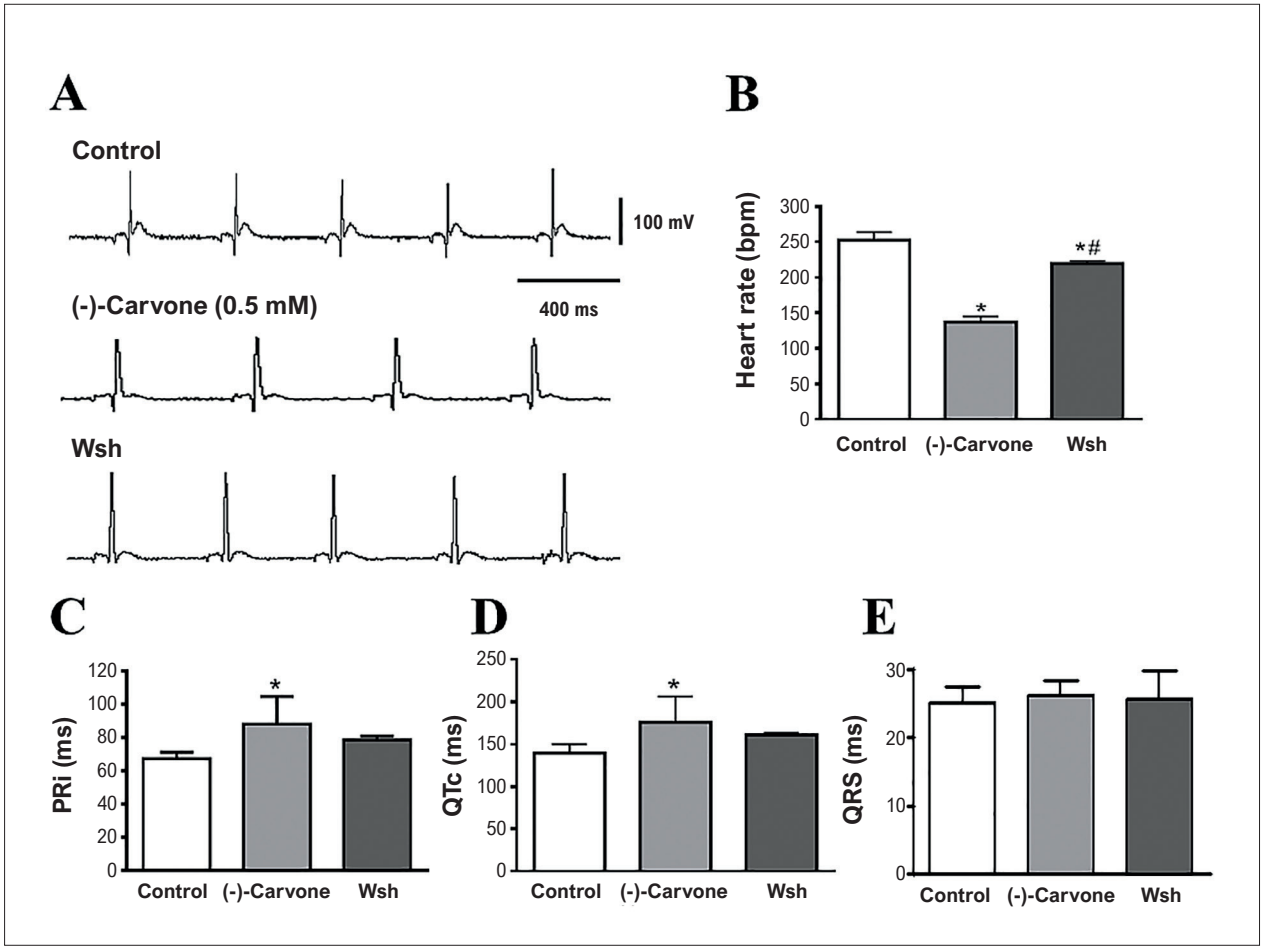

Figure 3 – *Effects of (-)-carvone on the electrocardiographic profile in the isolated rat heart. (A) Electrocardiogram records in control, with 0.5 mM (-)-carvone as washout (Wsh), (B) Heart rate, (C) PR interval (PRi), (D) QTc interval and (E) QRS complex duration (n = 5, *p < 0.05 vs control and #p < 0.05 vs (-)-carvone).*

was probably affected, and was responsible for decreasing heart rate, may be the $I_{Ca,L}$. The effect of (-)-carvone on calcium influx promoted a reduction in heart rate and an increase in the duration of the PRi interval, indicative of first-degree atrioventricular block. In this blockage, there is a delay in the transmission of electrical impulse from the atria to the ventricles, increasing the refractory period of myocardium. Other substances that promote this blockage are β-blockers, cardiac glycosides, and drugs that increase cholinergic activity.[28]

It was observed that (-)-carvone also increased the QTc interval, which reflects the period necessary for depolarization and ventricular repolarization to occur, i.e., an indirect parameter to estimate the ventricular action potential duration. QTc prolongation may be due to the blockage of potassium channels.[6,9] Class III antiarrhythmic agents are potassium channel blockers that prolong the duration of the action potential increasing the refractory period of atrial, nodal and ventricular tissues. An increase in the refractory period of the atrial cells is of great importance in the treatment of atrial tachyarrhythmia.[29] Amiodarone, a multiple-channel blocker, is considered one of the most effective antiarrhythmic drugs, and is widely prescribed. However, long-term use of antiarrhythmic drugs has been reported to cause torsades de pointes[30] and adverse effects.[29]

In isolated ventricular cardiomyocytes, 0.5 mM of (-)-carvone reduced the shortening fraction and accelerated the relaxation time, as was also observed in the isolated heart. It is known that the contractile force of the heart muscle depends on the free cytoplasmic Ca^{2+} concentration, and Ca^{2+} influx through L-type Ca^{2+} channels is essential to trigger calcium-induced calcium release from the SR. Then, whole-cell patch-clamp was performed to test whether (-)-carvone affects $I_{Ca,L}$. The results showed that (-)-carvone significantly reduced the $I_{Ca,L}$ in ventricular cardiomyocyte. As (-)-carvone reduces $I_{Ca,L,}$ it is reasonable to think that this monoterpene would profoundly affect the Ca^{2+} release from the SR. Our results showed that (-)-carvone also affected the Ca^{2+} transient amplitude and accelerated the time to 50% decay. It is known that the cardiac muscle relaxation is largely determined by reuptake of Ca^{2+} into the SR by sarco(endo) plasmic reticulum Ca^{2+} ATPase (SERCA2a) and by another

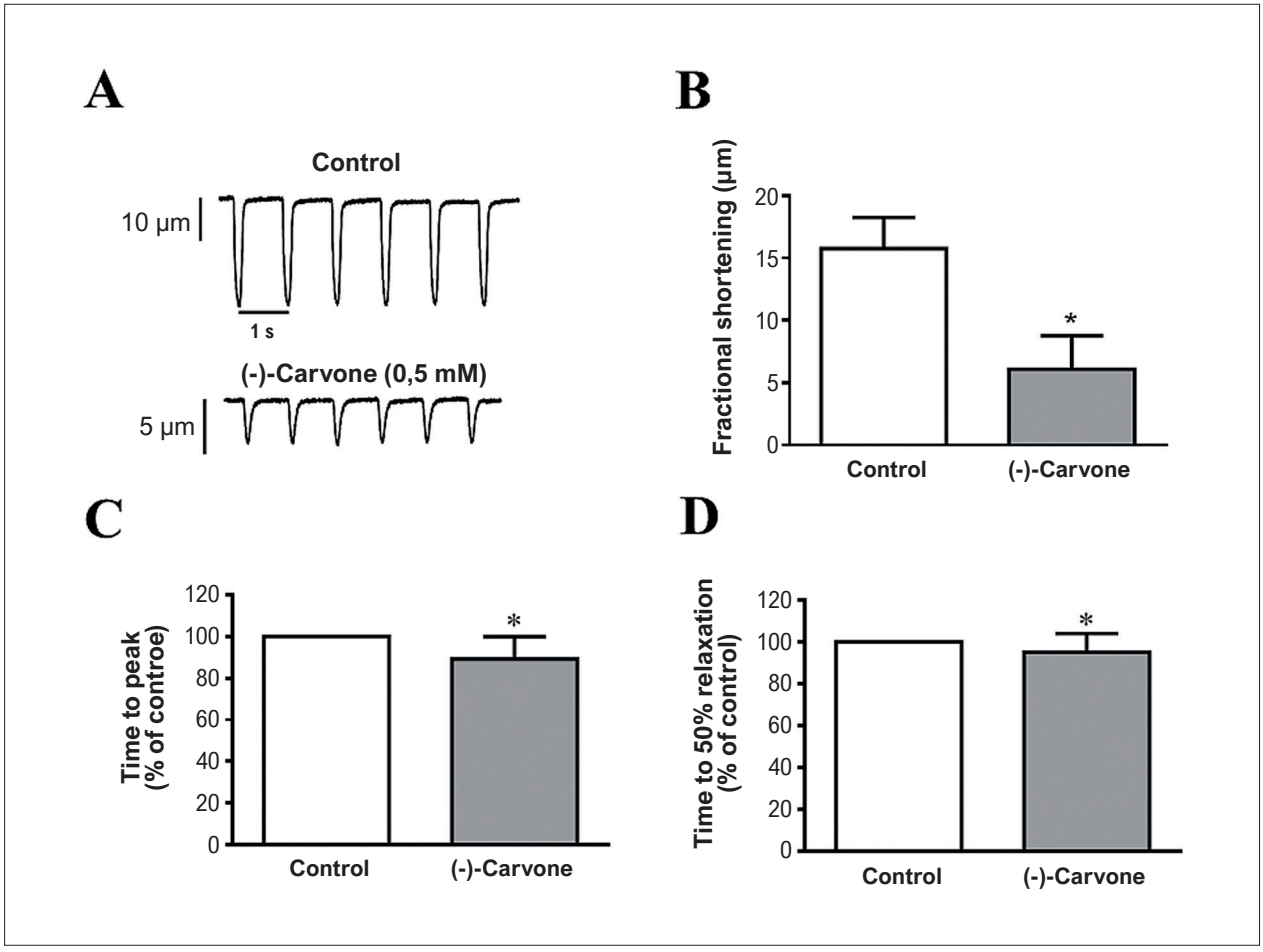

Figure 4 – *Effects of (-)-carvone on fractional shortening in the isolated ventricular cardiomyocyte. (A) Recording of cell shortening in control (top panel) and after incubation with 0.5 mM of (-)-carvone (bottom panel), (B) Fractional shortening in control and (-)-carvone, (C) Time to peak, (D) Time to 50% of relaxation (n = 5, *p < 0.05).*

transport protein such as Na^+/Ca^{2+} exchanger (NCX) and plasma membrane Ca^{2+} ATPase (PMCA).[17] Then, the decrease of the cytosolic Ca^{2+} may be associated with the activation of some of these pathways.

Nifedipine (10 μM), a L-type calcium channel blocker, reduced the amplitude of the Ca^{2+} transient by 79% in neonatal rat ventricular myocytes.[24] The blockade produced by nifedipine (1 μM) was totally reversible after washout with standard solution.[31] Our results indicate that (-)-carvone is a Ca^{2+} channel blocker, similar to nifedipine, but the effect on the $I_{Ca,L}$ was irreversible in the presence of 500 μM (-)-carvone. According to Vaughan-Williams (1970), calcium channel blockers belong to class IV of the antiarrhythmics, and are widely used in clinical medicine.[32,33]

As (-)-carvone reduced sarcolemal Ca^{2+} influx, we investigated their possible antiarrhythmic activity and observed a drastic reduction over time in events such as VF in an ex vivo model of calcium overload. Indeed, our results showed that (-)-carvone had a good antiarrhythmic effect, confirmed by decreased arrhythmia scores and reduction in the occurrence of ventricular fibrillation, considered a more severe type of arrhythmia. It is already known that active substances from plant material can have significant antiarrhythmic properties,[34] with great potential to be used as antiarrhythmics in preclinical and clinical studies. We can cite as example the terpenes geraniol, nerol, D-limonene and farnesol that have been shown to inhibit L-type Ca^{2+} channels and present antiarrhythmic activity.[6-9] Although many experimental studies have shown that terpenes exert antiarrhythmic effects, these compounds are not yet used in the clinic. In addition to the antiarrhythmic effect, (-)-carvone also had a cardioprotective effect against doxorubicin-induced cardiotoxicity *in vivo* and potentiated its anticancer toxicity *in* vitro.[14] These cardioprotective effects of carvone make it a promising molecule for use in clinical practice.

Study limitation

This study revealed that (-)-carvone reduces L-type calcium current, induces negative inotropic effect, and has antiarrhythmic effects in rat hearts. But we also can point some

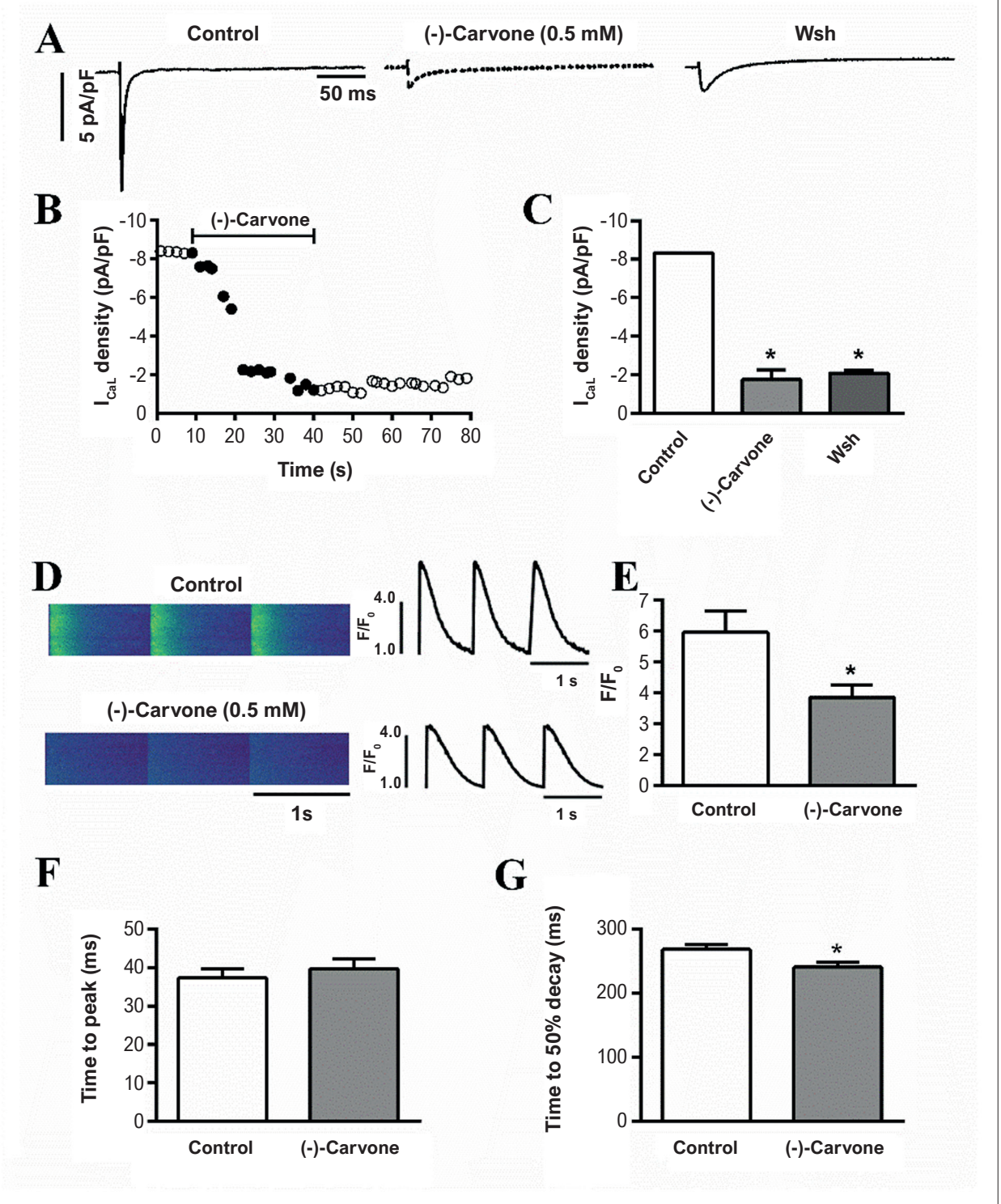

Figure 5 – *Effects of (-)-carvone on the L-type calcium current ($I_{Ca,L}$) and intracellular calcium transient in the isolated ventricular cardiomyocyte. (A) Typical recordings of $I_{Ca,L}$ in control, during the perfusion with 0.5 mM (-)-carvone and washout (Wsh), (B) Time course of the effect of (-)-carvone on $I_{Ca,L}$. Each symbol indicates the net amplitude of $I_{Ca,L}$ measured every 10 s at 0 mV membrane potential under control conditions (open circles), during exposure to 0.5 mM (-)-carvone (black circles), and after Wsh (open circles), (C) Summary of the effects of (-)-carvone on the $I_{Ca,L}$ density (pA/pF), (D) Images (left) and representative tracing (right) of the intracellular calcium transient in control (top panel) and after incubation with 0.5 mM of (-)-carvone (bottom panel), (E) Average calcium transient peak (F/F_0), (F) Time to peak of transient and (G) Time to 50% decay of calcium transient (n = 4-5, *p < 0.05 vs control; # p < 0.05 vs (-)-carvone).*

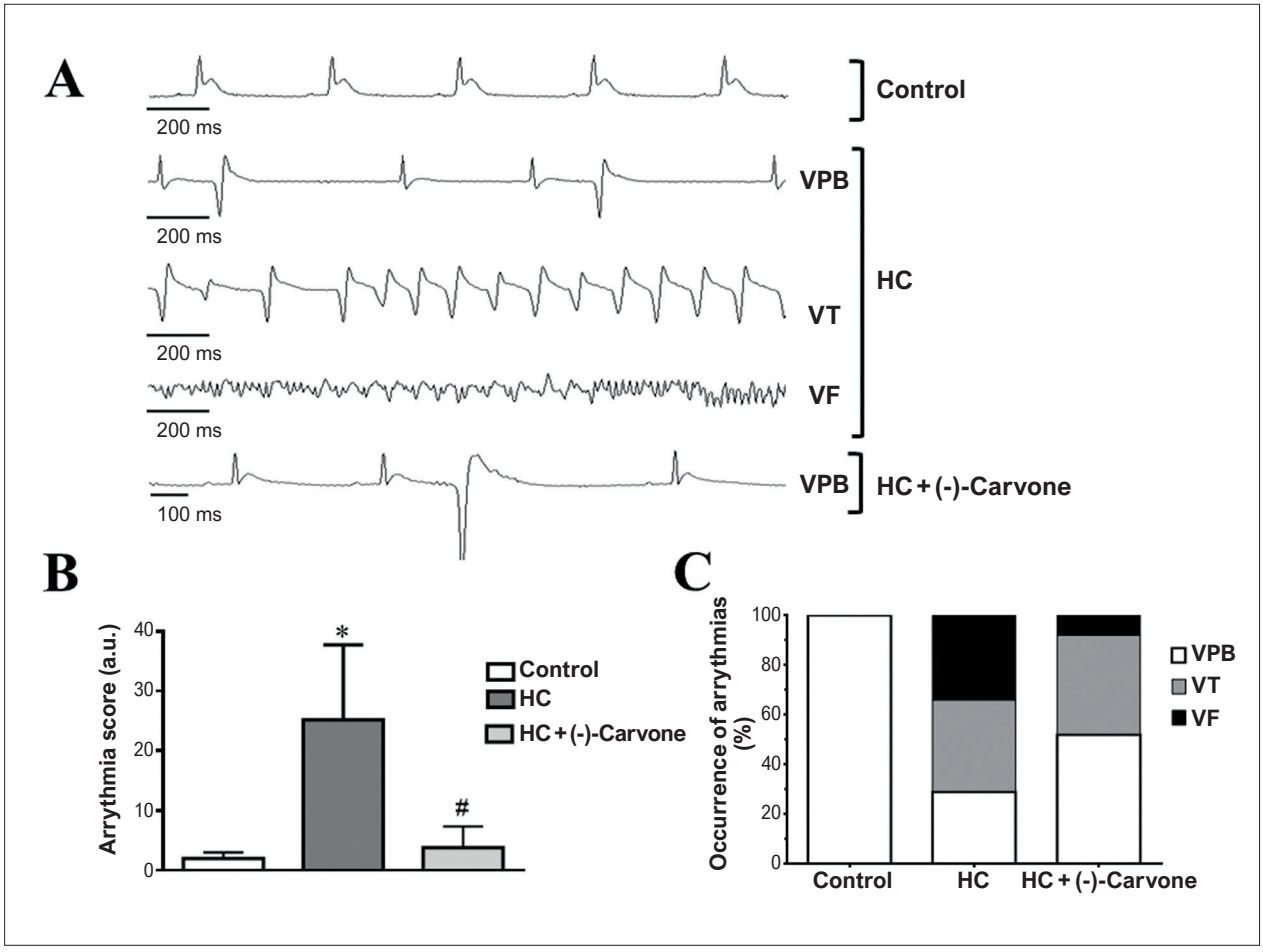

Figure 6 – *Antiarrhythmic effect of (-)-carvone in the calcium overload-induced arrhythmia model. (A) Representative electrocardiograms in control, with high calcium (HC) and HC plus (-)-carvone identifying the arrhythmias: ventricular premature beat (VPB), ventricular tachycardia (VT) and ventricular fibrillation (VF), (B) Arrhythmia score and (C) Occurrence of arrhythmia (n = 5, *p < 0.05 vs control and #p < 0.05 vs HC).*

limitations, as the lack of evaluation of antiarrhythmic effects of (-)-carvone in an *in vivo* model of arrhythmia and other *in vitro* models that indirectly generate calcium overload. Another limitation of this study is that we did not assess the effects of carvone on other important channels for cardiac excitation, nor evaluate its action on the SERCA2a. Furthermore, there are other limitations, including toxicological implications of the acute and long-term use of carvone, its metabolization, and pharmacodynamics.

Conclusion

We can conclude that (-)-carvone decreased L-type calcium current and intracellular calcium transient in the myocardium, promoting a reduction in atrial and ventricular contractility. In isolated rat hearts, (-)-carvone caused a decrease in heart rates and increase in PR intervals, typical of calcium channel blockers. In addition, a significant reduction in the severity of arrhythmias such as ventricular fibrillation in hearts submitted to (-)-carvone perfusion was observed. (-)-Carvone is, therefore, a highly promising natural substance in respect of the development of new antiarrhythmic drugs.

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Author Contributions

Conception and design of the research: Silva GBA, Souza DS, Silva-Neto JA, Cruz JS, Quintans-Júnior LJ, Vasconcelos CML; Acquisition of data: Silva GBA, Souza DS, Menezes-Filho JER, Silva-Neto JA, Roman-Campos DR, Quintans-Júnior LJ; Analysis and interpretation of the data: Silva GBA, Souza DS, Menezes-Filho JER, Silva-Neto JA, Cruz JS, Roman-Campos DR, Vasconcelos CML; Statistical analysis: Silva GBA, Souza DS, Menezes-Filho JER, Vasconcelos

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Where are We Going with Natural Products? Exploring the True Potential of New Plant-Based Drugs in the Cardiovascular Field

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Short Editorial related to the article: (-)-Carvone Modulates Intracellular Calcium Signaling with Antiarrhythmic Action in Rat Hearts

Cardiovascular diseases are a leading cause of death worldwide. In the Brazilian population, it is estimated that approximately 41.6% of women and 63.5% of men are at medium to high risk of developing cardiovascular diseases in the next 10 years.[1] Cardiac arrhythmias are common manifestations of cardiovascular diseases and configure an important cause of morbidity and mortality among cardiac diseases. After Vaughan-Williams' classification of antiarrhythmic drugs based on their pharmacological actions, several new therapies and drugs were proposed, aiming to achieve a high efficacy with the least adverse effects. However, treatments with antiarrhythmic drugs and other agents used to treat cardiovascular conditions such as heart failure are often prone to pro-arrhythmic adverse responses.[2,3] In addition, cardiac complications, such as arrhythmias, are also observed in treating other pathologies, including cancer, and during the use of antidepressants.[4,5]

Plant-based medicines have long been used in traditional/alternative medicine for the most diverse purposes. Its uses correlate with several factors, including family tradition, age, sex, education, socioeconomic status, and failure of conventional therapies.[6] Among plant-based drugs, different types of terpenes have been explored as fragrances/repellents but also according to their medical potential in treating parasitic diseases, bacterial infection, wound healing, and as anti-inflammatory antioxidant agents.[7] Moreover, the antiarrhythmic properties of some terpenes have been addressed using *in vitro* and experimental model approaches,[8,9] while other terpenes might actually have pro-arrhythmogenic activity.[10]

In this issue of the *Arquivos Brasileiros de Cardiologia*, the antiarrhythmic properties of the monoterpene (-)-Carvone was explored *in vitro* and *ex vivo* using diverse preparations that range from cellular assays to the isolated organ.[11] (-)-Carvone evoked a negative inotropic effect in the atria in a concentration-dependent fashion and reduced the contractility of isolated hearts after acute exposure to the terpene. The electrocardiogram (ECG) profile of isolated hearts exposed to this drug was marked with decreased heart rate, increased PR interval, and QTc. In freshly isolated cardiomyocytes, (-)-Carvone led to a decreased L-type calcium current, intracellular calcium transient, and cellular contraction, which aligns well with their isolated heart and atria findings. On top of their findings, (-)-Carvone reduced the severity of arrhythmias in an experimental model of isolated hearts exposed to a high Ca^{2+} media. The authors concluded that (-)-Carvone has a promising antiarrhythmic activity by decreasing Ca^{2+} entry through L-type Ca^{2+} channels.

Despite the well-presented data and properly performed experiments with well-supported conclusions, some questions are to be analyzed regarding the published work. First, it is important to highlight that although several terpenes display cardiovascular actions, including antiarrhythmic properties, there is very little, if any, well-conducted pre-clinical evidence of their potential to translate into the medical practice. One could then argue if terpenes are worth studying to this end. To add more doubt to this matter, most of these terpenes have low pharmacological potency when compared to other clinically used class IV antiarrhythmic like phenylalkylamines,[12] like Verapamil. Even when terpenes' pharmacological properties fall in the low micromolar range (around 0.3 mM for the Ca^{2+} current, according to the authors' findings for (-)-Carvone), many terpenes have multiple targets that could predictably lead to several undesirable side effects. In fact, the authors suggest that the prolonged Qtc may result from (-)-Carvone off-targets on other ion channels. Indeed (-)-Carvone was shown to activate other channels such as transient receptor potential (TRP) channels.[13]

With all these issues raised, what is the true potential of (-)-Carvone and other terpenes to the cardiovascular field? From my point of view, the time is now to explore exactly these features of multi targets and relative low potency of (-)-Carvone and other plant-based new drugs aiming to optimize specific cardiovascular conditions. (-)-Carvone has been demonstrated experimentally to have antiparasitic, anti-convulsant, antidiabetic, anti-inflammatory, anti-cancer, and immunomodulatory effects, among others.[14] Recently, (-)-Carvone was also shown to attenuate doxorubicin toxicity while potentiating its antitumoral effects.[15] Therefore, screening the biological properties of terpenes has a vast potential to create new and optimized therapies for cardiovascular diseases, especially in combination with already established drugs.

To address these questions more comprehensively, future studies should be focused on using (-)-Carvone and other terpenes in specific models of cardiovascular

Keywords

Cardiovascular Diseases/physiopathology; Anti-Arrhythmics; Risk Factors; Cardiotoxicity; Medicinal Plants; Patch-Clamp Techniques; Terpenes; Carvone

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diseases, exploring their biological properties that are currently investigated. Moreover, information on the pharmacokinetics and pharmacodynamics of many of these compounds and their toxicity after acute and long-term exposure are still lacking in the literature. Overall, (-)-Carvone and other terpenes do have a potential to be translated to clinical practice, either as an antiarrhythmic drug or due to other of its many biological actions; however, future studies are needed, covering more specific cardiovascular conditions and comparing currently used therapies with these new approaches using (-)-Carvone and other plant-based drugs

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Women Physicians: Burnout during the COVID-19 Pandemic in Brazil

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Abstract

Background: **COVID-19 has placed a tremendous burden on physicians worldwide, especially women physicians, affected by increased workload and loss of quality of life.**

Objective: **To assess the effects of the COVID-19 pandemic on the quality of life, burnout and spirituality of Brazilian women physicians directly or indirectly providing care to COVID-19 patients.**

Methods: **Prospective, observational study performed from July 28 to September 27, 2020, in Brazil, with women physicians from 47 specialities, the most frequent being cardiology (22.8%), with no age restriction. They voluntarily answered an online survey with questions on demographic and socioeconomic characteristics, quality of life (WHOQOL-brief), spirituality (WHOQOL-SRPB), and statements from the Oldenburg Burnout Inventory. Statistical analysis used the R software, beta regression, classification trees, and polychoric correlation matrix, with a 5% of significance level.**

Results: **Of the 769 respondents, 61.6% reported signs of burnout. About 64% reported wage loss of up to 50% during the pandemic. Some reported lack of energy for daily tasks, frequent negative feelings, dissatisfaction with capability for work, and caring for others not adding meaning to their lives. Negative feelings correlated negatively with satisfaction with sexual life and personal relations, and energy for daily tasks. The inability to remain optimistic in times of uncertainty correlated positively with feeling unsafe daily and not acknowledging that caring for others brings meaning to life.**

Conclusion: **This study showed a high frequency of burnout among Brazilian women physicians who answered the survey during the COVID-19 pandemic. Nevertheless, they presented with a relatively good quality of life and believed that spirituality comforted and reassured them in hard times.**

Keywords: **Physicians, Women; Burnout, Psychological; COVID-19; Brazil.**

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Introduction

Physicians on the front lines against the coronavirus disease-2019 (COVID-19) have faced unprecedented high levels of stress. Nevertheless, little attention has been paid to the vulnerability experienced by these professionals, mainly of the female sex. A systematic review carried out in the database Medline and Embase has shown an increase in the challenges related to the high workload and loss of quality of life during the COVID-19 pandemic, which are associated with physical and mental exhaustion.[1] The prevalence of burnout ranged from 23% to 76%, and female gender, high workload, and family-related concerns are predictors of burnout.[1] The authors recommended that studies on physician burnout take gender differences into account.

A study, conducting a cross-sectional survey to assess 2707 healthcare professionals (HCPs) from 60 countries, reported that 51% of them had burnout, which was associated with work impacting household activities, exposure to COVID-19 patients, inadequate training, and making life prioritizing decisions. Burnout was more frequent in high-income countries.[2] Another study reported an increase in burnout in women physicians as compared to men physicians, and the authors hypothesized that specific stressors included shortage of daycare options for children and imbalance between work and personal life. Women physicians with greater workloads and those without a partner experienced higher levels of burnout.[3] It is worth noting that women currently constitute a great proportion of the global health workforce and spend 15 hours more per week on unpaid domestic labor.[4,5]

The burnout dimensions have been significantly associated with an increased risk for diseases, independently of sociodemographic factors and depressive symptoms. A study with 5671 participants [predominantly physicians, mean age of 44.1 years (range, 18-70 years), 62.4% women] used a mobile health web application for an online survey of job burnout measured with the Maslach Burnout Inventory-General Survey. By using network analysis and logistic regression, the study has shown the association of high emotional exhaustion with arterial hypertension and other chronic diseases after adjusting for age, sex, educational level, and depressive symptoms.[6]

Another systematic review with 12 studies assessing burnout in HCPs working or not in frontline COVID-19 wards has shown controversial results.[7] Two of the studies reported higher levels of emotional fatigue in women as compared to men and that female sex was a risk factor for burnout among intensive care professionals.[8,9] However, another study has found no association with gender.[10] The heterogeneity of the studies regarding data collection and questionnaires used could have accounted for that, which emphasizes the need for further studies.[7]

Brazil has ranked second in number of COVID-19 cases and deaths since the beginning of the pandemic. However, to our knowledge, no study has assessed the burnout of Brazilian women physicians during the pandemic. Thus, this study aimed to assess the effects of the pandemic on the quality of life, burnout, and spirituality of women physicians directly or indirectly providing care to COVID-19 patients.

Methods

This is a transversal, observational study performed from July 28 to September 27, 2020 in Brazil, with women physicians from different medical specialities, directly or indirectly providing care to COVID-19 patients. There was no age restriction. The women physicians voluntarily answered an online survey with 68 questions, thus constituting a convenience sample.

The survey consisted of the following: 20 questions on demographic and socioeconomic characteristics; the 26 questions from the Brazilian Portuguese version of the WHOQOL-brief;[11] 9 questions based on the World Health Organization Quality of Life Spirituality, Religiousness and Personal Beliefs (WHOQOL-SRPB) field-test instrument;[12,13] and the 13 statements from the Brazilian Portuguese version of the Oldenburg Burnout Inventory (OLBI)[14-16] (Supplementary Material 1).

Through user identification, participants who answered the survey multiple times could be identified. All participants provided informed consent for the use of their anonymized data.

This study was approved by the Ethics Committee on Research (HUOL-CAAE: 34673520.7.0000.5292).

According to the methodology proposed by Schuster et al. and Demerouti et al., the 13 burnout statements of the OLBI were transformed into variables of the two dimensions 'disengagement' (7 variables) and 'emotional exhaustion' (6 variables).[15,17] Questions which answer was agree or disagree had the score inverted so as to the higher the score of each variable, the higher the burnout level. Each dimension was attributed a score corresponding to its mean score.

Statistical Analysis

Statistical analysis was performed through Beta Regression[18] which models rates and proportions outcomes. The two burnout dimensions were considered as outcomes and the 55 remaining questions, as independent variables.

In the OLBI, each outcome's score is limited to the 1-4 interval, thus a beta regression model was implemented, where each outcome was recalculated by using linear interpolation, so that values from 0 to 1 could be obtained. Three models were implemented for each outcome. The first model was composed of 55 variables. The second and third models used the independent variables that showed 10% significance in the previous model.

After the beta regression models, regression trees were implemented using the final model's independent variables and their respective outcomes. The Classification and Regression Trees (CART) is a nonparametric method used to obtain an association between the dependent variable and a set of covariates. Decision trees are used to identify the interaction between covariates. The leaves of the tree provide a graphical representation of the outcome for each group of individuals. The betareg[18] and partykit packages in R were used to implement the regression tree's beta regression models.[19,20]

Another graphical visualization was used based on a polychoric correlation,[21] a measure of association between ordinal categorical variables. A polychoric correlation matrix

was represented as a network where the nodes were the variables, and the weights on the edges represented the polychoric correlation coefficient. The thickness of the edges and the transparency was given by the magnitude of the correlation coefficient between the nodes. The colors red and green corresponded to negative and positive correlations, respectively. The 'qgraph' package in R was used for network visualization.[20-22]

For the statistical tests, we adopted a significance level of 5%.

Results

Of the 769 respondents, 474 (61.6%) reported signs of burnout. The criterion for classification of the respondents was provided by the cutoff points obtained from the classification trees: emotional exhaustion (<2.668 and ≥2.668) and disengagement (<2.143 and ≥2.143) (Supplementary Material 2).

Based on the answers to the questions, the characteristics of the sample were as follows: under 50 years of age, 50.2%; white skin color, 81.9%; married, 87.8%; and with 1 to 3 children, 67.5%. The distribution of the 47 medical specialities was as follows: Cardiology, 22.8%; Pediatrics, 15%; Internal Medicine, 6%; Obstetrics and Gynecology, 5.6%; Anesthesiology, 3.8%; Family and Community Medicine, 2.9%; and Intensive Care Medicine, 2.5%. All five Brazilian geographic regions were represented, the most frequent being the Southeastern (34.3%), Southern (31.7%), and Northeastern (28.3%) regions.

Most respondents worked in cities with more than 500 000 inhabitants (74.1%), were not in a leadership position (66.2%), had work stability (74.5%), and worked in two or three different places (59.7%). They spent 6 to 20 hours per week with household chores (54.8%) and up to 5 hours with leisure activities (59.0%). About 64% of the respondents earned US$ 1000 to US$ 4000, and 57.6% reported wage loss of as much as 50% during the pandemic. They reported good work conditions (61%) and availability of proper personal protective equipment (61.5%).

Most respondents reported having a good quality of life (71.7%) and being satisfied with their health (55%), while 64.8% reported not really enjoying life, almost 80% reported believing their lives had a purpose and 90.4% acknowledged that caring for others brought meaning to their lives. They considered the following aspects of their lives satisfactory: sleep, 62.9%; ability to perform daily chores, 54.7%; capability for work, 64.4%; personal relationships, 57.7%; support from friends, 61%; conditions of the household, 84%; and access to healthcare, 81.4%. Only 36.6% considered their sexual life satisfactory, and about 94% had, at least occasionally, negative feelings. Only 37% reported experiencing enough energy for daily tasks, and 48.6% accepted their physical appearance.

The respondents believed that spirituality comforted and reassured them (73.2%) and found spiritual force in hard times (70.6%), with good connection of body, mind, and spirit (67.8%), even though only 53.4% reported inner peace and 50.7% reported being optimistic. In addition, 72.7% of the respondents reported finding strength in faith, and 44.3% found support in religious or spiritual communities.

Tables 1 and 2 show the beta regression model for the outcomes 'emotional exhaustion' and 'disengagement', respectively.

For the outcome 'emotional exhaustion' (Table 1), the following were significant: place of work; time allocation for household chores; wage range; poor work environment; very poor quality of life; lack of energy for daily tasks; no time allocation for leisure; dissatisfaction with daily work commute. They reported significant dissatisfaction with their: capability for work; transportation; relationship skills; and sexual life. In addition, they reported experiencing negative feelings frequently.

For the outcome 'disengagement' (Table 2), the following were significant: marital status; place of work; time allocation for household chores; income reduction/increase during the pandemic; poor work environment; inability to concentrate; feeling unsafe on a daily basis; unhealthy physical environment; lack of energy for daily tasks; non-acceptance of physical appearance; great dissatisfaction with their ability for daily tasks, with their sexual life and with their capability for work; inability to remain optimistic in times of uncertainty; caring for others did not bring meaning to their lives; and considering that physical pain prevented them from doing what needed to be done.

In the classification tree corresponding to the outcome 'emotional exhaustion' (Figure 1), the respondents represented in leaves 12 (n=58, 7.5%), 13 (n=43, 5.6%) and 16 (n=35, 4.5%) had the highest scores of burnout, with mean and median equal to or greater than 3.4 (corresponding to 0.8 in the scale from 0 to 1). The respondents represented in leaves 12 and 13 reported experiencing very little or no energy for daily tasks and very frequent negative feelings. These two groups differed regarding their capability for work, and those in leaf 12 reported great dissatisfaction with that. The respondents in leaf 16 reported experiencing little energy for daily tasks and no or very few negative feelings, and not having good quality of life.

In the classification tree corresponding to the outcome 'disengagement' (Figure 2), the respondents represented in leaves 3 (n=97, 12.6%) and 5 (n=29, 3.8%) had the highest scores of burnout, with mean and median over 2.8 (corresponding to 0.6 in the scale from 0 to 1). The 97 respondents in leaf 3 reported dissatisfaction with their capability for work and having very little or no energy for daily tasks. However, the 29 respondents in leaf 5, despite their dissatisfaction with their capability for work and not acknowledging that caring for others brings meaning to life, considered having enough energy for their daily tasks.

For the outcome 'emotional exhaustion' related to women physicians with burnout, the polychoric correlation coefficient (Supplementary Material 3) identified that having negative feelings had a negative correlation with satisfaction with their sexual life and personal relations, and energy for daily tasks. Requiring medical treatment to cope with daily life correlated negatively with the presence of energy for daily tasks. However, lack of energy for daily tasks correlated positively with poor quality of life and dissatisfaction with capability for work (Figure 3).

For the outcome 'disengagement' related to women physicians with burnout, the polychoric correlation coefficient (Supplementary Material 3) identified that difficulty in concentrating correlated positively with

Table 1 – Beta regression model for the dimension of burnout emotional exhaustion, one of the dimensions of Burnout (Oldenburg Burnout Inventory)

Predictive variables	Estimate (95% CI)	p
Workplace (suburb or surroundings of a big city)	0.328 (0.139; 0.516)	0.001 ***
Workplace (mid-sized city)	0.358 (0.105; 0.611)	0.006 **
Workplace (small city)	-0.265 (-0.571; 0.04)	0.089 .
Time allocation for household chores (6-10 hours/week)	-0.05 (-0.184; 0.084)	0.469
Time allocation for household chores (11-20 hours/week)	-0.139 (-0.259; -0.019)	0.023 *
Time allocation for household chores (> 20 hours/week)	-0.122 (-0.226; -0.018)	0.022 *
Wage range (US$ 500-1000)	0.205 (-0.314; 0.724)	0.439
Wage range (US$ 1000-2000)	-0.374 (-0.816; 0.068)	0.097 .
Wage range (US$ 2000-4000)	0.252 (-0.047; 0.552)	0.099 .
Wage range (> US$ 4000)	-0.233 (-0.412; -0.054)	0.011 *
Work environment (poor)	-0.479 (-0.806; -0.153)	0.004 **
Work environment (regular)	0.193 (-0.084; 0.471)	0.172
Work environment (good)	-0.049 (-0.251; 0.152)	0.630
Work environment (excellent)	-0.005 (-0.136; 0.125)	0.937
Quality of life	-0.186 (-0.261; -0.111)	< 0.001 ***
Physical pain	0.06 (-0.004; 0.124)	0.064 .
Need for treatment	0.067 (0.01; 0.124)	0.020 *
Energy	-0.395 (-0.479; -0.311)	< 0.001 ***
Time allocation for leisure	-0.09 (-0.162; -0.019)	0.013 *
Work commute	0.102 (0.038; 0.167)	0.002 **
Capability for work	-0.183 (-0.258; -0.108)	< 0.001 ***
Satisfaction with personal relations	-0.109 (-0.176; -0.042)	0.001 ***
Satisfaction with sexual life	-0.058 (-0.108; -0.008)	0.023 *
Satisfaction with household	0.07 (-0.001; 0.142)	0.055 .
Satisfaction with transportation	-0.156 (-0.233; -0.078)	< 0.001 ***
Negative feelings	0.246 (0.181; 0.311)	< 0.001 ***

*Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1*

dissatisfaction with capability for work and feeling unsafe on a daily basis. The inability to remain optimistic in times of uncertainty correlated positively with feeling unsafe on a daily basis and the inability to see meaning for their lives in caring for others. The lack of energy for daily tasks correlated positively with dissatisfaction with capability for work (Figure 3). These network analysis findings corroborate those in the classification tree and beta regression.

Discussion

This study showed a high frequency of burnout among these Brazilian women physicians (61.6%) who answered the survey. Regarding the outcome 'emotional exhaustion,' women physicians with burnout have little or no energy for daily tasks, negative feelings, and dissatisfaction with their capability for work. Regarding the outcome 'disengagement', women physicians with burnout reported dissatisfaction with their ability for work, little or no energy for daily tasks, and not adding meaning to their lives from caring for others, which threaten their quality of life. Nevertheless, they presented with a relatively good quality of life and believed that spirituality comforted and reassured them in hard times.

Burnout has been defined as a psychological syndrome that results from chronic stress at work, and its key dimensions are exhaustion, cynicism, and lack of professional efficacy.[23] The condition is compounded by the COVID-19 pandemic that challenges mental health, questions personal beliefs, and threatens the quality of life of HCPs. The problem is aggravated by the household chores traditionally done by women.[24]

Brazil has ranked second in number of COVID-19 cases and deaths. This has stretched the Brazilian healthcare system

Table 2 – Beta regression model for the dimension of burnout disengagement, another dimension of Burnout (Oldenburg Burnout Inventory)

Predictive variables	Estimate (95% CI)	p
Marital status (married or with a partner)	0.231 (0.089; 0.373)	0.001 ***
Marital status (separated or divorced)	0.187 (0.008; 0.366)	0.041 *
Marital status (widow)	0.307 (-0.06; 0.674)	0.101
Workplace (suburb or surroundings of a big city)	0.364 (0.184; 0.544)	< 0.001 ***
Workplace (mid-sized city)	0.239 (-0.008; 0.485)	0.058 .
Workplace (small city)	-0.123 (-0.423; 0.177)	0.422
Workload (21-36 hours)	-0.045 (-0.194; 0.105)	0.560
Workload (37-48 hours)	0.038 (-0.089; 0.166)	0.557
Workload (49-60 hours)	-0.051 (-0.161; 0.059)	0.365
Workload (> 60 hours)	0.084 (-0.008; 0.177)	0.074 .
Time allocation for household chores (6-10 hours/week)	-0.119 (-0.251; 0.013)	0.078 .
Time allocation for household chores (11-20 hours/week)	-0.164 (-0.281; -0.047)	0.006 **
Time allocation for household chores (> 20 hours/week)	-0.238 (-0.338; -0.139)	< 0.001 ***
Time allocation for leisure (6-10 hours/week)	0.167 (-0.032; 0.366)	0.101
Time allocation for leisure (11-20 hours/week)	0.16 (-0.011; 0.33)	0.067 .
Time allocation for leisure (> 20 hours/week)	0.057 (-0.08; 0.194)	0.417
Pandemic income (20% reduction)	-0.141 (-0.282; 0)	0.050 *
Pandemic income (21-50% reduction)	0.016 (-0.119; 0.15)	0.820
Pandemic income (≥ 50% reduction)	0.134 (0.006; 0.262)	0.040 *
Pandemic income (increase)	0.114 (0.005; 0.223)	0.041 *
Work environment (poor)	-0.454 (-0.756; -0.153)	0.003 **
Work environment (regular)	0.01 (-0.242; 0.262)	0.938
Work environment (good)	-0.1 (-0.283; 0.083)	0.283
Work environment (excellent)	0.059 (-0.061; 0.178)	0.336
Physical pain	0.082 (0.027; 0.137)	0.004 **
Concentration	-0.144 (-0.226; -0.062)	0.001 ***
Life safety	-0.142 (-0.225; -0.059)	0.001 ***
Healthy environment	-0.12 (-0.193; -0.047)	0.001 ***
Energy	-0.201 (-0.283; -0.12)	< 0.001 ***
Acceptance of physical appearance	-0.065 (-0.125; -0.005)	0.034 *
Satisfaction with ability to perform daily tasks	0.109 (0.031; 0.187)	0.006 **
Capability for work	-0.249 (-0.332; -0.167)	< 0.001 ***
Satisfaction with sexual life	-0.08 (-0.128; -0.032)	0.001 ***
Caring for others adds meaning to life	-0.236 (-0.311; -0.161)	< 0.001 ***
Optimism	-0.12 (-0.188; -0.052)	0.001 ***

*Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1*

to the limit, affecting the care provided to patients with not only COVID-19, but other acute and chronic diseases as well. Almost all HCPs, especially physicians, have been involved in the fight against the pandemic.[25] According to Scheffer et al., Brazil has 477 982 physicians, 222 942 of whom are women, predominantly young, living in the Southeastern, Southern, and Northeastern regions, and most of them (59.5%) having a medical specialist title. Medicine in Brazil is undergoing

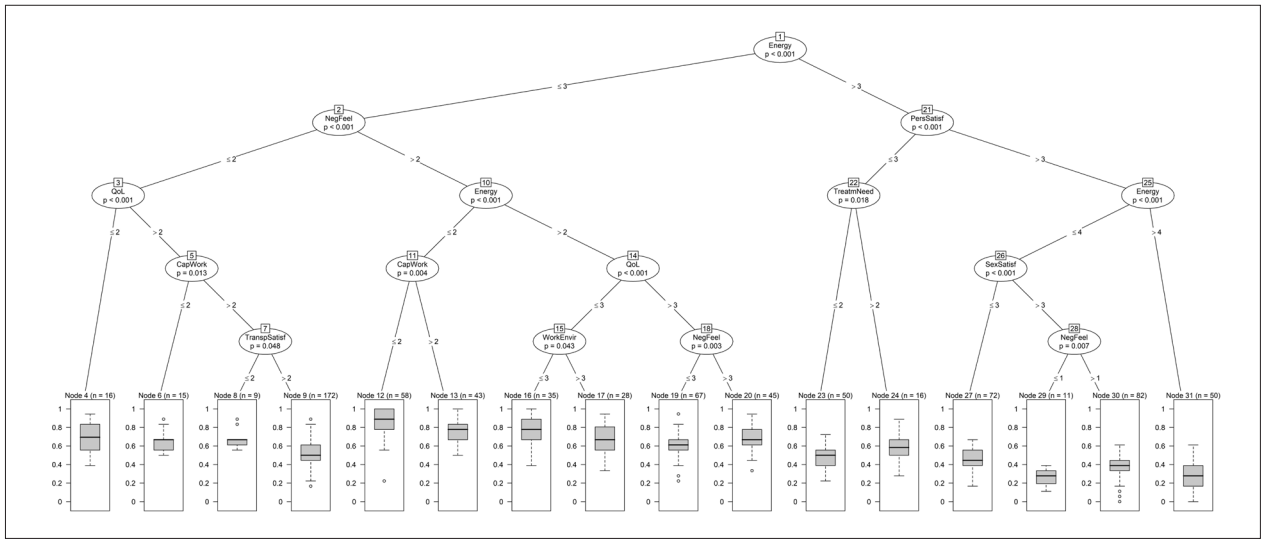

Figure 1 – *Classification tree corresponding to the outcome 'emotional exhaustion,' one of the dimensions of Burnout (Oldenburg Burnout Inventory). WorkEnvir: work environment; CapWork: capability for work; TreatmNeed: need for medical treatment; QoL: quality of life; NegFeel: negative feelings; PersSatisf: satisfaction with personal relations; SexSatisf: satisfaction with sexual life; TranspSatisf: satisfaction with transportation.*

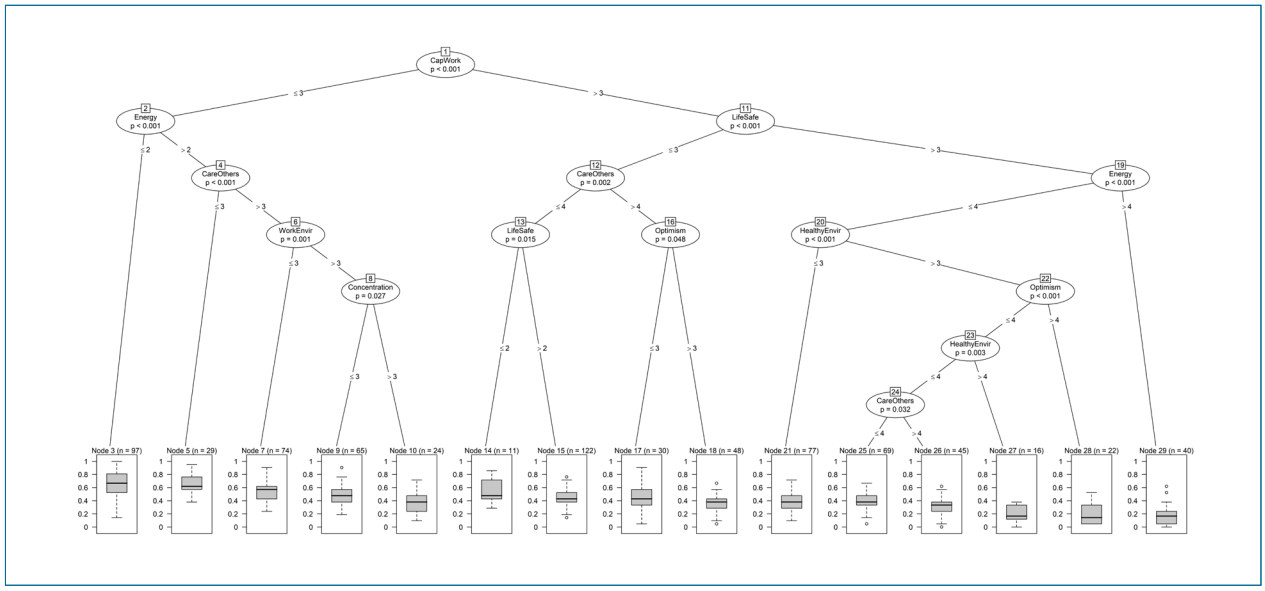

Figure 2 - *Classification tree corresponding to the outcome 'disengagement.', another dimension of Burnout (Oldenburg Burnout Inventory). CapWork: capability for work; CareOthers: care for others; HealthyEnviron: healthy environment; LifeSafe: life safety; WorkEnvir: work environment.*

feminization.[26] The distribution of our sample's characteristics is in accordance with that reported in the study by Scheffer et al.

Our study showed a higher prevalence of burnout (61.6%) among Brazilian women physicians as compared to other studies.[1-3,7-9] The ever-growing number of COVID-19 suspected and confirmed cases, huge workload, shortage of personal protective equipment, overwhelming media coverage, lack of specific medications, and the feeling of insufficient support may be contributing to the psychological damage to HCPs. Many of them feared to get infected or infect their families, friends, and colleagues, and reported high levels of stress, anxiety, and depression symptoms, which may have long-term psychological implications.[27,28]

In our study, most respondents reported having good quality of life and believing that their lives had a purpose and that caring for others brought meaning to their lives. In addition, they reported still having to overcome barriers in exercising their profession and receiving lower pay than their male counterparts. A large number reported frequent negative feelings, dissatisfaction with sexual life, and lack of sufficient energy for daily tasks, in addition to dissatisfaction with their physical appearance. Such findings might have been

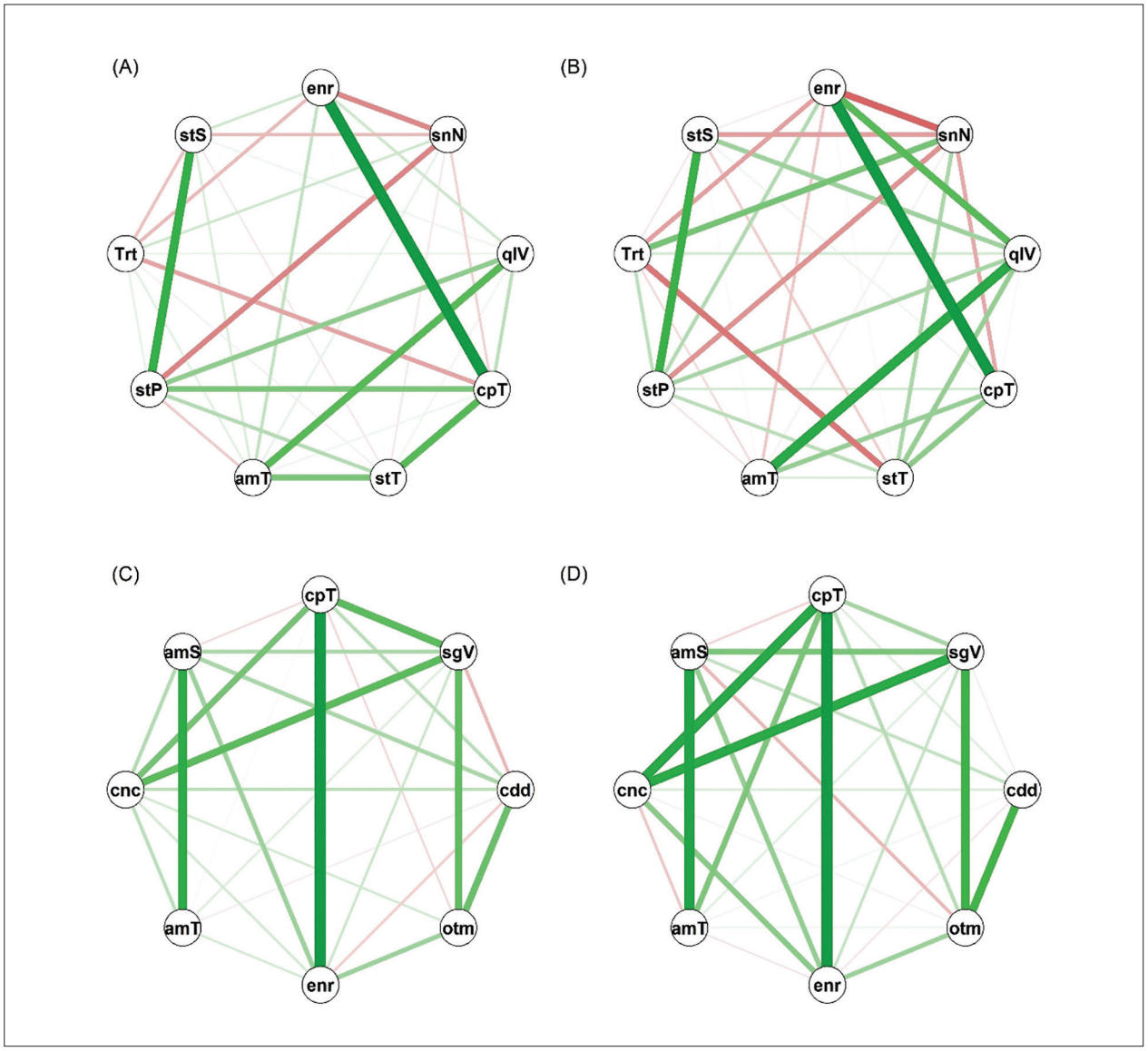

Figure 3 – *The polychoric correlation matrix is a network where the nodes were the variables, and the weights on the edges represented the polychoric correlation coefficient. The thickness of the edges and the transparency were given by the correlation coefficient's magnitude between the nodes. Dimensions of Burnout (Oldenburg Burnout Inventory): (A) Emotional exhaustion without burnout; (B) Emotional exhaustion with burnout; (C) Disengagement without burnout; (D) Disengagement with burnout. (*). With burnout: amS: healthy environment; amT: work environment; cdd: caring for others adds meaning to life; cnc: concentration; cpT: capability for work; enr: energy; otm: optimism in challenging times; qlV: quality of life; sgV: life safety; snN: negative feelings; stP: satisfaction with personal relations; stS: satisfaction with sexual life; stT: satisfaction with transportation; Trt: need for medical treatment. (*) More details for understanding the polychoric correlation matrix can be seen in the supplementary material.*

influenced by the effects of the pandemic on a country with a huge challenge to the health system.[25] Such findings are similar to those of the study with Turkish physicians, reporting that those involved in the fight against COVID-19 reported a strong sense of meaningfulness of work.[29] However, the frequency of burnout was much higher among Brazilian women physicians, which may be related to the magnitude of the effects of the pandemic in Brazil.

Medical practice is permeated by experiences of loss, stress, anxiety, and fear, which increase the psychological vulnerability of physicians and facilitate the appearance of anxiety-depression symptoms. In addition, resilience, spirituality, and personal beliefs seem to play a mediating role in some of these psychological variables. No study has assessed how these variables affect the exhaustion and psychological suffering of women physicians, mainly those acting in a country facing a broken health system.[30] We observed that women physicians rely on spirituality for comfort and reassurance, find spiritual strength in challenging times, and believe in getting strength for the daily challenges from faith.

In our study, the novel use of machine learning identified for the outcome 'emotional exhaustion' that women physicians with burnout often have little or no energy for daily tasks and negative feelings. For the outcome 'disengagement', women physicians reported dissatisfaction with their capability for work, little or no energy for daily tasks, and not adding meaning to their lives from caring for others (Figures 1 and 2). To our knowledge there is no assessment of burnout among women physicians using artificial intelligence techniques, which is the strength of our study.

In addition to confirming the beta regression and classification tree findings of women physicians with burnout, the network analysis (Figure 3) evidenced the correlation of their negative feelings with their dissatisfaction with personal relations and sexual life, as well as with their lack of energy for daily tasks. Moreover, it evidenced the correlation of their poor quality of life with their dissatisfaction with capability for work and their lack of energy for daily tasks, as well as the correlation of their difficulty to concentrate with their feeling of unsafety, which, in turn, correlated with their inability to remain optimistic in times of uncertainty. Moreover, this analysis showed graphically the strength of the relationship between the variables identified in the machine learning technique. Another study using this type of analysis has shown the association of elevated emotional exhaustion with arterial hypertension and other chronic diseases,[6] even outside the pandemic period.

A limitation of this study is it is a convenience sample, and the high frequency of burnout may be due to a sample bias; women with more problems may have answered the questionnaire more than other women. Although the distribution of the sample's characteristics is similar to that observed in the study of medical demography in Brazil.[26] The strength of this study is the joint analysis using machine learning of Burnout conditions, quality of life, and spirituality and their interrelationships during the COVID19 pandemic in female doctors, who faced the most significant challenges in dealing with unique working and living conditions personnel, in a country beset by cases and deaths related to SARS-COV-2 infection.

The pandemic's socioeconomic effects and how it affects a healthy lifestyle, as well as the female selfcare, well-being sensation, and quality of life represent major threats to the healthcare of women physicians with burnout. Yet, most of the time they are neither acknowledged nor addressed. In countries like Brazil, facing many cases and deaths, this challenge is bigger because of the inequalities of a continental country without target policies for physicians' health, especially for women physicians challenged by triple workload in pandemic times.

Therefore, it is essential to develop future studies to recognize the prevalence of burnout and its overwhelming impact on different populations to properly address it and prevent it. Our findings highlight the importance of creating an environment conducive to the construction of positive work relationships. In addition, government and healthcare agencies should provide resources and invest to protect healthcare professionals' psychological well-being by creating mental health programs. In parallel to this, partnerships with other social institutions should be established and remote assistance systems implemented, driven by resilience and comprehension of their unique situation, to help women physicians with burnout.

Conclusion

This study showed a high frequency of burnout among Brazilian women physicians who answered the survey during the COVID-19 pandemic. Nevertheless, they presented with a relatively good quality of life and believed that spirituality comforted and reassured them in hard times.

Author Contributions

Conception and design of the research: Oliveira GMM, Lemke VG, Paiva MSMO, Mariano GZ, Silva ERGA, Silva SCTF, Santos MA, Barbosa ICQ, Lantieri CJB, Duarte ER, Izar MCO, Anzolch KJ, Gerez MAE, Ramos MVO, Lopes MAAAM, Nascimento EM; Acquisition of data: Oliveira GMM, Lemke VG, Paiva MSMO, Mariano GZ, Silva ERGA, Silva SCTF, Santos MA, Barbosa ICQ, Lantieri CJB, Duarte ER, Izar MCO, Anzolch KJ, Gerez MAE, Ramos MVO, Lopes MAAAM; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Oliveira GMM, Lemke VG, Paiva MSMO, Mariano GZ, Silva ERGA, Silva SCTF, Santos MA, Barbosa ICQ, Lantieri CJB, Duarte ER, Izar MCO, Anzolch KJ, Gerez MAE, Ramos MVO, Lopes MAAAM, Nascimento EM, Wenger NK; Statistical analysis: Oliveira GMM, Lemke VG, Paiva MSMO, Nascimento EM; Writing of the manuscript: Oliveira GMM, Lemke VG, Paiva MSMO, Wenger NK

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 Supplemental Material 1, please click here.

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Much More Than Just Women: Wonder Women

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Short Editorial related to the article: Women Physicians: Burnout during the COVID-19 Pandemic in Brazil

The impact of the SARS-Cov2 pandemic hit the world quickly and overwhelmingly and highlighted the heroes of the white cover: healthcare professionals. It took more than two years of uninterrupted work, facing various challenges and external and internal conflicts to preserve the patient's life, colleagues, their families and themselves. A complicated scenario, not only due to the overload of professional demand but also the scientific lack of knowledge of what we were facing. Scientists worldwide have joined forces to disseminate scientific evidence, and, at the same time, medical societies have mobilized to optimize care procedures with protection for active professionals.[1]

Stress and Burnout syndrome are part of occupational diseases in health professionals.[2] However, the particular scenario of Covid-19 has shown that although it is not easy to be on the front lines in the fight against SARS-CoV2, nurses and doctors demonstrated high stress and exhaustion in studies, so behavioral/collective strategies can help.[3-6] This mini-editorial is dedicated to female doctors.

In addition to the challenges in the roles of woman, mother, daughter, friend, companion, housewife and many others, they also struggled in exhausting journeys to take care of the patient. In the study by Oliveira et al.,[7] women, who historically have a double shift, found themselves in Burnout during the SARS-cov2 Pandemic in Brazil. There were many accumulated demands, such as working hours in two or three different places, household chores, little leisure time and loss of salary, but they also struggled to maintain creativity and maintain a good quality of life. More than doctors, true Wonder Women sought spirituality, comfort, safety and stress reduction.

The pandemic has brought to light challenges that require reflection on our lifestyle and how they impact our quality of life. Doctors demonstrate bravery, courage and determination but still need more care for their well-being. Strategies to deal with difficult situations and cultivate well-being must be implemented in medical centers so their employees can experience and practice them. In addition to physical exercise and a balanced diet, behavioral tools such as cultivating positive thoughts and feelings of gratitude, practicing different forms of meditation, Yoga, Tai Chi or other practices similar can also calm the mind and reduce stress.[8-10]

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Keywords

COVID-19; SARS-CoV2; Pandemics; Betacoronavirus; Medicals; Health Occupations; Women/psychology; Professional Practice; Medical Profissional; Efficiency; Staff Development/ethics; Life Style; Epidemiology

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Evaluation of Endothelial Dysfunction in COVID-19 With Flow-Mediated Dilatation

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Abstract

Background: **Inflammation is known to play a crucial role in many diseases, including COVID-19.**

Objective: **Using flow-mediated dilatation (FMD), we aimed to assess the effects of inflammation on endothelial function in COVID-19 patients.**

Methods: **This study was conducted with a total of 161 subjects, of whom 80 were diagnosed with COVID-19 within the last six months (comprising 48 women and 32 men with a mean age of 32.10 ± 5.87 years) and 81 were healthy controls (comprising 45 women and 36 men with a mean age of 30.51 ± 7.33 years). We analyzed the findings of transthoracic echocardiography and FMD in all subjects. All results were considered statistically significant at the level of $p < 0.05$.**

Results: **The echocardiography and FMD of the COVID-19 group were performed 35 days (range: 25-178) after diagnosis. There was no statistically significant difference in echocardiographic parameters. Differently, FMD (%) was significantly higher in the control group (9.52 ± 5.98 vs. 12.01 ± 6.18, p=0.01). In multivariate analysis with the forward stepwise model, FMD was significantly different in the control group compared to the COVID-19 group (1.086 (1.026 - 1.149), p=0.04). A Spearman's correlation test indicated that FMD (r=0.27, p=0.006) had a weak positive correlation with the presence of COVID-19.**

Conclusion: **Our findings point to COVID-19-induced endothelial dysfunction, as assessed by FMD, in the early recovery phase.**

Keywords: **COVID-19/complications; Endothelial, Cells/infection; Endothelium Vascular/injuries; Diagnostic Imaging/methods; Echocardiography/methods; Ultrasonography/methods; Flow Dilatation; Myalgia; Olfaction Disorders; Taste Disorders.**

Introduction

A new type of coronavirus disease emerged in December 2019 and was named COVID-19 by the WHO. It primarily infects the respiratory tract and has spread rapidly around the world.[1]

As RNA viruses that can rapidly mutate and recombine, coronaviruses are known to primarily infect the respiratory tract or intestinal tract in humans and animals.[2] Coronaviruses enter the host cell by binding to the zinc peptidase angiotensin-converting enzyme 2, a surface molecule found in the endothelial cells of arteries and vessels, the respiratory tract epithelium, the arterial smooth muscle, the small intestinal epithelium, and immune cells.[3-5]

Endothelial activation and dysfunction develop as a result of endothelial cells being infected with COVID-19.[6] They lead to increased levels of pro-inflammatory cytokines (tumor necrosis factor-alpha, interleukin-1, and interleukin-6), chemokines (monocyte chemoattractant protein-1), von Willebrand factor (vWF) antigen, vWF activity, anti-hemophilic factor (AHF), and acute-phase reactants (IL-6, C-reactive protein, and D-dimer).[6]

Although COVID-19 primarily affects the upper and lower respiratory tracts, the vascular endothelium is another known target. Endothelial dysfunction may be caused directly by the activity of the virus or by the resulting systemic inflammatory response. Flow-mediated dilatation (FMD), which is a non-invasive ultrasonographic method, has been widely used to evaluate endothelial dysfunction due to its simplicity and cost-efficiency.[7] Several studies have addressed the effect of FMD on various inflammatory diseases such as rheumatoid arthritis, peripheral vascular disease, coronary artery disease, diabetes mellitus, and hypertension. To date, as far as we know, there are only a few reports on FMD being used to evaluate COVID-19.[8,9]

In this study, we used FMD to investigate the potential abnormal effects of COVID-19 on the vascular function of patients recovered from a COVID-19 infection.

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Methods

This single-centered study was carried out at Abant Izzet Baysal University Training and Research Hospital between October 2020 and February 2021. The study included 80 subjects diagnosed with COVID-19 within the last six months who did not require hospitalization and 81 healthy control subjects, with an age distribution of > 18 and < 45 years. All the COVID-19 patients were cured and free from symptoms at the time of study entry.

The exclusion criteria were as follows: age > 45 years, any presence of coronary artery disease, left ventricle systolic dysfunction (EF < 50%), moderate to severe valvular disease, congenital heart disease, atrioventricular conduction abnormality, moderate to severe kidney or liver disease, thyroid disease, electrolytic imbalance, systemic inflammatory disease, or poor acoustic echocardiography window. The study protocol was approved by the Local Ethics Committee and a written informed consent form was signed by each subject before participation.

Based on the COVID-19 Diagnosis and Treatment Plan by the National Health Commission (7th edition), COVID-19 cases were classified into four clinical types: mild (characterized by mild clinical symptoms without pneumonia on radiological imaging), common (characterized by fever, involvement of the respiratory tract, and other symptoms with pneumonia on radiological imaging), severe (characterized by respiratory distress, respiratory rate of ≥ 30 times/min, oxygen saturation ≤ 93% at rest, PaO2/FiO2 ≤ 300 mmHg), and critical (characterized by respiratory failure requiring mechanical ventilation, shock, and failure of another organ requiring monitoring and treatment at an intensive care unit).[10]

Lung involvement was classified using the "total severity score" (TSS) based on an assessment of chest computed tomography (CT) imaging. For this purpose, the percentages of involvement calculated for each of the five lobes were converted into one of the following score categories: none (0%) (Score 0), minimal (1-25%) (Score 1), mild (26-50%) (Score 2), moderate (51-75%) (Score 3), and severe (76-100%) (Score 4). Finally, the sum of all the scores yielded a TSS value ranging from 0 to 20.[11]

Laboratory parameters were obtained from hospital medical records at COVID-19 infection diagnosis. Laboratory data from the control group were obtained at study entry.

Patients and control subjects were evaluated with echocardiography and brachial Doppler ultrasonography for FMD measurement at study entry.

Echocardiographic evaluation

We used a Vivid S6 4-Mhz transducer (GE Vingmed, N-3191 Horten-Norway) to perform the required echocardiographic procedures.

All echocardiographic images were obtained using continuous ECG monitoring by a single-blind cardiologist with the subjects in the left lateral position. We considered the mean of three consecutive cardiac cycles and measured left ventricular end-diastolic and end-systolic diameters, left ventricular posterior wall thickness, left ventricular septum thickness, and left atrium diameters. A biplane modfied simpson's method was applied for measuring left ventricular ejection fraction. We performed two-dimensional and pulsed Doppler measurements based on the American Society of Echocardiography criteria[12].

Ultrasonographic evaluation

The parameters were measured in a quiet, dark, and air-conditioned room (i.e. room temperature of 22 - 25°C) after a rest period of at least 15 minutes. In addition, subjects were asked to fast and to avoid exercising, smoking, and consuming alcohol or caffeine for at least 8 hours before FMD measurements. We used a 7.5 MHz linear array transducer (GE Healthcare, M4S-RS, Tokyo, Hino-Shi, Japan) to measure the brachial artery diameter at the antecubital fossa. The skin was marked with a pencil, and thus all measurements were performed on the same line. We started with the basal diameter and flow rate of the brachial artery and then increased the pressure up to 50 mmHg above systolic blood pressure, and waited for 5 minutes at this level, so the arm remained ischemic. Then cuff pressure was lowered, and the diameter and flow rate of the brachial artery were measured again at 1 minute after pressure decrease.

FMD was calculated using the following equation:

FMD=100 x (maximum diameter at the 1st minute-baseline diameter)/baseline diameter.[13]

Statistical analysis

All statistical analyses were performed using SPSS 18.0 Statistical Package Software for Windows (SPSS Inc., Chicago, IL, USA). Normality data of the variables were evaluated with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were described using the mean and standard deviation; continuous variables without normal distribution were described using the median and interquartile range. The data are shown as numbers or percentages for qualitative variables. To analyze differences between independent groups, we used the Student's t-test (two-tailed) for normally distributed quantitative variables, the Mann-Whitney's U-test for variables without normal distribution, and the Chi-square test for qualitative variables. Spearman's correlation analyses were conducted to evaluate correlations between COVID-19 and lymphocyte level, neutrophil/lymphocyte ratio, glucose and creatinine levels, and FMD. For variables found to be significant in the univariate regression analysis, we employed multivariate logistic regression with the forward stepwise model to establish the independent prognostic factors of COVID-19. Spearman's correlation test was also performed between FMD and time elapsed from diagnosis. All results were considered statistically significant at the level of $p < 0.05$.

Results

Baseline clinical characteristics were similar between both groups. Among laboratory parameters, glucose,

creatinine, and neutrophil/lymphocyte ratio were significantly higher; lymphocyte counts were significantly lower in the COVID-19 group compared to the control group (Table 1).

Myalgia (65 %) and loss of smell and/or taste (61 %) were the most common symptoms in COVID-19 patients, whereas sweating was (8 %) the least common one (Table 2). None of the COVID-19 patients had a serious infection that required hospitalization. In our study, the patients belonged either to the mild type or the common type, according to the clinical classification, with TSS scores ranging from 0 to 5.

Echocardiography and FMD of the COVID-19 group were performed 35 days (25-178; IIQ: 38.5) after diagnosis. Echocardiographic measurements were similar between the two groups, whereas compared to the control group FMD (%), it was significantly lower in the COVID-19 patients (9.52 ± 5.98 vs. 12.01 ± 6.18, p=0.010) (Table 3). Spearman's correlation test showed that there was no statistically significant relation between FMD and the time elapsed after COVID-19 diagnosis (r=0.064; p=0.527).

Significantly different parameters in the univariate regression analysis (glucose, creatinine, lymphocyte, neutrophil/lymphocyte ratio, and FMD) were included in the multivariable regression analysis and only the FMD value was significantly different in the control group compared to the COVID-19 group (1.086 (1.026 – 1.149), p=0.04) (Table 4).

Spearman's correlation test showed that FMD (r=0.27, p=0.006) had a weak positive correlation with the presence of COVID-19.

Table 1 – Demographic and laboratory variables of the study population

Variables		COVID-19 (n= 80)	Control Group (n=81)	p
Demographics				
Age (years)		32.10±5.87	30.51±7.33	0.407
Male/Female (n(%))		32/48 (40/60%)	36/45 (44/56%)	0.313
SBP (mmHg) (IIQ)		105 (14)	110 (22)	0.307
DBP (mmHg) (IIQ)		70 (15)	70 (20)	0.343
Height (cm)		169.36±8.72	169.36±9.30	0.997
Weight (kg)		73.81±13.73	71.30±16.09	0.289
BMI (kg/m^2)		25.63±3.74	25.00±4.13	0.198
Hypertension n (%)	No	78 (97.5%)	79 (97.5%)	1.000
	Yes	2 (2.5%)	2 (2.5%)	
Diabetes mellitus n (%)	No	78 (97.5%)	81 (100.0%)	0.245
	Yes	2 (2.5%)	0 (0.0%)	
Hyperlipidemia n (%)	No	79 (98.8%)	80 (98.8%)	1.000
	Yes	1 (1.3%)	1 (1.2%)	
Family History of CAD n (%)	No	54 (67.5%)	59 (72.8%)	0.459
	Yes	26 (32.5%)	22 (27.2%)	
Smoking n (%)	No	61 (76.3%)	58 (48.7%)	0.502
	Yes	19 (23.8%)	23 (28.4%)	
Laboratory parameters				
Fasting Plasma Glucose (mg/dL) (IIQ)		93.50 (16.75)	91 (14)	0.038
Creatinine (mg/dL) (IIQ)		0.78 (0.19)	0.74 (0.11)	0.042
Hemoglobin (g/dL) (IIQ)		14.20 (2.05)	14.40 (1.95)	0.875
Hematocrit (%) (IIQ)		42.30 (5.51)	42.90 (5.40)	0.851
Platelet counts (K/uL) (IIQ)		250 (90.25)	263 (76.50)	0.659
Lymphocyte counts (K/uL) (IIQ)		1.83 (1.14)	2.24 (0.89)	0.017
Neutrophil counts (K/uL) (IIQ)		4.15 (2.12)	3.82 (1.73)	0.291
Neutrophil/ lymphocyte ratio (IIQ)		2.05 (1.63)	1.30 (1.06)	0.044

IIQ: Interquartile Range; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index.

Table 2 – Symptoms experienced by the COVID-19 patients

Symptoms	Number	%
Myalgia	52/80	65
Loss of smell and/or taste	49/80	61
Weakness	33/80	41
Headache	32/80	40
Cough	28/80	35
Fever	25/80	31
Dyspnea	19/80	24
Sore throat	15/80	19
Nausea	15/80	19
Diarrhea	13/80	16
Sweating	7/80	8

Discussion

The purpose of this study was to assess the vascular repercussions of COVID-19 using impaired FMD as a surrogate marker of endothelial dysfunction. Our study demonstrated that the FMD value was lower in COVID-19 patients compared to the control group. These results point to vascular involvement by COVID-19, as assessed by FMD, even in mildly affected patients. Within the limits of our knowledge, this is the first study to show vascular endothelial dysfunction defined by impaired FMD among young patients recovering from a mild COVID-19 infection.

We found a significant reduction in FMD even in such mildly affected patients early after recovery. This raises the question of whether the disease may have long-term abnormal effects on vascular function. Similarly to our findings, Ergul et al.[8] included 63 COVID-19 patients two months after recovery and found COVID-19 infection and increased body mass index as independent predictors of endothelial dysfunction evaluated by FMD.[8]

Likewise, Riou et al.[9] found a significant decrease in FMD among 16 mild-to-moderate COVID-19 patients, whereas FMD tended to be lower among 9 severe-to-critical COVID-19 patients three months after disease onset.[9] Contrary to these reports, we studied mildly affected non-hospitalized COVID-19 patients 35 days (25-178) after disease onset.

Endothelial dysfunction, associated with oxidative stress, is known to be the earliest factor for many diseases.[14] Although inflammation is part of the body's normal repair response to healing and is essential in protecting our body from infections and dangerous environmental substances, it would be overly optimistic to say that it is completely beneficial. When it gets out of control, it can become detrimental and destructive to the body.[15] Likewise, it is known that systemically out-of-control inflammation is associated with adverse COVID-19 outcomes.[16]

In a study where FMD was used to predict future cardiovascular events in patients who had undergone coronary bypass surgery, the lowest event rate was determined in patients with normal FMD (>8%), while a moderate event rate and the highest event rate were

Table 3 – Echocardiographic measurements of the study population

Variables	COVID-19 (n= 80)	Control Group (n= 81)	p
Left atrium diameter (cm)	3.03±0.5	2.92±0.32	0.332
LVDD (cm)	4.48±0.45	4.45±0.42	0.281
LVSD (cm)	2.80±0.30	2.81±0.29	0.711
PW (cm)	0.96±0.14	0.96±0.13	0.550
IVS (cm)	0.92±0.16	0.90±0.14	0.742
EF (%)	67.27±5.02	65.90±4.64	0.151
Transmitral E wave (cm/s) (IIQ)	96.9 (23.3)	94.7 (22.5)	0.409
Transmitral A wave (cm/s) (IIQ)	68.0 (16.1)	69.0 (15.3)	0.533
Mitral DT (ms) (IIQ)	198 (45)	188 (57)	0.531
Lateral E' (cm/s) (IIQ)	12.2 (3)	12.5 (3.5)	0.414
Lateral A' (cm/s) (IIQ)	9.35 (2.5)	9.0 (3)	0.515
Lateral S' (cm/s) (IIQ)	9.5 (2)	10.0 (2.1)	0.066
TAPSE (cm) (IIQ)	2.19 (0.44)	2.16 (0.40)	0.537
sPAB (mmHg)	23.79±5.13	25.14±5.63	0.268
FMD (%)	9.52±5.98	12.01±6.18	0.010

**LVDD: left ventricular diastolic diameter; LVSD: Left ventricular systolic diameter; PW: posterior wall; IVS: interventricular septum; EF: Ejection fraction; IIQ: Interquartile Range; DT: deceleration time; E': peak early diastolic myocardial tissue velocity; A': peak late diastolic myocardial tissue velocity; S: mitral annular systolic myocardial velocity; FMD: Flow-mediated dilatation; TAPSE: tricuspid annular plane systolic excursion; sPAB: systolic pulmonary artery pressure.*

Table 4 – Independent predictors of COVID-19 by multivariate logistic regression analysis

	OR (95%CI)	p
Glucose	0.981 (0.957–1.005)	0.116
Lymphocyte	1.022 (0.646–1.616)	0.926
Neutrophil/lymphocyte ratio	0.895 (0.744–1.077)	0.240
Creatinine	0.093 (0.005–1.595)	0.101
FMD	1.086 (1.026–1.149)	0.004

*FMD: flow-mediated dilatation; CI: Confidence interval; OR: Odds ratio.

found in patients with an FMD value of 4 to 8% and <4%, respectively.[17] In another study, patients with an FMD less than 6.2% had significantly lower ankle/brachial index compared to those with an FMD greater than 6.2%.[18] In addition, Maruhashi et al.[19] showed that FMD had an inverse correlation with the Framingham Risk Score, commonly used as a risk calculator and an index of cumulative cardiovascular risk for assessing the probability of a heart attack or death from heart disease within 10 years.[19]

Independent predictive factors of mortality from COVID-19 include advanced age, comorbidities such as diabetes mellitus (DM), cardiovascular disease or cancer, and chronic obstructive pulmonary disease at presentation.[20] However, neither infants nor children showed a significant increase in both morbidity and mortality during the COVID-19 pandemic.[21]

With increased age and age-related diseases, the chronic inflammatory state becomes dominant, and the anti-inflammatory response of the immune system becomes erratic and unable to suppress the inflammatory episode in a timely and effective manner.[22] In our study, we aimed to exclude the effects of such advanced age-related inflammation by including subjects under the age of 45 years.

Although still within the normal range, the COVID-19 patients had significantly slightly higher levels of blood glucose and creatinine than those of the control group. During the acute phase of infection, blood glucose levels may rise abnormally in patients under COVID-19 stress, even if they are not diagnosed with diabetes mellitus. Renal function has been also reported to be abnormally affected. High levels of blood glucose in COVID-19 patients can predict worse outcomes regardless of a DM history.[23] Kidney disease is associated with increased mortality from COVID-19.[24] It was found that 14.4% of 701 hospitalized patients with COVID-19 had increased serum creatinine levels, 13.1% had a decreased glomerular filtration rate, and approximately 5% had acute kidney injury.[24] Histopathological findings revealed acute tubular injuries, different impairments of the glomeruli, tubular necrosis, and glomerulosclerosis.[25] Our finding of slightly increased blood glucose and creatinine levels may be an incidental finding but also may suggest subclinical kidney injury and/or ongoing stress.

Lymphopenia has been used in the diagnosis of COVID-19 and has been associated with a poor prognosis.[26] The severity of COVID-19 was also correlated with the neutrophil/lymphocyte ratio and the lymphocyte/CRP ratio.[27] Accordingly, compared to the control group, lymphocyte counts were decreased and NLR was increased in our mild COVID-19 study subjects.

Limitations

The main limitations of this study lie in the fact that it is single-centered and that it was conducted on a relatively small number of patients. The results are limited to an early point in time during the disease process and cannot be extrapolated to reflect long-term findings. Another limitation is that laboratory parameters were not measured simultaneously with FMD measurement. Due to the exclusion criteria and age limit, the study population was strictly selected, and therefore the results can not represent all COVID-19 patients.

Conclusion

This study showed a decrease in FMD in young patients who were mildly affected by COVID-19 in the early recovery phase. Therefore, this parameter may be used as a marker for COVID-19-induced endothelial dysfunction. Undoubtedly, routine cardiovascular monitoring in patients with a history of COVID-19 may identify patients at risk of future cardiovascular events. To better understand the possible cardiovascular effects in these patients, larger-scale studies including long-term follow-up should be considered.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Mansiroglu AK, Seymen H, Sincer I, Gunes Y; Statistical analysis: Sincer I.

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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 bant Izzet Baysal University Hospital under the protocol number 2021/89. 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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COVID-19 and Late Cardiovascular Manifestations – Building Up Evidence

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Short Editorial related to the article: Evaluation of Endothelial Dysfunction in COVID-19 with Flow-Mediated Dilatation

In early 2020, the world faced the outbreak of a new pandemic, Coronavirus Disease 2019 (COVID-19), caused by a novel coronavirus (SARS-CoV-2 virus). We soon discovered that while the respiratory tract was the prime target, many other organ systems might also be affected. COVID-19 cardiovascular (CV) manifestations are among the most common and feared and may manifest as myocardial injury, arrhythmias, acute coronary syndromes, heart failure, vascular dysfunction, and thromboembolic disease.[1] Both pre-existing and comorbid cardiovascular disease and the concurrent presence of CV risk factors are harbingers of a poorer disease course and prognosis.[2] Notably, acute CV involvement is a strong independent predictor of COVID-19 in-hospital mortality.[3] The way in which the infection interacts with the CV system remains a subject of study, but apart from direct cell injury by the virus, the activation of inflammatory pathways is thought to play a key role. A comprehensive account of the pathophysiology of CV involvement in COVID-19 is beyond the scope of this commentary and has been extensively covered elsewhere.[4]

While it is now clear that both cardiac and vascular dysregulations are to be expected during the active stage of the infection, concerns now focus on long-term residual CV abnormalities. Huang et al.[5] reported that more than half of convalescent COVID-19 patients displayed signs of myocardial inflammation or fibrosis on cardiac magnetic resonance (CMR) imaging.[5] Similarly, the meta-analysis by Kim et al.[6] showed that nearly half of recovered COVID-19 patients exhibited one or more abnormal CMR results.[6] Likewise, and somewhat unsurprisingly, the infection may also induce enduring vascular injury. In light of the tropism of SARS-CoV-2 for membrane-bound angiotensin-converting enzyme 2-expressing cells, it is no wonder that the vascular endothelium is a major player in the infection. Nonetheless, the effects of COVID-19 infection on vascular endothelium and the complex interplay between the two are still poorly understood. In essence, CV homeostasis is primarily dependent on the role of the endothelium. It regulates vascular tone, cell adhesion, thromboresistance, smooth muscle cell proliferation, and ultimately, vessel wall inflammation. Whenever the endothelium is activated, resulting in endothelial dysfunction, cell-signaling shifts from nitric oxide - mediated vasodilatory to vasoconstrictor redox processes. This can occur as a transient acute phenomenon, with little to no consequences, or as a sustained detrimental endothelium activation, eventually leading to a pro-atherogenic, pro-thrombotic milieu.[7]

Endothelium-dependent vasomotion is widely acknowledged as a surrogate marker of endothelial function, and flow-mediated dilation (FMD), originally introduced in the 1990s, is the most endorsed non-invasive method for assessing it.[8]

In the study by Mansiroglu et al.[9] investigators used FMD to uncover subtle vascular involvement in young, mildly affected COVID-19 patients in the early post-infection period. The authors conducted a single-center, well-matched case-control investigation involving 80 recovered Covid-19 patients within 35 days (25-178;IQR: 38.5) of infection. Compared to the controls, the Covid-19 group had no echocardiographic signs of structural or functional cardiac affection from the recent infection. In contrast, they exhibited a significantly lower FMD response (9.52±5.98 *versus* 12.01±6.18, p= 0.010). These results expand on previous studies by restricting enrollment to individuals younger than 45, with mild infection not warranting hospitalization. The exclusion of competing conditions sharing the common denominator of endothelial dysfunction was also a distinctive feature. Notwithstanding, given the short timeframe from infection, it is arguable whether these findings extrapolate to any long-term consequence of the disease. Few studies on FMD response looked at young, otherwise healthy COVID-19 patients, getting equivalent results.[10] Similar findings have also been reported in a broader setting. Oikonomou et al.[11] prospectively studied 73 elder COVID-19 hospitalized patients (37% of whom required intensive care treatment) and found that FMD was significantly ($p < 0.001$) impaired in the COVID-19 group (1.65 ± 2.31%) compared with a propensity score-matched cohort (6.51 ± 2.91%). Another remarkable aspect is that this difference remained significant six months after discharge (5.24 ± 1.62% and 6.48 ± 3.08%, respectively, p=0,01).[11] Consistent with these results, the study by Gao et al., went a step further by demonstrating that FMD was reduced in survivors of COVID-19, even 327 days after diagnosis.[12]

Given the accumulating evidence, the long-term influence of a prior COVID-19 infection on vascular function is compelling. However, regardless of the involved mechanisms, the clinical implications of this vascular affection remain a mystery. Of special concern is the prospect of early onset of atherosclerosis in survivors of COVID-19. In this regard, it is unclear whether this vascular damage will impact on future CV events. As a result, further high-quality prospective

Keywords

Covid-19/complications; Ultrasonography/methods; Flow Dilatation; Endothelium, Vascular; Inflammation.

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longitudinal research on the association between COVID-19-induced endothelial dysfunction and long-term CV outcomes is necessary. As we stand, we are at the outset of unfolding the full long-term consequences of Covid-19-induced vascular injury. The research by Mansiroglu et al.[9], along with others', is ground-breaking.

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Screening, Diagnosis and Management of Atrial Fibrillation in Cancer Patients: Current Evidence and Future Perspectives

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population, carrying a high morbimortality burden, and this also holds true in cancer patients. The association between AF and cancer goes even further, with some studies suggesting that AF can be a marker of occult cancer. There is, however, a remarkable paucity of data concerning specific challenges of AF management in cancer patients. AF prompt recognition and management in this special population can lessen the arrhythmia-related morbidity and have an important prognostic benefit. This review will focus on current AF diagnosis and management challenges in cancer patients, with special emphasis on AF screening strategies and devices, and anticoagulation therapy with non-vitamin K antagonist oral anti-coagulants (NOACs) for thromboembolic prevention in these patients. Some insights concerning future perspectives for AF prevention, diagnosis, and treatment in this special population will also be addressed.

Introduction

Cardio-oncology has emerged as a key clinical field in the management of cancer patients, over the past decade. Cardio-oncology clinics now provide truly patient-centered clinical care and has proved useful in the prevention of cancer therapy-related cardiovascular toxicity.

Traditionally, oncology clinics were limited to the awareness of potential cardiomyocyte toxicity and risk of subsequent heart failure. We now have an ever more matured view of the varied cancer therapy-related cardiotoxicity. This includes a broad spectrum of inflammatory, thromboembolic and arrhythmic complications.

Keywords

Atrial Fibrillation; Neoplasms; Cardiotoxicity; Mass Screening; Cardio-Oncology; Arrhythmias, Cardiac; Anticoagulants; Blood Coagulation

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AF burden

Atrial Fibrillation (AF) is recognized as the most common sustained cardiac arrhythmia, with a prevalence of approximately 0.5 to 2% of the general population. Patients with AF have a five-fold increased risk of stroke and a three-fold increased risk of heart failure. Furthermore, AF is an independent predictor of cardiovascular morbidity and mortality.[1,2]

Factors predisposing to AF development include aging (with the prevalence of AF being as high as 10% in patients over 80 years old),[3] cardiovascular disorders such as hypertension, valvular heart disease, heart failure, pulmonary hypertension, and a variety of non-cardiovascular comorbidities such as diabetes, chronic pulmonary disease, obstructive sleep apnea, chronic kidney disease, thyroid dysfunction, inflammatory bowel disease, amongst others.

The association between AF and cancer has long been recognized and is somewhat expected based on the increasing prevalence of cancer with aging, and the high frequency of comorbidities predisposing to AF in cancer patients.

Several population-based cohort studies showed the remarkable, bidirectional association between these entities. A recent meta-analysis showed that the rate of cancer diagnosis was three times higher in the first 3 months following AF diagnosis. Conversely, the risk of AF was particularly increased in the first 3 months after cancer diagnosis (OR 7.62, CI 3.08 to 18.88).[4,5] Additionally, in a large population-based case-control study with 28,833 AF cases, 0.59% were diagnosed with colorectal cancer in the 90 days before AF diagnosis, compared with only 0.05% of the controls.[6] Another cohort study also found that AF was associated with a higher incidence rate of cancer diagnosis in the next two decades of follow-up, and, again, this holds particularly true within 90 days after the diagnosis of AF. In this 90-day period men had an approximately 3-fold

higher risk of having a cancer diagnosis, while women had a 4-fold higher risk.[7] In a recently published observational study including 4,324,545 individuals, of which 316,040 had a cancer diagnosis, AF remained independently associated with all major cancer subtypes.[8] The overall AF prevalence was 1.74% among cancer patients *vs*. 0.37% in the general population, and this difference increased with age. The strength of the association declined over time from the cancer diagnosis but remained significant even after 5 years (incidence rate ratio of 3.4 from day 0 to 90, and 1.1 from 2 to 5 years from cancer diagnosis). Another nationwide cohort study concluded that AF was strongly associated with metastatic cancer.[9]

It is known that AF can be an asymptomatic condition, especially in the elderly. The frequent paroxysmal nature of AF further complicates its early recognition. Studies have demonstrated that up to 45% of all AF-related strokes occurred in patients with asymptomatic and unknown AF.[10] The significant risk for thromboembolic complications posed by AF is thought to be even greater in cancer patients, in whom a procoagulant state usually prevails.

Screening and searching for AF may have a potential role in preventing complications if adequate treatment is prescribed early.

On the other hand, as the association between AF and cancer goes even further, some studies suggest that AF can be a marker of occult cancer. The authors of a meta-analysis comprising 5 population-based observational studies including more than 5,500,000 patients recommended that patients with new-onset AF should be screened for occult cancer.[5] This is, at present, highly controversial and has been contradicted by others.[7,11]

This review will focus on current AF diagnosis and management challenges in cancer patients, with special emphasis on AF screening, and anticoagulation therapy for thromboembolic stroke prevention in these patients. Some insights concerning future perspectives for AF prevention, identification, and treatment in this special population, will also be provided.

AF and Cancer: proposed pathophysiological links

Multiple pathophysiological links have been proposed to explain the strong association between the two entities (Figure 1).

The existence of shared risk factors for cancer and AF – such as preexisting cardiovascular disease, aging, obesity, diabetes, alcohol consumption and smoking – may explain a significant proportion of this epidemiological link.

Moreover, cancer patients frequently experience pain, hypoxia, electrolyte abnormalities and malnutrition, all of which can prompt several autonomic and endocrine-metabolic abnormalities contributing to AF.[12]

At the atria level, primary or metastatic tumor growth can elicit local compression or invasion, both potentially triggering AF.

It has been suggested that cancer increases the incidence of AF through the abnormal production of thyroid hormones-like peptides.[13] A variety of paraneoplastic syndromes may ultimately lead to endocrine or metabolic derangements and set the stage for AF development. Other auto-immune mechanisms involving targeting of atrial tissue have been postulated.[14]

Occult undiagnosed cancer, with its accompanying altered autonomic tone and a pro-inflammatory state, may precede AF and explain, at least in part, the association. In some of these cases, anticoagulation therapy may unmask the neoplastic disorder by promoting tumor-related bleeding events. Also, being more closely exposed to medical examination and diagnostic tests, recently diagnosed cancer patients have higher probability of new-onset AF diagnosis.

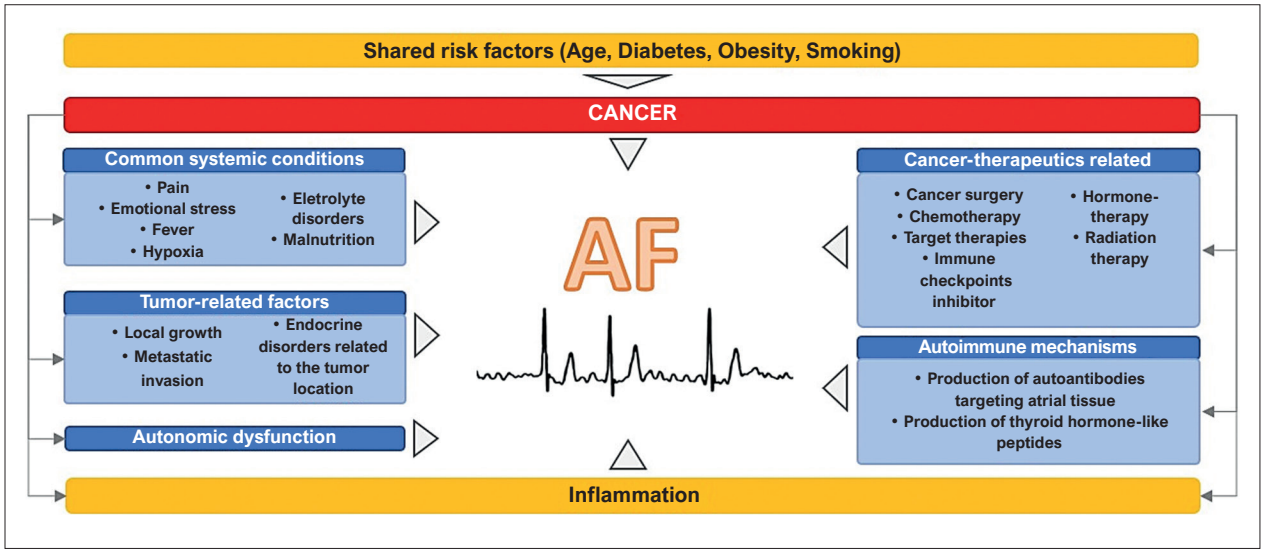

Figure 1 – *The multifactorial, bidirectional, interplay between cancer and atrial fibrillation. See text for further details.*

There is a large amount of evidence linking AF to inflammatory disorders. The high prevalence of AF in the postoperative period and in the acute stages of acute myocardial infarction (AMI) or myocarditis, provide a valuable insight into the relationship between AF and inflammation. Histological studies further explored this, with AF patients showing inflammatory cell infiltrates in their right atrial endocardium, which was not observed in controls.[15] Several studies evaluated inflammatory biomarkers in this context, showing C-reactive protein (CRP),[16,17] interleukin 2 (IL-2),[18] interleukin 6 (IL-6),[19] tumor necrosis factor α (TNF-α) and monocyte chemoattractant protein 1 (MCP-1)[20] to be significantly elevated in AF patients when compared to controls. The association between cancer and inflammation, being notably robust,[21,22] allows the hypothesis that inflammation is probably a common substrate for AF and cancer in some patients.[23]

AF is frequently seen following surgical therapy for cancer, and this is particularly evident after pulmonary resection for lung cancer, with a large observational study showing a prevalence of 12.6%.[24] This was also documented following surgery for esophageal, colorectal and breast cancers.[25-27]

Finally, several widely used anticancer drugs have been associated with an increased risk of incident AF (Table 1). A renewed interest in this field arose following the first reports of ibrutinib-related AF, a tyrosine-kinase inhibitor (TKi) used in patients with chronic lymphocytic leukemia, mantle cell lymphoma, and other hematological malignancies. The incidence of AF in patients undergoing ibrutinib therapy ranged from 3% to 16%.[28] The unique antiplatelet effects of ibrutinib, which appears to inhibit the initial steps of platelet adhesion and activation,[29] may pose therapeutic challenges when a decision must be reached about anticoagulation. It has been suggested that androgen deprivation therapy used to treat prostate cancer may lead to higher incidence of AF, possibly related to hormonotherapy-related hypogonadism.[30] This risk was more pronounced with abiraterone, a drug that also blocks CYP17 enzymes, and thus can cause hypermineralocortisolism, promoting hypokalemia and AF.[31] More recently, immune checkpoint inhibitors (ICI), have also been linked to new-onset AF because of their propension to cause myocardial and pericardial inflammation through auto-immune mechanisms.[32] Other autoimmune side effects of ICIs, such as thyroiditis, may predispose to AF development as well.

Chest radiotherapy is associated with myocardial fibrosis, potentially causing a restrictive cardiomyopathy over the long term, and the associated filling pressure elevation favors AF development. Enhanced myocardial fibrosis at the atria level may set the stage for subsequent mechanical and/or electrical remodeling, ultimately causing AF.

It must be acknowledged, however, that the real incidence of cancer therapy-related AF is likely to be underestimated, as routine rhythm monitoring is seldom performed or comprises only a single recording of a 12-lead ECG.

The rationale for AF screening

AF is not infrequently an asymptomatic condition, and the risk of stroke or death was found to be similar between symptomatic AF and silent AF.[33,34] Up to 5% of individuals with AF have a stroke as the initial clinical manifestation of their arrhythmia.[35] This may represent near one-third of all AF-related strokes. AF is associated with increased mortality risk in the general population,[36-39] and this has also proved to be true in cancer patients.[40,41]

Prevention of thromboembolic stroke due to an early introduction of oral anticoagulation in patients at risk is perhaps the most plausible benefit of AF screening programs.[42] Other proposed theoretical benefits of early AF recognition and management include reduction of AF-related morbidity and hospitalizations, and reduction of AF-related mortality.

The added value of opportunistic / systematic screening *versus* standard of care to detect silent AF in the general population is well established, and the rates of newly diagnosed AF ranged from 0.5 to 3.9% in most studies.[43-49] The increasing yield of screening programs seems to be more intimately related to the screened population and the duration of screening, rather than specific devices / test characteristics.

Factors such as age,[44] previous history of thromboembolic stroke,[50,51] CHA2DS2-VASc score,[52,53] and NT-proBNP levels,[54,55] have been proposed as potentially useful to optimize the "number needed to screen" of such programs, possibly allowing for improved net clinical benefit and cost-effectiveness.

Interestingly, CHA2DS2-VASc score not only predicts stroke risk among patients with known AF, but also performs fairly well when predicting newly diagnosed AF. This may be useful as a gatekeeper for screening programs, not only (1) helping to select those patients with higher pre-test probability for silent AF, but also because (2) it warrants all detected cases will derive clinical benefit from oral anticoagulant (OAC) prescription.

The clinical trial STROKESTOP included 75- and 76-year-old individuals, thereby selecting participants with a CHA2DS2-VASc score of at least 2 points (age >75). Previously unknown AF was found in 0.5% of the screened population in their first ECG, whereas intermittent ECG recordings increased new AF detection by 4-fold.[44]

The STROKESTOP II study also added the use of NT-proBNP, in a stepwise strategy for AF screening in 75- and 76-year-old individuals. The high-risk group (NT-proBNP ≥125 ng/L) was offered extended ECG-screening, whereas the low-risk group performed only one single-lead ECG recording. In the high-risk group 4.4% had newly diagnosed AF.[56]

Even in cohorts at higher risk for thromboembolic stroke (i.e. those with previous embolic stroke of undetermined source), empirical treatment with OAC failed to demonstrate a reduction in recurrent stroke. This reinforces the importance of effective AF documentation prior to the implementation of such therapies,[57,58] even in high prevalence and high-risk cohorts, such as cancer

Table 1 – Reported frequency of cancer therapy-induced atrial fibrillation

Therapeutic class	Drug agent	Reported frequency of AF
Alkylating agents	Anthracyclines	0.55 – 10.3%
	Melphalan	10.8 – 33%
	Busulfan	6.4%
	Cyclophosphamide	2%
Antimetabolites	5-Fluorouracil	5%
	Capecitabine	0.5 – 1.1%
	Gemcitabine	0-8.1% (*)
Taxanes	Paclitaxel	0.18 - 1%
IImmunomodulators	Talidomide	4.7%
	Lenalidomide	4.6 - 7%
Platinum derivates	Cisplatin	10-32%
Tyrosine kinase inhibitors	Ibrutinib (BTK)	3-16%
	Nilotinib (BCR-ABL1)	0.8%
	Ponatinib (BCR-ABL1)	3-7%
	Vemurafenib (BRAF)	1.5%
	Imatinib (BCR-ABL1)	0.55 – 33%
	Dasatinib (BCR-ABL1)	5.6%
	Sorafenib (VEGFR)	5.1% (**)
Proteasome inhibitors	Bortezomib	2.2%
	Carfilzomib	3.2 – 3.8%
Monoclonal antibodies	Trastuzumab (HER2/ERBB2)	1.2%
	Bevacizumab (VEFG)	2.2%
	Cetuximab (EGFR/HER1)	4.8%
	Alentuzumab (CD52)	1.2%
	Rituximab (CD20)	1%
Other	Interleukin 2	4.3 – 8%
ICIs	Nivolumab (anti-PD1)	13%
	Pembrolizumab (anti-PD1)	
	Ipilimumab (anti-CTLA4)	
CAR-T cell therapy		2.2%
Hormonotherapy	Degarelix	2%
	Abiraterone	1 – 5%
Radiation therapy		0.5 –3.2%

(*) AF incidence of 0% when used alone, 8% when associated with vinorelbine. (**) The reported prevalence was found in association with 5-FU, in a phase II study. It is noteworthy to recall that this association is not currently used in daily clinical practice.

patients. In patients with documented AF, OAC therapy reduced stroke rates by two-thirds.[50]

Strategies for AF screening

Several methods are available for AF screening (Figure 2). The simplest method for AF screening is pulse taking, which provides good sensitivity but only modest specificity (reported range of 65–91%). Other approaches include automated blood pressure devices (those able to perform oscillometric analysis),[59] non-invasive devices for a single-lead ECG registration, and cardiac rhythm monitoring patches.

More recently, smartphone and smartwatch-based ambulatory monitoring introduced the ability for patient-activated monitoring without the need for wearable devices, and for indefinite periods. Such a smartwatch device showed promising results in a study with 419,000 participants, concerning mass-screening for AF. Irregular rhythm patterns were detected in 0.52% of participants, and this prompted subsequent confirmation with an electrocardiography (ECG) patch. The positive predictive value of the irregular rhythms detected by the smartwatch as possible AF was 0.71. It must be noted, however, the unfavorable age profile of the enrolled individuals, which were mostly young (52% were younger than 40 years and only 6% were 65 or older).[46]

Artificial intelligence-based rhythm analysis is frequently dependent on heterogeneous algorithms and, therefore, subsequent validation of findings is needed. This applies not only to plethysmography analysis for pulse wave irregularities but also for single-lead ECG generation of some devices, whose diagnostic accuracy does not yet replace human judgement. This may represent a challenge for healthcare systems, potentially leading to human resources' shortness, since the great amount of data generated by these devices ultimately requires validation.

To date, randomized trials of AF screening have not demonstrated a reduction in stroke or other hard outcomes. It must be acknowledged, however, that none of these trials was adequately powered to demonstrate such an effect. Several trials are currently ongoing, aiming to give insights into this important topic (SAFER,[60] DANCANVAS,[61] LOOP,[62] GUARD-AF[63]).

Two important drawbacks have been pointed out regarding AF screening strategies. The first one concerns the risk of false positive results and potential for increased bleeding risk in patients in which OAC does not bring clinical benefit. The expected psychological consequences of a false positive result, concerning anxiety levels and diminished quality of life, may have redoubled their importance in oncologic patients. The second emphasizes the uncertain clinical significance of short episodes of AF documented with prolonged screening modalities. In fact, these short-lasting arrythmia episodes may not represent an increased risk of thromboembolic events.[64]

Following new-onset AF detection with whichever screening strategy used, it must be stressed, nevertheless, that ECG confirmation of AF is still mandatory in the guidelines.[2]

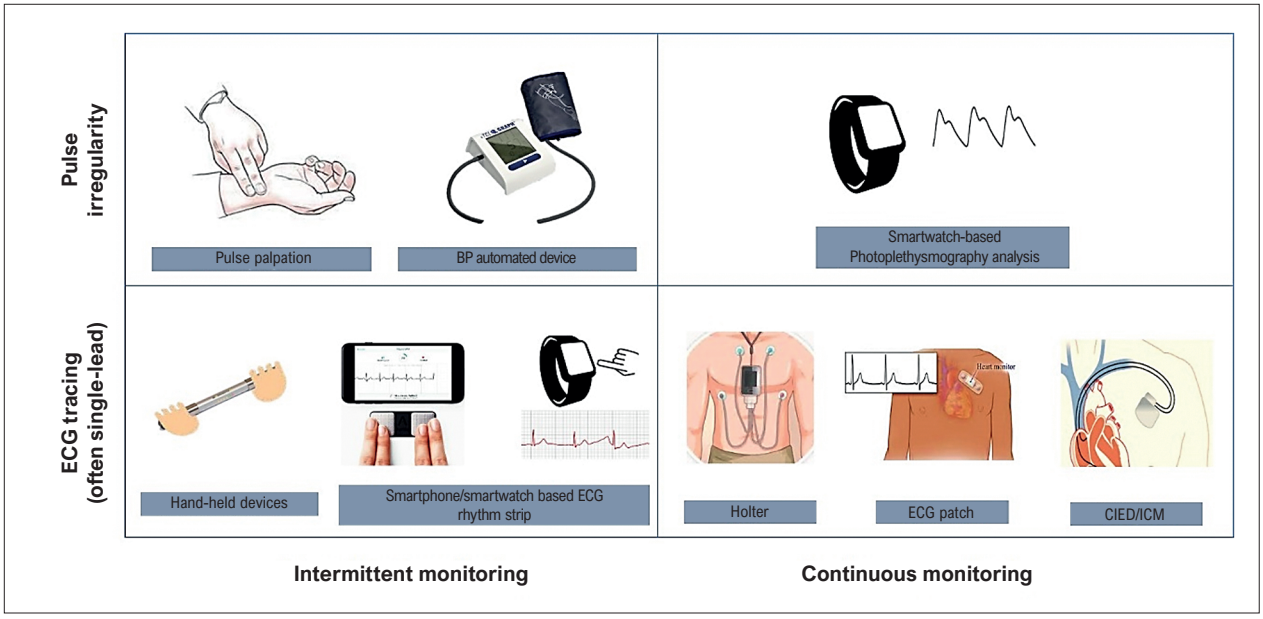

Figure 2 – *Several methods are available for outpatient atrial fibrillation screening. BP: blood pressure. CIED: cardiac implantable electronic device. ICM: implantable cardiac monitor*

Current recommendations for AF screening

The European Society of Cardiology (ESC) recommends opportunistic screening for AF by pulse taking or ECG rhythm strip in patients aged >65 years-old, with a Class of Recommendation (COR) I and a Level of Evidence (LOE) B.[2] According to the same recommendations, systematic ECG screening may be considered to detect AF in patients aged 75 years or older, or those at high stroke risk (COR IIb, LOE B). A position paper from the European Heart Rhythm Association (EHRA) adds that screening for AF is advised in high-risk populations, because of its cost-effectiveness.[42]

In contrast, the United States Preventive Services Task Force states that the current evidence is insufficient to assess the balance of benefits and harms of screening for AF with electrocardiography.[65]

Despite the high burden of AF in cancer patients, there are no specific recommendations regarding AF screening in these patients.

AF screening in cancer patients: what is the evidence?

There is an astonishing paucity of data concerning AF screening in cancer patients. Moreover, current malignancy and/or chemotherapy or radiotherapy exposure were considered the exclusion criteria in some trials on AF screening.[62, 66,67]

Intriguingly, most of AF screening studies do not even report cancer prevalence when it comes to the screened population characterization. Among the few studies that report cancer prevalence at baseline, no clear description exists regarding the rate of newly identified AF and/or "number needed to screen" in those patients.

A national cross-sectional study from Ireland randomly screened 2,200 patients aged 70 years and over using a three-lead ECG monitor in a primary care setting. The incident rate of newly diagnosed AF was 1.2%. This study reported a lung cancer prevalence of 0.3% in the overall screened population, but once again, no data on incident rate for newly identified AF is available for those patients.

Management of AF in cancer patients

The overall principles of AF prevention and treatment, and general management recommendations, also apply to cancer patients. For the sake of consistency, the author's will follow the guideline-recommended "ABC" approach to AF treatment (A: avoid stroke, anticoagulation; B: better symptom management, including patient-shared decisions on rate or rhythm control strategies; C: cardiovascular and comorbidity risk reduction). We also address some cancer patients' particularities that deserve consideration.

Antithrombotic regimen

In AF patients from the general population, the ischemic stroke risk is stratified with satisfactory precision by CHA2DS2-VASc score, and patients with a score ≥1 (except for female gender alone) are considered to have favorable risk/benefit under OAC therapy.[2] This must be balanced alongside the bleeding risk in each patient. The HAS-BLED score has been proposed for bleeding risk assessment in the general population.[68] The HEMORR2HAGES risk assessment scale has the unique feature of including cancer as a risk factor for bleeding in AF, although it lacks external validation. Risk factor modification is of utmost importance to minimize bleeding risk. Apart from their suboptimal performance and discriminatory capacity, the

numerous bleeding-risk scores available have the merit of highlighting such modifiable risk factors.

The OAC therapy reduces the risk of ischemic stroke rate by roughly 60%. Several landmark clinical trials have highlighted the superior safety profile of NOACs vs. VKAs with a comparable efficacy in the general population.[69-72] However, these studies directly (precluding patients undergoing active chemotherapy/radiation therapy) or indirectly (not allowing the enrollment of individuals with an expected survival <12 months) excluded active cancer patients.

Thrombotic events are the second leading cause of mortality in cancer patients.[73] However, cancer and many of its thrombotic-risk features are not incorporated into the CHA2DS2-VASc score calculation. Additionally, cancer-associated bleeding risk may theoretically shift the "net clinical benefit point" of OAC in these patients towards a higher CHA2DS2-VASc score (Figure 3).

Conflicting analysis have been made concerning the CHADS2 and CHA2DS2-VASc scores performance in cancer patients with AF. In a study including over 120,000 patients, those with cancer and a low CHA2DS2-VASc score (0–1) had a higher risk of stroke than noncancer patients, but in those with a score ≥2, the stroke risk was similar between cancer and noncancer patients.[74]

In a study comprising roughly 2000 patients, the CHADS2 score was more predictive of increased stroke risk in patients with cancer and pre-existing AF (each point increase was associated with a nearly 40% greater risk of stroke) than the CHA2DS2-VASc.[75] In the same study, notwithstanding, both scores accurately predicted the risk of stroke and survival. Intriguingly, the CHADS2 score lacked power to predict thromboembolism in cancer patients with new-onset AF in another study.[76]

On the other hand, patients with recently diagnosed cancer were at greater risk of bleeding, irrespective of the CHA2DS2-VASc score.[74] Cancer patients have a noticeable higher risk for bleeding events, either due to malignancy location, cancer surgery, thrombocytopenia, platelet dysfunction, chemotherapeutic agents, radiation therapy, iatrogenic and/or tumor-related kidney or liver failure, bone marrow suppression (by the neoplastic disorder or cancer-related therapeutics), disseminated intravascular coagulation or hyperfibrinolysis in specific subsets, mucositis, and acquired von Willebrand syndrome. In the Riete registry,[77] prior bleeding, creatinine clearance <30 mL/min, immobility ≥4 days and metastatic

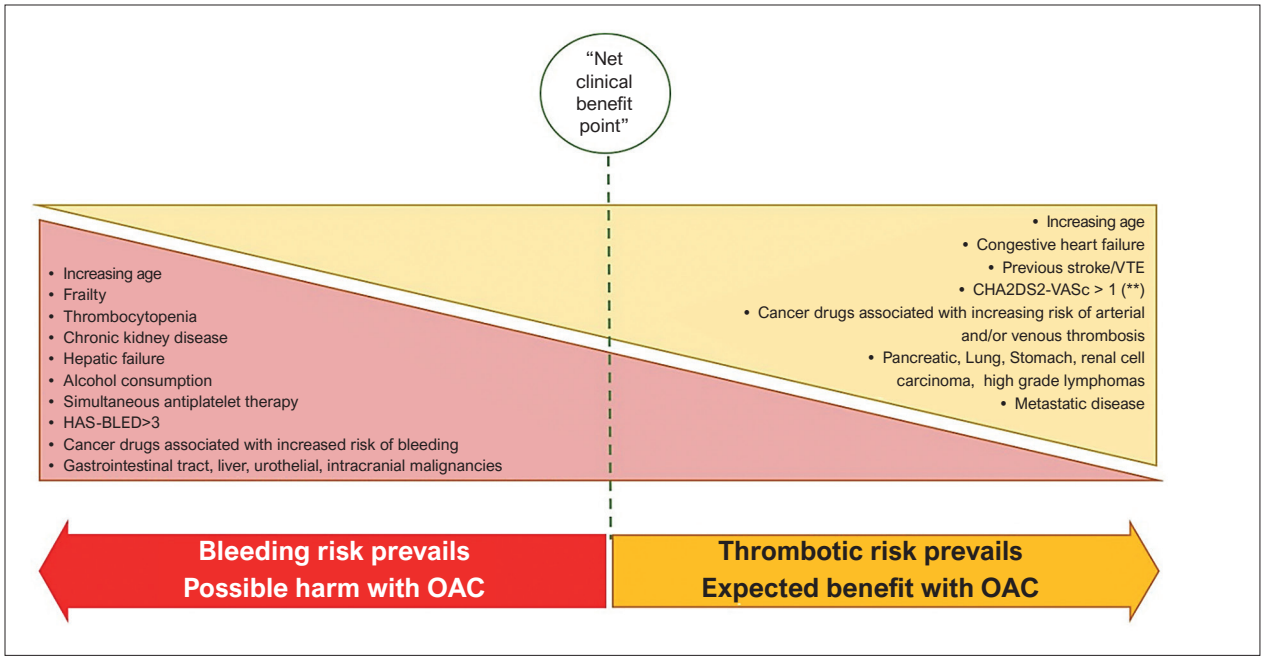

Figure 3 – *Cancer patients with AF are at simultaneously high thrombotic and bleeding risk. Patient factors, as well as tumor-specific risks and cancer therapeutics adverse effects pose additional challenges. The indication for anticoagulation in these patients must be individualized, and several factors, not included in classic risk scores, should be considered. (*) Vinca alkaloids, alkylating agents, monoclonal antibodies (aflibercept, bevacizumab, ramucirumab, trastuzumab emtansine), antiestrogens, antimetabolites (pentostatin), anthracyclines, bleomycin, campothecins, carfilzomib, epipodophyllotoxins, ibrutinib, BCR-ABL, BRAF, and VEGF/VEGFR inhibitors, interleukins, L-asparaginase, ruxolitinib, taxanes, temozolomide, cyclophosphamide, ifosfamide, megestrol, tamoxifen. (**) CHA2DS2-VASc score is a strong predictor of thromboembolic events in patients with previously known AF but performed poorly for stroke risk prediction in those with cancer and newly diagnosed AF. See text for further details. (***) Alkylating agents (carboplatin, cyclophosphamide, cisplatin, estramustine, oxaliplatin, temozolomide), gonadotropin-releasing hormone analogs, antiandrogens, monoclonal antibodies (aflibercept, bevacizumab, cetuximab, panitumumab), anthracyclines, antimetabolites (capecitabine, 5-fluorouracil, gemcitabine, methotrexate, pentostatin), immunomodulators (lenalidomide, pomalidomide, thalidomide), aromatase inhibitors, bleomycin, protein kinase inhibitors (axitinib, lenvatinib, pazopanib, sorafenib, sunitinib), mTOR inhibitors, proteosome inhibitors (carfilzomib), irinotecan, taxanes, tasonermin, tretinoin, megestrol, progestogens, raloxifene, tamoxifen, vinflunine, vorinostat, erythropoiesis-stimulating agents and granulocyte colony-stimulating factors.*

disease were the most important predictors of major bleeding in cancer patients undergoing anticoagulation therapy.

In a large registry data analysis, cancer patients had a two- to six-fold increase in the bleeding risk compared with patients without cancer.[78] Ischemic stroke rate was, however, comparable.

Evidence from randomized clinical trials comparing NOACs to either vitamin K antagonist (VKA) or low-molecular weight heparin (LMWH) for thromboembolic prevention in cancer patients with AF is not available at the present date.

Several RCTs recently emphasized NOAC's efficacy and safety profile for venous thromboembolism prophylaxis[79,80] and treatment[81-83] in cancer patients, compared to low molecular weight heparins (LMWH). In all these studies, the minor bleeding risk was greater with NOAC *versus* LMWH (driven by a higher rate of gastrointestinal bleeding). The major bleeding risk was similar between the two drug classes in some studies (Caravaggio[83] and SELECT-D[82]), but an increased risk with NOAC use was observed in one trial (Hokusai VTE Cancer[81]). To some extent, cautious extrapolation can be made from these trials, but the unique thromboembolic pathophysiology in AF patients deserves dedicated trials.

Recent observational data from a cohort of 16,096 patients with AF and cancer suggest NOACs may be at least as effective as warfarin for the prevention of ischemic stroke and have a safer bleeding profile.[84]

A summary of various subanalysis from major clinical trials on OAC therapy in AF assessing cancer patients is shown in Table 2. In a subanalysis of the ARISTOTLE trial, the safety and efficacy of apixaban *versus* warfarin were comparable between patients with and without active cancer.[85] Interestingly, cancer patients derived a greater benefit from apixaban therapy for the composite endpoint of stroke/systemic embolism, myocardial infarction (MI) and death. These results were replicated in an analysis of 1,153 patients initially included in the ENGAGE AF-TIMI 48 trial, who developed new or recurrent malignancy over a median follow-up of 495 days.[86] Overall, the efficacy and safety profile of edoxaban in relation to warfarin were preserved.

In a recently published meta-analysis comprising over 20,000 patients with AF and cancer undergoing OAC, NOACs showed lower or similar rates of thromboembolic and bleeding events when compared with warfarin (37% stroke risk reduction, 27% major bleeding risk reduction).[87] These results are still exploratory and should be interpreted with caution until RCTs are available. One important limitation concerns the limited data about cancer staging, which might have led to uncontrolled confounding factors if the type of OACs (NOACs vs AVK) varied by cancer staging. Furthermore, patients with greater disease severity (i.e. those with reduced life expectancy) were indirectly precluded by the analysis, as they were excluded by the numerous included studies.

The individualized assessment of thrombotic and bleeding risk profile, comorbidities, and expected drug-to-drug interactions in each patient remains crucial, either before the OAC strategy initiation, when evaluating the need for dose adjustment or scheme modification, or even therapy discontinuation.

Balancing thrombotic and/or bleeding risk remains particularly challenging in specific scenarios, according to comorbidities, tumor location, staging, and cancer-related therapies, some of which are addressed in Figure 3. Although, at present, there are no data to guide the choice of specific anticoagulants in most of these extreme scenarios, refraining from using rivaroxaban, dabigatran or edoxaban in gastro-intestinal cancer patients with high bleeding risk seems advisable.

LAA closure

Left atrial appendage (LAA) percutaneous closure was non-inferior to warfarin for the prevention of thromboembolic events and may be considered for those patients at the highest stroke risk who have contraindication for anticoagulation.[88] The OAC is not even necessary post-procedure, as dual antiplatelet therapy in the first 6 months showed to be equally safe.[89] It is noteworthy to

Table 2 – NOACs versus Warfarin for stroke prevention in patients with atrial fibrillation

NOAC	Primary Efficacy endpoint vs. Warfarin RR [95% CI]		Primary Safety endpoint * vs. Warfarin RR [95% CI]	
	General population **	Cancer ***	General population **	Cancer ***
Dabigatran	0.91 [0.53-0.82] †	0.14 [0.03 - 0.57] §	0.93 [0.81-1.07] †	0.23 [0.07-0.74] §
Rivaroxaban	0.79 [0.66-0.96]	0.52 [0.22-1.21]	1.03 [0.96-1.11]	1.09 [0.82-1.44] ††
Apixaban	0.79 [0.66-0.95]	1.09 [0.56-2.26]	0.69 [0.60-0.80]	0.80 [0.56-1.14] ††
Edoxaban	0.79 [0.63-0.99] ‡	0.60 [0.31-1.15] ‡	0.87 [0.73-1.04] ‡	0.98 [0.69–1.40] ‡

** Major bleeding results, unless otherwise specified. ** Data from landmark RCTs. *** Data from post-hoc subanalysis or observational studies. § Results from an observational retrospective study, which included 140 patients on Dabigatran, and counted two ischemic strokes and three major bleeding events in this study arm (Kim K, et al. 2018]. † The results for Dabigatran 150mg dosage are presented. †† Major or clinically relevant nonmajor bleeding events. ‡ The results for Edoxaban 60mg dosage are presented.*

remind that patients with either thrombocytopenia (platelet count <100.000) or anemia (hemoglobin <10g/dL) were excluded from major trials validating its use.

Heart rate and rhythm control specificities in cancer patients

For symptomatic control, a strategy of either heart rate control (rate control) or sinus rhythm restoration and maintenance (rhythm control) may be reasonable. The patient's age and functional status, comorbidities, AF duration, and predicted drug-drug interactions with rate-controlling and anti-arrhythmic drugs, are valuable aspects when deciding between the two strategies.

New-onset AF may arise in the context of systemic, infectious, metabolic, and/or endocrine disorders, and their correction may be enough to restore sinus rhythm.

Apart from these scenarios, in hemodynamically stable AF with >48h duration a rate control strategy is usually the first approach. Landmark RCT evidence showing lack of benefit with a rhythm control strategy and a lower potential for drug interactions with rate-controlling drugs have recently been questioned.[90,91] A lenient rate control strategy is advised, with a resting heart rate objective of 100-110bpm.[92] For this purpose, non-dihydropyridine calcium-channel blockers (diltiazem, verapamil) and digoxin carry the highest risk for relevant drug interactions with cancer treatments and beta-blockers not significantly metabolized by liver enzymes (atenolol, nadolol) may be preferred.

Antiarrhythmics have a narrow safety profile, and when choosing an antiarrhythmic agent, attention must be given to severe interactions with cancer drugs. Even in patients submitted to planned electric cardioversion for this purpose, antiarrhythmic drugs may increase the likelihood of sinus rhythm maintenance. Amiodarone is both a major CYP3A substrate and an inhibitor of P-glycoprotein and should be use with caution, when strictly necessary. Alternative antiarrhythmics in patients without structural heart disease (SHD) are sotalol, flecainide and propafenone. Mexiletine (class Ib antiarrhythmic) may be considered in those with SHD.

Data from the ORBIT-AF registry shows a 4% prevalence of prior catheter ablation procedure in AF patients with a history of cancer.[78] There is no information on whether these procedures took place before or after the cancer diagnosis. Patients with a history of cancer were less likely to have been submitted to catheter ablation of AF, when compared with those without cancer history.

The procedure has good long-term results in experienced hands, with low complication rates. Cancer patients with a perceived life expectancy > 12 months would theoretically be plausible candidates, aiming for symptomatic and/or prognostic benefit.

Drug-drug interactions

Although fewer food and drug-drug interactions are expected with NOAC use when compared with warfarin, some pharmacokinetic considerations have clinical relevance. A gut transporter, P-glycoprotein (P-gp), is responsible for gastrointestinal re-secretion of all NOACs. P-gp is also involved in NOAC renal secretion. Predictably, strong P-gp inhibitors result in increased NOAC plasma levels.

Cytochrome P450 3A4 (CYP3A4) enzymatic pathways are a critical step in the hepatic clearance of rivaroxaban and apixaban. Strong CYP3A4 inhibitors will potentially increase plasma levels of these drugs.

As a rule of thumb, strong inhibitors of both P-gp and CYP3A4 are not recommended in combination with NOACs. On the other hand, strong inducers of both P-gp and CY3A4, resulting in low NOAC plasma levels, may compromise treatment efficacy. Detailed drug-drug interactions and hazardous combinations have been detailed elsewhere.[93,94]

When the avoidance of severe drug-drug interaction compromises anti-cancer therapeutics efficacy, low-molecular weight heparins (LMWHs) may be considered as an alternative.

Pharmacodynamic considerations include not only the increased hemorrhagic risk with simultaneous antiplatelet therapy (e.g. in patients with acute coronary syndromes), but also the concomitant treatment with chemotherapeutic agents with antithrombotic activity. Individual assessment of thrombotic and hemorrhagic risk is advised.

Renal and Hepatic dose adjustments

In general, NOAC use is not advised in stage V chronic kidney disease (CKD) (creatinine clearance <15mL/min/m^2). Apixaban is considered a reasonable alternative to warfarin in these patients, according to some recommendations,[1,95] but the supporting evidence is still weak. Patients with stage IV CKD (CrCl between 15 and 30 mL/min/m^2) may be treated with a reduced-dose regimen of rivaroxaban, apixaban, or edoxaban. Stage III CKD (CrCl 30-60ml/min/m2) generally mandates NOAC dose adjustment, taking into account the patient's characteristics affecting the drug pharmacokinetics (i.e., age and weight).

All NOACs remain contra-indicated in end-stage hepatic disease (Child-Turcotte-Pugh C cirrhosis), due to lack of data. Rivaroxaban should also be avoided in those with Child B liver cirrhosis.[93]

Thrombocytopenia

Cancer patients with thrombocytopenia have increased bleeding risk, remaining at increased risk for thrombotic complications. To date, no robust data have emerged on which anticoagulation strategy should be pursued in this challenging scenario. It has been proposed either a strategy of platelet transfusion, or dose-modified anticoagulation regimen with LMWHs in those with severe thrombocytopenia (platelet count <50 x 109/L).[94,96] Some causes of thrombocytopenia involving immune-mediated mechanisms are characterized by a prominent thrombotic, as well as hemorrhagic, risk. That said, there is no consensus on a lower limit of platelet count when considering anticoagulation, as this is dictated by the clinical scenario and the prevailing risk.

Risk factor modification

Risk factor modification is crucial in AF prevention and recurrence avoidance. This includes weight loss, diabetes treatment, arterial hypertension control, sleep apnea identification and treatment, correction of thyroid dysfunction, smoke cessation, alcohol consumption avoidance, and treatment of any underlying structural / ischemic heart disease.

Future directions

AF prevention

Several interventions, focusing on lifestyle and risk factor modification, prompted a significant reduction in AF burden in the general population. These include weight loss in obese patients, optimal glycemic control in DM patients, hypertension and dyslipidemia management, obstructive sleep apnea identification and treatment, smoking cessation, and alcohol consumption reduction.[97] The extent to which cancer patients derive the same benefit with these interventions remains to be determined, but the high burden of classical cardiovascular risk factors in this population argues in favor of these interventions. Moderate aerobic exercise training is safe and provides QoL and cardiovascular benefit in cancer patients.[98] Those integrating Cardio-Oncology rehabilitation programs experience fewer cancer therapeutic-related adverse events.[99]

AF diagnosis

Artificial intelligence-based algorithms for the identification of subtle ECG changes associated with future AF development (e.g. LA enlargement, Bayés Syndrome)[100] may prove useful to identify patients who might benefit the most from AF screening. The same is true concerning echocardiographic parameters of LA dimensions and strain[101] and/or LV systo-diastolic function.[102] Cardiac magnetic resonance, allowing atrial morpho-functional characterization, may also become a crucial tool in early recognition of "fibrotic atrial cardiomyopathy", which is associated with incident and recurrent AF.[103] Genome-wide association studies (GWAS) have found several variants of atrial structural genes to be associated with AF development.[104] Also, OMIC sciences may help refine our knowledge of the biological processes underlying incident AF, perhaps helping clinicians in its early identification and treatment.

Risk stratification models exist for myocardial toxicity and overt heart failure development, according to chemotherapeutic classes.[105] New-onset AF may be the object of such baseline risk stratification tools in the future. This could help clinicians to better identify those patients who might benefit the most from AF screening.

The effectiveness of AF screening in cancer patients, concerning the prevention of major adverse cardio and cerebrovascular events, must be addressed in adequately powered prospective studies. The growing availability of user-friendly devices and apps, with potential for long-term screening in a large number of patients, may boost this research field.

AF management

Whether AF ablation carries a similar prognostic benefit in cancer patients with HFrEF, as demonstrated in the general population is currently unknown. Evidence from randomized clinical trials on NOAC use for stroke prevention in cancer patients with AF (compared with either VKA or LMWH) is also an important gap to be filled in the years to come.

Conclusion

Cardio-oncology clinics have allowed many cancer therapeutics-related cardiotoxicity events to be prevented, early recognized and optimally managed.

Despite the high frequency of AF in patients with active malignancy, this condition remains an under-recognized comorbidity in these patients. Its frequent paroxysmal nature, together with slack screening programs, may perpetuate this situation.

AF screening in cancer patients may have a role in early AF recognition and thromboembolic event prevention, through the timely prescription of anticoagulant therapy in individuals at risk. The best screening strategy and the optimal device to improve the yield of such screening programs are yet to be established.

In the future, clinical, genetic, analytical, electrocardiographic, and echocardiographic parameters may help to stratify the risk of subsequent AF development, thereby helping in the selection of patients who deserve more stringent screening protocols.

These challenging patients, simultaneously at higher thrombotic and hemorrhagic risk, deserve dedicated clinical trials. The prognostic impact of interventions aiming at the correction of underlying structural or functional heart disease, and the optimal anticoagulant regimen, require further investigation.

Multidisciplinary Cardio-Oncology teams are at a privileged position to carry on this mission, as they warrant a truly holistic approach to these challenging patients.

Author Contributions

Conception and design of the research: Gonçalves-Teixeira P, Costa T, Fragoso I, Leite-Moreira A, Sampaio F, Ribeiro J, Fontes-Carvalho R; Acquisition of data: Gonçalves-Teixeira P; Analysis and interpretation of the data: Gonçalves-Teixeira P, Costa T, Fragoso I, Ferreira D, Brandão M; Writing of the manuscript: Gonçalves-Teixeira P, Costa T, Fragoso I; Critical revision of the manuscript for intellectual content: Gonçalves-Teixeira P, Costa T, Fragoso I, Ferreira D, Brandão M, Leite-Moreira A, Sampaio F, Ribeiro J, Fontes-Carvalho R.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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Translational Medicine and Implementation Science: How to Transform What We Know Into What We Do

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Translational Medicine encompasses three areas: 1) acceleration of knowledge transmission from basic science to clinical practice; 2) analysis of the causes and pathophysiology of clinical observations through interaction with basic science; and 3) implementation of basic knowledge and concepts produced by clinical and experimental research in the general population, which is also known as "implementation science". In the past, some fundamental discoveries stayed confined to the basic science for long years before becoming diagnostic instruments or therapies applicable to practice.

An instructive example is the relationship between cholesterol and atherosclerosis. The first evidence that cholesterol induced atherosclerosis came from studies conducted on rabbits by Russians between 1908 and 1913.[1] The Framingham Heart Study,[2] published in 1961, was the first to demonstrate this fact in humans. However, statin was first produced only in 1976, starting the current era of pharmacological treatment of atherosclerosis.[3] This huge gap occurred in other contexts and represents a waste of knowledge and human lives.

Basis of preventive medicine: a healthy lifestyle

When medical knowledge is to be applied to the general population, the concept of healthy lifestyle should be highlighted, especially in terms of preventive medicine.

Most cardiovascular events, such as myocardial infarction and death, are associated with risk factors such as dyslipidemia, smoking, hypertension and diabetes.[4] Genetic factors are less representative. Another example is the Whitehall study, conducted with British civil servants,[5] that showed that servants in lower grades of employments had a mortality rate three to four times higher than of those in the higher grades. The basis of preventive medicine is related to a healthy lifestyle, including a diet composed predominantly of fruit, vegetable and fish, and low intake of meat and carbohydrates. At least 150 minutes per week of aerobic and strength exercises are strongly recommended, including for protection of cognitive functions and Alzheimer prevention.[6]

Exercise and diet are essential for preventing and treating diabetes, hypertension and obesity, and several anti-smoking programs are currently available, with remarkable success rates. In the book "Blue Zones",[7] American researchers evaluated the lifestyle of the five longest-lived communities in the world – Okinawa (Japan), Sardinia (Italy), Ikaria (Greece), Loma Lima (California) and Nicoya (Costa Rica). Some habits were shared by these communities – a diet mainly consisting of grains, fruits, vegetables, and fish, and poor in meat; active social life; religiosity; putting family first; manual labors like walking, taking care of animals, cooking, and taking care of the house; and restricted use of medications. Genetic factors cannot solely explain longevity of these populations, as they live in different countries and have no family relationship.

Emotional stress of any cause is a causal factor of cardiovascular events. The exponential increase of these conditions during the COVID-19 pandemic confirms these circumstances.[8,9]

It is noteworthy, however, that a healthy lifestyle is difficult to be implemented in adults. This represents an important challenge for translational medicine, particularly for its third component that concerns the general population. Results of initiatives to implement healthy habits in children and adolescents, as reported in Brazil and other countries,[10,11] for example, are impressive – children asking their parents not to smoke, to exercise and to follow a good diet! Hulsegge et al.[12] found that individuals who maintained four to five healthy lifestyle factors over a five-year period had 2.5 times lower risk of cardiovascular disease and all-cause mortality than those who did not.

In addition, it is important to consider in which context these initiatives have been implemented – in hospitals, educational programs, in the unified health system facilities or in private centers, by online consultations or others. Different contexts require different strategies.

Precision medicine

Today, medications are prescribed based on results of studies that showed their effective doses, which does not take into account individual responses, *i.e.*, doses have been established based on mean responses, without identifying who are responders and non-responders to the treatment. Side effects are described in a similar manner. On the other hand, randomized trials do not include patients with comorbidities and study only 6-8% of patients with the disease, which does not represent the real world. This causes errors and difficulties in adjusting medication doses.

Keywords

Translational Medical Research; Cholesterol; Atherosclerosis; Genome Human; Hydroxymethylglutaryl-CoA Reductase Inhibitors/therapeutic use; Cardiovascular Diseases/mortality; Exercises; Quality of Life; Preventive Medicine.

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Pharmacogenetics provides a more precise characterization of patients in terms of individualized responses to external agents and may form the basis for tailored therapies, as in preventing allergic reactions. Briefly, the knowledge of the human genome and the body responses will allow individualization of treatments considering the response to contrasts, intolerance to external agents, and sensitivity to salt, antiplatelet agents, and anticoagulants. Although this is not a current practice, it will be soon.

Socioeconomic inequality has a great impact on disease incidence

The Whitehall study[5] showed a relationship between a lower level of job satisfaction and higher mortality. Since then, several studies have shown that educational attainment, financial resources and social level have an influence on disease prevalence and mortality[13] due to factors other than psychological ones. Individuals with higher status are more aware of their diseases, have greater access to better health care and are more able to pay health costs. This is a universal problem that is more related to economy and social development, but affects health.

Comorbidities in the elderly and Multidisciplinarity

The population is aging. Comorbidities like cardiovascular diseases, cancers, rheumatic, renal, metabolic, inflammatory, urological, respiratory, neurological (dementia, Alzheimer disease) and psychiatric diseases are far more common among the elderly. It is rare to find an older patient with only one disease. For this reason, several specialists would be needed to provide the best care for patients with complex conditions.[14,15] In fact, a meta-analysis concluded that a teamwork is positively related to clinical performance.[16]

Establishment of medium and long-term risks

Although cardiovascular risk scores are imperfect, they are helpful in convincing patients to adopt a healthy lifestyle, to undergo periodic evaluations and to comply with medication regimens. Some diseases (e.g. hypertension, diabetes mellitus and atherosclerosis) are "silent" and hence the establishment of risks is of highly practical importance. Although the most used scores estimate 10-year risks, today the risk level of cardiovascular risks is estimated over a 30-year period.

Special techniques and parameters, like the coronary calcium score, radioisotopes and echocardiography allow recalculation of the risk, or more precisely, reclassification of patients.[17] Inflammatory markers like high-sensitivity C-reactive protein and genomic scores can also improve risk projections. Unconventional lipoproteins may also be helpful, including the lipoprotein(a), non-HDL cholesterol, triglyceride-rich lipoproteins, apolipoprotein CIII, angiopoietin-like protein 3 (ANGPTL3), angiopoietin-like protein 4 (ANGPTL4), apolipoprotein IV, apolipoprotein E, and genetic variants like PCSK9 can influence the cardiovascular risk.[18] The great advantage of risk calculation is to use it as an instrument to show patients the importance of continuous monitoring and decision making.

Judicious use of technologies: risks versus benefits

Technological advances are generally beneficial but may be hazardous. For example, the diagnosis of minimal lesions of thyroid, breast and prostate has led to "preventive", unnecessary interventions.[19] The same is true for imaging tests – scintigraphy, coronary computed tomography and percutaneous interventions – the indiscriminate use of these technologies overburdens the health care system, increases costs and causes patient anxiety. Countries like the United Kingdom and Canada have adopted measures to prevent "excesses". In Brazil, the quality of medical practice should be systematically evaluated (as performed by the Order of Attorneys of Brazil). The federal budget is insufficient to cover the health costs of the majority of the population, users of the federal public health system, and thus waste cannot be accepted. In addition, medical school hospitals play an important role in critically evaluating the innovative techniques.

Teamwork

Due to the complexity of some cases, presence of comorbidities, different institutional capacities and individual experiences, multidisciplinary teams are an effective way to provide the best care to the patients. In Cardiology, multidisciplinary teams should include a clinician, an interventionist, a surgeon and an arrhythmia specialist.[20,21]

In clinical practice, the indication for procedures is influenced by individual experiences. For example, while catheterization specialists may prefer percutaneous interventions, surgeons may be inclined to surgeries. In fact, there are arguments to support one or the other treatment option, based on its non-invasive character, long-term outcomes of the disease, as well as efficacy of previous drug treatments and patient lifestyle. Also, the fast development of assessment tools and therapeutic strategies, and individual experience of physicians and medical centers also contribute to differences of opinions. In this context, the Heart Team serves to minimize these biases. It is also worth emphasizing that the patient should be informed and asked about his/her preferences.

Research quality – basis of the translational process

The arguments mentioned above lead to the fundamental concept that translational medicine requires high-quality science in its every step. Scientific accuracy must exist from the collection of *in vitro*, *ex vivo* and *in vivo* data, development of phase I and II clinical trials, until the application of knowledge. Ideally, randomized clinical trials, with well-defined, relevant outcomes, and adequate number of patients and time of follow-up are preferred. A difficulty inherent to randomized studies is the high costs and long time to obtain results. There are some factors that have a clear influence on the implementation of good practice in the population, like the off-label use of drugs, economic issues, and an erroneous notion of free will among physicians. On the other hand, methods such as Mendelian randomization, Genome Wide Association Studies (GWAS), and the Big Data, with contributions from artificial intelligence and informatics, allow deeper investigations and elucidation of causes and pathophysiological mechanisms.[22,23] Regarding interventions,

clinical efficacy is the most important issue for physicians. Credibility in Medicine is then grounded in the principles of scientific method.

Author contributions

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Ethics approval and consent to participate

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Viewpoint

Predictors of Atrial Fibrillation in Holter Monitoring after Stroke – A Ten Year Flashback

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Introduction

Atrial fibrillation (AF) is a major risk factor for thromboembolic events, increasing five times the risk of stroke; it is also associated with more severe events and a higher risk of stroke recurrence. [1,2] On the other hand, the diagnosis of AF as the cause of ischaemic stroke shifts the therapeutic approach with a major prognostic impact.[3,4] Detection of previously unknown AF after stroke is crucial, and several studies have established the effectiveness of ECG monitoring for post-stroke AF detection.[1] According to ESO Guidelines for managing ischaemic stroke and transient ischaemic attack (TIA), after the acute phase, a 24-hour Holter ECG monitoring should be performed.[5] New ESC Guidelines recommend short-term ECG recording for at least the first 24 h and continuous ECG monitoring for at least 72 h whenever possible in cryptogenic stroke.[1]

Methods

We conducted a retrospective study in a single tertiary center in patients who suffered an ischaemic stroke or TIA and performed Holter monitoring between October 2009 and October 2011. All consecutive patients were selected, and those with AF or previous AF were excluded. We followed these patients for 8 to 10 years, observed the incidence of AF and evaluated the clinical, electrocardiographic and echocardiographic predictors of new-onset AF.

Excessive supraventricular ectopic activity (ESVEA) was defined as ≥ 500 premature atrial contractions per 24 hours or any sustained supraventricular tachycardia episode.[6]

Statistical analysis was performed in IBM SPSS Statistics version 25. Categorical variables were compared using the chi-square test, and differences were considered statistically significant when the p-value < 0.05.

Keywords

Atrial Fibrillation; Stroke/therapy; Tachycardia, Ectopic Atrial; Thromboembolis/therapy; Risk Factors; Electrocardiography, Ambulatory/methods.

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Results

In total, 104 patients were included; 79.5% had a stroke, and 20.5% had a TIA; 45.7% were female; the mean age was 63.8 ± 14.7-year-old at the time of the event (table 1). Concerning cardiovascular risk factors, 59.0% had hypertension, 47.4% had dyslipidemia, 19.5% had diabetes, 43.6% were smokers or previous smokers, and 66.7% were high alcohol consumers. Regarding echocardiographic features, 98% of patients had normal systolic ejection fraction, and only 2% had mildly impaired ejection fraction; medium left anteroposterior atrial diameter was 39 mm and 60% of patients had non-significative mitral regurgitation. 24-hour Holter monitoring revealed ESVEA in 13.5% of patients and paroxysmal AF in 1.9%. All patients with paroxysmal AF detected in Holter monitoring had a stroke and were older than 55.

Table 1 – Baseline characteristics and Follow-up results

N	104
Age, years (IQR)	63.8 (49.1-78.5)
Female, %	45.7
Hypertension, %	59.0
Dyslipidemia, %	47.4
Diabetes, %	19.5
Smoker or previous smoker, %	43.6
High alcohol consumers, %	66.7
Medium left atrial diameter, mm	39
Left systolic ventricular function, %	
• Normal	98.0
• Mildly reduced	2.0
Acute event, %	
• Stroke	79.5
• TIA	20.5
Holter results at baseline	
• AF, %	1.9
• ESVEA, %	13.5
At follow-up	
• AF, %	11.5

TIA: transient ischaemic attack; AF: atrial fibrillation; ESVEA: excessive supraventricular ectopic activity.

At a follow-up of 8-10 years, new-onset AF was detected in 11.5% of patients; these had similar mortality compared to those in sustained sinus rhythm (16.7% vs. 21.1%, p=0.724). Alcohol intake, an established risk factor for the development of AF, was associated with a non-significant increase in AF (18.0% vs. 11.5%, p=0.464), while cardiovascular risk factors, left atrium enlargement, mitral regurgitation was not associated with AF development. Regarding premature atrial contractions (PACs), documentation of ESVEA at presentation showed to be significatively associated with new-onset of AF at follow-up (35.7% vs. 8.1%, p=0.003). ESVEA also seems to be related to higher mortality at a long-term follow-up, although this difference was not statistically significant (35.7% vs. 18.6%, p=0.145) (Figure 1).

Conclusion

Our study corroborates previous reports suggesting that excessive PACs increased the risk of death and AF.[6,8] Copenhagen Holter Study showed that excessive PACs were associated with an increased risk of death, stroke, and admissions for AF at a median follow-up 6.3 years.[7] The same cohort was followed for 15 years, and the patients with ≥ 30 PACs/hour or with any runs of ≥ 20 PACs had an increased risk of ischemic stroke beyond developing AF. In that study, stroke was often the first clinical presentation than AF.[8] All these reports and the present study released whether patients with ESVEA benefit from anticoagulation. In fact, the assignment of atrial fibrillation as the cause of stroke totally changes patient's therapy, so it is of major importance to identify patients with paroxysmal AF and recognize which ones have more risk of having occult episodes of AF. 24-hour Holter monitoring allows the detection of paroxysmal AF, but apparently with low effectiveness. In our study, only 1.9% of patients were identified with AF promptly after stroke or TIA, while 11.5% exhibited AF in long-term follow-up.

Our study showed that ESVEA is a strong predictor of new-onset AF, highlighting the importance of ECG monitoring. This finding, combined with other risk factors such as embolic stroke of unknown source, can be used to identify patients at higher risk of developing AF who benefit from a long-term ECG monitoring or a more regular follow-up.

Author Contributions

Conception and design of the research: Proença T, Pinto RA, Carvalho MM, Sousa C, Campelo M; Acquisition of data, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Proença T, Pinto RA, Carvalho MM; Critical revision of the manuscript for intellectual content: Sousa C, Dias P, Campelo M, Macedo F.

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Ethics approval and consent to participate

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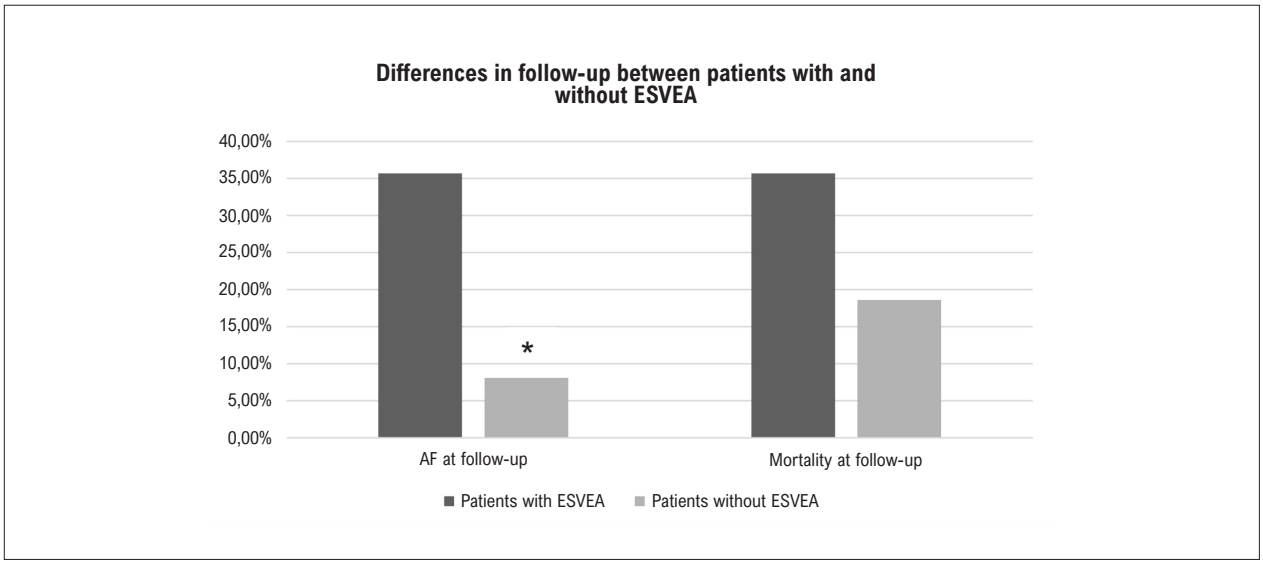

Figure 1 – *Differences in follow-up between patients with and without ESVEA. ESVEA at presentation was significatively associated with new-onset AF at follow-up (35.7% vs. 8.1%, p=0.003) and seemed to be related to higher mortality (35.7% vs. 18.6% p=0.145). ESVEA: Excessive supraventricular ectopic activit ; AF: atrial fibrillation.*

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An Incidental Finding of a Cardiac Sarcoma

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Introduction

Primary cardiac tumors are rare, and their clinical presentation ranges from incidental discovery on imaging tests to life-threatening presentations.[1-3]

We report a case of a young female with a history of atrial fibrillation (AF) who was found a left atrial mass in an elective cardiac computed tomography performed before AF-ablation and was qualified for surgical resection of the mass. A pathological exam revealed a primary undifferentiated pleomorphic cardiac sarcoma.

Case report

A 49 year-old Caucasian female with a previous history of paroxysmal AF, referred for elective percutaneous AF-catheter ablation, was referred to the hospital due to a left atrial (LA) mass incidentally identified at pre-interventional cardiac computed tomography (CCT). She had no symptoms related to the mass.

On initial evaluation, an electrocardiogram (ECG) was in sinus rhythm. Physical examination and full laboratory analysis revealed no abnormal findings.

Beyond the history of paroxysmal AF, diagnosed two years before, the patient was otherwise healthy. The medications on admission were edoxaban (in the last 2 weeks before ablation), flecainide and bisoprolol, with sub-optimal rhythm control.

Investigations

A homogenous, hypodense, slightly irregular sessile mass localized in the posterior wall of the LA, involving both ostia of the right pulmonary veins (RPV), was present in CCT (Figure 1). After this finding, the patient performed a complete imagological study.

The transthoracic echocardiographic study revealed a dense, irregular, thickened ceiling mass of the LA roof near to RPV entrance (Figure 2A). Transesophageal echocardiography showed voluminous LA mass extending into the posterior wall of the aortic root and LA appendage with an apparent anterior cleavage plane between the mass and LA wall (figure 2B to 2D).

At cardiac magnetic resonance (CMR) study, a clearly defined mass with a maximum 32 mm diameter was shown. This was isointense at T1-weighed sequences, bright at T2-weighed sequences, with some heterogeneous perfusion and late gadolinium enhancement (Figure 3).

Differential diagnosis

A myxoma was initially suspected as it represents the most common asymptomatic incidental mass, beyond thrombus, arising in the left atrium. In this case, the absence of a pedicle, several imagological features and its specific location along the posterior and superior LA wall raised the suspicion of another clinical entity, namely possible malignant behavior.

Management

Given the suspicion of malignancy, an F-18 FDG PET/CT was performed to identify both primary tumor and potential distant associated lesions. A solitary left atrial mass was identified. A complete body CT scan was performed for staging purposes, and it was negative for extra-cardiac disease.

Given the presumptive diagnosis of a primary cardiac tumor of potential malignant behavior, either for local extension or embolic risk, a decision was made to proceed with surgical resection for diagnostic and treatment purposes. Intraoperatively, the resected mass extended through the posterior wall of LA until the anterior commissure of the mitral annulus, without pulmonary veins infiltration. Posterior infiltration with incomplete mass detachment forced the need for both atrial and inter-atrial septum reconstruction using a pericardial patch. Postoperative recovery was uneventful.

The macroscopic evaluation revealed an irregular elastic fragment of 50x25x10 mm (Figure 4). Histopathological examination on hematoxylin and eosin stain showed that the lesion was composed of solid areas with a fine reticulate network of collagen and moderate nuclear pleomorphism with prominent focal nucleoli and mitotic activity (characteristic of an undifferentiated pleomorphic sarcoma) (Figure 4B). Immunohistochemistry revealed positivity for vimentin, a mesenchymal marker (Figure 4C) with negative epithelial and muscular markers. Ki67 was 40% positive in more proliferative areas (Figure 4D). The diagnosis of a primary undifferentiated pleomorphic cardiac sarcoma with possible MDM2 amplification was assumed.

The patient was discharged on the ninth day after surgery. She was referred for adjuvant therapy. At the fifth

Keywords

Heart Neoplasms; Sarcoma; Atrial Fibrillation.

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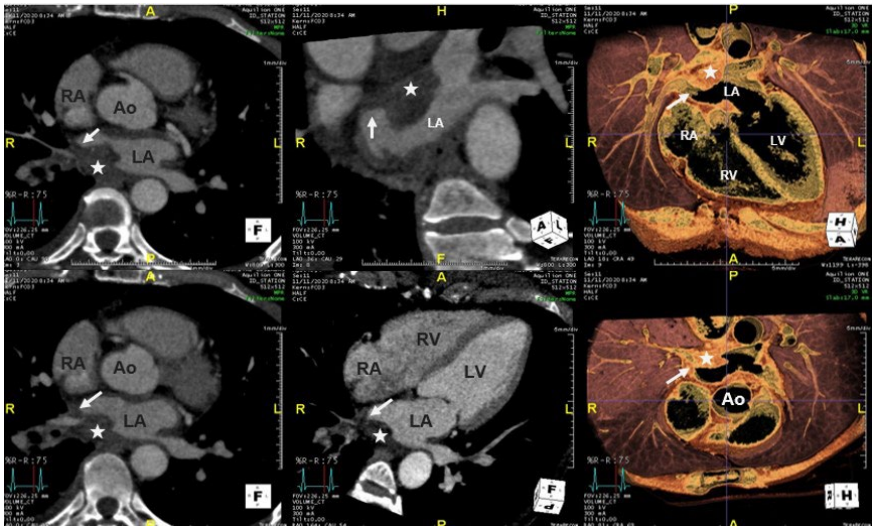

Figure 1 – *Cardiac computed tomography. A homogenous, hypodense, slightly irregular sessile mass (★), located in the posterior wall of the left atrium (LA), involving both ostia of the right pulmonary veins is depicted (arrows). Ao: Aorta; RA: Right atrium; RV: Right Ventricle; LV: Left Ventricle.*

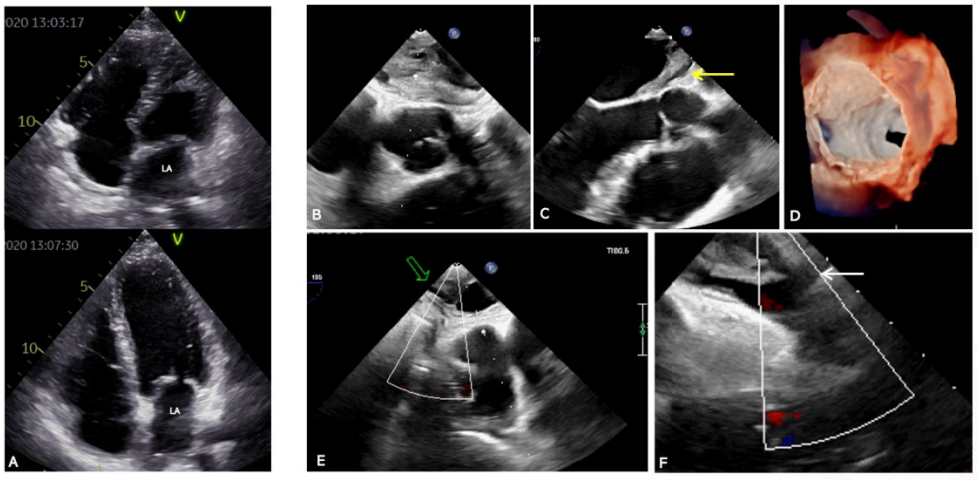

Figure 2 – *A) Transthoracic echocardiographic study showing a dense and irregular thickened ceiling mass of the LA near the right pulmonary veins ostia; B – D) Transesophageal echocardiogram showing an isoecogenic mass extending from the posterior wall of the aortic root towards the posterior left atrial wall; anteriorly there is a cleavage plane between the mass and left atrial wall (yellow arrow); posteriorly this is not the case as the limits of the mass are not clearly identified. E - F) Transesophageal echocardiogram showing LA mass related to the right pulmonary veins (right inferior pulmonary vein (RIPV) and right upper pulmonary vein (RUPV)). E) RIPV outflow compression as showed by ostial molding (green arrow). F) No interference with the RUPV outflow (white arrow). LA: left atrium.*

month of follow-up, she had already completed 2 cycles of chemotherapy with doxorubicin and ifosfamide and is now performing radiotherapy with an uneventful clinical course.

Discussion

Primary tumors of the heart are extremely rare entities, with less than 0.1 percent incidence.[1,2] They are aggressive tumors that may be symptomatic or, if they do not produce symptoms until they are locally advanced, as in the case reported, they are found incidentally during a cardiac imaging study.[2,3] They tend to occur in young patients with a mean age of 44 years and are approximately equally distributed between the sexes.[4] Cardiac sarcomas, albeit extremely rare, are the most common primary malignant lesions.[5,6] Depending on the subtype, they can arise from mesenchymal cells of ventricles, atria or pericardium. These malignancies proliferate quickly and cause death through

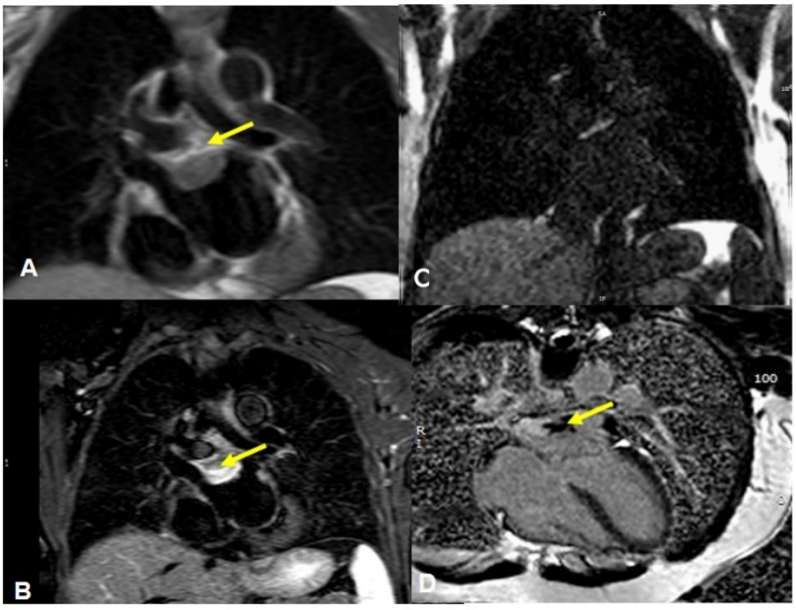

Figure 3 – *CMR study. LA mass (yellow arrows). A) T1-weighed sequence depicting an isointense posterior left atrium wall mass. B) corresponding T2-weighed sequence with fat-suppression showing high signal intensity across the mass. C) first-pass perfusion with contrast uptake. D) delayed enhancement sequence with a heterogeneous aspect positive for the presence of fibrosis.*

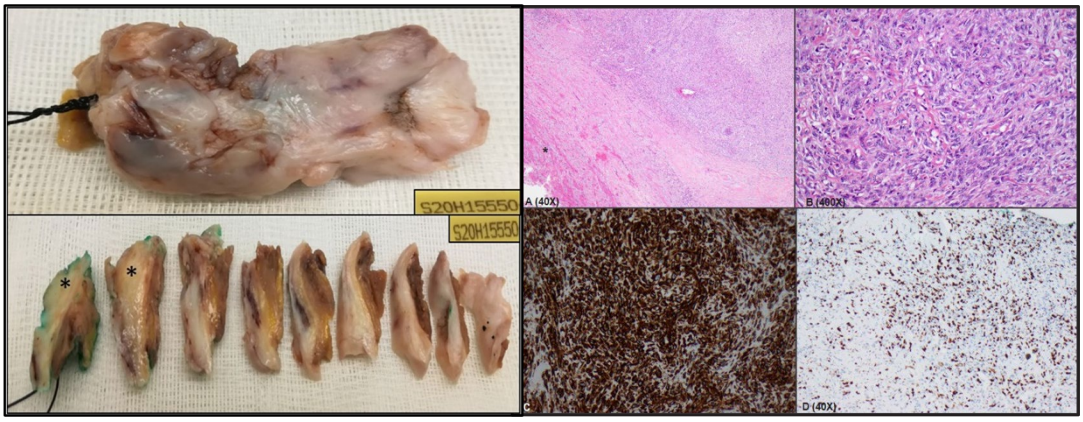

Figure 4 – *Macroscopic findings: 50x25x10mm irregular elastic mass. The cut surface showed an infiltrative and fibrous mass (*) without evident necrosis or myxoid changes. A (H&E): Tumor border with healthy myocardium (*); B (H&E): High power showing solid areas with a fine reticulate collagen network and moderate nuclear pleomorphism, prominent focal nucleoli, and mitosis; C – D: Immunohistochemistry study – positive for both vimentin and Ki67 (with ~40% positivity), respectively.*

widespread infiltration of the myocardium, obstruction of major cardiac vessels, and/or distant metastases.[7]

Surgical resection is the most effective local treatment for cardiac sarcomas, mainly in patients with nonmetastatic disease.[8,9] Although cardiac sarcomas are highly invasive tumors, clear surgical margins are difficult to obtain, and so they can easily recur, highlighting the need for more effective local and systemic treatments that may be used in conjunction with surgery to improve patient outcomes.[8-10] Median survival at diagnosis is 6 to 12 months even after complete surgical excision.[2,4]

Conclusions

Primary cardiac malignancies are very rare entities, being anecdotal as asymptomatic findings. Insertion location and some imaging features, only fully detailed under multimodality assessment, provide clues toward

differential diagnosis, namely with more common benign lesions. The use of advanced imaging tools for staging is key when defining the most appropriate treatment strategy. Complete surgical resection is prompted as the first option.

Author contributions

Conception and design of the research: Santos RR, Abecasis J, Gomes DA, Paiva MS, Trabulo M; acquisition of data: Santos RR, Gomes DA, Paiva M, Rocha B, Ribeiras R, Freitas P, Abecasis M, Trabulo M; analysis and interpretation of the data: Santos RR, Abecasis J, Rocha B, Ribeiras R, Freitas P, Abecasis M, Trabulo M; writing of the manuscript: Santos RR; critical revision of the manuscript for intellectual content: Abecasis J.

Potential Conflict of Interest

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Study Association

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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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Home Blood Pressure Monitoring and Blood Pressure Control in Treated Hypertensives

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Introduction

Blood pressure (BP) control rates are very low in Brazil and in the world, around 20% only.[1-3] Patients with uncontrolled hypertension despite treatment remain at high risk for cardiovascular (CV) events and mortality, comparably to untreated individuals.[4]

According to recent recommendations,[1,2,5,6] BP control should be monitored by both office BP and out-of-office BP measurements. In this way, it is possible to determine different hypertension phenotypes,[1,2,5,6] which is very important to determine the prognosis and individualized therapy.[1,2,5-7]

Home monitoring BP (HMBP) is the measurement of BP at home, performed by the patient or another trained person for several days, while awake, using an automated device and a pre-established protocol. HBPM has a low cost, good reproducibility, and good prognostic value. It is well accepted by patients[5-7] and is associated with lower therapeutic inertia and higher patient engagement and treatment compliance, especially when combined with education and counseling,[1,2,6] contributing to greater CV protection.[5,6,8]

Keywords

Hypertension; Control; Risk Factors; Arterial Pressure; Blood Pressure Monitors/methods; Telemonitoring; Telemedicine

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The present study aimed to compare BP control rates between office BP and HBPM in two treated hypertensive populations. The individuals were assessed in 2019 and 2020, after the implementation of HBPM into the practice of 274 centers in five different regions of Brazil.

Methods

This was a multicentric study, of two cross-sectional cohorts, part of the national registry of BP control, evaluated by office BP monitoring and HBPM.

Office BP was considered as the mean of two measurements performed using a validated oscillometric device (OMRON, model HEM-73,20) on the first day of the HBPM protocol. The same device was used for HBPM. Patients or their caregivers were instructed to take six BP measurements daily.[5] The tests were analyzed through the TeleMRPA platform (www.telemrpa.com), an instrument that allows remote BP data analysis by telemonitoring.

For analysis of office BP control, two BP cutoffs were considered – < 140/90mmHg and < 130/80mmHg – and for HBPM, the cutoff of < 130/80mmHg was used.[1] Although these values are lower than those adopted by Europeans,[2,6] they showed a higher correlation with an office BP of 140/90mmHg and were associated with lower risk of target organ damage, of CV outcomes and mortality.[9] The rates of BP control were analyzed by sex, age group (≥ 60 years and < 60 years), and body mass index (BMI) classification.

The frequency of hypertension phenotypes was determined in 2019 and 2020, considering a BP <140 and 90mmHg and <130 and 80mmHg as normal office BP and HBPM respectively.[1,5,6] The phenotypes were classified as: 1) controlled hypertension (CH): normal office BP and HBPM; 2) white coat uncontrolled hypertension (WCUH): abnormal office BP and normal HBPM; 3) masked

uncontrolled hypertension (MUH): normal office BP and abnormal HBPM; and 4) uncontrolled hypertension (UH): abnormal office BP and HBPM.

All patients read and signed the informed consent form. The study was approved by the ethics committee of the Federal University of Goias (CAAE 08208619.8.0000.5078). Data analysis was performed using the SPSS 27.0 (SPSS Inc.), by the Student's t-test and the chi-square test, rejecting the null hypothesis at the 5% significance level.

Results and discussion

A total of 5,324 individuals were included in the study, 2,538 in 2019 and 2,786 in 2020. Most patients were women (62;2%), as frequently observed in clinical studies conducted in Brazil,[10,11] which probably reflects the fact that women care more about their health than men.[3,12] Mean age of the 2020 cohort was significantly higher than the 2019 cohort. Mean systolic BP (SBP) and mean diastolic BP (DBP) were lower by HBPM than office BP (-6,6/-4,5mmHg, respectively), which is in accordance with previous studies.[1,5,6,10] In addition, mean DBP measured in the office and by HBPM was lower in 2020 compared with 2019, although the difference between the groups was lower than 1 mmHg (Table1). There was no record of antihypertensive medication use in 47.7% of the cases.

Rates of BP control were 57.7% by using an office BP < 140/90mmHg, 28.8% using an office BP < 130/80mmHg and 45.1% pela MRPA < 130/80mmHg (Figure 1). When the standard target (< 140/90mmHg) was adopted, BP control rates were higher (57.7%) than those registered in Brazil and other countries,[1,3] but similar to those reported in previous Brazilian studies when hypertensive patients were treated by specialists, particularly cardiologists.[10,11]

As compared with 2019, in 2020, there was an increase in the control rates for office BP < 130/80 mmHg (27.2% vs. 30.2%; p<0.02) and HBPM < 130/80mmHg (42.4% vs. 47.5%; p<0.0001) (Figure 1). The SPRINT[13] (Systolic Blood Pressure Intervention Trial) demonstrated that targeting lower systolic blood pressure than the standard target resulted in higher CV protection, which has been considered by the guidelines.

It is worth pointing out that the COVID-19 pandemic that started in 2020, could have negatively impacted the BP control rates, and yet, an increase in the control rates was observed instead. A recent Brazilian study with more than 50,000 individuals did not find any influence of the pandemic on BP control rates, determined by office BP or HBPM.[14]

Elderly patients usually show greater difficulty in controlling their BP,[1,2,12] and in the present study an increase in BP control rates by office BP <130/80mmHg and HBPM was observed in older patients. Studies with older hypertensive patients have emphasized the benefits of greater reductions in BP on CV protection.[15,16] Also, obesity is a condition that has a large impact on BP,[1,2] and we found an increase in BP control rates from 2019 to 2020, by both office BP and HBPM. These data reinforce the importance of evaluating BP by both methods.[1,2,5,6]

In the total sample, the distribution of hypertension significantly changed from 2019 to 2020, with increases in the rates of CH and WCUH, and reductions in MUH and UH (Figure 2). Therefore, the percentage distribution of the phenotypes improved from one year to the next, even adopting more strict cut-off criteria for HBPM. In addition, the phenotype distribution revealed higher rates of MUH and lower rates of WCUH than those estimated by the 2020 Brazilian Guidelines on Hypertension[1] and those reported in a Brazilian study with 6,500 patients,[10] which may be explained by the use of a lower cut-off point for HBPM.[17,18]

Some limitations should be noted: 1) the analysis of two cross sectional cohort of hypertensive patients precludes the evaluation of treatment course; 2) more detailed clinical data of the patients are not known, including the

Table 1 – Demographic characteristics, body mass index and blood pressure levels of the 2019 and 2020 cohorts

Variable	Total (n=5324)	2019 (n=2538)	2020 (n=2786)	Statistical test	p value
Sex (M/F) (%)	37.8/62.2	38.1/61.9	37.5/62.5	χ^2=0.193	0.671
Age (years)	61.66±14.9	59.72±15.1	63.43±14.5	t=9.085	<0.0001
Elderly (≥ 60 years) (%)	58.1	52.7	63.1	χ^2=58.825	<0.0001
Body mass index (Kg/m2)	28.6±5.2	28.6±5.1	28.7±5.3	t=0.804	0.421
Overweight/Obesity (%)	41.3/34.4	42.2/33.8	40.4/35.1	χ^2=1.663	0.435
Office SBP (mmHg)	132.2±19.8	132.4±19.4	132.1±20.2	t=0.610	0.542
Office DBP (mmHg)	82.5±11.9	82.7±12.0	82.1±11.8	t=2.373	<0.02
HBPM SBP (mmHg)	125.6±15.9	125.9±16.1	125.4±15.7	t=1.208	0.227
HBPM DBP (mmHg)	77.9±9.5	78.6±9.3	77.3±9.6	t=4.823	<0.0001

SBP: systolic blood pressure; DBP: diastolic blood pressure; HBPM: home blood pressure monitoring; t-test and chi-square test.

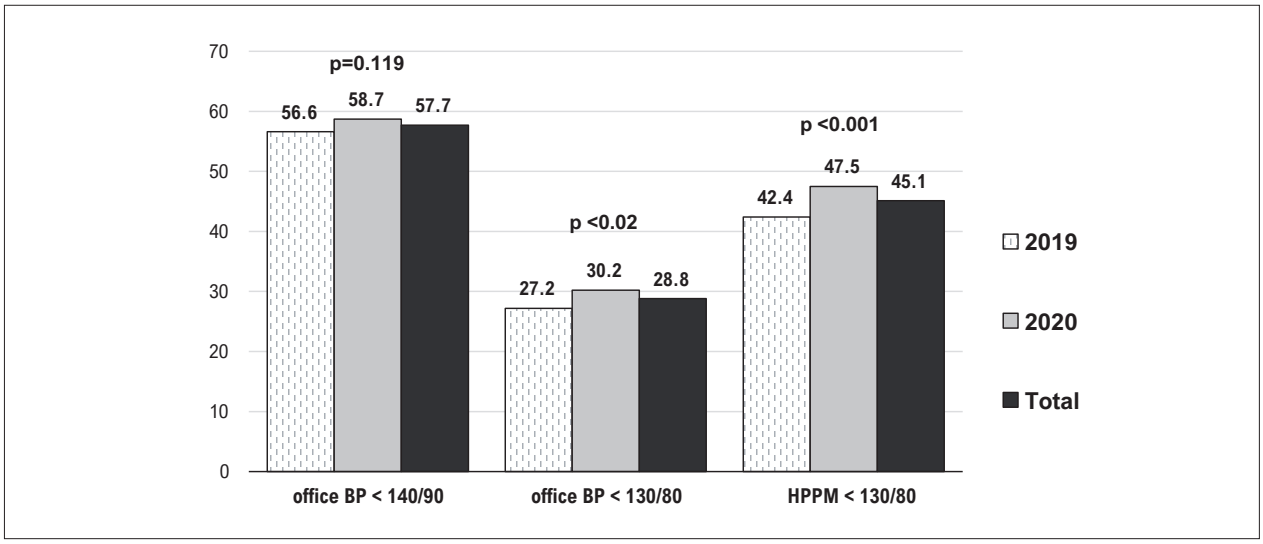

Figure 1 – *Office blood pressure and home blood pressure monitoring targets in 2019 and 2020; BP: blood pressure; HBPM: home blood pressure monitoring; chi-square test.*

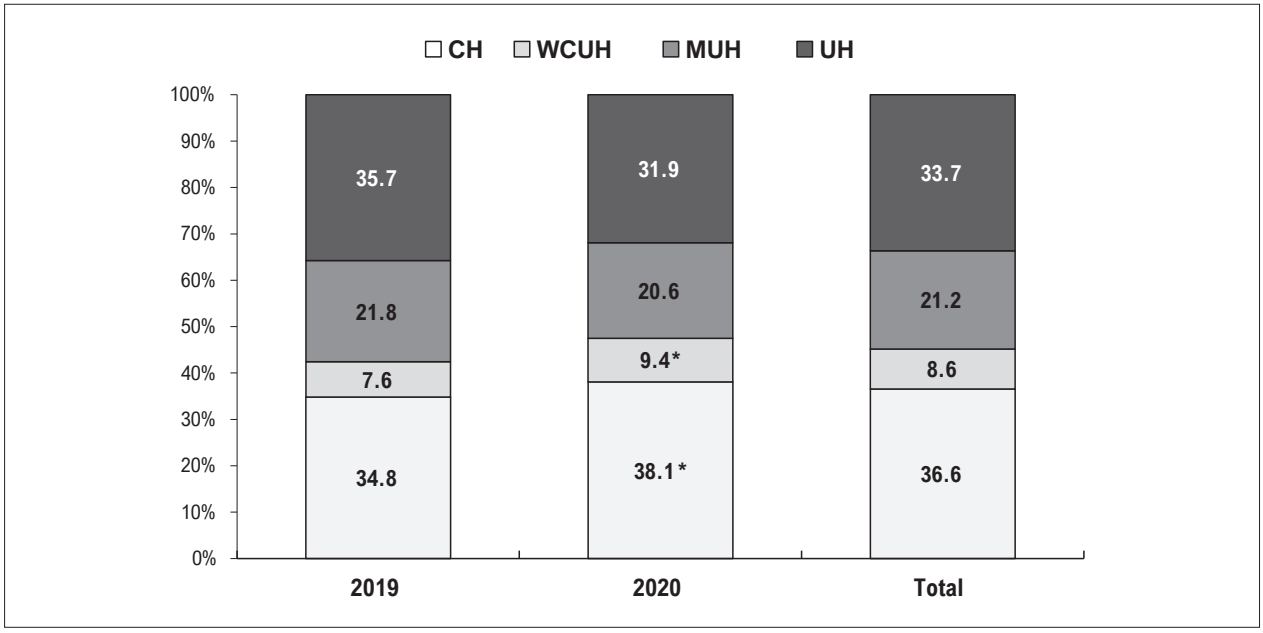

Figure 2 – *Distribution of hypertension phenotypes in 2019 and 2020; CH: controlled hypertension; WCUH: white coat uncontrolled hypertension; MUH: masked uncontrolled hypertension; UH: uncontrolled hypertension; chi-square test, *p < 0.05.*

stage of hypertension, the presence of comorbidities and other CV risk factors; 3) data on medication use were available (and incomplete) in less than half of patients. On the other hand, one strength of this study was the sample size, with relatively homogeneous cohorts in 2019 and 2020 for most of demographic and clinical features evaluated.

In conclusion, the data from this study revealed an increase in BP control rates using both office BP <130/80mmHg and HBPM in treated hypertensive patients. In 2019, HBPM was implemented to be used more frequently, and in a regular manner. This may have influenced the practice of physicians, towards greater attention to the measurement of BP levels out of the office, with a consequent increase in the rates of BP control from 2019 to 2020. In addition, HBPM has improved patient engagement in treatment, and has been associated with higher compliance and better blood pressure control.[19,20] Altogether, these data demonstrate the important contribution of HBPM in increasing the rates of BP control.

Author Contributions

Conception and design of the research: Brandão AA, Barroso WKS, Feitosa A, Barbosa ECD, Miranda RD, Ribeiro LP, Epelman A; Acquisition of data: Brandão AA, Barroso WKS, Feitosa A, Barbosa ECD, Miranda RD, Ribeiro LP, Saraiva GA, Silveira FS, Braga AA, Gomes MM; Analysis and interpretation of the data: Brandão AA, Barroso WKS, Feitosa A, Barbosa ECD, Miranda RD, Vitorino PVO, Pozzan R, Saraiva GA, Silveira FS, Braga AA, Gomes MM; Statistical analysis: Vitorino PVO, Pozzan R; Obtaining financing: Brandão AA, Barroso WKS, Feitosa A, Barbosa ECD; Writing of the manuscript: Brandão AA, Barroso WKS, Feitosa A, Barbosa ECD, Vitorino PVO, Pozzan R, Gomes MM; Critical revision of the manuscript for intellectual content: Brandão AA, Barroso WKS, Feitosa A, Barbosa ECD, Miranda RD, Vitorino PVO, Pozzan R, Ribeiro LP, Epelman A, Saraiva GA, Silveira FS, Braga AA, Gomes MM.

Potential Conflict of Interest

Dra. Andréa Araujo Brasdão – Servier do Brasil and Beliva.

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Dr. Audes Feitosa – Servier do Brasil and Beliva.

Dr. Eduardo Costa Duarte Barbosa – Servier do Brasil and Beliva.

Dr. Roberto Dischinger Miranda – Servier do Brasil and Beliva.

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*Supplemental Materials

For additional information, please click here.

"Lightning The Heart" with 3D Echo: Transillumination of a Prosthetic Mitral Valve Dehiscence

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Three-dimensional (3D) echocardiogram with transillumination (TI) is a novel 3D rendering tool that enhances specific image features not optimally displayed by conventional 3D imaging. Conventional 3D rendering lacks consistency regarding image details and depth perception, often presenting suboptimal images. Transillumination 3D imaging benefits from the integration of a movable virtual light source into the data set. The light source can be moved anteriorly or posteriorly and from side to side, being positioned at specific locations in order to highlight the region of interest, increase accuracy, improve depth perception, create shadows, and enable a more precise distinction between structures. Additionally, this new 3D rendering tool improves visualization and delineation of orifice and edges, cavities, masses, and structural abnormalities,[1,2] and is essential to perform detailed imaging during procedures.[3]

Transillumination may be particularly valuable in challenging scenarios, especially in the evaluation of cardiac prosthesis and devices that produce acoustic shadowing, leading to increased diagnostic accuracy.[4,5]

In the panel, we present two cases where 3D echocardiogram with TI conveyed additional diagnostic value in the evaluation of prosthetic valve dehiscence.

Case 1

A 55-year-old man underwent mitral valve replacement with a caged-ball prosthesis (3M Starr-Edwards) at the age of 29. He was admitted with acute heart failure, functional New York Heart Association (NYHA) class III. Transthoracic echocardiography (TTE) showed a moderate-severe mitral periprosthetic leak; 3D-transesophageal echocardiography (TOE) showed prosthesis dehiscence, with a severe periprosthetic leak (Figure 1A). TI improved depth perception and accurate definition of the degree of prosthetic dehiscence, demonstrating a disinsertion of the mitral prosthesis, involving more than 50% of mitral circumference (Figure 1B; Video 1).

Case 2

A 73-year-old man underwent mitral annuloplasty with a 34-mm complete ring. Four months later, he presented dyspnoea. TTE showed moderate mitral regurgitation (MR) and a hyperechogenic structure in the left atrium; 3D-TOE confirmed the presence of moderate MR and showed a partially detached ring (Figure 1C). In this case, TI enabled better visualization of the separation points of the prosthetic ring, showing the integrity of the posterior mitral leaflet, and provided additional information about MR mechanism, which was due to a dilated native mitral annulus that led to incomplete leaflet coaptation (Figure 1D; Video 2).

Despite 3D TI being highly feasible in a variety of cardiac conditions, including structural heart disease, it is not a widely available technique yet, and it still requires adequate training and further studies focusing on clinically relevant endpoints and effectiveness to validate the implementation of TI rendering in routine clinical practice. Furthermore, the current evidence is still limited regarding the added benefit of TI when compared to other techniques.

Nevertheless, this novel technique does not require a steep learning curve and is a relatively intuitive process to move the virtual light source in order to emphasize the structure of interest.[4] Transillumination rises as an alternative to conventional 3D imaging, especially in conditions where it is anticipated that conventional rendering will provide suboptimal images, particularly in the evaluation of prosthetic valve disease.[5]

These two cases highlight the importance of TI rendering in the evaluation of complex structural heart disease.

Keywords

Echocardiography, Three-Dimensional/méthods, Cardiovascular Diseases/diagnostic imaging; Cardiovascular Diseases/physiopathology; Image Interpretation, Computer Assisted; Observer, Variation; Transillumination; Mitral Valve/diagnosis.

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Author contributions

Conception and design of the research and Writing of the manuscript: Silva MR, Azevedo AI; Acquisition of data: Silva MR, Sampaio F, Ribeiro J; Analysis and interpretation of the data: Silva MR, Azevedo AI, Sampaio F, Ribeiro J, Fontes-Carvalho R; Critical revision of the manuscript for intellectual content: Silva MR, Azevedo AI, Sampaio F, Ribeiro J, Fontes-Carvalho R.

Potential Conflict of Interest

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

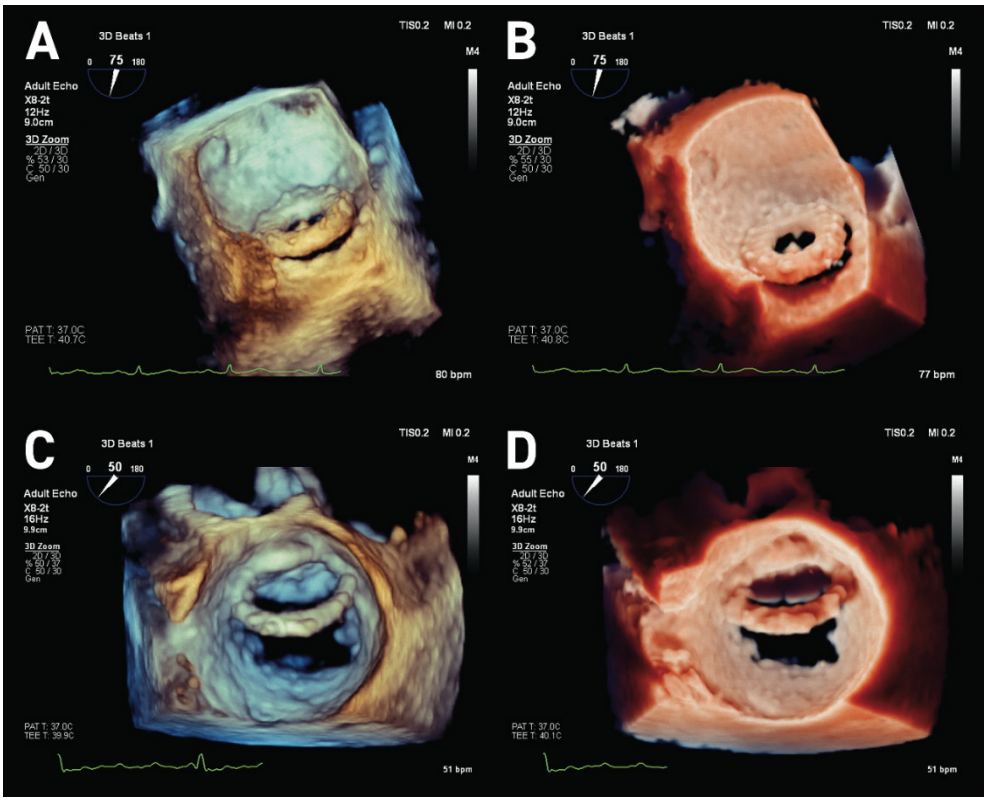
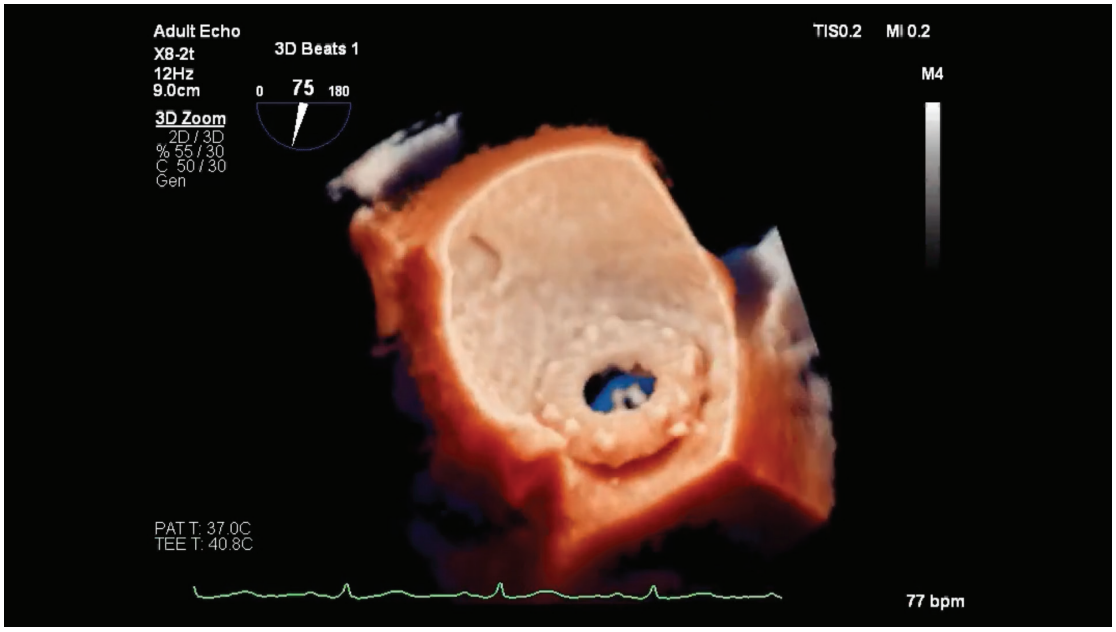
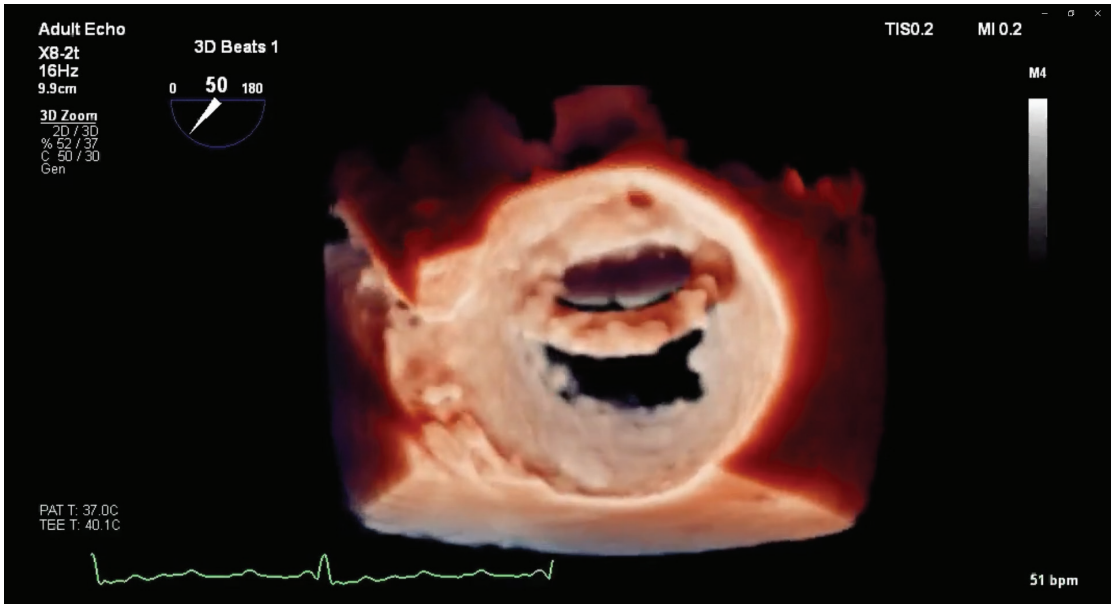


Figure 1 – *Panels A and B. 3M Starr-Edwards mitral prosthesis dehiscence viewed from left atrium (left atrial appendage at 9 o'clock position). Panel A: conventional 3D imaging. Panel B: TI rendering; the light is positioned below left atrial appendage. The shadowing effect improves depth perception and most accurate definition of the degree of prosthetic dehiscence. Panels C and D: Mitral ring dehiscence viewed from left atrium (aortic valve between 11 and 12 o'clock position). Panel C: conventional 3D imaging. Panel D: TI rendering; the light is positioned laterally near the left atrial appendage, enhancing the points of separation of the ring and depicting the integrity of the posterior mitral leaflet. 3D: three-dimensional; TI: transillumination.*



Video 1 – *URL: http://abccardiol.org/supplementary-material/2022/11902/2021-0655-video-1.mp4*



Video 2 – *URL: http://abccardiol.org/supplementary-material/2022/11902/2021-0655-video-2.mp4*

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This article does not contain any studies with human participants or animals performed by any of the authors.

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Previous Chronic Diseases and their Relationship with COVID-19 Infection

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Dear editor,

Due to the current global pandemic, the subject addressed is of great relevance. It is known that there is a certain urgency in the production and dissemination of scientific and epidemiological data about the new Coronavirus. Therefore, research that helps profile the population most vulnerable to this disease contributes to preventing an even greater number of deaths and sequelae resulting from COVID-19.

Although the Coronavirus infects people of all ages, complications are prevalent among two groups: the elderly and those with pre-existing comorbidities. Considering this last group, systemic arterial hypertension (SAH) and diabetes mellitus (DM) are two of the main risk factors for mortality from COVID-19.[1] In agreement with this data, a study on the multimorbidity of Brazilians published in Cadernos de Saúde Pública (CSP), showed that approximately 72% of patients admitted to the ICU for COVID-19 had previous chronic diseases compared to those who did not need this intensive care (37%).[2]

Consequently, there is a large contingent of people at risk of severe COVID-19 in the country, reinforcing that the profile of comorbidities in the Brazilian population is a worrying factor that needs to be considered. In this case, the adoption of non-pharmacological interventions becomes fundamental for the prevention of severe cases of infection,[2] since many of the aggravating factors are preventable, and ensuring a healthier lifestyle for the population would reflect positively on the battle against the pandemic.

Therefore, epidemiological studies are important tools for characterizing the typical behavior of the disease and guiding public policy decisions in health and epidemiological surveillance.[3] Thus, the estimate presented is important to plan people's monitoring strategies for chronic morbidities and prevention in the fight against the new Coronavirus.[3]

In this context, the Brazilian Unified Health System (SUS) and primary health care, through the coordination of care by the Family Health Strategy, will continue to have an important role in mitigating social inequities in health through the prevention of virus infection and management of chronic conditions and multimorbidity during and after the pandemic.[2]

Keywords

Diabetes Mellitus/prevalence; Hypertension/prevalence; COVID-19; Pandemic; Risk Factors; Epidemiologic Studies; Primary Health Care; Unified Health System

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Reply

The transformation of data into information, from information into knowledge and from knowledge into wisdom, while not an easy task – especially in times of a pandemic – is fundamental for timely intervention. Even more so when these interventions can save the lives of countless people [the term 'people' alluded to here has the geometric meaning of being a subject. They are real, concrete beings and owners of life and happiness projects]. Producing science is, therefore, an act of commitment to these subjects. The protected good is life itself – our and ours!

In Brazil, since 2006, the most important research on risk and protection factors for chronic diseases has been published in the capitals of 26 states and the Federal District, totaling 27 cities (Vigitel- Surveillance of risk and protection factors for diseases chronicles by telephone survey).[1] The data collected in 2020, although showing progress, is still worrying:

i. the frequency of adult (≥18 years) smokers in the 27 cities was 9.5%;

ii. overweight (BMI ≥ 25 kg/m2) was observed in 57.5% of the population, and obesity (BMI ≥ 30 kg/m^2) was observed in 21.5% of the individuals;

iii. the practice of physical activity in free time equivalent to 150 minutes of moderate activity per week was reported by just over a third of the population (36.8%);

iv. the frequency of arterial hypertension reached ¼ of the population (25.2%); and

v. the frequency of Diabetes Mellitus was 8.2%.[2]

The increase in the prevalence of risk factors and chronic diseases themselves is a worrying reality, not only in Brazil but throughout the world. In 2019 alone, 54.7% of deaths recorded in Brazil were caused by chronic non-communicable diseases.[3] This scenario requires a collective effort – managers, health professionals and civil society – and intersectoral, involving all levels of care and prevention. Only a broad set of policies can satisfactorily impact this scenario.

Considering this context, in 2021, Brazil launched the "Plan of Strategic Actions to Combat Chronic Diseases and Non-Communicable Diseases in Brazil 2021-2030"[4] with the objective of "strengthening the agenda for combating NCDs, violence and accidents at the federal, state, municipal and Federal District levels, as well as guide health promotion in health actions".[4] It should be noted that the plan in question is in line with global recommendations and adopts a bold indicator monitoring system.

The launch of the plan dialogues with the need to produce knowledge about the influence of risk factors (obesity, sedentary lifestyle and smoking, for example) and chronic diseases on the clinical outcome of individuals with COVID-19, as well as the impact of the pandemic - and its control measures – on the prevalence of these risk factors and diseases. There is a two-way street with many questions to be answered.

Finally, we were honored to receive the comment regarding our text[4] and thank you for the moment of discussion.

Carlos Souza
Lucas Santos
Jussara Baggio
Thiago Leal
Francisco Costa
Tânia Fernandes
Regicley Silva
Anderson Armstrong
Rodrigo Carmo

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