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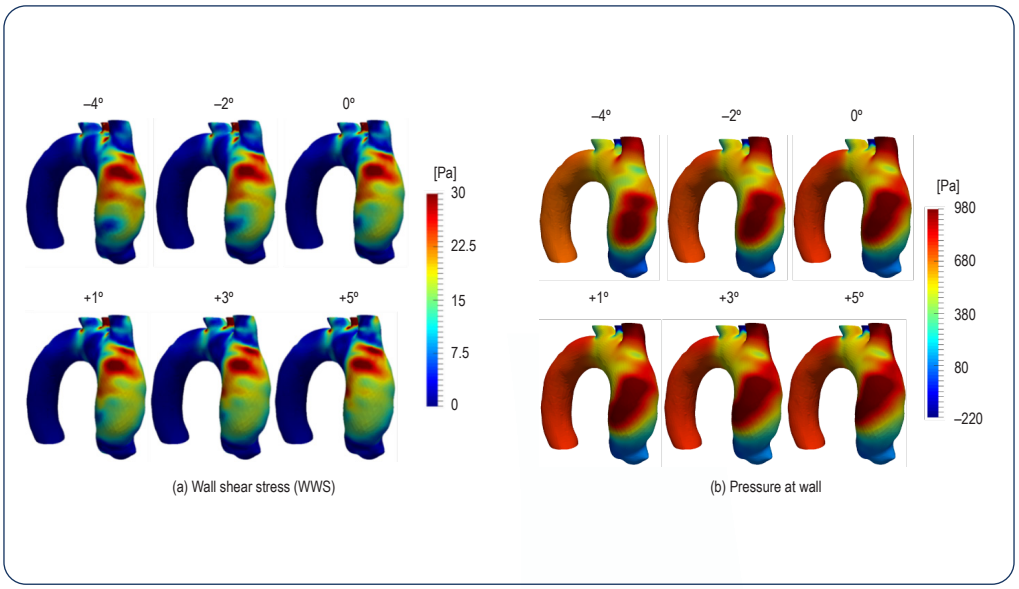

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Arquivos Brasileiros de Cardiologia
JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Overview of Recent Advances in Experimental Cardiovascular Research

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Basic research is essential to generate and expand knowledge in several research areas. In recent decades, cardiology practice has substantially changed in response to advances in experimental research, which have provided a better understanding of the molecular mechanisms involved in cardiovascular diseases. Consequently, new diagnostic evaluation tools have been introduced and new drugs have been indicated for treating cardiovascular diseases.[1]

Recent articles in *Arquivos Brasileiros de Cardiologia*, also known as ABC Cardiol, have shown great scientific advances in basic research, with studies originating from researchers from Brazil and from other countries. Additionally, knowledge from more diverse areas has been seen in national scientific output. In the last decade, the journal has seen a significant increase in the number of articles from different fields of research such as physical education, physiotherapy, nutrition, biology, biomedicine, etc. This Editorial focuses on basic research articles recently published in ABC Cardiol.

Currently, exercise is considered an important tool for preventing and treating cardiovascular diseases, particularly when considering population aging.[2] Consequently, the use of physical exercise has played an important role in cardiovascular diseases in the contemporary national and international scientific output. Recently, ABC Cardiol articles have shown that physical exercise contributes to redox and inflammatory balance in the heart in conditions of systemic agressions, such as obesity[3] and low-density lipoprotein receptor knockout associated with ovariectomy.[4] Exercise has also been shown to stimulate myocardial angiogenesis in diabetic cardiomyopathy.[5] Even passive exercise, such as whole-body vibration has produced beneficial effects by increasing myocardial tolerance to ischemia in rats.[6] These results add to the understanding of the mechanisms involved regarding the beneficial effects of exercise on cardiovascular disease prevention and treatment.

Another widely addressed strategy in cardiology is nutritional therapy.[7] A recent study highlighted the antioxidant effects of açaí berry and the improvement in energy metabolism, regardless of changes in left ventricular function after ischemia-reperfusion in rats.[8] Fat is another component under the experimental spotlight. Muniz et al.[9] reported that a high-lard diet increases body weight without inducing rat dyslipidemia. On the other hand, a high-lard high-cholesterol diet leads to dyslipidemia and severe liver damage.[9]

In addition to the potential non-pharmacological therapies described above, new drug effects have been studied in reports published in ABC Cardiol. Ramezani-Aliakbari et al.[10] evaluated the use of trimetazidine in diabetic rats with cardiomyopathy. The drug, often used to improve myocardial metabolism in coronary heart disease, reduced myocardial hypertrophy, and improved electrocardiographic and functional ventricular parameters [10]. Another drug, the angiotensin-II type 1 receptor blocker losartan, was shown to improve myocardial function in rats with high-fat diet-induced obesity.[11]

In the field of myocardial revascularization, rapamycin administered in combination with α-cyanoacrylate was superior in maintaining vascular patency than either used individually in vascular grafts in rats.[12] The positive effects seemed to be related to decreased intimal thickening, cell proliferation, and inflammatory response in the graft.[12]

Finally, studies investigating factors aggravating cardiovascular diseases have also been published. Vassallo et al.[13] described that mercury exposure impairs systemic arterial hypertension and increases myocardial oxidative stress and plasma activity of angiotensin-converting enzyme in spontaneously hypertensive rats. Physical stress, another risk factor for cardiovascular diseases, was also addressed.[14,15] Physical stress induction during the prenatal period resulted in sex-specific changes in the β1 adrenergic receptor gene expression of adult rat offspring.[14] On the other hand, applying physical stress 60 minutes before ischemia-reperfusion reduced the infarction area and improved ventricular function in rats.[15]

Despite the increase in information on the effect of physical exercise on signaling pathways, the systemic and cardiovascular effects of different diets, and the use of novel drugs for preventing and treating cardiovascular diseases, there is still a long way to go before knowledge can be incorporated into clinical practice. Hopefully, advances in translational medicine can help reduce the time lag between basic knowledge and its clinical application. ABC Cardiol has an important role in publishing scientifically relevant and important articles related to all areas of cardiology. Additionally, the journal promotes high-quality multi-professional and scientific debate, bringing together different professionals involved in the prevention and treatment of cardiovascular diseases.

Keywords

Cardiovascular Diseases/trends; Exercise; Heart Failure; Molecular Mechanisms/trends; Scientific Domaine; Scientific and Technical Activities/trends.

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Current Impact of Cardiopulmonary Bypass in Coronary Artery Bypass Grafting in São Paulo State

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Abstract

Background: **Previous results on the use of cardiopulmonary bypass (CPB) have generated difficulties in choosing the best treatment for each patient undergoing myocardial revascularization surgery (CABG) in the current context.**

Objective: **Evaluate the current impact of CPB in CABG in São Paulo State.**

Methods: **A total of 2905 patients who underwent CABG were consecutively analyzed in 11 São Paulo State centers belonging to the São Paulo Registry of Cardiovascular Surgery (REPLICCAR) I. Perioperative and follow-up data were included online by trained specialists in each hospital. Associations of the perioperative variables with the type of procedure and with the outcomes were analyzed. The study outcomes were morbidity and operative mortality. The expected mortality was calculated using EuroSCORE II (ESII). The values of p <5% were considered significant.**

Results: **There were no significant differences concerning the patients' age between the groups (p=0.081). 72.9% of the patients were males. Of the patients, 542 underwent surgery without CPB (18.7%). Of the preoperative characteristics, patients with previous myocardial infarction (p=0.005) and ventricular dysfunction (p=0.031) underwent surgery with CPB. However, emergency or *New York Heart Association* (NYHA) class IV patients underwent surgery without CPB (p<0.001). The ESII value was similar in both groups (p=0.427). In CABG without CPB, the radial graft was preferred (p<0.001), and in CABG with CPB the right mammary artery was the preferred one (p<0.001). In the postoperative period, CPB use was associated with reoperation for bleeding (p=0.012).**

Conclusion: **Currently in the REPLICCAR, reoperation for bleeding was the only outcome associated with the use of CPB in CABG. (Arq Bras Cardiol. 2020; 115(4):595-601)**

Keywords: **Extracorporeal Circulation; Risk Factors; Myocardial Revascularization; \epidemiology; Hospital Mortality; Postoperative Care; Morbidity.**

Introduction

The coronary artery bypass graft (CABG) surgery is one of the most studied procedures and, consequently, excellent results have been achieved.[1] The advent of cardiopulmonary bypass (CPB) has, undoubtedly, allowed establishing CABG as a safe, effective, and reproducible treatment, although there has always been a concern about the influence of CPB on morbimortality.[2] The first analysis that compared CABG with and without CPB was carried out in low-risk patients and did not show any significant differences.[3] Over time, CPB control was improved and short-term benefits began to be found only for subgroups at greater risks.[4] However, more recent randomized studies that did not find short-term differences disclosed problems with the technique without CPB, where complications occurred related to the patency of anastomoses and with the highest rates of incomplete revascularization.[5-7] Thus, although the criteria for CABG indication are well defined, the choice is based on the clinical profile and the surgeon's experience. The current opportunity for the technique without CPB might be related to the increased number of fragile patients referred for CABG,[8] based on the concept of applying the correct procedure to the correct patient. Current results for CABG with CPB show a reduction in the incidence of stroke,[9] although problems with an increase in bleeding and renal dysfunction persists for high-risk patients.

In Brazil, the proportion of patients who undergo CABG without CPB is variable, as are the morbimortality results.[10] The lack of a national guideline that recommends the handling of CPB through goal directed perfusion, security protocols, and

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real-time monitoring could be influencing the results; thus, there is a gap in our understanding of the impact of CPB on CABG.

The goal of this study was to evaluate the current impact of CPB on the morbimortality of patients undergoing CABG recorded in the REPLICCAR, the largest cardiovascular surgery registry in São Paulo State.

Methods

Samples

The total number of samples included 5222 patients, of which 2905 underwent CABG at the 11 participating institutions of the REPLICCAR study.[11] The patients were consecutively submitted to surgery from November 2013 to December 2016 at the following hospitals:

1- Instituto do Coração do Hospital das Clínicas da FMUSP
2- Beneficência Portuguesa de São Paulo
3- Hospital de Clínicas da UNICAMP
4- Irmandade da Santa Casa de Piracicaba
5- Irmandade da Santa Casa de São Paulo
6- Hospital Paulo Sacramento de Jundiaí
7- Hospital Pitangueiras do Grupo SOBAM
8- Hospital das Clínicas de Ribeirão Preto
9- Hospital São Paulo da UNIFESP
10- Hospital de Base de São José do Rio Preto
11- Irmandade da Santa Casa de Marília

Inclusion Criteria

All the patients were aged ≥18 years old and underwent CABG either electively, urgently, or because of an emergency during the established period.

Exclusion Criteria

Patients who underwent associated surgeries (including valve, thoracic aorta, and other surgeries) and alternative procedures to treat coronary insufficiency (laser, stem cell injections, and others) were excluded.

Data Collection, Definition, and Organization

The analysis was based on the REPLICCAR I database, which is a prospective, multicenter, mandatory registry that includes data collected between November 2013 and December 2016. The data collection was performed by people who had a degree and were trained for this exact purpose in each participating center. The data were incorporated into the website http://bdcardio.incor.usp.br/, through 4 available interfaces, including preoperative, intraoperative, postoperative, and evaluation after 30 days. Patient follow-up was performed through telephone interviews. The completeness and veracity of the data were overseen by the executive records committee. The definitions of variables were adopted from EUROSCORE II and the mortality calculation was performed using http://www.EuroSCORE.org/calc.html.

The analyzed outcomes were: morbidity (reoperation for bleeding, cardiogenic shock, stroke, surgical site infection, mediastinitis, pneumonia, acute myocardial infarction, and acute kidney injury) and surgical mortality in the period between the surgery and the 30-day evaluation, or otherwise, discharge from the hospital.

Statistical Analysis

The statistical analysis was performed using STATA software version 13.1 (StataCorp, Texas, USA). The *Shapiro-Wilk* test was used to evaluate data distribution normality. The variables: BMI (<18.5kg /m² low, 18.5-24.9kg /m² normal, 25-29.9kg / m² overweight and ≥30kg / m² obesity), NYHA Classification (I and II and III and IV), EuroSCORE II (<5% and ≥5%), glycosylated hemoglobin (≤7% and> 7%), ejection fraction (<30%, 30-50%, ≥50%), Hematocrit (<30% e; ≥30%) and creatinine levels (≤1.4mg / dL and> 1.4mg / dL) were categorized as absolute and relative frequencies, with the binomial confidence interval of 95%. Continuous variables were assessed for the difference using the *Mann-Whitney* test, due to the data distribution. However, the Chi-square or Fisher's Exact tests were used for the comparison of categories. Asymmetric continuous variables were described as median and interquartile range. The outcome variables (postoperative complications) were analyzed using univariate logistic regression and odds ratios and 95% confidence intervals were expressed. P values < 5% were considered significant.

Ethics and Consent Form

This study is a subanalysis of the project entitled "Heart Surgery Programs Innovation Using Surgical Risk Stratification at the São Paulo State Public Healthcare System" registered online under number 9696 at the Ethics Committee for Research Projects Analysis Extended Diagnosis Clusters (CAPPesq) of Hospital das Clínicas da Faculdade de Medicina Universidade de São Paulo (HCFMUSP).

Results

A total of 2905 patients who underwent coronary artery bypass graft surgery were analyzed during the study period. Of these, 542 (18.7%) did not undergo cardiopulmonary bypass during the procedure. There were no significant differences concerning the patients' age between the groups (p=00.81), as the median age of patients submitted to CPB was 63 years old (56-69), whereas in the group without CPB it was 64 years old (56-71). 72.9% of the patients were males.

Table 1 shows the preoperative characteristics of the evaluated groups, where the sample homogeneity was presented. A high prevalence of prior myocardial infarction were observed in both groups (>40%), however, it was significantly higher in the patients selected for the procedure with the use of CPB (p=0.005). There was no significant difference in relation to the median value of the EuroSCORE II (p=0.482) for both groups.

Table 2 shows that patients with glycosylated hemoglobin >7% underwent surgery with CPB (p=0.008). When the limitation was related to the heart, patients with ejection

Table 1 - Preoperative characteristics of the patients who underwent coronary artery bypass graft with and without CPB. REPLICCAR, São Paulo, 2019

Characteristics	CPB				95% CI	p Value
	Yes (n= 2363)		No (n= 542)			
	N	%	N	%		
Age, median, IQR	63 (56-69) *		64(56-71) *		62.4 – 62.6	0.081 †
Gender					0.25 – 0.29	0.125 ‡
Male	1737	73.5	381	70.3		
Female	625	26.5	161	29.7		
BMI					27.3 – 27.6	0.809 ‡
<18.5	14	0.6	4	0.7		
18.5–24.9	709	30	173	31.9		
25–29.9	1057	44.7	234	43.2		
≥ 30	583	24.7	131	24.2		
Prior myocardial infarction	1142	48.3	226	41.7	0.45 – 0.49	**0.005 ‡**
Prior stenting	389	16.5	98	18.1	0.15 – 0.18	0.363 ‡
Previous heart surgery	36	1.5	4	0.7	0.01 – 0.02	0.157 ‡
Insulin-dependent diabetes	382	16.2	96	17.7	0.15 – 0.18	0.381 ‡
COPD	17	0.7	4	0.7	0.004 – 0.01	0.963 ‡
Functional class IV angina	442	18.7	91	16.8	0.17 – 0.20	0.299 ‡
NYHA					0.32 – 0.36	0.917 ‡
I & II	1562	66.1	357	65.9		
III & IV	801	33.9	185	34.1		
EuroSCORE II					0.07 – 0.09	0.482 ‡
< 5%	2156	91.5	501	92.4		
≥ 5%	200	8.5	41	7.6		

*BMI: body mass index; COPD: chronic obstructive pulmonary disease. * Median and interquartile range (IQR), † Mann Whitney, ‡ Chi-Square or Fisher's exact test.*

fraction <50% were chosen to undergo surgery with CPB (p=0.031). The type of intervention was not associated with hematocrit and creatinine levels in the various cutoffs analyzed in this study.

The intraoperative factors (Table 3) verified that when the off-pump technique was chosen, in relation to the on-pump, there was a greater use of radial artery grafting (p<0.001) over the right internal thoracic artery (RITA) (p<0.001); however, the use of the left internal thoracic artery (LITA) grafts was not significantly associated (p=0.276) with any of the techniques.

The postoperative events (Table 4) did not identify a significant association with the occurrence of stroke up to 30 days after surgery, with a similar proportion between patients with and without CPB (p=0.473). The use of CPB was not related to surgical mortality (p=0.761). However, it was associated with reoperation for bleeding (p=0.001), leading to a 6.2-fold increased risk of bleeding (B=1.8, 95% CI, 0.41-3.23).

Discussion

Evidence has shown that the decrease in inflammatory response in off-pump CABG results in a decrease in organic dysfunctions,[2] as well as lower rates of vasoplegia and kidney injury.[12] This retrospective analysis in large populations confirms a significant decrease in morbimortality when CABG is performed without CPB.[13,14] Furthermore, an analysis of the 4 largest centers in the United States of America (USA) has shown benefits when CABG is performed without CPB, mainly in high-risk patients.[15] Two studies published regarding the same time period, one in the USA[16] and the other in Brazil,[17] also revealed an increased risk of death in patients undergoing CABG with CPB compared with those without CPB, especially in the high-risk group. Similarly, an analysis of 30 years of CABG without CPB showed a significant decrease in hospital mortality outcomes, such as stroke, severe postoperative complications, hospitalization time, and cost reduction.[18]

Nonetheless, randomized high impact trials did not show any difference in favor of CABG without CPB regarding the morbimortality.[19-21] In our analysis, with a current sample and multicentric study, the only difference found in favor of

Table 2 - Preoperative evaluation of the patients who underwent coronary artery bypass graft with and without CPB. REPLICCAR, São Paulo, 2019

	CPB				95% CI	p Value
Pre-operative exams	Yes (n=2362)		Yes (n=2362)			
	n	%	N	%		
Glycosylated hemoglobin					6.6 – 6.9	0.008 ‡
≤ 7%	784	68.0	159	77.0		
> 7%	369	32.0	47	23.0		
Ejection fraction					56.5 – 57.3	0.031 ‡
< 30%	36	1.5	4	0.7		
30 – 50%	474	20.1	87	16.1		
≥ 50%	1853	78.4	451	83.2		
Hematocrit					39.9 – 40.3	0.218 ‡
≥ 30%	2284	96.7	518	95.6		
< 30%	79	3.3	24	4.4		
Creatinine					1.1 – 1.2	0.651 ‡
≤ 1.4 mg/dL	2049	86.7	466	86.0		
> 1.4 mg/dL	314	13.3	76	14.0		

‡ Chi-Square or Fisher's exact test.

Table 3 - Intraoperative factors of the patients who underwent coronary artery bypass graft with and without CPB. REPLICCAR, São Paulo, 2019

	CPB					
Intraoperative	Yes (n=2362)		No (n=542)			
	N	%	n	%	95% CI	p value
LITA	2221	94	516	95.2	0.93 – 0.95	0.276 ‡
RITA	282	11.9	30	5.5	0.09 – 0.12	<0.001 ‡
Radial	134	5.7	114	21	0.08 – 0.1	<0.001 ‡

‡ Chi-Square or Fisher's exact test.

Table 4 - Univariate logistic regression of the postoperative complications of patients who underwent coronary artery bypass graft with and without CPB. REPLICCAR, São Paulo, 2019

Postoperative events and mortality	CPB				
	Yes (n=2362)	No (n=542)	OR	CI 95%	p Value
Reoperation for Bleeding	53 (2.2)	2 (0.4)	6.2	1.5 - 25.5	0.012
Cardiogenic shock	77 (3.3)	20 (3.7)	0.88	0.53 - 1.45	0.614
Stroke	19 (0.8)	5 (0.9)	0.87	0.32 - 2.3	0.784
Surgical site infection	286 (12.1)	55 (10.2)	1.2	0.9 - 1.7	0.203
Mediastinitis	16 (0.7)	6 (1.1)	0.61	0.24 - 1.6	0.303
Pneumonia	163 (6.9)	30 (5.5)	1.3	0.85 - 1.89	0.251
Acute myocardial infarction	38 (1.6)	12 (2.2)	0.72	0.37 - 1.4	0.330
Acute kidney injury	118 (5.0)	32 (5.9)	0.84	0.56 - 1.25	0.338
Death	102 (4.3)	25 (4.6)	0.93	0.57 - 1.46	0.761

OR: Odds ratio

CABG without CPB was the lower number of reoperations for bleeding. This was also verified in the analysis of Lamy et al.,[22] that when no significant difference occurred in morbidity and mortality, there was a decrease in the need for reoperation for bleeding. The rate of reoperation for bleeding found in this present study is similar to that found in another study,[23] but conversely, the mortality rate was 4.5 times higher in patients who had this complication.

The prevalence of CABG without CPB in our sample is similar to the values reported in other studies,[24] suggesting adherence to the guidelines regarding the choice of technique and the inclusion of all the patients in the registry. The analysis also evidenced that, when the surgical limitation was related to the heart manipulation, such as prior myocardial infarction and/or ventricular dysfunction, the group leaned towards choosing the technique with CPB. However, good results were also found when CABG was performed without CPB.[25] Conversely, when limitations were related to patient severity, NYHA IV or an emergency situation, the choice was off-pump surgery. This confirms the studies that showed a preference for CABG without CPB in unstable patients.[26] The higher utilization of radial arterial grafts in CABG without CPB can be explained by the shorter time required for graft preparation in relation to the double thoracic artery graft, mainly in acute cases.

Cantero el al.[27] reported a hospital mortality rate of 4.3% and 4.7% in a group without CPB and with CPB, respectively (p=0.92), similar values to those found in this study (p=0.76). However, the difference from this study is that patients submitted to surgery without CPB had fewer complications related to myocardial infarction (p=0.02) and the use of the intra-aortic balloon pump (p=0.01).

In this study, we did not find any significant correlation with the female gender and a higher index of negative outcomes, as described by Sá el al.,[28] which may be related to the sample size of the different studies.

The risk scores are prediction instruments that help patients and health professionals in their decision making about probable risks of complications or death. In a study conducted at InCor-HCFMUSP, a cutoff was found for the EuroSCORE and the 2000BP that would help in decision making to not use CPB with CABG.[17] This study uses EuroSCORE II, the same that underestimated our observed mortality, which would contradict its utilization in decision making regarding the studied sample. This confirms the recommendations of the last European guideline, where the total use of EII for the prediction of mortality after CABG is contraindicated.[29]

The limitations of this study are as follows: (1) The influence of variations in the handling of CPB and non-CPB protocols used in each participating center were not analyzed; (2) There were no important analyses, such as the use of antiplatelet agents and the use of antifibrinolytics in patients who underwent CABG. However, it is known that the use of protocols following current evidence has considerably reduced the increased risk of bleeding.[30,31]

In summary, randomized clinical trials did not find a short-term reduction in morbidity and mortality demonstrated in observational studies when CABG was performed without CPB. In the future, the use of a more monitored and real-time CPB, including online gasometry and goal-directed therapy, may highlight the advantages of using CPB. Finally, it is important to reiterate that the current state-of-the-art condition is that multidisciplinary groups define and choose the correct technique for the right patient.

Conclusion

Patients chosen for CABG with CPB were the most clinically stable, but with worse ventricular function than those without CPB. Reoperation for bleeding was the only outcome associated with the current CPB practice in São Paulo State; however, this complication did not influence the increase in the number of deaths.

Author Contributions

Conception and design of the research: Borgomoni GB, Mejia OAV, Lisboa LAF, Conte PH, Oliveira MAP, Petrucci Junior O, Tiveron M; Acquisition of data: Borgomoni GB, Mejia OAV, Conte PH, Oliveira MAP, Petrucci Junior O, Tiveron M, Dallan LAO, Jatene FB; Analysis and interpretation of the data: Borgomoni GB, Mejia OAV, Goncharov M, Lisboa LAF, Conte PH, Oliveira MAP, Fiorelli AI, Petrucci Junior O, Tiveron M, Dallan LAO; Statistical analysis: Borgomoni GB, Mejia OAV, Orlandi BMM, Goncharov M; Writing of the manuscript: Borgomoni GB; Critical revision of the manuscript for intellectual content: Mejia OAV, Lisboa LAF, Dallan LAO, Jatene FB.

Potential Conflict of Interest

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

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Cardiopulmonary bypass in Myocardial Revascularization Surgery in the State of São Paulo. The REPLICCAR Study

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Short Editorial related to the article: Current Impact of Cardiopulmonary Bypass in Coronary Artery Bypass Grafting in São Paulo State

Whether myocardial revascularization should be performed with or without the use of cardiopulmonary bypass, referred to as off-pump and on-pump CABG, is still up for debate. Intuitively, avoidance of cardiopulmonary bypass seems beneficial, as the systemic inflammatory response from extracorporeal circulation is omitted. Even so, no single randomized trial has been able to prove that off-pump CABG is superior to on-pump CABG, as regards the hard outcomes of death, stroke or myocardial infarction.

Nowadays, Off-pump coronary artery bypass grafting (OPCAB) has become a common practice for coronary artery bypass grafting (CABG). Also, it seems that organ dysfunctions (liver, kidney, bowel ischemia, stroke and other kinds of minor dysfunctions) should be definitively differentiated, considering the two myocardial revascularization operations. A limitation associated with the off-pump technique, namely hemodynamic instability, concerns the quality of the anastomosis, the ability to achieve complete revascularization and the on-pump conversion rate, constituting speculative concerns. Therefore, it is still unclear whether OPCAB is superior in terms of graft patency, the incidence of complications, long-term outcomes, and the associated mortality rate-compared with conventional CABG (CCABG).

The Brazilian Society of Cardiovascular Surgery (SBCCV) newsletter (April 2017) highlights a consensus published by the American Heart Association (AHA) for the use of appropriate criteria for myocardial revascularization in stable angina.[1] Unlike a standard guideline, this Consensus brings more than 60 real clinical settings, scored by a panel of 32 experts among clinicians, interventionists, and surgeons. The clinical, anatomical and functional characteristics were contemplated, and innovatively, the treatment with one or more antianginal drugs weighed in the intervention decision. This approach has been useful to establish an unambiguous standardization to correct regional discrepancies when, for example, EuroSCORE and STS are used. The Brazilian cardiac surgery, although it has high international prestige, never performed a great "trial" about coronary artery bypass grafting without cardiopulmonary bypass, since its introduction in surgical practice was carried out by Dr Enio Buffolo (in Brazil) and Dr Federico Benetti (in Argentina).[2]

At least two Trials in progress (BYPASS REGISTRY and the REPLICCAR) could become a valuable starting point for the real establishment of cardiac surgery conditions in Brazil. The BYPASS project is taking shape and accomplishing the aim of providing a picture of the Brazilian cardiovascular surgery scenario.[3,4] Despite several previous attempts to establish a national database, this project deserves to be incentivized. These two studies should be the beginning of a unified Brazilian cardiac surgery database.

In this *Arquivos Brasileiros de Cardiologia* issue, we have the pleasure to read the initial results of the REPLICCAR study, which considered data extracted from academic institutions from the state of São Paulo. The analyzed outcomes were: morbidity (reoperation due to bleeding, cardiogenic shock, stroke, surgical site infection, mediastinitis, pneumonia, myocardial infarction, acute renal failure and surgical mortality in the period between the surgery and the 30-day evaluation, or until hospital discharge. The study emphasizes that, although there are well-defined criteria for CABG indication, the choice of CPB remains based on the patient's clinical profile and the surgeon's experience. In the REPLICCAR, bleeding reoperation was the only outcome associated with the use of CPB in CABG.[5]

Finally, what is the best answer to the challenging question that is always repeated about the two techniques? Is the OPCAB better than the conventional CABG (CCABG) or vice versa? Yes or no? REPLICCAR and BYPASS studies were not helpful in answering that, and for now, the safest answer to the question remains "MAYBE"… Intuitively, one has the impression that, after more than 30 years, both techniques have found their place, including the increase in "hybrid grafts", which would be studied in partnership with the two aforementioned studies.

Keywords

Myocardial Infarction/surgery: Myocardial Revascularization/surgery; Extracorporeal Circulation; Epidemioloy; REPICCAR.

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Frailty Among Non-Elderly Patients Undergoing Cardiac Surgery

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Abstract

Background: **Usually viewed as a characteristic of old age, frailty may also occur in non-elderly people, primarily in those suffering from chronic disease. Frailty may increase operative risk.**

Objectives: **To determine the prevalence of frailty patients undergoing coronary artery bypass (CABG) and/or heart valve replacement or reconstruction and/or heart valve surgery, as well as the influence of frailty on postoperative outcomes.**

Methods: **Our study comprised 100 adults who underwent consecutive elective cardiac operations. Frailty was assessed using the Fried scale. Patients also performed a 6-minute walk test, and we measured maximal inspiratory and expiratory pressures. A p value <0.05 was considered significant.**

Results: **Of a cohort of 100 patients, based on the Fried frailty criteria, 17 patients (17%) were considered frail, 70 (70%) pre-frail and only 13 (13%) were non-frail. Among patients with valvular heart disease, 11 (18.6%) were considered frail and 43 (73%) pre-frail. Fifty three percent of the patients considered frail were less than 60 years old (median=48 years old). The differences in frailty phenotype between patients with valvular heart disease and coronary artery disease were not statistically significant (p=0.305). A comparison between non-frail, pre-frail, and frail patients showed no significant difference in the distribution of comorbidities and cardiac functional status, regardless of their cardiac disease. However, hospital mortality was significantly higher in frail patients (29.4%, p=0.026) than in pre-frail patients (8.6%) and non-frail patients (0%).**

Conclusions: **Frailty is prevalent even among non-elderly patients undergoing CABG or valvular heart surgery and is associated with higher postoperative hospital mortality. (Arq Bras Cardiol. 2020; 115(4):604-610)**

Keywords: **Frailty; Myocardial Revascularization/surgery; Heart Valves/surgery; Postoperative Care/mortality.**

Introduction

Frailty is a syndrome of increased vulnerability to stressors including hospitalization and is associated with a reduced physiological reserve secondary to a decline in the optimal function of multiple physiological systems, which predisposes individuals to high risk of adverse events.[1] It is a multidimensional syndrome comprising physical, psychological and social dimensions,[2] usually viewed primarily as a geriatric syndrome[3] characterized by low physical activity, muscle weakness, slowed performance, fatigue or poor endurance and unintentional weight loss. In this context, the Fried criteria are widely used for the physical domains of frailty, which can be easily interpreted by non-geriatricians and may have prognostic value.[4,5] Association of frailty with chronic comorbidities has been shown.[2,6] Therefore, even non-elderly patients may present with this condition.

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We have observed, in the course of our clinical practice, that several non-elderly patients undergoing open heart surgery demonstrate clinical features compatible with frailty, usually experiencing less favorable postoperative hospital outcomes.

Therefore, the objective of the present study was to determine the prevalence of frailty in non-elderly patients undergoing coronary artery bypass (CABG) and/or heart valve surgery, as well as to assess the influence of frailty on postoperative hospital outcomes.

Patients and Methods

Study Design and Participants

We studied a prospective cohort of adults regardless of gender and race, who underwent CABG or heart valve replacement or reconstruction. These patients were consecutively and electively operated between January 2016 and December 2017. Exclusion criteria were: patients with restricted mobility secondary to orthopedic or neurological conditions, those with unstable angina, those classified as class IV as per the New York Heart Association Functional Classification (NYHA) at the time of the operation, and patients diagnosed with acute myocardial infarction <30 days preoperatively.

Median sternotomy and cardiopulmonary bypass (CPB) were performed on all patients. The CPB circuit was primed using Ringer's solution, and the pump flow was adjusted to 2.4 L/min/m^2. No patient received corticosteroids. Inotropes, vasopressors, nitrates and sodium nitroprusside were administered intra- or postoperatively at the discretion of the anesthesiologist or the intensive care unit staff.

This study was approved by the institutional review board of Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto-USP (registry 15363/2014) and informed consent was obtained from each patient included in the study.

Assessment of Frailty

Frailty was assessed using the Fried frailty index, which includes 5 criteria (5-m gait speed test, handgrip strength, weight loss, exhaustion and inactivity). Those who met 3 of these 5 criteria were diagnosed with frailty. Patients who met 2 of the 5 criteria were considered as being in the pre-frail stage (a subset at high risk of progressing to frailty).[7] Physical activity was assessed using the International Physical Activity Questionnaire.[8]

For the 5-m gait speed test, the patient was positioned behind the 5-m start line and instructed to walk at a comfortable pace until a few steps past the 5-m mark. The timer was started with the first footfall after the 0-m line and stopped with the first footfall after the 5-m line. Handgrip strength was assessed by measuring the degree of isometric strength developed using a mechanical hand dynamometer (MN 70142-North Coast®).

Sarcopenia is known to affect respiratory muscle strength; thus, we evaluated maximal inspiratory and expiratory pressure using a portable digital manovacuometer (Mvd 300®, Globalmed, Porto Alegre, Brazil). Measurements were performed over a minimum of 3 trials with a 1-min interval between each repetition using a nasal clip. Any value showing >10% variation was disregarded, and measurements with the highest value were used.

Functional Capacity Assessment

A 6-minute walk test was performed based on the recommendations of the American Thoracic Society, 2002 statement, to assess the functional capacity of patients.[9]

Outcomes

Death from any cause until 1 month after hospital discharge was considered postoperative hospital mortality, which was the primary outcome measure of this study. Our secondary outcomes were the incidence of postoperative infection(s), and respiratory, renal or cardiovascular dysfunction.

Statistical Analysis

Data distribution was verified by analysis of distribution histograms, Q-Q graphs and the Shapiro-Wilk test. Since our data had non-normal distributions, we chose to use non-parametric statistical methods. Results were presented as median and interquartile range for continuous variables and percentages for categorical variables. Fisher's Exact Test was used to compare categorical variables. Mann-Whitney or Kruskal-Wallis test followed by a Dunn-Bonferroni post hoc test were used to compare continuous data. A p value <0.05 was considered statistically significant. Statistical analysis was performed using the software Statistical Package for the Social Sciences (IBM-SPSS) version 22.0.

Results

Our study included 100 patients: 59 underwent heart valve surgery and 41 underwent CABG. Table 1 shows the clinical characteristics of patients.

CPB time for valvular surgery and CABG was 122 min (100–165 min) and 110 (77–130 min), respectively (p=0.002), and the aortic cross-clamp time was 93 min (76–117 min) and 72 (49–95 min), respectively (p<0.001).

The median age for the whole cohort was 57 years (49-66 years) and 57% of the patients were younger than 60. Overall, based on the Fried frailty criteria, 17 patients (17%) were considered frail, 70 (70%) were considered pre-frail and only 13 (13%) were non-frail.

Table 1 – Clinical characteristics according to the heart disease

	VHD n=59	CAD n=41	p
Age (y)	54 (45–61)	62 (55–69)	0.002
Female	60%	29%	0.013
Weight	75 (64–87)	79 (72–86)	0.104
Height (cm)	164 (154–173)	165 (158–170)	0.501
Body mass index	29 (24–32)	29 (25–32)	0.342
Arterial hypertension	55.0%	82.4%	0.062
Diabetes mellitus	15.0%	64.7%	<0,001
Stroke	8%	2%	0.211
Previous MI	34%	4%	<0.001
Chronic atrial fibrillation	25.0%	0.0%	<0.001
Smoke	15.0%	35.3%	0.272
Pulmonary hypertension	17.5%	0.0%	0.005
Kidney failure	5.0%	0.0%	0.211
Previous operation	35.0%	5.9%	<0.001
NYHA class			
I	0.0%	5.9%	0.230
II	62.5%	52.9%	
III	37.5%	41.2%	
IV	0.0%	0.0%	
Ejection fraction	60 (48–66)	51 (44–63)	0.028
Serum creatinine (dg/l)	1.1 (0.9–1.4)	1.2 (1.1–1.3)	0.484
Hemoglobin	13 (12–14)	13 (12–14)	0.793

CAD: coronary artery disease; VHD: valvular heart disease; MI: myocardial infarction. Fisher's Exact Test (categorical variables) and Mann-Whitney (continuous data)

Among patients with valvular heart disease, 11 (18.6%) were considered frail and 43 (73%) were considered pre-frail. The percentage of patients showing frailty and pre-frailty among those who underwent CABG was 6 (14.6%) and 27 (66%), respectively. The difference in the percentage of frailty between patients with valvular and coronary artery disease was not significant (p=0.788).

CPB time was 110 min (85–135 min), 120 (95–147 min) and 107 min (75–145 min), respectively, in non-frail, pre-frail and frail patients (p=0.656), whereas aortic cross-clamp time was 76 min (67–100 min), 90 (71–113 min) and 86 min (46–114 min), respectively (p=0.361).

Distribution of Fried criteria between patients with valvular heart disease (VHD) and coronary artery disease (CAD) is shown in Table 2. The heart valvular disease group had significantly higher proportion of patients with change of body weight and transition time (5 min) was significantly longer in the CAD group.

Table 3 shows anthropometric characteristics, distribution of associated comorbidities, Fried frailty criteria, respiratory pressures and functional status (NYHA class, left ventricular ejection fraction, 6MWT distance) among non-frail, pre-frail and frail patients, regardless of the cardiac disease. Among frail patients, 53% were less than 60 years old (median=48 years, 44–54 years). The proportion of patients who experienced previous myocardial infarction among non-frail, pre-frail and frail patients with CAD was 50%, 37% and 50%, respectively. Etiologies of valve disease were rheumatic fever in 44%, degenerative in 37%, endocarditis in 5% and annular dilation due to ventricular enlargement in 13%. Table 4 shows the etiology and mechanism of valve dysfunction according the Fried phenotype.

Table 5 shows the valve disease characteristics according to the Fried phenotype.

Overall hospital mortality was 11%, 12% for valvular heart disease and 10% for CABG (p=0.762). Hospital mortality was significantly higher in frail patients (29.4%, p=0.026) than in pre-frail patients (8.6%) and non-frail patients (0%). No statistically significant differences were observed in the percentage of in-hospital complications (Table 5).

Discussion

Our results have shown that, overall, 17% of patients studied were frail and 70% pre-frail, despite the fact that non-elderly (<60 years) prevailed in the cohort studied (57%). In addition, except for the higher proportion of women among frail patients, frail, pre-frail and non-frail patients were similar regarding the distribution of comorbidities, left ventricle function and NYHA class.

It is well known that frailty is associated with adverse postoperative outcomes in those undergoing cardiac surgery.[10-14] However, most studies have reported frailty in elderly patients.[6,10,13,14] Our findings demonstrate that frailty occurs in a significant percentage of non-elderly patients diagnosed with valvular heart disease or coronary artery disease undergoing open heart surgery. This fact can be attributed to the association of socioeconomic factors with chronic disease, representing the concept of "secondary frailty," a term used to refer to frailty in the presence of chronic diseases.[15] The frail patients observed in our study did not differ from others in terms of the presence of comorbidities and cardiac functional status. They differed essentially in terms of psychological aspects and also in terms of sarcopenia, evidenced by the reported changes in body weight and low physical activity and mobility.

Although usually viewed as a characteristic of old age, frailty has been described in non-elderly people, primarily among the lower socioeconomic strata in societies.[16,17] Santos-Eggimann et al.[17] analyzed 18,227 randomly selected European communities and observed 4.1% frail and 37.4% pre-frail individuals in a middle-aged population. Moreover, they observed a strong relationship between education and frailty. Brothers et al.[18] observed higher levels of frailty among middle-aged and older European immigrants born in low- and middle-income countries, also suggesting that socioeconomic factors may significantly influence an individual's health throughout his/her life.

Risk assessment in these patients has been a concern among cardiothoracic surgeons. Consequently, different risk scoring systems have been developed to predict mortality and morbidity.[19-21] However, most scoring systems emphasize specific organic dysfunction and aspects of operation, with lesser emphasis on the physical and psychological consequences of chronic diseases and the effects of the socioeconomic dimension. In addition, we speculate that the high mortality found in the fragile group (29.4%), compared to previous information found in the literature, may result from the association between fragility and the preexisting chronic conditions.[22-24]

Table 2 – Fried's criteria distribution to according the heart disease

	All (%)	VHD n=59	CAD n=41	p (VHDxCAD)
Change in body weight	14%	20%	5%	0.028
Exhaustion	63%	68%	56%	0.223
Low physical activity	62%	68%	54%	0.152
Transition time (sec.)	4.7 (4.0–5.7)	4.5 (4.0–5.3)	5.1 (4.4–6.0)	0.019
Handgrip strength (kgf)	28 (20–35)	28 (20–35)	29 (20–36)	0.615

CAD: coronary artery disease; VHD: valvular heart disease; HVD: heart valve disease. Fisher's exact Test (categorical variables) and Mann-Whitney (continuous data)

Table 3 – Clinical characteristics to according the Fried's phenotype

	Non-Frail n=13	Pre-frail n=70	Frail n=17	p
Age	58 (51–60)	57 (49–66)	57 (48–69)	0.830
Female	38%	44%	76%	0.042
Body mass index	28 (25–30)	29 (25–32)	30 (24–34)	0.617
Arterial hypertension	92%	70%	71%	0.243
Diabetes mellitus	37%	30%	35%	0.793
Previous MI	31%	16%	23%	0.389
Previous stroke	8%	7%	0%	0.519
Kidney failure	0%	8%	0%	0.255
SAPH	8%	11%	6%	0.757
Atrial fibrillation	8%	18%	17%	0.629
Previous cardiac operation	8%	20%	29%	0.338
NYHA class				
I	8%	0%	6%	0.163
II	61%	67%	47%	
III	31%	33%	47%	
IV	0%	0%	0%	
Ejection fraction	56 (46–60)	58 (47–65)	60 (45–68)	0.605
Serum creatinine (dg/l)	1.1 (1.0–1.1)	1.2 (0.9–1.4)	1.1 (1.0–1.2)	0.565
6MWT distance (m)	417 (384–482)	423 (360–493)	307 (275–364)	0.005**
MIP (cm H_2O)	65 (52–106)	70 (49–96)	44 (40–66)	0.015*
MEP (cm H_2O)	77 (58–123)	90 (73–118)	64 (56–108)	0.160
Change in body weight	0%	9%	47%	<0.001**
Exhaustion	0%	66%	94%	<0.001*
Low physical activity	0%	69%	88%	<0.001*
5-m gait speed test (sec)	4.6 (3.5–4.7)	4.7 (4.0–5.6)	6.7 (5.3–8.4)	<0.001**
Handgrip strength (kgf)	34 (23–45)	30 (21–37)	20 (15–27)	0.018**

**significant for frail vs. non-frail; **significant for frail vs. non-frail and pre-frail. Fisher's exact test (categorical variables) and Kruskal-Wallis test followed by a Dunn-Bonferroni post hoc test (continuous data). IQR: interquartile range. Fisher's exact test (categorical variables). MI: myocardial infarction; SAPH: systolic arterial pulmonary hypertension; MIP: maximal inspiratory pressures; MEP: maximal expiratory pressures.*

Our findings demonstrate that in addition to comorbidities and specific organ dysfunctions, frailty phenotype should be considered an important factor for operative risk assessment, because it may reflect not only the consequences of a chronic disease, but also the socioeconomic dimension. Therefore, frailty phenotype, even in non-elderly, may contribute toward offering a more holistic view of the patient's health status that can assist the development of intervention actions of the multi-professional team.

In view of these facts, it is important when treating frail patients (both elderly and non-elderly) to decide if they would benefit from postponing their operation to engage in a preoperative multidisciplinary rehabilitation program. Evidence-based research has shown that several aspects related to frailty such as sarcopenia, physical inactivity and nutritional issues are potentially treatable[25-27] and might decrease operative mortality.[28,29]

Waite et al.[29] conclusively demonstrated that a home-based preoperative rehabilitation program for frail patients aged ≥65 years undergoing CABG or valvular surgery may improve their functional status and reduce the duration of hospitalization. Additionally, evidence suggests that psychological preparation may help reduce postoperative pain, negative effects, and the length of hospitalization, as well as improve behavioral recovery,[16] and, besides exercise, a preoperative nutritional support program can potentially reduce sarcopenia and improve postoperative outcomes.[27,30]

Although evidence-based research suggests the superiority of multicomponent exercise programs over a single component exercise program for the rehabilitation of frail patients,[31] a more focused program aimed at specific organ dysfunction may prove beneficial. Katsura et al.[32] reported that preoperative inspiratory muscle training was associated with reduced postoperative atelectasis, pneumonia and

Table 4 – Etiology and dysfunction of valve diseases

Valve dysfunction		FRIED					
		Non-frail		Pre-frail		Frail	
		n	%	n	%	n	%
Etiology	Mitral stenosis	0	0.0%	1	2.3%	0	0.0%
	Mitral regurgitation	1	20.0%	8	18.6%	3	27.2%
	Aortic regurgitation	1	20.0%	1	2.3%	0	0.0%
	Aortic stenosis	0	0.0%	3	7.0%	4	36.4%
	Double mitral lesion	0	0.0%	5	11.6%	0	0.0%
	Double aortic lesion	1	20.0%	4	9.3%	0	0.0%
	Mitro-aortic dysfunction	2	40.0%	21	48.8%	4	36.4%
	Degenerative	2	40.0%	13	30.2%	5	45.5%
	Rheumatic	1	20.0%	19	44.2%	3	27.3%
	Endocarditis	0	0.0%	2	4.7%	1	9.1%
	Secondary MR	1	20.0%	6	14.0%	1	9.1%
	Other						

Table 5 – Postoperative evolution according to the Fried's scale

	Non-frail n=13	Pre-frail n=70	Frail n=17	p
Hospital death	0%	8.6%	29.4%	0.026
Intensive care time (days)	3 (2–3)	3 (2–5)	3 (2–4)	0.946
Hospital time (days)	10 (7–11)	11 (7–16)	9 (6–22)	0.861
IMV time (hour)	15 (5–19)	17 (7–28)	13 (7–12)	0.615
Creatinine	1.2 (0.9–1.2)	1.3 (1.0–1.7)	1.1 (1.0–1.4)	0.231
Hemoglobin	10 (9–11)	10 (9–11)	10 (10–11)	0.994
Non-invasive ventilation	38%	40%	23%	0.448
Cardiogenic pulmonary congestion	46%	41%	47%	0.888
Pneumonia	8%	8%	23%	0.193
Urinary infection	0.0%	13%	23%	0.164
Superficial wound infection	8%	6%	12%	0.667
Mediastinitis	0%	3%	6%	0.640
Acute kidney failure	0.0%	8%	0%	0.255
Stroke	0.0%	3%	12%	0.178

IQR: interquartile range. Fisher's exact test (categorical variables). IMV: Invasive mechanical ventilation.

length of hospitalization in adults undergoing cardiac and major abdominal surgery. However, notwithstanding the favorable effects that an exercise program may provide, it is necessary to consider the risks and uncertainty associated with frequency, type, and duration of exercise for frail patients diagnosed with heart disease in whom a cardiac operation is essential.

We believe that our study is one of the first to investigate the prevalence of frailty among non-elderly patients diagnosed with valvular heart disease or coronary artery disease undergoing cardiac surgery and its consequences with regard to hospital outcomes.

The limitations of our study are the small-sized cohort, which might not provide the required statistical power to comment on the significance of findings/results or to analyze confounders. Moreover, a small cohort may not include all postoperative complications that may be associated with frailty. Therefore, future studies are necessary to corroborate our findings and to verify the risk-benefit ratio of using preoperative rehabilitation programs for frail patients.

Conclusion

We observed that frailty is prevalent even among non-elderly patients undergoing CABG or valvular heart surgery and is associated with higher postoperative hospital mortality.

Author Contributions

Conception and design of the research: Bottura C, Arcêncio L, Chagas HMA, Rodrigues AJ; Acquisition of data: Bottura C, Arcêncio L, Chagas HMA; Analysis and interpretation of the data: Bottura C, Rodrigues A; Statistical analysis: Rodrigues AJ; Writing of the manuscript: Bottura C, Arcêncio L, Rodrigues AJ; Critical revision of the manuscript for intellectual content: Arcêncio L, Evora PRB, Rodrigues AJ.

Potential Conflict of Interest

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

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Short Editorial: Frailty among Non-Elderly Patients Undergoing Cardiac Surgery

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Frailty is recognized as a geriatric syndrome characterized by an excess of vulnerability to stressors, with a low ability to maintain or recover homeostasis after a destabilizing event.[1] The analysis of frailty is a well-known and studied subject in elderly patients, having a direct relationship with the prognosis and even with measures to be instituted pre-procedure aiming to improve the quality of life and the outcome of the patients.

Despite the original description restricting the term to patients older than 65 years,[2] the syndrome also affects younger patients.[3,4] Frailty represents more biological and phenotypic aspects than age itself,[3] and precursors of the syndrome appear at a young age.[3]

The diagnosis and therapy of the syndrome has been almost exclusively limited to patients over 65 years of age.[5,6] Few studies that analyzed frailty included patients under 65 years old.[7,8] Factors classically related to frailty are advanced age, low educational level, smoking, use of hormone replacement therapy, not being married, depression, low intellectual level and, in the United States, being of African-American or Spanish ethnicity.[9,10]

Frailty is associated with an increase in overall mortality and also predicts worse outcomes in kidney transplant recipients, general surgery and cardiac surgery.[11-13] The most used tool to define fragility is Fried frailty criteria, which define as pre-fragile those who meets 2 criteria and as fragile those who meets 3 or more of the following criteria:[2] Weight loss (≥5 percent of body weight in last year), exhaustion (positive response to questions regarding effort required for activity), weakness (decreased grip strength), slow walking speed (gait speed) (>6 to 7 seconds to walk 15 feet) and decreased physical activity (Kcals spent per week: males spending <383 Kcals and females <270 Kcal).

When a surgical procedure has to be indicated, instantly a series of factors comes to mind: the right moment, the surgical risk and the patient's prognosis, with and without the procedure. The risk scores analyze the organic part through objective data, associated with the type of surgery proposed. However, we are often faced with extremely low values, which, subjectively, we know are not reliable.

In elderly patients with aortic valve stenosis, frailty scores are already routinely incorporated into the assessment of cardiovascular risk, helping in the indication or not of transcatheter exchange.[14] In an era that emphasizes costs in Medicine, identifying the most vulnerable patients, deciding an appropriate course of therapy, and targeting valuable resources are important priorities.[15]

The present study[16] reveals that the analysis of frailty is not related to comorbidities, ejection fraction and functional capacity, a very relevant fact. Another point that one must consider is that due to methodological reasons, the analysis did not include patients with orthopedic or neurological problems, with functional class IV or recent AMI, or those using corticosteroids - in this context, the risk would probably be exponential. The hospital mortality was significantly higher in frail patients (29.4%, p=0.026) than in pre-frail (8.6%) and non-frail patients (0%).

The study encompasses a series of characteristics that make it relevant. First, it deals with a common and still little explored topic. Second, it allows us to objectively estimate how much frailty contributes to the outcome of fragile, non-elderly patients undergoing cardiac surgery, regardless of the type. Finally, it draws the attention of physicians to the need to incorporate frailty scores into their daily routines in order to better stratify and even define when a procedure should or should not be indicated, providing the doctor, patient and family with tools that assist in the decision-making. TAVI or conventional surgery? CABG or PTCA? I hope that we have the appropriate strength of evidence to indicate to our patients the procedure with the best risk-benefit ratio.

Keywords

Frailty; Myocardial Revascularization/surgery; Heart Valves/surgery; Postoperative Care/mortality.

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Patients' Preferences after Recurrent Coronary Narrowing: Discrete Choice Experiments

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Abstract

Background: **Selecting the optimal treatment strategy for coronary revascularization is challenging. A crucial endpoint to be considered when making this choice is the necessity to repeat revascularization since it is much more frequent after percutaneous coronary intervention (PCI) than after coronary artery bypass grafting (CABG).**

Objective: **This study intends to provide insights on patients' preferences for revascularization, strategies in the perspective of patients who had to repeat revascularization.**

Methods: **We selected a sample of patients who had undergone PCI and were hospitalized to repeat coronary revascularization and elicited their preferences for a new PCI or CABG. Perioperative death, long-term death, myocardial infarction, and repeat revascularization were used to design scenarios describing hypothetical treatments that were labeled as PCI or CABG. PCI was always presented as the option with lower perioperative death risk and a higher necessity to repeat procedure. A conditional logit model was used to analyze patients' choices using R software. A p value < 0.05 was considered statistically significant.**

Results: **A total of 144 patients participated, most of them (73.7%) preferred CABG over PCI (p < 0.001). The regression coefficients were statistically significant for PCI label, PCI long-term death, CABG perioperative death, CABG long-term death and repeat CABG. The PCI label was the most important parameter (p < 0.05).**

Conclusion: **Most patients who face the necessity to repeat coronary revascularization reject a new PCI, considering realistic levels of risks and benefits. Incorporating patients' preferences into benefit-risk calculation and treatment recommendations could enhance patient-centered care. (Arq Bras Cardiol. 2020; 115(4):613-619)**

Keywords: **Coronary Artery Disease/surgery; Myocardial Revascularization; Intervention Coronary Percutaneous; Coronary Restenosis; Patient Preference; Surveys and Questionnaires.**

Introduction

Coronary heart disease is the leading cause of mortality and disability worldwide, responsible for about one-third of all deaths in people over 35 years of age.[1] There are two revascularization options: percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Besides the necessity of an open chest surgery for CABG, some crucial distinctions between these treatments are the perioperative risk of death, higher with CABG and the necessity to repeat revascularization, higher with PCI.[2] Recently, the use of drug–eluting stents have reduced the necessity to repeat revascularization, but the dilemma of the best revascularization strategy is still unanswered.[3,4] Therefore, the choice of optimal revascularization strategy is challenging and relies on many factors, such as the number, severity, and position of the narrowed or blocked arteries, patients' overall health, and their preferences for related endpoints, such as recovery time, short-time complications, the necessity to repeat revascularization and long-time survival.[5]

Health care providers have been trying to integrate patients more actively as partners in decisions and the provider must have the skills to involve patients in decision making.[6] Simply asking patients to rate treatment-related endpoints generally yield no substantial information since they will probably state that they want all the benefits (lower risks for all endpoints). Instead, choice experiments like discrete choice experiments (DCE) force patients to make a trade-off between realistic options, for instance, the option with the lower perioperative

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death (PCI) versus the option with lower risk to repeat revascularization (CABG).

DCE are frequently used to elicit preferences in a wide range of situations and became the most frequently applied approach in health care.[7] In a DCE, subjects are presented with a sequence of hypothetical scenarios and are asked to choose between competing alternatives that vary along several characteristics (attributes).

The DCE methodology is grounded in a random utility maximisation (RUM) framework, where the basic assumptions are: 1) any commodity, in this case treatment option (PCI and CABG) can be characterized by key attributes (eg, risk of perioperative death, risk to repeat revascularization) and their levels (e.g., 2%, 35%) and 2) whenever individuals have options to choose from (eg, PCI versus CABG), they make their choice for the option with the greatest utility, which is defined by comparing those attributes' levels.[8] Utility is a term used by economists to describe the measurement of "usefulness" and "desirability" that a consumer obtains from any good and represents the capacity of a commodity to give satisfaction.

In a recently published systematic review, our research team searched for studies that evaluated stated preferences between PCI and CABG. We identified a shortage of studies that addressed this theme and a lack of standardized methods for evaluating patients' preferences. Even so, fourteen endpoints used to compare PCI and CABG could be identified: atrial fibrillation, heart failure, incision scar, length of stay, long-term death, myocardial infarction, perioperative death, postoperative infection, postprocedural angina, pseudoaneurysm, renal failure, repeat CABG, repeat PCI, and stroke.[9]

Among those who had already undergone PCI, there is no study that evaluated patients' preferences between undergoing a new PCI or CABG, in case new revascularization is indicated. Therefore, this study aimed to provide insights regarding patients' preferences for PCI or CABG in the perspective of hospitalized patients who had to repeat revascularization.

Methods

Design

A DCE was developed and administered to a sample of hospitalized patients through individual and face-to-face interviews, from November 2017 to April 2018. The patients were randomly recruited based on their ward number using a list of random numbers at the Instituto Nacional de Cardiologia, a Brazilian tertiary public hospital specializing in cardiology. Patients 18 years old or over were deemed eligible if they had undergone previous PCI and were hospitalized due to coronary disease requiring new revascularization.

Patients who considered themselves unable to understand the experiment were excluded. There were no other exclusion criteria. Ethical approval was obtained from the Instituto Nacional de Cardiologia Ethics Board and written informed consent was obtained from each study participant (CAAE number 63684017.0.0000.5240).

Discrete Choice Experiment

The DCE was based on endpoints that were identified by the systematic review previously published.[9] In order to perform the DCE experiment, those endpoints were previously ranked and rated by patients to identify their relative importance. All endpoints were ranked considering a hypothetical scenario. The detailed method used for the patients to rank and rate the endpoints was previously published.[10] The selection of which attributes should be used in the DCE scenarios is an essential step, since it will only be possible to calculate the trade-offs between the attributes that will be used. We included only four attributes, since the use of all 14 attributes identified in the systematic review would make respondents tired or to use heuristics, a mental shortcut that allows people to make judgments quickly albeit leads to biased preference measures.[11] The four attributes chose to compose the DCE scenarios were selected considering: 1) long-term death should be included as the reference for marginal rates of substitution; 2) being the most relevant attributes accordingly to patients ranking, and 3) having a significant difference in incidence between PCI and CABG. The four attributes selected were: perioperative death, long-term death, myocardial infarction and repeat revascularization.

In order to use DCE in hospitalized patients, we used visual aids that were specifically developed for this project, in order to include patients with different socioeducational background.[12] Visual aids improve risk understanding and allow patients to consider themselves able to understand and participate in decisions with answers consistent with economic theory, choosing the alternatives with higher utility.

An example of a DCE scenario presented in this paper to patients is shown in Figure 1: the first attribute ("perioperative death") is shown with level 3% for PCI (angioplasty) and 8% for CABG (surgery); the second attribute is "death in 5 years", 22% risk for PCI and 15% for CABG. Each respondent had to choose between PCI and CABG in 12 different scenarios. All scenarios used were shown with the same four attributes, but with different levels combination according to pre-established values. PCI was always presented as the option with lower perioperative death and a higher necessity to repeat procedure (Table 1).

Development of the DCE Survey – Selection of Levels

When describing the treatment options in the DCE tasks, the four risk attributes were operationalized by classifying them into three specific levels. The levels for long-term death, revascularization, and myocardial infarction were derived from recent studies comparing PCI versus CABG[4,13-17] in order to make sure that actual levels of risk would be used. The level for perioperative death was selected based on the mean PCI and CABG perioperative mortality rates (2.21% and 6.23%, respectively), according to the Brazilian National Database years 2016 and 2017 (DATASUS)[18] and was presented in three levels: 1%, 2% or 3% for PCI, and 4%, 6% and 8% for CABG (Table 1).

Figure 1 – *A sample discrete choice experiment choice.*

Table 1 – Attributes and levels selected to describe treatment options in the DCE

Attribute	PCI	CABG
Perioperative death	1% - 2% - 3%	4% - 6% - 8%
Long-term death	8% - 15% - 22%	7% - 11% - 15%
Myocardial infarction	6% - 10% - 14%	3% - 5% - 7%
Repeat revascularization	13% - 24% - 35%	1% - 4% - 7%

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention.

Development of the DCE Survey – Designing the Choice Tasks

The NGene Software[19] was used to design the scenarios, which corresponded to the mechanism by which hypothetical profiles were presented to respondents for preference elicitation in DCE.[11] A D-Efficient design with no prior information about patients' preferences was used to generate the choice tasks. The order of the choice tasks was randomized among the participants.

All patients were individually and personally interviewed, choosing one option in 12 different scenarios presented in a paper-based questionnaire.

Statistical Analysis

A conditional logit model was used to analyse patients' choices using R software. Measurement data were presented as mean ± standard deviation ($x \pm SD$). A p value < 0.05 was considered statistically significant.

The four risk attributes entered the model as continuous and linear variables. Once patients' preferences for the risk attributes were estimated, it was possible to compute marginal rates of substitution (MRS). The MRS represented the trade-offs between attributes or how much of one attribute patients were willing to sacrifice to obtain more of another attribute. Due to the linear specification of the model, the MRS simply consisted of the ratio of two estimated coefficients.[20] We followed this approach to compute Maximum Acceptable Risks (MAR) with a 1% increase in the CABG long-term death as the reference.

Results

Out of 145 recruited patients, 144 gave written informed consent to participate in the study and considered themselves able to understand the experiment. The mean age was 57.5 ± 11.6 years; 74% were men and most patients were married (56%), with a low level of education and low income (Table 2).

Each respondent answered 12 choice tasks, providing thus a total of 1,728 (i.e., 144 times 12) observations for the analysis. Most patients (73.7%) preferred CABG over PCI

Table 2 – Baseline socioeconomic conditions and characteristics of respondents

Characteristic	Data (N = 144)
Age, years	57.5 (11.6)
Male sex, number (%)	106 (74%)
Annual income, U$	6,838.59 (10,586.82)*
Marital status	Married 81 (56%) Single 35 (24%) Other 28 (20%)
Level of education, years of study (%)	≤ 1 year: 5 (3.0%) 2 – 5 years: 39 (27%) 6 – 9 years: 31 (22%) 10 – 12 years: 40 (28%) College degree: 29 (20%)
Number of previous PCI	1 – 98 (68%) 2 – 23 (16%) 3 or more – 23 (16%)

*PCI: percutaneous coronary intervention; continuous data are presented as mean (standard deviation). *conversion based on http://www4.bcb.gov.br/pec/conversao/conversao.asp (1 U$ = 3.49 R$).*

Table 3 – Estimated Relative Preference Weights

Parameter	Estimate	Standard error	p value
PCI label	- 1.3226	0.6708	< 0.05
PCI perioperative death	- 0.0421	0.0975	NS
PCI long-term death	- 0.0371	0.0172	< 0.05
PCI myocardial infarction	- 0.0314	0.0165	NS
Repeat PCI	- 0.0005	0.0087	NS
CABG perioperative death	- 0.0956	0.0425	< 0.05
CABG long-term death	- 0.0582	0.0287	< 0.05
CABG myocardial infarction	0.0480	0.0407	NS
Repeat CABG	- 0.0657	0.0253	< 0.05

Log-likelihood = -952.35. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; NS: non-significant.

($p < 0.001$). The results for the estimation of preferences are reported in Table 3.

The regression coefficients were statistically significant at 5% level for PCI label, PCI long-term death, CABG perioperative death, CABG long-term death and repeat CABG. The negative coefficients indicate that patients considered the attributes as something undesirable (more risk is worse than less). Notably, the utility function used in the regression model included an alternative specific constant for PCI label and it was not only statistically significant but also the most important parameter, the one with the greatest negative value, meaning that most patients who had to repeat revascularization rejected PCI regardless of the associated risks presented.

Discussion

The present study is unique since, as far as we know, it is the first one that evaluated patients' preferences among those who had to undergo repeat revascularization after PCI and provides important insights, such as the evidence of a significant variation in the perceived utility of treatments and the noteworthy overall preference for the most invasive option (CABG).

There are few studies that used DCEs as a tool to elicit preferences for coronary revascularization. Our systematic review identified that most studies (83%) used ranking or rating as the method to identify patients' preferences and only two studies (33%)[21,22] used hypothetical scenarios. Hornberger et al.[22] studied a nationwide sample of respondents in a conjoint analysis study considering incision scar, pain, recovery time, days in hospital and repeated treatment. It is noteworthy that the participants considered that PCI would overcome CABG only if the 3-year risk of redoing revascularization declined to less than 28%. Kipp et al.[21] using a mixed logistic regression analysis, identified that for nearly all quoted risks, patients preferred PCI over CABG, even when the risk of death was double the risk with CABG or the risk of repeat procedures was more than three times that for CABG.

In contrast with the Kipp study, the majority of the patients (73.8%) in this study chose the most invasive option: CABG. This difference may be related to the different population since we considered only patients who had a past history of PCI. Besides that, we must consider some differences in the studies designs. While Kipp et al.[21] study was based on a threefold risk to repeat PCI over the risk to repeat CABG, with levels between 2 and 5%, we considered CABG risk between 1% and 7% and PCI risk between 13% and 35%. This high risk to repeat PCI was observed in diabetic patients in the Syntax trial,[23] where 35.3% of patients followed for 5 years had to undergo a new revascularization procedure.

Another important point raised by our findings is that different endpoints are seen differently by patients. However, guidelines' recommendations are based on the use of composite endpoints such as major adverse cardiovascular events (MACE). Endpoints such as death, stroke, myocardial infarction and repeat revascularization are frequently grouped as an attempt to capture the overall treatment effect and the main advantages are the reduction of the duration, sample size and costs of a clinical trial.[24] The use of MACE assumes that all its components are of equal clinical severity and patients and physicians have a similar perception of each component, assumptions that were false both in our study and in others.[24-26] Patients and physicians have distinct perspectives and none of them considered all clinical endpoints equally. The appropriate weight of each component of a composite endpoint would provide a more refined interpretation of the trial data.

An important decision in the application of DCE is whether to present the choices in a labeled or unlabeled form. We decided to adopt labeled scenarios, that is, patients chose between PCI and CABG, and not between option "A" versus "B". Unlabeled DCEs would be more suitable to investigate trade-offs between attributes, while labeled DCEs may be more suitable to explain real-life choices. Labeled choice sets

are considered less abstract and may increase the validity of the results, which may be better suitable to support decision-making at the policy level. The disadvantage is that labels may reduce the attention respondents give to the attributes and some patients may have chosen one option irrespective of their risks.[27] In our sample, each respondent answered an additional DCE validity test choice task at the end of the DCE section, a dominated question, where PCI represented the treatment with clearly dominant or better attribute levels, i.e., the less invasive option associated with the lesser risks of dying, having a myocardial infarction or repeat treatment. Respondents were expected to choose PCI, but 54 (37.5%) patients chose CABG, which may configure previous PCI rejection and the impact of the label utilization.

Strengths and Clinical Implications

There are just a few studies regarding patients' preferences between PCI and CABG and this is the first one to analyze patients' preferences specifically for repeated revascularization procedures.

Another strength is the selection of participants, composed of hospitalized patients, waiting for new revascularization. Currently, most health state value sets are obtained from members of the general public, who attempt to imagine what the state would be like, mainly argued for on the basis that the general population are the payers of healthcare. However, patients understand better the consequences of their choices and what it is like to live with that health condition. This minimizes one of the major concerns with DCEs that is the hypothetical bias related to patients' disinterest or inattention towards hypothetical scenarios, while patients facing the health problem would be more involved with the experiment.

Current cardiology guidelines may benefit from including patients' preferences into their recommendations. For instance, taking into consideration the results for patients with three-vessel disease of the Syntax trial, the 11.4% long-term mortality in the CABG group (coefficient value – 0.0582) would be equivalent to 17.9% ((-0.0582/-0.0371)*11.4) long-term mortality in PCI group (coefficient value -0.0371). Based on the value of the parameters identified in our regression model, even with the higher PCI long-term mortality (13.9%), this 2.5% long-term mortality difference, shown in the Syntax trial, would not be sufficient to influence patients' preferences in favour of CABG.

Limitations

The results of our study are limited by the use of a small sample size from a single tertiary hospital, which may limit the generalizability of our results.

There may be some interaction effects, since patients may have valued particular attributes or levels differently because of their previous particular experience. Another issue is that the attributes were modelled as continuous variables to make it easier to understand and we considered the effect of levels preferences as linear, which may not be realistic since the value of changing from low to moderate risk not necessarily is the same value of changing risk from moderate to severe.

Conclusion

Despite the important trade-offs between PCI and CABG, such as the necessity to repeat revascularization, patients` preferences have been poorly explored. In a DCE with a sample of hospitalized patients with coronary disease and previous PCI, our results support that most patients reject a new PCI and prefer CABG when facing realistic risk levels of each option.

Author Contributions

Conception and design of the research: Magliano C, Monteiro AL, Pereira CCA; Acquisition of data: Magliano C, Rebelo ARO, Santos GF; Analysis and interpretation of the data: Magliano C, Monteiro AL, Pereira CCA, Krucien N, Saraiva RM; Statistical analysis: Magliano C, Krucien N; Writing of the manuscript: Magliano C, Monteiro AL, Krucien N; Critical revision of the manuscript for intellectual content: Monteiro AL, Rebelo ARO, Santos GF, Pereira CCA, Krucien N, Saraiva RM.

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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Diastolic Function and Biomarkers of Long-Distance Walking Participants

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Abstract

Background: **The effects of long-distance walking on the cardiovascular system have been little studied.**

Objectives: **The general objective of this study was to verify these effects on the behavior of diastolic function and the cardiac biomarkers CK-MB (mass), troponin T, and NT-proBNP, in amateur athletes.**

Method: **This longitudinal study, conducted in 2015, evaluated participants during the following 5 stages: E0 (baseline) before starting the trajectory and the others, E1, E2, E3, and E4, at the end of each day, totaling 244.7 km. At all stages, the biomarkers NT-proBNP, CK-MB (mass), and troponin T were measured. Echocardiogram was performed to analyze the E, A and E' waves. P < 0.05 was adopted as significant.**

Results: **The study evaluated 25 participants, with an average age of 46 ± 10.5 years and body mass index of 20.2 ± 2.3 kg/m2. Increased values were found for NT-proBNP from E0 to E1, E2, E3, and E4 (p < 0.001), CK-MB (mass) from E0 to E2 (p < 0.001), and E' wave from E0 to E1, E2, E3, and E4 (p < 0.001). Positive correlations were identified between the following: CK-MB (mass) and troponin T (E1: r = 0.524, p = 0.010; E4: r = 0.413, p = 0.044); CK-MB (mass) and NT-proBNP (E4: r = 0.539, p = 0.006); and E/A and E' (E0: r = 0.603, p < 0.001; E1: r = 0.639, p < 0.001; E4: r = 0.593, p = 0.002). A negative correlation was found between CK-MB (mass) and E/A (E1: r = –0.428, p = 0.041).**

Conclusion: **The effects of intense, prolonged, and interspersed physical activity were verified based on significant variations in the behavior of CK-MB (mass), NT-proBNP, and the E' wave. Notwithstanding the alterations found, there were no criteria suggestive of myocardial damage (Arq Bras Cardiol. 2020; 115(4):620-627)**

Palavras-chave: **Walking; Biomarkers,Biological; Blood Pressure; Troponin-T; Natriuretic Peptide Brain; Athletes; Echocardiography, Doppler/methods.**

Introduction

Physical exercise is fundamental to general health maintenance and disease prevention.[1] Intensity, duration, and frequency, however, are factors that separate benefit from harm in the human organism. Recent evidence has asked whether the physiological demand of maintaining elevated cardiac output during a prolonged period of exercise may result in transient impairment of cardiac functions.[2]

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The acute effects of physical exercise on diastolic function and even variations in diastolic dysfunction are indirectly related to persistent stimulation, which also depends on intensity and duration. These adaptations, even when they are short-term, may cause decreased cardiac function, which is known as cardiac fatigue.[3]

The cardiac enzymes creatine kinase-MB (CK-MB) and cardiac troponin T (cTnT), and the amino acid precursor N-terminal pro B-type natriuretic peptide (NT-proBNP) are important biomarkers for evaluating the existence of myocardial lesions and diastolic function.[4]

CK-MB levels may also increase in states of rhabdomyolysis and even apoplexy; in this manner, they have variable sensitivity.[5] Troponin T is the preferred marker of myocardial lesion, and it is considered the gold standard.[6]

NT-proBNP is associated, in a direct and parallel manner, with brain natriuretic peptide (BNP) concentrations. It may be used for diagnostic and prognostic assessment of left

ventricular insufficiency, and it also increases in conditions that induce diastolic dysfunction. Little is known regarding the behavior of these biomarkers and especially their prognostic meaning in healthy individuals undergoing intense physical stress.[7]

Nonetheless, few studies have evaluated the effect of moderate to high intensity long-distance walking on the cardiovascular system based on evaluation of diastolic function and cardiac biomarkers. This was the first study to evaluate diastolic function and cardiac biomarkers in this type of exercise. Accordingly, the objective of this study was to verify, in amateur athletes, the effects of moderate to high intensity long-distance walking on the behavior of diastolic function and the cardiac biomarkers CK-MB (mass), troponin T, and NT-proBNP.

Methods

This was a longitudinal study, carried out during a long-distance walk, namely, the Goiás Ecological Walk, in the year 2015. Initially, approximately 200 people signed up via Internet to participate. The candidates participated in a selection process, during which they walked 56 km, divided into two days (28 km each), which had to completed in, at most, three hours and ten minutes for men and three and a half hours for women. Participants were ranked according to the best times in each age group, and a total of 29 participants, 25 male and 4 female, were selected. Women were not included in analysis, because they did not complete the previously established daily route.

The research project received approval from the Research Ethics Committee of the Pontifical Catholic University of Goiás under certificate number 1.107.021. The individuals approved during the selection process were invited to participate in the study. Following acceptance, a free and informed consent form was applied, and initial evaluation (E0) was carried out in a cardiovascular evaluation unit. Other evaluations took place 34 days after E0 during the 244.7-km trajectory, at the end of each day, at the resting places in each city on the trajectory, from July 21 to 24, 2015; evaluation days were named E1, E2, E3, and E4 (first, second, third, and fourth days of evaluation). Data collection was not carried out on the final day of the event, as participants were released to return to their home cities.

The predominant relief of the terrain was described as ascending, descending, and level, according to each day of the trajectory. This information was obtained from a previous study that had evaluated this.[8] The slope of the terrain was obtained using ArcGIS 10.3 software, through the slope tool (slope, arctoolbox), based on Shuttle Radar Topography Mission (SRTM) images provided by the American geological service, with pixel size of three arcsec. For meteorological monitoring of the trajectory days (E1 to E4), data were utilized from the Goiás station officially denominated by the Brazilian National Institute of Meteorology (INMET, acronym in Portuguese) of E014.

Organization of Collection

The study setting was subdivided into stations, one for each evaluation. Evaluations consisted of anamnesis (during E0 only) and echocardiography and blood collection for evaluation of biomarkers at all stages. Collection of echocardiographic data and biomarkers began around 6:00 p.m. (30 to 120 minutes after the end of each walk) on every day of the trajectory. In this manner, when participants arrived at the resting places, research stations had already been prepared, initiating the flow of identification of participants, followed by blood collection and echocardiographic evaluation; participants were subsequently free to return to the event. Collection was not possible in the morning, as participants woke up at 4:00 a.m., and this could have interfering with their periods of rest and recovery.

The researchers organized anamnesis in the form of an interview with questions regarding personal data such as age (years), sex (male and female), profession, and marital status; personal and family history of arterial hypertension, diabetes, and dyslipidemia; use of medication(s); tobacco use (current/prior); number of cigarettes per day, for smokers; physical exercise practice (weekly frequency, daily duration, and duration of practice); and the presence of orthopedic problems that might make it difficult to practice exercise.

Blood Biomarker Tests and Echocardiogram Procedures

The blood collection technique was via peripheral venous access in left cubital fossa.[9] Approximately 5 ml of blood were drawn from each participant. The blood was centrifuged at the collection site at 3,000 rpm for 10 minutes to obtain serum/plasma. The serum was collected in sample tubes with separator gel. The samples were promptly stored and frozen at −20 ºC in a specific freezer at the collection stations.[10] The samples were sent to an accredited laboratory for analysis. Kits registered by the Brazilian National Health Surveillance Agency (ANVISA, acronym in Portuguese) were used for the biomarker tests. The values of CK-MB (mass), troponin T, and NT-proBNP were obtained using the electrochemiluminescence immunoassay technique.[11] The assays were performed on a COBAS® Modular Analytics E170 system using the following kits: CK-MB STAT, Troponin T hs, and proBNP II, respectively. To ensure that assays were performed correctly, all instructions provided in the user's guide for analyzers were followed. A biomedical doctor handled all exams. The following units of measurement were used: pg/ml for NT-proBNP and troponin T and ng/ml for CK-MB (mass).[11]

Echocardiography

Echocardiogram was carried out individually at all stages of collection, during the day on E0 and around 6:00 p.m. from E1 to E4, after participants' arrival at the research stations. All exams were carried out by the same echocardiographer. One- and two-dimensional echocardiogram with color Doppler was performed using a Philips CX50® portable device, with an electronic transducer with 2 to 5MHz of frequency. The technique and reference standards used were those recommended by the American Society of Echocardiography [12]. The same angle of incidence was used for transmittal

analysis, attempting to align the ultrasound beam as parallel as possible to the color Doppler flow. The parameters used for analysis of diastolic dysfunction, with their respective units of measurement, were, for mitral flow, E in cm/s, A in cm/s, and E/A ratio. For tissue evaluation, E' in cm/s was used.[13]

Statistical Analysis

Data were analyzed using descriptive statistics with absolute and relative frequencies, averages, standard deviation, and confidence interval. The Shapiro-Wilk test was used to test the normality of the data distribution of the variables. To compare variables related to cardiac biomarkers between the days of the walk and echocardiographic parameters, the ANOVA test for repeated measures was applied, followed by Bonferroni's post hoc test. Pearson or Spearman tests were used for correlations. P value < 0.05 was adopted for statistical significance. Stata software, version 14, was used to carry out statistical analysis.

Results

Characteristics of the Sample

Evaluation included 25 men, with average age of 46 ± 10.5 years and body mass index 20.2 ± 2.3 kg/m^2 (Table 1). Four (16%) participants were using medications that did not influence the variables analyzed. The distance covered in four days was 244.7 km, with an average velocity of 7.6 km/h. All participants walked together as a group, thus maintaining the same velocity. The nocturnal resting period was between six and seven hours daily.

In relation to previous physical exercise, 24 participants (96%) practiced running; one (4%) practiced cycling, and four (16%) practiced bodybuilding. Average duration of aerobic activity was 13.3 years (0.5 ± 40), and average weekly distance of running, which was the most reported activity, was 64 km.

Table 1 – Social, health, and lifestyle characteristics of the participants of the Goiás Ecological Walk, Brazil, 2015 (n = 25*)

Variables	n	%
Age range (years)		
19 – 39	5	20
40 – 59	19	76
≥ 60	1	4
Medication use		
No	21	84
Yes	4	16
Diseases reported		
Diabetes mellitus	1	4
Dyslipidemia	1	4
Hypothyroidism	2	4
Orthopedic problems	3	12

** Number of participants evaluated.*

Environmental Characteristics of the Trajectory

Temperature during the days of the walk ranged from 19 to 32 ºC, and relative humidity ranged from 21% to 77%. On E1 and E3, the relief was predominantly ascending; on E2, it was descending (E2), and, on E4, it was level. The most accentuated variations in the slope of the terrain were found in sections of E2 and E3, ranging from 0 to −15.

Evaluation of Diastolic Function Biomarkers and Waves During the Long-Distance Walk

NT-proBNP showed a significant increase from E0 to all the other evaluations. CK-MB (mass) showed a significant increase from E0 to E2, and troponin T did not show any significant alterations. Regarding diastolic function, the E and A waves did not alter between the days of the walk. The E' wave increased from E0 to all the other days (Figure 1).

Correlations were made between all parameters collected regarding diastolic function biomarkers and waves; only significant correlations are shown. In relation to blood biomarkers, positive and moderate correlations were identified on the following days of exposure: E1, between troponin T and CK-MB (mass); and E4, between NT-proBNP and CK-MB (mass), as well as between troponin T and CK-MB (mass). In relation to diastolic function, positive and moderate correlations were identified between E/A and E' on E0, E1, and E4. With respect to diastolic function biomarkers and waves, a negative and moderate correlation was found between CK-MB and E/A on E1 (Table 2).

Discussion

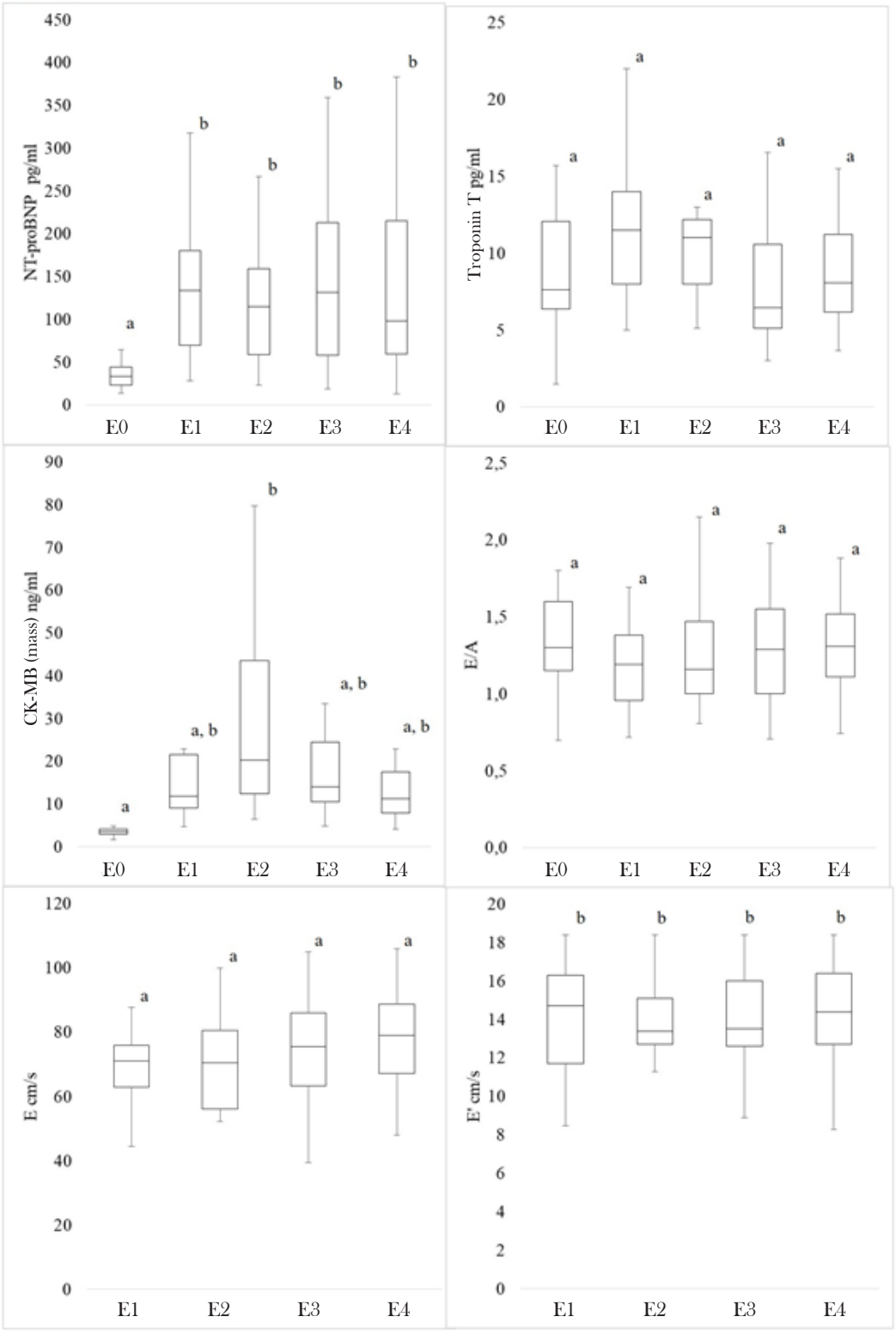
Although the participants were considered amateur athletes, the majority had prior experience with the trajectory and in prior editions of the Goiás Ecological Walk, with an average of 7.2 participations; in addition to this, the selection process resulted in a highly select sample.

The velocity of competitive running in half marathons or marathons solicits higher energetic and metabolic demands, and it increases the chances of cardiovascular outcomes, especially in individuals who are not conditioned.[14] In our study, the average velocity was 7.6 km/h, which is much lower than in marathons and half marathons; for this reason, there were lower energetic and metabolic demands on participants.

During the days they were exposed to exercise, in comparison to the 30 preceding days (E0), significant increases occurred in NT-proBNP, CK-MB (mass), and E' wave (tissue Doppler) values. We did not observe significant variations in the levels of troponin T and the mitral flow E/A ratio.

This increase has also been found in healthy individuals, adolescents, and adults, regardless of sex, when undergoing resistance exercises, with a return to baseline values during the first 24 hours after exercise.[15,16]

In the present study, we found an up to five-fold increase in serum NT-proBNP concentrations following exercise, when compared to baseline levels; these data corroborate the literature.[17-19] They also reinforce the importance of the natriuretic effect in the mechanism of acute and subacute adaptation of the cardiovascular apparatus to physical effort.



E0 (baseline); E1 (first day); E2 (second day); E3 (third day); E4 (fourth day). ANOVA and Bonferroni post hoc test; same letters: $p > 0.05$; different letters: $p < 0.001$.

Figure 1 – *Comparison between NT-proBNP, troponin T, CK-MB (mass), E/A, E, and E' values obtained during baseline evaluation and the four days of exposure to moderate to intense physical activity.*

Table 2 – Correlation of biomarkers, diastolic function, and biomarkers with diastolic function in participants of the Goiás Ecological Walk, Brazil, 2015 (n = 25)

Evaluation	Parameter	r	p
E0	E/A x E'	0.603	0.001*
E1	Troponin T x CK-MB (mass)	0.524	0.010**
	E/A x E'	0.639	0.001*
	CK-MB (mass) x E/A	−0.428	0.041**
E4	NT-proBNP x CK-MB (mass)	0.539	0.006**
	Troponin T x CK-MB (mass)	0.413	0.044**
	E/A x E'	0.593	0.001*

** Pearson test; ** Spearman test.*

Serum elevations of CK-MB (mass) have also been found in individuals after strenuous exercise. In a survey conducted in the United States, with young participants in a marathon, increased and sustained plasma levels of CK-MB were found up to 54 hours after exposure to exercise.[20,21]

Trained individuals, who perform high intensity exercise in sports, during the maximal effort test, tend to present acutely higher serum elevations of CK-MB than untrained individuals, thus suggesting cardiac involvement that is mainly benign in the nature of these serum levels.[22]

Scientists have also verified the effect of prolonged exercise and variations in environmental temperature on the behavior of creatine kinases, and they identified that the longer the exercise and the higher the environmental temperature, the greater the plasma release of these biomarkers.[23] The longer the stretch covered in a shorter amount of time, the greater the chances of muscle damage and, thus, the greater serum quantity of creatine kinases. Another important fact is that, during descent, the ground reaction force exerted against participants may also lead to increased musculoskeletal injuries, due to the greater source of impact, with a tendency toward more accentuated metabolic cost during descending slopes.[24,25]

In our study, significant variations in CK-MB (mass) were found only between E0 and E2. This increase may have been related to the characteristics of the trajectory in E2, namely, predominantly descending, with greater variation in slope and greater distance than the other days. The cumulative effect of CK-MB (mass) in E1 may have influenced the significant increase in the value of CK-MB (mass) in E2.

Evidence also exists regarding the limitations of evaluation of CK-MB in healthy individuals during physical exercise practice. Its specificity becomes impaired in the presence of inflammatory processes and skeletal muscle stress associated with a reduction during the first hours of exposure to effort, due to the slowed appearance of these markers in the blood, and it is more sensitive when cardiac injury is present.[26]

In studies on half marathons, marathons, and 48-hour ultra-marathons, carried out in amateur runners (non-athletes), elevated troponin T values were found during the first three hours of post-exposure, with important reductions immediately following, reaching baseline levels in a maximum of 48 hours.[20,27] In swimmers, 60 minutes after swimming, the same variation was found in troponin T as in amateur runners.[16]

Eijsvogels et al.[28] evaluated 82 people during a trajectory of 30 km daily for four days, and they also found that troponins increased only on the first day, with plasma reduction on all other days showing an association with walking speed.[28] A meta-analysis of 45 studies that evaluated the behavior of troponins and BNPs following exposure to resistance exercises observed that the elevated plasma values of troponins and BNP during and after intense and prolonged exercise are prone to change, and they may represent an acute characteristic with respect to exposure to exercise.[29] The biomechanics of the release of troponins induced by physical exercise are still unclear; it is also unclear whether this really reflects a physiological or pathological process.[30]

In this study, troponin T did not show a significant increase during the days of the trajectory; these results differ from those found in other studies mentioned. This may be related to following facts: the participants covered the trajectories at

an average speed below competition values, even for amateur runners; they alternated running and walking; and they were carefully hydrated throughout the journey. The behavior of troponin T was different than what is generally expected when related to CK-MB (mass). As troponin T has greater specificity for myocardial damage due to ischemia, it is possible that this is the reason for the lower increase between E0 and the other days. This fact may demonstrate that damage to the cardiovascular system seems to be minimal and this exercise modality seems to be safe.[31]

In our sample, we found a significant increase in the E' wave in relation to baseline values, without a reduction in the E/A wave ratio. These findings may be related to the characteristics of the population evaluated, which was well conditioned, and to the intensity of the effort, contributing to a greater adaptive capacity of myocardial remodeling. Other studies that have performed echocardiography in different populations have found different results. Left or right ventricular diastolic dysfunction was not found in amateur medium- and long-distance triathletes.[32] In contrast, in adult athletes, alterations in myocardial relaxation were demonstrated during diastole,[33] identified by increased E wave (mitral flow) in comparison with the E' wave (tissue Doppler). In ultra-resistance exercises, there were significant decreases in the E wave and the E/A ratio immediately after exercise.[34-36] A study, whose methodology was closer to the one we used, evaluated changes in cardiac function in participants of an ecological walk and found significantly decreased mitral E/A ratio and tissue Doppler E' wave, from 21 km.[37]

Regular aerobic training can minimize acute changes in diastolic function in response to the greater cardiac demand during intense exercise. This training effect can play a fundamental role in preserving diastolic filling in older athletes.[35,38]

We found positive correlations between the following: E/A and E'; CK-MB (mass) and troponin T; and CK-MB (mass) and NT-proBNP. A negative correlation was found only between CK-MB (mass) and E/A (the ratio of the velocities of rapid ventricular filling and atrial contraction).

Few studies have made correlations of diastolic function waves and serum variations of cardiac injury biomarkers with diastolic function variation waves. It is known that, in physiological patterns, variations in the behavior of mitral flow are reflected in the same direction as variations in ventricular tissue behavior.[13] Jouffroy et al.[37] succeeded in finding a positive correlation between E/A and E' in amateur participants of ultradistance running. The few studies that have evaluated these correlations have found discordant results.[37]

The direct relation of increased BNP(s) with troponins, creatine kinases, and diastolic alterations is known. Troponin T is also strongly associated with ventricular relaxation abnormalities.[16,20,39] The positive correlation of CK-MB (mass) with troponin T and NT-proBNP found in our study may be related to the fact that, even in situations where cardiac ischemia is absent, minimum levels of these biomarkers may be released into the bloodstream, in the same direction as the behavior of CK-MB (mass).

Consequently, we found an inverse correlation of CK-MB (mass) with the E/A wave ratio. The reason that the decrease in one leads to an increase in the other needs to be studied further, given that this correlation may be merely casual. We can speculate as to the possibility that reversible diastolic dysfunction is one of the possible mechanisms of plasma increase of CK-MB (mass) with the decreased E wave and the increased A wave.

Limitations

Data collection during the days of the trajectory had to adapt to the available times of the event, and this may have interfered with evaluation of acute variations in cardiac biomarkers, given that plasma levels vary according to time of exposure. It was also not possible to carry out collection in the morning in order to evaluate the behavior of the variables after resting, as this would have interfered with participants' rest and the recovery process, as they had to wake up at 4:00 a.m. to get ready and then walk the established route. Furthermore, evaluation of exposure would have helped better elucidate questions regarding the behavior of diastolic function biomarkers and waves, for instance, whether or not there was a return close to baseline values.

Conclusions

The effects of intense, prolonged, and interspersed physical activity were verified based on significant variations in the behavior of CK-MB (mass), NT-proBNP, and E'. It is worth underscoring that, notwithstanding the alterations found, there were no criteria demonstrative of myocardial damage during this exercise modality in trained individuals.

Author Contributions

Conception and design of the research: Euzebio MB, Vitorino PVO, Sousa WM, Sousa ALL, Jardim TSV, Arantes AC, Jardim PCBV, Barroso WKS; Acquisition of data: Euzebio MB, Sousa WM, Melo MA, Costa SHN, Arantes AC; Analysis and interpretation of the data: Euzebio MB, Vitorino PVO, Sousa WM, Melo MA, Costa SHN, Sousa ALL, Arantes AC, Jardim PCBV, Barroso WKS; Statistical analysis: Euzebio MB, Vitorino PVO, Sousa WM; Writing of the manuscript: Euzebio MB, Vitorino PVO, Sousa WM, Barroso WKS; Critical revision of the manuscript for intellectual content: Euzebio MB, Vitorino PVO, Sousa WM, Sousa ALL, Jardim PCBV, Barroso WKS.

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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Can Long-Distance Walking alter Cardiac Biomarkers and Echocardiographic Variables Related to Diastolic Function?

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Short Editorial: Diastolic Function and Biomarkers of Long-Distance Walking Participants

Walking is one of the most practiced physical activities worldwide. It is also included in physical exercise programs aiming at improving the health-related parameters in different populations.[1,2] Therefore, the demand for amateur events encompassing walking has been increasing, especially those related to nature and the culture of a specific region. One of the best known amateur events in the world that involves walking is the "*Camino de Santiago de la Compostela*". Moreover, here in Brazil, we have the "*Rota das Missões*", located in the south of the country. The trajectories can have different distances, reaching nearly 40km of walking on the same day. These are two examples of activities that involve walking and add a cultural experience to the event.

In addition to the two abovementioned events, there are long-distance ecological hikes, where participants experience direct contact with nature, going through different terrain characteristics on the same day, reaching a total walking distance of up to 250 km during a 4-day event. We know that each individual responds differently to a certain stimulus; however, walking more than 50 km in one day going up and down slopes, on rough terrain, can have a negative physiological impact on any individual who undergoes this type of modality.[3] In addition to the physiological damage, we are also concerned with the impact on the cardiovascular system in relation to the volume and intensity of this type of modality.[4,5]

Among the best known physiological markers, one can mention alterations in cardiac biomarkers such as Creatine Kinase-MB fraction (CK-MB), cardiac Troponin T (cTnT) and the NT-proBNP (N-terminal pro B-type natriuretic peptide), which may be related to myocardial damage.[4] Among the markers of altered cardiac function, we can highlight some echocardiographic variables, such as early (E) and late transmitral diastolic velocities (A), as well as the E / A ratio, as well as early diastolic velocity by tissue-Doppler (E'), all of which can be used to analyze diastolic dysfunction.[6]

The available scientific evidence on the effects of long-distance walking on cardiac biomarkers and diastolic function shows divergent results regarding cardiovascular risk for this type of modality. In this issue of the journal, Euzébio et al.[7] explore this topic in long-distance walking participants (mean age 46 ± 10.5). The authors verified these effects on the diastolic function behavior using the E, A waves and E / A ratio, in addition to the cardiac biomarkers CK-MB, Troponin-T and NT-proBNP. They also assessed correlations between diastolic function variables, cardiac biomarkers and whether there is a correlation between some diastolic function variable and some cardiac biomarker. For this purpose, the authors performed a longitudinal study with 25 adult participants (all men), after four women were excluded for not meeting the previous selection criterion, which consisted in walking 56 km, divided into two days, in up to three hours and ten minutes for men and three hours and 30 minutes for women. The evaluations were divided into five stages: A0, the moment before the event started, A1, the first day after the end of the trajectory; A2, the second day after the end of the trajectory; A3, the third day after the end of the trajectory; and A4, the fourth day after the end of the entire trajectory. The total trajectory comprised a distance of 244.7 km. As the main results, the authors found significant increases in CK-MB from A0 to A2, NT-proBNP from A0 to A1, A2, A3 and A4 and E' wave from A0 to A1. Interestingly, and unlike other studies, Troponin-T did not show any significant differences, as well as E and A waves. Moreover, positive correlations were identified between CK-MB and NT-proBNP, CK-MB and Troponin-T, between E/A ratio and E', and a negative correlation between CK-MB and E/A ratio.

Overall, the present study discloses important results on the effects of long-distance walking on parameters related to cardiac biomarkers and diastolic function, demonstrating that, despite the observed alterations , there are no criteria suggestive of myocardial damage, mainly because they did not find any alterations in Troponin-T, E wave and A wave.[7,8] The alterations found in NT-proBNP serum levels demonstrate the natriuretic effect on the physiological mechanism of acute and subacute adaptation of the cardiovascular system in relation to exertion.[9] It is also noteworthy that the increase in serum levels of CK-MB may be related mainly to higher temperatures during certain parts of the trajectory (that varied between 19 and 32ºC), and also to the type of terrain, distance walked and intensity in each part of the trajectory. Indeed, the variation found in this variable was between A0 and A2, predominantly comprising a downslope, promoting greater eccentric muscle contraction, and directly related to greater muscle damage, which may explain this behavior, in addition to a cumulative effect between the A1 and A2 trajectory.[10] Regarding the diastolic function, the significant increase only in the E' wave between A0 and A1 can be explained by the studied

Keywords

Walking; Physical Exertion; Biomarkers; Blood Pressure; Troponin T; Natriuretic Peptide Brain; Creatin Kinase; Echocardiography/methods.

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population. It is known that individuals with less physical conditioning are more susceptible to alterations in diastolic function when exposed to physical effort, when compared to individuals with more physical conditioning. Moreover, regular physical training can minimize acute alterations in diastolic function in relation to greater cardiovascular demands during prolonged and intense exercise.[11] In summary, one needs to pay attention mainly to the behavior of Troponin-T, which is specific to identify myocardial damage due to ischemia, demonstrating that the damage to the cardiovascular system seems to be minimal and that this type of exercise seems to be safe.[12]

Regarding the observed correlations, we can highlight the negative association between CK-MB and E/A (ratio between the rapid ventricular filling velocity and the atrial contraction velocity). One of the assumptions regarding this association can be attributed to the reversible diastolic dysfunction picture as one of the main mechanisms of CK-MB increase in plasma, with a consequent reduction in E wave and increase in A wave. However, this issue still needs to be better explored regarding the associations between cardiac biomarkers and diastolic function from the perspective of long-distance walking.

The study has some limitations, among which we can highlight the lack of standardization in relation to the time of data collection during the days of the event, since this can directly interfere with the assessments of the acute levels of cardiac biomarkers. It would also be important to collect the same variables at rest always on the day after the trajectory. However, the authors point out that this was not feasible due to the time that the journey started (4:00 am). Here, it is worth mentioning that despite the limitations, the study has its strengths. It is difficult to perform a randomized, controlled study in this scenario, which involves data collections outside a specific laboratory and with climatic adversities. Considering this fact, this is one of the greatest merits of the study, carrying out a complex investigation, with specific biochemical and echocardiographic measurements, outside a laboratory environment. Moreover, we believe that studies developed in the practical environment, further meets the demands and responds much more comprehensively about the behavior of a phenomenon. It is very important to know what the responses are in relation to cardiac biomarkers and diastolic function of long-distance walking, as this modality is one of the fastest growing in Brazil and worldwide.

Finally, the contribution of Euzébio et al.[7] published in this issue of the Brazilian Archives of Cardiology, in addition to providing important results for the scientific literature, will also be used to guide new studies that may improve the methods related to the design, data collection and variables to be studied. The final message of the present study is that trained adult individuals who participate in long-distance walking events comprising more than 240 km of total distance, do not suffer cardiovascular damage, analyzed through cardiac biomarkers and echocardiographic variables.

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Atorvastatin Reduces Accumulation of Vascular Smooth Muscle Cells to Inhibit Intimal Hyperplasia via p38 MAPK Pathway Inhibition in a Rat Model of Vein Graft

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Abstract

Background: The rate of saphenous vein graft failure one year after coronary artery bypass grafting ranges from 10% to 25%. The aim of this study was to explore whether atorvastatin can reduce accumulation of vascular smooth muscle cells to inhibit intimal hyperplasia via p38 MAPK pathway inhibition.

Methods: Forty-five Sprague-Dawley rats were randomized to three groups. Thirty rats received a vein graft operation, and they were randomized to be treated with vehicle or atorvastatin; fifteen rats received a sham operation. We detected intimal hyperplasia by hematoxylin-eosin staining and related protein expression by immunohistochemical and Western blot analysis. Comparisons were analyzed by single-factor analysis of variance and Fisher's least significant difference test, with $p < 0.05$ considered significant.

Results: The intima analyzed by hematoxylin-eosin staining was dramatically thicker in the control group than in the atorvastatin group and sham group ($p < 0.01$). The outcomes of immunohistochemical staining of α-SMA demonstrated that the percentage of α-SMA-positive cells in the control group was higher than in the atorvastatin group ($p < 0.01$). We also evaluated α-SMA, PCNA, p38 MAPK, and phosphorylation of p38 MAPK after statin treatment by Western blot analysis, and the results indicated that atorvastatin did not lead to p38 MAPK reduction ($p < 0.05$); it did, however, result in inhibition of p38 MAPK phosphorylation ($p < 0.01$), and it significantly reduced α-SMA and PCNA levels, in comparison with the control group ($p < 0.01$).

Conclusion: We have demonstrated that atorvastatin can inhibit accumulation of vascular smooth muscle cells by inhibiting the p38 MAPK pathway, and it is capable of inhibiting intimal hyperplasia in a rat vein graft model. (Arq Bras Cardiol. 2020; 115(4):630-636)

Keywords: Atorvastatin; Myocytes Smooth Muscle; Hyperplasia; Models, Animal; Mitogen Activated Protein Kinases; Myocardial Revascularization, Rats.

Introduction

Coronary artery disease and related complications are still the main causes of mortality around the world, although there have been many advances in medical therapy. Many studies and clinical guidelines have shown that coronary artery bypass grafting (CABG) surgery reduces morbidity and mortality of patients with three-vessel disease or left main disease, with reduced ejection fraction compared to percutaneous coronary intervention.[1] Notably, one year after CABG, the rate of saphenous vein graft (SVG) failure can be 10% to 25%, and in 1 to 5 years, the rate will be increased by 1 % to 2% per year.[2,3] Moreover, in 6 to 10 years, the failure rate will increase at a rate of 4% to 5% every year, due to atherosclerosis.[4] The mechanism of SVG restenosis includes thrombosis, intimal hyperplasia (IH) and atherosclerosis. The proliferation and migration of endothelial cells and vascular smooth muscle cells (VSMCs) are crucial to IH, and IH is the main cause of SVG restenosis.[5] However, the mechanism of IH is not clear, and it is still not known which prevention method and therapy would be most effective.

A substantial amount of evidence suggests that statin treatment reduces cardiovascular risk; therefore, when low-density lipoprotein cholesterol levels are higher than 100 mg/dL, statin therapy is recommended for patients with coronary artery disease.[6] Many observations have indicated that preoperative statin treatment could reduce morbidity, postoperative mortality, and complications, and recent evidence has indicated that statin treatment after CABG can reduce the rate of SVG disease by inhibiting IH, indicating that optimal statin treatment is crucial to the assessment of the long-term benefit of CABG.[7-9] The "response-to-injury" hypothesis proposed by Russell Ross is widely accepted; this hypothesis states that, following arterialization, SVGs instantly undergo injury (e.g. ischemia, hypoxia, shear stress, or surgical trauma), leading to an initiating event in the inflammatory response,

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followed by morphological and functional changes leading to IH, as the result of accumulation of VSMCs and endothelial cell dysfunction.[10] The dysfunction, proliferation and migration of these cells are stimulated by phosphorylation of p38 mitogen activated protein kinases (p38 MAPKs), extracellular signal-regulated kinases (ERK), c-Jun and N-terminal kinases.[11] Studies have demonstrated that inhibition of p38 MAPK could reduce the innate immune response and consequently inhibit IH following SVG arterialization.[12,13]

Based on these studies on IH, we hypothesized that atorvastatin could reduce the accumulation of VSMCs to inhibit IH by suppressing the p38 MAPK pathway. We verified our hypothesis by using a rat vein graft model with statin treatment to detect IH by hematoxylin-eosin staining and correlated protein expression by immunohistochemical and Western blot analysis. We found that atorvastatin was able to inhibit phosphorylation of p38 MAPK to reduce accumulation of VSMCs and, furthermore, inhibit IH.

Materials and Methods

Experimental Animals and Surgical Procedure

All animal experiments in this study were performed according to protocols approved by the Institutional Committee for Use and Care of Laboratory Animals. Forty-five male, pathogen-free, 8- to 10-week-old Sprague-Dawley rats, weighing 200 to 220 g were provided by the Anhui Lab Animal Research Center and identified by the Medical Ethics Committee of Anhui Medical University. They were randomized (completely randomized design) to 3 groups, containing 15 rats each, and fed for 4 weeks after operation. Thirty rats received a vein graft as described previously;[14] the method was used to construct rat models of right jugular vein grafts on common carotid artery, and the rats were randomized to be treated with vehicle (control group, administered with distilled water continuously by gavage for 4 weeks) or atorvastatin (atorvastatin group, 15 mg/kg, dissolved in distilled water). Fifteen rats received a sham operation (sham group), defined as simulation of the operation process, without venous arterialization and medical intervention.

Sample Collection

We collected each rat's vein graft at the fourth week after operation. Fully anaesthetized rats were fixed on the operating table, heparinized as before and operated in the same way, through the same approach. For histological analysis, vein grafts were placed in microtubes with paraformaldehyde, and fixed at 4 °C for 24 hours. Vein grafts with Western-Blot were placed in solvent-free microtubes and then stored at −80 °C. Rats were euthanized by cervical dislocation and handled properly.

Histologic and Immunohistochemical Analysis

Morphometric analysis of intima was performed by hematoxylin-eosin staining, using a hematoxylin and eosin staining kit (Beyotime Biotechnology, Shanghai, China). An Olympus microscope image acquisition system was used to collect images of sections (×40, ×100, and ×200 objective lens) and measure intimal thickness. Two independent researchers performed the measurements and data analysis. We selected sections of grafted veins; subsequently, we measured 16 points of intimal thickness and calculated the mean. Tissue sections were tested for cell proliferation using an immunohistochemistry analysis kit for α-smooth muscle actin (α-SMA) (R&D Systems, Bio-Techne, Minnesota, USA), the specific protein of VSMCs. All images (×100 and ×200 objective lens) were captured using an Olympus microscope image acquisition system (Olympus, Japan) and processed with Image-J 1.48u software (National Institutes of Health, Bethesda, USA). A total of 10 observation views were applied to calculate the average percentage of α-SMA-positive cells for each rat.

Western Blot Analysis

Four weeks after the operation, equivalent amounts of vein graft proteins from the three groups were electrophoresed in sodium dodecyl sulfate/10% polyacrylamide gel and blotted onto PVDF membranes (Sigma-Aldrich, USA). The membranes were subsequently incubated with anti-phospho-specific p38 MAPK antibodies, anti-non-phosphorylated p38 MAPK antibodies, anti-non-phosphorylated α-SMA antibodies, and anti-non-phosphorylated proliferating cell nuclear antigen (PCNA) antibodies, followed by incubation with an anti-mouse IgG-peroxidase. Western blotting was performed as previously described.[15] The antibodies (p38, p-p38, α-SMA, PCNA and β-actin) were acquired from R&D Systems (Bio-Techne, Minnesota, USA).

Statistical Analysis

Statistical analyses were performed using SPSS 17.0. Data are shown as mean ± standard deviation. As the data showed normal distribution, comparisons between multiple groups were analyzed by single-factor analysis of variance (ANOVA), and comparisons between two groups were made by Fisher's least significant difference test. P values < 0.05 were considered statistically significant.

Results

Rats Survived Well 4 Weeks After Operation

To simulate the pathophysiological changes of CABG, we used the improved cuff method to construct rat models of jugular vein graft on carotid artery in one side; after grafting, the transplanted veins were well filled, and the blood vessels had good pulse (Figure 1). Rats' vital status and incision were checked every day, and all rats survived and recovered well with good pulse in the grafted veins. All rats were euthanized 4 weeks after operation. Notably, only one rat had venous occlusion in the control group, and blood flow in other grafted veins was unobstructed. New granulation tissue was present in the veins of the control group, showing thickened tubes, edema, and mild stiffness. However, veins in the atorvastatin group had few fresh tissues with no obvious expansion, and they were easily separated.

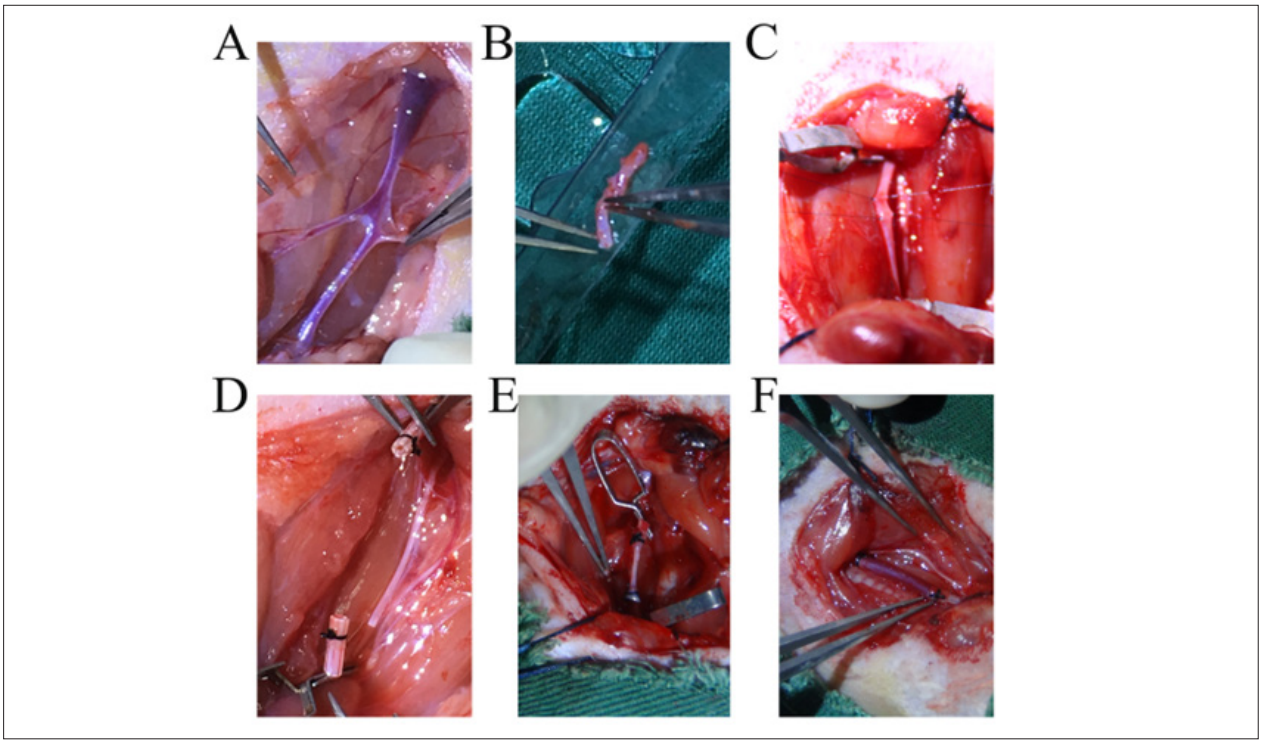

Figure 1 – *Model construction process. Operating procedure: 10% chloral hydrate was used to anaesthetize rats via intraperitoneal injection. Heparin (700 IU/kg) was injected through the caudal vein to induce heparinization. A vertical incision of approximately 1 cm was made in the middle of the neck (deflected to the operation side) and the veins were dissociated on one side (A and B). Epitheca of 1 to 2 mm were taken using 20G red arterial puncture needle (BD Company), used as cannula. The carotid artery was isolated until the branches. Then, two suture traction lines and hemoclips were placed at both ends of the artery to block blood flow (C). The middle of the artery was isolated and turned carefully to 1 to 1.2mm above the cannula to bring intima outside (D). 6/0 silk suture was used for knot and fixation; the vein was subsequently between isolated arteries, and we were able to open vascular clamps (E and F). The incision was sutured after we had verified that pulse in the vein graft was normal and that there was no bleeding.*

Atorvastatin Reduced Intimal Thickening of the Vein Graft

To evaluate the effect of atorvastatin on IH, we performed hematoxylin-eosin staining 4 weeks after surgery. Subsequently, a computer image analysis system was used to analyze IH. The results showed that the intima of the control group was significantly thicker than that of the atorvastatin group and the sham group (249.3 ± 14.5 versus 95.1 ± 3.6, 32.3 ± 1.7, $p < 0.01$; Figure 2A and B). The result indicated that atorvastatin is able to inhibit IH in the vein graft.

Atorvastatin Reduced Cell Proliferation in Intimal of The Vein Graft

We performed immunohistochemistry analysis of α-SMA and Western blot of α-SMA and PCNA, an indicator of cell proliferation status, in order to explore the cellular components and proliferation of IH. Furthermore, as shown in Figure 3, the results of immunohistochemical staining of α-SMA showed that the percentage of α-SMA-positive cells was significantly higher in the control group than in the atorvastatin group and the sham group (40.5% ± 3.1% versus 19.6% ± 1.4%, 4.7% ± 0.9%, $p < 0.01$; Figure 3A and B). Atorvastatin significantly decreased α-SMA and PCNA levels, in comparison with control group ($p < 0.01$; Figure 4C and D). These results indicate that VSMCs are the main cellular component of IH and that atorvastatin can inhibit the proliferation of VSMCs and reduce IH.

Atorvastatin Reduced Phosphorylation of p38 MAPK

We performed Western blot of p38 MAPK and phosphorylation of p38 MAPK in order to explore the relation between atorvastatin and the p38 MAPK pathway. The effects of atorvastatin on p38 MAPK and phosphorylation of p38 MAPK are shown in Figure 4A and B. Atorvastatin inhibited phosphorylation of p38 MAPK ($p < 0.01$, Figure 4B) but without significantly reducing p38 MAPK ($p > 0.05$, Figure 4A). These results indicate that atorvastatin was able to reduce IH by inhibiting phosphorylation of p38 MAPK.

Discussion

The results of this study indicate that atorvastatin was able to reduce the accumulation of VSMCs and inhibit IH by suppressing the p38 MAPK pathway. Other studies have shown that, with the help of angiotensin II, statin treatment induced phosphorylation of p38 MAPK and ERK 1/2 in cultured VSMCs;[16] however, the action mechanism of IH after coronary artery bypass has not been made clear, and it has not been verified in animal experiments. In our experiments of vein bridge restenosis in rats, we demonstrated that, after atorvastatin treatment, the protein expression of phosphorylation of p38 MAPK, α-SMA, and PCNA was reduced, and there was a significant reduction in the average thickness of IH, as well as a significant decrease in proliferation of α-SMA.

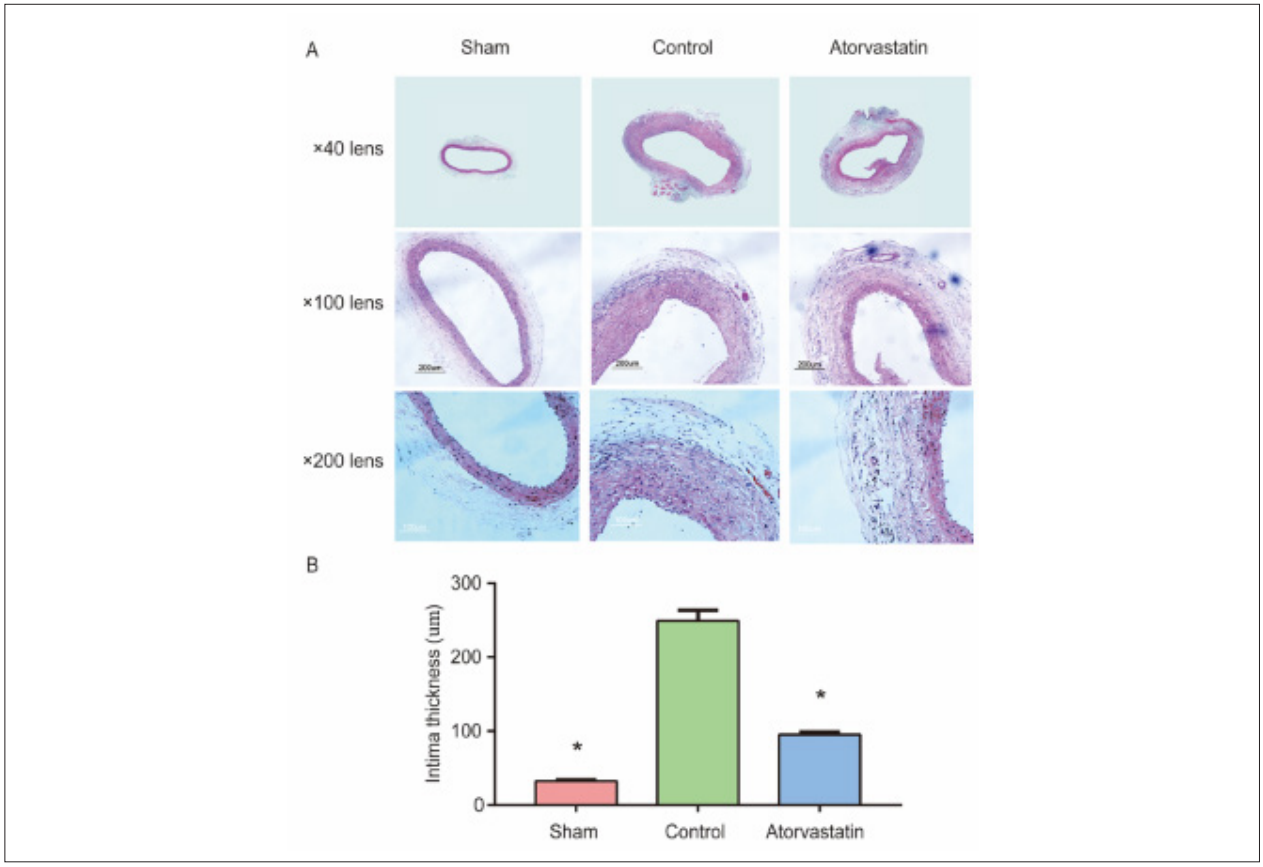

Figure 2 – *Atorvastatin reduced intimal thickening of the vein graft. The vessel tissue was collected 4 weeks after operation, fixed with formalin, sliced to 4 μm tissue sections, and stained with H&E. Images (×40, ×100, and ×200 objective lens) were collected and analyzed on an Olympus microscope imaging system. The intima of the control group was significantly thicker than that of atorvastatin group and the sham group (249.3 ± 14.5 versus 95.1 ± 3.6, 32.3 ± 1.7, p < 0.01). *The control group had an obvious difference with the other two groups.*

Statins have been able to improve clinical outcomes of patients with coronary heart disease, especially after percutaneous transluminal coronary intervention and CABG, due to pleiotropic, anti-atherosclerotic, and chronic inflammation effects, as well as inhibition of endothelial dysfunction.[17] However, studies about the effect of statins on vascular graft restenosis after CABG are rare. In the current study, using hematoxylin-eosin staining, we found that atorvastatin was able to inhibit IH of vein grafts. Our findings are in agreement with our previous work, which has suggested that rats treated with simvastatin showed significant growth in the mean lumen vessel area in a rat model of vascular access.[18] Furthermore, we detected α-SMA density by immunohistochemistry and the expression of α-SMA and PCNA by Western blot. These results indicated that atorvastatin was able to reduce accumulation of VSMCs to inhibit IH. Yiguan Xu et al. reported that atorvastatin can inhibit neo-IH and promote VSMC apoptosis in neointimal layers after carotid artery injury in rats.[19] This is the first time that we have observed the same phenomenon in a rat model of vein graft; namely, through a specific action mechanism, atorvastatin led to alleviation of the damage caused by vascular endothelial injury.

The mechanism of restenosis includes thrombosis, IH, and late atherosclerosis. Proliferation, migration, and secretion of endothelial cells and VSMCs are crucial to IH, the leading cause of restenosis.[20] In a previous study, we showed that p38 MAPK is phosphorylated in a model of arterialized vein grafts followed by activation of the innate immune response (inflammation), and a p38 MAPK inhibitor could reduce arterialization-induced cell proliferation and downregulate the early inflammatory response that follows vascular injury.[19] Hence, we tested the expression of α-SMA, PCNA, p38 MAPK, and phosphorylation of p38 MAPK after statin treatment, and the results showed that atorvastatin did not significantly reduce the level of p38 MAPK ($p > 0.05$). However, it inhibited phosphorylation of p38 MAPK ($p < 0.01$), and the α-SMA and PCNA levels showed a significant decrease, in comparison with the control group ($p < 0.01$). As reported by Antonio G. et al, statin treatment was able to inhibit proliferation of VSMCs in culture via the MAPK pathway. However, the cell experiments they completed were only *in vivo*, without validation of *in vitro* animal experiments, and they did not link this mechanism to IH of vascular restenosis.[16] The main strength of our study is that we performed our experiments in rats, with the construction of a highly complex model, in order to verify that statins were able to

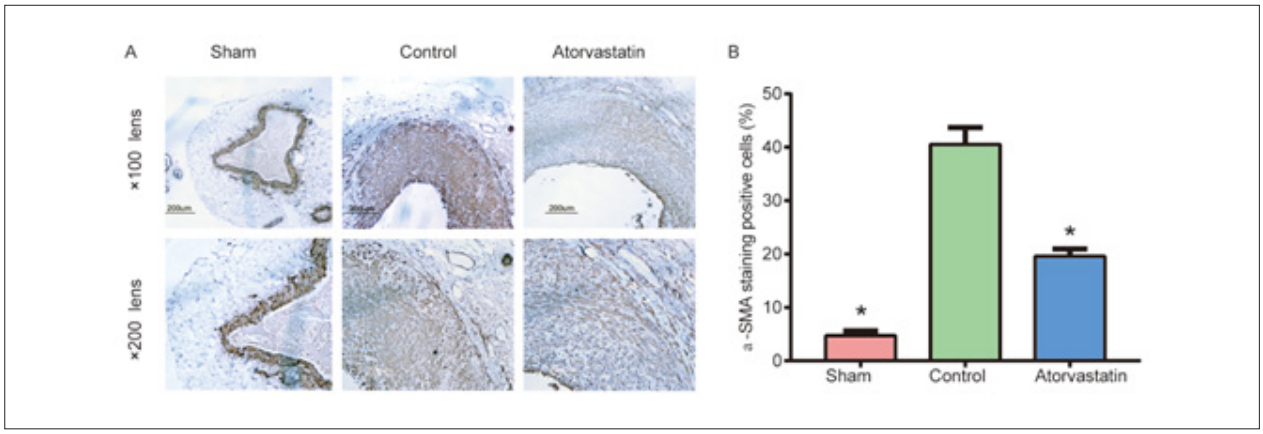

Figure 3 – *Atorvastatin decreased cell proliferating of the vein graft. The vessel tissue was collected 4 weeks after operation, fixed with formalin, sliced to 4 μm tissue sections, and stained with the primary antibody anti-α-SMA. Images (×100 and ×200 objective lens) were collected and analyzed on an Olympus microscope imaging system. The control group had a significantly higher percentage of α-SMA-positive cells than the atorvastatin group and the sham group (40.5% ± 3.1% versus 19.6% ± 1.4%, 4.7% ± 0.9%, p < 0.01). *The control group had an obvious difference the other two groups.*

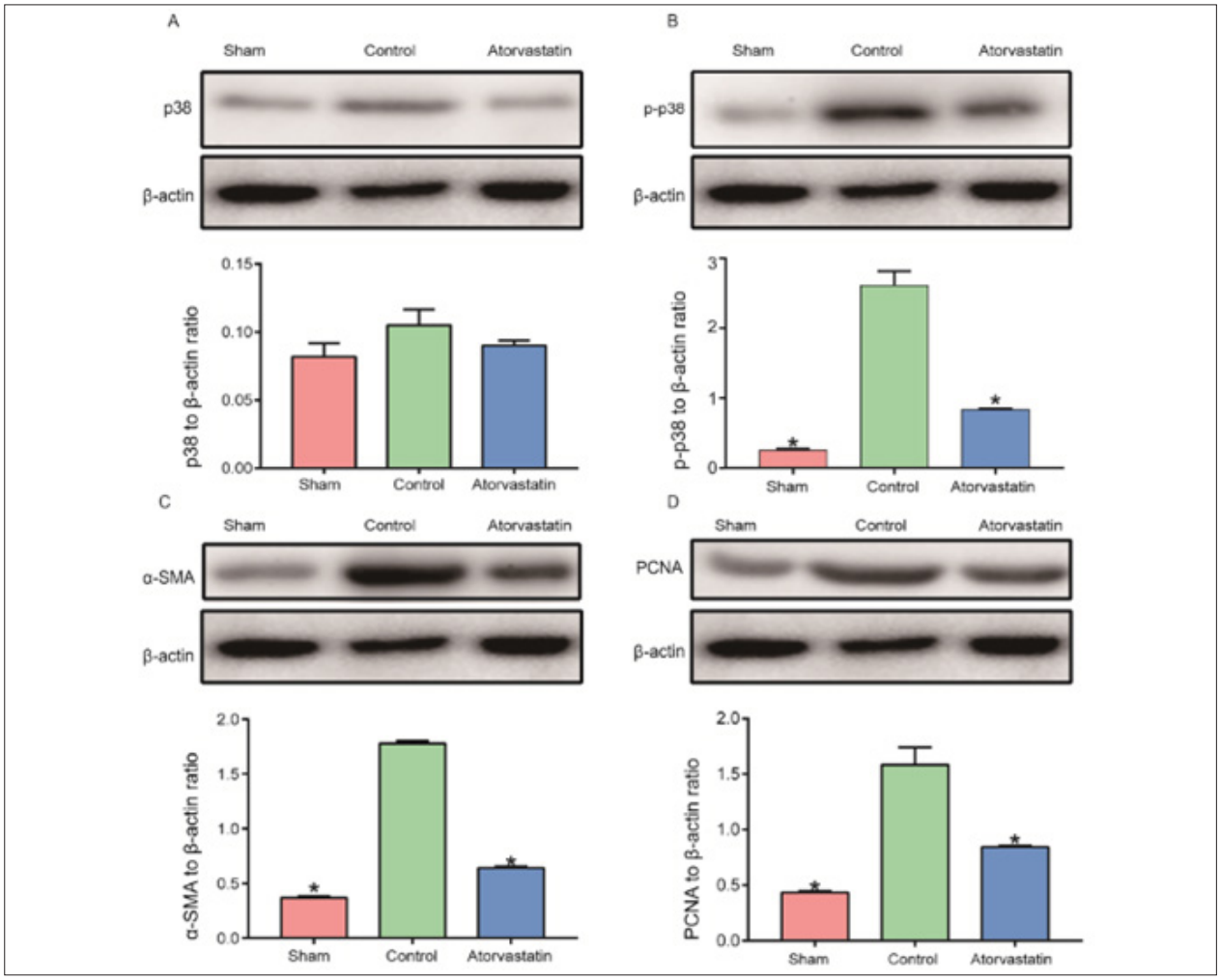

Figure 4 – *Atorvastatin reduced the expression of α-SMA, PCNA and phosphorylation of p38 MAPK. The vessel tissue collected 4 weeks after operation was placed in solvent-free microtubes, stored at −80 °C, and used for Western blot detection. Atorvastatin did not significantly reduce the level of p38 MAPK (p > 0.05, A). However, it inhibited phosphorylation of p38 MAPK (p < 0.01, B) and significantly reduced α-SMA and PCNA levels, in comparison with the control group (p < 0.01; C and D). *The control group had an obvious difference the other two groups.*

reduce accumulation of VSMCs and, furthermore, inhibit IH by suppressing p38 MAPK pathway.

Therefore, the findings from our study will contribute to future clinical work, and we should focus more on the application of statins in patients with CABG. In this study, we conducted only animal experiments *in vivo*, without *in vitro* cell experiments; future studies with more direct action mechanism research are needed to elucidate the action mechanism at the molecular level. As atorvastatin could reduce the accumulation of VSMCs to inhibit IH by suppressing the p38 MAPK pathway in rat models, we speculate that statins may also have a preventive effect in patients after CABG, but this still needs to be investigated in future studies. Our team is currently carrying out controlled clinical trials on the effects of statin application on the vascular patency rate after CABG.

In conclusion, we have demonstrated that atorvastatin can inhibit the accumulation of VSMCs by inhibiting the p38 MAPK pathway, leading to IH inhibition. We have verified this mechanism for the first time in a rat model of vein graft. These research results will lay a foundation for basic and clinical research on statin use for prevention of venous restenosis.

Author contributions

Conception and design of the research: Chu T, Zhao Z, Ling F; Acquisition of data: Chu T, Ling F, Cao J; Analysis and interpretation of the data: Chu T, Huang M, Zhao Z, Cao J; Statistical analysis: Chu T, Huang M; Writing of the manuscript: Chu T; Critical revision of the manuscript for intellectual content: Ge J.

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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Original Article

Influence of Atorvastatin on Intimal Hyperplasia in the Experimental Model

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Short Editorial related to the article: Atorvastatin Reduces Accumulation of Vascular Smooth Muscle Cells to Inhibit Intimal Hyperplasia via p38 MAPK Pathway Inhibition in a Rat Model of Vein Graft

Despite the significant advance in cardiovascular biomedicine in recent years, which provided a better understanding of the pathophysiology of coronary artery disease (CAD) as well as its prevention and treatment, this disease is still responsible for considerable mortality.[1]

The CAD results from the pathological accumulation of atherosclerotic plaques in the coronary arteries that can lead to their occlusion and ischemia of the cardiac tissue. Among the treatments used for CAD, stands out the venous graft (VG), a type of surgical intervention for coronary artery bypass grafting. However, in the long term, there is a high rate of obstruction of VG, with expansive remodeling and increased deposition of low-density lipoprotein (LDL), which can cause intimal hyperplasia (IH), atherosclerosis and thrombosis.[2,3] The IH is closely related to restenosis of the VG and begins in response to certain stress, which triggers inflammatory process and consequent endothelial dysfunction with proliferation and migration of vascular smooth muscle cells (VSMC).[4,5]

Statins are inhibitors of the enzyme HMG-CoA (3-hydroxyl-3-methylglutaryl coenzyme A), which is responsible for the synthesis of cholesterol.[6] Within this drug class, atorvastatin is commonly used in the treatment of patients with hypercholesterolemia and atherosclerosis and can decrease levels of lipids, platelets, and inflammatory processes, thus attenuating the occurrence of cardiovascular events.[7] It has been demonstrated by an experimental study using a carotid lesion model that atorvastatin is capable of suppressing IH by decreasing blood lipid levels and VSMC accumulation in the intima.[8] Another study with a similar model showed that the reduction in neointimal hyperplasia was due to increased VSMC apoptosis.[9]

The study published in the *Arquivos Brasileiros de Cardiologia* of this edition aimed to assess whether atorvastatin inhibits IH in rat vein graft[10] since few studies verified the effects of the statins on VG restenosis after coronary artery bypass grafting. These researchers observed that treatment with atorvastatin for four weeks after the VG was effective in reducing the intimal thickness, demonstrated by the decrease in VSMC using PCNA (nuclear cell proliferation antigen) and α-SMA (α-smooth muscle actin) as proliferation indicators of these cells.[10] The authors' curiosity in evaluating the effect of atorvastatin on cell hyperplasia is relevant because they demonstrated the inhibitory effect of this medication on the VSMC proliferation for the first time in an experimental VG model. Besides, the authors found that treatment with atorvastatin decreased p38MAPK phosphorylation in the VG tissue.[10] Some studies have been shown that statins are capable of suppressing p38MAPK pathway phosphorylation induced by angiotensin II in VSMC cultures[11] and that inhibition of this pathway by angiotensin-(1-7) infusion in an experimental jugular vein graft attenuated vascular remodeling.[12] However, the mechanism of action of p38MAPK in IH in the VG model had not yet been evaluated.[10] The p38MAPK involvement in IH has recently been verified by a study in which the authors showed that in experimental carotid lesions, there is decreased expression of miR-451. When this microRNA is highly expressed in VSMC, it occurs blockage of p38MAPK signaling and decreased migration of these cells to the injury site.[13]

The research on which this short editorial is based demonstrated that atorvastatin decreased the p38MAPK phosphorylation, and the authors associate this finding with reduced proliferation of VSMC in the VG, factors that were probably involved with the attenuation of IH. Thus, the findings of the present study indicate the importance of using statins to prevent restenosis in VGs, providing a basis for clinical studies. Also, the group will be able to elucidate in the future the possible molecular mechanisms involved with the benefits of this drug in this experimental model.

Keywords

Atorvastatin/prevention and control; Hyperplasia, Rats; Coronary Artery Dsease/physiopathology; Muscle, Smooth,Vascular; Models, Animal.

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Impact of Cardiorespiratory Fitness on the Obesity Paradox in Heart Failure with Reduced Ejection Fraction

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Abstract

Background: Higher body mass index (BMI) has been associated with improved outcomes in heart failure with reduced ejection fraction. This finding has led to the concept of the obesity paradox.

Objective: To investigate the impact of exercise tolerance and cardiorespiratory capacity on the obesity paradox.

Methods: Outpatients with symptomatic heart failure and left ventricular ejection fraction (LVEF) ≤ 40%, followed up in our center, prospectively underwent baseline comprehensive evaluation including clinical, laboratorial, electrocardiographic, echocardiographic, and cardiopulmonary exercise testing parameters. The study population was divided according to BMI (< 25, 25 – 29.9, and ≥ 30 kg/m²). All patients were followed for 60 months. The combined endpoint was defined as cardiac death, urgent heart transplantation, or need for mechanical circulatory support. P value < 0.05 was considered significant.

Results: In the 282 enrolled patients (75% male, 54 ± 12 years, BMI 27 ± 4 kg/m², LVEF 27% ± 7%), the composite endpoint occurred in 24.4% during follow-up. Patients with higher BMI were older, and they had higher LVEF and serum sodium levels, as well as lower ventilatory efficiency (VE/VCO_2) slope. VE/VCO_2 and peak oxygen consumption (pVO_2) were strong predictors of prognosis (p < 0.001). In univariable Cox regression analysis, higher BMI was associated with better outcomes (HR 0.940, CI 0.886 – 0.998, p 0.042). However, after adjusting for either VE/VCO_2 slope or pVO_2, the protective role of BMI disappeared. Survival benefit of BMI was not evident when patients were grouped according to cardiorespiratory fitness class (VE/VCO_2, cut-off value 35, and pVO_2, cut-off value 14 mL/kg/min).

Conclusion: These results suggest that cardiorespiratory fitness outweighs the relationship between BMI and survival in patients with heart failure. (Arq Bras Cardiol. 2020; 115(4):639-645)

Keywords: Heart Failure; Obesity; Body Mass Index; Breathing Exercises; Stroke Volume; Cardiorespiratory Fitness; Respiratory Function Tests.

Introduction

Obesity impacts most cardiovascular disease risk factors, and it is an independent risk factor for the development of heart failure (HF), being present in approximately 20% to 30% of patients with advanced HF.[1-3] However, multiple investigators have demonstrated that elevated body mass index (BMI) is paradoxically associated with improved clinical outcomes in the setting of established HF, which has been termed the "obesity paradox".[4-6]

Various competing and often contradictory mechanisms have been proposed to explain the HF obesity paradox. Possible reasons include increased levels of serum lipoproteins,[7] low levels of adiponectin,[8] and decreased response to sympathetic activation.[9] Confounding factors have also been suggested as a potential explanation.[10]

Cardiorespiratory fitness, measured variously as peak oxygen uptake (pVO_2) or ventilatory efficiency slope (VE/VCO_2 slope), has been identified as an important predictor of survival in HF.[11,12] A strong obesity paradox has been demonstrated in patients with coronary heart disease,[13,14] but not in patients with high levels of exercise tolerance.[15,16]

We aim to investigate the impact of exercise tolerance and cardiorespiratory capacity on the obesity paradox.

Methods

The investigation conforms to the principles outlined in the Declaration of Helsinki. All participants filled out a written informed consent form, and the institutional ethics committee approved the study protocol.

Selection of patients and complementary evaluation

We performed a prospective cohort study including all patients with HF with reduced ejection fraction (HFrEF) (≤ 40%), in New York Heart Association (NYHA) class II or

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III, followed in the Heart Failure Clinics of our institution. All patients referred to the Heart Failure Clinics underwent comprehensive complementary evaluation, from 2000 to 2009. Clinical, laboratorial, electrocardiographic, echocardiographic, and cardiopulmonary exercise test data were prospectively collected; all exams were performed within a period of one month for each patient.

Patients with any of the following factors were excluded: age under 18 years old, planned percutaneous coronary revascularization or cardiac surgery, exercise-limiting comorbidities (including cerebrovascular disease, musculoskeletal impairment, and severe peripheral vascular disease), and previous heart transplant.

A maximal symptom-limited treadmill cardiopulmonary exercise test was performed using the modified Bruce protocol (GE Marquette Series 2000 treadmill). Minute ventilation, oxygen uptake, and carbon dioxide production were obtained breath-by-breath, using a SensorMedics Vmax 229 gas analyzer. Before each test, the equipment was calibrated in standard fashion using reference gases. Patients were encouraged to perform exercise until the respiratory exchange ratio (ratio between carbon dioxide production and oxygen consumption, RER) was ≥ 1.10. The pVO_2 was defined as the highest 30-second average achieved during exercise and was normalized for body mass; surrogate for fat-free mass was considered in obese patients (BMI ≥ 30 kg/m^2). Percentage of predicted pVO_2 was calculated according to Hansen et al[17]. The VE/VCO_2 slope was calculated by least squares linear regression, using data acquired throughout the whole exercise[18]. The electrocardiographic data was interpreted by a physician during the exam. Weight and height were obtained, using a 110-CH Welmy anthropometric scale, before the cardiopulmonary exercise test was performed.

A GE Vivid 9 ultrasound system was used to acquire parasternal long- and short-axis views, as well as apical two-, three-, and four-chamber views. Echocardiographic parameters, including left ventricle end-diastolic and end-systolic volumes and left ventricle ejection fraction, were determined according to the American Society of Echocardiography's recommendations.

Follow-up and endpoint

All patients were followed-up for 60 months. Patients were evaluated for the occurrence of death, heart transplant, or the need for mechanical circulatory support. Data was obtained from the outpatient clinic visits and review of medical charts, with a complementary standardized telephone interview for all patients at 12, 36, and 60 months of follow-up.

The combined endpoint was defined as cardiac death, urgent heart transplant (occurring during unplanned hospitalization due to worsening of HF, requiring inotropes), or need for mechanical circulatory support.

Statistical analysis

Patients were divided into the following three groups according to BMI: < 25, 25 – 29.9, and ≥ 30 kg/m^2. Cardiorespiratory fitness was dichotomized into low- and high-risk according to VE/VCO_2 (cut-off value of 35[19]) and pVO_2 (cut-off value of 14 mL/kg/min[11]). Categorical data are presented as frequencies (percentages), and continuous variables as mean (standard deviation), as appropriate. Continuous variables were analyzed using the unpaired Student's t test after normality was verified (Kolmogorov-Smirnov test); categorical variables were analyzed using the chi-squared or Fisher's exact tests. One-way analysis of variance (ANOVA) was used for between-group comparison, when appropriate. Univariable and multivariable Cox regression models were applied to analyze time until the combined endpoint. Survival was estimated by Kaplan-Meier analysis and compared by log-rank test. Further analysis of the lower BMI group (< 25 kg/m^2) was performed, separating BMI < 20 and BMI 20 – 24.9 kg/m^2. However, due to the small percentage of patients with BMI < 20 kg/m^2 (only 17 patients), only baseline characteristics were evaluated (Supplementary Table S1 and Supplementary Figure S1), and no further statistical analysis was performed. All statistical tests were two-sided. P value < 0.05 was considered significant. SPSS version 21 software (SPSS Inc., Chicago, Illinois, USA) was used for computation.

Results

A total of 282 patients were included, with mean age of 53.7 ± 12.1 years; 75.5% were male, with mean BMI 26.8 ± 4.3 kg/m^2, and 37.6% had ischemic cardiomyopathy. Mean left ventricular ejection fraction (LVEF) was 27.4% ± 7.3%, and 23.0% of patients were in NYHA class ≥ III. Regarding therapy, 96.8% were receiving an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; 80.1% were receiving a beta-blocker; 68.1% were receiving a mineralocorticoid antagonist, and 26.2% had biventricular pacing. All patients were followed up during 60 months. The combined endpoint of cardiac death, urgent heart transplant, or need for mechanical circulatory support occurred in 24.4% of patients.

Body mass index groups

Baseline characteristics of patients according to BMI groups are shown in Table 1. Patients with higher BMI were older, and they had higher LVEF and serum sodium levels. Exercise effort was, on average, maximal in all BMI groups (RER > 1.05), although higher BMI was associated with lower RER value. Elevated BMI was associated with lower VE/VCO_2 slope (p 0.005), as well as numerically higher pVO_2 and percentage of predicted pVO_2, which did not reach statistical significance, however.

In an unadjusted Cox proportional hazards model, BMI was a predictor of event-free survival when expressed as a continuous variable (hazard ratio [HR] 0.940, CI 0.886 – 0.998, p 0.042, Table 2) or a dichotomous variable (log-rank p value 0.047, Figure 1).

Cardiorespiratory fitness

Both VE/VCO_2 slope and pVO_2 were strong predictors of event-free survival in univariable analysis (p < 0.001, Table 2).

Table 1 – Baseline characteristics according to BMI class

Baseline characteristics	BMI < 25 kg/m² (n = 99)	BMI 25 – 29.9 kg/m² (n = 119)	BMI ≥ 30 kg/m² (n = 64)	p
Age, years, mean (SD)	49.0 (± 9.6)	59.3 (± 4.5)	57.3 (± 8.5)	0.022
Male sex, n (%)	70 (70.7%)	92 (77.3%)	51 (79.7%)	0.359
Ischemic etiology, n (%)	37 (37.4%)	44 (37.0%)	25 (39.1%)	0.961
Diabetes mellitus, n (%)	8 (8.0%)	30 (25.2%)	22 (35.1%)	<0.001
LVEF, % mean (SD)	24.0 (± 5.2)	28.3 (± 0.6)	27.8 (3.6)	0.003
NYHA class ≥ III, n (%)	29 (29.6%)	24 (20.3%)	12 (19.0%)	0.184
ACE inhibitors / ARBs, n (%)	98 (99.0%)	113 (95.0%)	62 (96.9%)	0.241
Beta-blockers, n (%)	75 (75.8%)	99 (83.2%)	53 (82.8%)	0.335
Mineralcorticoid antagonist, n (%)	63 (63.6%)	86 (72.3%)	44 (68.6%)	0.364
Biventricular pacing, n (%)	21 (21.2%)	33 (27.7%)	19 (29.7%)	0.402
ICD, n (%)	23 (23.2%)	30 (25.2%)	16 (35.0%	0.938
Hb, g/dL mean (SD)	15.0 (± 1.3)	12.4 (± 1.1)	13.6 (± 1.7)	0.075
eGFR, mL/min/1.73 m² mean (SD)	103.4 (± 48.5)	69.0 (± 23.3)	73.0 (±23.5)	0.140
Sodium, mEq/L mean (SD)	134.5 (± 7.1)	139.0 (±2.6)	136.4 (± 4.8)	0.025
BNP, pg/mL mean (SD)	534.3 (± 365.3)	350.7 (± 89.0)	573.4 (± 300.6)	0.710
RER, mean (SD)	1.13 (± 0.14)	1.06 (± 0.49)	1.07 (± 0.15)	0.023
pVO_2, mL/kg/min mean (SD)	15.0 (± 2.6)	15.2 (± 3.9)	16.1 (± 2.8)	0.758
% predicted pVO_2, % mean (SD)	43.0 (± 8.4)	55.3 (± 9.3)	60.3 (± 16.1)	0.207
VE/VCO_2 slope, mean (SD)	43.4 (± 6.6)	33.8 (± 6.0)	33.1 (± 8.1)	0.005

BMI: body mass index; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; ICD: implantable cardioverter defibrillator; Hb: hemoglobin; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; RER: respiratory exchange ratio; pVO_2: peak oxygen consumption; VE/VCO_2 slope: ventilator efficiency slope. P calculated by analysis of variance.

Table 2 – Composite endpoint according to unadjusted body mass index and cardiopulmonary exercise test parameters

Dependent variable	HR (95% CI)	p
BMI, unadjusted	0.940 (0.886 – 0.998)	0.042
VE/VCO_2 slope, unadjusted	1.164 (1.135 – 1.194)	< 0.001
pVO_2, unadjusted	0.791 (0.742 – 0.842)	< 0.001

BMI: body mass index; HR: hazard ratio; VE/VCO_2 slope: ventilator efficiency slope; pVO_2: peak oxygen consumption.

When patients were grouped into low- and high-risk cardiorespiratory fitness classes according to VE/VCO_2 slope, BMI was not a predictor of clinical outcomes on univariate Cox regression analysis (p 0.771 for VE/VCO_2 slope > 35 and p 0.439 for VE/VCO_2 slope ≤ 35). Figure 2 illustrates the event-free survival characteristics of each cardiorespiratory fitness group. Furthermore, BMI did not affect event-free survival when patients were grouped for pVO_2 (p 0.170 for pVO_2 ≤ 14 mL/kg/min and p 0.164 for pVO_2 > 14 mL/kg/min).

Although BMI was a predictor of prognosis on univariable analysis, after using a Cox regression analysis adjusting for VE/VCO_2 slope, BMI lost its prognostic capacity (p 0.786, Table 3). Moreover, there was no relationship between BMI and event-free survival after adjusting for pVO_2 (p 0.201, Table 3).

Discussion

In this study, we evaluated whether cardiorespiratory capacity affects the obesity paradox. The findings can be summarized as follows: (1) obesity paradox is present in this HF population; (2) VE/VCO_2 slope and pVO_2 are strong prognostic predictors, and (3) most importantly, the prognostic capacity of BMI is lost when considering either of these two cardiorespiratory fitness parameters.

Obesity is a major risk factor for the development of HF. In the Framingham Heart Study, with 5,881 participants, the risk of HF doubled in obese subjects (HR 1.90 for men and HR 2.12 for women).[20] These results were similar in larger studies, including one with over 59,000 participants free of HF at baseline, where the multivariable-adjusted HRs for developing

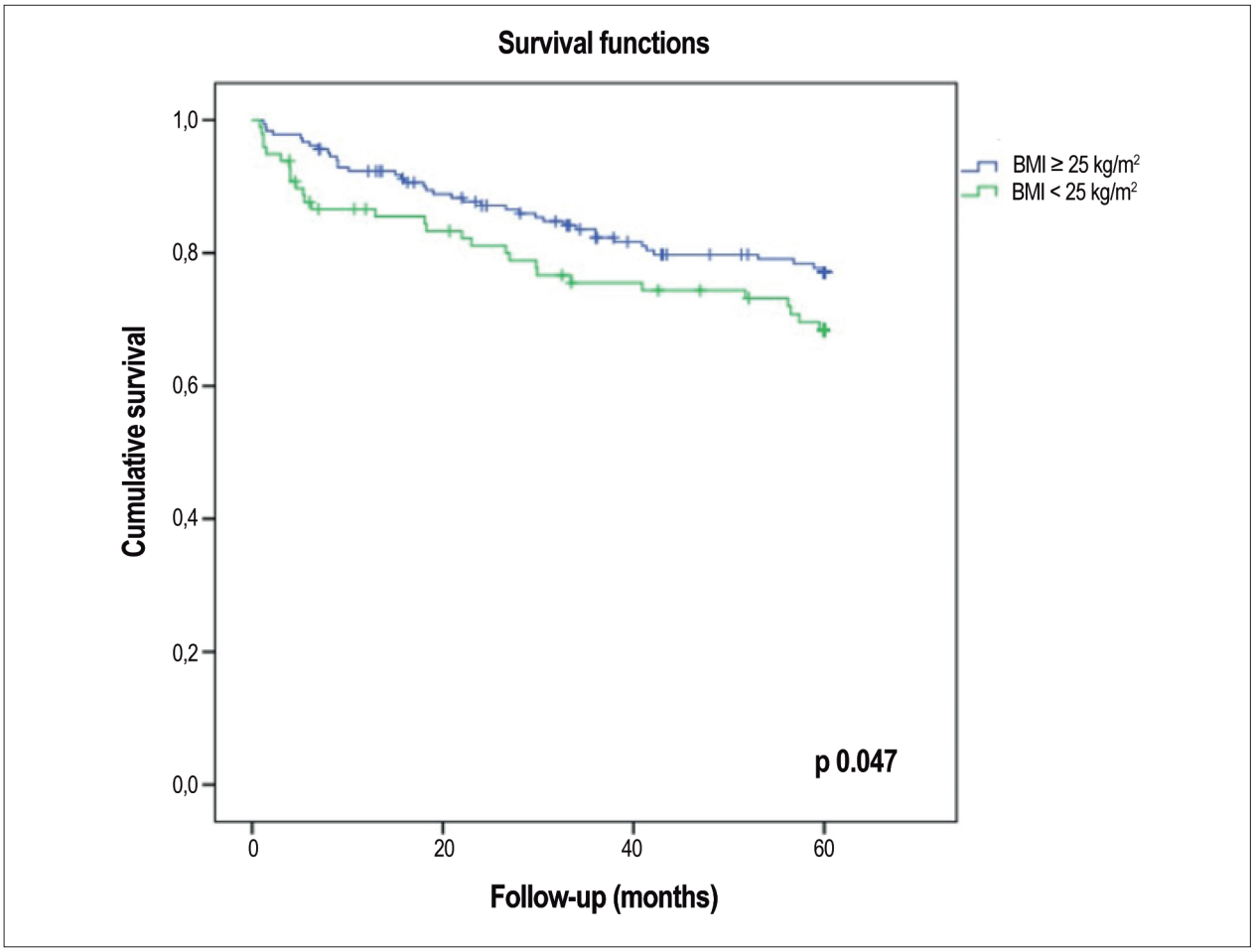

Figure 1 – *Kaplan-Meier analysis according to body mass index (BMI) in the overall group.*

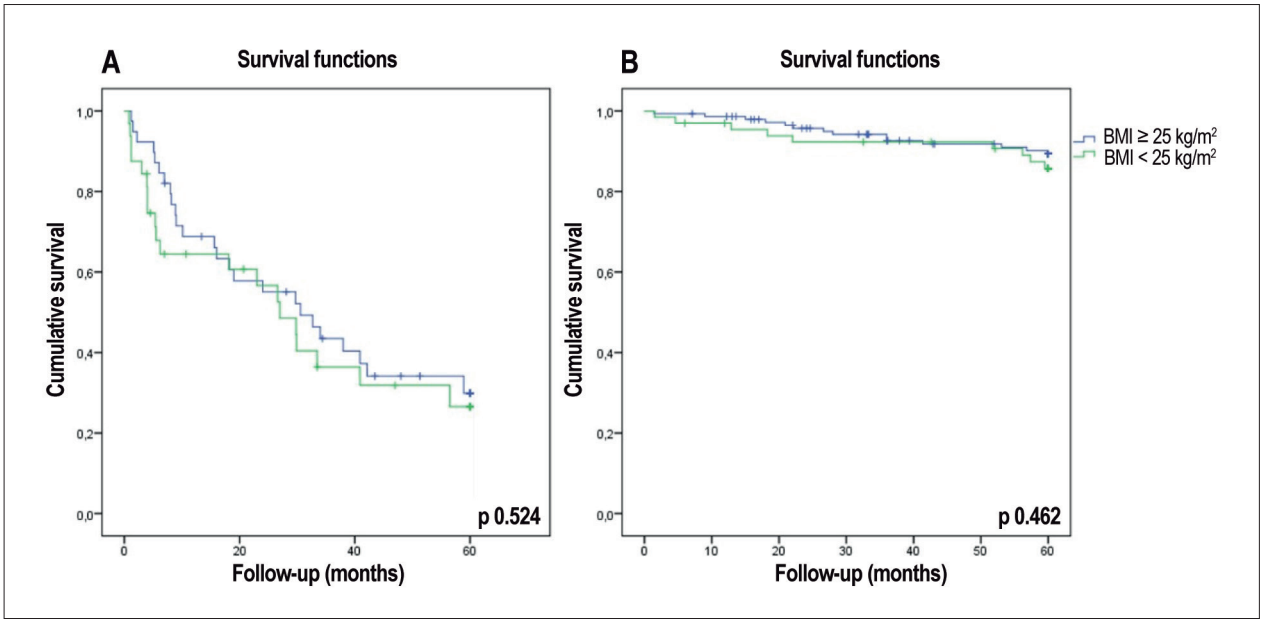

Figure 2 – *Kaplan-Meier analysis according to body mass index (BMI) in the (A) low cardiorespiratory fitness group (VE/VCO_2 slope > 35) and (B) high cardiorespiratory fitness group (VE/VCO_2 slope ≤ 35).*

Table 3 – Composite endpoint according to body mass index adjusted to cardiopulmonary exercise test parameters.

Dependent variable	HR (95% CI)	p
BMI, adjusted by VE/VCO_2	1.008 (0.949 – 1.072)	0.786
BMI, adjusted by pVO_2,	0.949 (0.892 – 1.020)	0.201

BMI: body mass index; HR: hazard ratio; VE/VCO_2 slope: ventilator efficiency slope; pVO_2: peak oxygen consumption.

HF at different levels of BMI (< 25, 25 – 29.9, and ≥ 30 kg/m²) were 1.00, 1.25, and 1.99 for men and 1.00, 1.33, and 2.06 for women, respectively.[21]

Although elevated BMI constitutes an independent risk factor for HF, multiple investigations have shown a reverse association between BMI and mortality, leading to the concept of "obesity paradox." One of the first studies in 2001, with 1,203 patients with advanced HFrEF, showed that BMI > 27.8 kg/m² was associated with a statistically significant survival benefit.[5] An analysis of in-hospital survival and BMI in more than 100,000 patients with decompensated HF identified that mortality risk was lowered by 10% for every 5-unit increase in BMI.[22] Furthermore, a meta-analysis including > 22,000 patients with chronic HF showed that the risk of cardiovascular mortality and hospitalization was lowest in overweight patients (relative risk 0.79 and 0.92 compared to normal BMI, respectively).[23] In our cohort of patients with HF, patients with higher BMI also presented better prognosis (Figure 1).

Historically, pVO_2 has been the cardiorespiratory exercise test variable most widely used for determining HF prognosis and timing of transplant.[11] However, other variables, including VE/VCO_2 slope, are also strong predictors of prognosis.[19] The additional advantage of VE/VCO_2 slope measurement is that its value is still reliable if a patient does not reach a maximal effort (RER > 1.05) and therefore does not achieve his or her "true" pVO_2.[24]

In our study, VE/VCO_2 slope and pVO_2 were both strong predictors of prognosis. Chase et al.[12] demonstrated that VE/VCO_2 slope maintains prognostic value irrespective of BMI in patients with HF[12]. We also demonstrated that higher BMI conveys a better outcome in unadjusted analysis. However, when either VE/VCO_2 slope or pVO_2 were considered, BMI lost its prognostic capacity. Moreover, when the patients were grouped according to their cardiorespiratory fitness class, BMI did not influence outcomes. Analyzing our HF population by BMI class, we were also able to observe that patients with higher BMI had better prognostic parameters (including LVEF, sodium levels, and VE/VCO_2 slope), indicating that these patients presented a less advanced HF condition.

These findings indicate that the obesity paradox might be mitigated and even negated by cardiorespiratory fitness, and it may only represent a survival or index event bias. HF is a catabolic state, and elevated BMI may represent metabolic reserve, while lower BMI may be a consequence of unintentional weight loss and cardiac cachexia, which is associated with poor prognosis.[25] Additionally, the clinical experience in our Heart Failure Clinics has shown that obese patients may experience greater functional impairment due to increased body mass and therefore seek medical assistance first, leading to earlier implementation of prognostic therapy. Additionally, it is possible that some of the patients identified as "obese," in fact, have increased muscle mass and muscular strength.[26]

The obesity paradox has previously been challenged in other studies. Lavie et al.[16] demonstrated that, in patients with HFrEF, BMI was a significant predictor of survival in the group with low cardiorespiratory fitness (pVO_2 < 14 mL/kg/m²), but not in the high cardiorespiratory fitness group.[16] More recently, Piepoli et al.[27] verified that the prognostic role of BMI disappeared when age, gender, LVEF, and pVO_2 were taken into consideration.[27]

These previous studies that evaluated the influence of cardiorespiratory fitness on the obesity paradox only analyzed the influence of pVO_2, which is effort-dependent and highly influenced by patient motivation.[28] In our study, we also demonstrated that VE/VCO_2 slope, which is a maximal effort-independent parameter, mitigated the obesity paradox. Therefore, the relationship between cardiorespiratory fitness and the obesity paradox is not influenced by maximal exercise effort performed during the test.

Despite the benefit of weight loss in the prevention of adverse cardiac remodeling, HF, and other cardiac diseases, there is no clear consensus regarding weight loss in patients with HF. Large clinical trials are needed to better understand the benefits and risks of weight reduction in patients with HF. Given the current state of evidence, it may be reasonable to advise purposeful weight loss, particularly in those with more severe degrees of obesity, incorporating the benefits of physical activity, exercise training, and cardiorespiratory fitness.[29,30]

Limitations

This is a single center study, which limits the generalization of results. Nevertheless, this made it possible for the cardiorespiratory exercise test protocol to be homogeneous in all cases, and it may have reduced the number of physicians responsible for interpretation of the exam, thus reducing interobserver variability. Additionally, the population comprised patients with HFrEF (mean systolic LVEF 27.4% ± 7.3%) who were able to perform exercise and, therefore, the results may not apply to the entire HF population. A further limitation is that patients with higher BMI presented lower RER. However, these patients had the highest exercise performance, and analysis with VE/VCO_2 slope overcomes this limitation, as it is a maximal effort-independent parameter.

Conclusion

In the studied HF population, BMI was not related to outcomes when cardiorespiratory exercise test variables

were taken into consideration. Therefore, cardiorespiratory fitness affects the relationship between BMI and survival in HF patients.

Author contributions

Conception and design of the research and Statistical analysis: Moreira RI; Acquisition of data: Moreira RI, Silva TP, Gonçalves AV, Feliciano J, Rio P; Analysis and interpretation of the data: Moreira RI, Gonçalves AV; Writing of the manuscript: Moreira RI, Silva TP; Critical revision of the manuscript for intellectual content: Soares R, Ferreira RC.

Potential Conflict of Interest

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

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Study Association

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

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Is the Obesity Paradox in Heart Failure Dependent on Cardiorespiratory Fitness?

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Short Editoral related to the article: Impact of Cardiorespiratory Fitness on the Obesity Paradox in Heart Failure with Reduced Ejection Fraction

Heart failure (HF) is a global public health menace which is associated with increased hospitalization, morbidity, mortality and high economic costs.[1] However, HF which has ischemic heart disease as a common underlying disease, is a preventable condition. Cardiorespiratory fitness (CRF) is an index of habitual physical activity levels and is considered the gold standard for aerobic exercise capacity. Cardiorespiratory fitness, an important component of physical fitness and directly measured by peak oxygen uptake (pVO_2), and ventilatory efficiency slope (VE/VCO_2 slope), has been identified as one of the most important predictors of health outcomes and survival.[2] We have previously reported that directly assessed pVO_2 is strongly, independently and inversely related to a lowered risk of cardiometabolic conditions such as HF,[2,3] atrial fibrillation,[3,4] ventricular fibrillation,[5] diabetes[6] as well as mortality from cardiovascular diseases (CVDs).[7,8] Our recent population-based study based on UK Biobank suggests that CRF is a strong risk indicator for mortality and addition of CRF to a conventional risk factor score improved the overall discrimination of mortality risk and, more importantly, the predictive value of CRF varied across levels of some relevant risk factors, including age, sex, and smoking.[8] This is an indicator of the potential of CRF to be a valuable risk assessment tool in clinical practice.

It is well-known that obesity, as measured by body mass index (BMI), is related to the development of cardiovascular outcomes. However, the combined effect of obesity and CRF on the risk of future HF still requires further study. It is of clinical relevance to understand if CRF attenuates the association of obesity with later risk of HF due to other underlying CVDs.[9] The majority of previous studies on higher BMI, other obesity parameters, and HF risk have not taken into account the differences in CRF levels. Though high BMI is a risk factor for HF, there are findings of a non-linear relationship between BMI and CVD outcomes in HF patients which indicates an unusual relationship. In patients with established HF, accumulating evidence suggests that overweight and obese (higher BMI) individuals have improved survival compared to those with normal BMI, a known concept which has been called the "obesity paradox" or "reverse epidemiology".[10] Some mechanisms have been proposed to explain the HF obesity paradox which includes HF therapy being more effective in obese patients. It has been reported that CRF might play also play a role by either mitigating or negating the "obesity paradox".[10,11]

There is limited evidence on the association and interactions between CRF, BMI, HF and HF outcomes. This was the rationale for the new study by Moreira et al. published in the recent issue of the journal, which aimed to investigate the impact of exercise tolerance and cardiorespiratory capacity on the obesity paradox among HF patients with low ejection fraction.[12] All patients referred to the Heart Failure Clinics underwent clinical evaluation with collection of laboratory, electro- and echocardiographic, and cardiopulmonary exercise test data. A maximal symptom-limited treadmill cardiopulmonary exercise test was performed using the modified Bruce protocol (GE Marquette Series 2000 treadmill). Minute ventilation, oxygen uptake, and carbon dioxide production were acquired using a breath-by-breath gas analyzer. A total of 282 HF patients were included (75.5% male) with a mean age of 53.7 years and BMI of 28.6 kg/m^2. Patients were followed-up for 60 months for a combined composite endpoint comprising of cardiac death, urgent heart transplant, or need for mechanical circulatory support.[12] Interestingly, patients with higher BMI had higher LVEF but lower ventilatory efficiency (VE/VCO_2) slope.[12] Association analysis showed BMI, VE/VCO_2 slope and pVO_2 to be each an indicator of the primary outcome. However, the association between BMI and outcome was attenuated to null when patients were grouped into low and high CRF (based on VE/VCO_2) and after controlling for VE/VCO_2 or pVO_2.

Consistent with findings of this study, Chase et al. have earlier demonstrated that VE/VCO_2 slope maintained its prognostic value irrespective of BMI in patients with HF.[13] However, when either VE/VCO_2 slope or pVO_2 were taken into account in their analyses, the association between BMI and cardiac outcomes were not significant. Moreover, when the patients were grouped and analyzed according to their CRF subgroups, BMI was not related to outcomes.[13]

Keywords

Heart Failure; Obesity; Cardiorespiratory Fitness; Body Mass Index; Exercise; Hospitalization; Morbity and Mortality.

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Given that the absolute risk of adverse CVD outcomes depends largely on age, employing a single relative metric cannot allow quantification of absolute risk differences across increasing ages with different BMI levels. Zaccardi et al.[14] recently suggested a new approach to evaluate the interplay were to estimate residual life expectancy across CRF levels and BMI.[14] Based on the large UK Biobank cohort including 474,919 participants, the authors demonstrated that participants with a brisk walking pace have a longer life expectancy across the spectrum of BMI and other fatness measures, providing additional data evidence that walking pace, as a marker of fitness level, is an easily available indicator of health status.

The strengths of the current study include the use of a clinically relevant sample based on high-risk HF patients and the assessment of CRF measures using reliable respiratory gas analysis, which is a more objective and quantitative assessment method for CRF. Several limitations include (i) the small sample size; (ii) inability to adjust for many potential confounders; (iii) lack of data on medications, biomarkers, and physical activity patterns during follow-up, which could have at least partly influenced CRF and BMI levels; (iv) lack of formal risk prediction analyses as measures of association are insufficient for making clinical judgments about the prognostic relevance of an exposure; and (v) the potential for regression dilution given the absence of repeat measurements of CRF, given the potential for changes in CRF levels due to errors in measurements and changes in the clinical course of the disease. In our reproducibility substudies of CRF measurements within the Kuopio Ischemic Heart Disease (KIHD) prospective cohort study, we have demonstrated a high within-person variability in CRF levels measured many years apart (regression dilution ratio=0.58);[15] which suggests that analyses using only single baseline measurements of CRF could underestimate associations with outcomes. Overall, these new findings highlight the fact that an "obesity paradox" exists in HF patients and there is an interplay between obesity, CRF and outcomes in HF. Cardiorespiratory fitness as measured by VE/VCO_2 or pVO_2 appeared to negate the obesity paradox.[12]

CRF is influenced by genetic and environmental factors; approximately 50 % of the variation in CRF has been attributed to heritable factors, with the contribution of inherited factors to the response of CRF to physical activity and exercise training.[7,8,11] It also depends on several factors such as baseline health and fitness status, type, duration, and intensity of PA. The level of CRF is also an indicator of a chain of multiple physiological processes that include: pulmonary ventilation and vascular function, right and left ventricular function, the capacity of the vasculature to efficiently transport blood from the heart to other organs matching their oxygen requirements, the ability of the muscle cells to use the oxygen and essential nutrients, and the ability to activate all necessary muscle fibres needed for body movement.[11] Left ventricular stroke volume, maximal heart rate, and arteriovenous oxygen difference at exercise have essentially determined CRF levels. Left ventricular function is a key measure of HF and CRF level may reflect LV function. As CRF is related to the integration of human body function under physiological stress conditions, it can be employed as a very accurate indicator of the risk for HF, reflecting whole body functional status among patients with existing HF. Given the central role normal cardiac function plays in defining maximal aerobic capacity, disease, or dysfunction that detrimentally affects cardiac output will also compromise maximal VO_2. High-intensity aerobic exercise training is safe and effective in improving functional capacity in many patient populations with cardiac conditions.[11] Participation in a long-term aerobic exercise training program produces a host of positive morphological and physiological cardiovascular adaptations in apparently healthy individuals, irrespective of age and sex. Commonly reported morphological adaptations associated with regular aerobic exercise training is left ventricular dilation (ie, increased end-diastolic diameter) and hypertrophy (ie, increased wall thickness), referred to as exercise training-induced cardiac remodelling.[16]

The current findings throw more light on a possible interaction between CRF, obesity and outcomes in HF. However, given the limitations of small sample size and inability to adjust for relevant covariates, these observational study findings need caution when being interpreted. Findings add to the minefield of accumulating evidence that CRF (using peak VO_2 and measures of ventilatory efficiency) is a clinically useful tool in HF risk assessment. High levels of CRF can be achieved through regular physical activity and this should be promoted extensively via population wide approaches. The health benefits associated with regular physical activity, which includes aerobic and strength training components, cannot be overemphasized.[11,14,16] Efforts to improve CRF with a healthy body weight could become a standard part of clinical encounters for the treatment of HF with low ejection fraction.

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Stress in Women with Acute Myocardial Infarction: A Closer Look

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Abstract

Background: Women seem to be more susceptible to psychosocial stress than men, and stress is associated with worse outcomes after acute myocardial infarction (AMI).

Objectives: To investigate whether the female gender is an independent predictor of risk for stress and to compare stress levels between women and men after AMI.

Methods: Cross-sectional study of a case series. Patients aged 18 to 65 years who were treated for AMI at the study facility between January 2017 and June 2018 were eligible. The presence of stress was assessed using Lipp's Stress Symptoms Inventory for Adults (ISSL), which categorizes stress into four phases (alertness, resistance, near-exhaustion, and exhaustion), through a list of physical and psychological symptoms. Data were analyzed using SPSS Version 24.0. The significance level was set at $p<0.05$.

Results: Of the 330 respondents, 89% of women and 70% of men experienced stress. The female gender was associated with nearly threefold higher odds of experiencing stress (EXP (B)2.79, $p = 0.02$). Regarding the phases of stress, women were more often in the near-exhaustion and exhaustion phases, while men were more often in the resistance phase.

Conclusions: This study showed that women are most often in the third and fourth phases of stress, i.e., in situations of long-standing psychosocial stress. These findings can assist in the development of gender-specific strategies for health promotion and disease prevention, aiming to minimize the effects of stress in this population. (Arq Bras Cardiol. 2020; 115(4):649-657)

Keywords: Women; Myocardial Infarction; Stress, Psychological; Coronary Artery Disease; Vascular Diseases; Risk Factors.

Introduction

Selye was the first to identify stress as a set of reactions that the body exhibits when it is required to adapt to a situation by exerting an effort.[1] Stress is thus understood as a reaction to any stressful event, or *stressor*, and can trigger behavioral, psychological, and physical symptoms.[2]

In the intercontinental INTERHEART study,[3] conducted with 11,119 cases and 13,648 controls across 52 countries, the presence of stressors was shown to double the risk of acute myocardial infarction (AMI). Data from a U.S. National Health Interview Survey[4] confirm these findings, and demonstrate that stress and psychological distress can double the risk of AMI (OR: 2.0; 95%CI, 1.4 to 3.0).

Chronic psychological stress produces the overactivation of the sympathetic nervous system, which exacerbates coronary atherosclerosis and endothelial dysfunction.[5,6] In the long term, this may increase the risk of coronary events and death.[7]

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Studies have shown that women are more susceptible to psychosocial stress.[8,9] Women's daily lives involve multiple social and family roles, which makes them as much as or more susceptible to cardiovascular diseases than men.[10] Acute myocardial infarction (AMI) and stroke are the leading causes of death in women over the age of 50. In this age group, there are more cardiovascular deaths than by any other cause, including breast cancer.[11]

In Brazilian studies, younger women have been found to experience a higher frequency of stress symptoms compared to men.[12,13] However, in studies on stress and ischemic heart disease, women are less prevalent and older than males.[14,15] Within this context, the objective of the present study was to investigate predictors of stress, mainly to investigate whether female gender is an independent predictor of stress risk , as well as to compare sociodemographic and clinical characteristics, medical history, in-hospital events and stress levels between women and men with acute myocardial infarction.

Methods

Design and Participants

Cross-sectional study of a case series conducted over an 18-month period. Patients were included according to the following criteria: Age 18 to 65 years (i.e., working age); treated for acute myocardial infarction with ST-segment

elevation (STEMI), within 12 hours of symptom onset, at a cardiology referral center. According to the 5th Brazilian Society of Cardiology Guideline on the Treatment of STEMI (2015),[16] AMI is defined as an acute ischemic syndrome with ST-segment elevation >1.0 mm on contiguous ECG leads. Increased and/or decreased levels of cardiac markers, especially troponin (>99th percentile), are essential for the diagnosis. Exclusion criteria: Prolonged time from symptom onset until hospital arrival; need for mechanical ventilation; development of delirium; previous history of dementia, cognitive impairment; or known psychiatric conditions, according to the attending physician, which would preclude comprehension of the informed consent form.

Participants were interviewed during the first 48 hours of hospitalization. Data on sociodemographic variables, past medical history, and risk factors for ischemic heart disease were collected. Race was self-reported by the participants. Hypertension was defined as a previous diagnosis or current use of antihypertensive agents. Dyslipidemia was considered present in patients with a previous diagnosis or those currently using lipid-lowering drugs. Diabetes mellitus was defined by a documented fasting glucose >126 mg/dL on two occasions or a history of use of insulin or antidiabetic agents. Family history of CAD was considered positive if any first-degree relatives had a history of AMI or sudden cardiovascular death before age 55 (men) or 65 (women). BMI (body mass index) was calculated using the self-reported weight and height data. Depression was defined by the occurrence of at least one major depressive episode requiring pharmacological treatment. Angina was defined as pain or discomfort in the anterior chest, epigastric region, jaw, shoulder, back or upper limbs, triggered or worsened by physical activity or emotional stress (class II or higher), according to the Stable Coronary Disease Guidelines.[17] Medical records were checked for any intercurrent events occurring during hospitalization.

Instruments

The presence of stress was assessed using the LIPP's Stress Symptoms Inventory for Adults (ISSL),[2] which has been validated by the Brazilian Federal Board of Psychology. The ISSL consists of a list of 53 physical and psychological symptoms, divided into time periods: in the last 24 hours, in the last week, and in the last month. In addition to detecting the presence or absence of stress, the instrument categorizes stress into four phases: alertness (corresponding to the score obtained for symptoms present in the last 24 hours), resistance, near-exhaustion (corresponding to the scores for the last week), and exhaustion (corresponding to symptoms that were present in the month preceding the interview). This instrument thus allows the diagnosis of stress, establishing the stage of stress the respondent is currently experiencing, and whether there is a predominance of physical, psychological, or mixed symptoms.

Phases of Stress

The alertness phase is characterized by sympathetic nervous system reactions, elicited by the initial perception of the stressor. The resistance phase develops when a stressor persists over time – causing the person to resist and find the strength to continue coping with the stress, although the symptoms remain present. In the near-exhaustion phase, the actual pathological process begins, and organs that have a greater genetic or acquired vulnerability start to show signs of deterioration. If the stress is not relieved, whether by removal of the stressor or the use of coping strategies, the exhaustion phase is reached. Various conditions arise, such as stress ulcers, gingivitis, psoriasis, hypertension, depression, and anxiety, among others.[2]

Ethical Considerations

This study was approved the institutional Research Ethics Committee (CAAE: 62727416.5.0000.5333). All participants agreed to participate in the study and signed the Free and Informed Consent Form (ICF), pursuant to the provisions of Brazilian National Health Council Resolutions 466/12 and 510/2016.

Sample Size

The sample size was calculated using the WinPepi software, version 11.29. Considering that the difference between the proportion of men and women with stress ranges from 30%[12] to 50%[13] and that 70% of patients with acute myocardial infarction are males,[18] for a significance level of 0.05 and a statistical power of 80%, the minimum sample size would comprise 194 participants (114 men, 80 women).

Statistical Analysis

Data were entered into a Microsoft Excel database and analyzed using the Statistical Package for Social Sciences (SPSS), Version 24.0. The Kolmogorov–Smirnov test was used to verify the normality of the variables. Continuous variables were expressed as mean and standard deviation, and categorical variables, as absolute and relative frequencies. The multivariate logistic regression was performed for the predictors of stress. Variables that reached $p<0.10$ in the bivariate analysis were retained for the multivariate model. A *t*-test for independent samples or chi-square test was used for comparison of variables between participants with and without stress and by gender. A p-value < 0.05 was considered statistically significant. The prevalence of stress, its phases, and symptoms were presented as relative frequencies and compared with the chi-square test as necessary, following the rules of the ISSL Instrument, in which the responses are categorized.[2]

Results

Patients were included consecutively from August 2017 through June 2018. According to the study flowchart diagram (Figure 1), of the 632 patients with AMI assessed for eligibility, 211 did not meet the inclusion criteria, 32 were excluded according to the established criteria, 40 died, and 19 were excluded because they were not interviewed within the first 48 hours of hospitalization. Thus, the final sample consisted of 330 participants.

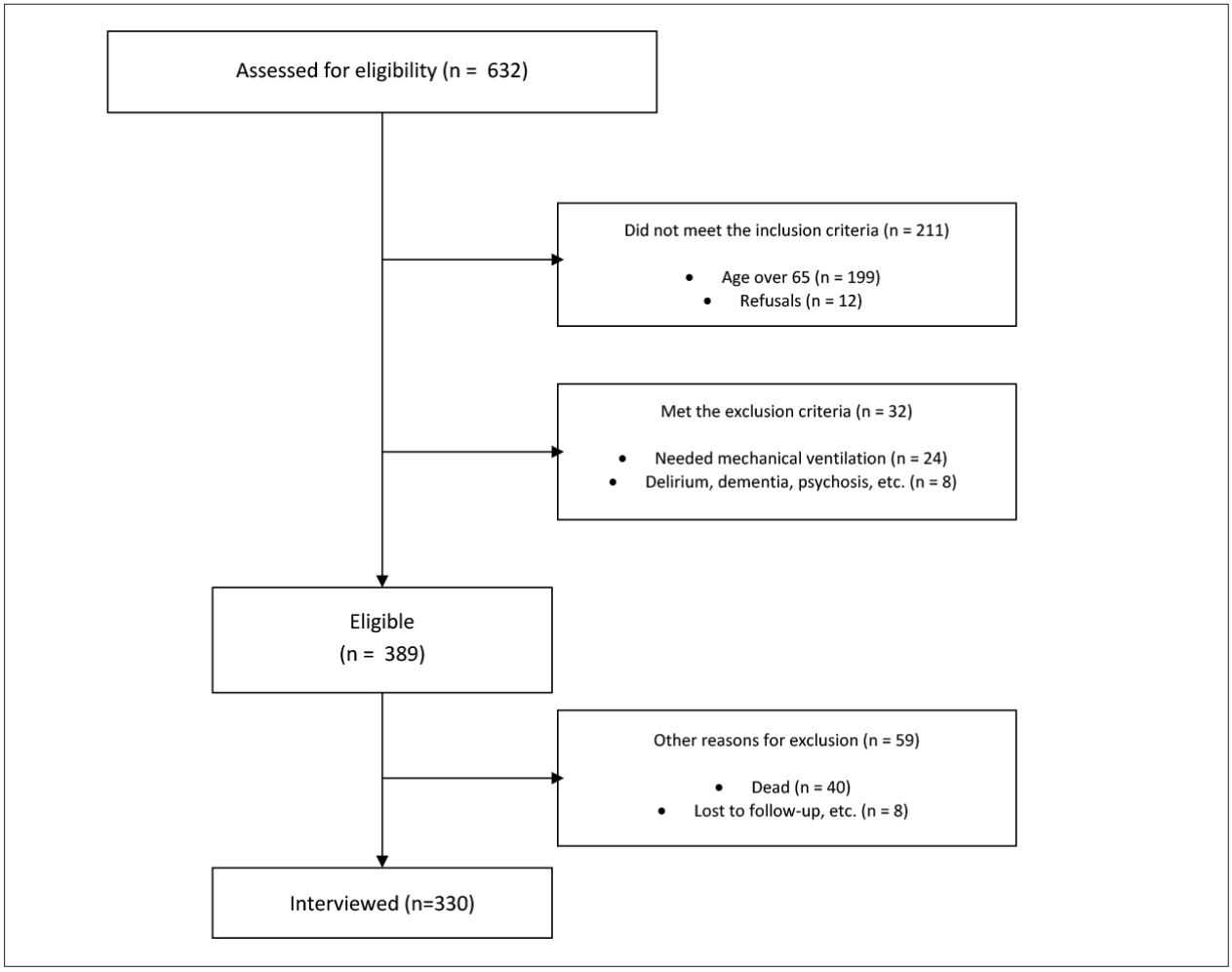

Figure 1 – *Study flowchart diagram. January 2017 to June 2018.*

Of these 330 respondents, 80 were women and 250 were men. Overall, 74% were experiencing stress (89% of women and 70% of men). Table 1 shows the clinical characteristics of the sample, stratified by the presence or absence of stress. We observed that those respondents with stress were mostly women, with fewer years of formal education, and had been admitted under the care of the Unified Health System (SUS). There were no significant differences between the risk factors; however, regarding the past medical history, patients with stress were more likely to have angina and depression. There were no differences regarding complications and intercurrent events occurring during hospitalization in these patients.

After the bivariate analysis of the characteristics of patients with *vs*. without stress, we selected those with $p<0.10$ for inclusion in the multivariate analysis model (Table 2). The results showed that female gender and being admitted under the Brazilian public healthcare system (Unified Health System) were independent predictors of stress. The relative risk of exposure to stress—Exp(B)—in women was 2.79 (95% CI 1.21 to 6.40, $p=0.02$), which suggests that being female nearly triples one's odds of experiencing stress.

The analysis by gender included only those patients with stress, i.e., a total of 245 participants (71 women and 174 men). As seen in Table 3, women with stress had a lower level of schooling than men, and a greater proportion of them had a lower household income. Women were also hospitalized under the care of the public system more frequently than men (89.7% vs 75.5%, $p=0.014$). There were no significant differences in relation to age or body mass index (BMI). Regarding the risk factors, smoking was more prevalent among women than men. Hypertension, diabetes, and family history of coronary heart disease were similar in both groups. There was an apparent trend toward dyslipidemia among women. Women were also more likely than men to have a history of depression and chronic obstructive pulmonary disease (COPD). Regarding the clinical course, the in-hospital mortality was higher in women.

Assessment of the phases of stress showed that women were more likely than men to be in the near-exhaustion (18.6% vs. 9.2%, $p= 0.041$) and exhaustion (32.9% vs. 16.7%, $p = 0.005$) phases, while men were more likely to be in the resistance phase (40.0% vs. 62.6%, $p<0.001$). The

Table 1 – Difference in stress prevalence between genders

Characteristics	Overall n=330	Stress n=245	No stress n=85	p*
Sociodemographic characteristics				
Female gender, n%	80 (24.2%)	71 (29.0%)	9 (10.6%)	0.001
Age, years	54.6 ± 7.7	54.4 ± 8.10	55.4 ± 7.0	0.28
BMI, kg/m²	27.8 ± 5.1	27.6 ± 5.0	28.2 ± 5.5	0.33
Level of schooling, years	9.0 ± 4.0	8.7 ± 4.4	9.9 ± 3.3	0.02
Caucasian, n (%)	249 (81.0%)	186 (81.0%)	63 (80.8%)	0.32
Household income <5× minimum wage, n (%)	243 (76.0%)	186 (78.2%)	57 (69.5%)	0.11
Unified Health System, n (%)	231 (76.0%)	184 (79.7%)	47 (64.4%)	0.008
Risk factors				
HTN, n (%)	180 (54.5%)	132 (54.0%)	48 (56.2%)	0.68
DM, n (%)	75 (22.7%)	55 (22.4%)	20 (23.5%)	0.84
Smoking, n (%)	120 (49.0%)	120 (49.0%)	38 (44.7%)	0.09
Dyslipidemia, n (%)	68 (27.8%)	68 (27.8%)	21 (24.7%)	0.58
FH+, n (%)	81 (24.8%)	62 (25.6%)	19 (22.4%)	0.55
Past medical history				
Prior AMI, n (%)	64 (19.7%)	52 (21.7%)	12 (14.1%)	0.13
Prior PCI, n (%)	48 (14.8%)	40 (16.7%)	8 (9.4%)	0.10
Prior stroke, n (%)	20 (6.2%)	14 (5.8%)	6 (7.1%)	0.68
CHF, n (%)	16 (5.0%)	12 (5.1%)	4 (4.7%)	0.90
Angina, n (%)	87 (26.8%)	74 (30.8%)	13 (15.3%)	0.005
COPD, n (%)	9 (2.8%)	9 (3.8%)	0	-
CKD, n (%)	4 (1.2%)	3 (1.3%)	1 (1.2%)	0.95
Depression, n (%)	51 (15.8%)	45 (19.0%)	6 (7.1%)	0.01
In-hospital events				
Arrhythmia, n (%)	9 (2.8%)	7 (3.0%)	2 (2.4%)	0.75
Recurrent AMI, n (%)	2 (0.6%)	2 (0.9%)	0	–
Stroke, n (%)	1 (0.3%)	1 (2.5%)	0	–
Death, n (%)	4 (1.3%)	4 (1.7%)	0	–

*AMI: acute myocardial infarction; BMI: body mass index; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; FH+: family history of coronary artery disease; HTN: hypertension; PCI: percutaneous coronary intervention. *Chi-square or Student's t-test for independent samples.*

Table 2 – Multivariate analysis of independent predictors of stress

Characteristics	Exp(B)	95% confidence interval	p
Females	2.79	1.21-6.40	0.02
Level of schooling	0.98	0.91-1.06	0.66
Angina	1.90	0.94-3.87	0.07
Depression	1.52	0.57-4.02	0.40
Smoking	1.06	0.60-1.86	0.84
Unified Health System	1.93	1.00-3.70	0.05

Table 3 – Comparison of profiles between women and men with stress

Characteristics	Women n=71 (89%)	Men n=174 (70%)	p*
Sociodemographic characteristics			
Age, years	55 ± 9	54 ± 7	0.667
BMI, kg/m²	27 ± 7	28 ± 4	0.168
Level of schooling, years	8 ± 4	9 ± 4	0.016
White ethnicity, n (%)	59 (86.8%)	127 (78.4%)	0.308
Household income <5× minimum wage, n (%)	63 (91.3%)	123 (72.8%)	0.006
Unified Health System, n (%)	61 (89.7%)	123 (75.5%)	0.014
Risk factors			
HTN, n (%)	44 (62.0%)	88 (50.6%)	0.114
DM, n (%)	20 (28.2%)	35 (20.1%)	0.170
Smoking, n (%)	46 (64.8%)	77 (44.4%)	0.005
Dyslipidemia, n (%)	25 (35.2%)	41 (23.6%)	0.062
FH+, n (%)	19 (26.8%)	45 (25.9%)	0.885
Past medical history			
Prior AMI, n (%)	16 (22.9%)	36 (21.3%)	0.791
Prior PCI, n (%)	12 (17.1%)	28 (16.6%)	0.914
Angina, n (%)	21 (30.0%)	53 (31.4%)	0.836
CHF, n (%)	5 (7.1%)	7 (4.2%)	0.350
Depression, n (%)	26 (37.7%)	19 (11.3%)	<0.001
COPD, n (%)	5 (7.1%)	3 (1.8%)	0.037
CKD, n (%)	1 (1.4%)	2 (1.2%)	0.877
Prior stroke, n (%)	4 (5.7%)	10 (5.9%)	0.952
Intercurrent events			
Arrhythmia, n (%)	4 (5.8%)	3 (1.8%)	0.105
Recurrent AMI, n (%)	1 (1.4%)	1 (0.6%)	0.526
Stroke, n (%)	0	1 (0.6%)	-
In-hospital death, n (%)	3 (4.3%)	1 (0.6%)	0.045

*AMI: acute myocardial infarction; BMI: body mass index; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; FH+: family history of coronary artery disease; HTN: hypertension; PCI: percutaneous coronary intervention. *Chi-square or Student's t-test for independent samples.*

prevalence of the alertness phase (7.1% vs. 8.6%, p=0.703) and a predominance of physical symptoms (77.1% vs. 73.6%, p=0.586) were similar in the two groups. Figure 2 illustrates the distribution of these percentages.

Discussion

In this study, the prevalence of stress in patients admitted with acute myocardial infarction was 74%. The overall prevalence of stress was similar to that described in previous studies of patients with cardiovascular disease, ranging from 72%[14] up to 85% in patients with hypertension.[19] Therefore, there is a high prevalence of stress in patients undergoing primary percutaneous coronary intervention for the treatment of myocardial infarction.

Women experienced more stress than men, as described elsewhere in the literature. In a study by Calais and Lipp[12] on the differences in stress manifestations by gender and level of schooling, the authors, using the ISSL, found an overall stress prevalence of 79.30% in women and 51.72% in men. In a survey of magistrate court employees[13] using the same instrument, 82% of female and 56% of male magistrate employees were stressed, demonstrating a significant difference between the genders. Although these surveys described higher percentages of stress in women, neither of them evaluated whether female gender alone was an independent predictor, which is a strength of our study. We found a higher prevalence in both genders, although it was higher in women (89% and

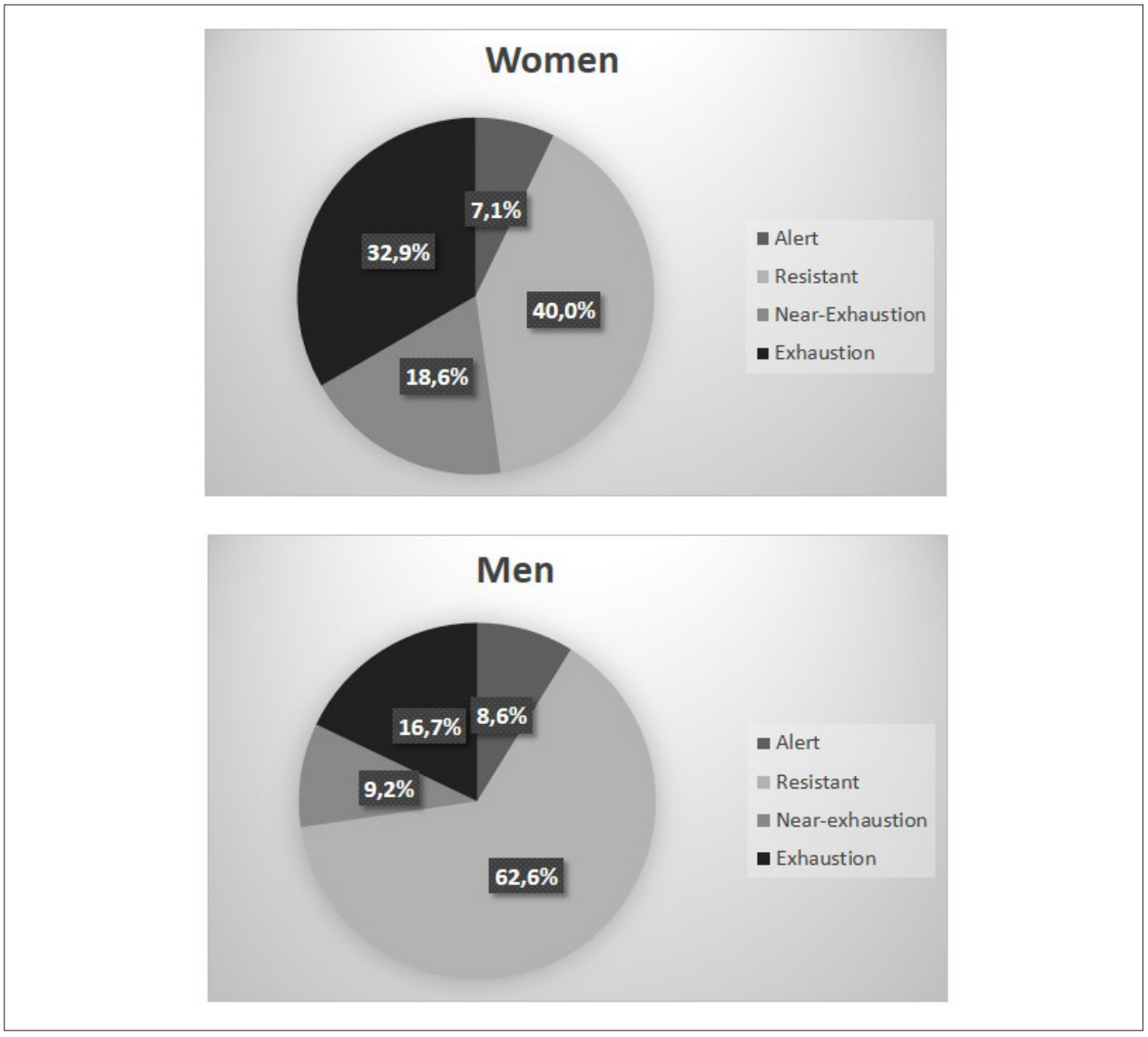

Figure 2 – *Comparison of stress phases in women and men.*

70%, respectively). The multivariate analysis showed that female gender was associated with nearly threefold higher odds of stress.

The healthcare model was also an independent predictor for the occurrence of stress, with patients treated by the Unified Health System (SUS) being the most affected. Similar data were found in a study by Santos et al.[20] in which more patients in the SUS group showed more stress as compared to health-insured patients. This suggests that patients treated by the public system are more vulnerable, probably due to the lower socioeconomic status of these patients, lower level of schooling, and lower income—all factors associated with higher levels of stress.[21] In our study, however, we did not perform any subgroup analyses to check for possible differences between the SUS group and patients with private health insurance. This remains a possibility for future research.

On a subgroup analysis restricted to patients with stress, stratified by gender, we found that women with stress were more likely to have a history of depression. It has been described that women are significantly more likely to have a history of depression diagnosis,[22,23] especially during menopause,[24] as compared to men. There is a growing interest in finding out whether this gender difference in rates of depression might be driven by greater exposure and reactivity to stressors.[25] Women are substantially more likely to be victimized by traumatic experiences (such as sexual abuse and assault), than men. Such experiences, especially in childhood or adolescence, are commonly predictive of depressive episodes.[25] Chronic stressors often associated with depression, such as poverty and single parenthood, are far more common in women than in men.[25] Experiencing chronic illness and being the primary caregiver for sick family members also seem to be experiences far more common for women than for men. These

conditions are likewise associated with depression.[25,26] Studies have suggested that "chronic strain" related to traditional female roles, manifested by reduced agency and decision-making (such as submissiveness in intimate relationships, role overload, domestic inequalities, childcare responsibilities), were predictive of depression over time and partially mediated gender differences in depression.[25,27]

In a study by Hammen et al.[28] evaluating the stress-depression relationship in women, the onset of depression was significantly associated with chronic and acute stress. There was a trend, consistent with a sensitizing effect, that chronic stress would moderate the effects of acute stressful events in major depression, so that high levels of chronic stress amplified the impact of acute events; conversely, the association between acute stress and depression was lower among women with lower levels of chronic stress. These findings confirm the importance of taking into account the effects of chronic stress on the stress-depression relationship in women.

Our subgroup analysis restricted to stressed patients, and stratified by gender, found that stressed women smoke more and are more likely to have a history of COPD than men. Epidemiological data support a higher prevalence of smoking in men,[29] and rates of tobacco-related illnesses in men are more than double those in women, with particular focus on COPD, AMI, pneumonia, and stroke.[30] The higher prevalence of smoking and COPD in women when we consider only the stressed population warrants further analysis. Stress itself may be influencing these findings.

According to Bussoleto,[15] when dealing with day-to-day challenges and seeking relaxation and rewards, patients resort to smoking and inadequate nutritional strategies. This not only worsens their level of stress, but also worsens heart disease. This premise may have been held true in our study, because, although it was not powered to detect significance, the percentage of dyslipidemia was higher in women than in men. We consider that, although women were not older than men in this sample (a factor known to be associated with mortality in women),[31] this buildup of risk factors—which also highlighted the lower level of schooling and income of women as compared to men – may have contributed to the higher percentage of in-hospital deaths found in women. Nevertheless, we must emphasize that this study was not designed to assess mortality.

Although women experience more emotional stress, most studies, especially those of ischemic patients, have included few women. Lucinda,[14] analyzing stress in post-AMI patients who remained active in the job market, found that 71% of the sample was in the resistance phase, with 91% of the sample consisting of men and only 9% of women. Likewise, Bussoleto[15] found 78.6% of his sample in the resistance phase, in a study that included 83.87% men and 16.13% women. In our study, 57.6% of participants were in the resistance phase, including 76% of men, that is, a higher percentage than among women (24%). Thus, we were able to observe differences in the phases of stress between men and women. Women were predominantly in the near-exhaustion and exhaustion phases, i.e., in the phases of chronic stress. These results corroborate the findings of Wottrich,[19] who also used the ISSL to analyze stress in hypertensive patients according to gender. The author also found that women were mostly in the exhaustion phase of stress (41.4% vs. 15.2%), while men were in the resistance phase (60.6%). Interestingly, this sample of 103 patients consisted predominantly (70%) of women.

Limitations

The women in the present study had lower level of schooling and lower household income than the men. Thus, it is assumed that socioeconomic conditions also act as mediators in the presence of stress, in addition to contributing to cardiovascular diseases. However, our design precludes any inference as to whether women had lower income because they lived alone or were widowed. We are also unaware of any other psychosocial factors, such as the number and age of children and grandchildren, or about social vulnerability conditions. We have no information about their family support networks. In other words, there may be other factors related to our findings.

This study used Lipp's Stress Symptoms Inventory for Adults (ISSL), an instrument that measures the presence of symptoms in the last 24 hours, in the last week, and in the last month. However, it is subject to reporting bias by the respondents when completing the questionnaire.

Conclusion

In this study, female gender and being admitted to the hospital under the Unified Health System (SUS) were independent predictors of risk for stress in patients with recent AMI. Women were most often in the third and fourth phases of stress, i.e., in situations of long-standing psychosocial stress. Women also had fewer years of schooling and lower household income and appeared to use tobacco smoking quite often as a coping strategy. Depression was also more prevalent in women than in men. These findings can assist in the development of gender-specific strategies for health promotion and disease prevention, aimed at minimizing the effects of stress on patients.

Author Contributions

Conception and design of the research: Moraes MA, Schmidt MM; Acquisition of data and Writing of the manuscript: Schmidt K, Lima AS, Schmitt KR; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Schmidt K, Schmidt MM; Statistical analysis: Schmidt MM.

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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Stress, Women and Acute Myocardial Infarction: What is known?

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Short Editorial related to the article: Stress in Women with Acute Myocardial Infarction: A Closer Look

For decades, women were excluded from health research. This fact has been criticized by the National Institutes of Health (NIH),[1] which sought to encourage the inclusion of women in clinical research trials, with little progress in the 1980s. Some of the most well-known examples occurred in cardiovascular research. The Harvard Physicians Health Study,[2] which analyzed the relationship between moderate use of aspirin and heart disease, did not include women in the sample studied. In that occasion, the result could not be conclusive for its application to women. The Multiple Risk Factor Intervention Trials (MR. FIT)[3] was another major research on heart disease that did not include female individuals. This national study examined how cholesterol levels, blood pressure and smoking affected the development of heart disease.

The omission of women from these and other studies at the time deserves to be highlighted in view of the cardiovascular mortality rates among women.[4]

The history of Western civilization shows the predominant male domination inside and outside home, how women were submissives, and the roles that were reserved for them, namely, domestic and family responsibilities.[5] The search for a professional space in modern society has made women protagonists in the job market, although most of them have not been able to stop playing the second round when they are back home after a busy workday.

The World Health Organization (WHO)[6] presents in the Atlas of Heart Disease and Stroke, in the topic Cardiovascular Disease, among other subjects, the risk factors and points out among the *Other modifiable risk factors* psychosocial stress ("chronic life stress, social isolation and anxiety") which increases the risk of heart disease and stroke. Likewise, it mentions "depression" as associated with that increase. In this atlas, item 12 is entitled *Women: a special case?* There, *Risks for women only* quotes: "use of oral contraceptives; hormone replacement therapy; polycystic ovary syndrome; greater risk of heart attack at the beginning of each menstrual cycle". Women carry with them such singularities and also the tensions experienced in the management of personal, familiar and professional life that generate emotional overload, despite advances in attention and care for women in this scenario of cardiovascular diseases. Good to be so, because in that chapter it is written that women are wrong to think that they are more prone to cancer than to cardiovascular diseases.

The article "Stress in women with Acute Myocardial Infarction: A close look"[7] studied a sample that also included men and used an instrument with four stages (alertness, resistance, near-exhaustion and exhaustion). The "alert" phase, with the reactions of the autonomic nervous system to the stressor; "resistance", the individual looks for ways to deal with stress; and the "near-exhaustion" and "exhaustion" phases, that are characterized by the beginning of the process of illness targeting the most vulnerable organs or when, effectively, the diseases manifest themselves. In this study,[7] the greater susceptibility of women to suffering from stress was evident, as they scored twice as many men in the "near-exhaustion" (32.9% x 16.7%) and "exhaustion" (18.6% x 9.2%).

Psychosocial stress should be studied using a composite measure, as there are several manifestations in the subjective, biological and behavioral sphere, justifying an integrated approach. A study[8] that evaluated symptoms of depression, anxiety, anger, perceived general stress, post-traumatic stress and hostility and used specific instruments, prospectively studied a sample of women with stable coronary disease. The authors standardized the scales and combined them into a composite index to analyze them statistically. They found women with a high level of psychological stress and who had a significantly higher incidence of cardiovascular events. The measure of perceived stress levels is also widely used in patients with acute myocardial infarction (AMI) and a study found that women reported higher levels of stress than men in the 12-month period after an AMI.[9] Nevertheless, another important prospective study (18 years of follow-up) investigated in a large sample of women and men the association between the perception of the impact of stress on self-rated health and the incidence of coronary artery disease (CAD).[10] This study predicted CAD incidence regardless of the perceived stress level scale and the authors claim that it is reasonable to assume that the only question "To what extend do you feel that the stress or pressure you have experienced in your life has affected your health?" can be used in general or specialized care settings.

Finally, there is still a lot to know about psychological stress and cardiovascular disease. It is a subject that has a lot to be studied and, considering the question of the study above, we suggest researches to use qualitative method and to listen to people's voices, regardless of sex, in counterpoint and as a complement to the countless investigations with quantitative research method.

Keywords

Cardiovascular Diseases; Women; Myocardial Infarction; Psychological Stress.

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Original Article

Prognostic Value of Troponin-T and B-Type Natriuretic Peptide in Patients Hospitalized for COVID-19

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Abstract

Background: **COVID-19 causes severe pulmonary involvement, but the cardiovascular system can also be affected by myocarditis, heart failure and shock. The increase in cardiac biomarkers has been associated with a worse prognosis.**

Objectives: **To evaluate the prognostic value of Troponin-T (TNT) and natriuretic peptide (BNP) in patients hospitalized for Covid-19.**

Methods: **This was a convenience sample of patients hospitalized for COVID-19. Data were collected from medical records to assess the association of TnT and BNP measured in the first 24 hours of hospital admission with the combined outcome (CO) of death or need for mechanical ventilation. Univariate analysis was used to compare the groups with and without the CO. Cox's multivariate model was used to determine independent predictors of the CO.**

Results: **We evaluated 183 patients (age = 66.8±17 years, 65.6% of which were males). The time of follow-up was 7 days (range 1 to 39 days). The CO occurred in 24% of the patients. The median troponin-T and BNP levels were 0.011 and 0.041ng/dL (p <0.001); 64 and 198 pg/dL (p <0.001), respectively, for the groups without and with the CO. In the univariate analysis, in addition to TnT and BNP, age, presence of coronary disease, oxygen saturation, lymphocytes, D-dimer, t-CRP and creatinine, were different between groups with and without outcomes. In the bootstrap multivariate analysis, only TnT (1.12 [95% CI 1.03-1.47]) and t-CRP (1.04 [95% CI 1.00-1.10]) were independent predictors of the CO.**

Conclusion: **In the first 24h of admission, TnT, but not BNP, was an independent marker of mortality or need for invasive mechanical ventilation. This finding further reinforces the clinical importance of cardiac involvement in COVID-19. (Arq Bras Cardiol. 2020; 115(4):660-666)**

Keywords: **Betacoronavirus; SARS-CoV-2; Pandemics; Biomarkers; Inpatients; Troponin T; Natriuretic Peptide, B Type; Cardiovascular Diseases/complications**

Introduction

The world is currently experiencing the pandemic of a disease called COVID-19 by the World Health Organization (WHO), caused by a new coronavirus (SARS-Cov-2). The International Committee on Taxonomy of Viruses then called the virus SARS-CoV-2[1] (severe acute respiratory syndrome coronavirus-2). The current pandemic originated in China in December 2019 in the city of Wuhan, capital of the Hubei province. It quickly spread globally and by the time this article was written, it has already infected more than 4.5 million people, causing more than 300,000 deaths. In Brazil, more than 200,000 people have already been infected, of which 15,000 died due to COVID-19.

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Coronaviruses usually cause acute lung and intestinal disease, of which its main symptoms are cough, fever, dyspnea, diarrhea, nausea and vomiting. However, since its appearance in China, there have been growing reports of its cardiovascular system involvement, which have alerted the scientific community. Elevated cardiac biomarkers, such as Troponin-T (TnT) and brain natriuretic peptide (BNP) has been associated with a worse prognosis[2]. Guo et al.,[2] in a cohort of 187 hospitalized patients in the city of Wuhan, found that 27.8% of the patients had an increase in TnT and the presence of complications, such as the need for mechanical ventilation, was higher in this group. The levels of N-terminal-pro-brain natriuretic peptide (NT-Pro-BNP) had a significant positive linear correlation with TnT. Liu et al.[3] showed that BNP levels >100pg/mL were also associated with a higher risk of complications in patients with COVID-19. However, both studies were limited to performing the univariate analysis of data.

In a recent analysis of patients that recovered from COVID-19, Huang et al.[4] demonstrated that cardiac magnetic resonance (CMR) imaging was abnormal in 58%. Late enhancement and myocardial fibrosis expression were present

in 31% of patients. However, there were no differences in either TnT or BNP levels between groups with and without changes in CMR imaging.

Cardiac involvement in COVID-19 is a reality, but the predictive potential of cardiac markers still needs to be better assessed.

In the present article, we evaluated the presence and impact of cardiac biomarkers TnT and BNP, measured within the first 24 hours of hospital admission on the clinical evolution of patients admitted for COVID-19.

Methods

This was a convenience sample obtained from the database analysis of patients admitted for COVID-19 in a tertiary hospital in the city of Rio de Janeiro, Brazil. The medical records of patients who met the criteria for a clinical syndrome compatible with COVID-19 by the WHO[5] and who later had their diagnosis confirmed by a nasopharyngeal swab using the real-time polymerase chain reaction (RT-PCR) method were reviewed. Clinical and laboratory data were collected from this population. The ultrasensitive TnT was measured using the electrochemiluminescence method (Elecsys® Troponin T Gen 5 STAT, Roche Laboratory) and its cutoff value was <0.014ng/mL, whereas the BNP was measured by the fluorescence immunoassay method (Triage® BNP; Alere) and its cutoff value was <100 pg/mL.

Gender, weight, height, presence of comorbidity (coronary artery disease [CAD], pulmonary disease, stroke, diabetes, arterial hypertension, chronic kidney disease [CKD] and cancer), time of symptom onset on arrival at the hospital (days), systolic blood pressure (SBP; mmHg), heart rate (beats per minute) and arterial oxygen saturation (%) on hospital admission, total leukocytes (cells/mm^3), lymphocytes (cells / mm3), titrated C-reactive protein (t-CRP; mg/dL), Creatinine (mg/dL), D-dimer (ng-dL) and Ferritin (ng/mL) were also assessed. All clinical and laboratory parameters were obtained within the first 24 hours of hospital admission.

The assessed clinical outcome was the combination of death from all causes or the need for mechanical ventilation (MV).

The study was carried out according to the standards of the Helsinki declaration for human research. The need for the Free and Informed Consent was waived by the Research Ethics Committee, as it is an observational, retrospective study, performed through the analysis of medical records.

Statistical Analysis

The continuous variables were expressed as mean and standard deviation or median and interquartile range and compared by unpaired Student's *t* test or Mann-Whitney-U test according to the presence or not of normal distribution. The presence of normal distribution was assessed by the Kolmogorov-Smirnov test. Categorical variables were expressed as frequencies (%) and compared using the Chi-square test and Fisher's exact test.

The patients were grouped in quartiles according to the troponin-T values and the evolution of their groups was compared using the Kaplan-Meier curve, whereas the difference between groups was established by the log rank test. Cox multivariate survival analysis was developed aiming to identify independent predictors of death and or the need for mechanical ventilation. Variables with an alpha error < 5% in the univariate analysis were included in these models. The multivariate analysis of survival was used, as it was considered more appropriate for a prognostic study.

To verify the stability of the result, and any biases generated by overfitting, the bootstrapping technique with 1,000 samples was used.[6,7]

Statistical significance was defined by an alpha error probability <5%. Statistical analysis was performed using the SPSS program (SPSS 22.0 for Windows, IBM SPSS, IL, USA).

Results

A total of 183 patients were analyzed. The median follow-up time was 7 days (1 to 39 days). Table 1 describes the characteristics of the population.

Twenty-eight patients died and 31 required mechanical ventilation during the analyzed period. The combined outcome (death and/or mechanical ventilation was present in 44 (24%) of the patients.

Table 2 shows the univariate analysis in the groups with and without the combined outcome. The patients with a combined outcome were older; had a higher prevalence of CAD; lower oxygen saturation, fewer lymphocytes; and higher levels of t-CRP, creatinine, BNP, TnT and D-dimer than the group without the outcome. These were the variables included in the COX multivariate model, of which results are shown in table 3.

All mentioned biomarkers were included in the multivariate analysis and after the bootstrap analysis, only TnT and t-CRP were independently associated with the combined outcome.

Figure 1 illustrates the differences in the combined outcome per TnT quartile. Mortality more than doubles between Q1 and Q2; and between Q3 and Q4 and increases by more than 60% between Q2 and Q3. Figure 2 shows the probability of the event over time for each of the TnT quartiles. After 20 days of admission, the event-free survival rate for the first interquartil (Q1) of troponin T (TnT≤0.006ng/dl) was 89.8% and for the last interquartil (Q4) (TnT≥0.03ng/dl) was 15.2%.

Discussion

This study reinforces the idea previosuly raised by other authors that the increase in TnT, in addition to being prevalent, is associated with the evolution to severe forms of COVID-19. To the best of our knowledge, this is the second study, the first in Brazil, to identify TnT as an independent predictor of a worse prognosis in patients with COVID-19. Shi et al., studying a Chinese cohort with a similar design, demonstrated that increased troponin levels at hospital admission increased the risk of death in patients with COVID-19 by 3.41-fold (95%CI, 1.62-716). In this cohort, patients with increased troponin levels had a higher rate of invasive mechanical ventilation compared to those who did not have an increase in troponin (18 of 82 [22.0%] *vs*. 14 of 334 [4.2%]; p <0.001).

Table 1 – Characteristics of the population

N	183
Age (years)	66.8±17
Weight	80±19
Height	169±15
Male gender (%)	65.6
CAD (%)	19.1
Pulmonary disease (%)	15.8
Stroke (%)	4.4
Diabetes (%)	19.7
SAH (%)	53.6
Cancer (%)	9.8
CKD (%)	2.2
Time of symptom onset	6(3;8)
SBP	128±19
HR	85±16
$SatO_2$	93.6±5.4
Leukocytes	6710(4760;9100)
Lymphocytes	1070(740;1400)
CRP	9.94(5.48;18.39)
Creatinine	0.98(0.78;1.26)
BNP	84(21;197.5)
TnT	0.011(0.006;0.033)
D-Dimer	906(482;1429)
Ferritin	720(378;1303)
Deaths (%)	15.3
Mechanical Ventilation – MV (%)	16.9
Death and/or MV (%)	24
Admission at ICU (%)	42.6

CAD: coronary artery disease; SAH: systemic arterial hypertension; CKD: chronic kidney disease; SBP: systolic blood pressure; HR: heart rate; $SatO_2$: oxygen saturation; t-CRP: C-reactive protein; BNP: B-Type Natriuretic Peptide; TnT: Troponin-T; MV: mechanical ventilation; ICU: intensive care unit.

Additionally, mortality was also higher in those with myocardial injury compared to those without injury (42 of 82 [51.2%] vs 15 of 334 [4.5%]; p <0.001). However, the epidemic of other viral diseases such as dengue in China showed very different prevalence rates and prognosis of myocarditis than Brazil, and other countries.[9,10] Our study shows that this does not seem to be the case for COVID-19, where, in both western and eastern populations, the prevalence of myocardial injury is prevalent and associated with a worse prognosis. Among the unfavorable outcomes are heart failure, arrhythmias, mechanical ventilation and death.[11]

Among the mechanisms proposed for myocardial injury caused by SARS-CoV-2, there is mainly the so-called "cytokine storm", which is triggered by an imbalance in the cell responses of Type-1 and Type-2 T-helper lymphocytes. Interleukin-6 (IL-6) is a cytokine that increases as a result of this cell imbalance and it is an already identified marker of mortality. These cytokines attack the myocardium, causing elevation in troponin levels and cardiac dysfunction.[12]

A meta-analysis of 4 Chinese studies involving 341 patients was recently published as correspondence.[13] The prevalence of troponin elevation (above the 99th percentile) ranged from 8 to 12%, and its values were significantly higher in patients with more severe forms of COVID-19. Therefore, the monitoring of troponin levels may help to identify a subgroup with a greater chance of a worse clinical course.

An important finding in the study by Guo et al.[5] was that the increase in troponin levels was a stronger marker for mortality than the presence of previous cardiovascular disease (CVD). Patients with a history of CVD, but with normal troponin levels had lower mortality rates than those without a history of CVD, but who had increased troponin levels at hospital admission. Moreover, both TnT and NT-pro-BNP increased significantly during hospitalization in those who died, and this increase was not observed in those who survived.

In our cohort, the association between troponin-T elevation and the combined outcome of death or MV was very well demonstrated, to the point that more than half of the patients in the last quartile of troponin (> 0.03ng/dL) had an unfavorable evolution. This can constitute a practical way to identify those patients with the highest in-hospital risk of a worse clinical course on admission.

As for the BNP/NT-pro-BNP, some studies also suggest that it is an important prognostic marker. Possible mechanisms for the increase in BNP levels in the presence of SARS-Cov-2 infection range from the previously described elevation secondary to inflammatory myocardial injury (cytokine storm), which results in cardiac dysfunction and increased ventricular filling pressures, to the direct injury to the cardiomyocyte by the virus through the angiotensin-converting enzyme-2 binding site and due to the myocardial hypoxemia induced by acute lung injury. The first study that showed that NT-Pro-BNP is a marker of mortality was published by Gao et al.,[14] evaluating 54 patients with significant respiratory dysfunction (respiratory rate ≥30/min or Sat O_2≤93% or ratio of Partial Pressure Arterial Oxygen and Fraction of Inspired Oxygen ≤ 300mmHg). Patients with NT-proBNP >88.64 pg/mL showed a significantly lower cumulative survival during the 15-day follow-up than those with levels below this value. In our cohort, despite being a risk predictor in the univariate analysis, BNP was not an independent risk marker when the multivariate model was used. This fact can be explained by a collinearity effect between TnT and BNP, as a great correlation has been demonstrated between these markers in COVID-19.

In addition to TnT, the titrated C-reactive protein was also independently associated with a worse prognosis in our cohort. In fact, other studies have already indicated the presence of a correlation between t-CRP and the severity of infection by Covid-19,[15,16] which supports the findings of our study.

The present study showed an association between elevated TnT levels and the risk of death or need for MV. In contrast, the increase in BNP levels, although it was shown to be a risk factor for the combined outcome of MV or death in the

Table 2 – Univariate Analysis

	Alive without MV	Death or with MV	p-value
N	139	44	
Age (years)	64±16	75.7±16	<0.001
Weight	82±20	75.5±14	0.116
Height	169.8±14	168.6±19	0.858
Men/Women	86/53	34/10	0.061
CAD (%)	14.4	34.1	0.004
Pulmonary disease (%)	14.4	20.5	0.337
Stroke (%)	3.6	6.8	0.401
Diabetes (%)	20.1	18.2	0.775
SAH (%)	51.1	61.4	0.233
Cancer (%)	8.6	13.6	0.311
CKD (%)	1.4	4.5	0.244
Time of symptom onset	6(3;8)	4(2.25;7)	0.14
SBP	127.9±19	128.3±21	0.911
HR	85.6±17	87±13	0.405
$SatO_2$	94.3±5	91.7±7	0.036
Leukocytes	6510(4715;8905)	7490(5680;10190)	0.083
Lymphocytes	1120(832.5;1470)	750(540;1190)	0.001
CRP	9.54(4.5325;16.9525)	13.64(7.04;24.74)	0.011
Creatinine	0.92(0.7575;1.0925)	1.3(1.01;1.91)	<0.001
BNP	64.5(16.75;138)	198(45;619)	<0.001
TnT	0.01(0.006;0.017)	0.041(0.012;0.072)	<0.001
D-Dimer	741(452.75;1254.75)	1315(776;2200)	<0.001
Ferritin	654(375.5;1204.75)	976(401.5;1543)	0.255

CAD: coronary artery disease; SAH: systemic arterial hypertension; CKD: chronic kidney disease; SBP: systolic blood pressure; HR: heart rate; $SatO_2$: oxygen saturation; TnT: Troponin-T; MV: mechanical ventilation; ICU: intensive care unit; CRP: C-reactive protein.

Table 3 – Cox multivariate analysis with 1000 bootstrapped

Variables	HR (95%CI)	HR (95%CI) bootstrapped
Age (years)	1,02(0,99-1,04)	1,02(0,97-1,05)
CAD (%)	1,09(0,47-2,53)	1,09(0,36-2,84)
$SatO_2$ (%)	0,92(0,87-0,97)	0,92(0,85-1,01)
Lymphocytes (each 100 cells/mm^3)	1,01(0,95-1,07)	1,01(0,87-1,06)
D-Dimer (500Ung/mL)	0,99(0,97-1,01)	0,99(0,92-1,03)
CRP (mg/dL)	1,04(1,01-1,08)	1,04(1,00-1,10)
Creatinine (mg/dL)	0,9(0,62-1,3)	0,9(0,55-2,17)
TnT (increment of 0.014ng/dL)	1,13(1,05-1,21)	1,12(1,03-1,47)
BNP (increment of 100pg/mL)	1,05(0,95-1,15)	1,05(0,81-1,23)

CAD: coronary artery disease; $SatO_2$: oxygen saturation; CRP: C-reactive protein; BNP: B-Type Natriuretic Peptide; TnT: Troponin-T.

univariate analysis, was not shown to be an independent predictor in our sample. In fact, a recent review article by Costa et al.[17] established a flowchart for the cardiological approach of patients with COVID-19 and troponin was the only laboratory marker suggested to define admission in the intensive care unit, regardless of the presence of a history of cardiovascular disease.

Limitations

Electrocardiogram and echocardiogram data were not included in the analysis, as less than 70% of patients in the sample had these data available. The patient with COVID-19 is a major consumer of hospital resources, notably PPE, which is why these tests are only requested when strictly necessary and indicated. This was also the reason for not evaluating biomarkers as continuous variables over time. We did not use routine serial collections of these biomarkers. Every time a healthcare professional enters the isolation area for the collection of biomarkers or other tests, unless strictly necessary, results in increased costs, the use of PPE and a risk for the entire health team. Therefore, including them (ECG, ECHO and serial collections of biomarkers) would require a strategy for treating the missing data, which in our opinion would compromise the analysis.

Another limitation is that with many predictors in the univariate analysis and a number of relatively small outcomes for the sample size, the bootstrap technique does not eliminate the possibility of overfitting.

Conclusion

Troponin T, but not BNP, was an independent risk marker for mortality or need for invasive mechanical ventilation in patients hospitalized for COVID-19. These data further reinforce the use of this biomarker in the risk stratification of patients with COVID-19.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

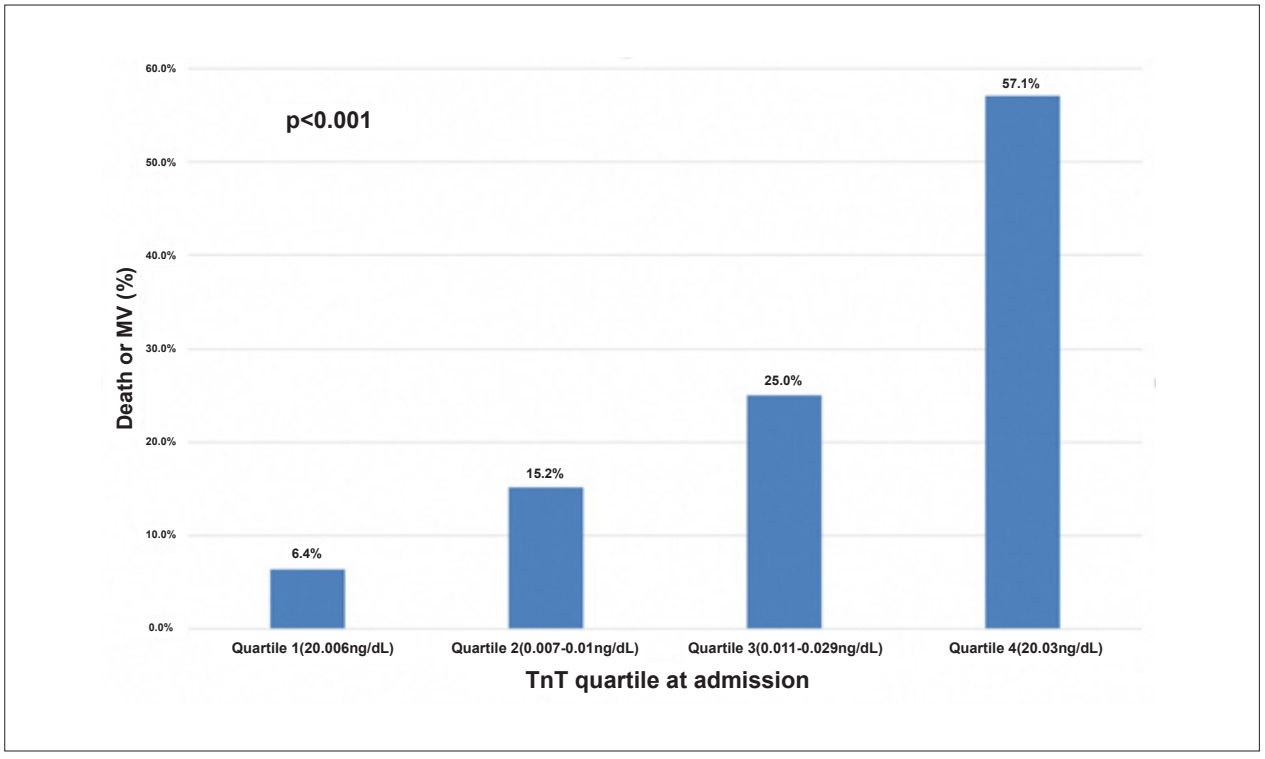

Figure 1 – *Differences in combined outcome by Troponin quartile. MV: mechanical ventilation; TnT: Troponin-T.*

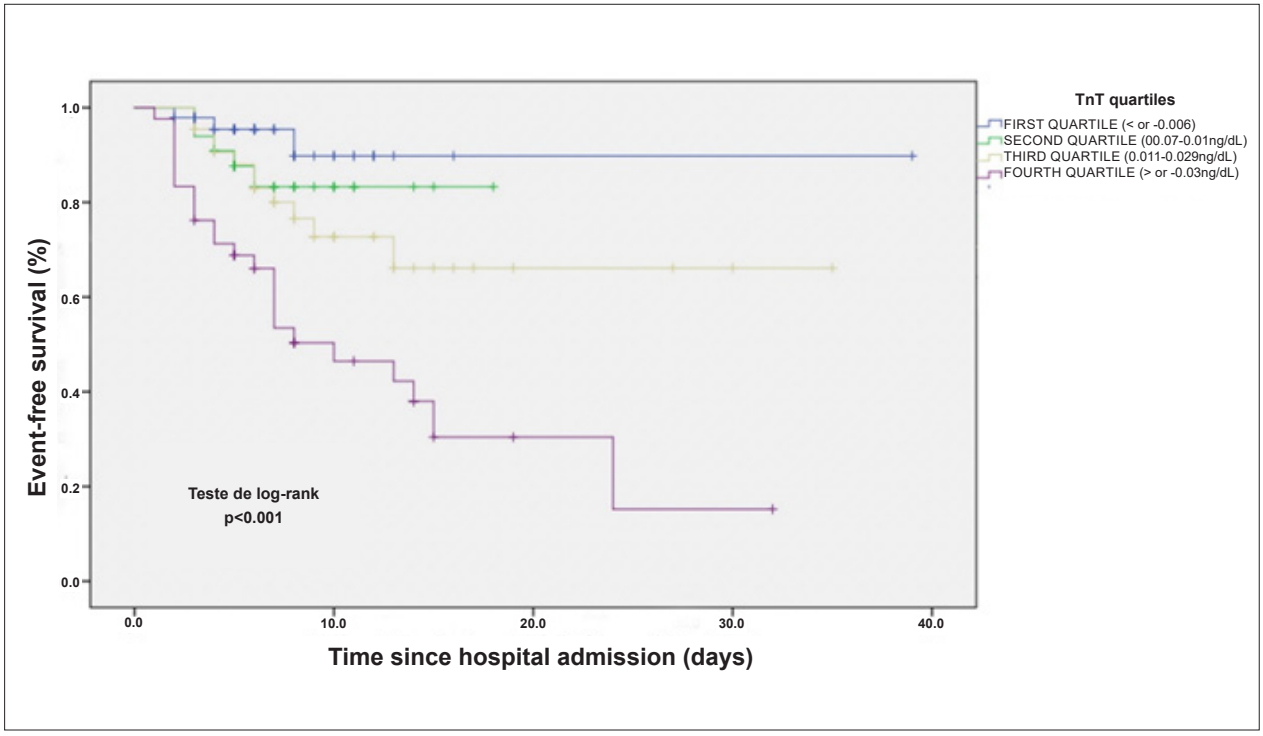

Figure 2 – *Probability of the combined outcome over time for each of the Troponin quartiles. TnT: Troponin-T.*

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Cardiac Troponin as a Predictor of Myocardial Injury and Mortality from COVID-19

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Short Editorial related to the article: Prognostic Value of Troponin-T and B-Type Natriuretic Peptide in Patients Hospitalized for COVID-19

In Brazil, until August 1, 2020, 2,707,877 cases of COVID-19 were diagnosed, with 93,563 deaths. the lethality rate for the country, in this period, was 3.5% with mortality variable mortality depending on the region studied. It is the lowest in the South (11.1 deaths/100,000 inhabitants) and the highest in the North (60.2 deaths/100,000 inhabitants).[1] Up to 20% of infected individuals require hospitalization and, of these, about 25% need to be taken to an intensive care unit (ICU).[2] In severe cases of COVID-19, intense inflammatory response and hypercoagulability enhanced by hypoxemia justify the main clinical and laboratory findings.[3]

In this population, the presence of Myocardial Injury (MI) is not uncommon, and increased cardiac troponin (cTn)I behaves as a predictor of in-hospital mortality.[4] There is also a possibility of direct injury by a virus that could generate myocarditis.[5] A necropsy study that documented the presence of a virus in 61.5% did not observe the inflow of inflammatory cells in the myocardium in the acute phase, and the long-term consequence of this cardiac infection is not yet known.[6] However, the incidence of MI in patients admitted for this disease in Brazil is little known, and its prognostic impact is still poorly elucidated. A multicenter study with cardiac biomarkers is hampered by different laboratory tests between institutions.

Diagnosis of (MI) is based on the identification of at least one cTn value above the normal upper range. Variations in serial analyses of this biomarker suggest acute cardiac cell damage, though not being able to determine the underlying pathophysiological mechanism just by measuring it. Reasons for its occurrence can be grouped as ischemic cardiac, non-ischemic, and systemic cardiac causes.[7,8] Increased cTn is common in ICU patients and is related to more significant adverse events regardless of the underlying disease.[9]

A pioneering study developed in Rio de Janeiro with a convenience sample of 183 confirmed cases of COVID-19 admitted to a tertiary hospital assessed the prognostic value of cTn T and BNP in this population. They concluded that cTn T, but not BNP, was an independent risk marker for in-hospital death or need for invasive mechanical ventilation.[10] One of the study limitations was the lack of electrocardiography and echocardiography data, justified by an institutional policy aimed at better distribution of financial resources and at protecting healthcare professionals. Besides, troponin was checked only in the first 24 hours of hospitalization.

We know that the inflammatory condition secondary to cytokine storm (phase III) occurs after the pulmonary phase (phase II), with an average interval of 5 days. Thus, the serial dosage of troponin would be the best approach as it would help to identify patients with myocardial injury not detected at admission.[11]

A meta-analysis carried out in March 2020 by Giuseppe Lippi et al. found that significant increases in troponin corresponding to myocardial injury are found in about 8 to 12% of all cases of COVID-19, and is more frequent in critically ill patients.[12] A recently published study carried out with 2,736 patients with COVID-19 found that myocardial injury, quantified by a rise in troponin, even if this is a modest rise, and especially in those with a history of cardiovascular disease, was associated with a high death rate.[13]

Data obtained by this Brazilian study[10] reinforce the impression raised by other authors that increased cTn in COVID-19 is associated with worse clinical outcomes.[11-14] The use of this biomarker in risk stratification in patients with COVID-19 may be a feasible strategy to identify cardiac involvement without exposing healthcare professionals to electrocardiography and echocardiography scans.

In conclusion, MI is common in COVID-19 patients and could be explained by different pathophysiological mechanisms. So far, there is no recommendation for specific IM therapy related to infection by a new coronavirus. However, measurement of cTn during hospitalization can facilitate the risk classification of these patients with the advantage of being an easily reproducible method with minimal exposure of the health team involved in its execution, which is specifically useful for controlling viral spread in a hospital environment.

Keywords

COVID-19/complications; Betacoronavirus/complicações; Cardiovascular Diseases; Cardiomyopathy, Hypertrophic Familial; Mortality; Hospitalization; Troponin T.

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Effect of Diterpene Manool on the Arterial Blood Pressure and Vascular Reactivity in Normotensive and Hypertensive Rats

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Abstract

Background: Many studies have shown that the diterpenoid classes exert a significant effect on the cardiovascular system. Diterpenes, in particular, are among the main compound links to cardiovascular properties such as vasorelaxant, inotropic, diuretic and hypotensive activity. While the manool vasorelaxation mechanism is visible, its effect on blood pressure (BP) is still unknown.

Objective: To evaluate the in vivo hypotensive effect of manool and check the ex vivo vasorelaxation effect in rat aortic rings.

Methods: The animals were divided randomly into two groups: normotensive and hypertensive. The normotensive group was sham-operated, and the 2K1C model was adopted for the hypertensive group. Invasive BP monitoring was performed for manool tests at different doses (10, 20 and 40 mg/kg). Concentration-response curves for manool were obtained in the aorta rings, with endothelium, pre-contracted with phenylephrine (Phe) after incubation with Nω-nitro-L-arginine methyl ester(L-NAME) or oxadiazole [4,3-a]quinoxalin-1-one (ODQ). Nitric oxide (NOx) plasma levels were measured by chemiluminescence assay.

Results: After manool administration, BP was reduced in normotensive and hypertensive groups, and this effect was inhibited by L-NAME in hypertensive animals only in 10 mg/kg dose. Ex vivo manool promoted vasorelaxation, which was inhibited by L-NAME and ODQ incubation or endothelium removal. NOx plasma levels increased in the hypertensive group after manool administration. Manool elicits endothelium-dependent vascular relaxation in rat aorta mediated by the NO/cGMP signaling pathway and BP reduction, also by NOx plasma increase. These combined effects could be involved in modulating peripheral resistance, contributing to the antihypertensive effect of diterpene.

Conclusion: These effects together could be involved in modulating peripheral resistance, contributing to the antihypertensive effect of diterpene. (Arq Bras Cardiol. 2020; 115(4):669-677)

Keywords: Cardiovascular Diseases; Hypertension; Diterpenes; Manool; Reactivity; Nitric Oxide; Rats.

Introduction

Diterpenes is a broad class of chemical metabolites, which are widely distributed in the flora, with more than 12,000 known compounds.[1,2] They can be divided into two types: specialized (secondary) metabolism diterpenes and general (primary) metabolism diterpenes. Secondary diterpenes can have functions in the ecological interactions of plants with other organisms and benefits in pharmaceuticals, perfumes, resins and other industrial bioproducts with great economic relevance.[1,2] Several secondary metabolites, such as terpenes, phenolic acids, polyphenols, flavonoids and anthocyanins, have been reported from Salvia species. These species are seen as excellent sources of diterpenes.[3] According to chemotaxonomic findings, manool was previously reported in the following Salvia species: *S. sclarea*, *S. pubescens*, *S. lavandulifolia*, *S. hypoleuca*, *S. miltiorrhizae*. It is also present in other species, such as *Pinuscaribaea (Pinaceae)*, *Lourteigiastoechadifolia (Asteraceae)* and *Halocarpusbiformis (Podocarpaceae)*. However, manool is the main diterpene of the various species of Salvia, and it is found in higher concentration in *Salvia officinalis*.[4]

The biosynthesis of the isoprene structural units of a wide variety of terpenes, including diterpenes, occurs by the deoxyxylulose pathway. This pathway rises to two distinct products: isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). More specifically, manool, whose chemical composition is $C_{20}H_{34}O$, is a bicyclic labdane diterpene. Its structure is based on a 2E, 6E, 10E-geranylgeranyl pyrophosphate (GGPP) carbon skeleton.[5-7]

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The discovery of new substances with antihypertensive activity, with low cost and few adverse effects, is still desirable and important to clinical use.[8] However, several difficulties are encountered for this purpose, such as the choice of experimental model, obtaining standardized extracts and the difficulty of obtaining, isolating and identifying the active substances.[9,10] The option to conduct research, from the indication of plants used by communities, shortens the route of developing a new drug, as researchers have, before starting scientific studies, a hint of which biological activity this medication might present.[11,12]

Diterpenes, in particular, are among the primary compound links to cardiovascular properties, such as vasorelaxant, inotropic, diuretic and hypotensive activity. The vascular action exerted by these compounds appears to involve multiple mechanisms. Such mechanisms are either independent or endothelium-dependents, prostacyclin, and increased blocking of voltage-dependent calcium channels.[13-17]

As previously described in the literature review, manool — $C_{20}H_{34}O$ — is a labdane-type diterpene, commonly found in various plant families, it is the main diterpene of several species of Salvia, and is present in higher concentrations in *Salvia officinalis* (Figure 1).[1,3,18,19] It is a species of the family *Lamiaceae (Labiateae)*, originating in southern Europe. It presents a habit of herbaceous growth or small shrub; it is a perennial plant that flourishes in the Southern Hemisphere between August and December.[20]

Li et al.[21] found that although manool possesses cardiovascular activity that is still unknown, it must be considered a crucial factor to be investigated. Moreover, it can be seen as a new driver for the treatment of heart disease and deserves further research.[4,21,22] The experimental protocol included observations on plasma levels of nitric oxide (NO) in hypertensive animals and the impact of manool on the BP of animals following the administration of different doses of the compound.

Knowing that manool belongs to the class of diterpene compounds, with potential use in the treatment of hypertension, the present investigation was designed to assess the possible vasodilator effect and the cellular mechanisms involved in the relaxation response of aortic rings of rats. Therefore, the aim was to evaluate the in vivo hypotensive effect of manool and check the ex *vivo* vasorelaxation effect in aortic rings of rats.

Material and Methods

Ethics Statement and Animals

Animal handling policies and experimental procedures were reviewed and approved by the Institutional Committee for Animal Care from Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (n. 060/210), following the directions of the European Commission's Directive 2010/63/EU. Thirty-four male Wistar rats (180–220 g) were housed under standard laboratory conditions (12 h light/dark cycle at 21 °C) with water and food ad libitum. The animals were allocated randomly into five groups of 7 animals for normotensive and hypertensive blood pressure protocols (normotensive vehicle, normotensive manool; hypertensive vehicle, hypertensive manool and hypertensive manool + L-NAME). The animals allocated to the normotensive groups were sham-operated, while animals allocated to the hypertensive groups underwent the surgical procedure 2K1C (two-kidney-one-clip hypertensive rats) for hypertensive induction. Another group of 6 animals that did not undergo any procedure (intact) was used for *ex vivo* vascular reactivity studies.

Drugs

Manool, acetylcholine (ACh), 1H-[1,2,4]oxadiazole[4,3-a] quinoxalin-1-one (ODQ), and phenylephrine (Phe) were from Sigma Chemical Company (St. Louis, MO, USA); Nω-nitro-L-arginine methyl ester (L-NAME) was obtained from Calbiochem (San Diego, CA, USA); Vetec Química Fina Ltda furnished isoflurane from Abbott and all the salts used for Krebs solution preparation. Almost all the drugs were prepared with distilled water, and manool was solubilized in dimethyl sulfoxide (50 uL) and diluted in ethanol/water (2:10, total volume 200 uL). For vascular reactivity experiments, 100

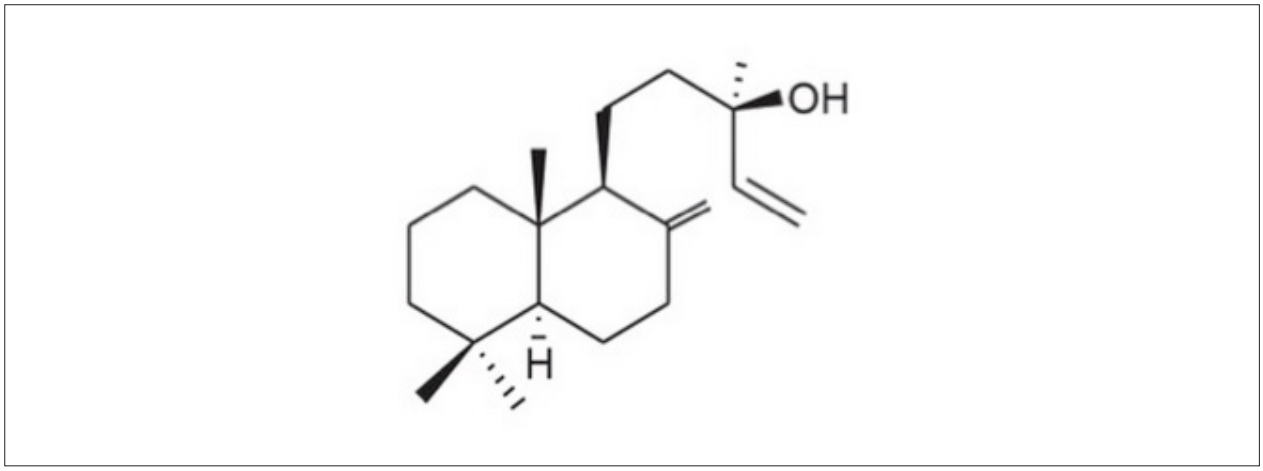

Figure 1 – *Manool chemical structure.*[10,11]

uL was diluted in 900 uL of water, making the stock (10^{-3}). From this stock, the curve was prepared. The volume used from this curve was 10 uL in a 10 ml cube. Therefore, after so many dilutions, the vehicle does not promote any effect on vascular reactivity.

Induction of Hypertension

After i.p. anesthesia with ketamine (50 mg/kg) and xylazine (10 mg/kg), the renal artery was exposed. The hypertensive groups had partial constriction of the main left renal artery with a silver clip of 0.10 mm gap (2K1C), while the normotensive groups had the main left renal artery isolated but did not receive the clip (sham). To monitor hypertension development, systolic blood pressure (SBP) was noninvasively measured using a tail-cuff, once a week. (Kent Scientific Corporation, Connecticut, USA). The 2K1C rats were considered hypertensive with tail SBP ≥ 160 mmHg at the 3rd week after the surgical procedures. The 2K1C rats with SBP < 160 mmHg at the 3rd week were euthanatized. Less than 10% of animals had SBP < 160 mmHg. The sham-operated rats were included in the normotensive group.

Manool Effect on Systolic Blood Pressure

Three weeks after hypertension induction, the animals were anaesthetized, and the femoral artery and vein were respectively cannulated for continuous measurement of systolic blood pressure (SBP) and drugs administration. After anesthesia (urethane, 2 mg/kg, intraperitoneal), vascular cannulation and stabilization period (20 minutes) with continuous real-time SBP recording, three doses of manool (10, 20 and 40 mg/kg) or vehicle (Dimethyl sulfoxide — DMSO — and water+ethanol) were administered to the normotensive and hypertensive rats. Each dose was given in a 200 μL intravenous bolus, and the interval between each consecutive dose was 6 minutes. The animals that received vehicle did not receive manool. For each animal, the variation in systolic blood pressure (ΔSBP) was calculated subtracting the mean of the lowest SBP values immediately after manool administration from the average of the baseline SBP values before manool or vehicle bolus. Mean blood pressure was measured using MP System 100 A (BioPac System, Inc., Santa Barbara, CA, USA).

Vascular Reactivity

Experiments were conducted in aortic rings from normotensive rats. Six male Wistar rats (280–300 g) were anaesthetized with inhalational isoflurane, followed by abdominal aorta exsanguinations and thoracotomy for thoracic aorta harvesting. The thoracic aorta was carefully dissected, confirmed to be free of connective tissue, and immediately immersed in Krebs solution. The Krebs solution was composed of NaCl (118.0 mM), KCl (4.7 mM), CaCl2 (2.5 mM), KH2PO4 (1.2 mM), MgSO4 (1.66 mM), glucose (11.1 mM), and NaHCO3 (25.0 mM); the solution had pH 7.4. The thoracic aorta immersed in Krebs solution was cut into rings that were 4–5 mm in length. For tests, the endothelium-denuded ring was removed by gently rubbing the internal surface vessel with a thin steel rod. This procedure effectively removes the endothelium, but it does not affect the ability of the vascular smooth muscle to contract or relax. The aortic rings were placed in 10 mL isolated organ bath containing Krebs solution, at 37 °C, and 95% O_2/5% CO_2 (pH 7.4) to measure the isometric force with Grass FT03 equipment (Grass Instrument Company, Quincy, MA, USA). Each ring was stretched to the optimal 2.0 g length-tension, determined in a pilot study, and was allowed to equilibrate for 60 min. During this time, tissues were washed every 15 min. The endothelium was considered to be present (E+) recording the Ach-induced 80% relaxation (10^{-6} M) after pre-contraction with Phe (10^{-7} M). Endothelium was considered absent (E−) when the relaxation response did not occur. Next, each ring was washed and re-equilibrated for 30 min. The aortic rings were precontracted with Phe (10^{-7} M) after a stable plateau was reached, and dose-response curves of manool were obtained. The concentration-response assays in the organ baths were carried out in the presence or absence of: L-NAME ($2x10^{-4}$ M), a nonspecific nitric oxide synthase inhibitor and ODQ (10^{-4} M), a guanylyl cyclase inhibitor.[20] The preparations were incubated with the inhibitors for 30 min. We did not perform dose-response curves with a vehicle because the dilution was performed in water. The initial solution 1 M (50 uL DMSO + 30 uL ethanol + 120 uL water) suffered serial dilution for 10^{-1} M in water.

Indirect Plasma Measurements of NO

Blood samples (1 ml) were collected from the femoral artery, after the last dose-response curve from a normotensive vehicle and hypertensive manool, and placed in heparinized tubes. After blood centrifugation (3000×g, 10 minutes, 4 °C), the plasma was immediately immersed in liquid nitrogen and kept at -70 °C until nitrite and nitrate (NOx) measurements. Samples were analyzed in duplicates for NOx by ozone-based chemiluminescence assay. The plasma samples were briefly treated with cold ethanol (1 volume of plasma: 2 volumes of ethanol for 30 minutes at −20 °C) and centrifuged (4000×g, 10 minutes). The NOx levels were measured by injecting 25 μL of the supernatant in a glass purge vessel containing 0.8% of vanadium (III) in HCl (1 N) at 90 °C, which reduces NOx to NO gas. A nitrogen stream was bubbled through the purge vessel containing vanadium (III), then through NaOH (1 N), and then into a NO analyzer (Sievers® Nitric Oxide Analyzer 280, GE Analytical Instruments, Boulder, CO, USA).

Statistical Analysis

The data are presented as mean ± standard error of the mean (SEM). We performed statistical analyses with Student's T-test, one-way (ANOVA), Bonferroni post-test and two-way repeated-measures of variance (ANOVA) with the Bonferroni post-test to detect potential differences between the values in the study. For each figure, the legend describes which test was performed for analysis. $P<0.05$ was considered significant (Prism 5.0, GraphPad Software, San Diego, CA, USA). A sample size of (N = 5–7) per group provided 95% power with a 0.05% significance level in protocols of in vivo blood pressure measurement. Moreover, a sample size of (N = 6–8) animals per group provided 95% power with a 0.05 significance level to detect a relative 10% reduction in the maximal contraction in precontracted vessels. The number of animals was based on the literature.[20,23,24]

Results

Before surgical procedures, there were no differences in the BP between normotensive and hypertensive groups. However, after hypertension induction, from the 1st to the 3rd week, the BP was significantly higher in the hypertensive rats (130,6 mmHg versus 193,0 mmHg) (Figure 2).

The evaluation of body weight showed that, in the first week, the groups had similar loads. However, at the end of three weeks, the hypertensive group showed significantly lower values compared to the normotensive group (Table 1).

In the *in vivo* SBP analysis, only the surgery (2K1C) was able to change the blood (normotensive vehicle versus hypertensive vehicle). Manool promoted a dose-dependent response on SBP, reducing the pressure significantly from the dose of 20 mg/kg in the normotensive group, and there is not any difference between 20 and 40 mg/kg in this group for manool. In the hypertensive group, only a lower dose of manool (10 mg/kg) reduced the SBP compared to the control (hypertensive vehicle) group, and the previous administration of L-NAME prevented the manool effect. In the hypertensive group, the manool effect was not dose-dependent (Figure 3).

The plasma NOx is a little high in the normotensive group after manool administration, but it is not significant. However, in the hypertensive group, manool promoted an increase in plasma NOx levels (Figure 4).

About vascular reactivity experiments, manool promoted a dose-dependent relaxation only in intact rings (Figure 5), precontracted with Phe. Incubation with either L-NAME or ODQ blocked the relaxation induced by manool in endothelium-intact rings in the same way of endothelium removal (Figures 6A and 6B).

Discussion

Previous research has shown that labdane diterpenes have a wide range of pharmacological effects, such as the ability to inhibit HIV replication, prevent common colds, it is antimalarial, antibacterial, anti-inflammatory, antihyperglycemic, prevents dysentery, besides suppressing various cancerous cells.[6,13] On the cardiovascular side, they showed: significant reduction of stenosis in atherosclerotic arteries, associated with the fewer restenosis rates after angioplasty in rabbits; reduction of *ex vivo* platelet aggregation, and antihypertensive action in rats.[13,15-17,25] They are thus seen as a promising source of new prototypes for the discovery and development of new agents of cardiovascular therapeutics.

Diterpenes, in particular, are among the significant compounds with binding to cardiovascular properties, such as vasorelaxant, inotropic, diuretic and hypotensive activity.[26] The vascular action exerted by these compounds seems to involve multiple mechanisms, such as dependent and independent endothelium, increase of prostacyclin and blockade of voltage-dependent calcium channels.

In the present study, we used the 2K1C model for investigating the possible antihypertensive effect of manool. This model produced satisfactory results, for hypertension induction, with a significant increase in blood pressure in animals, after three weeks of surgery. Even the first week post-surgery, the 2K1C SBP was higher than in a normotensive

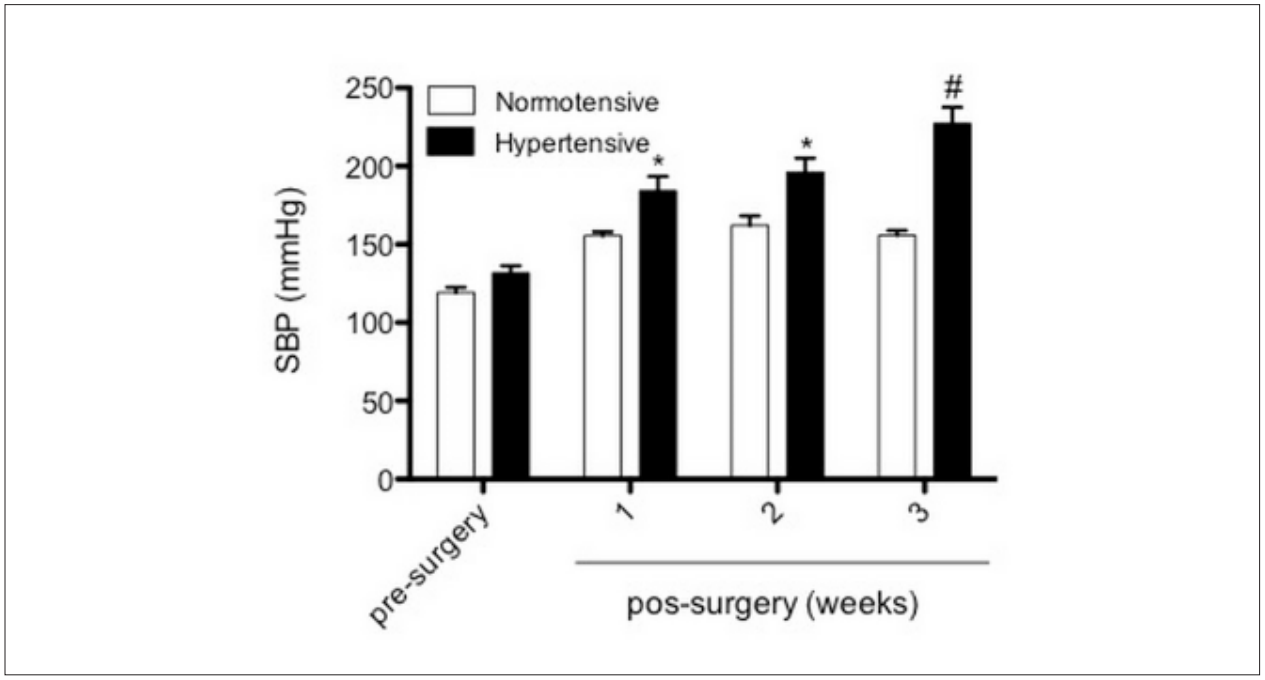

Figure 2 – *Temporal evolution of systolic blood pressure (SBP) non-invasively in normotensive and hypertensive animals. The values represent mean ± standard error of mean arterial pressure before the clip placement surgery (pre-operative) and at three weeks following the surgery. * p<0.05 and # p <0.01 indicate a significant difference between the hypertensive group and the normotensive group. Two-Way ANOVA, Bonferroni post-test. n=14 normotensive and n=14 hypertensive.*

Table 1 – Time evolution of body weight normotensive and hypertensive animals

Evolution of body weight (g)		
Groups	Initial	Final
Normotensive	233.4±7.1	480.2±10.2
Hypertensive	239.4±7.7	404.8±18.2*

*Each value represents mean ± SEM. * p<0.05 indicates significant difference between the hypertensive group and the normotensive group. Student's T-test.*

animal. SBP found in hypertensive animals agree with other authors who evaluated a similar model.[23,27,28]

The results obtained after administration of 3 increasing doses of manool showed that this compound was able to reduce BP in both normotensive and hypertensive rats. In normotensive animals, manool presents a positive dose-response effect. This finding is different from other natural compounds, including Rosmarinic acid, which reduced BP only in hypertensive animals.[23] This response profile is not observed in hypertensive animals, where the dose increase does not represent a more significant effect. ΔSBP is the same after 10, 20 and 40 mg/kg of manool in hypertensive animals; in other words, regardless of the doses, maximum blood pressure was about 40–50 mmHg. However, as in the hypertensive vehicle group there was a reduced SBP, only the 10 mg/kg was able to effectively reduce the pressure.

Our hypothesis to this antihypertensive effect of manool was based on recent studies about the vasodilator activity of diterpenes mediated by NO.[13,15,16,26] It has been demonstrated that hypertension has a strong association with the formation of reactive oxygen species (ROS).[29] Consequently, inactivation of NO by superoxide induces the development of endothelial dysfunction in cardiovascular diseases.[30] The property of some compounds to increase NO can be attractive to reducing the endothelial dysfunction of hypertension. Our findings indicate that the antihypertensive effect of manool can be partially mediated by NO once L-NAME administration before manool injection blocks SBP reduction in hypertensive animals only at a dose of 10 mg/kg. Corroborating these findings, the plasma NOx concentration was increased significantly only in the hypertensive animals that received manool. Some NOx studies in the 2K1C model show that hypertension can reduce these levels, but our finding is in disagreement with this data, perhaps because of the time of 2K1C surgery.[31,32] Though the full antihypertensive effect of manool remains unknown, other hypotheses can be raised, such as ACE (angiotensin-converting enzyme) inhibition and modulation.[33] It was demonstrated that, in the 2K1C model, there is an increase in plasma ACE activity and some natural peptides from rice, terpenes, phytoestrogen and polyphenol compounds can reduce this ACE activity,[20,34,35] which could characterize this mechanism as complementary to NO on BP maintenance.

It would be possible to attribute the antihypertensive effect of manool to a direct effect on vascular reactivity that does not include an increase of systemic NO. The present study showed that manool induces relaxation in rat aorta only in the presence of endothelium and pre-incubation of the aortic rings with nitric oxide synthase (NOS) or guanylyl cyclase (GC) inhibitors. The cardiovascular properties of diterpene are related to Ca^{2+} channels blockade and NO/cGMP (cyclic guanosine monophosphate) activation.[13] The endothelium produces potent vasodilators, such as the endothelium-derived relaxing factor (EDRF, NO), prostacyclin,

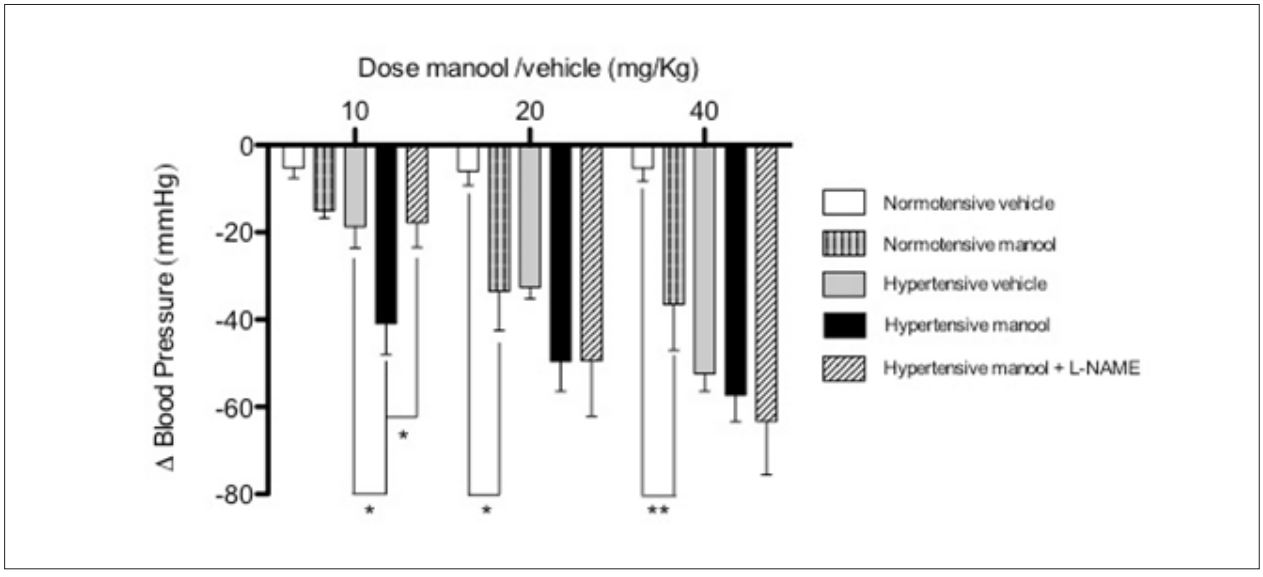

Figure 3 – *Change in systolic blood pressure (ΔSBP) after administration of manool or vehicle in normotensive and hypertensive rats. Data are presented as mean ± standard error of the mean. Normotensive vehicle (n=7), normotensive manool (n=7), hypertensive vehicle (n=7), hypertensive manool (n=7) and hypertensive manool + L-NAME (n=7), * p< 0.05, ** p <0.01 indicates significant difference. Two-way ANOVA, Bonferroni post-test.*

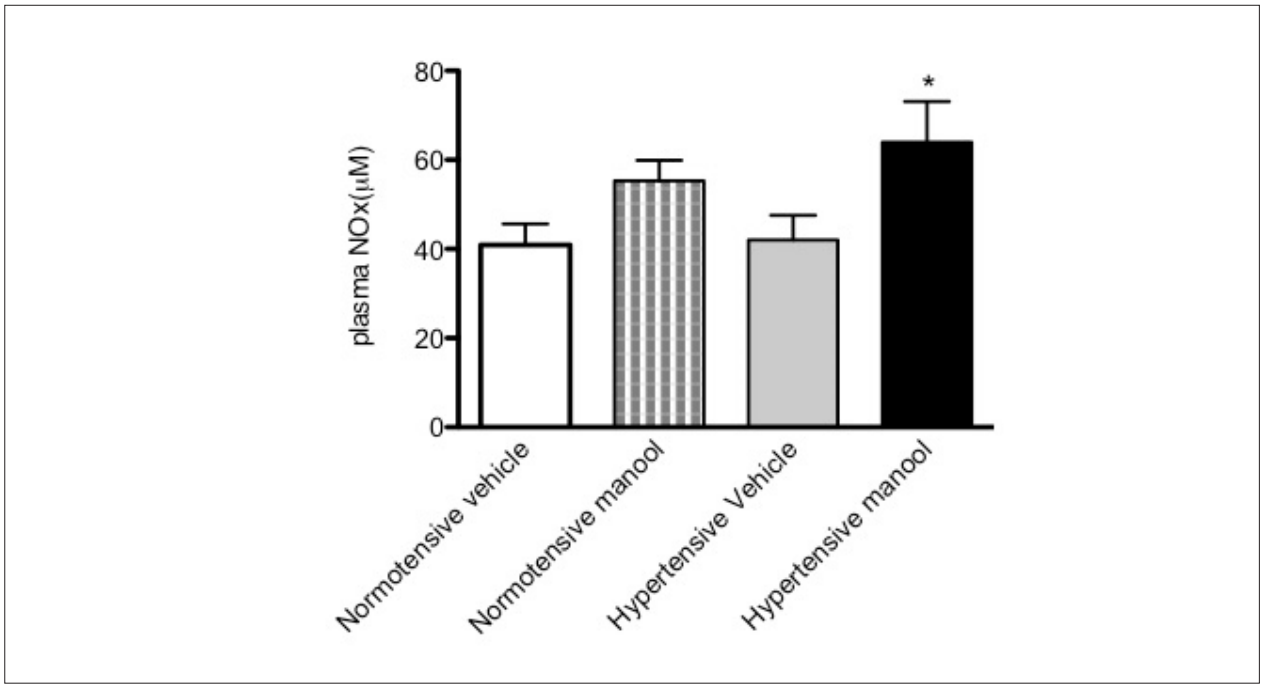

Figure 4 – *Nitrite and nitrate levels (NOx) plasma in normotensive vehicle and manool and hypertensive vehicle and manool animals. One-way ANOVA, Bonferroni post-test (n=7). *p<0.01 indicates significant difference between hypertensive vehicle and hypertensive manool.*

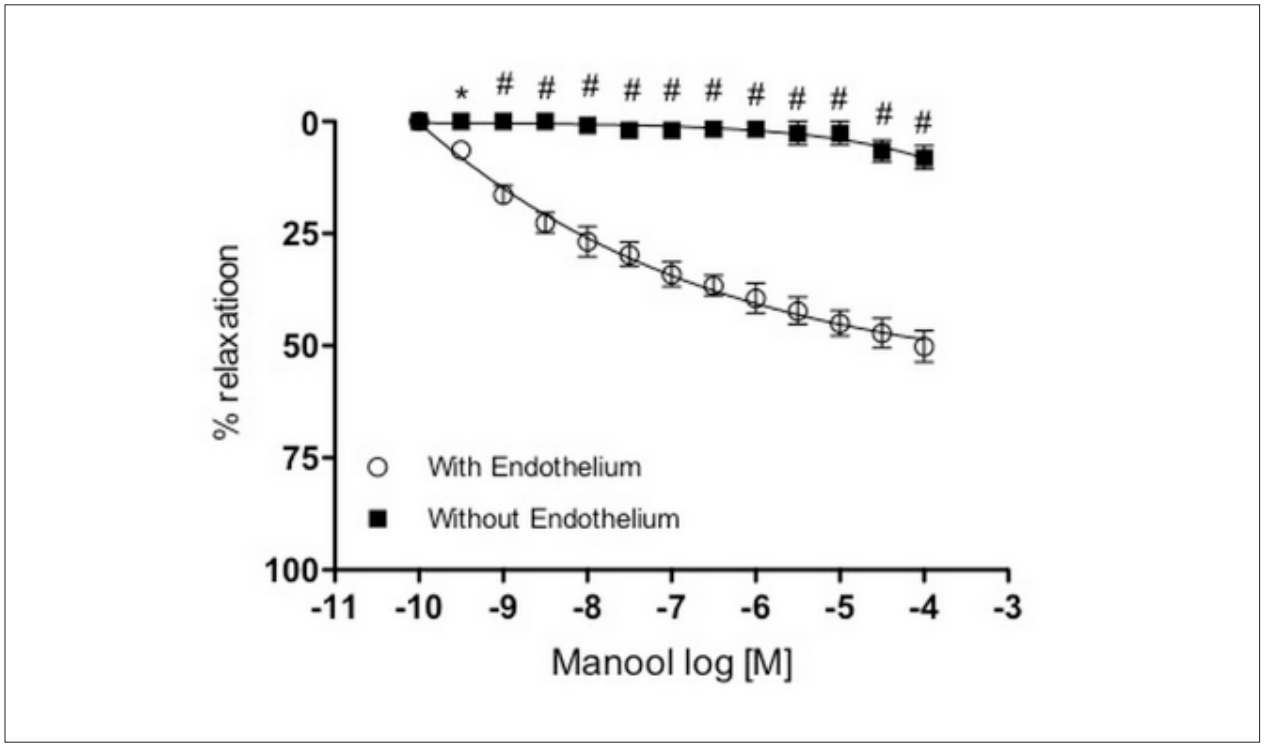

Figure 5 – *Relaxation curve in endothelium-intact and endothelium-denuded rat thoracic aortic rings exposed to manool. The rings were pre-contracted with phenylephrine (Phe) (10-7.M). All values correspond to the mean ± SEM (n = 6). * p<0.05 and # p <0.001. Two-way repeated-measures ANOVA and Bonferroni post-test.*

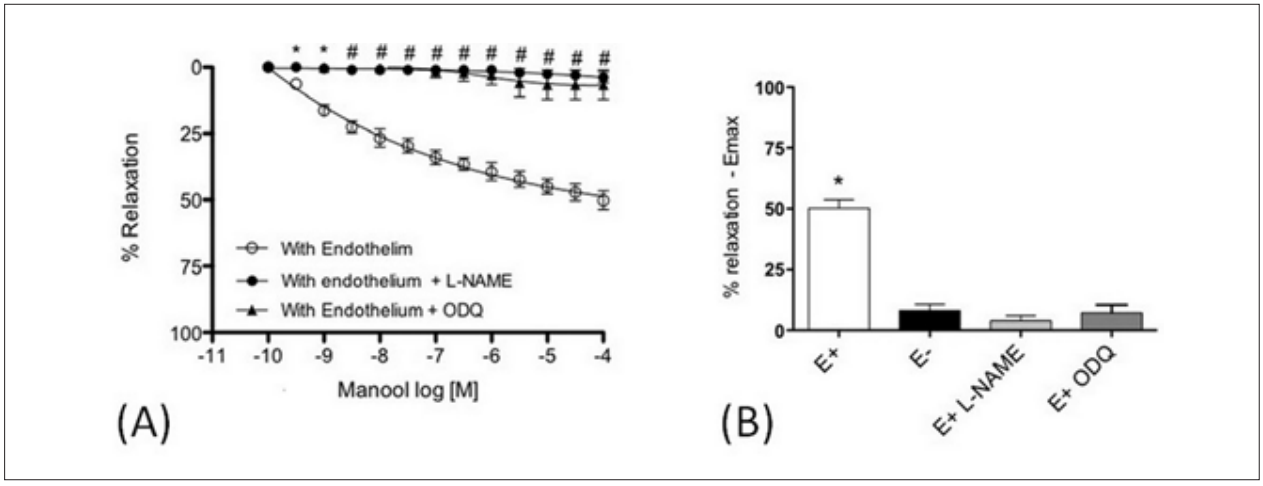

Figure 6 – *Relaxation curve in endothelium-intact rat thoracic aortic rings exposed to manool in the presence and absence of L-NAME (2x10-4 M) or oxadiazole [4,3-a]quinoxalin-1-one (ODQ) (10-4 M). (A) dose-response curve and (B) Bar graph Emax. The rings were pre-contracted with phenylephrine (Phe) (10-7.M). All values correspond to the mean ± SEM (n = 6). *p< 0.05 and # p< 0.001 indicate significant differences between each group and the control group (vessels with endothelium); Two-way repeated-measures ANOVA and Bonferroni post-test.*

and endothelium-derived hyperpolarizing factor (EDHF). NO is the predominant mediator in conductance and large arteries, whereas EDHF and prostacyclin are more prevalent in smaller arteries, such as the mesenteric vessels, coronary arteries and peripheral resistance vessels.[36] Corroborating our findings, some diterpenes, such as 14-deoxy-11,12-dihydroandrographolide and 14-deoxyandrographolide have been reported to dilate aortic rings. The compound 14-deoxy-11,12-dihydroandrographolide had a hypotensive effect in anaesthetized rats. Both compounds exert their vasorelaxant activity by the release of NO and activation of the guanylate cyclase pathway, as well as the blockade of Ca^{2+} influx through both voltage- and receptor-operated Ca2+ channels.[13,37-39] In the present study, we also suggest that manool has an endothelium-dependent vasorelaxant effect operating via the NO/cGMP pathway.

Conclusion

In summary, manool elicits endothelium-dependent vascular relaxation in rat aorta mediated by the NO/cGMP signaling pathway and BP reduction also by NOx plasma increase. These effects together could be involved in modulating the peripheral resistance, contributing to the antihypertensive effect of this diterpene.

Author Contributions

Conception and design of the research: Monteiro ASN, Albuquerque AAS, Evora PRB, Ferreira LG, Celotto AC; Acquisition of data: Monteiro ASN, Campos DR, Albuquerque AAS, Ferreira LG; Analysis and interpretation of the data: Monteiro ASN, Campos DR, Albuquerque AAS, Ferreira LG, Celotto AC; Statistical analysis: Monteiro ASN, Campos DR, Albuquerque AAS, Celotto AC; Obtaining financing: Evora PRB, Celotto AC; Writing of the manuscript: Monteiro ASN, Campos DR, Albuquerque AAS, Evora PRB, Ferreira LG, Celotto AC; Critical revision of the manuscript for intellectual content: Albuquerque AAS, Evora PRB, Celotto AC.

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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Cardiovascular Effects of the Diterpene Manool in Normotensive and Hypertensive Rats

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Short Editorial related to the article: Effect of Diterpene Manool on the Arterial Blood Pressure and Vascular Reactivity in Normotensive and Hypertensive Rats

The World Health Organization estimates that cardiovascular diseases (CVD) are the leading cause of death globally, accounting for 17.5 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030.[1] Similarly, in Brazil, diseases of the circulatory system caused 30.68 % of the total deaths in 2014.[2]

Hypertension is quantitatively the most important risk factor for CVD, such as stroke, myocardial infarction, and cardiac failure.[3] The global prevalence of hypertension in adults aged 18 years and over was around 22% in 2014. The high incidence of hypertension and other CVD also generates an important economic problem since they are responsible for high rates of mortality and disability in the economically active population.[3]

It is important to note that even with the great diversity of drugs currently available, there is still an increase in the prevalence of CVD. This emphasizes the importance of studies with purposes of discovering new substances with antihypertensive or cardioprotective effects, low cost, and few adverse effects. In this sense, the therapeutic potential of plant-derived products for treatment of CVD has been documented in previous studies.[4-6] Indeed, some commercial drugs have been developed from substances found previously in plants, such as digoxin, derived from *D lanata*, used in the treatment of congestive heart failure for many decades, and the reserpine, derived from *R serpentine*, which was one of the first drugs used on the treatment of hypertension.[5]

Monteiro et al.[7] evaluated the effect of manool on blood pressure in two-kidney one-clip (2K1C) renovascular hypertension animal model. The manool promoted a reduction in the systolic blood pressure in both normotensive and hypertensive rats. The effect found in hypertensive animals was, at least in part, mediated by nitric oxide pathways, since the pre-treatment with a nonspecific nitric oxide synthase inhibitor, L-NAME, attenuated the antihypertensive effect of manool. Additionally, manool promoted an increase in plasma nitrite/nitrate (NOx) levels in hypertensive, but not normotensive rats. This data suggest a possible difference in action mechanisms of the manool between normotensive and hypertensive animals. Unfortunately, the authors did not show whether the changes in blood pressure were accompanied by alterations of the heart rate. Interestingly, the authors demonstrated that manool seems to act on vascular endothelium. It was observed that manool evoked vasorelaxation only in endothelium-intact aortic rings from normotensive rats. However, it was not demonstrated the effects of manool in aorta of the hypertensive rats.

Manool belongs to the class of diterpene compounds and is found in higher concentrations in the species *Salvia officinalis*.[8] There are very few studies directed to evaluate the effect of manool on the cardiovascular system. However, many experimental and clinical studies have shown the beneficial effects of several classes of diterpenoids for CVD.[6] Diterpenoids promote vascular relaxation and reduction in systolic blood pressure in spontaneously hypertensive rats[9] and diuresis and natriuresis in normotensive rats.[10] Clinical studies demonstrated that stevioside administered orally reduces systolic and diastolic blood pressures.[11] Also, intravenous administration of labdane-type diterpene forskolin reduces diastolic blood pressure and improved left ventricular function in patients with cardiomyopathy.[12]

These studies pointed out the diterpenoids as a potential target for the development of novel cardiovascular therapeutic agents. In this sense, Monteiro et al.[7] showed that manool, a diterpenoid labdane also has some beneficial actions on the cardiovascular system. Besides, this study provides information on the mechanisms of action elicited by manool that can form a basis for future studies aiming at the development of new drugs for the treatment of CVD. However, further experimental studies, including other animal models and clinical studies are essential to confirm this hypothesis.

Keywords

Cardiovascular Diseases; Hypertension; Rats; Plants; Diterpenes Manool; Plants, Medicinal.

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Prediction of Stress Map in Ascending Aorta - Optimization of the Coaxial Position in Transcatheter Aortic Valve Replacement

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Abstract

Backgroud: Transcatheter aortic valve replacement (TAVR) can reduce mortality among patients with aortic stenosis. Knowledge of pressure distribution and shear stress at the aortic wall may help identify critical regions, where aortic remodeling process may occur. Here a numerical simulation study of the influence of positioning of the prosthetic valve orifice on the flow field is presented.

Objective: The present analysis provides a perspective of great variance on flow behavior due only to angle changes.

Methods: A 3D model was generated from computed tomography angiography of a patient who had undergone a TAVR. Different mass flow rates were imposed at the inlet valve.

Results: Small variations of the tilt angle could modify the nature of the flow, displacing the position of the vortices, and altering the prerssure distribution and the location of high wall shear stress.

Conclusion: These hemodynamic features may be relevant in the aortic remodeling process and distribution of the stress mapping and could help, in the near future, the optimization of the percutaneous prosthesis implantation. (Arq Bras Cardiol. 2020; 115(4):680-687)

Keywords: Aortic Valve Stenosis/surgery; Aortic Valve Stenosis/diagnostic imaging; Comorbidity; Heart Valve Prosthesis Implantation/trends; Echocardiography/methods; Computed Tomography Angiography/methods Treatment Outcome.

Introduction

For many years, the open-chest aortic valve replacement was the standard-of-care treatment for cases of severe aortic stenosis,[1-3] reducing symptoms and improving survival.[4–7] However, some high-risk patients cannot undertake open-chest surgery,[8,9] either because of their advanced age, left ventricular dysfunction, or the presence of multiple coexisting conditions.[10-12] For this class of patients, in 2002 [13] a powerful less invasive alternative was developed, called transcatheter aortic valve replacement (TAVR).[14]

When performed by open surgical procedure, valve placement is precise, but invasive. In the TAVR procedure, prosthesis is released in the region of the aortic annulus, replacing the damaged valve without removing it, through the use of catheters and with the aid of fluoroscopic images. However, the method is subject to greater variability in the positioning of the prosthesis, due to the nature of the procedure.[15,16] Also, the presence of eccentric calcifications in the aortic annulus may avoid the complete expansion of the percutaneous prosthesis, thereby affecting its coaxial position after the release process.[17]

The valve position can be defined based on the relationship between its effective orifice and the annulus, with its inclination determined as the angle formed between aortic annulus centerline and the effective orifice centerline. Variations in prosthesis composition as well as in its positioning (coaxial position of the aortic prosthesis) in relation to the patient's native valve can generate significant hemodynamic changes in the aortic root, such as the turbulence intensity, flow direction and pressure drop increase. It is well known that blood flow variations in the ascending aorta are related to the aortic remodeling process and pathological conditions, such as dilatation, aneurysmal formations and tortuosity.[18,19] Identification of high shear stress and pressure is important due to their association with aneurysmal dilatation of the ascending aorta.[20]

The helical patterns of blood flow, before and after a patient have undergone a TAVR procedure, vary considerably by the effect of the geometry of the prosthesis implanted, its inclination and final positioning.[21] Currently, little is known about the hemodynamic consequences of the lack of coaxiality of the percutaneous prosthesis. These variations have not been completely understood and it is of great interest to analyze the influence of this procedure on aortic remodeling, to improve its design and assembly. Therefore, in the present work, a study

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is performed to investigate the influence of small variations in the coaxial angle of the valve on the flow field inside the aorta.

The definition of the aortic flow pattern based on computed tomography angiography (CTA), without using an invasive procedure, may help to define the best care strategy. This could be considered as a good practice in health care and maybe a step further on direction of precision medicine.

Methods

To better represent the aorta geometry, a vascular model was constructed from a pre-TAVR electrocardiogram gated-scan CTA of the aorta from a 77-year-old male patient. The patient had mild systolic left ventricular dysfunction, and severe degenerative aortic stenosis with New York Heart Association functional class III. The valve implanted was an Edwards-SAPIEN. The patient provided a free, prior and informed consent for participation in the study, which was registered in the National Council of Ethics in Research (Ministry of Health - Brazil) and approved by the Research Ethics Committee, National Institute of Cardiology.

The CTA was performed on a 64-slice scanner (Somatom Sensation 64, Siemens, Germany). A series of CTA slices were selected, covering from the aortic annulus to the thoracic aorta. The DICOM images were transferred to the FIJI software, in order to allow the segmentation of the desired aortic region and study of the systolic phase of the cardiac cycle. Segmentation of a pre-implant CTA is a valid extrapolation, since there is no major difference between pre- and post-operative CTA data. The effective diameter *D* of the aortic prosthesis was determined from post-operative transthoracic echocardiogram measurements, using the continuity equation.

Although the cardiac cycle is naturally transient, the focus of the present work is the systolic period, when the aortic walls are distended, providing their maximum diameter, with small variation due the vascular complacency. Further, the aortic prosthesis completely opens in a very short time interval, reaching its effective diameter *D* very fast. Thus, to analyze the influence of the positioning of the aortic valve on the flow field and stress distribution, a few simplifications of the model were made:

(1) The aortic surface was considered rigid, *i.*e., its complacency was neglected. This approximation is less conservative, since due to complacency, the pressure inside the aorta is reduced in aortic dilatation.

(2) The valve was placed at the inlet region, centered in the aortic annulus. The leaflets of the aortic prosthesis were not modeled. At systolic peak, they are completely open, resulting in an orifice with the effective diameter *D*. The coronary arteries were also not included in the model because of the low flow through them at systolic peak. These simplifications were introduced due to the cost-effectiveness of model simulation, and we believe that they do not have a significant impact on the results of peak systolic flow rate.

(3) The flow was modeled in steady state, corresponding to the moment of systolic peak, which can be considered as the critical condition (maximum flow rate).[22] This approximation allows inferring the time average stress and velocity distribution. However, the oscillatory shear index, which is associated to aneurysmal degeneration,[23] cannot be determined.

(4) Gravity effects were neglected since the pressure variations are dominant.

(5) According to Sun and Chaichana,[24] blood can be considered as a Newtonian fluid, i.e., the viscous stress is directly proportional to the fluid element deformation rate. This approximation can be applied if the shear rate is above 100 s^{-1}. [25,26] In addition, under normal conditions at 36°C, the blood can be considered as an incompressible fluid, with constant viscosity.[27,28]

(6) At the systolic peak (maximum flow rate), the jet flow leaving the valve orifice is turbulent. Following previous studies on turbulent hemodynamic flows,[29–32] the turbulence was determined with the Reynolds-Average model. Based on a comparison between numerical and experimental data,[33] the turbulence model κ–ω SST,[34] which is recommended for low Reynolds number situations, was selected.

Based on the hypothesis presented above, the flow field through the aorta can be obtained by the solution of the Reynolds-Averaged Navier-Stokes equations:

$$(1)\ \frac{\partial u_i}{\partial x_i} = 0\ ;\ \frac{\partial \rho u_j u_i}{\partial x_j} = -\frac{\partial \hat{p}}{\partial x_i} + \frac{\partial}{\partial x_j}\left[\left(\mu + \mu_t\right) 2 S_{ij}\right]\ ;\ S_{ij} = \frac{1}{2}\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_j}\right)$$

where x_i represents the coordinate axes and u_i the time-average velocity component; ρ is the density, $\hat{p} = p + 2/3\ \rho\kappa$ is the modified pressure, which includes the turbulent dynamic pressure (κ is the turbulent kinetic energy); μ and μ_t are the molecular and turbulent viscosity; μ_t is determined based on the solution of the differential equations for the turbulent kinetic energy κ and the specific rate of dissipation ω.[34]

Figure 1 illustrates schematically the computational domain corresponding to the aorta. The outer boundary of the computational domain is the inner layer (intima) of the aorta, which will be referred here simply as aortic wall. The blood enters the aorta through the prosthesis, with an effective orifice area of 1.54 cm^2, at the base of the aortic root (Figure 1a). The inlet plane is coincident with the plane x-y, and perpendicular to the axial z coordinate. The tilt angle θ of the valve is defined in relation to the z-axis, where negative θ is in the direction of the right coronary artery, and positive to the posterolateral aortic wall (Figure 1b).

The volumetric flow rate Q is defined at the entrance. According to Ku D.N.,[35] for the situation under consideration, since the Womersley number is high (>10), a uniform profile for the velocity components, as well as for the turbulent quantities is reasonable. Based on the data of Gomes B.A.A.,[36] 10% of turbulent intensity was prescribed at the inlet.

The flow leaves the aorta through four exits, as illustrated in Figure 1b, with null diffusive flux. The flow rate was split at the outflow regions, based on average values found in the human body, following the recommendation of Alastruey et al.[37], and Nardiet al.[38], Output 1 (descending aorta): 69.1%; Output 2 (brachiocephalic trunk): 19.3%; Output 3 (left common carotid artery): 5.2% and Output 4 (left subclavian artery): 6.4%.

At the aortic surface, a non-slip condition was defined as a boundary condition. The boundary condition of κ at the solid surface is also zero, and the specific dissipation in the walls (ω_w) is defined based on the thickness of the molecular sublayer.[34]

Since the flow was modeled as incompressible, the pressure level is irrelevant, thus, the pressure distribution was determined in relation to the pressure at the aortic valve, p_{in}.

Numerical modeling

The conservation of mass, momentum, and turbulence equations that characterize the problem were solved with ANSYS Fluent software v17.0, based on the finite volume method.[39] A mesh with 400,000 nodes was defined for all cases. The mesh was designed based on a mesh independence test, performed to guarantee the quality of the solution in the valve inlet region and at the aorta wall, with the dimensionless wall distance of the first node, $y^+ = \rho u_\tau y/\mu$ smaller than 4.5 at the aortic surface, as recommended for the $\kappa - \omega$ SST model. Here, $u_\tau = \sqrt{\tau_w / \rho}$ is the friction velocity, where $\tau_w = \mu \partial u / \partial n|_w$ is the wall shear stress (WSS) (based on the normal gradient at the wall). The defined mesh provided variation of the pressure drop at the ascending aorta region, indicated in Fig. 1a, inferior to 0.3%, when the mesh was doubled.

Results

The influence of the tilt angle on the axial velocity, pressure and WSS was evaluated here. Based on a previous study,[36] six different inlet valve angles were analyzed: -4°, -2°, 0°, 1°, 3° and 5°. The most critical situation corresponding to the systole peak, *i.e.*, maximum flow rate during the systole period (25 L/min) was considered.

To visualize the internal fields, a central plane with 6cm of height and oriented with respect to the right coronary artery (Fig. 1a) was selected. According to the position of the chosen center plane, the left wall of the plane corresponds to the anterior wall of the aorta and the right wall corresponds to the posterior wall.

To analyze the stress distribution on the walls, the complete geometry was examined, although emphases were given to the wall where the inlet jet impinges (right anterolateral wall of the ascending aorta).

Figure 2 compares, for all inlet angles studied, the isocontours of the axial velocity component (u_z) and relative pressure ($p - p_{in}$) at the central plane of the aorta (Figure 1). It can be seen a progressive displacement of the axial velocity field with the variation of the inlet valve angle, without substantial modification of the jet diameter. When the jet is tilted to the left (negative angles), it reaches the anterior aortic wall. Furthermore, a region with negative velocity to the right of the jet is identifiable, indicating the presence of a recirculation. On the other hand, the inclination of the valve to the right (positive angles) displaces the jet away from the anterior wall, approaching the posterior aortic wall. The jet undergoes a spreading, and a smaller region of negative velocities occurs at the posterior side of the aorta. As the inlet jet impinges the aorta surface, the pressure increases substantially, and a downward flow is induced. Note a change in the location of the high-pressure areas, which are located at the anterior wall at negative tilt angles and move to the posterior wall at positive tilt angles.

For three representative angles (-4°, 0° and +5°), Figure 3 presents an iso-surface corresponding to the constant axial velocity component, u_z =1.3 m/s. The surface is colored by the relative pressure. To better visualize the flow, front and back views are presented. For the three tilt angles, the inlet jet impinges at the left side of aortic wall, where the pressure reaches its maximum value. Due to the aortic wall curvature, the jet is bent in direction of the aortic arch. For the negative angle (opposite direction than the aortic curvature), a stronger curvature of the jet can be observed. For the positive tilt angle, the inlet jet is more aligned with the aortic shape, and the jet is more vertical.

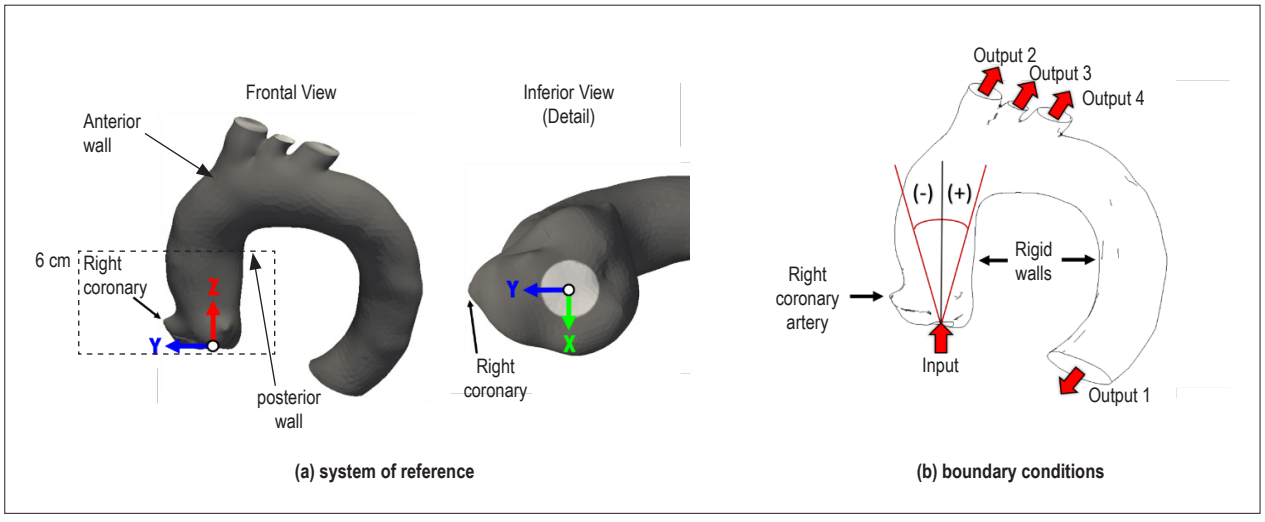

Figure 1 – *Computational domain: system of reference and boundary conditions.*

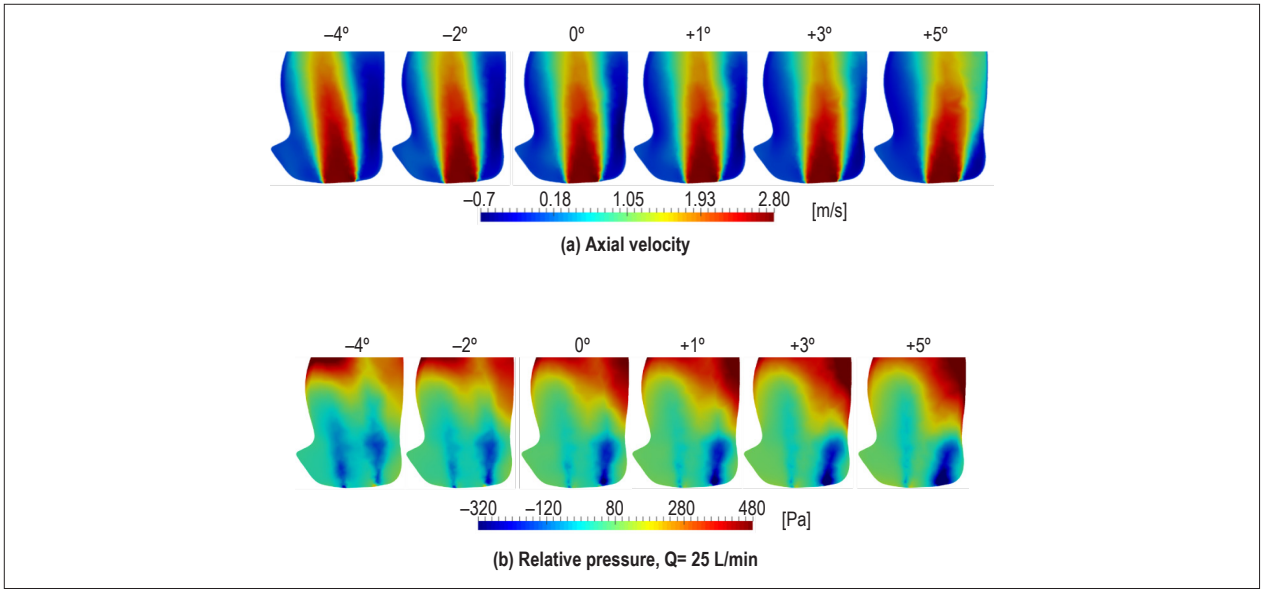

Figure 2 – *Axial velocity and relative pressure at different tilt angles.*

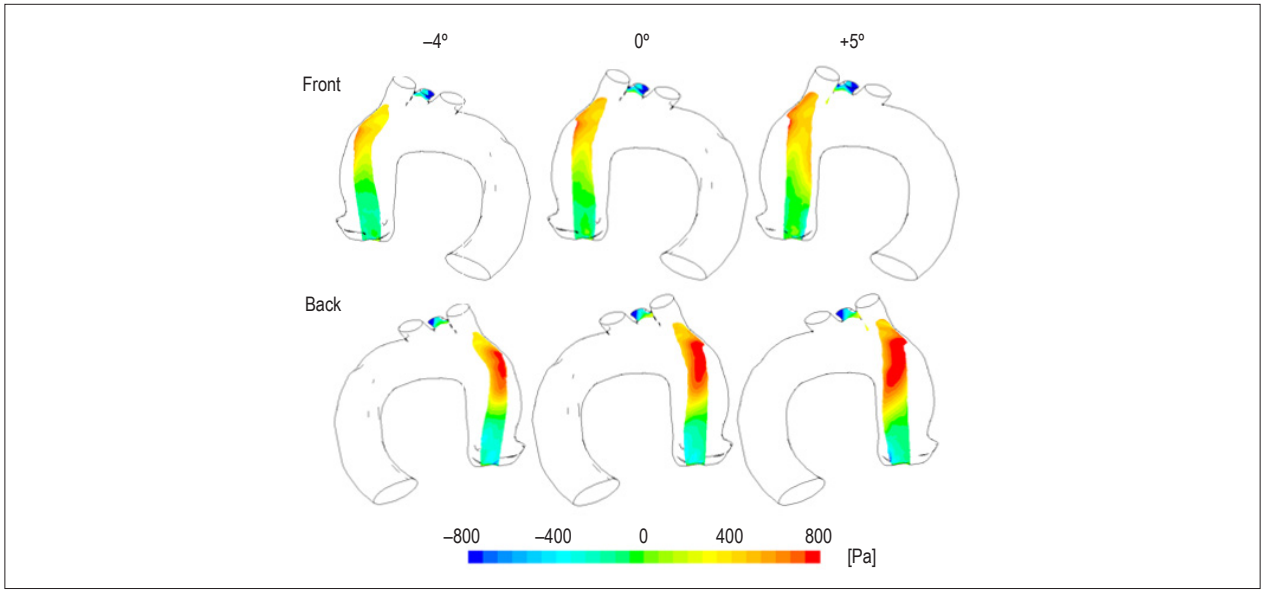

Figure 3 – *Influence of tilt angle of the valve. Iso-surface of u_z=1,3 m/s, colored by relative pressure. Q=25L/min.*

In Figure 4, the WSS and the pressure at the aortic wall are shown for six angles and Q=25L/min. The aorta is visualized in such a way as to focus on the region where the greatest effects occur, which in this case occurs in the right anterolateral wall of the ascending aorta. It can be clearly seen that the high stress region corresponds to the right anterolateral wall of the ascending aorta. WWS values up to 30 Pa were obtained, as also observed by several authors.[40-42] This high WSS values are concentrated in a region near the brachiocephalic trunk. Analyzing the figure, it can be perceived that when the angle is modified from negative values to positive values there is a displacement and a reduction of the higher values of WSS, showing that the region of high pressure corresponds to the region where the inlet jet impinges the aortic wall. It can also be seen that higher pressures occur in the anterior region for the negative angles cases. As the angles increase and become positive, the higher-pressure region is displaced to the posterior zone. This implies a displacement and decrease of mechanical stress on the ascending aortic wall by modifying the inclination of the prosthetic valve on the direction of the posterior wall.

To better identify the region of the ascending aorta surface with elevated WSS and pressure, a critical sub-region (corresponding to the right anterolateral wall, Fig. 1a) where

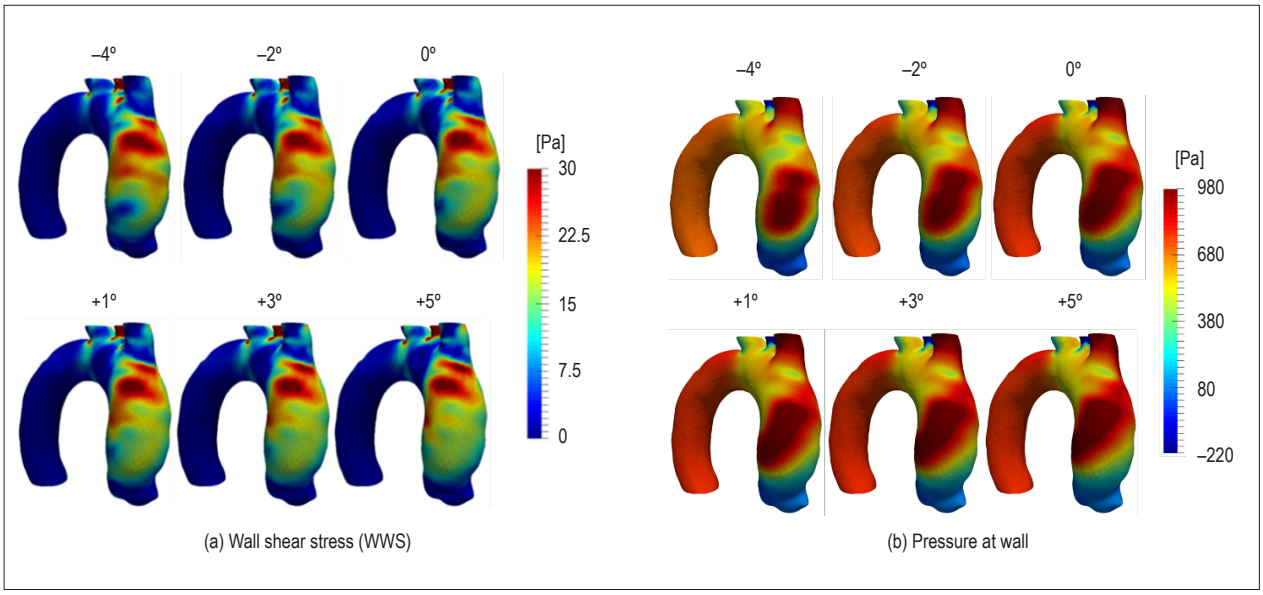

Figure 4 – *Influence of the tilt angle of the valve on shear stress and pressure at aortic wall. Q=25L/min.*

the major effects occur was defined. This region was taken as reference to the analysis. Further, three subranges of WSS and relative pressure values were defined, where blue corresponds to lower values, green to intermediate values and red to higher values. Analyzing Figure 5, it can be seen a significant reduction in the size of the region with high WSS when the flow inclination increases from -4° to +5°. Although a reduction of the area with high pressure is also observed when the valve position angle is increased, the reduction is much less striking. To determine the variation of the size of the region with high stress values (WSS and pressure), the percentage of superficial area covered by each stress range in relation to the reference area was determined (Figure 5). Note that the size of the low WSS zone tends to remain at a constant value of approximately 47%, while the size of the high WSS zone is progressively reduced by varying the tilt angle. Pressure variation due to valve inclination is relatively small, with very small changes in the size of the region with high-pressure values.

In Figure 6, it is possible to observe reduction up to 15% of the size of area with the highest values of WSS, when the flow angle changes from -4° to +3°. The influence of the flow angle on the size of the area with high pressure is much smaller, with a reduction of only 6% with the increase of the inlet angle.

Discussion

From the results of this study, it was observed that the tilt angle of the prosthetic valve induces changes in the hemodynamic patterns of the aorta. However, in all cases, the jet tends to hit the right lateral wall of the ascending aorta. Negative tilt angles incline the jet towards the anterior wall, without a substantial modification of the jet diameter considering the values of the central position. This change concentrates the pressure and WSS on this wall, increasing its mechanical stress.

As the prosthetic valve takes positive angulation, the jet tilts toward the posterior wall, with a small widening of the jet diameter. This angle variation relieves the mechanical stress on the anterior wall of the ascending aorta, decreasing and displacing higher WSS values in all aortic walls.

Although the present analysis is limited to only one patient, it provides a perspective of great variation in the flow behavior due angle changes, without influence of other bias like the aortic shape.

The significant impact of the inclination of the prosthetic valve on the hemodynamic properties of the aorta flow leads us to recommend that manufacturers consider this parameter in the design of percutaneous prosthesis. One can also suggest, in the near future, that a hemodynamic study of the influence of the tilt angles of the prosthesis should be performed on each candidate before being submitted to the TARV procedure. It is known that each patient has differences in the aortic geometry and in the aortic wall resistance; therefore, such analysis should be individualized. The study could contribute to the implementation of TAVR, by recommending strategic adjustments in the positioning of prosthetic valves, thereby preventing high mechanical stress, which can influence the aortic remodeling process.

Compliance with Ethical Standards

The authors were supported by grants from the Brazilian Government agencies: CNPq and CAPES. There was no conflict of interest by any of the authors. All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration, and approved by ethics and research committee of the National Institute of Cardiology, INC-MS CAAE number: 10998912.2.0000.5272. Registered Informed consent was obtained from each participant in the study.

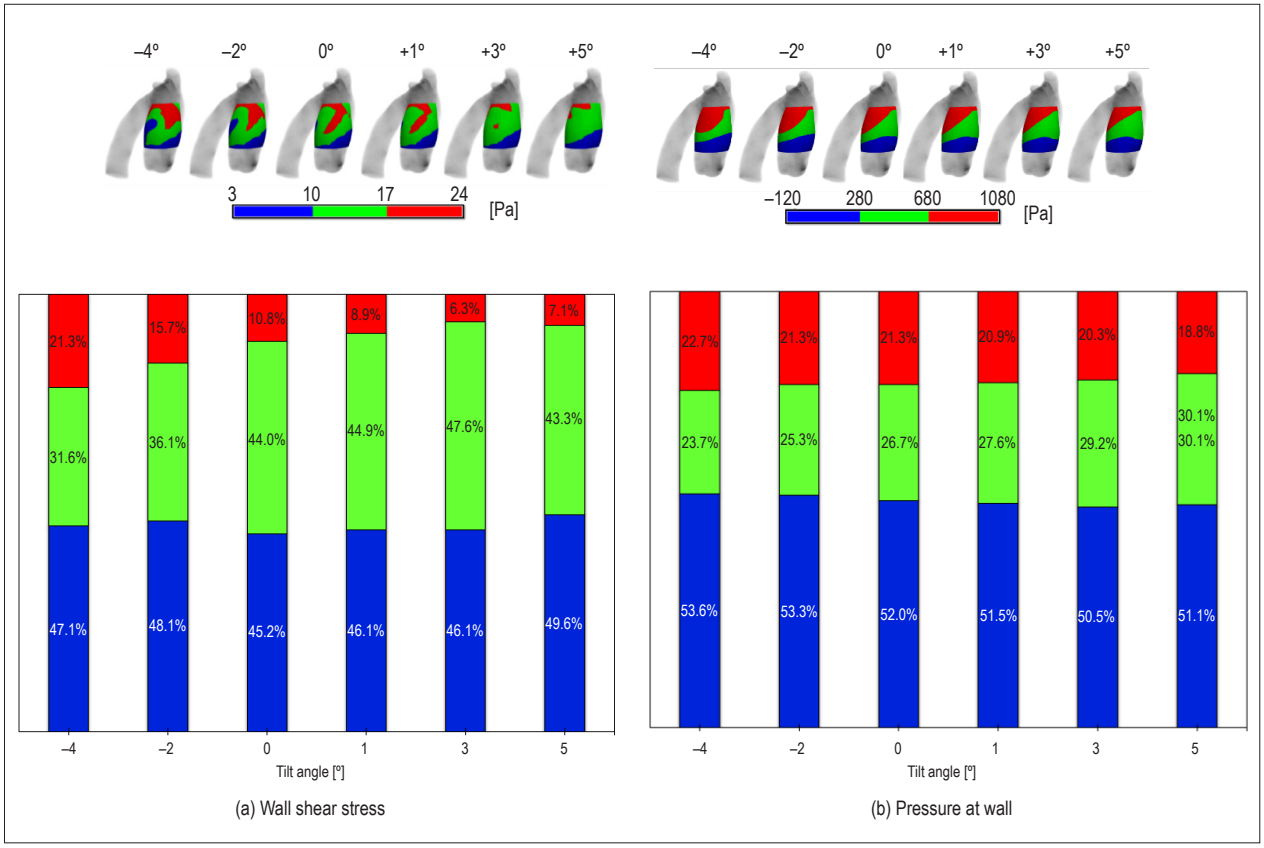

Figure 5 – *Identification of the area with high wall shear stress and pressure, with percentage distribution on the anterolateral wall, as a function of the tilt angle, Q=25L/min.*

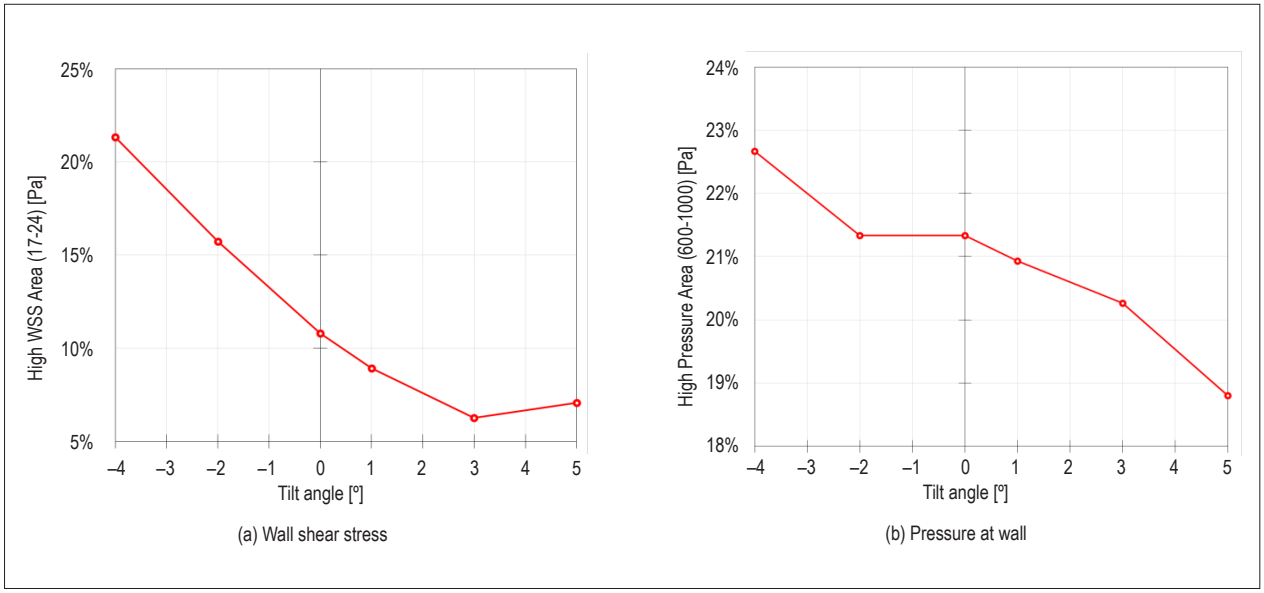

Figure 6 – *Percentage of the area (right anterolateral wall of the ascending aorta) with high wall shear stress and high-pressure values by changes in the tilt angle.*

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: Celis D, Gomes BAA, Ibanez I, Azevedo PN, Teixeira PS, Nieckele AO.

Potential Conflict of Interest

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

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Computational Analysis of Fluid Dynamics in the Transcatheter Aortic Valve Replacement

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Short Editorial related to the article: Prediction of Stress Map in Ascending Aorta - Optimization of the Coaxial Position in Transcatheter Aortic Valve Replacemento

Transcatheter aortic valve replacement (TAVR), a minimally invasive heart surgery, was introduced by Cribier et al.[1] as an alternative to the traditional open-heart surgery in the treatment of individuals with severe aortic valve stenosis and at high surgical risk due to advanced age or the presence of multiple comorbidities.[2] After the first pioneering efforts, the advent of innovative prosthetic valves, and more technologically refined approaches and devices, the use of TAVR for patients with intermediate surgical risk has been a worldwide trend.[3] However, variation in the prosthetic valve positioning and orientation post TAVR procedure can produce significant changes in the aortic hemodynamics and the corresponding stresses in the vessel wall.[4]

Within the aorta, there are two categories of vessel wall stress. The first category of stress is the result of the friction between the moving blood and the vessel wall, which is proportional to the blood speed, moving away from the intimate layer of the vessel wall. This kind of stress is known as wall shear stress (WSS). The second category of stress is due to the variation in pulse pressure generated during the cardiac cycle. In this category, there are circumferential, axial and radial stress transferred to all vessel wall layers. With advancing age, the aorta enlarges, the arch changes shape from a near-perfect semicircle, and the vessel generally becomes more tortuous.[5] Moreover, the change in the natural curvature of the aorta introduces secondary flow dynamics and flow asymmetry, which directly influence WSS distribution and magnitude over the vessel wall.

Among the available imaging modalities, computed tomography (CT) is widely considered the gold standard method for studying and analyzing the aorta, coronary and femoral arteries. Recent developments using a wide coverage detector design (256 or 320 slices) or high-frequency dual-source CT have made it possible to use less contrast and a lower radiation dose. Although CT can present the geometrical and functional complexities of the aorta, it is currently limited to capture a snapshot of the blood flow at a defined instant of time during the cardiac cycle.

Keywords

Flow Mechanics; Transcatheter Aortic Valve Replacement/methods; Hemodynamics; Regional Flood Flow.

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On the other hand, four-dimensional (4D) flow magnetic resonance imaging (MRI) is a novel technique with the capability of assessing aortic blood flow in three-dimensional space as a function of time, which permits the quantification of aortic hemodynamics.[6] This new imaging acquisition technique may improve our understanding of the inherent dynamicity of aortic blood flow. However, CT can be improved with computational fluid dynamics (CFD) modeling, which can compute previously unmeasurable hemodynamic parameters to understand the biomechanical behavior of blood flow in both normal and diseased vessels.

In the absence of a readily applicable means to directly measure WSS, CFD has been applied in CT and MRI images to understand both the spatial and temporal patterns of WSS and the influence of aortic flow dynamics on this parameter.[7–9] Using CT images as the input of a CFD model, Celis et al.[10] demonstrated that small variations of the aortic valve tilt angle could modify the nature of the flow and produce changes in the distribution of the WSS over the aorta wall.

CFD is a feasible method that has been used for ages[11] in determining fluid flow and 3D model of coronary arteries and can simulate an accurate vessel flow based on a set of given parameters. For incompressible fluids, most CFD analysis solve the Navier-Stokes and continuity equations that govern fluid motion. This set of equations includes non-linear and partial differential equations based on the principle of conservation of mass and momentum. Navier-Stokes equation describes the viscous motion of fluids[12] and, according to Newton's law of viscosity, the relationship between the shear stress and shear rate of a fluid, subjected to mechanical stress, is a constant for a given temperature and pressure, and is defined as the viscosity or coefficient of viscosity. Physiologically, this means that the blood flow in the cardiovascular system is equal to the change of blood pressure divided by the system resistance.[13]

Despite the availability of powerful CFD software packages to model fluid flow, such as ANSYS FLUENT, OpenFOAM, SIMVascular, and ADINA,[14] the current CFD methods have large computational time cost, which prevents them from being used in large patient cohorts. This time cost basically comes from the complexity of the models, which need patient anatomic geometries, tissue properties, hemodynamics loading conditions, and proper selection of modeling techniques. A potential paradigm-changing solution to the bottlenecks in current CFD methods is to incorporate machine learning (ML) algorithms[15] to expedite computational analysis, starting from geometry modeling to computational model setup, and simulation completion.

Liang et al.[16] have recently developed a novel machine learning approach that demonstrated the feasibility of using ML as a fast and accurate surrogate of CFD to estimate steady-state hemodynamic fields of human thoracic aorta. In their approach, CFD is treated as a black box, and the ML algorithm learns the nonlinear relationship between CFD input and output. On average, the proposed method took minutes to run a CFD simulation for each aorta model, which seems to be fast enough for clinical applications.

In vivo measurements of parameters hemodynamics and the corresponding stress in the aorta are not practical. Therefore, CFD is widely used to estimate these parameters, but it is time consuming and computationally expensive. ML models can be a promising alternative for CFD simulations to aid clinical decisions and treatment based on specific patients. This can lead to better clinical results in many studies, such as the identification of the best position and orientation of the prosthetic valve in the TAVR procedure.

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Review Article

Pharmacogenomics and Cardiovascular Disease: Where are We and Where do We go from Here?

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Abstract

Pharmacogenomics (PGx) studies the interaction between genes and drugs. By analysis of specific regions of DNA, it is possible to obtain information on patient's metabolization profile of a given drug, as well as the expected profile of response to treatment. The results obtained are allies in the treatment of patients who are not responding adequately to a certain medication, either due to the lack of expected effects or presence of adverse effects. The aim of this review is to inform clinical cardiologists about this important area of knowledge and to update them on the topic, seeking to fill the gaps of the costs and benefits of PGx in cardiovascular diseases, and to provide information for the implementation of PGx-guided therapy in clinical practice.

Introduction, the DNA and the Genes

Pharmacogenomics (PGx) is the science of understanding the interaction between genes and drugs. The analysis of specific areas of the DNA provides information about a certain drug metabolism and about the expected response to a certain treatment. PGx also aims to reduce the incidence of adverse drug events (ADEs).[1,2] Many studies in this area have focused on the identification of genes that predispose to diseases, modulate drug response, affect drug concentration and correlate with adverse effects of patients exposed to different types of drugs, so the desired therapeutic benefit is achieved.[4]

The causes of individual responses to a same drug dosage include age, genetic and immunological factors, comorbidities and interaction between active principles.[5] Genetic variability may influence not only pharmacodynamics, but also pharmacokinetics, which studies the relationship of the absorption, metabolism and excretion of the drug to its systemic concentration.[1]

Keywords

Cardiovascular Diseases; Genes; Heredity; Genome; Genetic Profile; Pharmacogenetics; Biotransformation; Drug Therapy/adverse effects; Public Health.

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ADEs are a public health problem in the world, as they significantly increase the length of hospital stay, and are considered the fourth of the six main causes of death in the United States in the last 20 years.[6,7] Also, in the United States, more than two million people are hospitalized[8] and at least 55,000 people die each year from abscence of treatment response or from ADE per se. In Brazil, data is still scarce and PGx could be a useful tool in the treatment of patients and optimization of financial expenses.[10] The most common drug classes were antiretrovirals, anticoagulants and antihypertensives. In this study,[10] the mean cost to treat a patient for ADE was BRL2,200, with a total cost of 18 million Brazilian reals.

In a recent publication, a national estimate of drug-related morbidity and mortality was conducted by the Brazilian Unified Health System (SUS) using data from the Datasus database.[11] The estimate showed that of 150 million Brazilians that go to the doctor at least once a year, 86% leave the doctor with a drug prescription. The adverse events caused by the drugs are severe, not only from a clinical point of view, but also from an economical perspective – for every Brazilian real spent on drug provision, five Brazilian reals are spent on the treatment of drug-related comorbidities. The most expensive events are those caused by adverse reactions (39.3% of the expenses), non-adherence to treatment (36.9% of the expenses) and unusual dose regimens (16.9% of the expenses). Half of the cases could be prevented by a more careful and effective supervision of different therapies. Finally, it was estimated that 60 billion Brazilian reals were spent annually on drug-related morbidity and mortality by the SUS, corresponding to 30% of its initial budget.[11]

Cardiovascular disease (CVD) is the main cause of death in the world, significantly contributing to the increasing economic burden of health costs. In 2016, 31% of all deaths in the world (17.9 million) were caused by CVDs. These diseases cost the United States approximately $555 billion in that year, and estimates say that this cost will reach $1.1 trillion in 2035.[12]

For this reason, the use of PGx tests, which is more widespread in countries like the United States, Spain and Canada, has gained importance in Brazil, with the potential to improve the drug-physician-patient relationship. With the aid of PGx, the physician could prescribe, in a safer and more assertive way, the most appropriate drug at the correct dose, since, in addition to other important factors, information about patient's genetic profile would be now available.[13] Thus, CVDs are at the forefront of PGx-guided therapy, and cardiologists should be alert to this area of knowledge.

Several classes of drugs are known to reduce the risk of CVDs, but it is also known that there is a significant individual variation in treatment response.[14] In addition to variations attributable to sociodemographic characteristics, there are genetic determinants of drug and responses that may affect how the drugs are metabolized, absorbed and distributed.[1,14-16] Therefore, genetic data can be used in the identification and evaluation of drug response, control of side effects, and prediction of results.[17-19] With recent advances in gene cloning, genotyping and DNA sequencing, PGx has emerged as a useful component. Current knowledge may be applied at an individual gene level, to a therapeutic area or to specific drug: (a) PGx tests to predict an individual dose of the drug; (b) PGx tests to predict individual risk of drug toxicity in response to a drug prescribed or administered.

There are many clinical guidelines available in this area of knowledge, and the most relevant ones are: the Clinical Pharmacogenetics Implementation Consortium (CPIC),[20] the Dutch Pharmacogenetics Working Group (DPWG),[21] the Canadian PGxs Network for Drug Safety (CPNDS),[22] the Groupe de Pharmacologie Clinique Oncologique (GPCO/Unicancer),[23] the Réseau National de Pharmacogénétique Hospitalière (RNPGx),[24] and the American College of Rheumatology (ACR).[25]

A Little of History

Some of the main therapies based on a specific mutation, that changed significantly the prognosis of diseases, are trastuzumab therapy against HER2-positive breast cancer and imatinib in chronic myeloid therapy.[26,27] Since then, Oncology has bet on the use of genetic information and today it serves to guide the therapeutic decision making, having included the genomic test in 39% of the clinical trials in the field in 2018.[28] In addition to oncology, other areas have identified and improved therapies based on genetic variations. For cystic fibrosis, more than 100 causative mutations have been identified, that, even though make the development of a specific treatment for each variant difficult, enables the grouping of subtypes that seem to respond to similar treatments.[29]

Advances in genomic medicine are not limited to drugs that act at the protein level. Techniques like the clustered regularly interspaced short palindromic repeats (CRISPR) system, which refers to a specialized DNA region, have been used to silence genes and prevent the development of diseases in embryos and/or modify disease-related genes in adults.[30] These techniques are part of what is known as genetic therapy and, although at embryonic stage, they are expected as potentially revolutionary alternatives.

Drug Metabolization

The main PGx guidelines have adopted terms that aim to facilitate clinical application of genetic results and harmonize reports from different laboratories.[31] This classification varies with different types of genes, and takes into account the combination of variants identified in the same gene and its zygosity. One example is the consensual classification of cytochrome P450 2D6 (CYP2D6), one of the main enzymes of drug metabolism, which is involved in the metabolism of approximately 25% of the commercialized drugs. Patients may be classified into one of four phenotypes regarding the type of drug metabolizers: poor metabolizers, intermediate metabolizers, extensive metabolizers and ultrarapid metabolizers, as detailed below:

- **Slow Metabolizers**

Patients experience a very slow breakdown of medications, making side effects more pronounced. Patients of this group have two alleles with variants that cause a reduction, or even inactivity of the enzyme. Also, standard doses of certain drugs may not work as expected. Up to 15% of the population are in this group.[32]

- **Intermediate Metabolizers**

Intermediate metabolizers may somehow affect the breakdown of medications, causing effects similar to those in poor metabolizers, but not as pronounced.[33]

- **Extensive Metabolizers**

The rate of metabolism of these patients is considered "normal". Medication is likely to work as planned, and these individuals will take the dose recommended in the package insert of the medication;[34]

- **Ultrarapid Metabolizers**

Patients in this group metabolize medications very quickly, due to the presence of two alleles that produce highly active enzymes or of extra copies of the alleles (e.g. gene duplication or triplication).[35]

The CYP2D6 gene, responsible for the metabolism of nearly 25% of the medications prescribed,[36] has the alleles that generate the four metabolizer types, previously described.[37] The prevalence of these alleles varies with ethnicity. For example, one of the main known nonfunctional alleles, the CYP2D6*4, has an estimated prevalence of 25% among Caucasians, whereas the CYP2D6*10 and the CYP2D6*17 (both with reduced function) are more common in African and Asian populations, with an allele frequency of about 40%.[38]

Randomized Clinical Trials

Over the last years, several studies have been conducted to test the role of PGx in clinical practice. A randomized clinical trial (RCT)[39] involving 1,956 patients infected with human immunodeficiency virus were randomly assigned to one of two groups – to undergo prospective HLA-B*5701 screening, with exclusion of HLA-B*5701-positive patients from abacavir treatment, or to undergo a standard-of-care approach of abacavir use without prospective HLA-B*5701 screening (control group). The incidence of hypersensitivity reaction was lower in the prospective-screening group (3.4%) than in the control group (7.8%). This result made the US Food and Drug Administration (FDA) require the inclusion of PGx test in the package insert of the medication.[39] More recently,

Smith et al.[40] reported a reduction by 30% in pain intensity in chronic opioid users when the therapy was guided by the presence of CYP2D6. A meta-analysis including five RCTs found that individuals receiving genotyping-guided therapy were 1.71 times more likely to achieve symptom remission compared with individuals who received standard treatment.[41]

Regarding studies on CVDs, most are related to antiplatelet and anticoagulation agents. After retrospective observations that the presence of genetic variants classified as loss of function had an impact on the effects of clopidogrel, initiatives have emerged to evaluate the benefits of including PGx tests as a routine approach. The Implementing Genomics in Practice (IGNITE) investigators observed, in a group of 1,815 patients, higher rates of cardiovascular events in patients with a CYP2C19 loss-of-function allele prescribed clopidogrel compared with alternative antiplatelet therapy, including prasugrel or ticagrelor (hazard ratio [HR] 2.26, 95% confidence interval [CI] 1.18-4.32; p=0.013).[42] Another RCT showed an important decrease in late coronary events with implementation of PGx strategy for clopidogrel prescription.[43]

Regarding warfarin, most studies evaluated genetic variants related to its metabolization in CYP2C9 and VKORC1 genes. The European Pharmacogenetics of anticoagulant therapy (EU-PACT) showed that a genotype-guided therapy significantly increased the percentage of time in the therapeutic range of 2.0 to 3.0 for the international normalized ratio (INR).[44] More recently, the Genetics Informatics Trial of Warfarin to Prevent Deep Vein Thrombosis (GIFT) study showed a significant reduction in major bleeding, venous thromboembolism and death in patients on genotype-guided therapy with warfarin during the perioperative period of elective surgeries of hip or knee arthroplasty.[45] These two studies involving warfarin included a predominantly white populations and therefore, further studies including CYP2C9 variants that are more common African-descendant populations are needed to obtain in accurate results related to these groups. Interestingly, the largest study on warfarin, the Clarification of Optimal Anticoagulation Through Genetics (COAG) study, showed contrasting results, reporting no difference in initiating warfarin therapy based on clinical information and initiating warfarin therapy based on individual's genotype (search for CYP2C9 variants, which are far more common in European-descendant populations, in a cohort composed of 27% of African-Americans).[46] On the other hand, considering the cost-benefit of the use of warfarin and clopidogrel, a recent systematic review including 31 RCTs showed that, the PGx test was superior to standard therapy in 81% of the times.[13]

Parallel to studies on one type of medication, the concept of preventive test has gained importance and shown evidence of benefit. In 2012, Schildcrout et al.[47] estimated that 64.8% of 52,942 medical home individuals were exposed to at least one medication with a mechanism influenced by genetic variants. The authors also estimated that 398 potential adverse events could have been prevented with an effective preemptive genotyping. The study on genotype data of 44,000 participants of the Estonian Biobank showed that 99.8% of these individuals had a genotype associated with increased risks to at least one medication.[48] Concordant results were reported in the RIGHT (Right Drug, Right Dose, Right Time Using Genomic Data to Individualize Treatment) protocol, created by the Mayo clinic/eMERGE initiative, which performed sequencing of a panel that included solute carrier organic anion transporter family member 1B1 (SLCO1B1), CYP2C19, CYP2C9, VKORC1 and CYP2D6. The study demonstrated that 99% of 1,013 individuals had at least one variant associated with increased risks to a medication.[49]

In the United States, medications with recommendations related to PGx constitute 18% of all prescriptions[50] and 30% of the most prescribed medications that have a high PGx risk represent 738 million prescriptions a year.[51] These data corroborate the idea of a positive impact of the preemptive PGx test, not only for the increase in therapeutic efficacy and cost-benefit, but also for the potential in preventing ADEs. In addition, a Dutch study showed a beneficial effect by reducing the risk of fluoropyrimidine-induced toxicity from 73% to 28% by genotype-guided dosing and reduction of drug-induced death from 10% to 0%.[52]

Importance of Pharmacogenomics

Over the last years, PGx has emerged as an area of increasing interest and enthusiasm, as it essentially leads with the so-called "personalized medicine", considering the influence of patients' genomic variation on drug responses.[53]

Many benefits can be achieved with deployment of PGx:

- To increase therapeutic power and reduce likelihood of intoxication;
- To initiate a therapy in more appropriate time.

In addition, PGx may contribute to the reduction of costs in healthcare, as presented in Figure 1. It is important to mention that a large amount of deaths per year are related to ADEs, with a cost of approximately €80 billion.[54]

It is estimated that a considerable proportion of patients do not show a satisfactory response to drug treatment.[55,56] In this regard, the FDA recommends, for example, that PGx tests be carried out before chemotherapy with mercaptopurine (a drug commonly used in the treatment of patients with acute leukemia) is initiated.[57] This recommendation is based on the fact that, since the drug may cause severe side effects and increase the risk of infection, depending on individual's genetic variant, the therapy may not achieve intended results.

The Genomics and Targeted Therapy Group, an arm of the FDA's Office of Clinical Pharmacology, works to ensure that PGx strategies are applied appropriately by means of its functions of regulatory review, research, policy development, and professional education. Part of this work included the construction of a table describing pharmacological instructions of 161 drugs that display PGx information on the label. The last update provides a remarkable number of biomarkers associated to drugs used in several areas of medicine, many of them widely used in clinical practice[58] (Table 1).

Finally, it is expected that PGx soon become more accessible and that its responsible use contribute to more accurate drug prescription, with a higher likelihood of therapeutic success and a lower risk of ADEs.

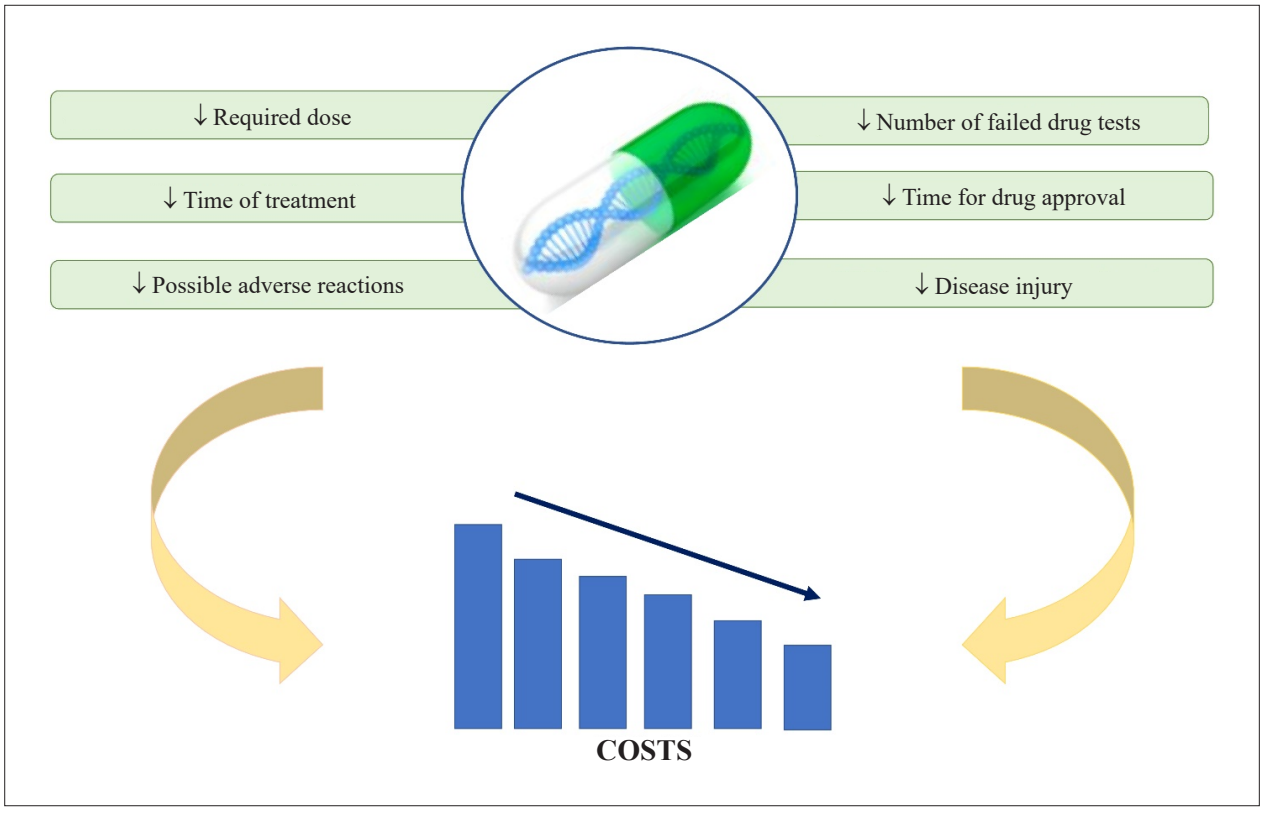

Figure 1 – *Advantages of pharmacogenomics and potential health cost reduction. *Due to possible earlier detection.*

Table 1 – Number of pharmacogenomic biomarkers in drug labeling by medical field, based on the US Food and Drug Administration table

Area	Biomarkers
Oncology	167
Infectious disease	35
Psychiatry	34
Neurology	29
Hematology	25
Anesthesiology	23
Cardiology	22
Gastroenterology	17
Rheumatology	11
Pneumology	10
Endocrinology	7
Inborn errors of metabolism	7
Urology	5
Dermatology	4
Toxicology	2
Transplant	1

Association Between Genetic Variants and Drug Responses in Cardiovascular Diseases

It is widely known that factors like age, comorbidities, weight, and demographic aspects can contribute to significant differences in the response to a certain medication, as well as to the development of ADE.[59,60] In this context, genetic variation may represent a cornerstone in this outcome. It is believed that many deaths could be prevented if physicians were aware of PGx profile of patients and prescribe them medications at correct doses.[61] Patients diagnosed with the same disease are treated following the same therapeutic protocol although their responses to drug treatment may vary significantly. A tailored therapy can reduce ADEs and increase efficacy rates, as described in Figure 2. For example, there is a huge variation (up to 20 times) in the daily dose of one of the most used anticoagulants in clinical practice, warfarin, among patients.[62] The dose of propranolol, a medication of the beta blocker class, may vary up to 40 times among users.[60] Some medications widely used in cardiology, that may have important genetic associations, are listed in Table 2.

Warfarin

Warfarin is a vitamin K antagonist that has been largely used for the prevention of thrombotic events.[63] Evidence has suggested that the individual response to warfarin and to other vitamin K antagonists, may be influenced by genetic variations in cytochrome P450 2C9 (CYP2C9) and vitamin K

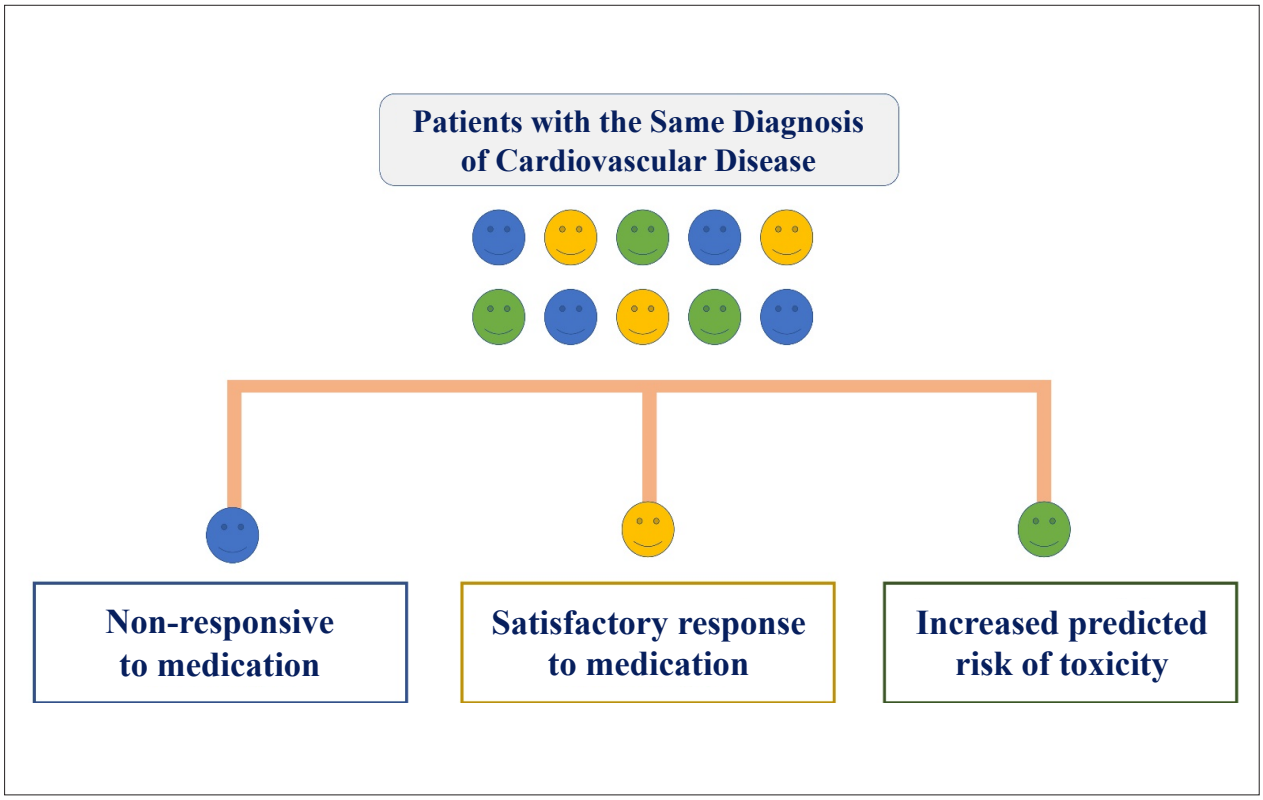

Figure 2 – *Potential clinical applications of Pharmacogenomics; Adapted from Johnson, 2003.*[99]

Table 2 – Association between genes and medications

Genes	Medications	Class	Genetic variant	Allele effect
CYP2C9, VKORC1	Warfarin	Vitamin K antagonist	CYP2C9*2 (p.Arg144Cys; rs1799853)	Reduced drug clearance; reduced dose required
			CYP2C9*3 (p.Ile359Leu; rs1057910)	Reduced drug clearance; reduced dose required
			VKORC1 (-1639G>A; rs9923231)	↑ Sensitivity to medication; Reduced dose required
CYP2C19	Clopidogrel	Receptor $P2Y_{12}$ inhibitor	CYP2C19*2 (c.681G>A; rs4244285)	↑ Risk of cardiovascular events; loss of function; lower antiplatelet effect.
			CYP2C19*17 (c.-806C>T; rs12248560)	↑ Sensitivity to medication; loss of function; ↑ risk of bleeding
SLCO1B1	Simvastatin	HMG-CoA reductase inhibitor	SLCO1B1*5 (p.Val174Ala; rs4149056)	↑ Risk of myopathy or rhabdomyolysis
ADRB1	Atenolol, metoprolol	Beta blocker	ADRB1 (p.Ser49Gly; rs1801252)	Better blood pressure control; ↑ LVEF
			ADRB1 (p.Arg389Gly; rs1801253)	
CES1	Dabigatran	Direct oral anticoagulant	CES1 (G143E, rs71647871)	↑ Metabolism of medication and its metabolites
ITGB3	Aspirin	Antiplatelet agent	ITGB3 ($PI^{A1/A2}$ [T1565→C], rs5918)	↓ Antiplatelet effect

LVEF: left ventricular ejection fraction; CYP2C9: Cytochrome P450 2C9; VKORC1: vitamin K epoxide reductase C1; CYP2C19: P450 2C19; SLCO1B1: Solute carrier organic anion transporter family member 1B1; CYP4F2: cytochrome P450 family 4 subfamily F member 2; ADRB1: beta-1 adrenergic receptor; CYP11B2: Cytochrome P450 family 11 subfamily B member 2; FUT4: Fucosyltransferase 4; CES1: carboxylesterase 1; ITGB3: Integrin beta-3.

epoxide reductase C1 (VKORC1), target of these drugs,[64,65] and polymorphisms of cytochrome P450 family 4 subfamily F member 2 (CYP4F2).[66] Variations in the CYP2C9*2 and CYP2C9*3 have been shown to reduce enzymatic activity of CYP2C9 and inhibit the anticoagulant metabolism,[67] whereas the polymorphism of VKORC1- 1639G>A seems to influence the pharmacodynamic response to vitamin K antagonists.[68] For these issues, the FDA indicated the need for displaying PGx information in the package insert of warfarin.

In practice, heterozygous carriers for CYP2C9*2 or CYP2C9*3 may require a reduced warfarin dose, by approximately 30% and 47%, respectively, and homozygous carriers for CYP2C9*3 may require greater reductions (~80%).[69-71] The -1639 G>A variant of the VKORC1 gene seems to reduce the expression of proteins, which in theory represents the requirement of a lower maintenance dose of warfarin compared with non-carriers of the variant.[72] Also, combinations of some variants associated with ultrarapid metabolism limit the systematic definition of a therapeutic INR of these patients.[73] In this scenario, the CPIC guidelines recommend considering a direct oral anticoagulant (e.g. edoxaban).[74]

Clopidogrel

In the United States, it is estimated that more than three million individuals are prescribed clopidogrel after stent implantation.[75] Clopidogrel belongs to the class of thienopyridines and exerts antiplatelet effect.[76] The individual response to clopidogrel may be altered by the polymorphism of CYP2C19.[77]

The CYP2C19*2 loss-of-function variant allele was associated with an increased risk of adverse cardiovascular events, including stent thrombosis during clopidogrel therapy.[78] More specifically, the CYP2C19*2 (rs4244285) allele causes loss of function and was associated with reduced antiplatelet effect of the drug.[79] Also, carriers of the CYP2C19 *3 (rs4986893) allele show poor response to clopidogrel and higher rates of recurrent adverse cardiovascular events as compared with non-carriers.[80,81] It is important to mention that the frequencies of CYP2C19 *2 and CYP2C19 *3 are higher in Asian populations, suggesting that these individuals are more likely to be resistant to this medication.[82] In contrast, the CYP2C19*17 (rs3758581) allele promotes gain of function and has been associated with increased enzymatic activity and improved platelet inhibition. Carriers of the CYP2C19*17 variant have been called ultrarapid metabolizers.[83]

In addition, race seems to play an important role in this scenario. Cresci et al.[84] compared the effect of polymorphism of CYP2C19 on cardiovascular adverse events between patients with acute myocardial infarction in Caucasians and African Americans treated with clopidogrel. The authors found a significant association of the CYP2C19*2 allele with increased one-year mortality and an increasing trend in the incidence of recurrent myocardial infarction in Caucasians. The CYP2C19*17 was associated with higher one-year mortality and higher risk of bleeding in African Americans. Also, it is of note that CYP2C19*2 carriers that undergo percutaneous coronary intervention may have higher risk of stent thrombosis. In a RCT in which nearly 2,500 patients that were pre-treated with 600mg clopidogrel, there was a significanly higher stent thrombosis rate amongst CYP2C19*2 allele carriers, in 30 days, when compared with wild-type CYP2C19 allele carriers.[85] In this same line, the meta-analysis conducted by Mega et al.,[86] including studies on more severely ill patients receiving more aggressive treatment, found an increased risk of stent thrombosis when the allele *2 was identified by PGx.

Despite these evidences, a systematic review and meta-analysis including 15 studies did not corroborate these findings and did not show a clear influence of polymorphisms of the CYP2C19 gene on the clinical efficacy of clopidogrel,[87] suggesting that the use of individualized antiplatelet regimens guided by CYP2C19 genotype is not justified.

Today, the American College of Cardiology, in conjunction with the American Heart Association, does not recommend PGx tests for CYP2C19 as a routine approach.[88] However, a more recent meta-analysis demonstrated that patients who may benefit from the PGx study are those with coronary artery disease, undergoing percutaneous myocardial revascularization.[89] In this context, the CPIC officially recommends that patients with acute coronary syndrome and even those undergoing percutaneous coronary intervention undergo PGx testing. The CPIC emphasizes that those patients with one or two copies of loss-of-function variants should receive alternative antiplatelet agents (prasugrel or ticagrelor), to reduce the risk of adverse cardiovascular events.[90] On the other hand, PGx testing is not indicated for other patient populations (e.g. atrial fibrillation patients), in which the use of clopidogrel is debatable.

Claassens et al.[91] conducted a recent RCT to evaluate the results of a genotype-guided antiplatelet therapy in patients with acute myocardial infarction with ST segment elevation. Patients were assigned to receive either clopidogrel, based on early CYP2C19 genetic testing (non-carriers of loss-of-function alleles received clopidogrel) or standard treatment with either ticagrelor or prasugrel. No difference was found between the groups in the incidence of thrombotic events and therefore, the genotype-guided strategy was noninferior to standard treatment with ticagrelor or prasugrel, which is more expensive and associated with higher incidence of bleeding.[91]

Results of the TAILOR PCI clinical trial were recently published. The authors assessed a genotype-guided strategy (n=2,652) versus standard therapy (n=2,650) in patients with stable or unstable coronary artery disease, aiming to determine whether genetic testing could identify the best anti-platelet therapy in these individuals. In the genotype-guided group, CYP2C19 *2 or *3 carriers received ticagrelor 90 mg twice a day or non-carriers received clopidogrel 75 mg daily. In the standard therapy group, patients received clopidogrel 75 mg daily and underwent genotyping test at 12 months. The primary outcome was cardiovascular death, myocardial infarction, stroke, stent thrombosis or recurrent ischemia in 12 months. The primary outcome and the incidence of bleeding were not different between the treatment groups. However, it is worth mentioning the 34% reduction in these events at one year and a 40% reduction in the number of events per patient in the genotype-guided group. Finally, a post-hoc analysis revealed a reduction of approximately 80% in the adverse

event rate in the first three months of treatment in the group of patients randomized to the genotype-guided therapy arm.[92,93]

Beta Blockers

This class of medications has been extensively used in the treatment of cardiac arrhythmias, chest pain, myocardial infarction, and hypertension.[94] The genes associated with individual response to beta blockers include the CYP2D6, the beta-1 adrenergic receptor (ADRB1), the beta-2 adrenergic receptor (ADRB2) and G protein-coupled receptor kinase 5 (GRK5).[95] For example, some beta-blockers, including propranolol and metoprolol, are metabolized by the CYP2D6, which very frequently presents with a 'loss of funtion' variant.[34] Evidence has suggested that hypertensive patients, homozygous for the wild-type allelic variant Arg389, showed a 3-fold greater reduction in diurnal diastolic pressure with metoprolol compared with carriers of the allelic variant Gly389.[96] Other findings,[97] despite not so consistent, indicated that patients homozygous for the ADBR1 Arg389 haplotype seem to present a more satisfactory response to the family of beta-blockers, with a better left ventricular ejection fraction as compared with carriers of the Gly389 allele.[97]

Regarding the skin color, the higher frequency of the Gly389 allele in African Americans compared with white skin may be a plausible explanation for the reduced response to beta blockers. Although ethnicity and polymorphisms of ADRB1 have been reported as independent predictors of responses to beta blockers,[98] further prospective studies to elucidate the role of these genetic variants in ethnicity-specific responses are needed.

Therefore, there are no recommendations for the use of PGx in guiding the use of beta blockers in heart failure treatment.

Statins

Statins represent a class of medications that target the HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) inhibition, and are used to reduce cholesterol levels, especially LDL cholesterol.[99] Combined with changes in lifestyle, these drugs are considered first-line therapy for primary and especially secondary prevention of CVDs. However, large interindividual variability has been observed in the extension of LDL reduction, explained, in part, by environmental and genomic factors.[100] Thus, a dose tailoring may be needed for each patient, to obtain a more effective response.

More recently, Licito et al.[101] evaluated association of the PGx profile and neuromuscular pain in 76 type 2 diabetes mellitus patients and previous CVD using anti-diabetic and anti-cholesterolemic agents, such as statin. Different variants were studied, including the SLCO1B1, ABCB1, ABCC8, and drug biotransformers of cytochrome P450 Family (CYP) including CYP2C9*2 CYP2C9*3 CYP2C8*3, and CYP3A4*22. Approximately 17% of 35 patients treated with statin had neuromuscular pain. The PGx analysis showed a lack of any correlation between candidate gene polymorphisms and toxicity, except for the SLCO1B1 T521C allele. Thus, when available, analysis of the SLCO1B1 T521C variant is suggested, to enable clinicians to optimize the therapy prescribed, aiming at minimizing neuromuscular pain and maximizing the benefits from statins.

Also, the most strongly associated variant (with SLCO1B1), c.521T>C, reduces SLCO1B1 transport function, which can affect statin clearance, resulting in increased risk for toxicity in skeletal muscle. A meta-analysis of nine case-control studies, involving 4,500 patients, showed that individuals with the variant allele C were likely to experience statin-related myopathy (CT + CC versus TT: odds ratio = 2.09; 95%CI = 1.27-3.43).[102]

Possible Barriers to the Implementation of Pharmacogenomics

Due to the advances in technology and sequencing techniques, the costs of PGx analysis have drastically reduced in the last years (Moore's law), facilitating its use in clinical practice. However, the relatively high cost of PGx tests represents a barrier to its wider implementation. Also, there is a lack of familiarity by healthcare providers, a lack of a platform standardizing investigation and academic thinking and an insufficient volume of studies demonstrating the benefits of PGx. Those are factors that contribute to a low acceptance.

Nevertheless, there is currently a global effort to overcome these obstacles, including the development of large studies,[103] like the UK's 100.000 Genomes Project,[104] the PREemptive PGx testing for prevention of Adverse drug REactions (PREPARE), with participation of seven European countries.[105] On the other side of the North Atlantic, in the United States, the Electronic Medical Records and Genomics (eMERGE),[106] the Network and the Implementation of Genomics in Practice (IGNITE),[107] and the Clinical Sequencing Evidence Generating Research Consortium,[108] are part of a series of projects funded by the National Human Genome Research Institute, with an estimated investment of at least U$ 775 million in genetic research from 2007 to 2022. In Asia, the South East Asian PGxs Research Network (SEAPharm) is a collaborative effort of five Asian countries to develop studies in PGx.[109] In general, these studies are aimed to define, provide and analyze evidence of the clinical usefulness of genomic sequencing to guide treatment, cost-efficacy and the costs of its broad implementation in clinical practice. Of the available results, a review including 44 cost-benefit analyzes showed that 30% of them showed cost-effectiveness and 27% even showed a cost reduction.[110] This may lead to an optimistic perspective of the future of PGx.

Among global initiatives' many contributions for the expansion of PGx in clinical practice, some of the crucial aspects worth to highlight are: education and training of healthcare providers, investment in technology, in research and in healthcare centers' structure. Projects involving PGx not only contribute to knowledge in the area, but also promote training of healthcare professionals to an adequate practice of genomic medicine, which requires the adoption of basic routines that may be less relevant to other medical specialties. For example, the involvement of family members in counseling and treatment planning, and confidentiality that ensures that genetic information is being used exclusively for the purpose of assistance (thereby avoiding the inappropriate use of PGx in relation to legislation, insurance, marketing or employment

relationship). Education and training play a central role for the acceptance of genomic medicine in clinical practice, and acceptance, in turn, is the key to. The effort for data generation is of significant help, but commitment and involvement of healthcare providers that seek excellence are essential. The scale and the progress of efforts and investments in the world make clear the importance and potential attributed to genomic medicine, as it may be considered a component of high-quality medicine and one of the cornerstones of precision medicine.

Final Considerations

1) Area of consensus: PGx tests may be helpful in the optimization of drug treatments, allowing greater pharmacological safety;

2) Area of controversy: whether PGx tests may be extensively applied, including for the prescription of medications whose benefits are not so clear;

3) Area of expansion: individual genotype data have become more and more available to consumers. This will probably increase the demand for a personalized prescription, indicating that prescribers should consider PGx data. For example, we can site the 100,000 Genomes Project. This amazing project will provide complete genome sequences that may someday be included in patients' medical records. This seems to be a valuable information in personalized prescription.

4) Promising research areas: development of novel drugs targeting specific genetic risk factors of diseases. These medications could be prescribed for individuals with a high-risk genotype. It is likely that PGx information become routinely available in the future, mainly in technologically advanced environments. This could influence the prescription of several drugs other than those requiring PGx tests prior to prescription.

Author Contributions

Conception and design of the research: Stein R; Acquisition of data and Writing of the manuscript: Stein R, Beuren T, Cela LR, Ferrari F; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Stein R, Beuren T, Ferrari F.

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

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Study Association

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ACE2 Expression and Risk Factors for COVID-19 Severity in Patients with Advanced Age

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Understanding the relationship between aging and COVID-19 severity is key from multiple perspectives: for the clinical management of patients with SARS-CoV-2 infection, drafting of health policies and repositioning of drugs and/or the development of potential therapeutic targets for this population. Focusing on the underlying molecular and pathophysiological mechanisms, we will discuss the potential risk factors that may contribute to COVID-19 severity in patients with advanced age: ACE2 (angiotensin-converting enzyme 2) expression, immunosenescence/inflammaging and the presence of multimorbidity or frailty.

ACE2, SARS-CoV-2 Infection and Aging

Abnormalities induced by aging in metabolic pathways may partly explain the higher rate of COVID-19 morbidity and mortality in elderly patients. These include those belonging to the renin-angiotensin system (RAS), given the crucial role that this system plays both in viral transmissibility[1] and in the pathogenesis of acute lung injury and its most severe form: acute respiratory distress syndrome (ARDS).[2]

ACE2 is known to act as a receptor for SARS-CoV-2 1 structural protein S (spike),[1] through which the virus gains access to the host cell. This mechanism involves interaction of viral S protein with ACE2 extracellular domain, triggering conformational changes that destabilize the cell membrane, allowing the internalization of SARS-CoV-2 and ACE2, viral replication, and cell-to-cell transmission.[1,3]

With aging, there is a considerable reduction in the expression of ACE2 in the lungs.[4] Knowing that ACE2 is the gateway to SARS-CoV-2, it can be affirmed that the greater the expression of ACE2 in the cell membrane, the greater the infectivity. However, despite the decline in tissue ACE2 expression with age, elderly patients have greater severity of lung damage and higher lethality rate from COVID-19 compared to young individuals.[5] A possible explanation to this apparent inconsistency between old age, level of tissue ACE2 and severity of SARS-CoV-2 infection[6] is that younger people with higher ACE2 expression are more likely to have the infection while elderly individuals, with lower ACE2 expression may present more severe conditions when infected due to exacerbated effects mediated by Angiotensin II (Ang II). This is supported by the fact that, with aging, in addition to reduced tissue ACE2 expression, there is greater activation of pro-inflammatory signaling pathways resulting from hyperactivity of the ACE/Ang II pathway.[7-9] Also, there is ample evidence of the protective role of ACE2 against pulmonary insufficiency and a causal relationship between the ACE/Ang II pathway and ARDS, established in animal models.[10,11] The complex interrelationship between ACE2, SARS-CoV-2 infection and aging is illustrated in Figure 1.

Immunosenescence, Inflammaging and COVID-19

Significant abnormalities in the immune system, which affect both innate and adaptive immunity, have been associated with aging. This set of abnormalities are broadly referred to as immunosenescence, characterized by a decline in immune system responsiveness, leading to more serious viral and bacterial infection outcomes, and increased incidence of autoimmune diseases, neoplasms, and others.[12]

Based on current knowledge of the abnormalities caused by immune system senescence, and based on studies related to the pathophysiology of COVID-19, it is possible to come up with explanations about the high frequency of severe cases in the elderly or patients with chronic diseases. Healthy individuals in general, in contrast to the elderly and immunosuppressed, have efficient innate immunity, which, associated with intact cellular and humoral immunity, limit the progression of infection and recovery in a few weeks. This controlled immune response supposedly acts in the initial phase of the infectious process, limiting viral replication and dissemination, which, unfortunately, frequently occur in the elderly critically ill from COVID-19.[13,14] In the elderly, weakened innate and adaptive immune systems would allow higher and persistent viral loads — an assumption that is in line

Keywords

Aging; COVID-19; Immunosenescence; Frailty; Multimorbidity.

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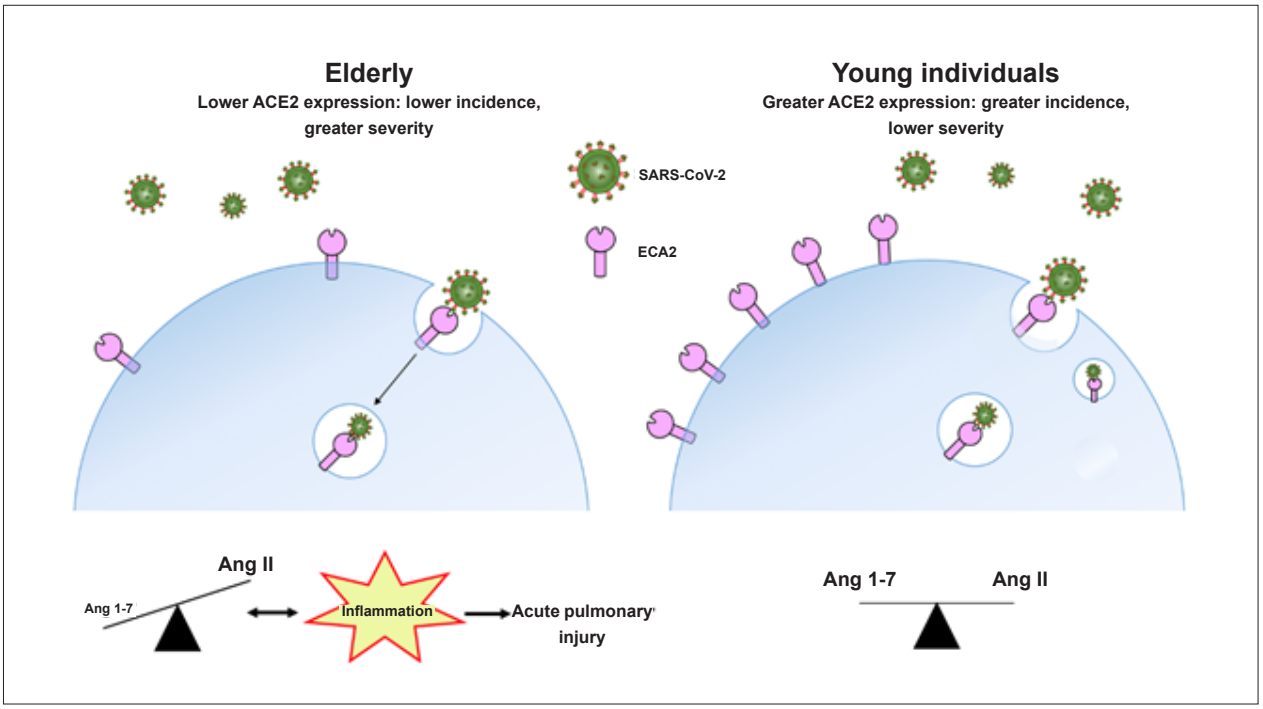

Figure 1 – *Association between age, ACE2 expression and COVID-19 severity. Reduced expression of ACE2 in the membrane of pulmonary epithelial cells (type II pneumocytes) with aging increases the levels of angiotensin II (Ang II) to the detriment of Ang-(1-7) formation, exaggeratedly triggering pro-inflammatory pathways and predisposing elderly patients to greater severity of acute lung injury and mortality from COVID-19. Such predisposition is enhanced by the fact that SARS-CoV-2 binding to ACE2 leads to the internalization of both, further reducing the expression of this enzyme in the cell membrane. In young patients, expression of ACE2 in the cell membrane is greater than in the elderly, enabling a balance between the actions of Ang II and Ang-1-7. Greater expression of ACE2 may cause increased infectivity by SARS-CoV-2, but the generation of Ang-1-7 triggers anti-inflammatory effects that are opposed to those of Ang II, protecting young individuals against the development/progression of acute lung injury. This model is hypothetical and has not been validated experimentally.*

with a recent description of patients with COVID-19, in which the viral load detected in the posterior oropharynx correlates with age.[15] This increased viral load represents intense and persistent antigenic stimulus in the elderly, concomitantly with lower immune system regulation. The relationship between changes in the immune system, advanced age and COVID-19 severity is shown in Figure 2. To better understand this, it is necessary to define and describe the processes of immunosenescence and inflammaging.

Dendritic cells (DC) are cells of the innate immune system that connect the innate and adaptive immune systems[16] — this cell subtype seems important in the host's defense against SARS-CoV-2, given the location of this cell type (present in the skin, nasal cavity, lungs, peripheral blood, the sites where we can find the virus). In the elderly, DCs: 1) have poorer phagocytic capacity — which may result not only in a less efficient immune system response, but also in reduced physiological capacity to remove proper components (including apoptotic cells); 2) are less able to instruct an adaptive immune response through coordinated signaling; 3) remain capable of secreting inflammatory cytokines under stress conditions, contributing to a chronic inflammatory state.[17-19]

In addition to DCs, monocytes and macrophages act on innate immunity by producing pro-inflammatory cytokines and processing and presenting antigens to T lymphocytes. With aging, there may be reduced generation of macrophage precursors and their phagocytic function.[20] Signaling dysregulation by Toll-like receptors (TLR) has also been described, generating insufficient production of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and contributing to poorer activation of essential immune cells in immune response, such as lymphocytes.[21]

Senescence also causes an imbalance in Natural Killer (NK) cell populations — which play an early role in the immune response to infectious processes and participate on orchestrating the subsequent steps of the adaptive immune response. There is an increase in the subtype CD56dim (high cytotoxic capacity) and a decrease in the subtype CD56bright (low cytotoxic capacity, but with high immunoregulatory activity through secretion of cytokines and chemokines) impacting both adaptive immune response and regulatory capacity of the immune system.[22-25]

In addition to changes in innate immunity, aging directly impacts the adaptive immune response mediated by T and B lymphocytes. Elderly people are known to have attenuated antibody production and reduced vaccine response. Several mechanisms contribute to this deficiency: 1) the balance between different subtypes of B lymphocytes is altered, with a higher proportion of memory B cells, which produce large amounts of inflammatory cytokines and contribute to the status of systemic inflammation in this population (these cells possibly have a role in the generation and maintenance

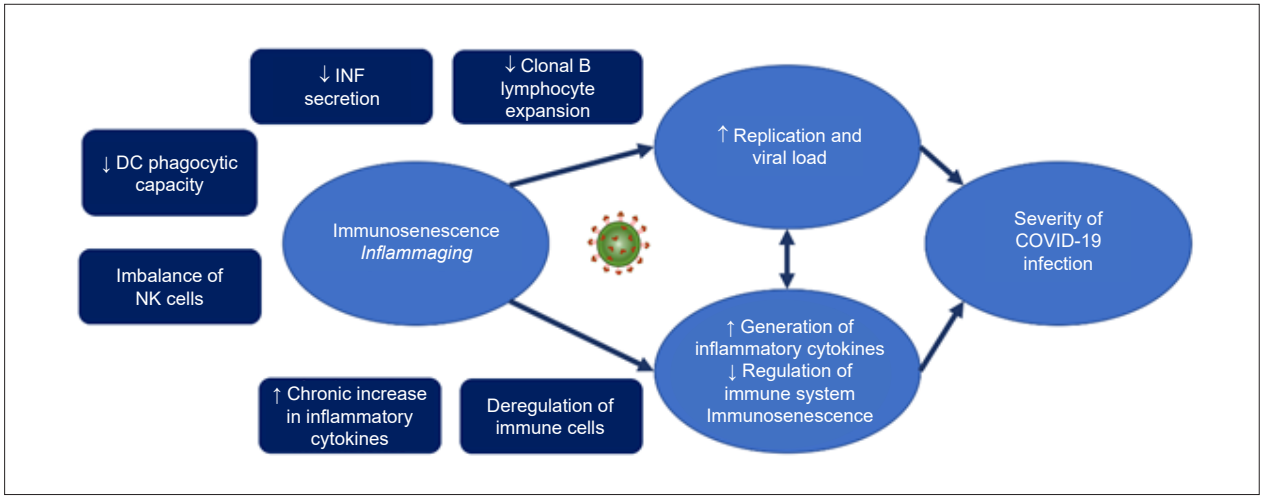

Figure 2 – *Relationship between immunosenescence, inflammageing and severity of infection by COVID-19. Note that changes in the immune system and inflammatory status can contribute to the severity of the infection both by impacting viral replication and by increasing inflammatory cytokines.*

of systemic inflammation, known as inflammaging);[26] 2) Naïve B lymphocytes in the elderly are capable of producing IL-10 and TNF-α with physiological stimulus, while naïve B lymphocytes in young individuals require more potent stimuli; 3) plasmocytes have reduced clonal expansion with aging, culminating in the production of antibodies with lesser antigenic affinity;[27,28] 4) decreased B lymphocyte repertoire caused by increased memory cell compartment impacts the ability to respond to new antigenic stimuli. Reduced primary humoral response capacity, in turn, is associated with disturbances both in the switch of immunoglobulin class and in the generation of specific antibodies with different functions. Therefore, there is greater susceptibility to infections.[29]

In patients affected by the severe form of COVID-19, lung parenchyma damage would be caused mainly by severe inflammatory response and less by the direct virus action. Exacerbated immune (or immunopathogenic) response partly accounts for severe pneumonia, respiratory failure in these individuals, and often for disorders in other organs and systems. One of the problems related to aging is that some elderly people or patients with chronic diseases are unable to modulate inflammatory immune response, leading to an overflow of immune cells and inflammatory cytokines in the lungs, an event called "cytokine storm".[13] Several of the cytokines described in the context of inflammaging, such as IL-6, TNF-α and interferon gamma (IFN-γ) participate in this storm of cytokines. IL-6 is also related to frailty, loss of muscle mass, cognitive decline and risk of hospitalization for pneumonia, frequent manifestations in frail elderly people. This cytokine triggers inflammation and tissue injury, which may facilitate the invasion of pathogens.[30,31] Elderly people have high levels of TNF-α after stimulation with lipopolysaccharides (LPS) and IFN-γ.[32] This cytokine reduces the expression of CD28 by inhibiting its transcription (in which the molecular mechanisms are not yet well known).[32-34] In patients with COVID-19, increased levels of TNF-α, IL-6, IFN-γ and IL-10 have been reported; whereas reduced levels of these cytokines were related to the resolution of the disease.[35] Similar findings were described by Huang et al., but an even larger panel of inflammatory cytokines was analyzed and included interleukin 1 beta (IL-1β), IL-12 and monocyte chemoattractant protein 1 (MCP1).[36]

Multimorbidity

Individual-multimorbidity interaction is complex and interferes with the clinical management of patients with COVID-19. If in the routine follow-up of people with multimorbidity disease-disease, disease-treatment and treatment-treatment interactions should already be considered, in the context of infection with the novel coronavirus, an additional variable[37] is introduced, often accompanied by new organic dysfunctions and poorly understood effects.

In a theoretical example, one can imagine a 72-year-old patient with Hypertension, heart failure with reduced ejection fraction, chronic obstructive pulmonary disease (COPD), dyslipidemia, depression and mild cognitive impairment using statins, angiotensin II type 1 receptor blocker (ARB), beta-blocker, inhalation device with long-acting beta-2-agonist/inhaled corticoid and selective serotonin reuptake inhibitor (SSRI). If this patients is hospitalized with COVID-19 presents acute hypoxemic respiratory failure and requires admission to the Intensive Care Unit (ICU) with mechanical ventilation. Chloroquine and azithromycin are initiated and, during hospitalization, the patient presents acute confusional state, acute kidney failure and ventricular arrhythmia. Figure 3 exemplifies the various possible interactions in this scenario (interaction between diseases (blue lines), interaction between treatment for one disease impacting another disease (black lines) and interactions between treatments (red lines). This complex scenario illustrates the importance of patient-centered care to define the therapeutic plan, given that interactions between diseases and treatments can be harmful to patients with multimorbidity.[37,38]

Although the available information suggests an association between multimorbidity and severity of COVID-19, it is still unclear whether there are specific situations in which the

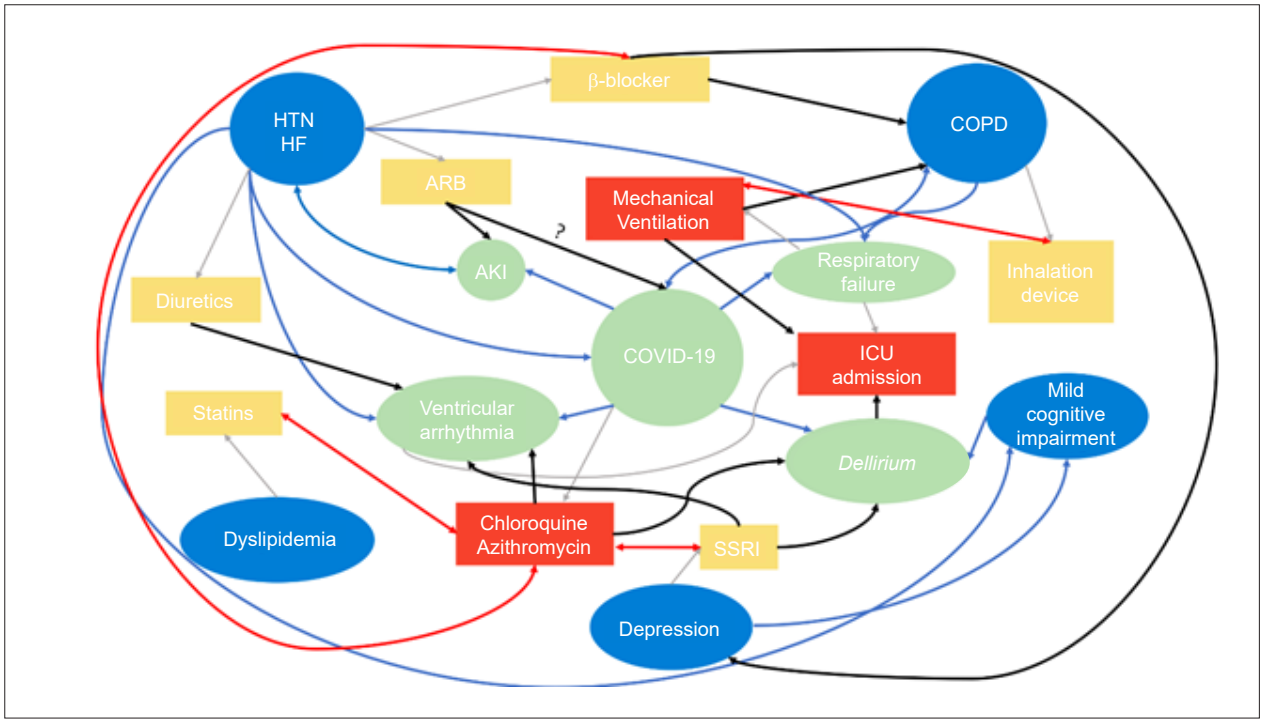

Figure 3 – *Theoretical model of a patient with multimorbidity with COVID-19. Blue balloons represent chronic diseases; green balloons, COVID-19 complications; yellow rectangles, treatment for chronic diseases; and red rectangles, new therapy initiated on admission. Gray lines represent usual treatment based on the disease; blue lines, potential disease interactions; red lines, potential interactions between the proposed treatments; and black lines, potential interactions between the proposed treatment for two different diseases. COPD: chronic obstructive pulmonary disease; HTN: Hypertension; HF: heart failure; AKI: Acute Kidney Injury; SSRI: selective serotonin reuptake inhibitor; ICU: intensive care unit. Adapted from.[37,38]*

treatment of chronic diseases may have a beneficial effect on infection control (e.g.: HIV using antiretroviral, permanent atrial fibrillation using oral anticoagulation). Thus, while there is no more information about SARS-CoV-2 infection, care should be taken before untimely suspending medications to which the patient is accustomed. The healthcare team is responsible for weighing, on a case-by-case basis, the risks and benefits of each drug in use in view of possible interventions against COVID-19. This avoids the unwanted cascade in which disease number 1 (COVID-19) is controlled today and diseases number 2, 3, 4 ... (chronic diseases) become even bigger problems tomorrow.[37-39]

Frailty

Although every elderly person has some risk of developing frailty, it is more common among those with multimorbidities, physical inactivity and inadequate nutrition.[40] Frailty is associated with a chronic pro-inflammatory state characterized by increased cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), whose levels can predict loss of functionality and other adverse health outcomes.[41] Taking this information into account, and knowing that there are outcomes suggesting an association between high levels of IL-6 and higher mortality in individuals with COVID-19,[42] frailty is likely a more robust prognostic marker than age, in the disease.

Unfortunately in the context of a pandemic, during which clinical decisions and limited resources need to be arranged quickly, it is common for purely age criteria to be used to define the best candidates for certain managements.[43] However, it is essential to understand that the geriatric population is much more heterogeneous than other age groups, and that, therefore, it is not possible to determine an automatic correlation between age and the potential for treatment benefits.[43] This caveat is particularly true when treatment includes general clinical support measures and proper medical and hospital assistance, as in COVID-19.

On the other hand, classifying people of the same age group according to frailty, at different levels of risk for adverse outcomes, can assist in the prognostic assessment of those infected with COVID-19. Its identification is possible through simple scales, such as the FRAIL scale and the Frailty Index, as these screening instruments are currently validated for filling in information from patients, family members or medical records, an interesting flexibility in a scenario where isolation measures are necessary.[44,45]

The identification of frailty from the emergency care unit can help understand acute illness in the context of an individual's baseline health conditions, hence helping the team to predict adverse events. Therewith, it is possible to implement interventions aimed at preventing these adverse events and guide the decisions on allocation of resources.[46] Such work is part of the global assessment of the elderly, the cornerstone in the multidisciplinary teams' work of managing

medications, preventing falls and delirium, and implementing care transitions.

Frailty syndrome has not been sufficiently studied in the context of COVID-19. Exploring its usefulness for assessing prognosis and defining the proportionality of support measures can be a fundamental step so that health professionals may act with justice and security, without omission or negligence in the application of health resources.

Prospects

It is clear that the elderly will be those who will be most impacted by the pandemic, regarding morbidity and mortality — this includes different aspects discussed in this study, connected in some aspects and acting synergistic in others: expression of ACE2 and renin-angiotensin system, immunosenescence, inflammaging, multimorbidity and frailty, summarized in Figure 3.

The SARS-CoV-2 imposes a range of challenges on health system managers, government officials, health professionals and society in general. In a scenario with finite resources and saturation of health services, a rational allocation of the health system will be necessary.[47] Decision-making, however, should never be based solely and exclusively on an individual's chronological age — healthcare professionals relocated to see patients with COVID-19 must be familiar with the application of frailty scores determined by their institutional practice and complete mandatory training. Cardiologists are aware of the impact of frailty in the treatment of cardiovascular diseases.[48,49]

The knowledge generated during this pandemic can be essential to provide answers about the peculiarities of aging in several other contexts. Human, technological and scientific community engagement is possibly the greatest in our history and this unique resource may allow the implementation of new therapies, vaccines, expand our diagnostic capacity with an inestimable impact on the health of the elderly, both for COVID-19 and for other diseases related to aging.[50]

Author Contributions

Conception and design of the research: Tavares CAM, Avelino-Silva TJ, Girardi ACC, Jacob Filho W; Acquisition of data: Tavares CAM, Avelino-Silva TJ, Benard G, Fernandes JR, Cardozo FAM, Girardi ACC, Jacob Filho W; Writing of the manuscript: Tavares CAM, Avelino-Silva TJ, Benard G, Fernandes JR, Cardozo FAM, Girardi ACC; Critical revision of the manuscript for intellectual content: Tavares CAM, Avelino-Silva TJ, Benard G, Girardi ACC, Jacob Filho W.

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COVID-19, Renin-Angiotensin System, Angiotensin-Converting Enzyme 2, and Nicotine: What is the Interrelation?

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The World Health Organization (WHO) declared COVID-19, an infection caused by the new Coronavirus (SARS-CoV-2),[1] as a pandemic on March 11, 2020. By the beginning of June, 7 million positive cases and around 400 thousand deaths from the disease had been reported worldwide.[2] In the same period, Brazil accounted for approximately 700 thousand cases and 40 thousand deaths.[3]

Although the virus can infect individuals of any age, so far the most serious cases have been described in people aged 55 and over, with associated comorbidities—many of them related to the cardiovascular system.[4,5] Therefore, the medical community's great concern about knowing how to act against COVID-19 is justifiable, especially in this population at higher risk and with many cardiovascular comorbidities, and the aim is reducing morbidity and mortality rates.[4,5]

SARS-CoV-2 uses as a cell receptor the angiotensin-converting enzyme type 2 (ACE-2),[6] a molecule abundantly expressed on the surface of cells in the endothelium, kidneys, lungs, and other organs. It is a component of the renin-angiotensin system (RAS), whose genomic sequence was discovered in 2000.[6] Since then, a compensatory axis of the classic actions of the RAS ("protective" axis) was recognized to counteract the harmful axis caused by production angiotensin 2. From a structural point of view, ACE-2 is similar to the classic one; but, from the functional point of view, they are opposed.[7] This is because ACE converts angiotensin 1 into angiotensin 2 and causes deleterious effects resulting from the stimulation of AT1 receptors, such as increased sympathetic activity, salt and water reabsorption, vasoconstriction, inflammation, aldosterone and vasopressin release, all contributing to tissue fibrosis, endothelial dysfunction, and arterial hypertension.

Keywords

COVID-19; Coronavirus/complicações; Betacoronavirus, SARS-CoV2; Syndrome Respiratory Acute; SARS-CoV2.

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ACE-2 breaks down angiotensin 2 into its metabolites, including angiotensin (1 to 9) and angiotensin (1 to 7), and activates MAS receptors (MasR), which are potent vasodilators and therefore can be a negative regulator of SARS.[7] ACE-2 is expressed in a variety of different tissues, including the upper and lower airways, the myocardium and the gastrointestinal mucosa.[8] Although its function in human health and disease has not been fully elucidated, it appears to have an important regulatory role in blood pressure and cardiac function. The physiological role of ACE-2 in the airways is still unclear, but, in mice, it was shown to protect against severe lung injury related to aspiration and sepsis.[9]

The issues underlying the relationship between increased availability of ACE-2 receptors and possibly greater susceptibility to SARS-Cov-2[2] infection are widely debated in cardiology, as the use of drugs as angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor blockers (ARB) increases the expression of ACE-2 receptors in different tissues such as the lung,[10] although it is fundamental for the treatment of arterial hypertension and heart failure.[11,12] Discussions about the replacement of these drugs have taken place during the pandemic; however, due to their relevance in terms of efficacy and safety in the treatment of cardiovascular diseases and, to date, the absence of evidence of a relationship between their use and the increase in mortality by COVID-19, there is a consensus[13] regarding their maintenance until there is reliable evidence that indicate otherwise. In fact, the good news is that studies even suggest a protective effect of ACE inhibitors in reducing mortality during SARS-CoV-2 infection, and no evidence of increased risk in ARB users.[14]

It is interesting to note that another very relevant and controversial aspect also involves the expression of ACE-2 and is related to smoking. Some authors[15,16] have raised the hypothesis that the low prevalence of smokers hospitalized with COVID-19 in China and France, in comparison with the higher prevalence of smoking in the general population, may be related to the lower expression of ACE-2 caused by nicotine.[17] Oakes et al.[17] reviewing the effects of nicotine and RAS, demonstrated that inhaled nicotine alters the SARS pulmonary homeostasis by stimulating its classic axis (increased expression and concentration of ACE-2) to the detriment of the protective axis (reduced expression and concentration of ACE-2 and angiotensin 1-7), thus determining less expression of ACE-2. Thus, supporters of the hypothesis[16] of a "protective" effect of nicotine speculate that this would make it difficult for SARS-Cov-2 to adhere to the respiratory epithelium. It should be noted that the average age of patients hospitalized with COVID-19 is higher,[4] and the prevalence of smoking drops significantly with aging, because smokers either die early[18] or stop

smoking when they get sick.[18] Again, this is a paradox involving the expression of ACE-2 receptors and RAS.

In this context, some questions remain unanswered: are there epidemiological data that indicate this "protective" effect? What is the action of nicotine on the RAS in the bronchial epithelium? Is the relationship between ACE-2 expression in the pulmonary epithelium similar between smokers and non-smokers? What are the consequences of the interruption in RAS homeostasis by nicotine in the lung?

Data on mortality show a higher risk of death from COVID-19 among smokers with or without chronic obstructive pulmonary disease (COPD),[19-21] and the risk of intubation is doubled[19] when comparing smokers with non-smokers. These data corroborate what occurs in other viral infections, with a worse course in smokers.[22,23] Considering the complexity of RAS, nicotine can affect elements other than those discussed, causing effects not yet elucidated.

Recent studies have shown increased expression of ECA-2 in the epithelium of small airways in smokers and COPD patients with COVID-19. Brake et al.,[24] using immunohistochemistry, identified for the first time an increased expression of ACE-2 in the lung tissue of patients with COVID-19. However, it was higher in COPD patients, whether they were smokers or not, and was present in a lesser extent in smokers without COPD. There was no increase in the expression of ACE-2 in nonsmokers. Leung et al.[25] also reported a greater expression of ACE-2 in the epithelium of the small airways of patients with COPD and smokers with COVID-19, analyzing bronchial lavage material and correlating this with the severity of the disease. Russo et al.[26] investigated *in vitro* the mechanism by which nicotine could lead to an increase in ACE-2 in this population. Different airway cells, such as bronchial epithelial cells, type 2 alveolar epithelial cells, and interstitial fibroblasts express nicotinic acetylcholine receptors (nAChR), specifically the α7-nAChR subtype, and also the components of the RAS. By quantifying the expression of ECA-2 in cultured bronchial epithelial cells, they demonstrated that nicotine promotes a positive regulation (increased expression of ACE-2) mediated specifically by its binding with α7-nAChR receptors. Thus, smoking could cause an increase in the cellular uptake mechanism for SARS-Cov-2 by signaling the α7-nAChR pathway.

With these data, the reasoning would be that patients who smoke and have COPD would, in fact, be more susceptible to SARS-Cov-2 infection. This mechanism was formulated and represented in a schematic model (Figure 1) by Olds and Kabbani[27]

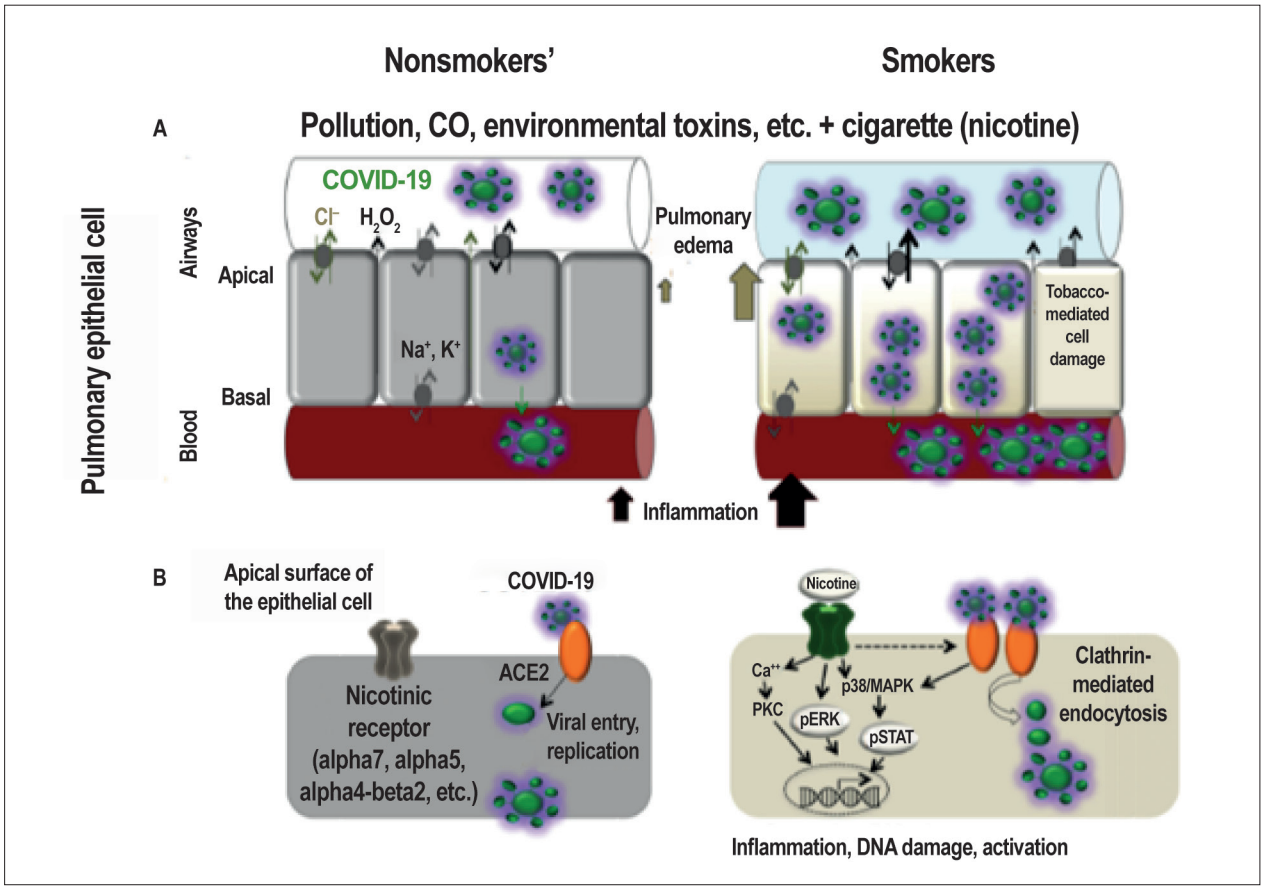

Figure 1 - *Schematic model of how exposure to nicotine increases the risk of SARS-CoV-2 entering the lung of the human host. A. Pulmonary and immune responses to virus infection in smokers' (right) and nonsmokers' (left) epithelial cells. B. Cellular mechanisms triggered by the activity of nicotinic receptors promote the entry and proliferation of SARS-CoV-2 in epithelial cells through the co-expression of ACE-2. The activation of nicotinic receptors by nicotine can cause greater activation of proteases, cell death (apoptosis) and inflammatory signaling through mechanisms that converge in ACE-2 regulation and pathways signaling.*

and explains how exposure to nicotine increases the risk of the virus entering the lung cells and, consequently, how smoking can have a negative impact in the pathophysiology of COVID-19.

In this context, we can interpret that the role of the RAS in the severity of SARS-CoV-2 infection depends less on the expression of ACE-2 in the cardiovascular system and more on its expression in the respiratory epithelium. This may justify the non-interference in COVID-19 morbidity and mortality in ACEI and ARB users, as well as the lack of protection for this disease in smokers and COPD patients.

In addition to the therapeutic guidelines being to quit smoking and maintain cardiovascular medication, knowledge about the interrelation of nicotine with the expression of ACE-2 in the cells of the respiratory epithelium and its interface with α7-nAChR receptors suggests the possibility of therapeutic actions for the treatment of COVID 19. The use of selective α7-nAChR antagonists such as methylglycaconitin[28] and α-conotoxin[29] can significantly alter the expression of ACE-2, and may be a therapeutic option to prevent the entry of SARS-CoV-2 in the respiratory tract epithelium. Further studies should confirm or not these hypotheses.

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Safety of Interventional Cardiology Procedures in Chronic Coronary Syndrome during the COVID-19 Pandemic

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Cardiovascular disease (CVD) is the leading cause of mortality in Brazil and in the world, with increased morbidity and well-defined risk factors. Acute coronary heart disease has very well-established indications for interventional treatments. In chronic coronary syndrome (CCS), the indications for intervention are based on the degree of ischemia and the symptoms of each patient.[1,2] The pandemic triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, has radically changed the indications for interventional procedures, regardless of clinical presentation.[3]

Wide community transmission, severe involvement and complexity of the disease, and a mortality rate that may reach up to 12% in risk groups, mainly those with CVD, have been observed.[3] COVID-19 has triggered a paradigm shift in cardiology care worldwide, especially in interventional cardiology settings.[4-8]

In acute coronary syndrome (ACS), there has been a significant reduction in the number of patients seeking emergency rooms, perhaps due to fear of infection or even because they were less symptomatic during lockdown. Delays in the public service regulation system have also occurred, certainly caused by overload in hospital admissions.[6] Conversely, interventional cardiology departments have restricted care to these patients, and new routines have been created to perform interventions only in more severe situations, with real demobilization in chest pain protocols.[7,8] Many tertiary care hospitals have recommended thrombolysis rather than primary angioplasty, and others have performed interventional procedures only after rapid testing to exclude SARS-CoV-2 infection. All actions have been supported or guided by interventional cardiology societies worldwide.[4,5,7,8]

Invasive diagnostic tests have been fully suspended for elective patients with CCS, with no schedule for appointments. This has occurred in the Brazilian Unified Health System (SUS), whose suspension of elective appointments has also had an indirect impact on the reduction in procedures. In the private health insurance system, authorization passwords have been suspended by several insurers.

Acknowledging that patients with CCS are less severe does not represent the data seen in the literature, which demonstrate incidence of significant obstructions in more than 50% of cases.[9-11] In contrast, we found no data suggesting interventional procedures for stable individuals during the pandemic. Based on the assumption that procedures in patients with CCS should not be delayed, as they potentially have severe coronary heart disease, we organized a cohort of patients to conduct effective guidance during appointments. Regardless of the stage of social distancing imposed by the pandemic, the procedures were conducted in the safest way possible. Our primary objective was to evaluate whether performing coronary angiography with or without percutaneous coronary intervention (PCI) was safe regarding the risk of SARS-CoV-2 infection in an initial population of 105 SUS patients with CCS. We analyzed clinical profile, angiography results, need for revascularization, mortality, and whether tests were suspended due to diagnosis or suspicion of the infection.

Methods

In this prospective study conducted during the COVID-19 pandemic, 105 SUS patients with CCS undergoing elective coronary angiography at a teaching hospital between March and May 2020 were evaluated. Four patients were excluded for not attending the test on the scheduled date. All patients were previously evaluated by a cardiologist in a medical appointment, including data on each patient's clinical profile. During the appointment and when signing the informed consent form, patients were advised to make social isolation, and the guidance was understood by all. The procedures were performed safely with both staff and patients wearing personal protective equipment (PPE). The approaches were taken based on the coronary lesions. Those above 70% of the lumen in epicardial coronary vessels and those above 50% in the left main coronary artery (LMCA) were considered severe. The lesions were assessed by two or more experienced observers. The assessment of clinical symptoms for presence of COVID-19 was made during the appointment, in the hospital stay, and after 15 days of being at the hospital. The guidance for performing the test was scheduled only in case of suspicion of the disease. The study was approved by the institution's research ethics committee (registration number: CAAE 31784420.7.0000.5259; opinion number: 4.035.853).

Keywords

Pandemics; SARS- CoV-2; Betacoronavirus; Coronary Artery Disease/mortality; Percutaneous Coronary Intervention; Health Profile

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Statistical analysis

Data were analyzed using IBM SPSS, version 25.0. Continuous variables were described as mean and standard deviation, and categorical variables were described as absolute numbers and percentages.

Results

In total, 194 precatheterization outpatient appointments were made and 105 patients had their tests scheduled between March and May 2020. With regard to appointments, two patients (1.03%) had flu-like syndrome on the day of the appointment and were advised to maintain isolation at home for 15 days and to seek care at the hospital if their condition deteriorated. Both patients did not attend the scheduled test and no further information was obtained about their progress. Two other patients missed the exam and there was no further contact. Onde hundred and one patients attended the test. One patient had cardiovascular death before the procedure (ventricular tachycardia). We considered 101 patients for analysis, including 100 patients undergoing catheterization either combined with PCI or not and 15 (14.8%) admissions for the procedure. There were 11 PCIs and 3 coronary artery bypass grafts (CABGs). Mean age was 61.88 ± 10.3 years, and 51.5% were male. Hypertension, diabetes mellitus, and dyslipidemia were the most prevalent risk factors for coronary artery disease (CAD) (Table 1).

The prevalence of obstructive CAD was 54%, of which 22% had triple-vessel involvement, with 8% involving the LMCA and 35% involving the left anterior descending artery (LAD) (Table 2). In patients with LMCA involvement, 87.5% were associated with multivessel CAD and only one patient had isolated stenosis in the LMCA (Figure 1). Obstructive CAD was found in 66.6% of men and 40.8% of women. CAD occurred in 63% of patients aged > 60 years. Radial access was used in 97% of cases.

PCI or urgent CABG was performed in 14% of patients with obstructive CAD. Of all PCIs performed, 70% treated only one vessel.

Among the eight examiners and staff members, none had suspected or confirmed COVID-19 during the study. None of the admitted patients had COVID-19 symptoms during hospitalization. All patients who underwent procedures were kept in isolation according to previous guidance. Regarding the patients who underwent the procedure, none had flu-like syndrome within 15 days of the test.

Discussion

This preliminary study showed safety for both patients and staff in conducting elective tests, even during the

Table 1 – General characteristics of the population

Baseline characteristics		Patients analyzed (N = 101)
Age (years)		61.88 ± 10.3
Male		52 (51.5)
Female		49 (48.5)
Smoking		19 (18.8)
Hypertension		89 (88.1)
Diabetes mellitus		41 (40.6)
Dyslipidemia		31 (30.7)
Previous AMI		31 (30.7)
Previous Cath		8 (7.9)
Previous CABG		7 (6.9)
Clinical presentation		
SA		101 (100)
NIT		
Performed		37 (37)
	Obst. CAD	19 51.4
	No obst. CAD	18 48.6
Not performed		63 (63)
	Obst. CAD	35 (55.6)
	No obst. CAD	28 (44.4)

Values shown as n (%). AMI: acute myocardial infarction; CABG: coronary artery bypass graft; CAD: coronary artery disease; Cath: coronary catheterization; NIT: noninvasive test; Obst.: obstructive; SA: stable angina.

Table 2 – Angiographic characteristics and approaches

Angiographic characteristics		Procedures (N = 100)
Cath		89
Cath and PCI		11
	Ad hoc	4 (36.4)
	Urgent	7 (63.6)
CABG		3
Death		1
	Single-vessel	20
	Double-vessel	12
	Triple-vessel	22
Location of lesions in the arteries		
	LMCA	8
	LAD	35
	LCX	32
	RCA	32
Access routes		
	Radial	97
	Femoral	3

Values shown as n (%). CABG: coronary artery bypass graft; Cath: coronary catheterization; LAD: left anterior descending artery; LCX: left circumflex artery; LMCA: left main coronary artery; PCI: percutaneous coronary intervention; RCA: right coronary artery.

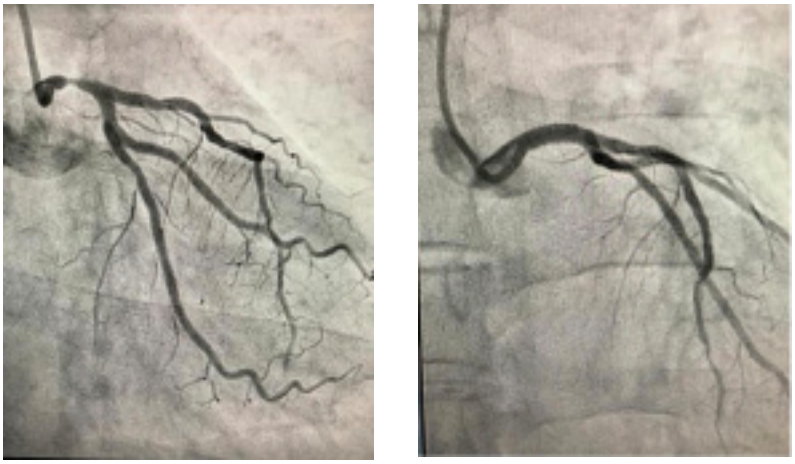

Figure 1 - *coronary angiography in two projections showing a 75% lesion in the left main coronary artery (LMCA) and then following 4.0 x 12 mm drug-eluting stent implantation in the LMCA.*

pandemic. We do not have comparative data because there are no studies in the Brazilian literature evaluating this type of population. By evaluating all the patients in this series, we observed that, despite CCS, a significant percentage of 14.8% of the patients had serious events, including 1 death and 14 indications for admission for immediate (ad hoc) revascularization or within the first week following the procedure, 3 of which were indicated for surgery. The mean age of 61.8 years and the higher incidence of hypertension and diabetes mellitus were similar to those of other studies of patients undergoing coronary angiography.[9,10]

The rate of normal test results (46%) was within that found in the literature according to a study conducted by Costa et al.,[9] who investigated a cohort of 1844 patients undergoing coronary angiography. Those authors also found a significant percentage (52.9%) of severe CAD in CCS.

Sant'Anna et al. reported 45% of normal coronary arteries in an evaluation of 503 patients, but the prevalence was found in a population consisting of young, female, nonsmoker patients.[10] An American study[11] of 1 989 779 tests found a prevalence of moderate-to-severe CAD of 41.0% in patients with CCS. Regarding patients with obstructive CAD, 26% required urgent intervention because of the severity of the lesion.

The presence of LMCA disease (8%) and triple-vessel involvement (22%) exceeded expectations for stable patients, as well as the occurrence of 1 death before the test. Also, the severity of LMCA disease does not correspond to that found in patients with CCS, and 1 patient was treated urgently by percutaneous route (Figure 1). Approximately 74% of patients with indication for CABG or PCI were advised to have their procedures scheduled electively. Among those with obstructive CAD (54%), only 26% (14) have already undergone a procedure for revascularization, and 74% (40) have known obstructive coronary anatomy awaiting a procedure.

The guidelines for ACS care during the pandemic are better established, with the support of several cardiology societies, always respecting the balance between staff's exposure and patient's benefit.[3,4,6,7] In cases of ST-segment elevation myocardial infarction (STEMI) and active COVID-19, fibrinolysis may be considered an option in relatively stable patients.[3-6] In unstable patients or those with potential clinical deterioration, primary PCI should be performed. In a national multicenter study involving 54 hospitals in Italy, there was a significant reduction of 48.4% (319 x 618, $p < 0.001$) in the number of infarctions during a comparative week between 2019 and 2020; however, the number of fatal cases increased by 13.7% compared to 4.1% that was previously recorded in 2019 (RR = 3.3, 95% CI 1.7–6.6; $p < 0.001$).[12] A New York (United States, US) registry also showed increased mortality in households, about 8-10 times, compared to the same period in previous years.[13] These results are consistent with those of a Spanish registry[14] that showed a 40% reduction in STEMI cases and those of different US states whose reduction in admissions ranged from 38 to 48%.[13]

In non-ST-segment elevation myocardial infarction (NSTEMI), the reports also demonstrated a sharp decrease in the number of weekly admissions, as shown in the Italian study, in which the number reduced from 350 to 122 (65.4% reduction; 95% CI 60.3–70.3; $p < 0.001$).[12] The most accepted recommendation for NSTEMI is, if possible, performing COVID-19 tests before cardiac catheterization, and more severe patients should undergo early intervention.[3,4,6,7]

The recommendations for CCS interventions are less consistent and superficially consider that the procedures should be individualized and indicated only for high-risk patients.[6,8] Welt et al.[8] suggested reducing the number of procedures, with delays in elective cases, and dividing

the staff into shifts to rotate professionals, with a focus on reducing the risk of staff contamination.

Those restrictive measures for stable patients provided a comfort zone in relation to reducing the spread of COVID-19; however, in objective terms, we observed that coronary heart disease care was not included, with regard to the good practices established before the pandemic.

In Brazil, the pandemic has dramatically changed medical care in several specialties with suspension of elective procedures and appointments. Most medical professionals advised their patients, either private health insurance clients or SUS clients, to postpone their elective procedures and to seek emergency rooms in case of severe symptoms of chest pain, dyspnea, etc. This guidance undoubtedly protects individuals who remain asymptomatic or oligosymptomatic from SARS-CoV-2 but exposes patients who may need urgent care to infection. Conversely, individuals who believe their symptoms are not so severe or who are more tolerant of pain may be affected by a reckless reflection. In such cases, delaying care may have serious consequences, including cardiac death at home.

Resolution number 2004 of March 18, 2020 issued by the Rio de Janeiro State Health Department[15] suspended elective outpatient care services in public units but correctly maintained essential outpatient care services, including those of oncology and cardiology. Nonetheless, access to patients was affected and the resolution was not widely accepted. As a rule, SUS patients are more severe and have more risk factors. In those patients, there are great difficulties in separating those who are overall stable from those who may be affected by an acute condition requiring hospitalization.

It seems reasonable to us to preserve the capacity of hospital beds, avoiding unnecessary elective procedures in stable patients with significant comorbidities or in those whose post-intervention length of stay is more than 24 to 48 hours.However, despite being in line with most protective measures for patients and staff, we highlight that patients with CCS may require procedures and this warrants cautiously breaking the restrictive measures with no additional risks of exposure to the virus.

In this case series, an active search was made to select patients who were symptomatic, ischemic, and with multiple risk factors, thus preventing them from attending any type of appointment or going to an emergency room. We understand that such rapid action in the diagnosis and treatment of those patients was a measure that prevented a more severe outcome in terms of coronary events. Conversely, strict care and guidance provided in the appointment, reinforced isolation, procedural routines, and the attempt to reduce length of stay have minimized the risks of coronavirus infection.

In the health crisis triggered by COVID-19, there was no objective guidance on the performance of procedures in stable patients exactly because they were suspended or delayed. In our real-world experience, providing patients with suspected CAD with care based on clinical assessment and rapid knowledge of coronary anatomy should be done before any possible clinical instability. In this population, we clearly demonstrated that the risk of cardiac events to which patients were exposed was much greater than the possibility of having complications of the disease caused by the virus.

Although they do not determine that this is effectively the best approach, our data suggest a reflection so that care in catheterization laboratories during the pandemic is reassessed and not systematically suspended or delayed.

Limitations

The main limitations are the small number of patients, the low-prevalence variables that require much larger samples, and the fact that this is a single-center study. In addition, under the guidance of the Hospital Infection Control Committee, we did not perform COVID-19 tests on any of the patients and staff because they were all asymptomatic at the time of the procedure and remained as such for at least 15 days. Despite the limitations, this study may encourage other services to generate multicenter observations and analyses with greater statistical robustness.

Conclusions

As shown in this study, the performance of elective tests in patients with CCS was safe for both patients and professionals even during the pandemic, contrasting with most recommendations from other services. The study demonstrated that the anatomical angiographic evaluation revealed patients at high risk of morbidity and mortality, requiring interventions in those with complex lesions, thereby contributing to reduce the number of ACS in this population.

Author contributions

Conception and design of the research: Ferreira E, Mourilhe-Rocha R, Esporcatte R, Albuquerque DC; Acquisition of data: Ferreira E, Alves TS, Lacerda ALI; Analysis and interpretation of the data: Ferreira E, Alves TS, Mourilhe-Rocha R, Albuquerque FN, Spineti PPM, Setta DXB, Esporcatte R, Albuquerque DC; Statistical analysis: Ferreira E, Mourilhe-Rocha R, Spineti PPM; Writing of the manuscript: Ferreira E, Alves TS, Mourilhe-Rocha R, Albuquerque FN, Spineti PPM, Setta DXB, Esporcatte R, Albuquerque DC; Critical revision of the manuscript for intellectual content: Ferreira E, Mourilhe-Rocha R.

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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Thrombocytopenia-Related Problems in Patients with Concomitant Atrial Fibrillation Requiring Antithrombotic Prevention: A Retrospective Cohort Study

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Abstract

Low-dose edoxaban and enoxaparin sodium have been the subject of a retrospective comparison implemented with the propensity score technique in order to mitigate the effects of the differences in the basal clinical features of two cohorts and minimize the risk of bias.

Subsequently, using a Cox proportional-hazards model, the association of each type of therapy with the risk of the composite of all-cause death, stroke/transient ischemic attack, hospitalizations and major bleeding events was assessed. For this analysis, a p-value < 0.05 was considered statistically significant. Therapy with enoxaparin and liver cirrhosis as causing thrombocytopenia were associated with increased risk of the composite endpoint (enoxaparin: hazard ratio (HR): 3.31; 95% CI: 1.54 to 7.13; $p = 0.0023$; liver cirrhosis, HR: 1.04; 95% CI: 1.002 to 1.089; $p = 0.0410$). Conversely, edoxaban therapy was significantly associated with decreased risk of the composite endpoint (HR: 0.071; 95% CI: 0.013 to 0.373; $p = 0.0019$). Based on this retrospective analysis, edoxaban at low doses would appear as an effective and safe pharmacological tool for the prophylaxis of cardioembolic events in patients with AF and thrombocytopenia.

Introduction

A common problem is the presence of atrial fibrillation (AF) in patients suffering from thrombocytopenia, which obviously contraindicates the administration of full-dose anticoagulant drugs.[1] Moreover, in these cases, the implementation of an AF ablation program involves non-negligible risk, because the first three months following ablation, the so-called "blanking period," coincide with the need to administer, given the high risk of AF relapses, not only antiarrhythmics, but also anticoagulants at full doses.[2] Instead, the administration of fractionated low-molecular-weight heparin, namely enoxaparin sodium[3] at a dose of 4000 I.U. per day, appeared to be a viable option. Alternatively, a widely practiced therapeutic approach was the non-vitamin K antagonist edoxaban[4] at the prefixed dose of 30 mg per day.

In the present retrospective cohort study, which encompassed a median period of 40 months (interquartile range: from 36 to 48 months), 220 patients were included according to an arbitrary criterion, namely without doing power and sample size calculations. The patients subjected to edoxaban were 90 altogether, whereas 130 patients were assigned to enoxaparin.

The requirements for inclusion in the retrospective study were: moderate thrombocytopenia, defined by a platelet concentration between 99,000 and 30,000 thrombocytes per mm^3; chronic AF, subject to the rate control strategy; absence of newly diagnosed paroxysmal AF.

Recruitment of cases was based on the constitution of homogeneous groups according to the "propensity score matching" method[5] to decrease the risk of bias ensuing from the differences in the basal clinical features of the two groups. Patients on unfractionated heparin were paired to patients on a low dose (30 mg per day) of edoxaban with basal clinical features as similar as possible, with a 1:1 ratio. We applied a logistic regression model. Several variables were found to be significantly associated with the probability of belonging to one of the groups, based on a backward stepwise elimination ($p = 0.05$ cut-off) methodology. The following variables were finally used to calculate the propensity score for each patient: age and care level at index date, previous anticoagulant use, antianginal drug use, insulin use, stroke, hospitalization costs in the baseline period. Patients were matched 1:1 within gender-specific 5-year age groups, based on their propensity score with a maximum allowable difference of 0.001.

The statistical analysis subsequently adopted was the construction of a Cox proportional-hazards regression model. A composite endpoint was chosen including all-cause death, stroke/transient ischemic attack, hospitalizations and major bleeding events. The exposure variables taken into account were low-dose edoxaban therapy, enoxaparin therapy, hypertension, left atrium anteroposterior diameter > 40 mm, left ventricular ejection fraction < 40%, age > 85 years, liver cirrhosis as a cause of thrombocytopenia, Werlhof's disease as a cause of thrombocytopenia. In all statistical analyses, p value < 0.05 was considered to be statistically significant.

The calculations were made using Excel 2016 (version 16.0, Seattle, WA, USA) as well as MedCalc Version 18.6 (Acacialaan 22, 8400 Ostend, Belgium) and Epi-Info version 7.1.5.0

Keywords

Cohort Studies; Thrombocytopenia; Atrial Fibrillation; Anticoagulants; Edoxaban; Enoxaparine; Hemorrhage; Stroke; Liver Cirrhosis; Heparin/therapeutic use

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for Windows (Centers for Disease Control and Prevention, Atlanta, Georgia — USA). Increased risk of being affected by the composite endpoint was associated with exposure to the therapy with enoxaparin (hazard ratio (HR): 3.31; 95% CI: 1.54 to 7.13; p = 0.0023) and liver cirrhosis as causing thrombocytopenia (HR: 1.04; 95% CI: 1.002 to 1.089; p = 0.0410). Even hypertension was associated with increased risk (HR: 1.104; 95% CI: 1.011 to 1.966; p = 0.0477). Conversely, edoxaban therapy was significantly associated with decreased risk of the primary endpoint (HR: 0.071; 95% CI: 0.013 to 0.373; p = 0.0019).

Heparin is a non-negligible cause of thrombocytopenia. This seems to apply also to low-molecular-weight fractioned heparin, i.e., enoxaparin sodium, judging by the results we have found, which advise against the use of enoxaparin therapy in patients with documented thrombocytopenia. Furthermore, the ominous progression of liver cirrhosis might have played a role in causing a significantly higher risk of the composite endpoint. Indeed, the bleeding events due to the rupture of gastroesophageal varices are likely to have played a substantial role in determining the conclusive inference that the composite is unfavorably influenced by liver cirrhosis as an exposure variable. Vice versa, edoxaban therapy at low doses in thrombocytopenic patients has proved to be protective against the composite of all cause-death, stroke/transient ischemic attacks, hospitalizations and major bleeding events. The main limitation of the study is its retrospective nature, which does not allow to draw definitive conclusions about the comparison between enoxaparin and edoxaban due to the possibility of confounding by indication despite the fact that the propensity score matching technique has been adopted as a countermeasure. However, based on our retrospective analysis, edoxaban at low doses would appear as an effective and safe pharmacological tool for the prophylaxis of cardio-embolic events in patients with AF and thrombocytopenia.

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: De Vecchis R, Paccone A, Soreca S; Statistical analysis: De Vecchis R.

Potential Conflict of Interest

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Temporal Evolution of the iFR (Instantaneous Wave-Free Ratio) Employment Results Analysis

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Dear Editor,

We read with interest the short editorial written by authors Chamié and Abzaid[1] regarding the paper "Evaluation of Myocardial Ischemia with iFR (instantaneous wave-free ratio) in the catheterization laboratory: a pilot study".[2] The short editorial clearly translates to us the historical evolution reasoning that we must follow when interpreting coronary physiology studies in therapeutic decision-making. Although medicine is full of binary situations for resolution, such as the presence or absence of fever by the thermometer, it is very clear that different levels of values refer to different diagnoses, prognosis and treatments. With regard to coronary functional assessments, after an enormous amount of binary studies to demonstrate their validity, recent trials cited in the short editorial directed us to a phase where clinical decision-making power has an important weight once again,[3] and the dissertation of this change in direction occurred brilliantly in the editorial. We did not neglect the clinical reasoning and other factors in our study, since the stent placement predictor was iFR < 0.87 in this group, despite the cutoff value established for iFR being 0.89, with a significant reduction in the use of stent.

It is worth mentioning that our study was conducted with data collected from 2014 to 2018, covering a long period in which the iFR did not have a still well-established binary cutoff value. Until the publication of Swedeheart and Define-Flair trials in 2017, the values of iFR > 0.86 and iFR < 0.93 were considered as gray zone, where the guidelines for the method indicated the use of *fractional flow reserve* (FFR).[4,5] In this time scenario, the placement of stents in patients with value of iFR ≤ 0.92 cannot be considered unnecessary as mentioned, due to the lack of literary data that definitively corroborated the 0.89 cutoff value, which only occurred after comparison between the FFR and iFR methods in the trials aforementioned.

I am grateful for the opportunity to clarify these points and corroborate that the editorial directs us and clarifies not only the need to increasingly use coronary physiology, but also how to use it today, contributing exquisitely in this area of interventional cardiology study.

Keywords

Myocardial Ischemia; Fractional Flow Reserve, Myocardial; Stents; Coronary Artery Disease; Percutaneous Coronary Intervention/methods.

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Update

Update of the Brazilian Guidelines for Valvular Heart Disease – 2020

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Note: These updates are for information purposes and are not to replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Update of the Brazilian Guidelines for Valvular Heart Disease – 2020	
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List of Abbreviations:

βHCG: beta-human chorionic gonadotropin
ACC/AHA: American College of Cardiology/American Heart Association
AF: atrial fibrillation
AR: aortic regurgitation
aPTT: activated partial thromboplastin time
AS: aortic stenosis
ASA: acetylsalicylic acid
AVA: aortic valve area
PBMV: percutaneous balloon mitral valvuloplasty
BNP: brain natriuretic peptide
PBTV: percutaneous balloon tricuspid valvuloplasty
CHC: combined hormonal contraceptive
DOACs: direct oral anticoagulants
ECG: electrocardiogram
EOA: effective orifice area
EROA: effective regurgitant orifice area
ESC/EACTS: European Society of Cardiology/European Association for Cardiothoracic Surgery
FC: functional class
IE: infective endocarditis
INR: international normalized ratio
IUD: intrauterine device
LA: left atrium
LV: left ventricle
LVDD: left ventricular diastolic diameter
LVEF: left ventricular ejection fraction
LVSD: left ventricular systolic diameter
MAC: mitral annulus calcification
MR: mitral regurgitation
MS: mitral stenosis
MVA: mitral valve area
NYHA: New York Heart Association
PH: pulmonary hypertension
PHT: pressure half time
RA: right atrium
RF: rheumatic fever
rTPA: recombinant tissue plasminogen activator
SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology)
SPAP: systolic pulmonary artery pressure
STS: Society of Thoracic Surgeons
TAVI: transcatheter aortic valve implantation
TR: tricuspid regurgitation
TS: tricuspid stenosis
TTR: time in therapeutic range
VHD: valvular heart disease
VKA: vitamin K antagonists

Update

Content

1. Introduction

There are currently a wide modalities of interventional strategies - both transcatheter and surgical - which can be indicated for patients with valvular heart diseases (VHD), with the objective of reducing the morbidity and mortality. The correct timing for indication and the type of interventional treatment are linked to the precise anatomical and functional diagnosis of the VHD, and comprehensive global evaluation of the patient. The 2020 Update of the Brazilian Guidelines for VHD, in addition to compiling scientific evidence and expert opinion, continues with the ideal of being useful in supporting decision making for patients with VHD, and has three unique characteristics, namely:

• Maintenance of the innovative flowcharts proposed in the 2017 edition, with sequential steps guiding anatomical, etiological, and functional diagnosis, defining conduct aligned with best practices and rational use of resources (Figure 1);

• The increase of the recommendations number in the attempt to contemplate the diverse possibilities in view of increasing complexity of patients;

• Comparison of the recommendations of these guidelines with the leading international ones, the American College of Cardiology/American Heart Association (ACC/AHA) 2017 and the European Society of Cardiology/European Association for Cardiothoracic Surgery (ESC/EACTS) 2017 Guidelines, allowing for individualization of the Brazilian population.[1,2]

This 2020 edition considers the evaluation process for patients with non-severe VHD, and it emphasizes the need to weigh the possibility of transcatheter intervention in elderly patients, regardless of surgical risk, in addition patients with native or prosthetic valves with high surgical risk. Notwithstanding great advances and increased availability of imaging exams, these guidelines maintain the recommendation of detailed clinical evaluation, which continues to be indispensable to diagnosis, decisions making, and the doctor-patient relationship.

Bellow, the 5 recommended steps:

• First step: verify whether the VHD is anatomically severe; if so, proceed to the second step. In the event of non-severe valvular disease, investigate differential diagnoses in symptomatic patients and monitor evolution in asymptomatic patients;

• Second step: evaluate etiology, including clinical and past history, beside complementary exams;

• Third step: evaluate symptoms; this is fundamental to intervention decision making. Pharmacological treatment is indicated to alleviate symptoms until interventional takes place;

• Fourth step: evaluation of anatomical and/or functional prognostic factors (especially pulmonary hypertension [PH], ventricular remodeling, systolic dysfunction, aneurysmatic dilation of the aorta, and atrial fibrillation [AF]). This can be decisive regarding intervention in asymptomatic patients;

• Fifth step: type of intervention. The procedure can be surgical or transcatheter, with individualized indication depending on operative risks, comorbidities, and the Heart Team's decision.

2. The Heart Team

The Heart Team is a group of different professionals with experience in valve diseases who share the decision regarding the most appropriate treatment for a given patient. Given the wide variety of interventional strategies available, the Heart Team is fundamental to risk-benefit and cost-effectiveness analyses and decision making. The Heart Team comprises diverse cardiological subspecialties; the members will play different fundamental roles during each step of care, from the clinical cardiologist, who is responsible for patient selection and indication, besides pre- and post-intervention follow-up, to the cardiac surgeon and the hemodynamicist, who will be responsible to perform the procedures indicated by the Heart Team. The radiologist will also be important to data analysis in order to evaluate the technical possibility of each intervention, and the echocardiographer, in addition to evaluating preoperative data, will also monitor the procedure, collaborating for better results.[1,2]

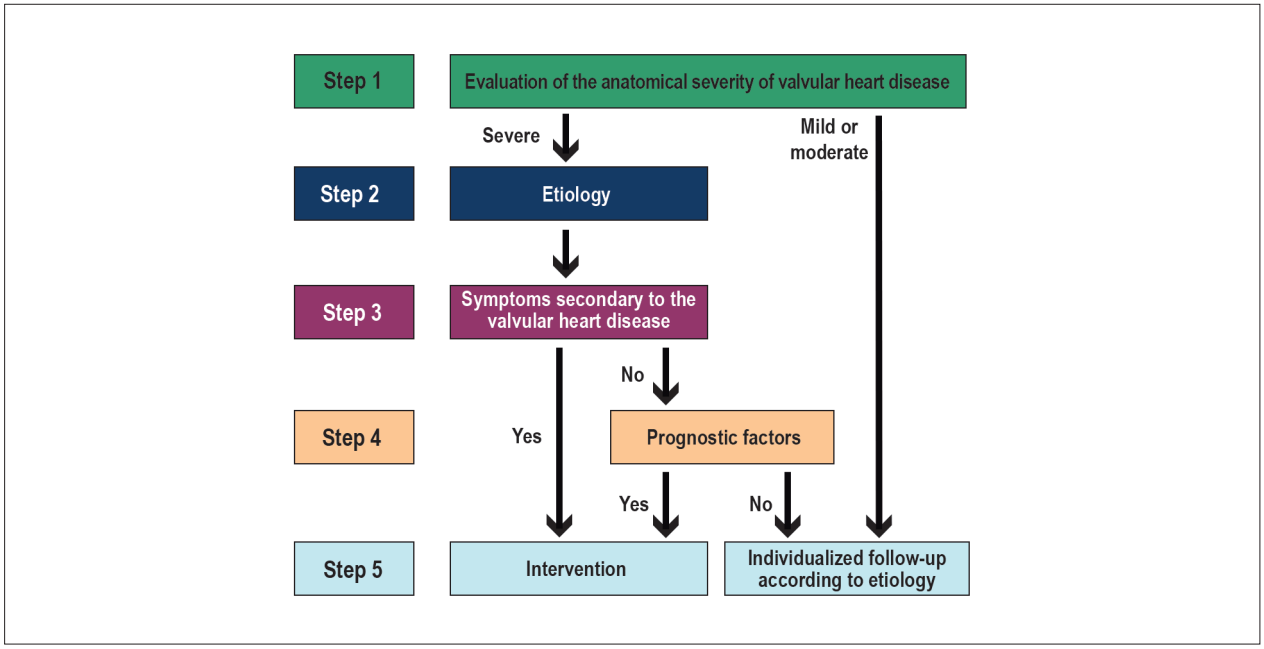

Figure 1 – *Flowchart showing steps of anatomical, etiological, and functional diagnosis, in addition to the intervention decision making.*

3. Operative Risk Evaluation

Indication of intervention for patients with VHD should always be based on the benefits and risks of the proposed procedure. For this purpose, we utilize online scores, including the EuroSCORE II (http://www.euroscore.org/calc.html) and the Society of Thoracic Surgeons (STS) score (http://riskcalc.sts.org/stswebriskcalc/#/calculate), which have been validated in different populations regarding their predictive ability of 30-day mortality. Patients with STS < 4% are conventionally considered at low surgical risk, while those with scores between 4% and 8% have intermediate risk, and those with scores > 8% have high risk. Rearding the EuroSCORE II, patients are considered low risk when it is lower than 4%, and, if the score is > 4%, they are considered at high surgical risk. In the event of a discrepancy between the two scores, we must use the one whose estimated higher risk.[3-8]

It is important to point that both scores omit some factors related to prognostic outcomes, such as frailty and specific contraindications to procedures, such as porcelain aorta. Furthermore, risk evaluation does not substitute the individual clinical evaluation, and the decision regarding intervention should always be shared with patients and their families.

4. Frailty

Frailty is an entity that denotes a state of vulnerability in elderly patients, associated with physical weakness and low physiological reserve. It is extremely relevant to individualized evaluation, mainly due to the following two factors:

- It is a predictor of events, such as mortality, length of hospital stay, and functional decline, after surgical or transcatheter intervention;

- It is not taken into consideration in conventional risk scores.

Several scores and tools are available for evaluating and quantifying frailty, through measurement of data related to functional status, instrumental daily activities, nutrition, cognition, independence for activities, and other factors. It is important that evaluation of frailty is not only subjective ("eyeball test"), but rather a set of clinical impression associated with different objective measurements and scores.[9-14]

5. Mitral Stenosis

Physical examination is the first resource applied for anatomical evaluation of mitral stenosis (MS). Patients with mild to moderate MS may already present an opening snap as well as a decrescendo rumbling diastolic murmur in the mitral area, starting immediately after the click. In patients in sinus rhythm, the murmur shows presystolic reinforcement in the end of diastole. In patients with severe MS, however, these clinical changes become more evident, as electrocardiographic and radiologic changes get evident. The characteristics present in patients with severe MS are shown in Table 1.

Echocardiography is the main complementary exam for mitral valve anatomical evaluation, and it is fundamental for defining the severity of VHD, hemodynamic repercussions, and parameters regarding intervention success, with evaluation of the components of the valve (valve annulus, valve cusps, and subvalvular apparatus).

The echocardiographic parameters of severe MS are mitral valve area (MVA), which may be measured by planimetry, pressure half time (PHT), or the continuity equation, and transmitral diastolic gradient.[15]

From the epidemiological point of view (Table 2), the main etiology of MS continues to be rheumatic fever (RF),

Table 1 – Step 1: Diagnosis of severe mitral stenosis[15]

	Characteristics of severe mitral stenosis
Physical examination	• *Facies mitralis* • Early opening snap • Hyperphonetic first heart sound • Hyperphonetic second heart sound • Rumbling diastolic murmur, with presystolic reinforcement for patients in sinus rhythm • Signs of pulmonary congestion and right heart failure • Presence of TR
Electrocardiogram	• LA enlargement • Right chambers overload • AF
Chest radiography	• Normal cardiothoracic index • Signs of enlarged LA: Elevated left main bronchus ("ballerina sign") Double atrial contour on the right 4th arch in the cardiac silhouette on the left • Signs of pulmonary congestion
Echocardiogram	• MVA < 1.5 cm^2 • Average diastolic transmitral gradient ≥ 10 mmHg • Resting SPAP ≥ 50 mmHg • SPAP ≥ 60 mmHg during exertion
Hemodynamic study	• Indicated in the event of discordance between clinical and echocardiographic findings • Diastolic transmitral gradient ≥ 10 mmHg (spontaneous or after atropine and volume) • SPAP ≥ 50 mmHg

AF: atrial fibrillation; LA: left atrium; LV: left ventricle; MVA: mitral valve area; SPAP: systolic pulmonary artery pressure; TR: tricuspid regurgitation.

Table 2 – Step 2: Evaluation of etiology of severe mitral stenosis [16,17]

	Etiological characteristics
Rheumatic fever	• > 90% of cases in developing countries • Symptoms between the third and fourth decades of life • Commissural fusion, thickening of cusps • Compromised subvalvular apparatus • Dome opening of the anterior cusp and reduced mobility of the posterior cusp • Mitral-aortic involvement
Degenerative	• 12% to 26% of cases in developed countries • More common in elderly patients • May reach 60% of cases in patients over 80 years • Calcification of the mitral valve annulus • Absence of commissural fusion • Related to aortic and coronary calcification
Rare causes	• Congenital • Rheumatologic diseases (lupus or rheumatoid arthritis) • Medication (methysergide or anorexigenic drugs) • Carcinoid syndrome • Fabry disease • Actinic injury – post-radiotherapy

which remains prevalent in developing countries, including Brazil. In these countries, rheumatic valve disease maintains an estimated prevalence of 1 to 7 per 1,000 children in clinical studies; this number is up to 10 times higher when echocardiography is used for population screening. Regarding developed countries, statistics indicate that MS is responsible for 9% of all VHD in Europe, and 0.1% in the United States. In these countries, cases occur predominantly in elderly patients and young immigrants from developing countries.[16-18]

In addition to the rheumatic etiology, there is a proportional increase in the number of patients with mitral annulus calcification (MAC), which may extend to the base of the valve leaflets, leading to restricted cusp movement and restriction of atrial emptying. The estimated prevalence of MAC is around 10% of the elderly population and approximately 1% to 2% of these patients develop MS.[19]

Other rare causes of MS include: rheumatologic diseases (systemic lupus erythematosus or rheumatoid arthritis), deposit

diseases (such as Fabry disease), Whipple disease, therapy with methysergide or anorexigenic drugs, carcinoid syndrome, or congenital anatomical abnormalities of the mitral valve, such as parachute mitral valve or mitral valve hypoplasia.

In patients with severe MS, it is necessary to pay attention to the symptoms (Table 3), the most common being dyspnea (New York Heart Association [NYHA] functional class [FC] II to IV). In particular, dyspnea may appear in situations that lead to increased pulmonary capillary pressure (physical exertion, pregnancy, or AF). Over time, it may also appear at rest, even with orthopnea. Other symptoms that may appear are palpitations, hemoptysis, dysphonia, dysphagia, cough, and embolic events.

In parallel to the evaluation of symptoms, possible prognostic factors should be investigated (Table 4). With respect to severe MS, relevant signals are the presence of significant PH (systolic pulmonary artery pressure – SPAP above 50 mmHg when resting or above 60 mmHg during exertion) or recent onset AF (triggered in the recent months).

Types of intervention and their indications are described in Tables 5 and 6 and Figure 2. Percutaneous balloon mitral valvuloplasty (PBMV) remains the treatment of choice for patients with MS of rheumatic etiology, wherein calcification and commissural fusion are predominant. There is need for favorable valve anatomy (as evaluated by the Wilkins-Block score [Table 7]) and no procedure contraindications (moderate to severe mitral regurgitation [MR] and left atrium [LA] thrombus). The Wilkins-Block score consists of echocardiographic evaluation of the mitral valve, with emphasis on description of structural aspects. The following four parameters are taken into consideration: leaflet mobility, valve thickening, degree of cuspid calcification, and involvement of the subvalvular apparatus. Values from 1 to 4 points for each item result in scores ranging from 4 to 16 points. Patients with Wilkins-Block score less than or equal to 8 are candidates for PBMV, since there are no contraindications. Surgical treatment of the mitral valve is the treatment of choice for patients with unfavorable anatomy or contraindications for PBMV in the presence of symptoms (NYHA FC III or IV) or prognostic factors. Surgery may consist of mitral commissurotomy or, in cases of very significant valve impairment, valve replacement with a biological or mechanical prosthesis.[20,21]

For patients with degenerative MS, on the other hand, PBMV is not a therapeutic option, as there is no commissural fusion or calcification, but rather valve annulus calcification. Furthermore, in these patients, who are usually elderly and often have multiple comorbidities, surgical risk is significantly higher. The surgical procedure is technical difficulty and is more likely to have complications, including atrioventricular disjunction, circumflex artery injury, and ventricular wall bleeding. The initial treatment of choice is, thus, clinical: heart rate control with betablockers, calcium channel blocker or ivabradine (for patients in sinus rhythm who have not tolerated previous medications), associated with diuretics.[22] If this strategy works, patients may continue with medical treatment, without indication for further interventions. For patients who are refractory to clinical treatment, however, it is necessary to consider the possibility of surgical intervention, in cases with low to moderate risk, or eventual transcatheter implantation of a mitral prosthesis. In these cases, transcatheter implantation uses the MAC to support the valve prosthesis, in a procedure routinely referred to as valve-in-MAC. There is still limited experience with this procedure, which is most frequently performed in clinical studies via the transeptal or transapical route. It still has a high rate of complications, including paravalvular leak, left ventricle (LV) outflow tract obstruction, and prosthesis embolization, and the mortality rate may reach 25% in 30 days and 54% in 12 months. Further studies are needed in order to broaden its indications.[23-25]

Clinical follow-up of patients, as long as they present non-severe VHD, consists of periodic consultations and echocardiographic reevaluation (Table 8). In patients

Table 3 – Evaluation of severe mitral stenosis symptoms

	Symptoms
Dyspnea (NYHA FC II to IV)	• Main symptom • Initially with situations that increase pulmonary capillary pressure (physical exertion, atrial fibrillation, or pregnancy) • Resting dyspnea and nocturnal paroxysmal dyspnea • May be accompanied by palpitations, hemoptysis, dysphonia, dysphagia, cough • May be accompanied by embolic events (cerebral, mesenteric, or extremities)

FC: functional class; NYHA: New York Heart Association.

Table 4 – Step 4: Evaluation of severe mitral stenosis prognostic factors

	Prognostic Factors
Pulmonary hypertension	• Resting SPAP ≥ 50 mmHg • SPAP ≥ 60 mmHg during exertion (exercise test or echocardiography with pharmacological stress)
Recent onset AF	• Relation to LA enlargement • Maintain INR between 2.0 and 3.0

AF: atrial fibrillation; LA: left atrium; INR: international normalized ratio; SPAP: systolic pulmonary artery pressure.

Table 5 – Step 5: Type of mitral stenosis intervention[15,17,20-25]

Type	Considerations
Percutaneous balloon mitral valvuloplasty	• Treatment of choice in rheumatic etiology • Indications: Symptoms (NYHA FC II to IV) and/or prognostic factors Wilkins-Block echocardiographic score ≤ 8 * (subvalvular apparatus and calcification ≤ 2) • In pregnant women or patients with high surgical risk, consider if: echocardiographic score 9 to 10 (subvalvular apparatus and calcification ≤ 2) • Contraindications: - LA thrombus - Moderate or severe MR - Recent embolic phenomenon
Surgical treatment (commissurotomy/ valve replacement)	• Rheumatic MS with NYHA FC III to IV and contraindications to PBMV • Rheumatic MS with prognostic factors, not eligible for PBMV • Degenerative MS, refractory to medical treatment
Transcatheter mitral valve implantation (valve-in-MAC)	• Degenerative MS, refractory to medical treatment, with contraindication or high surgical risk (currently under study)

* Individualize in cases with echocardiographic scores 9 to 10. Patients with calcification and subvalvular apparatus scores below 3 have higher rates of successful PBMV.
PBMV: percutaneous balloon mitral valvuloplasty; FC: functional class; LA: left atrium; MAC: mitral annulus calcification; MR: mitral regurgitation; MS: mitral stenosis.

Table 6 – Mitral stenosis: Recommendations[1,2,15,17,20-25]

Intervention	Clinical condition	SBC	AHA	ESC
Percutaneous balloon mitral valvuloplasty	• Rheumatic MS, NYHA FC II to IV, in the absence of contraindications	I A	I A	I B
	• Asymptomatic rheumatic MS, with prognostic factors, in the absence of contraindications	I C	IIb C (if AF)	IIa C (if high thromboembolic risk or risk of hemodynamic deterioration)
Surgical treatment (commissurotomy/valve replacement)	• Rheumatic MS, NYHA FC III to IV, with contraindications to PBMV	I B	I B	I C
	• Asymptomatic rheumatic MS with prognostic factors, not eligible for PBMV	IIa C	IIb C (Recurrent embolism)	-
	• Degenerative MS refractory to medical treatment	IIb C*	-	-
	• Asymptomatic rheumatic MS with other concomitant heart surgery	I C	I C	-
Transcatheter mitral valve implantation (valve-in-MAC)	• Degenerative MS refractory to medical treatment, with contraindication or high surgical risk	IIb C*	-	-

** Consider evaluation of the Heart Team. AHA: American Heart Association; PBMV: percutaneous balloon mitral valvuloplasty; ESC: European Society of Cardiology; FC: functional class; MAC: mitral annulus calcification; MS: mitral stenosis; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).*

with non-severe MS, reevaluation may be performed on a yearly basis. Patients with valve area ≥ 1.5 cm^2 are not normally expected to develop symptoms or prognostic factors. In the event that these changes occur, before the patient develops anatomically severe VHD, it is imperative to consider the possibility that other differential diagnoses are present. Patients with severe MS, on the other hand, should be reevaluated at shorter intervals, usually every 6 to 12 months.

6. Primary Chronic Mitral Regurgitation

For the clinical decision making in primary chronic MR, it is recommended that the 5 steps of the flowchart for treating VHD are followed, as detailed below and subsequently summarized in Figure 3.

In addition to confirming the presence of VHD, transthoracic echocardiogram is the main exam used to define the anatomical severity of MR. Diverse parameters may be used

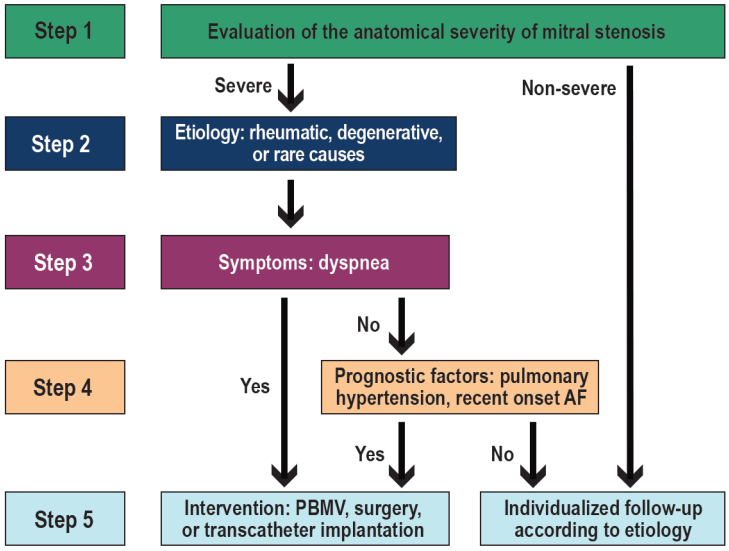

Figure 2 – *Flowchart for decision making in mitral stenosis. AF: atrial fibrillation; PBMV: percutaneous balloon mitral valvuloplasty.*

Table 7 – Wilkins-Block echocardiographic score

Leaflet mobility: 1 - High valve mobility with restriction only in the extremities of the leaflets 2 - The medial and basal regions show normal mobility 3 - The valve continues moving forward in diastole, mainly at the base 4 - Minimal or no movement of the leaflets in diastole
Subvalvular thickening: 1 - Minimal subvalvular thickening exactly below the mitral leaflets 2 - Chordal thickening extending for more than a third of length 3 - Thickening extending to the distal third of the chordae 4 - Extensive thickening and shortening of all structures of the chordae extending to the papillary muscles
Leaflet thickness: 1 - Thickening of the leaflets, with thickness close to normal (4 – 5 mm) 2 - Normal medial layers, considerable thickening of margins (5 – 8 mm) 3 - Thickening extending throughout all the layer (5 – 8 mm) 4 - Considerable thickening of the entire tissue layer (> 8 – 10 mm)
Valve calcification: 1 - Single area of increased brightness 2 - Minimal areas of brightness confined to the leaflet margins 3 - Brightness extending inside the middle portion of the leaflets 4 - Extensive brightness, beyond the limits of the leaflets

Table 8 – Mitral stenosis: Individualized follow-up[1,2]

Mitral stenosis	Follow-up	SBC	AHA	ESC
Severe and asymptomatic, without prognostic factors	• Clinical and echocardiographic evaluation	Every 6 to 12 months	Every 12 months	Every 12 months
	• Concomitant surgical intervention in patients who will undergo other cardiac surgical procedure (coronary revascularization, ascending aorta, or other valve procedures)	I C	IIb C	-
Non-severe (MVA > 1.5 cm² and mean transmitral gradient < 5 mmHg)	• Clinical and echocardiographic reevaluation	Every 1 years	Every 3 to 5 years	Every 2 to 3 years

AHA: American Heart Association; ESC: European Society of Cardiology; LA: left atrium; LV: left ventricle; MVA: mitral valve area; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).

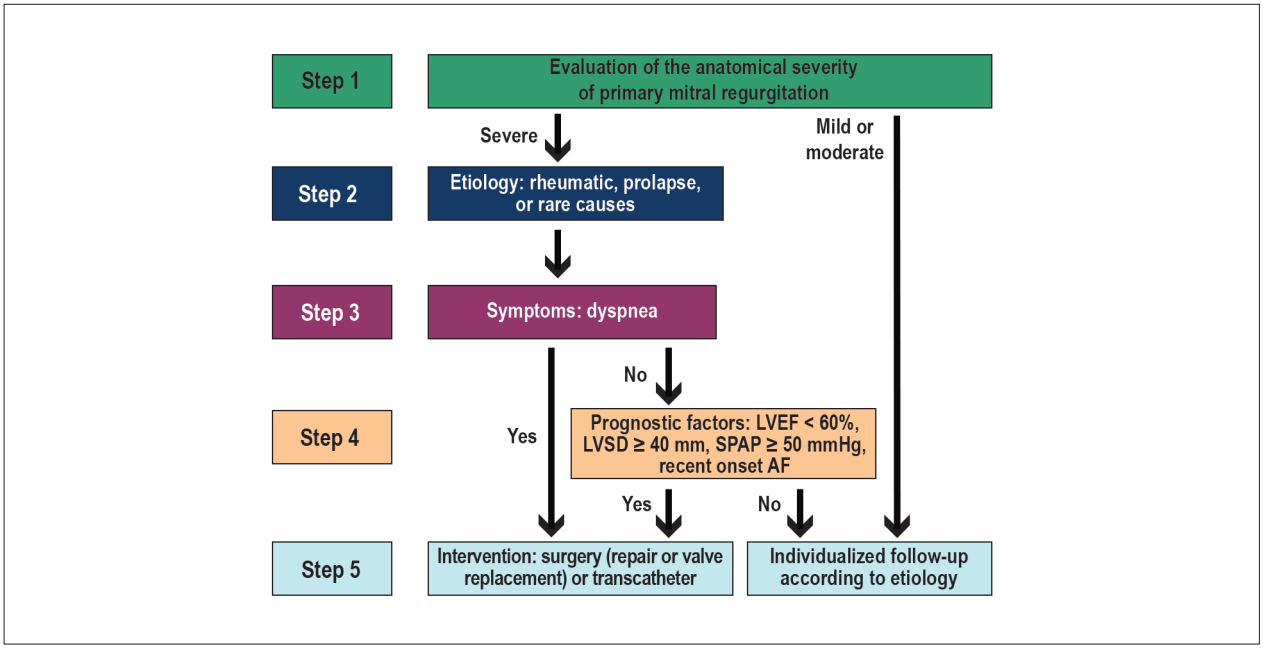

Figure 3 – *Flowchart for decision making in primary chronic mitral regurgitation. AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; SPAP: systolic pulmonary artery pressure.*

for this quantification; detailed, thorough examination is of fundamental importance (Table 9).

Patients with anatomically mild or moderate MR should continue with periodic clinical and echocardiographic follow-up, and there is no indication for intervention (medical or surgical) in order to interrupt the natural history of the valve disease. On the other hand, patients with severe MR should proceed as per the flowchart for specific evaluation, investigating symptoms that are secondary to the VHD and/or the presence of prognostic factors.

In patients with MR, it is necessary to define the etiology of the VHD, given that clinical follow-up and therapeutic planning (timing and type of intervention), when indicated, can be different according to the cause of MR (Table 10). In spite of advances in diagnostic tests, transthoracic echocardiogram remains the first and main exam indicated for anatomical quantification and etiological evaluation of patients with MR. [33-35]

The main symptom in patients with anatomically severe MR is dyspnea, which should be taken in account, even if it does not limit routine activities (NYHA FC II). If there are doubts regarding the presence of symptoms, an exercise test or cardiopulmonary test may be requested (Table 11). Once the presence of symptoms has been confirmed, and if they are secondary to MR, patients should be referred for valvular intervention, as described in Step 5 (Table 12).

Patients with severe asymptomatic MR should be periodically reevaluated to determine the development of anatomical and/or functional changes secondary to valve disease (Table 13). The following prognostic factors are associated with MR: LV systolic dysfunction (left ventricular ejection fraction [LVEF] < 60%), LV dilation (left ventricular systolic diameter [LVSD] ≥ 40 mm), PH (SPAP ≥ 50 mmHg at rest or ≥ 60 mmHg during exertion), and new onset AF (recent months).[36-38] Increased LA volume (especially ≥ 60 ml/m^2) may be considered an anatomical prognostic factor in MR, and it should be taken into consideration for intervention decision, given that it is associated with worse prognosis. In addition, if there is a progressive decline in LVEF or progressive dilation of the LV on serial imaging tests, mitral valve intervention should be considered, even before the previously mentioned limits have been reached.

After confirming the existence of anatomically severe MR, with a defined etiology, and, finally, verifying the presence of symptoms that are secondary to the VHD and/or the presence of prognostic factors, the patient should be referred for valvular intervention, if there is no contraindication (Table 13 and 14). In these cases, surgical mitral repair is the treatment of choice, provided that the etiology (especially prolapse) and the anatomy are favorable and that the procedure is performed in a qualified hospital with an experienced surgeon. Otherwise, surgical mitral valve replacement is indicated.[39-52]

Indication of transcatheter interventions is restricted to patients with primary MR, and the decision should be made following discussion with the Heart Team. In the same manner, for patients with contraindication or high risk associated with conventional surgery, prior discussion with the Heart Team needs to take place for the best decision making.

When patients, notwithstanding the presence of anatomically severe MR, do not show symptoms or have prognostic factors, they should receive individualized follow-up, with biannual clinical follow-up and echocardiographic evaluation at maximum 1-year intervals (Table 15).

Table 9 – Step 1: Diagnosis of severe primary mitral regurgitation [26-32]

	Characteristics of severe primary mitral regurgitation
Physical examination	• Apex beat shifted to the left and downward • Hypophonetic S1 (frequently audible in patients with rheumatic MR and MR due to prolapse, and loss of intensity may be considered a marker of severity of ventricular dysfunction, chordal rupture, among others) • Hyperphonetic S2 • Regurgitative systolic murmur ≥ +++/6+ • Clinical signs of right heart failure
Electrocardiogram	• Left ventricular hypertrophy • Left atrial enlargement Arial or ventricular arrhythmias (PVCs, tachycardia) and AF
Chest radiography	• Enlarged cardiac silhouette with LV and LA dilation Signs of pulmonary congestion
Echocardiogram	• Jet area ≥ 40% of LA area • Regurgitant fraction ≥ 50% • Regurgitant volume ≥ 60 mL/beat • *Vena contracta* ≥ 0.7 cm Effective regurgitant orifice area (EROA) • ≥ 0.40 cm²
Hemodynamic study	• Indicated in cases of disagreement between clinical and echocardiographic findings • Left ventriculography (severe if > 3+) • Evaluation of intracavitary pressures
Magnetic resonance	• In cases of disagreement between clinical and echocardiographic findings or limited quality of echocardiographic image • Confirmation of degree of MR before scheduled mitral valve intervention • Degree of MR • Evaluation of mitral annulus disjunction in the complex of myxomatous disease and mitral valve prolapse

AF: atrial fibrillation; LA: left atrium; LV: left ventricle; MR: mitral regurgitation; PVCs: premature ventricular contractions.

Table 10 – Step 2: Evaluation of severe primary mitral regurgitation etiology [33-35]

	Etiological characteristics
Rheumatic	• Most prevalent cause in Brazil • Thickening with cusp retraction • Commissural involvement • Mitral-aortic involvement • Frequent in young adults
Mitral valve prolapse and associated diseases (Barlow syndrome)	• Second most frequent cause in Brazil • Cusp protrusion into the LA ≥ 2 mm • More frequent in middle-aged and elderly populations
Other causes	• Infective endocarditis • Marfan syndrome • Systemic lupus erythematosus • Traumatic lesions • Congenital deformities

LA: left atrium.

Table 11 – Step 3: Evaluation of severe primary mitral regurgitation symptoms

	Symptoms
Dyspnea (NYHA FC II-IV) and fatigue/weakness	• Pulmonary congestion • Initially with events that increase pulmonary capillary pressure (physical exertion, AF, pregnancy) • Resting dyspnea and nocturnal paroxysmal dyspnea • May be accompanied by palpitations, coughing, edema • May be accompanied by embolic events

AF: atrial fibrillation; FC: functional class.

Table 12 – Step 5: Type of severe primary mitral regurgitation intervention [39-52]

Type of intervention	Considerations
Mitral valve repair	• Treatment of choice • Rheumatic patients: less favorable results. • Prolapse of the posterior cusp of the mitral valve (isolated P2): better results.
Mitral valve replacement	• Indicated in cases where valve repair is not possible.
Percutaneous mitral valve repair	• Reserved for high-risk patients or patients with surgical contraindication and refractory symptoms • Degenerative MR due to prolapse • Favorable anatomical conditions • Indicated following decision by the Heart Team

MR: mitral regurgitation.

On the other hand, patients with anatomically moderate MR should receive annual clinical evaluation and undergo echocardiogram every 2 years.

7. Secondary Mitral Regurgitation

Secondary MR results from ventricular changes (dysfunction and/or dilation), while the mitral valve leaflets and chordae are normal. In this context, additional LV overload occurs due to mitral regurgitation, culminating in worse prognosis. The main etiologies are coronary artery disease (ischemic MR) and dilated cardiomyopathy (annular dilation and/or poor positioning). For these reasons, the ideal treatment is controversial, given that valve correction is not curative. In general, intervention is indicated in patients who remain symptomatic, in spite of optimized medical treatment. Even so, the therapeutic decision must be individualized and, whenever possible, shared with the Heart Team.[53]

As physical examination for diagnosis of secondary MR is often poor, transthoracic echocardiogram is a fundamental test. There is evidence that lower limits of the regurgitant orifice area and the regurgitant volume are associated with worse prognosis, in comparison with primary MR. Nevertheless, for quantification of anatomical severity of secondary MR, the echocardiographic limits applied are the same as those for primary MR. In the event of

Table 13 – Step 4: Evaluation of severe primary mitral regurgitation prognostic factors[36-38]

	Prognostic factors
Echocardiogram	• LVEF ≤ 60% or progressive decline in LVEF (within normal range) • Progressive remodeling (LVSD ≥ 40 mm) • Resting SPAP ≥ 50 mmHg or ≥ 60 mmHg during exercise • LA volume ≥ 60 ml/m²
Electrocardiogram	• Recent onset AF (< 1 year)

AF: atrial fibrillation; LA: left atrium; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; SPAP: systolic pulmonary artery pressure.

Table 14 – Primary mitral regurgitation: Recommendations[1,2,39-52]

Intervention	Clinical condition	SBC	AHA	ESC
Mitral valve repair (centers with experience)	**Rheumatic**			
	• Symptomatic (NYHA FC ≥ II)	IIb C	IIb C	-
	• Asymptomatic, with prognostic factors: - LVEF between 30% and 60% and/or LVSD ≥ 40 mm	IIb B	IIb B	-
	- SPAP ≥ 50 mmHg or AF	IIb B	-	-
	Rheumatic, asymptomatic MR without prognostic factors	III	-	-
	Non-rheumatic			
	• NYHA FC ≥ II, with favorable anatom	I B	I B	I B
	• Asymptomatic, with favorable anatomy and prognostic factors: - LVEF between 30% and 60% and/or LVSD ≥ 40 mm	I B	I B	I B (LVSD ≥ 45 mm)
	- SPAP ≥ 50 mmHg or AF	IIa B	IIa B	IIa B
	• Asymptomatic MR due to prolapse, with favorable anatomy, without prognostic factors	IIa B	IIa B	IIa C (LA ≥ 60 ml/m² and sinus rhythm)
Mitral valve replacement	**Rheumatic**			
	• Symptomatic (NYHA FC ≥ II)	I B	-	-
	• Asymptomatic, with prognostic factors: - LVEF between 30% and 60% and/or LVSD ≥ 40 mm	I B	-	-
	- SPAP ≥ 50 mmHg or AF	IIa B	-	-
	• Rheumatic, asymptomatic MR, without prognostic factors	III	-	-
	Non-rheumatic			
	• NYHA FC ≥ II, with unfavorable anatomy for valve repair	I B	I B	I B
	• Asymptomatic, with unfavorable anatomy for valve repair, and prognostic factors: - LVEF between 30% and 60% and LVSD ≥ 40 mm	I B	I B	I C (LVSD ≥ 45 mm)
	- SPAP ≥ 50 mmHg or AF	IIa C	IIa C	IIa B
	• Asymptomatic MR due to prolapse, with unfavorable anatomy for valve repair, without prognostic factors	III	III	III
Percutaneous mitral valve repair	• Non-rheumatic MR, with high risk or contraindication to surgery, with refractory symptoms	IIa B *	IIb B	IIb C

** In centers with a Heart Team. AF: atrial fibrillation; AHA: American Heart Association; ESC: European Society of Cardiology; FC: functional class; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology); SPAP: systolic pulmonary artery pressure.*

disagreement between clinical and echocardiographic findings, hemodynamic study with left ventriculography or magnetic resonance may assist in definition (Table 16).[27-32,54]

Echocardiogram provides the main information required for establishing the etiology of secondary MR, especially regarding analysis of LV changes (Table 17). Coronary cineangiography, in turn, plays an important role in diagnosis of obstructive coronary artery disease, which may be the cause of MR.[53]

Tests for myocardial viability evaluation (such as nuclear magnetic resonance) may be useful in patients with ischemic MR who are scheduled for myocardial revascularization.

Table 15 – Primary mitral regurgitation: Individualized follow-up[1,2]

Primary mitral regurgitation	Follow-up	SBC	AHA	ESC
Severe and asymptomatic, without prognostic factors	• Clinical and echocardiographic reevaluation	Every 6 months to 1 year	Every 6 months to 1 year	Every 6 months
	• Concomitant intervention in patients who will undergo another cardiac surgical procedure (coronary revascularization, ascending aorta, or other valve procedures)	I B	I B	-
Moderate (Jet area 20% – 40% of LA area, regurgitant fraction 30% – 49%, regurgitant volume 30 – 59 mL/beat, vena contracta 0.3 – 0.69 cm, EROA 0.2 – 0.39 cm²)	• Clinical and echocardiographic reevaluation	Every 1 to 2 years	Every 1 to 2 years	Every 1 to 2 years
	• Concomitant intervention in patients who will undergo another cardiac surgical procedure (coronary revascularization, ascending aorta, or other valve procedures)	IIa C	IIa C	-
Mild (Jet area < 20% of LA area, regurgitant fraction < 30%, regurgitant volume < 30 mL/beat, vena contracta < 0.3 cm, EROA < 0.2 – 0.39 cm²)	• Clinical and echocardiographic reevaluation	Every 2 to 3 years	Every 3 to 5 years	-

AHA: American Heart Association; EROA: effective regurgitant orifice area; ESC: European Society of Cardiology; LA: left atrium; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).

Table 16 – Step 1: Diagnosis of severe secondary mitral regurgitation[27-32,54]

	Characteristics of severe secondary mitral regurgitation
Physical examination	• Hypophonetic or normophonetic S1 • Protomesosystolic or holosystolic murmur, radiating to the axillary line
Electrocardiogram	• Left ventricular hypertrophy • Left atrial enlargement Signs suggestive of the underlying pathology
Chest radiography	• Enlarged cardiac silhouette due to dilation of left chambers
Echocardiogram	• Quantification of regurgitation*: - Regurgitant fraction ≥ 50% - Regurgitant volume ≥ 60 mL/beat - EROA ≥ 0.40 cm²
Hemodynamic study	• Disagreement between clinical and echocardiographic findings • Degree of MR on left ventriculography
Magnetic resonance	• Disagreement between clinical and echocardiographic findings or limited quality of echocardiographic image • Confirmation of the degree of MR before scheduled mitral valve intervention • Degree of MR

** Consider the possibility of anatomically severe mitral regurgitation if EROA is between 0.3 and 0.4 cm ² when associated with severe systolic dysfunction. EROA: effective regurgitant orifice area; MR: mitral regurgitation.*

Table 17 – Step 2: Evaluation of severe secondary mitral regurgitation etiology[53]

	Etiological characteristics
Ischemic	• Segmental changes in contractility • Inadequate arrangement of the papillary muscles or leaflets (tenting leaflet or with apical traction – tethering – and/or due to failed leaflet coaptation) • Mitral annular dilation or deformity • Evaluation of coronary arteries on coronary cineangiography • Evaluation of viability on cardiac magnetic resonance
Dilated	• Valve annulus dilation – ventricular dilation • Ventricular systolic dysfunction • Inadequate arrangement of the papillary muscles or leaflets (tenting leaflet or with apical traction – tethering – and/or due to failed leaflet coaptation) • Ventricular dyssynchrony • Altered atrioventricular mechanical coupling

The main symptom present in patients with secondary MR is dyspnea, which may result from LV dysfunction and/or associated mitral regurgitation (Table 18).

Patients with important symptoms (NYHA FC III and IV) that persist in spite of optimized treatment for heart failure (including resynchronization therapy, when indicated) should be considered for intervention in an individualized manner.

There are no specific prognostic factors for patients with secondary MR, given that the origin of the problem lies in ventricular disease (Table 19). Nonetheless, in the event that LV dilation and/or dysfunction worsen, without any clear causal factor, the concomitant mitral valve disease may be considered responsible.[55,56]

Indication of intervention for patients with secondary MR is controversial (Tables 20 e 21). In patients with ischemic MR who are candidates for myocardial revascularization surgery, simultaneous approach to the mitral valve disease should be considered. On the other hand, in patients who are not indicated for revascularization, isolated surgical approach to MR is associated with high mortality and high rates of MR recurrence, and there is no evidence of its benefit in terms of survival.[53,57-66]

In patients with MR secondary to dilated cardiomyopathy, indication of intervention in mitral valve disease is even more restricted. While isolated mitral valve surgery has not demonstrated a benefit in this scenario, new evidences have

Table 18 – Step 3: Evaluation of severe secondary mitral regurgitation symptoms

	Symptoms
Dyspnea and fatigue/weakness	• Increased end diastolic pressure • Pulmonary capillary congestion • May be accompanied by palpitations, cough, ascites, edema, or chest pain • May be accompanied by embolic events

Table 19 – Step 4: Evaluation of severe secondary mitral regurgitatio nprognostic factors[55,56]

Prognostic factors	
Clinical and echocardiographic evaluation	• Worsening of underlying conditions without other attributable causes (increased SPAP, increased ventricular diameters, or decreased LVEF) • Symptoms refractory to optimized clinical treatment

LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary artery pressure.

Table 20 – Step 5: Type of severe secondary mitral regurgitatio n intervention[53,57-72]

Type	Considerations
Surgery (valve repair or replacement)	• Valve replacement or repair + myocardial revascularization, when indicated
Percutaneous mitral valve repair	• May be considered after evaluation by the Heart Team, especially in patients with LVEF ≥ 20% and LVSD < 70 mm

LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter.

Table 21 – Secondary mitral regurgitation: Recommendations[1,2,53,57-72]

Intervention	Clinical condition	SBC	AHA	ESC
Mitral valve replacement or repair	**Ischemic**			
	Symptomatic (NYHA FC ≥ III)	IIb B	IIb B	IIb C
	Associated revascularization	IIa B	IIa B	I C (LVEF > 30%) IIa C (LVEF < 30%)
	Dilated			
	Symptomatic (NYHA FC ≥ III)	IIb B	IIb B	IIb C
Percutaneous mitral valve repair	**Ischemic**			
	Refractory symptoms (NYHA FC ≥ III), with high risk or contraindication to surgery	IIa B	-	IIb C (LVEF < 30%)
	Dilated			
	Refractory symptoms (NYHA FC ≥ III) with high risk or contraindication to surgery	IIa B	-	IIb C (LVEF < 30%)

AHA: American Heart Association; ESC: European Society of Cardiology; FC: functional class; LVEF: left ventricular ejection fraction; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).

shown a benefit to transcatheter intervention in patients with secondary MR and LVEF ≥ 20%, who remained symptomatic in spite of optimized clinical treatment, provided that the procedure is not indicated in more advanced phases of the natural history of VHD. [67-72]

For more appropriate indication and more thorough approach, cases of secondary MI should be discussed with the Heart Team before the decision is made (Figure 4).

8. Aortic Stenosis

Aortic stenosis (AS) shows a growing prevalence due to increased life expectancy and consequent aging of the Brazilian population. The most common cause of AS is aortic calcification/degeneration, which mainly affects elderly patients. Transcatheter treatment has become an alternative to surgical valve replacement, not only in frail and high-risk patients, but also in patients with intermediate or low risk. Therefore, Heart Team is becoming increasingly important and necessary in decision making regarding intervention in these patients.73

According to current evidence and following the recommendations of the 2017 Brazilian guidelines, the first step for evaluating patients with AS is to define the VHD severity (Table 22). To date, only patients with anatomically severe AS benefit from intervention. Severe AS is defined in echocardiography as an aortic valve area (AVA) ≤ 1.0 cm^2 and/or indexed AVA ≤ 0.6 cm^2/m^2 in the presence of mean transaortic gradient ≥ 40 mmHg or maximum aortic jet velocity ≥ 4.0 m/s. Patients with low-flow, low-gradient AS (AVA ≤ 1.0 cm^2 and mean transaortic gradient < 40 mmHg), once anatomical severity has been confirmed, may also undergo intervention. In cases with low-flow, low-gradient AS and preserved LVEF, it is necessary to measure aortic calcium score (severe AS if over 1,300 AU for women and over 2,000 AU for men).[74-82] In patients with low-flow, low-gradient AS and low LVEF, dobutamine stress echocardiogram is indicated. Severe AS is defined when, in the presence of contractile reserve, AVA remains reduced,.[83-86] In the absence of contractile reserve, it is also necessary to measure valve calcium score in order to define anatomical severity.[74-78,87] Patients with no contractile reserve also benefit from surgical or transcatheter intervention.

The second step is the evaluation of etiology (Table 23).[88,89] In developed countries, there is greater prevalence of degenerative/calcification etiology in elderly patients, whereas, in developing countries, rheumatic and bicuspid etiologies are predominant in young patients. In Brazil, we may observe a bimodal peak in the prevalence AS. In other words, there are patients with all etiologies in different age ranges due to the transitional age pyramid typical of developing countries. The etiology of AS also reflects in the choice of treatment (Step 5). Patients with rheumatic AS are usually young, and have not been considered in transcatheter aortic valve implantation (TAVI) studies. The majority of patients studied had degenerative etiology. There is, however, already evidence regarding the procedure's feasibility in patients with bicuspid aortic valve.[90]

The third step is the evaluation of symptoms related to the VHD (Table 24). Intervention is unequivocally indicated for patients with severe AS and dyspnea, angina, or syncope.

In cases where there are no symptoms, we must evaluate the presence of prognostic factors that justify indication of intervention (Table 25).[91-95] The following prognostic factors are currently taken into consideration in the current guidelines:

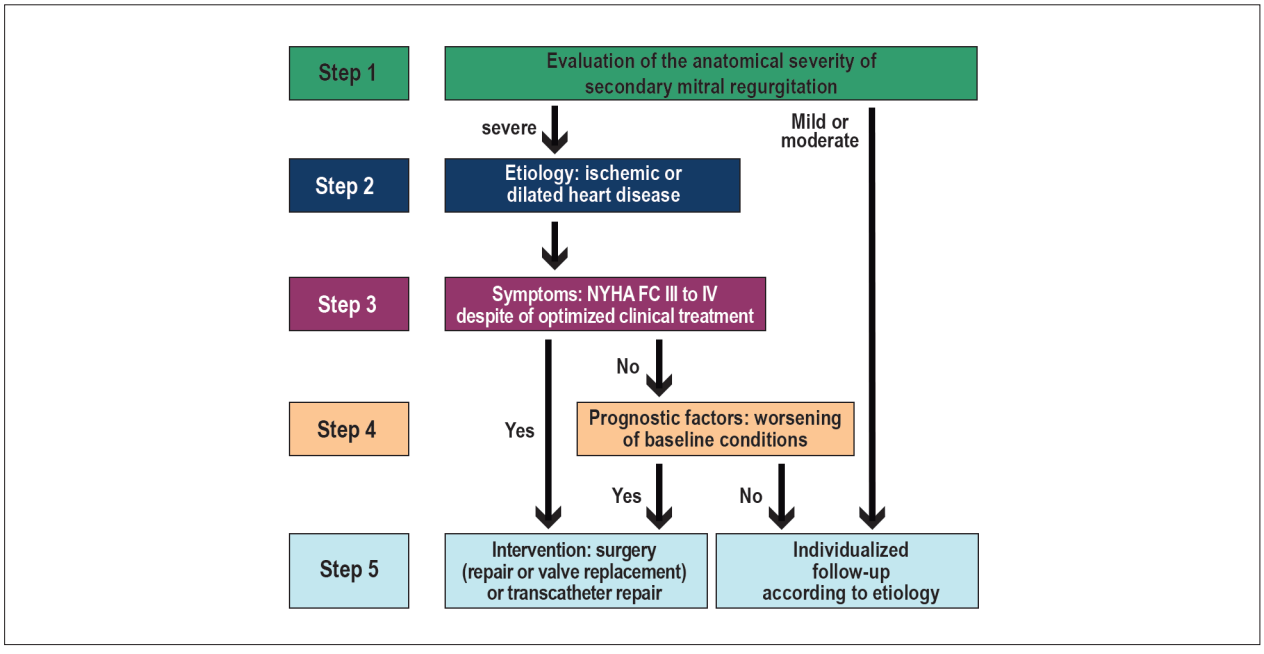

Figure 4 – *Flowchart for decision making in secondary mitral regurgitation.FC: functional class.*

Table 22 – Step 1: Diagnosis of severe aortic stenosis[74-87]

	Characteristics of severe aortic stenosis
Physical examination	• *Pulsus parvus et tardus* • Ejective systolic murmur with telesystolic peak • Hypophonetic second heart sound • Hypophonetic first heart sound • Gallavardin phenomenon • Paradoxical double second heart sound or single second heart sound
Electrocardiogram	• Left chamber overload • Altered ventricular repolarization (strain pattern)
Chest radiography	• Cardiothoracic index may be normal • Signs of pulmonary congestion
Echocardiogram	• AVA ≤ 1.0 cm^2 • Indexed AVA ≤ 0.6 cm^2/m^2 • Mean transaortic gradient ≥ 40 mmHg • Maximum aortic jet velocity ≥ 4.0 m/s • Flow rate ratio between LV outflow tract and aortic valve < 0.25
Dobutamine stress echocardiogram	• Indicated for evaluation of anatomical severity in patients with low-flow, low-gradient AS, with low LVEF, defined as AVA ≤ 1.0 cm^2, LVEF < 50% and mean transaortic gradient < 40 mmHg* • In the presence of contractile reserve (increase of ≥ 20% in stroke volume and/or increase of > 10 mmHg in mean transaortic gradient), patients with reduction or preservation in peak AVA during stress have severe AS (increase of up to 0.2 cm^2 in AVA is accepted as a criterion of preserved AVA). Patients with increasing in AVA ≥ 0.3 cm^2 are defined as moderate AS (pseudo-severe AS) • In the absence of contractile reserve, it is necessary to corroborate anatomical severity with the aortic calcium score
Multidetector chest computed tomography	• Aortic valve calcium score above 1,300 AU for women and 2,000 AU for men confirms severe AS
Hemodynamic study	• Transaortic gradient (peak) ≥ 50 mmHg
Special situation	• Low-flow, low-gradient AS with preserved LVEF ("paradoxical"), defined as: AVA ≤ 1.0 cm^2, LVEF > 50%, and transaortic mean gradient < 40 mmHg*. In these cases, we must evaluate the following parameters for defining severe AS: - Indexed AVA ≤ 0.6 cm^2/m^2 - High aortic valve calcium score - Systolic arterial pressure ≤ 140 mmHg - Indexed stroke volume < 35 mL/m^2 • Patients with all of the above parameters, but normal indexed stroke volume (> 35 ml/m^2) are defined as having normal-flow, low-gradient AS. This entity has been recently described; evidence is scarce, and these patients appear to benefit from valve intervention when they are symptomatic[88,89]

** In cases of low-flow, low-gradient AS with preserved or low LVEF, we must pay attention to possible errors in echocardiographic measurement. AS: aortic stenosis; AVA: aortic valve area; LV: left ventricle; LVEF: left ventricular ejection fraction.*

Table 23 – Step 2: Evaluation of severe aortic stenosis etiology[88,89]

	Etiological characteristics
Atherosclerotic/degenerative	• Associated with old age • Prevalence: 3% to 5% of the population over 75 years old • Related to aortic valve calcification • Presence of risk factors related to atherosclerosis
Rheumatic	• Commissural fusion • Mitral-aortic involvement • Younger patients • Associated with a range of aortic regurgitation degrees
Bicuspid	• Prevalence: 2% of the population • Associated with aortopathy (70% of cases) • Latero-lateral orientation of the commissural cleft: predictor of the evolution of aortic stenosis

- Echocardiogram: LV dysfunction (LVEF < 50%) and/or markers of very severe AS (AVA < 0.7 cm^2, maximum aortic jet velocity > 5.0 m/s, mean transaortic gradient > 60 mmHg).[96]

- Exercise test (ergometry): absence of inotropic reserve and/or low functional capacity, arterial hypotension during exertion (20 mmHg decrease in systolic arterial pressure) and/or presence of symptoms with low loads.[97,98]

The fifth and final step is choice of intervention (Tables 26 and 27 and Figures 5, 6, and 7). Transfemoral TAVI is preferable in relation to other thoracic access approaches (transaortic and

Table 24 – Step 3: Evaluation of severe aortic stenosis symptoms

	Symptoms
Dyspnea	• Diastolic dysfunction: LV hypertrophy → reduced compliance → shifting of the ventricular pressure/volume curve up and to the left → increased filling pressures → pulmonary capillary hypertension • Systolic dysfunction: related to afterload mismatch and low-flow/low-gradient states • Patients with unclear symptomology (pseudo-asymptomatic) may undergo exercise test (ergometry or ergospirometry) for evaluation of dyspnea during exertion
Angina	• Imbalance in oxygen supply/consumption in the hypertrophic myocardium • Reduced myocardial perfusion gradient (elevated end diastolic pressure)
Syncope	• Results from inability to increase cardiac output in situations of significant reduction in total peripheral resistance • May result from use of vasodilators (common triggering agents) • 50% of cases are associated with cardioinhibitory reflex

Table 25 – Step 4: Evaluation of severe aortic stenosis prognostic factors[91-98]

	Prognostic factors
Echocardiogram	• LV dysfunction: LVEF < 50% • Markers of very severe AS: AVA < 0.7 cm^2, maximum aortic jet velocity > 5.0 m/s, mean transaortic gradient > 60 mmHg
Ergometry/ergospirometry test	• Limited functional capacity • Inadequate pressure response: increase in systolic arterial pressure less than 20 mmHg or systolic arterial pressure with a decrease greater than 10 mmHg • Arrhythmias: ventricular tachycardia or more than 4 successive ventricular extrasystoles • ST segment horizontal or descending depression ≥ 2 mm • Contraindicated in symptomatic patients and/or patients with LV dysfunction

AVA: aortic valve area; LV: left ventricle; LVEF: left ventricular ejection fraction.

Table 26 – Step 5: Type of severe aortic stenosis intervention[90,99-132]

Type	Considerations
Aortic valve replacement surgery*	• First choice for patients under 70 years without contraindication or high surgical risk* • May be indicated for patients with intermediate risk or elderly patients with low risk, depending on the Heart Team's decision and the availability of the transcatheter procedure
TAVI	• Requires evaluation of the institutional Heart Team • Transfemoral approach is preferred • First choice in patients with prohibitive surgical risk, contraindications to surgery, frailty, or intermediate risk • Expanded indication for patients with low surgical risk (STS < 4%, EuroSCORE II < 4%, logistic EuroSCORE < 10%) * Transfemoral access appears to be better than surgery in these patients There is a lack of data regarding TAVI in patients < 70 years and prosthesis durability Thus, in patients with low risk, age < 70 years, without other specific indications for TAVI, this procedure should be avoided • Angiotomography of the aorta is the exam of choice for evaluating which access to use, valve size, type of valve, and feasibility of the procedure, as well as for predicting possible complications. • Contraindicated in patients with estimated life expectancy of less than 12 months
Percutaneous balloon aortic valvuloplasty	• "Bridge" for definitive procedures (surgery or TAVI) in patients with hemodynamic instability or advanced symptoms • Palliative in cases with definitive contraindications to conventional surgery or TAVI.

** All current guidelines consider TAVI the preferred intervention, rather than surgery, for patients who are inoperable or frail and/or patients with high surgical risk (evaluated by the STS and EuroSCORE II scores). However, following the publication of American and European guidelines, 4 studies comparing TAVI and surgery in patients with low surgical risk were published. Meta-analysis of these studies demonstrated reduced 1-year mortality in transfemoral TAVI. These results suggest that transfemoral TAVI should be the preferred treatment in these patients. However, it is relevant to note that the mean age of the studied population was 75.4 years. Thus, in low-risk patients, extending to intermediate risk, we should avoid TAVI in patients under 70 years of age, until more robust data have been published regarding the durability of the prostheses. STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation.*

transapical). Transfemoral approach is less invasive, and has a lower rate of complications. For this reason, other approachs are recommended only when there is a technical contraindication to femoral access.

All current guidelines consider TAVI the preferred intervention, rather than surgery, for patients who are inoperable or frail and/or patients with high surgical risk (evaluated by the STS and EuroSCORE II scores).[99-113] However, following the publication of American and European guidelines, 4 studies comparing TAVI and surgery in patients with low surgical risk were published. Meta-analysis of these studies demonstrated reduced 1-year mortality in transfemoral TAVI. These results suggest that transfemoral TAVI should be the preferred treatment in these patients. However, it is relevant to note that the

Table 27 – Aortic stenosis: Recommendations[1,2,90,99-132]

Intervention	Clinical condition	SBC	AHA	ESC
Surgical aortic valve replacement or TAVI*	• Symptoms (NYHA FC ≥ 2, syncope and angina)	I A	I A	I B
	• Asymptomatic, with prognostic factors: LVEF < 50%	I B	I B	I C
	Exercise test +	IIa B	IIa B	I C
	• Asymptomatic, with very severe AS: AVA < 0.7 cm^2 Maximum jet velocity > 5.0 m/s Mean transaortic gradient > 60 mmHg	IIa C	IIa B	IIa C (Elevated BNP; SPAP > 60 mmHg; maximum jet velocity > 5.5 m/s)
	Special situations			
	• Severe low-flow, low-gradient AS with low LVEF: - With contractile reserve	IIa B	IIa B	I C
	- Without contractile reserve + elevated aortic calcium score	IIa C	-	IIa C
	• Severe symptomatic paradoxical AS	IIa C	IIa C	IIa C
Choice of intervention, between surgery and TAVI**	• Inoperable, prohibitive risk and/or frailty - TAVI	I A	I A	I B
	- Surgery	IIb A	-	-
	• High surgical risk - TAVI	I A	I A	I B
	- Surgery	IIa A	I A	-
	• Intermediate surgical risk - TAVI	I A	IIa B	I B
	- Surgery	IIa A	I B	I B
	• Low risk > 70 years - TAVI	I A	-	-
	- Surgery	I A	I B	I B
	• Low risk < 70 years - TAVI	IIb C	-	-
	- Surgery	I A	I B	I B
Percutaneous balloon aortic valvuloplasty *	• Symptomatic patients with important hemodynamic instability, temporarily impossible to perform definitive intervention (TAVI or conventional surgery) — "therapeutic bridge"	IIa C	IIb C	IIb C
	• Palliative treatment in symptomatic patients, with contraindications to surgery and/or TAVI.	IIb C	-	-

** Mandatory prerequisite: evaluation by the institutional Heart Team, evaluating surgical risk, frailty, anatomical conditions, and comorbidities. ** Other aspects, such as the technical feasibility, risks and benefits of each procedure, patient choice, local experience, and availability of procedures, should also be taken into consideration when choosing the technique. The American and European guidelines were published before the studies on TAVI in low surgical risk patients. We should take these data into consideration when comparing the evidence of the 3 guidelines (SBC, AHA, and ESC). AHA: American Heart Association; AS: aortic stenosis; AVA: aortic valve área; ESC: European Society of Cardiology; FC: functional class; LVEF: left ventricular ejection fraction; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology); TAVI: transcatheter aortic valve implantation.*

mean age of the studied population was 75.4 years. Thus, in low-risk patients, extending to intermediate risk, we should avoid TAVI in patients under 70 years of age, until more robust data have been published regarding the durability of the prostheses. [100,114-120]

Another relevant aspect which is unanimous in Brazilian and international guidelines is the need for a Heart Team to evaluate each case. Other aspects, such as technical feasibility, risks and benefits of each procedure, patient choice, local experience, and availability of procedures, should also be taken into consideration when choosing the type of intervention.

The following groups of patients should be monitored frequently, due to the risk of progression of the VHD (Table 28):

- Severe asymptomatic AS, without prognostic factors: To date, these patients are indicated for valve surgery only if other invasive cardiovascular procedures are indicated (coronary revascularization, ascending aorta, or other valve procedures). Studies are underway to evaluate the benefit of early intervention in this group of patients.

- Moderate AS, defined as AVA between 1.0 and 1.5 cm^2 and mean transaortic gradient 25 to 39 mmHg:

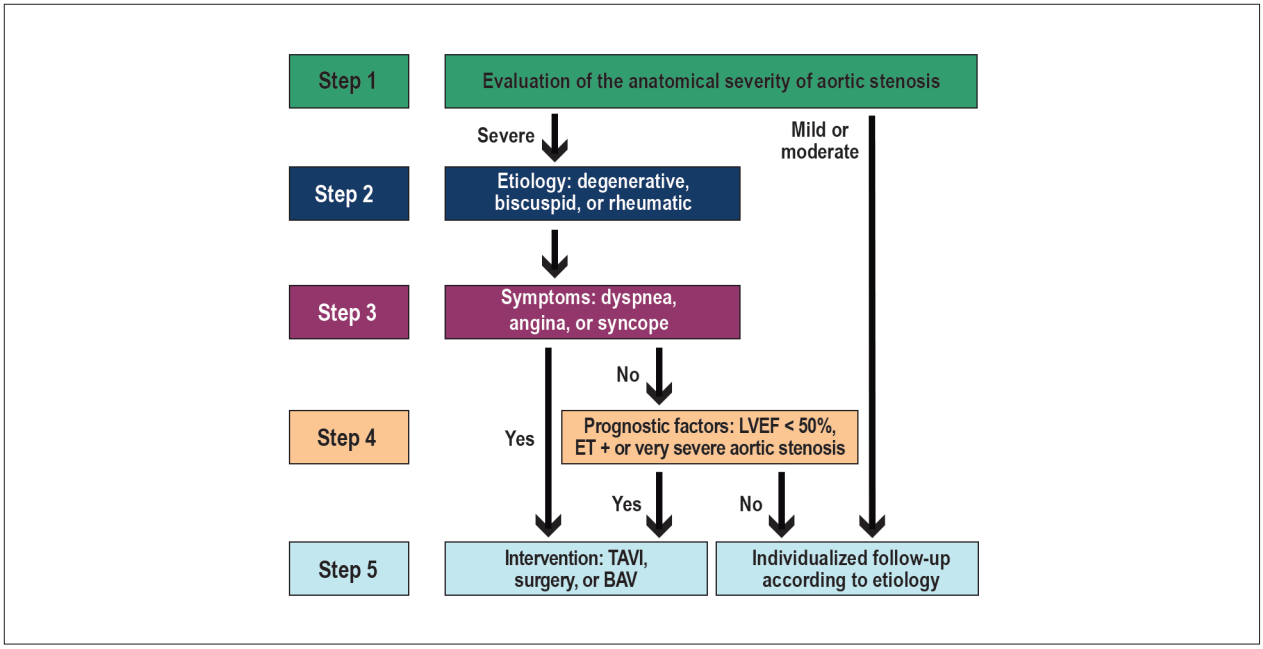

Figure 5 – *Flowchart for decision making in aortic stenosis. BAV: balloon aortic valvuloplasty; ET: exercise test; LVEF: left ventricular ejection fraction; TAVI: transcatheter aortic valve implantation.*

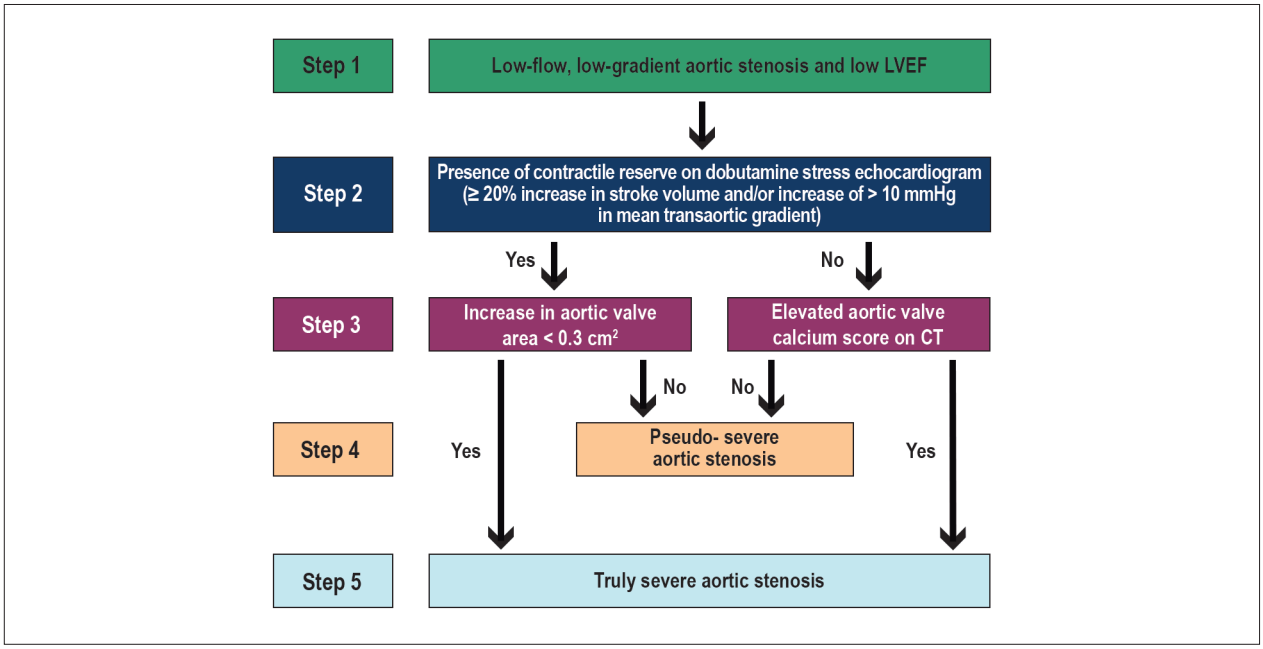

Figure 6 – *Flowchart for confirming anatomical severity of low-flow, low-gradient aortic stenosis with low ejection fraction. CT: computerized tomography; LVEF: left ventricular ejection fraction.*

These patients are indicated for valve surgery only if other invasive cardiovascular procedures are indicated (coronary revascularization, ascending aorta, or other valve procedures).

- Mild AS, defined as AVA > 1.5 cm² and mean transaortic gradient < 25 mmHg: Clinical and echocardiographic follow-up.

9. Chronic Aortic Regurgitation

The five-step clinical approach (Figure 8) is also recommended for management of chronic aortic regurgitation (AR). The first step consists of charactering AR anatomical severity, especially identifying patients with anatomically severe AR. Table 29 shows the main findings of clinical

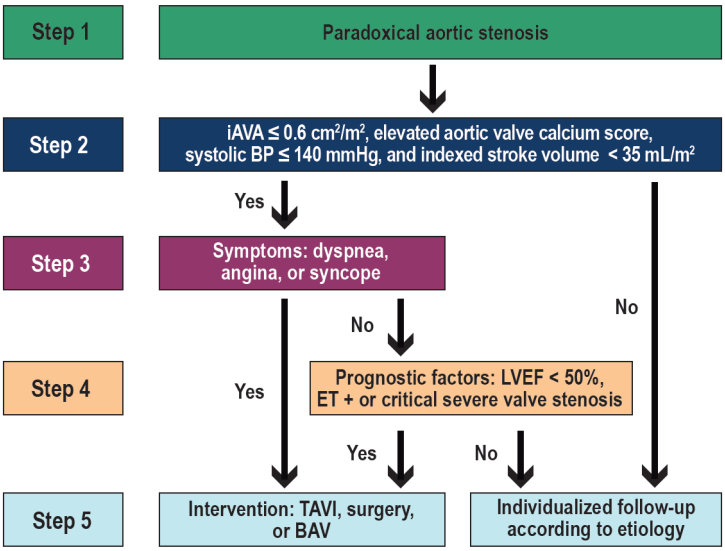

Figura 7 – *Flowchart for decision making in paradoxical aortic stenosis. BAV: balloon aortic valvuloplasty; BP: blood pressure; ET: exercise test; iAVA: indexed aortic valve area; LVEF: left ventricular ejection fraction; TAVI: transcatheter aortic valve implantation.*

Table 28 – Aortic stenosis: Individualized follow-up[1,2]

Aortic stenosis	Follow-up	SBC	AHA	ESC
Severe and asymptomatic, without prognostic factors	• Clinical and echocardiographic evaluation	Every 6 months	Every 0.5 to 1 year	Every 6 months
	• Concomitant intervention in patients who will undergo another cardiac surgical procedure (coronary revascularization, ascending aorta, or other valve procedures)	I C	I B	I C
Moderate (AVA between 1.0 and 1.5 cm² and mean transaortic gradient 25 – 39 mmHg)	• Clinical and echocardiographic evaluation	Every year	Every 1 to 2 years	Every year
	• Concomitant intervention in patients who will undergo another cardiac surgical procedure (coronary revascularization, ascending aorta, or other valve procedures)	IIa C	IIa C	IIa C
Mild (AVA > 1.5 cm² and mean transaortic gradient < 25 mmHg)	• Clinical and echocardiographic evaluation	Every 2 to 3 years	Every 3 to 5 years	Every 2 to 3 years

AHA: American Heart Association; AVA: aortic valve area; LV: left ventricle; SC: European Society of Cardiology; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).

examination and complementary methods for defining severe AR.[133,134] In general, transthoracic echocardiogram continues to be the main tool for diagnosing and scoring the severity of AR. Three-dimensional echocardiography has been increasingly incorporated into complementary evaluation, especially in cases where two-dimensional analysis is limited (eccentric jets or anatomical determination, for example, in bicuspid valve disease). Furthermore, there has recently been an increase of studies on cardiac magnetic resonance for evaluation of AR, making it possible to acquire new diagnostic and prognostic parameters, such as regurgitant fraction and estimated LV end diastolic volume.[134]

For the second step (Table 30), it is necessary to verify the etiology of AR. From the etiopathogenic point of view, chronic AR is related to anatomical abnormalities related to the valve leaflets and/or pathologies of the aortic valve annulus. The following causes are related to dysfunction of the valve leaflets: rheumatic fever (still one of the main etiologies in Brazil), infective endocarditis (IE), degenerative causes, congenital malformations such as bicuspid valve disease, and myxomatous degeneration. With respect to abnormalities related to the aortic valve annulus, it is worth underscoring dissection of the ascending aorta, aneurysmatic dilatation (mainly provoked by systemic arterial hypertension and collagen diseases

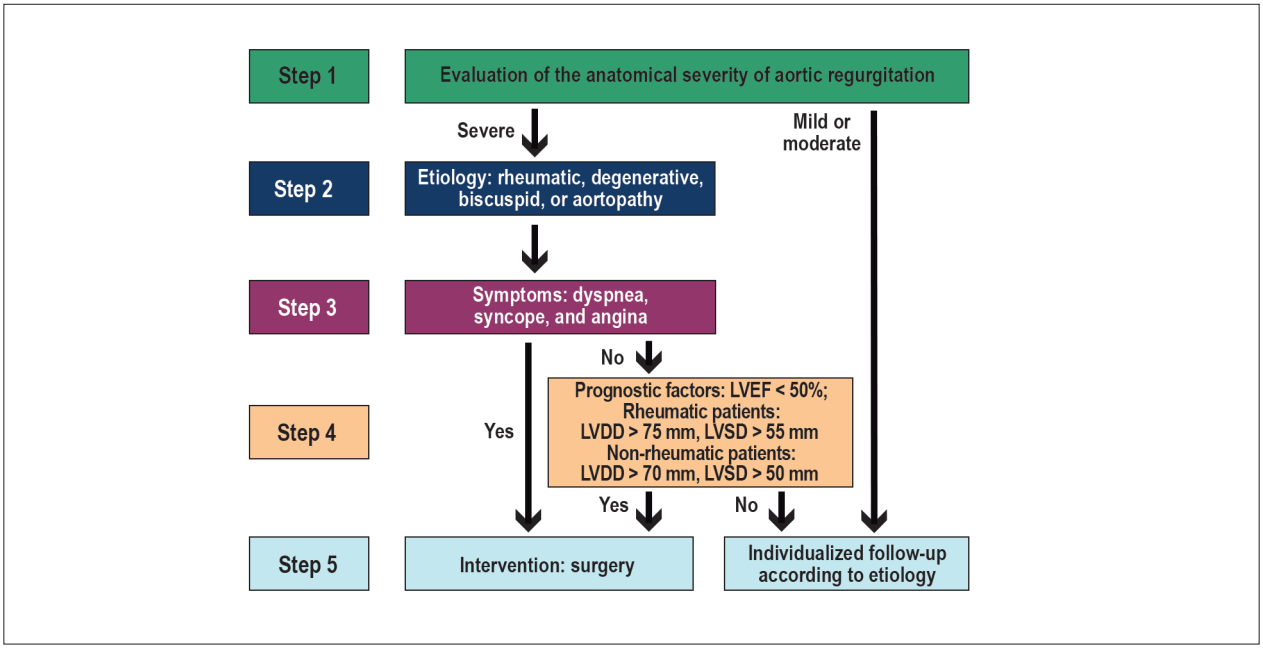

Figure 8 – *Flowchart for decision making in chronic aortic regurgitation. LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter.*

Table 29 – Step 1: Diagnosis of severe aortic regurgitation [133,134]

	Characteristics of severe aortic regurgitation
Physical examination	• Decrescendo blowing diastolic murmur with hypophonetic second heart sound • Hyperflow midsystolic murmur • Austin-Flint murmur (AR jet does not allow mitral valve opening, generating a rumbling diastolic murmur) • Water hammer pulse or Corrigan's pulse: rapid increase and high amplitude • Divergence between systolic and diastolic pressures • Clinical signs of increased pulse pressure: Musset's sign, Becker's sign, carotid dance, Muller's sign, Quincke's sign, Rosenbach's sign, Gerhard's sign, Traube's sign, Duroziez's sign, Mayne's sign, and Hill's sign
Electrocardiogram	• Signs of left chamber overload
Chest radiography	• Enlarged cardiac silhouette due to LV dilation • Signs of aortic dilation or ectasia
Echocardiogram	• Evaluation of the valve disease etiology, ascending aorta diameter, ventricular diameters, and ventricular function. • Quantification of regurgitation: - *Vena contracta* > 0.6 cm - Jet width > 0.65 cm - Jet area ≥ 60% - Regurgitant fraction ≥ 50% - Regurgitant volume ≥ 60 mL/beat - EROA ≥ 0.30 cm²
Hemodynamic study	• Necessary in cases of discordance between clinical and echocardiographic findings (elevated left ventricular end diastolic pressure, aortic regurgitation during aortography)
Magnetic resonance	• Evaluation of the aorta • Evaluation of ventricular function in borderline cases • Evaluation of valve function in cases of disagreement between clinical and echocardiographic findings • New prognostic factors: regurgitant fraction and LV end diastolic volume
Angiotomography of the aorta	• Evaluation of the aorta

AR: aortic regurgitation; EROA: effective regurgitant orifice area; LV: left ventricle.

Table 30 – Step 2: Evaluation of severe aortic regurgitation etiology[135,136]

	Etiological characteristics
Rheumatic	• High prevalence in Brazil • Generally associated with mitral lesion • Frequent in young adults
Atherosclerotic	• Generally associated with AS • Frequent in the elderly population
Bicuspid	• Associated with abnormalities in the aorta (40% of cases – aneurysm, dissection, coarctation) • Frequent in young adults
Diseases related to altered geometry of the aortic root	• Systemic arterial hypertension, dissection of the ascending aorta, Marfan syndrome, ankylosing spondylitis, syphilitic aortitis, osteogenesis imperfecta, Ehlers-Danlos syndrome, Reiter's syndrome, subaortic stenosis, and interventricular septal defect with prolapse of the aortic cusp
Others	• Infective endocarditis, myxomatous degeneration, traumatic lesions, rheumatoid arthritis

AS: aortic stenosis.

such as Marfan and Ehlers-Danlos syndromes), seronegative spondyloarthropathies (ankylosing spondylitis and Reiter's disease), syphilitic aortitis, and Takayasu arteritis.[135,136]

The third step (Table 31) is characterized by evaluation of symptoms related to AR. Identification of symptoms may be a difficult task during routine healthcare, especially in elderly patients who frequently have physical self-limitation. In these cases, provocative functional tests, such as ergospirometry, can assist in identification of these "pseudo-asymptomatic" patients. Given the high morbidity and mortality related to symptoms, once they are identified, patients should be referred for surgical intervention.

The fourth step (Table 32) focuses on evaluation of prognostic factors. This step is especially relevant for asymptomatic patients. The main prognostic factor of AR is low LV systolic function, related to systolic stress and ventricular dilation. In a retrospective study, Chaliki et al. found reduced survival in patients who had AR with LVEF below 50%. Postoperative mortality rates were also influenced by ventricular function (14% for patients with LVEF below 35%, 6.7% for LVEF between 35% and 50%, and 3.7% for patients with LVEF above 50%, p = 0.02). [137]

Ventricular remodeling continues to show clinical ambivalence: on one hand, increased ventricular diameters is an adaptive mechanism to volume overload; on the other hand, ventricular remodeling may determine worse prognosis, especially in non-rheumatic populations. In a Brazilian study carried out with 75 asymptomatic patients with rheumatic severe AR, the strategy of indicating surgical treatment based on the appearance of symptoms, even in patients with LV diastolic diameter (LVDD) greater than 75 mm and LVSD greater than 55 mm, with normal LVEF, was capable of promoting improvement in quality of life and reversal of dilation, with a 10-year survival rate of 90.6%.[138] On the other hand, prospective studies with predominant non-rheumatic AR patients found that LVSD above 50 mm was associated with composite clinical outcomes (death, symptoms, and/or ventricular dysfunction) of up to 19% yearly. There is also evidence that it would be more appropriate to used diameters indexed by body surface area, especially in women. A study of 246 patients with asymptomatic AR found that indexed LVSD values equal to or greater than 25 mm/m^2 were associated with outcomes (mortality, symptoms, and ventricular dysfunction).[139] More recently, studies have evaluated the role of brain natriuretic peptide (BNP) in AR. Cutoff values of 130 pg/mL for BNP and 602 pg/mL for NT-pro-BNP have been associated with adverse clinical outcomes. The combination of these values of BNP with echocardiographic parameters may improve the ability to stratify asymptomatic patients. Persistent elevations in BNP during clinical follow-up have also been related to adverse clinical events.[140]

Echocardiographic parameters such as longitudinal stress are also predictors of evolution in asymptomatic AR, and they also influence postoperative results. The limitation to the clinical use of longitudinal stress in AR lies in the divergence regarding cutoff points.

Another prognostic factor related to AR is late enhancement myocardial fibrosis. Cardiac magnetic resonance with late enhancement is the main imaging method capable of quantification. Studies have demonstrated that the presence of myocardial fibrosis influences the postoperative period, and it is associated with persistence of symptoms, failure to recover ventricular function, and higher mortality.[141] Also with respect to magnetic resonance, new studies have demonstrated that regurgitant fraction above 33% and LV end diastolic volume above 246 ml were associated with lower surgery-free survival. These new parameters may improve stratification of asymptomatic patients, thus ensuring more precise surgical indications.[134]

Finally, the fifth step is to define the intervention in AR (Tables 33 and 34). Surgical aortic valve replacement remains the first choice.[142,143] Surgical mortality rates range from 1% (valve replacement procedure alone) to 7% (combined procedures). The presence of symptoms, reduced LVEF, and excessive LV remodeling entail worse prognosis, and they are, therefore, the main indications for surgical treatment. As previously stated, new prognostic factors related to myocardial fibrosis, left ventricular remodeling, and biomarkers may represent potential future parameters for intervention. The clinical follow-up of patients without indication of intervention is described in Table 35.

Table 31 – Step 3: Evaluation of severe aortic regurgitation symptoms

Symptoms	
Dyspnea	• Occurs due to increased end diastolic pressure secondary to blood volume overload in the LV and consequent pulmonary capillary congestion.
Angina	• Occurs due to reduced myocardial reserve. Nocturnal angina may occur due to increased valve regurgitation resulting from bradycardia during sleep.
Syncope	• Low effective cardiac output

LV: left ventricle.

Table 32 – Step 4: Evaluation of severe aortic regurgitation prognostic factors[134,137, 137-139,141]

	Prognostic factors
Echocardiogram	• LVEF < 50% • LVDD > 70 mm (non-rheumatic) and > 75 mm (rheumatic) • LVSD > 50 mm (non-rheumatic) and > 55 mm (rheumatic) • Indexed LVSD > 25 mm/m²
Magnetic resonance	• Presence of late Gadolinium enhancement images • Regurgitant fraction > 33% • LV end diastolic volume > 246 mL
Angiotomography	• Bicuspid valve with indication of intervention + aortic root > 45 mm

LV: left ventricle; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter.

Table 33 – Step 5: Type of severe aortic regurgitation intervention[142,143]

Type of intervention	Considerations
Surgery (aortic valve replacement)	Treatment of choice Valve replacement combined with correction of the ascending aorta, when indicated
TAVI	Requires further studies

TAVI: transcatheter aortic valve implantation.

Table 34 – Aortic regurgitation: Recommendations[1,2,142,143]

Intervention	Clinical condition	SBC	AHA	ESC
Aortic valve replacement surgery	• Symptoms	I B	I B	I B
	• LVEF < 50%	I B	I B	I B
	• Ventricular diameters	IIa B Rheumatic LVDD > 75 mm or LVSD > 55 mm IIa B Non-rheumatic LVDD > 70 mm or LVSD > 50 mm or indexed LVSD >25 mm/m²	IIa C LVDD > 70 mm or LVSD > 50 mm or indexed LVSD > 25 mm/m²	IIa B LVDD > 70 mm or LVSD > 50 mm or indexed LVSD > 25 mm/m²
Transcatheter aortic valve implantation – TAVI *	• Symptomatic, with life expectancy > 1 year and contraindications/prohibitive risk of conventional surgery	IIb C*	-	-

** Consider discussion in the Heart Team. AHA: American Heart Association; ESC: European Society of Cardiology; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).*

Table 35 – Aortic regurgitation: Individualized follow-up[1,2]

Aortic regurgitation	Follow-up	SBC	AHA	ESC
Severe and asymptomatic, without prognostic factors	• Clinical and echocardiographic evaluation	Every 0.5 to 1 year	Every 0.5 to 1 year	Every 3 to 6 months
	• Concomitant intervention in patients who will undergo another cardiac surgical procedure (coronary revascularization, ascending aorta, or other valve procedures)	I C	I C	I C
Moderate (Vena contracta 0.3 – 0.6 cm, jet width 0.25 – 0.64 cm, regurgitant fraction 30% – 49%, regurgitant volume 30 – 59 mL/beat, EROA 0.10 – 0.29 cm²)	Clinical and echocardiographic evaluation	Every 1 to 2 years	Every 1 to 2 years	Every 1 to 2 years
	Concomitant intervention in patients who will undergo another cardiac surgical procedure (coronary revascularization, ascending aorta, or other valve procedures)	IIa C	IIa C	-
Mild (Vena contracta < 0.3 cm, jet width < 0.25 cm, regurgitant fraction < 30%, regurgitant volume < 30 ml/beat, EROA < 0.10 cm²)	Clinical and echocardiographic evaluation	Every 3 to 5 years	Every 3 to 5 years	Every 1 to 2 years

AHA: American Heart Association; EROA: effective regurgitant orifice area; ESC: European Society of Cardiology; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).

10. Tricuspid Stenosis

Tricuspid stenosis (TS) is a rare VHD, usually associated with tricuspid regurgitation (TR). Echocardiography remains the main tool to define anatomical severity (Table 36). [144]

The most common etiology of TS is rheumatic disease. It generally occurs concomitantly to mitral valve and/or aortic valve disease. Thickening and cusp retraction occur with commissural involvement. Other possible causes of TS, which are even rare, are described in Table 37.[145-147]

Both symptoms and physical examination are usually limited to patients with anatomically severe TS. The most commonly found symptom is fatigue, which may be associated with symptoms of right-sided heart failure (Table 38).

When asymptomatic patients have severe TS, it is necessary to evaluate whether or not there present prognostic factors (Table 39).

In the presence of these symptoms or prognostic factors, intervention is indicated. In spite of the rarity of cases and the scarcity of data in the literature, percutaneous balloon tricuspid valvuloplasty (PBTV) remains the treatment of choice (Tables 40 and 41 and Figure 9).[148]

11. Tricuspid Regurgitation

Patients with mild TR usually do not require any type of treatment. Patients with moderate to severe TR will need specific follow-up, especially in order to identify the etiology of the VHD and the repercussions associated (Table 42).[149]

TR is usually functional, secondary to dilation of the tricuspid valve annulus, mainly secondary the left heart chambers valve diseases or cardiomyopathies and/or PH. Cases of primary TR are generally related to rheumatic disease, interventions (repeated endomyocardial biopsies, presence of pacemaker electrodes, or implanTable cardioverter defibrillator), consequence of IE or other rare causes (Table 43).[150]

During severe TR natural history, symptoms may arise which will have a significant impact on decision making (Table 44).

On the other hand, even in asymptomatic patients, right ventricular remodeling can develop, which may justify valve intervention. Thus, right ventricular dilation or dysfunction (except for severe right ventricular dysfunction) should be considered as a prognostic factor (Table 45).

New data have shown the prognostic importance of TR. A recently published study found a prevalence of moderate to severe TR of 0.55%, where 72% of cases were secondary to left VHD (49.5%) or PH (23%). Only 8% of cases were isolated TR. Patients with moderate to severe TR alone show a higher mortality rate (relative risk 1.68, with 95% CI 1.04 to 2.6, p = 0.03), confirming data from the same group published in 2014.[151] The increase in mortality has also been shown in a recent meta-analysis, including 70 studies, which found almost two-fold mortality in patients with moderate to severe TR (relative risk 1.95, 95% CI 1.75 to 2.17). TR was an independent mortality predictor even after adjusting for the presence of right ventricular dysfunction, PH, AF, MR, or LV dysfunction.[152]

The interventional treatment of choice, when indicated, is tricuspid valve repair, with a prosthetic ring capable of reducing the tricuspid annulus diameter, improving valve leaflet coaptation, and correcting regurgitation. Valve replacement is reserved for patients who do not have anatomical conditions for repair. It should be noted that the isolated surgical approach to the tricuspid valve currently continues to be rarely indicated, and has surgical mortality rates varying from 8.8% to 9.7%. However, there are still no data showing improved survival with TR surgical treatment alone, despite the increased mortality rate in

Table 36 – Step 1: Diagnosis of severe tricuspid stenosis[144]

	Characteristics of severe tricuspid stenosis
Physical examination	• Early opening snap • Hyperphonetic first heart sound • Rumbling diastolic murmur, with presystolic reinforcement in patients in sinus rhythm in the left sternal border, increasing with inspiration • Systemic congestion: hepatomegaly, ascites, lower limbs edema, jugular venous stasis, Kussmaul's sign
Electrocardiogram	• Overload of the RA • AF
Chest radiography	• RA enlargement
Echocardiogram	• Tricuspid valve area ≤ 1.0 cm^2 • Mean diastolic RA/right ventricle gradient ≥ 5mmHg • Isolated RA enlargement • Tricuspid PHT ≥ 190 ms
Hemodynamic study	• Cases of clinical and echocardiographic discordance • Diastolic RA/right ventricle gradient ≥ 5 mmHg
Magnetic resonance	• Cases of clinical and echocardiographic discordance or limited quality of echocardiographic image

AF: atrial fibrillation; PHT: pressure half time; RA: right atrium.

Table 37 - Step 2: Evaluation of severe tricuspid stenosis etiology[145-147]

	Etiological characteristics
Rheumatic	• Most prevalent cause • Associated with other valvular heart diseases • Thickening with cusp retraction • Commissural involvement • Frequent in young adults
Other	• Infective endocarditis • Systemic lupus erythematosus • Carcinoid syndrome • Congenital deformities • Atrial myxoma • Actinic injury (post-radiotherapy) • Deposit disease: amyloidosis, Fabry disease • Whipple disease

Table 38 – Step 3: Evaluation of severe tricuspid stenosis symptoms

	Symptoms
Fatigue	• Main symptom • Associated with lower limbs pain and edema • Absence of dyspnea • May be associated with palpitations, ascites, or signs of hepatic dysfunction

Table 39 – Step 4: Evaluation of severe tricuspid stenosis prognostic factors

	Prognostic factors
Electrocardiogram	• AF
Systemic congestion	• Evaluation of hepatic impairment (altered enzymes or coagulogram)

AF: atrial fibrillation.

Table 40 – Step 5: Type of severe tricuspid stenosis intervention[148]

Type	Considerations
Percutaneous balloon tricuspid valvuloplasty	• Treatment of choice • Moderate TR is not a contraindication • Contraindicated in the presence of atrial thrombus despite anticoagulation and/or vegetation
Tricuspid valve replacement	• Option when balloon valvuloplasty is contraindicated • Bioprosthesis is preferable • Preferable if associated with surgery for treatment of mitral valve disease

Table 41 – Tricuspid stenosis: Recommendations[1,2,148]

Intervention	Clinical condition	SBC	AHA	ESC
Percutaneous balloon tricuspid valvuloplasty	• Severe symptomatic TS alone, without contraindications	IIa C	IIb C	-
	• Concomitant PBMV	I C	I C	-
	• PBTV with severe TR	III	-	-
Tricuspid valve replacement or repair (commissurotomy)	• Severe, symptomatic TS with contraindication to PBTV	I C	I C	I C
	• Severe, symptomatic TS alone	IIa C	I C	I C
	• Bioprosthesis is preferable, when valve replacement is indicated	I C	-	-

AHA: American Heart Association; PBMV: percutaneous balloon mitral valvuloplasty; PBTV: percutaneous balloon tricuspid valvuloplasty; ESC: European Society of Cardiology; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology); TR: tricuspid regurgitation; TS: tricuspid stenosis.

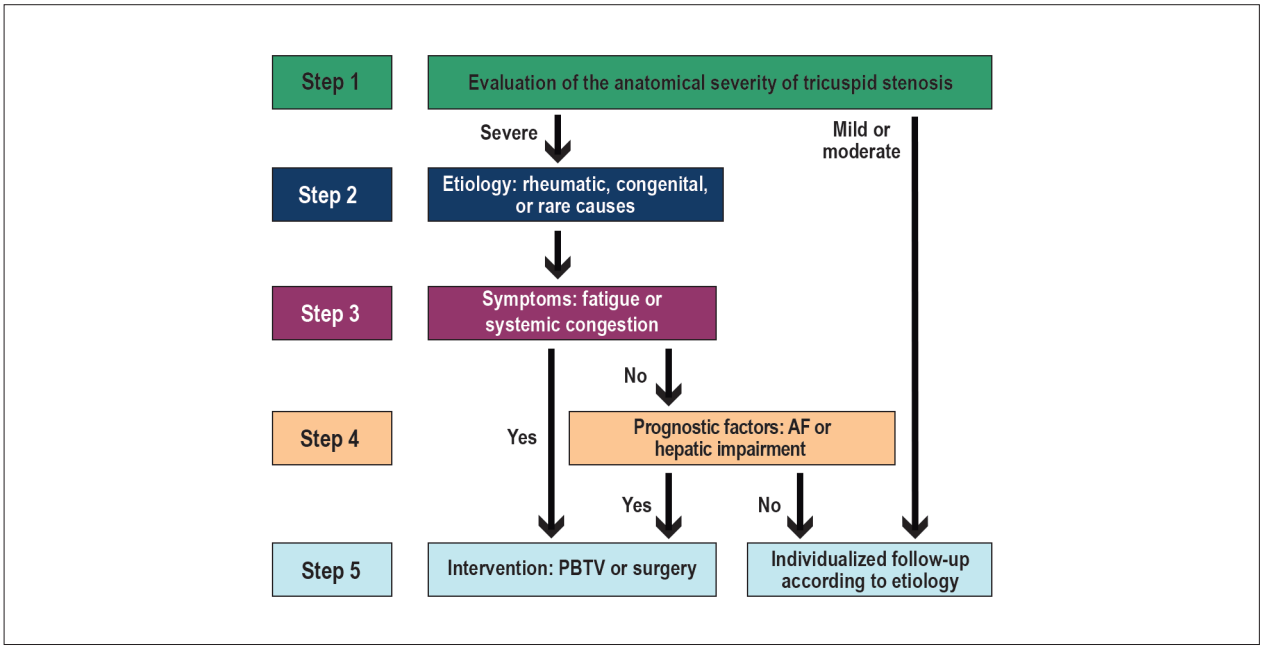

Figure 9 – *Flowchart for decision making in tricuspid stenosis. AF: atrial fibrillation; PBTV: percutaneous balloon tricuspid valvuloplasty.*

Table 42 – Step 1: Diagnosis of severe tricuspid regurgitation [149]

	Characteristics of severe tricuspid regurgitation
Physical examination	• Pathological jugular venous stasis • Hyperphonetic second heart sound (pulmonary arterial hypertension) • Regurgitative systolic murmur in the left sternal border associated with Rivero-Carvallo sign • Hepatomegaly
Electrocardiogram	• Right chamber overload • AF
Chest radiography	• Signs of enlarged right chambers • Pulmonary congestion, only when associated with left side valvular disease • Enlargement pulmonary trunk
Echocardiogram	• EROA ≥ 0.40 cm² • Reverse flow in hepatic veins • Regurgitant volume > 45 ml/beat • Dense, triangular regurgitant volume, with early peak on continuous Doppler. • *Vena contracta* ≥ 0.7 cm • Annulus diameter ≥ 40 mm • Failed cusp coaptation
Hemodynamic study	• Case of clinical and echocardiographic discordance • Measures SPAP in cases with failed cusp coaptation
Magnetic resonance	• Case of clinical and echocardiographic discordance or limited quality of echocardiographic image

AF: atrial fibrillation; EROA: effective regurgitant orifice area; SPAP: systolic pulmonary artery pressure.

Table 43 – Step 2: Evaluation of severe tricuspid regurgitation etiology[150]

	Etiological characteristics
Primary	• Rheumatic fever • Prolapse and myxomatous degeneration • Actinic injury due to radiation (post-radiotherapy) • Closed chest trauma • Infective endocarditis • Repeated endomyocardial biopsies • Carcinoid syndrome • Congenital (Ebstein) • Pacemaker electrodes or defibrillator
Secondary	• Dilation of the tricuspid annulus (> 40 mm or > 21 mm/m²) • Left heart valve disease • Long-duration AF • Primary PH • Right ventricular cardiomyopathy (ischemic, arrhythmogenic dysplasia, non-compacted myocardium, hypertrophic cardiomyopathy) Constrictive pericarditis
Rare causes	• Rheumatologic diseases • Medication (methysergide or anorexigenic drugs) • Fabry disease

AF: atrial fibrillation; PH: pulmonary hypertension.

Table 44 – Step 3: Evaluation of severe tricuspid regurgitation symptoms

Symptoms	
Dyspnea (NYHA FC II to IV)	• Secondary to left heart disease (pulmonary capillary congestion, pulmonary arterial hypertension). • Dyspnea during exertion and nocturnal paroxysmal
Fatigue	• Main symptom • Associated with lower limbs pain and edema • More common in right heart failure

FC: functional class; NYHA: New York Heart Association.

Table 45 – Step 4: Evaluation of severe tricuspid regurgitation prognostic factors

Prognostic factors	
Echocardiogram	• Primary TR: progressive right ventricular dilation or dysfunction

TR: tricuspid regurgitation.

patients with moderate to severe TR in clinical treatment. For this reason, the main reason for surgical indication, in this population, is still to improve symptoms and prevent severe right ventricular dysfunction.[153-155]

The number of studies on percutaneous interventional treatment of TR has increased. Several devices have been developed, with strategies based on reducing the tricuspid valve annulus, improving coaptation between the leaflets, or even on transcatheter valve implantation. Further data will be available soon (Tables 46 and 47 and Figure 10) [149,156-158]

12. Prosthetic Valve Dysfunction

After valve replacement surgery, periodical clinical and echocardiographic follow-up is needed for early detection of prosthesis dysfunction, as well as identification of anatomical and functional symptoms or prognostic factors.

The main test for diagnosis of prosthesis dysfunction is transthoracic echocardiogram. Nonetheless, transesophageal echocardiogram and aorta angiotomography triggered with electrocardiogram (EKG) are useful especially in the evaluation of bioprosthesis thrombosis (Tables 48 and 49).[159]

The most frequently symptom is dyspnea, resulting from pulmonary capillary congestion (Table 50).

The definition of prognostic factors in prosthesis dysfunction is complex. Patient usually already has PH, ventricular dilation, or ventricular dysfunction as a result of prior VHD. Accordingly, the progression of these abnormalities should be taken into consideration for indication of intervention (Table 51).

New procedures, such as percutaneous treatment of paravalvular regurgitation and valve-in-valve, are already included in recent guidelines (Tables 52 and 53).[159-162]

13. Multivalvular Disease

Multivalvular disease is a primary involvement of two or more valves. This classification excludes valve involvement secondary to a primary VHD, which is the case with functional TR as a consequence of mitral valve disease and MR secondary to LV remodeling as a consequence of aortic VHD (Table 54).[163-165]

In Brazil, multivalvular disease is the result of rheumatic involvement in most cases; there has been, however, a progressive increase in degenerative calcific mitral-aortic disease (Table 55).[159]

Symptoms are generally associated with the most severe valvular disease, and, in cases where both are equally severe, the most proximal valvular disease tends to prevail (Table 56).

Prognostic factors, when present, result from the most severe valvular disease (Table 57).

The standard treatment of mitral-aortic diseases with symptoms and/or prognostic factors is surgical; nonetheless, transcatheter strategies may be indicated in select cases, especially in patients assumed to be at high risk for conventional surgery (Tables 58 and 59).[163-165]

14. Evaluation of Coronary Artery Disease

Before cardiac valve surgery or transcatheter intervention for VHD, patients must undergo evaluation of coronary artery disease with coronary angiography if they meet any of the following criteria: 40 years of age or older, suspected coronary artery disease (risk factors for atherosclerosis [diabetes, dyslipidemia, arterial hypertension, and others], prior events, or angina), LV dysfunction, or in order to evaluate the etiology in secondary MR.[166-168] Coronary tomography angiography may be used in patients with low or intermediate probability of coronary artery disease. If coronary tomography shows significant or unclear lesions, the patient should undergo coronary angiography (Table 60).[169-171]

15. Anticoagulation

The two prognostic factors with the greatest impact on the natural history of valve disease are hemodynamic repercussions and thromboembolism. Stroke is the most clinically significant thromboembolic event, affecting up to 20% of individuals with AF associated with valve disease. The CHA_2DS_2-VASc score is recommended for decision making regarding anticoagulation, except for patients with rheumatic MS or those with mechanical prostheses. The criteria for anticoagulation are the same for patients with paroxysmal, persistent, or permanent AF. The main indications for anticoagulation are described in Table 61.

Oral anticoagulation, as a means of preventing thromboembolic events in patients with valve disease, is still predominantly carried out with vitamin K antagonists (VKA); warfarin currently represents this class of drugs in Brazil. It is a safe strategy to start warfarin at a dose of 5 mg/day in individuals under 65 years of age and 2.5 mg/day in individuals over 65 years. Prothrombin time should be measured on the third day to evaluate hyper-responsiveness to the medication and again on the fifth day, after which the dose proceeds to be adjusted. During this phase, exams should be carried out at 5-day intervals until the therapeutic level has been reached. The international normalized ratio (INR) should remain between 2.0 and 3.0, except in patients who have mechanical prostheses in the mitral position, aortic mechanical prosthesis associated with AF, hypercoagulable states, and cardioembolic events while INR is between 2.0 and 3.0. In these cases, the target becomes 2.5 to 3.5. INR control is usually performed on a monthly basis; in patients whose doses have been sTable for a long time and who have not been exposed to any new factors

Table 46 – Step 5: Type of severe tricuspid regurgitation intervention[149,151-158]

Type	Considerations
Tricuspid repair with a prosthetic ring	• Treatment of choice
	• Indications: - Left valvular heart disease intervention in the presence of tricuspid annulus ≥ 40 mm and/or moderate to severe tricuspid regurgitation - tricuspid regurgitation alone, refractory to clinical treatment, low surgical risk, without contraindications.
	• Contraindications: severe right ventricular systolic dysfunction
Surgical valve replacement	• If repair is possible • Bioprosthesis is preferable
Transcatheter tricuspid valve implantation	• Refractory symptoms, with contraindication or high surgical risk (currently under study)

Table 47 – Tricuspid regurgitation: Recommendations[1,2,149,151-158]

Intervention	Clinical condition	SBC	AHA	ESC
Tricuspid repair with a prosthetic ring	• Left valvular heart disease intervention and severe TR	I C	I C	I C
	• Left valvular heart disease intervention and tricuspid annulus ≥ 40 mm	IIa C	IIa B	IIa C
	• Left valvular heart disease intervention, severe TR, and signs of right ventricular dysfunction	IIa C	IIa B	IIa C
	• Left valvular heart disease intervention, moderate to severe TR, and/or annulus ≥ 40 mm and SPAP ≥ 70 mmHg	IIa C	IIb C	IIa C
	• Severe TR alone, refractory to clinical treatment	IIa C	IIa C	IIa C
	• Severe primary asymptomatic TR alone, with right ventricular dilation or progressive dysfunction	IIb C	IIb C	IIa C
Surgical valve replacement	• Repair not possible	I C	I C	I C
	• Bioprosthesis preferable	I B	-	-
Transcatheter tricuspid valve implantation	• Refractory to clinical treatment, with contraindication or high surgical risk (currently under study)	IIb C*	-	-

** Consider discussion in the Heart Team. AHA: American Heart Association; ESC: European Society of Cardiology; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology); TR: tricuspid regurgitation.*

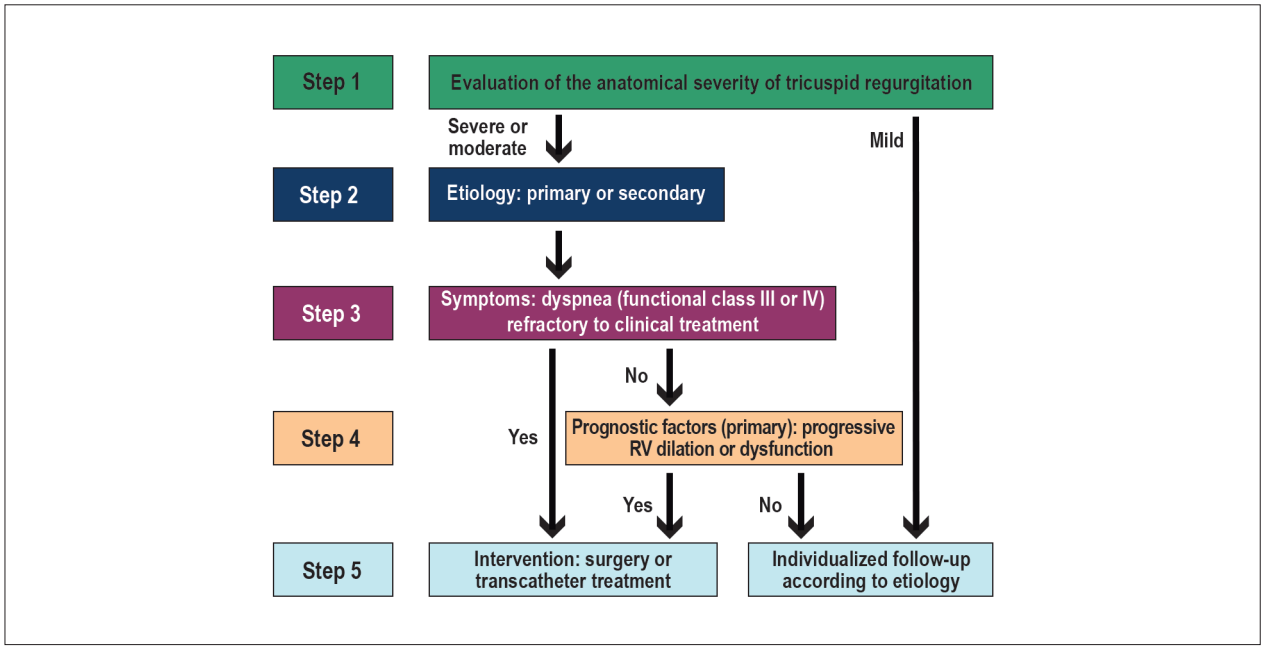

Figure 10 – *Flowchart for decision making in tricuspid regurgitation. RV: right ventricular.*

Table 48 – Step 1: Diagnosis of severe prosthetic valve dysfunction

	Characteristics of severe prosthetic valve dysfunction
Physical examination	• Clinical signs according to the predominant type of prosthesis dysfunction
Electrocardiogram	• Abnormalities according to the predominant type of prosthesis dysfunction
Chest radiography	• Abnormalities according to with the predominant prosthesis dysfunction
Transthoracic echocardiogram	• Evaluation the type of valve dysfunction and confirmation severity of the dysfunction - thickening of leaflets - calcification and mobility of leaflets - reduced EOA - transvalvular gradient - valve regurgitation • Evaluation of ventricular systolic dysfunction • Progressive evaluation of the cardiac chambers diameters
Transesophageal echocardiogram	• Inadequate window for transthoracic echocardiogram • Severe paravalvular regurgitation with favorable anatomy for percutaneous intervention • Indicated to improve anatomical evaluation
Hemodynamic study with manometry	• Cases of clinical and echocardiographic discordance
Angiotomography of the aorta triggered with EKG	• Evaluation of the aorta • Evaluation of bioprosthesis thrombosis and TAVI

EOA: effective orifice area; EKG: electrocardiogram; TAVI: transcatheter aortic valve implantation.

Table 49 – Step 2: Evaluation of severe prosthetic valve dysfunction etiology[159]

	Etiological characteristics
Prosthesis stenosis	• **Mechanical prosthesis:** thrombosis pannus • **Biological prosthesis:** leaflets degeneration leaflets calcification prosthesis-patient mismatch (indexed EOA ≤ 0.85 cm^2/m^2)
Prosthesis regurgitation	• **Central:** leaflets degeneration (rupture, perforation) leaflets calcification • **Paravalvular:** infective endocarditis annulus degeneration

EOA: effective orifice area.

Table 50 – Step 3: Evaluation of severe prosthetic valve dysfunction symptoms

Symptoms	
Dyspnea (NYHA FC II to IV)	• Pulmonary capillary congestion according to predominant dysfunction

FC: functional class; NYHA: New York Heart Association. FC: functional class; NYHA: New York Heart Association.

Table 51 – Step 4: Evaluation of severe prosthetic valve dysfunction prognostic factors

	Prognostic factors
Echocardiogram	• Progression of ventricular systolic dysfunction • Progression of LV remodeling (in the event that initial diameters are elevated) • PH • Severe bioprosthesis calcification
Hemolytic anemia	• Occurs in cases of severe prosthetic valve regurgitation, especially if it is paravalvular

LV: left ventricle; PH: pulmonary hypertension.

Table 52 – Step 5: Type of severe prosthetic valve dysfunction intervention[159-162]

Type	Considerations
Surgery (valve re-replacement)	• Treatment of choice • Indications: severe prosthetic valve dysfunction, with symptoms and/or severe hemolytic anemia
Transcatheter intervention – valve-in-valve	• Mitral or aortic bioprosthesis dysfunction in symptomatic high surgical risk or inoperable patients (before Heart Team evaluation)
Percutaneous occlusion of paravalvular regurgitation	• Severe paravalvular regurgitation associated with hemolytic anemia or heart failure symptoms (NYHA FC III/IV), in patients with high surgical risk and favorable anatomy for the procedure

FC: functional class.

Table 53 – Prosthetic valve dysfunction: Recommendations[1,2,159-162]

Intervention	Clinical condition	SBC	AHA	ESC
Prosthesis replacement surgery	• Symptomatic severe prosthetic valve dysfunction	I B	I B	I C
	• Hemolytic anemia	IB	I B	I C
	• Severe asymptomatic prosthetic valve dysfunction, with low surgical risk	IIa C	IIa C*	IIa C
Percutaneous occlusion of paravalvular regurgitation	• Hemolysis or symptoms, with favorable anatomy and high surgical risk, before Heart Team evaluation.	IIa B	IIa B	-
Valve-in-valve	• Severe bioprosthesis dysfunction, in high surgical risk or inoperable symptomatic patients, before Heart Team evaluation.	IIa B	IIa B	IIa C

** Aortic bioprosthesis with regurgitation. AHA: American Heart Association; ESC: European Society of Cardiology; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).*

Table 54 – Step 1: Diagnosis of severe multivalvular disease[163-165]

	Characteristics of severe multivalvular disease
Physical examination	• Presence of murmurs distinctly characterized as mitral and aortic – regurgitation, stenosis, or double lesion. • Rule out the possibility of murmur caused by hemodynamic interference (for example, Austin-Flint murmur) • Rule out the possibility of valve involvement secondary to a primary valvular heart disease (for example, TR secondary to mitral disease) • Physical examination is especially important for defining predominance of one of the valvular heart diseases
Electrocardiogram	• Left ventricular hypertrophy and/or left atrial enlargement, depending on the predominant valvular heart disease • AF in severe mitral valvular heart diseases
Chest radiography	• Increased cardiothoracic index, especially in association with regurgitant valvular diseases • Signs of pulmonary congestion • Signs of right ventricular overload in associated mitral stenotic lesion
Echocardiogram	• Echocardiographic findings vary by valvular heart disease
Hemodynamic study	• Indicated when there is disagreement between clinical and echocardiographic findings

AF: atrial fibrillation; LV: left ventricle; TR: tricuspid regurgitation.

Table 55 – Step 2: Evaluation of severe multivalvular disease etiology[159,163-165]

	Etiological characteristics
Rheumatic fever	• > 95% of cases • Typical in young patients • Frequent extemporaneous evolution • Symptoms between 20 and 40 years • Commissural fusion, thickening of leaflets, frequent double dysfunction – complex pathophysiology • Impaired subvalvular apparatus
Infective endocarditis	• Valve regurgitation due to destruction of the mitral and/or aortic apparatus • Aortic-mitral metastatic infection
Valvular apparatus calcification	• Elderly patients • Associated with degenerative aortic valvular disease • Calcification of the mitral valve annulus with caseous calcification • Absence of commissural fusion • Related to aortic and coronary calcification
Marfan or Ehlers-Danlos syndrome	• Mitral and aortic valve regurgitation • Investigate involvement of the ascending aorta

Table 56 – Step 3: Evaluation of symptoms

	Symptoms
Dyspnea (NYHA FC II to IV)	• Main symptom • Initially with events that increase pulmonary capillary pressure • May be accompanied by palpitations, hemoptysis, dysphonia, dysphagia, or cough • Associated right heart failure in patients with pulmonary hypertension
Precordial pain	• Especially when associated with regurgitant or stenotic aortic valvular heart disease • May be caused by PH
Low output or syncope	• Especially present with associated AS and MR

AS: aortic stenosis; MR: mitral regurgitation; PH: pulmonary hypertension.

Table 57 – Step 4: Evaluation of severe multivalvular disease prognostic factors

	Prognostic factors
Pulmonary hypertension	• Resting SPAP ≥ 50 mmHg • Most often present with associated MS • Symptoms of right heart failure • Related to increased surgical risk
Recent onset AF	• Related to LA remodeling
Increased ventricular diameters	• Consider diameters depending on the type of valve lesion

LA: left atrium; MS: mitral stenosis; SPAP: systolic pulmonary artery pressure.

Table 58 – Step 5: Type of severe multivalvular disease intervention[163-165]

Type	Considerations
Percutaneous balloon mitral valvuloplasty	• Cases of severe MS with favorable anatomy and moderate aortic valvular heart disease
Surgical treatment (commissurotomy or valve replacement)	• Conservative mitral valve surgery when stenosis is predominant • Avoid aortic valve repair – frequent recurrence of valvular heart disease and symptoms, even with good immediate results • Treatment of anatomically moderate valvular heart disease concomitant to intervention for severe valvular disease
Transcatheter treatment – valve-in-valve	• Mitral and aortic bioprosthesis dysfunction, in symptomatic patients who have high surgical risk or are inoperable (following evaluation by the Heart Team)
Transcatheter treatment – TAVI and percutaneous mitral repair	• Severe AS and severe primary MR, in patients with symptoms and/or prognostic factors, when there is a high surgical risk or contraindication to surgery (following evaluation by the Heart Team)

MR: mitral regurgitation; MS: mitral stenosis; TAVI: transcatheter aortic valve implantation.

Table 59 – Multivalvular disease: Recommendations[1,2,163-165]

Intervention	Clinical condition	SBC	AHA	ESC
Percutaneous balloon mitral valvuloplasty	• Severe symptomatic MS with favorable anatomy and aortic moderate lesion	I A	-	-
Surgical treatment/valve replacement	• Symptomatic multivalvular disease	I B	I B	I B
	• Multivalvular disease with prognostic factors	IIa C	-	-
	• Treatment of moderate valve lesion concomitant to treatment of severe valvular disease or other cardiac or ascending aorta surgery	I C	I C	I C
Transcatheter treatment – valve-in-valve	• Mitral and aortic biological prosthesis dysfunction with symptoms and high surgical risk	IIb C	-	-
	• Mitral and aortic biological prosthesis dysfunction with prognostic factors and high surgical risk	IIb C	-	-
Transcatheter treatment – TAVI and percutaneous mitral repair	• Severe AS and severe primary MR with symptoms and high surgical risk	IIb C	-	-
	• Severe AS and severe primary MR with prognostic factors and high surgical risk	IIb C	-	-

AHA: American Heart Association; AS: aortic stenosis; MR: mitral regurgitation; MS: mitral stenosis; ESC: European Society of Cardiology; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology); TAVI: transcatheter aortic valve implantation.

Table 60 – Intervention in coronary artery disease concomitant to valve Intervention: Recommendations[1,2,166-171]

Intervention	Clinical condition	SBC	AHA	ESC
Myocardial revascularization surgery	Indication of valve surgery and coronary lesion ≥ 70%	I C	IIa C	I C
Coronary angioplasty	Indication of transcatheter valve intervention and coronary lesion ≥ 70% in a proximal segment	IIa C	IIa C	IIa C

AHA: American Heart Association; ESC: European Society of Cardiology; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).

Table 61 – Indications for oral anticoagulation[1,2, 172-183]

Clinical condition	Medication	SBC	AHA	ESC
Native valve				
• MS with AF and/or LA thrombus*	Warfarin	I B	I B	I B
	DOACs	III C	III C	III C
	ASA	IIb B	-	-
• Other valvular heart diseases with AF	Warfarin	I B	I C	I B
	DOACs	IIa C	IIa C	IIa B
	ASA	IIb B	-	-
• Previous embolic event without AF	Warfarin	I B	I B	-
	DOACs	III C	-	-
	ASA	IIb C	-	-
Biological prosthesis				
• AF	Warfarin	I B	I B	I C
	DOACs	IIb B	-	-
	ASA	IIb C	-	-
• Sinus rhythm – mitral bioprosthesis (first 3 to 6 months)	Warfarin	IIb	IIa B	IIa C
	DOACs	III C	-	-
	ASA	IIb	-	-
• Sinus rhythm – aortic bioprosthesis (first 3 to 6 months)	Warfarin	IIb B	IIa B	IIb C
	DOACs	III C	-	-
	ASA	IIb B	-	IIa C
TAVI				
• AF	Warfarin	I B	-	-
	DOACs	IIb C	-	-
	ASA + clopidogrel	III B	-	-
	ASA	III C	-	-
• Sinus rhythm	Warfarin	III B	IIb B (3 months)	IIb C (3 months)
	DOACs	III B	-	-
	ASA or clopidogrel, indefinitely	IIa B	-	IIb C
	ASA + clopidogrel, 3 to 6 months	IIb B	IIb C	IIa C
• Sinus rhythm + angioplasty with stent (chronic coronary artery disease)	ASA + clopidogrel up to 12 months, according to stent type	IIa C	IIb	-
• AF + angioplasty with stent (chronic coronary artery disease)	DOAC + clopidogrel	IIa C	-	-
	Warfarin + ASA + clopidogrel 1 month, followed by warfarin + clopidogrel up to 12 months	IIb C	-	-
Mechanical prosthesis				
	Warfarin	I B	I A	I B
	DOACs	III B	III B	III B
	Warfarin + routine ASA	III C	IIa B	-
	Warfarin + ASA after a thromboembolic event within therapeutic INR	IIa B	-	IIa C

** Consider anticoagulation with warfarin in individuals with MS and episodes of sustained atrial tachycardia or enlarged LA (≥ 50 mm anteroposterior diameter or ≥ 50 ml/m² LA volume) and spontaneous contrast. AF: atrial fibrillation; AHA: American Heart Association; ASA: acetylsalicylic acid; DOACs: direct oral anticoagulants; ESC: European Society of Cardiology; INR: international normalized ratio; LA: left atrium; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology); TAVI: transcatheter aortic valve implantation.*

that interact with warfarin (Table 62), the control may be done every two months. In the event that INR is above the target, a new exam should be performed on an earlier basis, in 1 to 2 weeks. Dose adjustments should be, on average, 10% to 15% of the weekly dose, and it is necessary to investigate which factors caused the oscillation in INR. Monitoring of prothrombin time with point of care devices provides quick and reliable information; its availability, however, is still limited due to the high cost of the device and the strips.

It is known that greater time in therapeutic range (TTR) is associated with lower risk of thromboembolic events and bleeding. In a study including 119 patients with mitral valve disease and AF, 78.2% of individuals had INR < 2.0 at the time of the thromboembolic event. For INR values < 1.7 the likelihood doubled, and it tripled for values < 1.5. The difficulties of managing VKA are result of the wide variability in individual dose and interactions with foods and medications, in addition to the need for frequent monitoring. Patients should be advised to avoid alcohol consumption and to maintain a balanced diet, especially in relation to foods that are rich in vitamin K, such as greens and vegetables. These foods should not be excluded from the dietary routine.

Over the past years, the role of direct oral anticoagulants (DOACs) has progressively increased. Dosages of medications available in Brazil can be found in Table 63. Multiple clinical trials involving patients with VHD are underway. Most of the current information is from analyses of subgroups of the main studies on DOACs, as well as retrospective cohort studies.

In patients with mechanical prostheses, pre-clinical trials involving animals have suggested that the use of DOACs could be as safe as warfarin. However, the clinical Dabigatran versus Warfarin in Patients with Mechanical Heart Valves (RE-ALIGN) study, which compared dabigatran and warfarin, was prematurely terminated due to greater occurrence of the combined outcome of stroke, transient ischemic attack, systemic embolism, myocardial infarction, and death (9% versus 5%; hazard ratio 1.94, 95% CI 0.64 to 5.86) and bleeding (27% versus 12%, p < 0.05) in the first group. The study included 252 patients, and it used dabigatran at doses of 150, 220, and 300 mg, administered every 12 hours, according to creatinine clearance, with dose adjustments for serum level above 50 ng/mL. For this reason, we do not indicate the use of DOACs in patients with mechanical prostheses.[176]

Although the large clinical trials that have validated the use of DOACs in AF excluded individuals with severe MS and mechanical valve prostheses, these studies did include individuals with other VHD. In the Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) study, 26.4% of participants had moderate or severe VHD; in the Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY) study, 21.8%; in the Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) study, 14.1%; and, finally, in the Edoxaban versus Warfarin in Patients with Atrial Fibrillation (ENGAGE AF) study, 13%. Subanalyses of these studies suggest the efficacy of DOACs in comparison with warfarin in individuals with AF and valve disease,

Table 62 – Warfarin dose adjustments

INR value	Dose adjustment
≤ 1.5	Increase weekly dose by 15%
1.51 – 1.99	Increase weekly dose by 10%
2 – 3*	Maintain dose
3.01 – 4.0	Reduce weekly dose by 15%
4.01 – 4.99	Suspend 1 dose and reduce weekly dose by 10%
5.0 – 8.99	Suspend warfarin until INR is 2 to 3 then start again with weekly dose reduced by 15%
≥ 9.00	Hospitalization, suspend warfarin for an average of 4 days, prescribe vitamin K at a dose of 1 to 2.5 mg orally, repeating 24 to 48 hours later if INR does not decrease to < 5.0, and restart anticoagulation once INR is close to target value (below 4)

** Consider maintaining the weekly dose of warfarin with INR up to 3.5, provided that the medication has not been initiated recently, and perform new measurement in 1 to 2 weeks. In case of the therapeutic INR goal is between 2.5 and 3.5, dose adjustments should occur adding 0.5 to the above values, with the exception of INR ≥ 9.0. INR: international normalized ratio.*

Table 63 – Dose of direct oral anticoagulants for prophylaxis of thromboembolic events in atrial fibrillation[177-180]

Anticoagulant	Usual dose	Dose adjustment	Contraindications
Dabigatran	150 mg twice daily	≥ 80 years of age and/or high risk of bleeding: 110 mg twice daily	Creatinine clearance < 30 mL/min, concomitant use of ketoconazole
Rivaroxaban	20 mg once daily	15 mg once daily if creatinine clearance is < 50 mg/dL	Creatinine clearance < 15 mL/min, hepatic disease associated with coagulopathy
Apixaban	5 mg twice daily	2.5 mg twice daily in patients with at least 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL	Creatinine clearance < 15 mL/min, hepatic disease associated with coagulopathy
Edoxaban	60 mg once daily	30 mg once daily	Creatinine clearance > 95 mL/min or < 15 mL/min

excluding patients with mechanical prostheses and severe MS. The ARISTOTLE and ENGAGE-AF studies included individuals with bioprostheses. [177-180]

Notwithstanding the negative results in individuals with mechanical valve prostheses, dabigatran has been shown to be effective in preventing intracardiac thrombus formation in individuals with aortic and/or mitral biological prosthesis in a Brazilian single-center study, Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively (DAWA).[175]

A South Korean cohort with 2,230 patients evaluated individuals with AF and MS of different etiologies and degrees of anatomical severity, comparing off-label use of DOACs in relation to warfarin. Ischemic events occurred in 2.22% yearly in the DOAC group versus 4.19% yearly in the warfarin group (hazard ratio 0.28; 95% CI 0.18 to 0.45), and intracranial bleeding occurred in 0.49% in the DOAC group versus 0.93% in the warfarin group (hazard ratio 0.53; 95% CI 0.22 to 1.26). This study reinforces the hypothesis of the efficacy of DOACs in MS. Attention should be paid to the fact that TTR of INR was not evaluated in this cohort. [181] In a multi-center observational study, Korean patients had only 31% of INR values within the therapeutic target.

The first antithrombotic regimen adopted for individuals undergoing TAVI in sinus rhythm was dual antiplatelet therapy with ASA and clopidogrel for 6 months, inferring from experience with stents and based on the expected period for endothelialization of the prosthesis to occur. In a meta-analysis of three recent small clinical trials, antiplatelet therapy with ASA or clopidogrel alone did not show an increase in 30-day mortality (odds ratio 5.2 versus 3.2%, p = 0.447) or ischemic events (3.8 versus 3.8%, p = 0.999), when compared with dual antiplatelet therapy; furthermore, there was a higher chance of bleeding in the dual antiplatelet therapy group (odds ratio 2.24; 95% CI 1.12 to 4.46; p = 0.022). [173]

There is evidence, from transesophageal echocardiogram and computed tomography angiography, of the occurrence of thickening of the leaflets after TAVI in up to 13% of patients, which may correspond to the formation of thrombi, and it has been associated with increased incidence of transient ischemic attack and stroke.[174] Observational cohort studies where individuals received VKA or DOACs have indicated that the use of these medications could be safe for prevention of events. However, the recently published multi-center Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) study, which included 1,644 patients without established indication for dual antiplatelet therapy or anticoagulation, comparing the use of rivaroxaban 10 mg/day (associated with ASA 75 – 100 mg/day during the first 3 months) versus ASA 75 – 100 mg (associated with clopidogrel 75 mg/day during the first 3 months). The study was prematurely terminated due to greater occurrence of thrombotic events (9.8 and 7.2 per 100 person-years; hazard ratio 1.35, 95% CI 1.01 to 1.81; p = 0.04), bleeding (4.3 and 2.8 per 100 person-years; hazard ratio 1.5, 95% CI 0.95 to 2.37; p = 0.08), and death (5.8 and 3.4 per 100 person-years; hazard ratio 1.69, 95% CI 1.13 to 2.53) in the rivaroxaban group. [172]

15.1. Surgical Procedures

In surgical procedures with low risk of bleeding, where hemostasis is possible, such as cataract surgery, glaucoma surgery, small dermatological surgeries, dental or gum surgeries, periodontal scraping and simultaneous extraction of up to 3 teeth, it is suggested to maintain oral anticoagulation. In the case of warfarin, INR should be within the therapeutic range, as measured 24 to 48 hours before the procedure. In the case of DOACs, ideally, the procedure should not be performed during the hours following use of these medications, in order to avoid their peak plasma concentrations.

With respect to procedures that imply higher risk of bleeding due to the size of the surgery or difficulty in achieving hemostasis, heparin bridging is indicated in individuals using VKA. These procedures include coronary angiography, endoscopy or colonoscopy with polypectomy, postectomy, vasectomy, internal organ biopsies, and larger surgeries. In these cases, warfarin should be suspended during the 5 days preceding the procedure, starting heparin 3 days before the procedure. In the case of low molecular weight heparin, the last dose should be administered 24 hours before the procedure, and unfractionated heparin should be suspended 4 to 6 hours before the surgery. Heparin is generally reintroduced 12 hours later, provided that hemostasis is adequate. Warfarin is, generally, restarted on the following day. INR should be measured in 5 days, and heparin should be suspended as soon as the therapeutic target has been reached. In emergency surgeries, 50 IU/kg prothrombinic complex should, ideally, be administered intravenously.

The rapid onset of action of DOACs (2 to 4 hours) and their short elimination half-life dispense with the need of using a heparin bridge. For elective procedures with low risk of bleeding, suspension is recommended 24 hours before surgery, and, in cases with elevated risk of bleeding or sites with difficult hemostasis, the recommendation is to suspend 48 hours before. In emergency surgery, use of the antidote idarucizumab is recommended in individuals using dabigatran, with a total dose of 5 g endovenously (two 2.5-g aliquots). Andexanet alfa (Andexxa), an antidote to factor Xa inhibitors, is not yet available in Brazil.

16. Prosthetic Valve Thrombosis

Prosthetic valve thrombosis is an uncommon event; it is more frequent in mechanical prostheses, especially in the mitral position, and it is associated with high morbimortality. It may be asymptomatic or it may manifest with heart failure syndrome, low output, and even death. Diagnosis and suspicion are usually made after transthoracic echocardiogram, and they may be confirmed by the transesophageal method (Tables 64, 65, and 66).

The main prognostic factor of thrombosis is thrombus size, due to the risk of embolism and valve obstruction (Table 67).

Table 64 – Step 1: Diagnosis of prosthetic valve thrombosis

	Characteristics of prosthesis thrombosis
Clinical evaluation	• Symptoms and signs suggestive of acute or exacerbated heart failure (dyspnea, chest pain, low output, or syncope) • Murmur compatible with stenotic valvular heart disease • Muffled clicking sound • Possibility of ineffective anticoagulation (INR outside therapeutic range)
Electrocardiogram	• Compatible with the baseline disease that was the reason for valve surgery • Rarely shows acute alteration
Chest radiography	• Compatible with the baseline disease that was the reason for valve surgery • Rarely shows acute alteration of the cardiac silhouette • Pulmonary congestion may be present
Echocardiogram	• Key test for diagnosis • Ideally transesophageal • Documentation of thrombus adhering to the prosthesis, identification of location and size of the thrombosis
Hemodynamic study (fluoroscopy)	• Inadequate mobility of one or more leaflets of the mechanical prosthesis

INR: international normalized ratio.

Table 65 – Step 2: Evaluation of prosthetic valve thrombosis etiology

	Etiological characteristics
Ineffective anticoagulation	• Interruption of anticoagulation • Drug/behavioral interaction • INR below therapeutic target

INR: international normalized ratio.

Table 66 – Step 3: Evaluation of prosthetic valve thrombosis symptoms

	Symptoms
Dyspnea	• Main symptom • Distinguish between mild worsening (NYHA FC I) and more evident symptoms (NYHA FC II to IV)
Precordial pain	• Possibility of coronary embolism
Low output or syncope	• Indicative of a severe obstruction

FC: functional class.

Table 67 – Step 4: Evaluation of prosthetic valve thrombosis prognostic factors

	Prognostic factors
High risk of embolization associated with thrombolysis	• Thrombus > 8 mm • Mobile thrombus (pedunculated)
Pulmonary hypertension	• Resting SPAP ≥ 50 mmHg • More frequent when there is associated MS • Clinically – symptoms of right heart failure • Related to increased surgical risk
Recent onset AF	• Related to significant LA remodeling

AF: atrial fibrillation; LA: left atrium; MS: mitral stenosis; SPAP: systolic pulmonary artery pressure.

The recommendations of international guidelines are heterogeneous in relation to treatment, and there is a lack of randomized studies in this area (Tables 68 and 69). In prosthesis thrombosis without significant hemodynamic repercussion (NYHA FC I and II), without valve obstruction on complementary tests, oral anticoagulation and outpatient monitoring with imaging are indicated. In the event of a large (especially greater than 8 mm) and/or mobile thrombus, which has an elevated risk of embolization, hospitalization with parenteral anticoagulation is indicated. In the event that the thrombus is not reduced on imaging tests, performed every 5 to 7 days, fibrinolysis and/or surgery may be considered.[184,185]

In cases where there is a more significant hemodynamic impairment (NYHA FC III and IV), fibrinolytic therapy or

Table 68 – Step 5: Type of prosthetic valve thrombosis intervention[184,185]

Type	Considerations
Thrombolysis	• Priority therapy • rTPA 10 mg (bolus), followed by 90 mg in 2 hours OR Streptokinase 500,000 IU in 20 minutes, followed by 1,500,000 IU in 10 hours
Valve surgery	• Reserved for cases with high risk of hemorrhagic or embolic complications associated with thrombolysis

rTPA: recombinant tissue plasminogen activator.

Table 69 – Prosthesis thrombosis: Recommendations[1,2,184,185]

Intervention	Clinical condition	SBC	AHA	ESC
Thrombolysis	• Valve thrombosis in a right chamber	IIa B	IIa B	-
	• Small thrombus (< 0.8 cm²), NYHA FC I to III, left chambers if the thrombus persists after parenteral anticoagulation	IIa B	IIa B	-
Valve surgery	• NYHA FC IV, left chambers	IB	I B	I C
	• Mobile or large (> 0.8 cm²) thrombus, left chambers	IIa C	IIa C	IIa C (thrombus > 10 mm)

AHA: American Heart Association; ESC: European Society of Cardiology; FC: functional class; NYHA: New York Heart Association; SBC: Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology).

valve surgery is usually indicated. Recently, there has been a trend to prioritize fibrinolysis over surgery, based on data from a meta-analysis of 48 studies. When deciding on these two strategies, discussion with the Heart Team is recommended, and the risks of fibrinolysis (preferred procedure) and surgery should be weighed individually. The following factors make fibrinolysis favorable: high surgical risk, low risk of bleeding, involvement of the right valves, first episode of valve thrombosis, and thrombus smaller than 1 cm². If there is hemodynamic instability, the treatment of choice is surgery, and fibrinolysis may be considered in individuals with elevated surgical risk. The following factors make surgical procedure favorable: contraindication to fibrinolysis, high risk of bleeding, low surgical risk, suspicion of pannus associated with thrombosis, and need for other concomitant cardiac surgical procedures (for example, myocardial revascularization).[184,185]

17. Prophylaxis of Rheumatic Fever

RF and consequent chronic rheumatic heart disease remain the most important cause of acquired VHD in Brazil. Rheumatic disease is one of the most costly diseases for the Brazilian Unified Health System and the community in general, because it affects very young individuals, and it frequently leads to multiple hospitalizations and surgeries. It continues to be the main cause of acquired VHD in Brazil. The goal of decreasing its incidence is of the utmost importance, considering that it is certainly the most easily prevenTable cardiovascular disease.

17.1. Primary Prophylaxis of Rheumatic Fever

In order to decrease the incidence of RF, the measure with the greatest impact is primary prophylaxis, preventing susceptible individuals from contracting the disease (Tables 70 and 71). We have recently encountered serious difficulties in carrying out primary prophylaxis; supplies of benzathine penicillin G are unreliable, with frequent shortages of the medication. Furthermore, restrictions on locations where the medication may be administered, due to concerns regarding allergic reactions and lack of familiarity with intramuscular application on the part of primary healthcare professionals, have made it increasingly difficult to perform primary prophylaxis via the intramuscular route. This fact will certainly contribute to increased incidence of the disease in the coming years.

Oral therapies should not be used routinely, because 10 days of therapy are generally necessary in order to completely eradicate streptococci from the oropharynx. For this reason, there is a very high risk of non-adherence to the complete treatment, placing patients at the risk of developing a rheumatic attack. Treatments based on 5 days of azithromycin have been proposed, but there are still no clinical studies validating its use in pharyngotonsillitis.[186-193]

17.2. Secondary Prophylaxis of Rheumatic Fever

For patients who have already been diagnosed with RF, secondary prophylaxis is indicated in order to prevent new attacks of acute RF (Tables 72 and 73). The drug of choice is benzathine benzylpenicillin, at the same doses of 600,000 IU for children weighing up to 27 kg and 1,200,000 IU above this weight, at a maximum interval of three weeks. Monthly applications of benzathine penicillin do not promote adequate protection in patients with rheumatic disease in countries with high endemicity of the disease, like Brazil.[194-198] For patients who are allergic to penicillin, sulfadiazine is indicated at a dose of 1 g daily, and it is necessary to control possible leukopenic conditions.

Table 70 – Medications and posology indicated for streptococcal pharyngotonsillitis – primary prophylaxis of rheumatic fever[186-193]

Medication		Dose	Route of administration / Duration	Comments
Penicillins and derivatives				
	Benzathine benzylpenicillin	600,000 IU up to 25 kg, 1,200,000 IU over 25 kg	Intramuscular Single dose	Medication of choice: single dose, high efficacy and low cost
	Amoxicillin	50 mg/kg for children and 1.5g daily for adults, divided in 2 to 3 doses	Oral 10 days	Low adherence to complete treatment
	Phenoxymethylpenicillin	250 mg 2 to 3 times daily up to 25 kg, 500 mg 3 times daily > 25 kg	Oral 10 days	Low adherence to complete treatment
For patients who have allergy to penicillin				
	Clindamycin	20 mg/kg divided 3 times daily, adults: 300 to 600 mg 3 times daily	Oral 10 days	Frequent gastrointestinal intolerance
	Azithromycin	12 mg/kg in a single daily dose. For adults, 500 mg once daily	Oral 5 days	The only oral antibiotic therapy that may eradicate streptococcus in less than 10 days
	Clarithromycin	15 mg/kg twice daily or, for adults, 250 mg twice daily	Oral 10 days	

Table 71 – Recommendations for primary prophylaxis of rheumatic fever[186-193]

Class I - Benzathine benzylpenicillin in patients with streptococcal tonsillitis - Benzathine benzylpenicillin in patients with suspected streptococcal tonsillitis, even without diagnostic confirmation - Oral antibiotic therapy in patients with streptococcal tonsillitis who are allergic to penicillin
Class IIa - Use of oral antibiotics for treatment of streptococcal pharyngotonsillitis in patients who are not allergic to penicillin - Rapid tests to detect streptococci in the oropharynx in order to make the decision regarding treatment with penicillin.
Class III - Oropharynx culture in patients with suspected tonsillitis in order to make the decision regarding treatment with penicillin.

Table 72 – Secondary prophylaxis of rheumatic fever: Recommended medications and posology[194-200]

Medication		Dose and frequency	Recurrence / Notes
	Benzathine benzylpenicillin G	< 25 kg – 600,000 IU > 25 kg – 1,200,000 IU Every 15 days during the first two years after the attack Every 21 days during subsequent years	Recurrence of 0.3% yearly Medication of choice
	Phenoxymethylpenicillin	250 mg orally twice daily	Recurrence of 5%/year Should not be used as an alternative to benzathine penicillin G
For patients who have allergy to penicillin	Sulfadiazine	< 25 kg – 500 mg daily > 25 kg – 1 g daily	Recurrence of 1.3% yearly May be used until penicillin desensitization is concluded
For patients who have allergy to penicillin and sulfadiazine	Erythromycin	250 mg twice daily	Empirical regimen of prophylaxis, has not been the subject of studies on secondary prophylaxis of RF – should only be used in exceptional cases

RF: rheumatic fever.

Table 73 – Recommendations for secondary prophylaxis of rheumatic fever[194-200]

Class I
- Benzathine benzylpenicillin G for secondary prophylaxis of RF, every 15 days during the first two years after the attack and every 21 days during the following years.
- Use of benzathine benzylpenicillin G until 18 years of age, or 5 years after the last attack in patients with RF without carditis.
- Use of benzathine benzylpenicillin G until 25 years of age, or 10 years after the last attack in patients with RF and carditis, without cardiac sequelae or mild sequelae, provided that there are no stenotic lesions.
- Use of benzathine benzylpenicillin G until 40 years of age in patients with RF and carditis, with severe sequelae or cardiac surgery to correct valvular heart disease.
- Use of benzathine benzylpenicillin G after 40 years of age in patients who are occupationally exposed to streptococci.
- Sulfadiazine for antibiotic prophylaxis of RF in patients who are allergic to penicillin
Class IIa
- Use of oral antibiotic prophylaxis for patients with RF who are not allergic to penicillin
Class IIb
- Use of erythromycin for antibiotic prophylaxis for patients with RF who are allergic to penicillin and sulfa medications
Class III
- Suspension of antibiotic prophylaxis for RF after cardiac surgery with implantation of valve prosthesis, even when other valves do not have apparent lesions.

RF: rheumatic fever.

Considering the recent shortage of benzathine penicillin G, the alternative is sulfadiazine, which is frequently available for rheumatologic diseases in the public health system and is listed in high-cost medication regimens. We must also remember that only benzathine penicillin G and sulfadiazine have proven efficacy for secondary prophylaxis of RF, based on controlled studies. [199-200]

17.3. Criteria for Suspending Prophylaxis (Table 74)

- Patients without cardiac involvement, with only joint manifestation or "pure" chorea – suspend at 18 years of age or 5 years after the last rheumatic attack;

- Patients with carditis during the acute attack who do not have late sequelae or who have very mild sequelae – suspend at 25 years of age or 10 years after the last rheumatic attack;

- In patients whose prophylaxis is suspended and symptoms recur, prophylaxis should be maintained for 5 more years.

- Patients with even mild cardiac involvement should receive prolonged prophylaxis, preferably lifelong; when this is not possible, until the fourth decade life. When deciding to suspend the prophylaxis, we must always investigate occupational exposure to sources of streptococci.

18. Prophylaxis of Infective Endocarditis in VHD

IE is a severe complication of VHD, and it is frequently fatal. For this reason, when prophylaxis is possible, it should be applied. For this purpose, several antibiotic regimens have been utilized, with little evidence from controlled studies, mainly due to the difficulty of conducting large controlled studies with medications that are already in the public domain.

Streptococci are part of the normal oropharynx and gastrointestinal tract flora, and they cause at least 50% of acquired IE cases in the Brazilian community. Bacteremia due to viridans streptococci has been demonstrated in up to 61% of patients following tooth extraction and periodontal surgery (36% to 88%), and experimental studies in animals have shown that antibiotic prophylaxis was capable of avoiding IE due to viridans streptococci and enterococci.[201,202]

More recently, it has been observed that spontaneous bacteremia, especially originating in the teeth and gums, occurs in everyday situations. Thus, ordinary routine activities, such as tooth brushing (0% to 50%), use of dental floss (20% to 68%), use of toothpicks, and even chewing during meals (7% to 51%), are associated with bacteremia. In this manner, the burden of spontaneous bacteremia, not caused by dental intervention, would be higher than that caused by dental treatments. A theoretical study of cumulative bacteremia, lasting approximately one year, calculated that everyday bacteremia is six times greater than bacteremia caused by isolated tooth extraction. Considering that dental prophylaxis indications recommend two annual visits to the dentist, everyday activities have a greater impact on the generation of bacteremia than dental intervention itself. Recent epidemiological studies have not shown a relation between dental treatment two weeks before and episodes of IE.[203-208]

For this reason, maintenance of optimal oral health in patients with VHD is more important than prophylaxis before dental procedures. Patients with good oral health have lower chances of bacteremia from everyday activities. We must, thus, focus more on non-pharmacological prevention than on pharmacological prophylaxis. Part of non-pharmacological prophylaxis of IE is to reinforce, during all consultations, the need to maintain excellent oral health and to increase the frequency of dental consultations, from two (recommendation for the general population) to four times a year. It is necessary to underline that many of the dental conditions that most frequently cause IE are oligosymptomatic, such as gingivitis and periapical endodontic lesions.[209]

For patients undergoing dental interventions, there is growing evidence that antibiotic prophylaxis prevents only a very small number of cases of IE. There is, however, recent evidence that completely abolishing antibiotic prophylaxis could lead to increased incidence of IE. The British National Institute for Health and Care Excellence (NICE) proposed that prophylaxis of IE should not be applied on any occasion.[210] As a consequence, a decrease was observed in the prescription of antibiotic prophylaxis before dental treatments, followed by an increase in the number of cases of IE.[211] We thus have empirical evidence that completely abolishing antibiotic

Table 74 – Duration of secondary prophylaxis of rheumatic fever

Category	Duration
RF without carditis: clinical of pure arthritis or chorea	Until 18 years of age or 5 years after the last attack of RF, whichever is longer
RF with carditis, without sequelae or with very mild valvular sequelae (excluding stenotic lesions, even if they are very mild)	Until 25 years of age or 10 years after the last attack
RF with carditis and severe sequelae; patients undergoing cardiac surgery	Until 40 years of age, at least; lifelong if occupationally exposed

RF: rheumatic fever.

prophylaxis could lead to an increase in cases of IE. We accordingly recommend maintaining antibiotic prophylaxis before dental, gastrointestinal, and genitourinary procedures.

All patients with moderate to severe VHD, whether of rheumatic or degenerative etiology, and patients with prosthetic valves should receive non-pharmacological and pharmacological prophylaxis for IE, once all patients with IE have high morbimortality.

18.1. Non-pharmacological Prophylaxis of Infective Endocarditis

Non-pharmacological prophylaxis of IE may be more effective than pharmacological prophylaxis, as it acts toward primary prevention of proven sources of bacteremia (Table 75). As priority measures for patients with VHD, we highlight maintaining excellent oral health and avoiding invasive body art procedures, such as piercings and tattoos.

Body art (procedures such as tattoos and piercings) should be contraindicated. Piercings lead to the formation of a tract that needs to be epithelialized, and until that process is complete, it is a source of continuous bacteremia, with many reports of IE related to piercings in the literature, some of them with fatal outcomes. It is important for patients to be informed regarding the risks of this procedure, in the same manner that physicians should always cover this issue when treating patients who have or intend to have body art.[212]

18.2. Prophylaxis of Infective Endocarditis for Dental Procedures (Tables 76, 77, and 78)

The antibiotic should be administered one hour before the procedure. The regimen used should prevent bacteremia due to streptococci viridans, whenever tissue from the gums or the periapical region of the tooth is to be manipulated. The antibiotic of choice, if the patient is not allergic, is amoxicillin, due to its adequate absorption and to the susceptibility of the infectious agent. However, resistance to the antibiotic has been reported in several strains of the microorganism. For patients who are allergic to penicillin, the following may be used: clindamycin, azithromycin, or clarithromycin.

18.3. Prophylaxis of Infective Endocarditis for Respiratory Tract Procedures

Patients who will undergo incision or biopsy of the mucosa of the respiratory tract, such as otorhinolaryngological surgery, should receive antibiotic regimens similar to those used for conditions affecting the mouth.

18.4. Prophylaxis of Infective Endocarditis for Genitourinary or Gastrointestinal Tract Procedures

Enterococci are part of the the gastrointestinal tract flora, and they can cause IE. Thus, considering the lack of adequate scientific evidence, American and European guidelines no longer indicate antibiotic prophylaxis before interventions in these locations.[213,214] Though, considering the severity of an eventual occurrence of IE by these sources, in the current document, we have chosen to consider prophylaxis for patients with high risk of severe IE who will undergo genitourinary or gastrointestinal procedures associated with mucosal injury. (Table 79).[215] In the presence of infections that have installed in the genitourinary and gastrointestinal tracts, treatment should include antibiotics that act against enterococcus.

19. Pregnancy, Family Planning, and Contraception

19.1. Pre-Pregnancy Counseling

Risk stratification of valve diseases during pregnancy planning must be based on anatomical diagnosis of the valve lesion in order to classify the risks of pregnancy as high, intermediate, or accepTable (Table 80).

Concomitance of prognostic factors should be considered as worsening maternal and fetal prognosis (Table 81). [216]

During pregnancy planning, keep in mind that percutaneous or surgical valve intervention should be indicated in patients with severe valve disease, even in asymptomatic patients, because NYHA FC I/II does not mean good maternal evolution in severe obstructive lesions (Table 82).[217]

In contrast, regurgitation lesions have better prognosis when LVEF fraction is preserved, and the rare cases with complications are those that already had surgical indication prior to pregnancy.

During pregnancy, the basic principle for prevention and treatment of complications is to prioritize general measures and to choose non-teratogenic drugs with doses adjusted to gestational age. Table 83 lists the drugs and daily doses most frequently used to control complications of valve disease during pregnancy.[218]

Interventional measures in valve diseases during pregnancy are reserved for cases that are refractory to clinical treatment. Percutaneous procedures should be

Table 75 – Non-pharmacological prophylaxis of infective endocarditis

Recommendation	Class of recommendation	Level of evidence
During medical consultations, reinforce the need to maintain good oral health and appropriate hygiene habits	I	C
Quarterly dental consultations	I	C
Tattoo	III	C
Skin piercings	III	C
Piercings of the tongue and mucous membranes	III	C

Table 76 – Indications of prophylaxis for dental procedures

High likelihood of significant bacteremia	Without high likelihood of significant bacteremia
Procedures that involve manipulation of gum or periodontal tissue or perforation of oral mucosa.	Local anesthesia in non-infected tissue
	Dental radiography
	Placement or removal of orthodontic appliances
	Adjustment of orthodontic appliances
	Placement of parts in orthodontic appliances
	Natural loss of deciduous teeth
	Bleeding due to trauma of the oral mucosa or the lips

Table 77 – Antibiotic prophylaxis of IE in VHD

Indication	Recommendation	Level of evidence
Patients with moderate and severe valvular heart disease, or patients with prosthetic valves, who will undergo dental procedures with high likelihood of significant bacteremia.	I	C
Patients with an elevated risk of severe infective endocarditis* who will undergo genitourinary or gastrointestinal procedures associated with lesion of the mucosa.	IIa	C
Patients with elevated risk of severe infective endocarditis* who will undergo esophagus or respiratory tract procedures associated with lesion of the mucosa.	IIa	C
Patients with MVP without regurgitation, patients after myocardial revascularization surgery or stent placement, patients with functional heart murmur, patients with pacemaker or defibrillator, patients with Kawasaki disease or RF without valvular dysfunction, who will undergo dental, respiratory tract, genitourinary, or gastrointestinal procedures.	III	C
Patients undergoing procedures that do not involve risk of bacteremia.	III	C

** Elevated risk of severe IE: prosthetic heart valve; prior IE; congenital heart disease that is unrepaired, partially corrected, or corrected with prosthetic material; heart transplant with VHD. MVP: mitral valve prolapse.*

Table 78 – Regimens for prophylaxis of infective endocarditis before dental procedures

Route of administration	Medication	Single dose 1 hour before the procedure	
		Children	Adults
Oral	Amoxicillin	50 mg/kg	2 g
Oral (penicillin allergy)	Clindamycin	20 mg/kg	600 mg
	Azithromycin or clarithromycin	15 mg/kg	500 mg
Parenteral (endovenous or intramuscular)	Ampicillin	50 mg/kg	2 g
	Cefazolin or ceftriaxone	50 mg/kg	1 g
Parenteral (endovenous or intramuscular) (penicillin allergy)	Clindamycin	20 mg/kg	600 mg

Table 79 – Parenteral antibiotic prophylaxis for procedures in the gastrointestinal and genitourinary tracts

Route of administration	Medication	Single dose 1 hour before the procedure	
		Children	Adults
Parenteral (intravenous)	Ampicillin +	50 mg/kg	2 g
	Gentamicin	1.5 mg/kg	
Parenteral (intravenous) - penicillin allergy	Vancomycin +	20 mg/kg	1 g
	Gentamicin	1.5 mg/kg	

Table 80 – Classification of risks of valve diseases to pregnancy

High risk	Intermediate risk	AccepTable risk
Severe MS	Biological prosthesis with moderate dysfunction	Mild valve disease
Severe AS Stenotic/calcified biological prosthesis Mechanical prosthesis with dysfunction	Pulmonary valve stenosis	Biological prosthesis without dysfunction
	Mitral mechanical prosthesis > Aortic mechanical prosthesis	No prognostic factors

AS: aortic stenosis; MS: mitral stenosis.

Table 81 – Conditions that worsen prognosis of pregnancy in patients with valve disease[216]

- Prognostic factors: AF, PH, ventricular dysfunction, previous events (heart failure, thromboembolism, or infective endocarditis)
- Moderate to severe left-sided obstructive lesions
- Aortic diseases associated with increased diameters of the ascending aorta
  - Marfan syndrome (diameter of the aorta > 40 mm)
  - Bicuspid aortic valve (diameter of the aorta > 45 mm)
- NYHA FC III/IV
- Valve disease with indication of surgical or percutaneous intervention
- Need to anticoagulant use (transitory or permanent)

AF: atrial fibrillation; FC: functional class; NYHA: New York Heart Association; PH: pulmonary hypertension.

given preference over surgery, and the proposed treatments should be discussed with the Heart Team and shared with the Obstetric Team. Balloon valvuloplasty in AS has been indicated when etiology is congenital or as an attempt to save the mother's life in extremely severe cases. In contrast, PBMV is safe, with results equivalent to those of surgery; it nevertheless requires the classical indication criteria, such as absence of thrombus in the LA, no more than mild MR, and Wilkins-Block echocardiographic score ≤ 8.

19.2. Valve Prostheses

From the hemodynamic point of view, both mechanical and biological prostheses improve functional capacity, and they promote similar clinical evolution during pregnancy; nevertheless, biological prostheses appear to be more advantageous because they do not require anticoagulation (Table 84). Their limited durability, with the possibility of short-term reoperation, including during pregnancy, are the main restrictions to implantation of biological prostheses in young women.

The management in cases of prosthesis dysfunction during pregnancy should always prioritize the mother's life, and the proposed treatments should be discussed with the Heart Team and shared with the Obstetric Team (Table 85).

Anticoagulation regimens for patients with mechanical prosthesis remain controversial.[218,219] To date, there are no uniform guidelines that have been widely accepted. Factors that must be considered include the following: patient preference, expertise of the attending doctor, local resources, and availability of adequate coagulation control.

The recommendations for preventing thromboembolism in mechanical prostheses are intended to meet the ideal requirements of a position based on the literature and on the authors' experience, and they should be effective for the reality of diverse healthcare services. It is understood that the dynamics of permanent anticoagulation in patients with mechanical prostheses is multidisciplinary, and it is divided into five phases: pre-conception, each trimester, delivery, and postpartum, shown in Table 86 and Figure 11. Vigilant control of anticoagulation and doses of anticoagulants should be adjusted according to conventional targets.

Phase 1 - *orientations regarding early diagnosis of pregnancy:* Clarify that it is mandatory to maintain anticoagulation and discuss the availability of anticoagulants and their risks during all phases of pregnancy, delivery, and postpartum. Advice includes information regarding the importance of early diagnosis of pregnancy in order to reduce the occurrence of embryopathy, which occurs between

Table 82 – Recommendations for treatment in acquired native VHD, during family planning and pregnancy[217]

Valve disease	Family planning Intervention	Pregnancy		
		Maternal risk	Fetal risk	Intervention
Severe mitral stenosis MVA < 1.5 cm²	Consider PBMV or surgery: NYHA FC III/IV or NYHA FC I/II + SPAP > 50 mmHg or Recent onset AF	Increased risk: NYHA FC III/IV and/or AF	Prematurity Restricted intrauterine growth Fetal loss Increased if NYHA FC III/IV	Betablocker Diuretic Anticoagulation if AF If refractory maternal NYHA FC III/IV consider PBMV or surgery
Severe aortic stenosis AVA ≤ 1 cm²	Consider balloon valvuloplasty or surgery: Symptomatic or Asymptomatic + Altered ergometry test or LVEF < 50% or AVA < 0.7 cm² mean gradient > 60 mmHg or Bicuspid valve + diameter of the aorta > 45mm	Increased risk Heart failure Arrhythmia Syncope Sudden death Aortic dissection	Complications Prematurity Restricted intrauterine growth Fetal loss	Rest Use of diuretics is controversial Consider betablocker or calcium channel blocker + Anticoagulation if AF Consider balloon valvuloplasty or surgery if heart failure or syncope
Severe mitral regurgitation	Consider surgery (repair/ prosthesis): NYHA FC ≥ II or Asymptomatic + LVEF ≤ 60% + SPAP ≥ 50 mmHg + LVSD ≥ 40 mm	Heart failure AF Increased risk if LVEF < 35%	Low risk	Diuretic, vasodilator Digoxin, betablocker Consider surgery or percutaneous mitral repair if refractory heart failure
Severe aortic regurgitation	Consider surgery: Symptomatic NYHA FC ≥ II or Prognostic factors LVEF < 50% LVDD > 70 mm (75 if rheumatic) LVSD > 50 mm (55 if rheumatic) Consider intervention in proximal aorta: Isolated bicuspid valve and diameter of the aorta > 45 mm	Low risk if asymptomatic and normal LVEF Risk of heart failure if NYHA FC > II and/or AF or LVEF < 35%	Low risk	Diuretic, vasodilator, Digoxin Consider surgery if refractory heart failure Consider intervention in proximal aorta: Isolated bicuspid valve and diameter of the aorta > 45 mm

AF: atrial fibrillation; AVA: aortic valve área; PBMV: percutaneous balloon mitral valvuloplasty; FC: functional class; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; MVA: mitral valve area; SPAP: systolic pulmonary artery pressure.

Table 83 – General and pharmacological recommendations during pregnancy[218]

- Restricted physical activities and low-sodium diet (4 g/day)
- Prophylaxis of rheumatic disease should be maintained (except sulfadiazine)
- If pharmacological treatment is indicated, consider:
  - Diuretic: furosemide (< 80 mg/day)
  - Betablockers: propranolol (<80 mg/day) or metoprolol succinate (< 100 mg/day), carvedilol < 50 mg
  - Non-dihydropyridine calcium channel blockers: verapamil (< 240 mg/day)
  - Vasodilator: hydralazine (< 100 mg/day)
  - Digitalis: digoxin (0.25 mg/day)

Table 84 – Prosthetic valve with normal function and risks to pregnancy

Biological prosthesis with normal LVEF		Mechanical prosthesis with normal LVEF	
Maternal risk	**Fetal risk**	**Maternal risk**	**Fetal results**
Low risk	Low risk	Intermediate risk Requires anticoagulation	High risk
Does not require anticoagulation		Systemic embolism Prosthesis thrombosis Hemorrhage	Warfarin embryopathy Fetal loss Prematurity Perinatal hemorrhage

LVEF: left ventricular ejection fraction.

Table 85 – Treatment in prosthesis dysfunction during pregnancy

Biological prosthesis		Mechanical prosthesis	
Maternal risk	**Fetal risk**	**Maternal risk**	**Fetal risk**
Dysfunction with predominant regurgitation, NYHA FC I/II and normal LVEF Consider pharmacological measures	Low risk	Dysfunction with mild to moderate "paravalvular" regurgitation, without significant hemolysis or severe heart failure Consider pharmacological measures for heart failure and anemia Severe MR or significant hemolysis Consider intervention Heart failure and/or symptomatic hemolysis Consider percutaneous closure of the paravalvular leak or surgery (high risk of relapse)	High fetal risk, if surgery
Dysfunction with predominant valve stenosis and calcification (mitral, aortic, or tricuspid) Risks of severe heart failure, shock, sudden death Always consider percutaneous or transapical (valve-in-valve) implantation or surgery	High fetal risk Fetal loss Prematurity	Mechanical prosthesis thrombosis Consider emergency intervention (thrombolysis or surgery) Mechanical prosthesis stenosis due to intravalvular endothelial growth – pannus or mismatch Need for intervention is rare If necessary, consider surgery	High fetal risk, if surgery

FC: functional class; LVEF: left ventricular ejection fraction; MR: mitral regurgitation.

Table 86 – Anticoagulation control in patients with mechanical prosthesis during pregnancy

Gestational age (weeks)	Anticoagulant	Control
Between 6 and 12	Subcutaneous low-molecular-weight heparin 1.0 mg/kg every 12 hours or Intravenous unfractionated heparin 18 IU/kg/hour in an infusion pump (< 30,000 IU)	Anti-Xa: 0.8 to 1.2 U/ml aPTT 1.5 to 2.0 times control value
12 to 36	Warfarin, dose according to INR	Aortic INR between 2.5 and 3.0 Mitral INR between 3.0 and 3.5
After 36, until delivery	Low-molecular-weight heparin 1.0 mg/kg subcutaneous every 12 hours or Intravenous unfractionated heparin 18 IU/kg/hour in an infusion pump (< 30,000 IU)	Anti-Xa: 0.8-1.2 U/ml aPTT 1.5 to 2.0 times control value
Postpartum	Subcutaneous low-molecular-weight heparin 1.0 mg/kg every 12 hours Intravenous unfractionated heparin 18 IU/kg/hour in an infusion pump (< 30,000 IU) Warfarin must reach target INR before hospital discharge	Anti-Xa: 0.8 – 1.2 U/ml aPTT 1.5 to 2.0 times control value INR between 2.0 and 2.5

aPTT: activated partial thromboplastin time; INR: international normalized ratio.

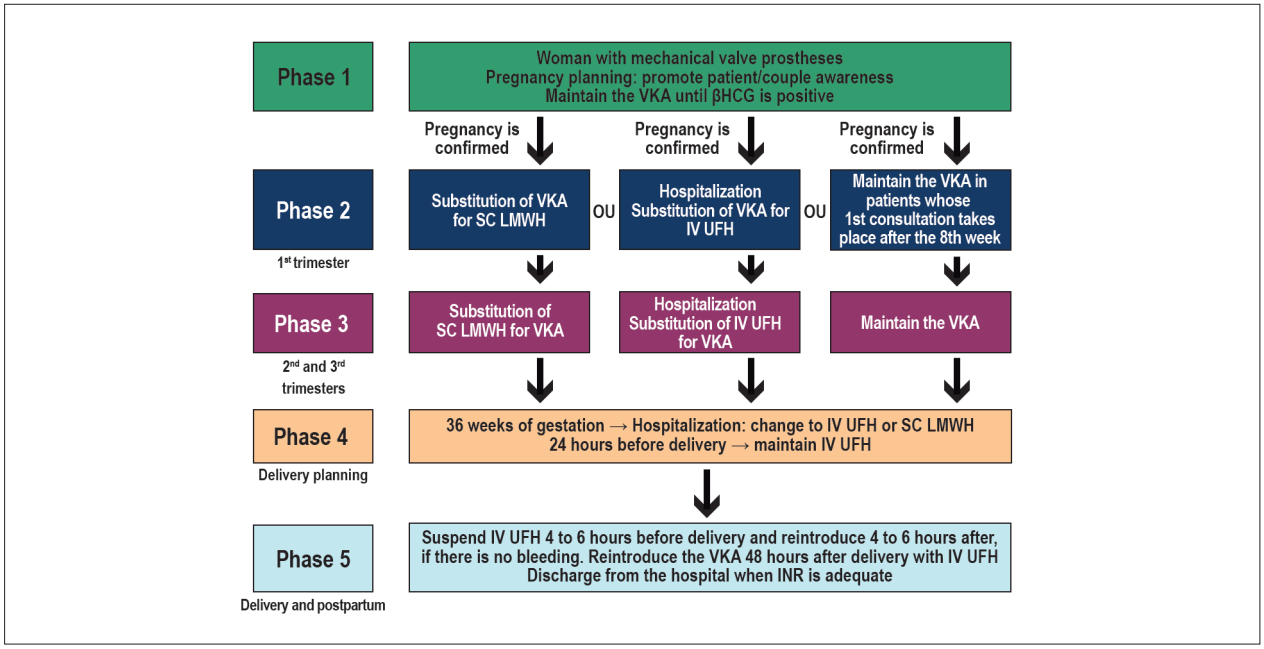

Figura 11 – *Flowchart with recommendations for anticoagulation in patients with mechanical prostheses during pregnancy, delivery, and postpartum. βHCG: beta-human chorionic gonadotropin; IV UFH: intravenous unfractionated heparin; SC LMWH: subcutaneous low-molecular-weight heparin; VKA: vitamin K antagonist.*

the sixth and ninth week of pregnancy. During this consultation, t

he patient receives a request for beta-human chorionic gonadotropin (βHCG) measurement, which should take place as soon as there are doubts regarding late menstruation.

Phase 2 - *first trimester:* Once pregnancy has been confirmed (βHCG and obstetric ultrasound), warfarin should be substituted by heparin which makes it possible to balance between the benefit of preventing maternal thrombosis and the harm of embryopathy. In patients whose first medical consultation occurs after the sixth week of gestation, warfarin should not be suspended. The couple should be informed that there is a possibility of embryopathy and that the risks of substituting warfarin for heparin are no longer justified.

Phase 3 - *second trimester:* Return to oral anticoagulant. The return to warfarin is based on the benefit of shortening the use of heparin and lowering the risk of embryopathy. The proposal is to maintain the warfarin dosage in accordance with pre-pregnancy goals, with weekly or biweekly INR control. Reintroduction of warfarin should take place simultaneously with the use of subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin until the target INR has been reached.

Phase 4 - *third trimester:* Consider hospitalization, return to parenteral anticoagulation and schedule delivery. Hospitalization should be scheduled at week 36 of pregnancy for use of subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin.

Phase 5 - *postpartum:* Reintroduction of oral anticoagulation and hospital discharge. Six hours after delivery, if there are not maternal complications, intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin should be reintroduced in therapeutic doses. Warfarin should be prescribed 48 hours after delivery, following the transition dynamic in conjunction with heparin until the INR value of 2.0 has been reached, at which point the patient is discharged from the hospital.

19.3. Delivery and Postpartum

Delivery planning should be multidisciplinary, starting at week 34 of pregnancy. Vaginal delivery is considered to be more advantageous because it is associated with less blood loss and lower risks of thrombosis and infection. Sequential anesthesia techniques, with neuraxial anesthesia, have hemodynamic advantages because they allow a gradual form of sympathetic block. In general, cases of maternal indication for cesarean delivery require general anesthesia (Table 87).

19.4. Contraception

The choice of contraceptive method for women with valve diseases requires multidisciplinary effort, involving the gynecologist and the cardiologist, in order to seek safety, efficacy, tolerance, and easy access. Accordingly, guidelines for prescription should be based on the Contraceptive Eligibility Criteria, which classify contraceptives in four risk categories, and on the Pearl index, which calculates the effectiveness of a method considering the number of pregnancies per 100 women during the first year of use.[220,221] For patients with valve disease, the current tendency is to indicate methods that contain only progesterone or combinations of progesterone and natural estrogen in monthly injecTable forms, because they are safe, effective, and easily accessible (Table 88). Although intrauterine devices are classified as category 2, they have not been indicated in patients with valve diseases, due to the presumed inherent risk of IE.

Table 87 – Recommendations for route of delivery and anesthesia in patients with valve disease

- Vaginal birth and spinal epidural anesthesia are preferable in cases with low- and intermediate-risk valve disease
- Cesarean delivery should be considered in the event of:
  - High-risk valve disease (severe obstructive lesions)
  - Diseases of the thoracic ascending aorta
  - Delivery under anticoagulation
  - History of aortic dissection
- Antibiotic prophylaxis at the moment of delivery is no longer routine. Nevertheless, it may be considered in patients with valve prostheses or history of infective endocarditis:
  - Ampicillin 2.0 g intravenous + gentamicin 1.5 mg/kg/day intramuscular, one hour before delivery
- There are no restrictions with respect to breastfeeding

Table 88 – Medical eligibility criteria (modified)* and index of effectiveness for contraceptive use in patients with valve disease[220,221]

Available contraceptives	Oral CHC	Monthly injection	Progesterone pills	InjecTable progesterone	Implantation of progesterone	Copper IUD	Levonorgestrel IUD
Valve disease							
Not complicated	2	1	1	1	1	3/4	3/4
Prognostic factors	4	4	1	1	1	4	4
Effectiveness	8	3	3	3	0.05	0.8	0.1

** Prognostic factors: Effectiveness (Pearl Index) calculated as the number of pregnancies per 100 women who routinely use the method. Eligibility criteria: category 1: there are no restrictions to using the method; category 2: the advantages of using the method generally outweigh the theoretical or proven risks; category 3: the theoretical or generally proven risks outweigh the advantages of using the method; category 4: condition that represents an unacceptable health risk of using the contraceptive method. CHC: combined hormonal contraceptive; IUD: intrauterine device.*

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Statement – Protocol for the Reconnection of Cardiology Services with Patients During the COVID-19 Pandemic – 2020

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Note: These statements are for information purposes and are not to replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Statement – Protocol for the Reconnection of Cardiology Services with Patients During the COVID-19 Pandemic – 2020	
The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these update, 2020.	
Expert	**Type of relationship with industry**
Andréa Araujo Brandão	FINANCIAL DECLARATION A - ECONOMICALLY RELEVANT PAYMENTS OF ANY KIND MADE TO (i) YOU, (ii) YOUR SPOUSE/PARTNER OR ANY OTHER PERSON LIVING WITH YOU, (iii) ANY LEGAL PERSON IN WHICH ANY OF THESE IS EITHER A DIRECT OR INDIRECT CONTROLLING OWNER, BUSINESS PARTNER, SHAREHOLDER OR PARTICIPANT; ANY PAYMENTS RECEIVED FOR LECTURES, LESSONS, TRAINING INSTRUCTION, COMPENSATION, FEES PAID FOR PARTICIPATION IN ADVISORY BOARDS, INVESTIGATIVE BOARDS OR OTHER COMMITTEES, ETC. FROM THE BRAZILIAN OR INTERNATIONAL PHARMACEUTICAL, ORTHOSIS, PROSTHESIS, EQUIPMENT AND IMPLANTS INDUSTRY: - Servier: Lectures - Libbs: Hypertension - Novartis: Heart failure - EMS: Hypertension - Sandoz: Hypertension - Abbott: Hypertension OTHER RELATIONSHIPS FUNDING OF CONTINUING MEDICAL EDUCATION ACTIVITIES, INCLUDING TRAVEL, ACCOMMODATION AND REGISTRATION IN CONFERENCES AND COURSES, FROM THE BRAZILIAN OR INTERNATIONAL PHARMACEUTICAL, ORTHOSIS, PROSTHESIS, EQUIPMENT AND IMPLANTS INDUSTRY: - Servier: Hypertension
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Érique José Farias Peixoto de Miranda,	FINANCIAL DECLARATION A - ECONOMICALLY RELEVANT PAYMENTS OF ANY KIND MADE TO (i) YOU, (ii) YOUR SPOUSE/PARTNER OR ANY OTHER PERSON LIVING WITH YOU, (iii) ANY LEGAL PERSON IN WHICH ANY OF THESE IS EITHER A DIRECT OR INDIRECT CONTROLLING OWNER, BUSINESS PARTNER, SHAREHOLDER OR PARTICIPANT; ANY PAYMENTS RECEIVED FOR LECTURES, LESSONS, TRAINING INSTRUCTION, COMPENSATION, FEES PAID FOR PARTICIPATION IN ADVISORY BOARDS, INVESTIGATIVE BOARDS OR OTHER COMMITTEES, ETC. FROM THE BRAZILIAN OR INTERNATIONAL PHARMACEUTICAL, ORTHOSIS, PROSTHESIS, EQUIPMENT AND IMPLANTS INDUSTRY: - Bayer: Xarelto OTHER RELATIONSHIPS EMPLOYMENT RELATIONSHIP WITH THE BRAZILIAN OR INTERNATIONAL PHARMACEUTICAL, ORTHOSIS, PROSTHESIS, EQUIPMENT AND IMPLANTS INDUSTRY, AS WELL AS ANY EMPLOYMENT RELATIONSHIP WITH HEALTH INSURANCE COMPANIES OR MEDICAL AUDIT COMPANIES (INCLUDING PART-TIME JOBS) IN THE YEAR TO WHICH YOUR DECLARATION REFERS: - Bayer
Evandro Tinoco Mesquita	OTHER RELATIONSHIPS EMPLOYMENT RELATIONSHIP WITH THE BRAZILIAN OR INTERNATIONAL PHARMACEUTICAL, ORTHOSIS, PROSTHESIS, EQUIPMENT AND IMPLANTS INDUSTRY, AS WELL AS ANY EMPLOYMENT RELATIONSHIP WITH HEALTH INSURANCE COMPANIES OR MEDICAL AUDIT COMPANIES (INCLUDING PART-TIME JOBS) IN THE YEAR TO WHICH YOUR DECLARATION REFERS: - UnitedHealth Group
Fernando Bacal	FINANCIAL DECLARATION A - ECONOMICALLY RELEVANT PAYMENTS OF ANY KIND MADE TO (i) YOU, (ii) YOUR SPOUSE/PARTNER OR ANY OTHER PERSON LIVING WITH YOU, (iii) ANY LEGAL PERSON IN WHICH ANY OF THESE IS EITHER A DIRECT OR INDIRECT CONTROLLING OWNER, BUSINESS PARTNER, SHAREHOLDER OR PARTICIPANT; ANY PAYMENTS RECEIVED FOR LECTURES, LESSONS, TRAINING INSTRUCTION, COMPENSATION, FEES PAID FOR PARTICIPATION IN ADVISORY BOARDS, INVESTIGATIVE BOARDS OR OTHER COMMITTEES, ETC. FROM THE BRAZILIAN OR INTERNATIONAL PHARMACEUTICAL, ORTHOSIS, PROSTHESIS, EQUIPMENT AND IMPLANTS INDUSTRY: - Novartis: Entresto
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Statement

Content

1. Introduction and General Concepts

The pandemic resulting from the novel coronavirus (SARS-CoV-2) infection, named COVID-19, emerged in Wuhan, China, in December 2019.[1,2] Since then, millions of people around the world have been affected and hundreds of thousands have died.

The virus spreads mainly from person to person,[1,2] directly via the airways or indirectly through contact with contaminated surfaces and objects. Respiratory infections occur through the transmission of virus-filled droplets (> 5 μm, approximate extension of 1.5 m) or aerosols (≤ 5 μm, approximate extension of 8 m) exhaled by infected individuals.[3,4] Recent data have suggested the possibility of airborne transmission. The contact of the contaminated respiratory droplets, eliminated when infected persons breath, talk, sneeze and cough, with the ocular, oral and nasal mucosa of susceptible individuals results in SARS-CoV-2 transmission. With the dissemination of COVID-19 and the fast increase in the number of cases, studies have shown the viability of the virus in the environment as well as the role played by contaminated surfaces in SARS-CoV-2 hospital spread.[5] Based on droplet transmission, the Centers for Disease Control and Prevention of the United States have recommended the practice of physical distancing of at least 1.5 m and hand hygiene to reduce viral spread.

The COVID-19 clinical presentation can range from mild/moderate illness, which affects 80% of the cases, to more severe illness, which affects the other 20% with findings that in Brazil are comparable to those of the severe acute respiratory syndrome (SARS).[6] The most sensitive symptoms of mild to moderate illness are dry cough and fever, which might or not be present at disease onset, while the most specific symptoms are olfactory and gustative disorders.[7,8] The SARS is defined as a influenza-like illness (ILI) associated with dyspnea/respiratory distress OR persistent chest pressure OR O_2 saturation <95% on room air OR bluish coloration of lips and face, with tachypnea, cyanosis and severe pulmonary impairment.

Because of the virus spread potential, the severe clinical presentation of some cases and the lack of a specific viral treatment, or even a vaccine, nonpharmacological measures have been the most effective interventions to contain disease spread.[9,10] Such non-pharmaceutical interventions are aimed at reducing the person-to-person viral transmission by limiting the contact between infected and susceptible individuals, either by increasing the distance between people or reducing the intensity and duration of the contact or by using measures and physical or chemical devices that help prevent the person-to-person viral spread.

The non-pharmaceutical interventions can be as follows:

- Physical distancing: consists in keeping a minimum physical distance of 2.0 m between individuals, some examples being school dismissal, closure of crowded places, and travel restrictions.
- Measures of transmission blockade: hand hygiene with water and soap or alcohol, respiratory etiquette, and use of face masks or other physical contact barriers.
- Identification and isolation of cases of suspected or confirmed COVID-19: maintain individual isolation.

• Quarantine of contacts: active tracing of contacts of confirmed cases and their household confinement, in addition to clinical course monitoring of suspected cases.

This pandemic is a daunting challenge to the population. The current humanitarian crisis is due not only to COVID-19 itself, but also to the collateral damage associated with the following: the delay and reduction in the care provided to other diseases in emergency settings; the reduction in the access to care provided to chronic illnesses in outpatient settings; and the higher exposure to risk factors for the development of other diseases (sedentary lifestyle, obesity, anxiety, and emotional stress). Moreover, economic losses pile up, as do the psychological impact and burnout associated with the COVID-19 pandemic. The decrease in the proper delivery of general healthcare can occur mainly in two circumstances. First, there is a reduction in the number of routine medical consultations and tests. This disruption in the chronic patients' care might lead to acute decompensation of some conditions, such as arterial hypertension, diabetes, and heart failure. Similarly, other severe consequences to face might be related to the reduction in the search for urgency and emergency healthcare for time-sensitive circumstances, such as acute coronary syndromes, acute heart failure, and stroke, for which delay compromises outcomes.[11-13]

To minimize those adversities, the Brazilian Society of Cardiology (SBC) has compiled recent evidence, which is limited and sometimes grounded in expert opinions or preliminary reports, to create structured guidance aimed at reconnecting physicians to patients for a planned reopening of cardiological services. Such guidance is intended for risk reduction for not only patients and patient companions, but also healthcare professionals involved in the clinical activities of Cardiology.

The recommendations presented in this document are based on evidence available at the time of its elaboration and on expert opinions. The knowledge about COVID-19 progresses fast and dynamically, thus the protocols for the safe return of medical care, as well as of invasive and non-invasive procedures, are constantly being updated. This project was conceived by the SBC to be a source of reference material for its associates. The recommendations presented, however, should not be used as the sole base to define local protocols, and other updated sources should be considered as the knowledge in the field evolves.

This position paper was aimed at aligning the following demands:

• To minimize the risk of SARS-CoV-2 transmission among patients, healthcare personnel and others involved in the patient's care.

• To early identify patients with suspected COVID-19 and conduct triage to assign proper levels of care, to reduce the risk of complications from COVID-19 and ongoing cardiovascular diseases, and to reduce the risk of viral transmission.

• To provide patients and healthcare professionals with safe and reliable information on COVID-19-related care.

• To reduce the negative impact from the lack of outpatient management of pre-existing conditions on the emergency and hospital admission settings.

• To optimize the use of personal protective equipment (PPE).

Thus, to deliver excellent care, ensuring the safety of healthcare professionals and patients with cardiovascular disease, we should consider the following assumptions:

• Because the clinical presentation varies, the definition of the presence or absence of SARS-CoV-2 infection might not be possible based only on initial clinical assessment. Clear screening protocols should be used to minimize the traffic of patients with suspected COVID-19 in the healthcare setting, except for urgency or emergency care. When necessary, that traffic should occur with the lowest possible risk of contamination.

• All healthcare professionals should undergo continuous training regarding good practices, institutional protocols, and patient care flowcharts.

• The delivery of emergency care should follow the same protocol of the care provided to patients with confirmed/suspected COVID-19, since COVID-19 cannot be ruled out timely for the proper care in the emergency setting, which should continue to operate at full capacity.

• Elective and semi-elective procedures will be resumed after thorough planning, but should be restricted to limited capacity, with continuous reassessment by the steering committee, always respecting authorizations and occasional traffic restrictions, and reopening of medical services defined by competent authorities.

• Separate pathways for traffic, with access routes to diagnostic equipment clearly indicated using adequate signage to the transportation services, patients and other workers who do not belong to the medical sector, aiming at minimizing contact and exposure. For individuals with suspected or confirmed COVID-19 requiring a test or procedure, the healthcare flows and pathways, as well as the corresponding waiting areas, should be set up apart from the flows and pathways for those without suspected SARS-CoV-2 infection.

• Reduction in the traffic and exposure of healthcare workers (receptionists, and hygiene and administrative professionals).

Finally, the hierarchy of the healthcare flows in different areas of Cardiology requires the definition of the patient's clinical profile, of the physical distancing between the patient and the healthcare team, of the type of their contact during the delivery of care, in addition to the level of urgency for the treatment of heart diseases.

The reopening time of Cardiology services should align with institutional policies and follow the recommendations of competent authorities. Important considerations include the local incidence of patients with SARS-CoV-2 infection, the trend in the number of disease cases, and the institutional resources available, including facilities, human resources, and PPE supply chains. For example, if the PPE storage is limited, the transitory suspension of elective care delivery might be necessary to prevent PPE shortage in the urgency and emergency care.

As the Brazilian regions tend towards the COVID-19 epidemic control after its transforming impact on healthcare services, that guidance might relax restrictions on a regional

basis. Therefore, monitoring patients and healthcare workers is crucial to identify the progression of possible local transmission and the need to increase the response level inside medical institutions, particularly those with hospital beds. Thus, the medical community must remain on the alert and attentive to the evolving character of the recommendations both in the state or municipal level and even in their offices, clinics, and hospitals.

2. Healthcare and Patient's Clinical Profiles, and Healthcare Environment

a. General Guidance to all Healthcare Settings

To resume healthcare activities safely, it is essential that all medical services define a local plan elaborated with the active participation of the medical staff, of the professionals with experience in infection control and patient's safety, as well as of all healthcare professionals involved. Thus, the following initial measures, applicable to all healthcare levels, are proposed:

• Activities should resume with limited capacity, for example, 25% of the pre-COVID-19 maximum capacity, enabling the controlled implementation of interventions and assessment of healthcare flow. After obtaining an appropriate flow, the healthcare volume can be increased in a staggered way. However, reaching the pre-COVID-19 flow volumes should not be expected during the period of relaxation of restrictions because of the adaptations required. The potential impact of these measures on the financial sustainability of the health service should be considered.

• The care of more symptomatic patients and those with illnesses most likely to decompensate within the next few weeks or months should be prioritized, lowering the chance of hospitalizations and complications in the short and medium term, and helping fight the overload of the hospital admission system.

• Aiming at ensuring physical distancing, adaptations in the physical structure, such as flooring demarcation, are required in association with the installation of physical barriers in the workplace, such as acrylic or glass panels.

• Ensure that hygiene and cleaning materials, such as alcohol gel, tissue papers and hand soap, are readily available and easily reached, in addition to ensuring the proper disposal of residues.

• Elaborate visual reminders, such as banners and posters, which should be made available to patients digitally or displayed at the entrance of the service and at strategic places disclosing key information on hand hygiene, respiratory etiquette, and COVID-19 major signs and symptoms.

• Make sure all healthcare personnel wear proper PPE continuously during the entire time of care delivery (Figure 1).

• Make sure all patients and patient companions older than 2 years wear a mask, and, for those who do not, provide one at the time of triage. It is worth emphasizing that some healthcare settings with proper characteristics, such as hospitals, might have specific regulation enforcing the use of disposable surgical masks. These specifications should be considered by the health services when defining which mask the patient is required to wear.

• For bigger-size medical services with larger teams of workers, a reopening committee should be constituted for the continuous discussion of the adjustments required in the interventions and healthcare volume to reduce the risk of transmission.

• On the day before the consultation or test, the Screening Questionnaire of Symptoms and Exposures (Appendix A) should be applied via email or telephone contact. All patients

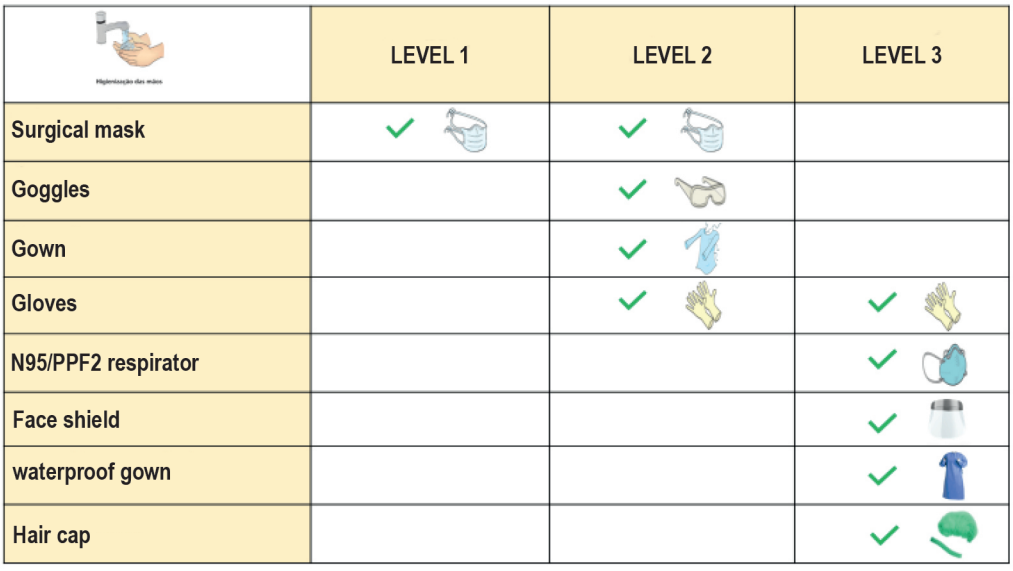

Figure 1 – *Guidance on PPE according to the risk levels. For level 2, goggles can be replaced with face shield. At level 3, the face shield is mandatory and cannot be replaced by goggles. Adapted from GVIMS/GGTES/ANVISA.*

should complete that questionnaire verbally (telephone) or in writing (e-mail or printed).

• Upon arrival for healthcare, all patients should have their body temperature measured.

• When a consultation or test is required for a patient with suspected or confirmed COVID-19, a separate room should be reserved for it.

• In the hospital setting, barriers should be placed for outpatients, creating 'clean' entrances and exits, that is, preventing contact with inpatients.

• For urgency and emergency care (definition in section 2b), where neither previous screening nor healthcare delay is possible, apply objectively, after standard cardiac assessment, the Screening Questionnaire of Symptoms and Exposures to define the epidemiological status.

In case of any positive answer to that questionnaire (Appendix A):

Make sure the patient wears a surgical mask.

• Keep the patient in a separate waiting room, with doors closed and, if possible, adequate signage.

• Keep physical distancing of 2.0 m.

• The supervisor and medical care provider should be informed, and all healthcare personnel involved should be wearing proper PPE.

• Urgency and emergency services should define a specific healthcare flow according to the local structure available.

b. Definition of the Cardiological Care Profile According to its Urgency

Defining the healthcare protocol requires considering the patient's clinical condition and its urgency. Therefore, four care profiles were defined according to the patients' clinical characteristics and risk of worsening due to postponing the care:

• Profile A: emergency care setting: when the care, assessment and intervention should be performed within the next minutes or hours.

• Profile B: urgent care setting: when the care, assessment and intervention should be performed within the next days.

• Profile C: semi-elective care setting: when the care, assessment and intervention should be performed within the next weeks, ideally within 3 months.

• Profile D: elective care setting: when the care, assessment and intervention are not deemed necessary in the short term and could be postponed for more than 3 months.

Table 1 shows the major clinical presentations of the cardiovascular diseases according to the above classification of healthcare required.

c. Definition of the Patient's Clinical Profile (COVID-19 Status)

The clinical presentation compatible with suspected or confirmed COVID-19 should consider the definition of FLS and SARS as shown in Table 2.

Table 1 – Major clinical presentations of cardiovascular diseases according to the urgency of the healthcare required

Emergency healthcare setting
ST-elevation myocardial infarction
High-risk acute coronary syndrome
Refractory ventricular arrhythmia
AF due to ventricular pre-excitation syndrome
Acute aortic syndromes
Corrections of cardiac anatomical dysfunctions leading to cardiogenic shock
Dysfunction of an intra- or extracorporeal MCAD
Bradyarrhythmias and tachyarrhythmias with hemodynamic repercussion
Cardiac tamponade
Acute pulmonary edema
Urgency healthcare setting
Moderate-risk acute coronary syndrome
Low-risk acute coronary syndrome
Significant valve anatomical dysfunction, symptomatic
AF and recurrent supraventricular tachycardia with clinical repercussion
NYHA functional class IV decompensated heart failure
Urgent heart transplant
High-risk cardiac tumors
Severe congenital heart disease, symptomatic
Severe hypertriglyceridemia > 1000 mg/L
Dysfunction of any component of the CIED
CIED at the end of battery life
Semi-elective healthcare setting
Stable angina
Uncontrolled hypertension
NYHA functional class III decompensated heart failure
Uncontrolled diabetes
Moderate valve anatomical dysfunction
Aortic aneurysm
Significant valve anatomical dysfunction, asymptomatic
Patients assessed for MCAD implantation
New cardiac anatomical change in a previously healthy patient
CIED with battery requiring non-urgent replacement
Elective healthcare setting
Other cases

AF: atrial fibrillation; CIED: cardiac implantable electronic device; MCAD: mechanical circulatory assistance device; NYHA: New York Heart Association.

Table 2 – Definition of influenza-like illness (ILI) and severe acute respiratory syndrome (SARS)

Classification	Clinical characteristics
ILI	Respiratory symptoms, such as cough, runny nose, sore throat, with or without fever*
SARS	O_2 saturation <95% on room air AND/OR respiratory rate ≥24 bpm

** Fever may not be present in some cases, such as elderly and immunocompromised patients, when the clinical assessment should be taken into consideration.*

The clinical criterion, however, does not allow to establish the etiology, and other agents should enter in the differential diagnosis, based on epidemiological evidence, laboratory tests, and radiological findings.

Regarding the SARS-CoV-2 infection, a patient's clinical profile can be as follows:

• *With suspected COVID-19*: case suspected of FLS or SARS based on presumptive clinical, radiological or laboratory criterion.

• *With confirmed active COVID-19*: case suspected of FLS or SARS with SARS-CoV-2 infection confirmed by use of a definitive laboratory method (positive RT-PCR for SARS-CoV-2) or IgM serology AND:

◦ within 10 days from symptom onset or from the test date, if asymptomatic; OR

◦ within 3 days from the last COVID-19-related symptom.

• *With confirmed resolved COVID-19:* confirmed COVID-19 with evidence of improvement of clinical findings, defined as absence of fever for >3 days and improvement of the respiratory symptoms (cough, shortness of breath) AND:

◦ at least 10 days have passed since the first symptoms OR

◦ positive IgG serology with clinical history compatible with previous COVID-19

• *Contact of a suspected or confirmed case*: an individual who came into contact (workplace, household) within the last 14 days with another classified into one of the three clinical profiles above.

• *Asymptomatic individual without recent contact with a case:* an individual with neither symptom suggestive of SARS-CoV-2 infection within the last 10 days nor contact with a suspected or confirmed case within the last 14 days.

• *COVID-19 ruled out*: Case suspected of FLS or SARS without laboratory confirmation of SARS-CoV-2 infection during the diagnostic window of opportunity OR laboratory confirmation of another etiological agent, such as influenza virus or respiratory syncytial virus. In highly suspected cases, it might be necessary to repeat the RT-PCR test in 48 hours due to its limited sensitivity.

d. Definition of the Healthcare Environment

The above described clinical profiling is useful not only to define the urgency the medical care requires, but also its structural model of approach. Whenever possible, the risk of exposure of healthcare personnel, patients and patient companions should be minimized, prioritizing a safer, even though effective, care. Thus, the healthcare environment was classified according to the distance and contact duration between patients and healthcare workers:

• *Environment I: Remote care,* where there is no physical contact between the patient and the healthcare team.

• *Environment II: Moderate-contact setting,* where there is in-person contact between the patient and the healthcare team, with short-time exposure (< 15 minutes) and/or greater physical distancing (> 1.5 m).

• *Environment III: Close-contact setting,* there is close or prolonged physical contact between the patient and the healthcare team (>15 minutes, in a closed environment).

• *Environment IV: Invasive contact and potential airway manipulation,* there is either direct contact with the patient or patient's airway manipulation, and consequent exposure to aerosols.

To make it clearer, Table 3 depicts examples of several environments of routine cardiological care. It is worth emphasizing that diagnostic/procedural reports, whenever possible, should be elaborated and issued remotely.

3. COVID-19 Precautionary Measures and Confinement

Four levels of occupational risk from exposure to SARS-CoV-2 have been distinguished: extremely high, high, intermediate, and low (Figure 2). The occupational risk assessment depends on the distance and duration of contact between the professional and the patient, on the type of procedure performed and its risk of aerosol generation, in addition to the patient's clinical profile regarding the SARS-CoV-2 infection.

Therefore, in addition to standard precautionary measures, the following should be implemented by the healthcare services:

◦ Precautionary measures against contact

◦ Precautionary measures against droplets

◦ Precautionary measures against aerosols

Some aerosol-generating procedures are as follows: tracheal intubation or aspiration, non-invasive mechanical ventilation, cardiopulmonary resuscitation, manual ventilation before intubation, nasotracheal sample collection, bronchoscopy. For the healthcare in which these aerosol-generating procedures are routine or potentially necessary, precautionary measures against droplets should be replaced with precautionary measures against aerosols.

Thus, the necessary PPE for healthcare delivery to suspected or confirmed cases of COVID-19 are as follows:

a. Standard Precautionary Measures

Instituted for all patients and comprise:

• Hand hygiene.

• Masking – during the COVID-19 pandemic, face masks should be worn for standard precaution, as detailed below for level 1 PPE.

If there is risk of exposure to blood or secretions:

• Wear procedural gloves.

• Wear goggles and gown.

Dispose PPE waste into appropriate containers.

b. Precautionary Measures Against Contact + Droplets:

• Surgical face mask.

• Googles or face shield.

•Gown with minimum weight of 30 g/m^2.

• Procedural gloves.

c. Precautionary Measures Against Contact + Aerosols:

• N95/PPF2 respirator or equivalent.

• Face shield.

Table 3 – Classification of Cardiology care environments according to person-to-person contact

Cardiology care environments
Remote care
Decision-making support systems
Teleconsulting, including telephonic guidance
Tele Regulation
Telediagnosis and remotely issued reports
Teleducation
Moderate-contact environment
Parking lot (valet parking)
Receptionists and administrative workers
Security professionals
Close-contact environment
In-person medical appointment
Presence of healthcare personnel in nuclear medicine tests
Presence of healthcare personnel in imaging tests (CT, MRI, echocardiography)
Presence of healthcare personnel in cardiology graphical methods
Invasive contact and potential airway manipulation
Oroscopy and physical exam
Transesophageal echocardiography
Invasive procedures in electrophysiology
Invasive procedures in interventional cardiology

CT, computed tomography; MRI, magnetic resonance imaging.

- Fluid-resistant gown.
- Hair cap.
- Procedural gloves.

In addition to aerosol-generating procedures, when managing patients with sputum, bleeding, vomiting or diarrhea, the healthcare professional should wear a fluid-resistant gown. The rational use of PPE in healthcare services is required, and because of the risk of PPE shortage, the recommendations on PPE use may change due to contingency plans during the COVID-19 pandemic.

d. Recommendation on PPE Use According to the Procedure Complexity and the Patient's Clinical Profile (Figures 1 and 2, Table 4)

Level 1 PPE: For intermediate risk, moderate-contact environment.

Standard Precautionary Measures

Indicated for NON-invasive procedures when performed electively AND in patients without suspected COVID-19.

- Professionals involved in activities favoring contact between one another greater than 2.0 m can wear a cloth face mask.
- If the 2.0 m physical distancing from patient is not guaranteed, a surgical mask should be worn during the activities (Table 5).
- Physical barriers, such as acrylic plaques and flooring demarcation, should be installed to favor distancing of at least 2.0 m (Table 5).

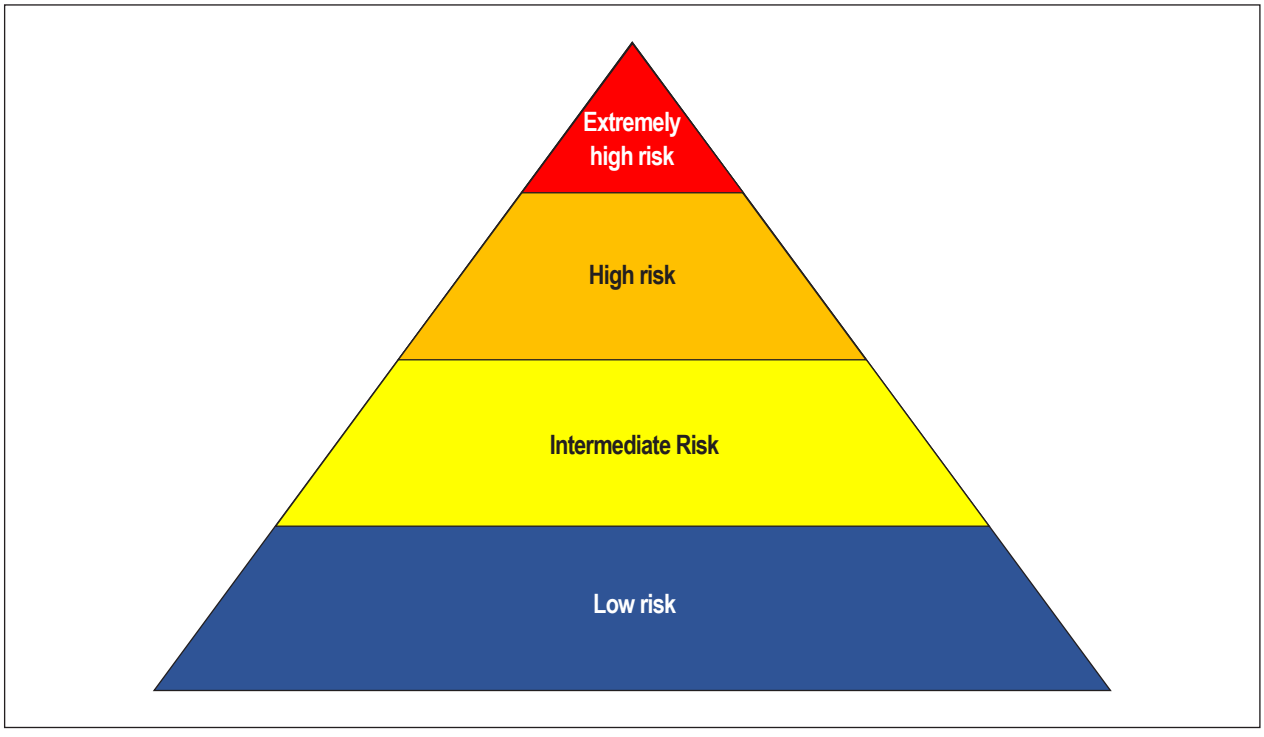

Figure 2 – *Pyramid of occupational risk for COVID-19 (adapted from Occupational Safety and Health Administration - OSHA).*[14]

Table 4 – Definition of the PPE usage level according to risk

Risk	Exposure type	Healthcare type	PPE level
Extremely high risk Invasive contact of airways	Exposure to patients with confirmed or suspected COVID-19 Aerosol-generating procedures	Oroscopy and ophthalmoscopy TEE, exercise stress testing Invasive procedures in electrophysiology and interventional cardiology	Level 3
High risk Close-contact environment	Exposure to patients with confirmed or suspected COVID-19	Nuclear medicine tests Imaging tests (CT, MRI, TTE) Graphical methods in cardiology	Level 2
Intermediate risk Moderate-contact environment	Frequent and in-person contact	Receptionists Administrative workers Parking lot In-person appointment	Level 1
Low risk Remote care	No contact with patients	Tele Regulation Telediagnosis Teleducation	No specific PPE

CT: computed tomography; MRI: magnetic resonance imaging; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography. For in-person consultations of patients with suspected or confirmed COVID-19, level 2 PPE should be worn. Some guidelines consider that imaging tests and graphic methods, except for exercise test, require the use of only surgical mask, particularly when the likelihood of active COVID-19 is low, when COVID-19 is resolved or in cases with neither symptoms nor recent contact and a recent negative test for COVID-19.

Table 5 – Standard precaution according to distancing

Precaution type	Standard
Professionals > 2.0 m from patient	Cloth face mask
Professionals < 2.0 m from patient	Surgical mask

A cloth face mask should not be used by healthcare personnel during care delivery.

Level 2 PPE: For high risk, close-contact environment.

Precautionary Measures Against Contact + Droplets

Indicated for NON-invasive procedures when performed in an emergency situation OR in patients with confirmed OR suspected COVID-19.

Level 3 PPE: For extremely high risk, invasive contact of airways.

Precautionary Measures Against Contact + Aerosols

Indicated for invasive and **aerosol-generating** procedures performed:

• electively AND in patients with **no** suspected COVID-19.

• in an emergency situation OR in patients with confirmed OR suspected COVID-19.

Note: For invasive procedures, replace the PPE (gloves, gowns) with properly sterilized equipment.

It is worth emphasizing that cloth face masks are not PPE, thus they should not be worn by healthcare or ancillary personnel in situations requiring the use of either a surgical mask (during healthcare or direct contact, in which the minimum 2.0 m distance between one another cannot be kept) or an N95/PFF2 respirator (during aerosol-generating procedures).

e. Surface cleaning and disinfection

There is no differentiated recommendation for surface cleaning and disinfection after contact with cases of suspected or confirmed COVID-19. However, it is mandatory that healthcare services revise their operational procedures for cleaning and disinfection of environment and surfaces to ensure better practices and increased periodicity of cleaning.[14,15,16]

• All specific equipment in cardiological management should be cleaned at the end of the workday and professionals should be wearing PPE to prevent contact with infected materials.

• Monitors and surfaces of the ultrasound device can be covered with a disposable plastic wrap to reduce the risk of contamination and facilitate cleaning.

• After a patient with suspected or confirmed COVID-19 leaves the procedure room, the equipment and all areas that the patient and healthcare professionals had contact with should be cleaned/disinfected with usual sanitizers.

4. Strategic Approach in the Healthcare Environment

a. In-person Healthcare Environment

Classification: Environment II (moderate contact)

Risk: Low to intermediate

In-person healthcare is provided in the out-of-hospital environment, which comprises basic healthcare units, outpatient

speciality clinics, hospital outpatient clinics, clinics, and medical offices. These are an essential part of the health system response, because of the potential increase in cardiovascular outcomes in the medium-term due to the deficit in the medical care for that population. Adaptations of the healthcare protocol should include the following changes in routine care:[16]

Scheduling

• Appointments should be scheduled remotely (telephone or online), using dedicated digital platforms or message apps.

• Fewer appointments should be scheduled and at longer intervals, allowing a patient to leave the healthcare facility, including the waiting room, before the next one arrives, minimizing contact between one another.

• The triage of patients with respiratory symptoms should be performed during scheduling and upon appointment confirmation by using the Screening Questionnaire of Symptoms and Exposures (**Appendix A**).

• The use of a face mask by the patient and patient companion should be advised and required regardless of either the presence of symptoms or their responses to the Screening Questionnaire of Symptoms and Exposures.

• The patient should be advised to attend the appointment alone, whenever possible. When strictly necessary, indicate that only one companion is allowed, and this person should also complete the same Screening Questionnaire of Symptoms and Exposures.

Physical Structure/ Waiting Room

• Keep the environment ventilated (air conditioning with ventilation, which ensures air exchange, or opened windows).

• Downsize the reception personnel that has physical contact with patients.

• Install physical barriers in the reception to reduce contact, such as acrylic plaques and flooring demarcation to remind people to maintain at least 2.0 m between one another.

• Display visual reminders at the service entrance and strategic places disclosing key information on hand hygiene, respiratory etiquette, and signs and symptoms of suspected COVID-19.

• Provide tissue paper for nasal hygiene or respiratory etiquette in the waiting room, in addition to foot-pedal trash cans for discarding tissues and paper towels.

• Provide dispensers with alcoholic preparations for hand hygiene and sinks with liquid soap dispensers, paper towel and its support, touchless garbage can.

• Encourage waiting in an open or external environment, observing the minimum 2.0 m physical distancing.

• Demarcate the minimum 2.0 m distance between the seats.

• Provide disposable cups for water and coffee.

• Remove shared objects from the room, such as magazines and newspapers.

• Advise on hand hygiene before and after completing the forms, using pens, and paying with credit card. Clean the credit card payment machine and, to facilitate the process, the device can be covered with a disposable plastic wrap and cleaned after each use.

• Provide surgical masks for patients with respiratory symptoms and instruct them on the correct mask wearing during their entire stay in the unit, if the care is strictly necessary. Patients requiring elective or semi-elective care, however, should return home for individual confinement and investigation for COVID-19, and a new appointment rescheduled for later. Masks should be replaced whenever moist or dirty.

• A patient with respiratory symptoms should be referred to a separated room or area, isolated from other patients.

• Increase the cleaning and disinfection frequency of the environment, objects and higher-contact surfaces.

• Neither carpets soaked in sanitizing solutions nor disinfection booths at the entrance of the service are recommended due to lack of documented efficacy.

• No product should be sprayed onto patients, patient companions or healthcare workers because of the high risk of intoxication and lack of scientific evidence for its use.

Patient Companion

• Advise patients to come to the appointment alone.

• If a companion is required for a patient who needs supervision or for any other reason, allow the presence of only one person who does not belong to the risk group (Table 6).

• On the day prior to the appointment, apply the Screening Questionnaire of Symptoms and Exposures to the patient companion.

• Patients requiring elective or semi-elective care with companions who have symptoms or had recent contact with suspected or confirmed COVID-19 cases should not attend a medical appointment.

Table 6 – Risk group assessment for screening the patient companion

Age > 65 years
Obesity
Systemic arterial hypertension
Diabetes mellitus
Smoking
Heart failure
Chronic obstructive pulmonary disease
Chronic kidney disease
Sickle cell anemia
Continuous immunosuppression (transplants, HIV infection, oncological diseases, chronic use of immunosuppressants)
Asthma (moderate to severe)
Cerebrovascular disease
Pregnancy
Liver disease

• Patient companions should follow all the instructions and recommendations provided to patients.

b. Healthcare Via Telemedicine

Classification: Environment I (remote)

Risk: None

Telemedicine plays a fundamental role in the rational return to healthcare activities and was detailed in the 2019 Brazilian Society of Cardiology Guideline on Telemedicine in Cardiology.[17] In the context of that guideline, we should emphasize the teleconsultation and telemonitoring concepts and highlight that their use is recommended, except for urgency and emergency patients, who require in-person care. In addition to the general recommendation for telemedicine use, it is worth noting that remote care should be preferred when the healthcare provider belongs to the risk group.

• All telemedicine consultations must take place with synchronous image and sound, in addition to equipment that ensures patient privacy and confidentiality, as well as proper recording of information in a patient's medical record.

• Telemedicine can be used routinely for pre-consultation by the physician, who should assess the patient's need for an in-person visit, define the risk of the patient's clinical findings, refer the patient to a hospital, when necessary, or even solve the case providing complete healthcare via telemedicine.

• Remote healthcare should be preferably provided with digital certification and electronic signature, ensuring originality of the information, as well as safety for both physician and patient.

c. Remote Follow-up

Classification: Environment I (remote)

Risk: None

• Telemonitoring of necessary vital signs and test results can be performed via other remote access media. Some examples of telemonitoring: follow-up of heart failure symptoms and blood pressure levels; telemetry of cardiac implantable electronic device; remote control of laboratory test results, such as kidney function, anticoagulation etc.

• Telemonitoring can and should be used for the remote follow-up of patients to reduce the number of in-person medical visits and, thus, the traffic of patients, whenever possible.

5. Strategic Approach in the Context of Non-Invasive Tests

a. Graphical Methods in Cardiology

The complementary graphical methods in Cardiology can be classified according to the environment they are performed in and the distance between patients and healthcare professionals required, as follows:

Remote Healthcare

• Home Blood Pressure Monitoring (HBPM).

Moderate-contact Environment

• Electrocardiography at rest.

• Holter.

• Ambulatory Blood Pressure Monitoring (ABPM).

Close-contact Environment

• Tilt-table test.

Similarly to the instructions provided to other Cardiology areas, appointments should be scheduled remotely and at programmed hours to reduce the number of people at the same time in the waiting room. The Screening Questionnaire of Symptoms and Exposures should be applied on the day before the procedure for both the patient and the patient companion, which should only be present if essential and not belonging to the risk group for COVID-19 (Table 6).

In the specific context of the graphical methods, remote diagnostic media should be encouraged, such as remote access and real-time telediagnosis, which reduce not only the number of healthcare professionals exposed but the duration of their exposure as well. When these tests cannot be delayed, the instructions include:

• Issue electrocardiogram, Holter, ABPM and HBPM reports remotely.

• Prioritize the use of HBPM over ABPM, whenever possible.

• Follow the institutional protocols of distancing and hygiene/cleaning for the facility and the return of Holter and ABPM devices.

• To assess myocardial ischemia, consider an alternative to exercise testing, with association of imaging techniques and pharmacological stress to reduce the personnel exposure to droplets and aerosols.

b. Exercise Stress Testing

Classification: Invasive contact of airways

Risk: Extremely high

Exercise testing is a valuable tool, considering its widespread use, and the major method for assessing myocardial ischemia in several services across the country. However, one should be cautious during the period of sustained community transmission of COVID-19, because of the higher risk of disease spread resulting from the increase in the patient's respiratory rate and emission of droplets during the test, as well as the long length of stay in the testing room, which is a closed environment. Therefore, elective and semi-elective tests should be considered on a case-by-case basis. Postponing an exercise test is recommended during the phase of higher community transmission of SARS-CoV-2.

In the rare situation in which exercise testing is deemed necessary for a patient with recent suspected or confirmed COVID-19, it should be performed observing the specific level 3 (contact precaution + aerosols). Due to the fact that scientific evidence is still uncertain regarding this type of exposure, there is a possibility of a change in the recommendation in future publications.

With regard to the tilt test, although there is prolonged exposure by the health professional, there is no increase in respiratory work, and it can be inferred that the risk of transmission is not so increasing. Therefore, level 3 precaution is recommended.

• When undergoing an exercise test, patients should wear a surgical mask during all the procedure.[18]

• Other people should not be present in the testing room (relatives, coaches etc.).

• Automatic blood pressure cuffs should be used whenever available.

• The healthcare team should wear proper PPE according to their distance from the patient, specific level 2 precaution.

• During the entire procedure, the healthcare team should stay at least 2.0 m away from the patient.

• The testing room should be actively ventilated and ideally at least 60 minutes between individual tests should be observed for each treadmill, allowing enough time for proper hygiene of the equipment.

• All equipment used for the test should be thoroughly cleaned between each patient assessed.

c. Echocardiography

The reopening of echocardiography services should contemplate the already described measures regarding remote scheduling, larger interval between appointments, recommendations for patient companions, environment cleaning and hygiene, and physical distancing. Because of the close contact between the equipment operator and patients required during image acquisition, postponing elective and semi-elective tests should be considered during the sustained community transmission period, mainly for patients of the risk groups (Table 7).

d. Transthoracic Echocardiography (TTE)

Classification: Close-contact environment

Risk: High

• In the initial phase of reopening, schedule high-priority tests first and then intermediate-priority ones, according to local epidemiological status and reopening success;

Table 7 – Priority regarding eligibility for echocardiography testing

Urgency and emergency healthcare environment
Recent clinically relevant cardiovascular symptoms (FC III or IV heart failure, syncope of cardiac origin, chest pain, arrhythmias)
Recent procedure requiring urgent follow-up
Arrhythmias after device implantation
Pericardial effusion
Post-operative assessment in cardiac surgery
Initial assessment before beginning oncological drug treatment (chemotherapy/immunotherapy)
Suspected infective endocarditis with high pre-test probability
Semi-elective healthcare environment
Asymptomatic patient with chronic cardiac disease that requires monitoring
Assessment of stable heart valve disease (aortic and mitral stenosis or regurgitation)
Pulmonary hypertension
Disease progression after intervention (recurrent coarctation, duct stenosis)
Non-cardiological therapy requiring continuous monitoring
Pulmonary artery systolic pressure estimation in patients on specific therapy
Assessment of rejection after heart transplant
Treatment for Kawasaki disease
Follow-up assessment of the VAD function in stable patients
Non-urgent pre-operative echocardiography
Elective healthcare environment
Routine follow-up of chronic diseases: hypertension, coronary artery disease, annual assessment of aorta disease or of prosthetic valve function (normal function on the previous test and no new symptom)

FC: functional class; VAD: ventricular assistance device.

• Apply in advance the Screening Questionnaire of Symptoms and Exposures and repeat triage before the procedures;

• Healthcare personnel should wear proper PPE.

e. Transesophageal Echocardiography (TEE)

Classification: Invasive contact of airways

Risk: Extremely high

The general considerations for performing TEE follow the same principles already described. However, additional precaution is recommended because of the aerosol-generating potential related to the cough reflex in patients with unprotected airways. Therefore, proper complete and universal PPE should be worn, and thorough cleaning of the testing room and equipment performed.

Ideally, aerosol-generating procedures should be carried out in a respiratory isolation unit with negative pressure and HEPA (High Efficiency Particulate Arrestance) filter. When such unit is not available, the patient should be placed in an individual room with doors closed, and the number of healthcare professionals should be restricted during those procedures. Because of the high risk TEE poses, its indication should be assessed on an individual basis during the COVID-19 pandemic.

Recommended PPE

All professionals in contact with the patient's airways and the support team in the procedure room should take specific level 3 precaution (precaution against contact + aerosols).

Equipment Cleaning

Detailing the TEE equipment cleaning is beyond the scope of this document. Other cleaning and disinfection protocols provided by hospital infection control services and institutional technical rules should be followed routinely.

f. Stress Echocardiography

Classification: Close-contact environment

Risk: High

Echocardiography performed with physical stress promotes the same respiratory rate changes described for exercise testing, compounded by the fact that the operator cannot keep proper distance from the patient. Thus, physical stress should be considered rather an exception and not applied routinely until the COVID-19 community transmission is properly controlled. An alternative is performing stress echocardiography with pharmacological agents or using other imaging methods when necessary. In exceptional cases, when physical stress echocardiography must be performed, specific level 3 precaution (precaution against contact + aerosols) should be taken by all professionals in the testing room.

Stress echocardiography with dobutamine or other pharmacological agents should be the preferred alternative during the pandemic, and all precautionary measures recommended for performing an echocardiography at rest should be observed.

Patients with Confirmed or Suspected COVID-19

In patients with acute findings and diagnosed with confirmed or suspected COVID-19, echocardiography should be performed only in case of urgency and emergency, when the result of the test is expected to really impact on the clinical management. The use of portable devices is recommended, with special attention being paid to team protection.

• Plan echocardiography in advance to analyze only the windows necessary for decision making.

• Use the time at the patient's side only to acquire images and videos, leaving measurements to be taken later with a dedicated software.

• Reassign training professionals and less experienced echocardiographers to non-COVID-19 areas to minimize test duration.

• The healthcare team should wear the recommended PPE according to their proximity to the patient, specific level 3 precaution (precaution contact + aerosols).

g. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) of the Heart

Classification: Moderate-contact environment

Risk: Intermediate

Radiology services and their imaging rooms worldwide have not been projected contemplating restrictive measures against the transmission of infectious diseases. However, imaging tests are essential tools for the diagnosis and treatment of COVID-19 and its complications.

The previously mentioned initial measures related to remote appointment scheduling, longer intervals between appointments, recommendations regarding patient companions, healthcare environment cleaning/disinfection, and physical distancing must be observed.

In the adaptation process for service reopening under the current uncommon conditions, patients with suspected or confirmed COVID-19 should undergo tests preferably using devices/equipment dedicated to their clinical profile, to prevent crossed contamination between infected and non-infected individuals. This is particularly important, because CT is frequently used in the investigation of cases with suspected or confirmed COVID-19. When that is not possible, it is necessary to define, in the equipment available, time slots dedicated to the clinical profile 'suspected or confirmed COVID-19', preferably at the end of the workday. Because SARS-CoV-2 remains viable on several surface types and environmental conditions, the imaging room must be cleaned and disinfected after being used for each patient with suspected or confirmed COVID-19 and before acquiring images from a patient without suspected or confirmed COVID-19, and that cleaning should follow institutional protocols.

Elective and semi-elective tests should be rescheduled during the most intense COVID-19 community transmission period. Urgency and emergency tests should be considered according to the clinical need and the expectation of management definition based on test results.

For in-patients, cardiovascular imaging can be used to replace invasive tests or tests that involve airway manipulation, such as TEE and coronary angiography. Thus, in some selected cases, cardiac

CT can be used to search for left atrial appendage thrombus, or coronary tomography angiography used in non-ST- elevation acute coronary syndrome. For clinical profile A or B patients, for whom the tests are deemed necessary and irreplaceable, or in selected clinical profile C patients who need the tests, level 2 precaution is recommended. Because of the low level of evidence, this recommendation is made for the purpose of safety and other guidelines might recommend the use of only surgical mask for the care of patients with no suspected COVID-19. This strategy is particularly acceptable in cases of resolved COVID-19 or in cases with no symptom and a recent negative test for COVID-19.

Cardiac MRI, because of the long time it requires to be performed, and thus, longer exposure of the healthcare personnel, should be indicated for patients with suspected or confirmed COVID-19 only exceptionally, such as for the differential diagnosis between myocarditis, Takotsubo syndrome, and myocardial infarction with no obstructive coronary artery disease (MINOCA). Table 8 details the indications and priority levels for CT and MRI.

h. Nuclear Medicine

Classification: Moderate-contact environment

Risk: Intermediate

Similarly to echocardiography, it is important to define the priorities of nuclear medicine tests, observing the patient's clinical profile. Elective and semi-elective tests (profiles C and D) should be considered for later rescheduling during COVID-19 sustained community transmission. This is particularly important for patients with risk factors for COVID-19, such as age > 60 years, systemic arterial hypertension, diabetes, chronic pulmonary disease, and other chronic illnesses, characteristics frequently found among those undergoing nuclear medicine tests. For clinical profile A or B patients, for whom the tests are deemed necessary and irreplaceable, or in selected clinical profile C patients who need the tests, level 2 precaution is recommended. The risks described for exercise testing should always be weighed when physical stress is considered. Because of the low level of evidence, this recommendation is made for the purpose of safety and other guidelines might recommend the use of only surgical mask for the care of patients with no suspected COVID-19. This strategy is particularly acceptable in cases of resolved COVID-19 or in cases with no symptom and a recent negative test for COVID-19. Thus, the following instructions are intended to align test planning with international guidelines:

- **To shorten test duration**
- Select the protocol with the shortest acquisition duration;
- Consider initiating the protocol at the stress phase and performing the test in one single day, mainly for patients with low probability of myocardial ischemia;
- Consider protocols restricted to stress imaging;

Table 8 – Indications for cardiac computed tomography / magnetic resonance imaging during COVID-19 pandemic

Urgency healthcare environment
Non-ST-elevation acute coronary syndrome – differential diagnosis, to rule out:
Coronary artery disease
Acute myocarditis
MINOCA
Takotsubo syndrome
Exclusion of pulmonary embolism (triple rule-out protocols)
Detection of left atrial thrombus in AF in an in-patient
Heart valve dysfunction with acute decompensation
Suspected valvular endocarditis
Pre-TAVI planning
Assessment of VAD dysfunction
Surgery or biopsy programming for suspected malignant cardiac tumors
Semi-elective healthcare environment
Detection of left atrial thrombus in persistent AF
Subacute or chronic heart valve dysfunction
Investigation of coronary artery disease in stable angina
Stable structural cardiac disease
Probably benign cardiac tumors with no surgery or biopsy programming
Elective healthcare environment
Other clinical conditions

AF: atrial fibrillation; MINOCA: myocardial infarction with no obstructive coronary artery disease; TAVI: transcatheter aortic valve implantation; VAD: ventricular assistance device.

• Prefer pharmacological agents requiring the shortest time of infusion.

• **To reduce the healthcare professional's risk of exposure**

• Strictly assess the physical stress criterion for exercise testing to minimize its use during the pandemic, prioritizing protocols with pharmacological stress;

• Consider using automatic blood pressure cuffs, when available;

• Consider remote video surveillance during the test;

• In stress protocols with adenosine and dipyridamole, extenders can be used to maintain the distance between professionals and patient;

• For endocarditis, 18F-FDG PET should be considered an alternative to TEE, which determines extremely high exposure to the risk of droplets for device operators.

In addition to the measures implemented in the context of the COVID-19 pandemic, its rapid progression and high impact can result in shortage or difficult distribution of medications and radiotracers. Thus, stricter control of their flow is essential, mainly when the number of new COVID-19 cases is high or in situations of possible disruption of the logistics of medication distribution.

6. Catheterization Laboratory and Interventional Cardiology

Classification: Invasive contact of airways
Risk: Extremely high

a. Elective Procedures

General Recommendations

• In the cardiac catheterization laboratory (cath lab), elective patients should follow different flows from those of emergency patients.

• In services with more than one intervention room, an exclusive room for elective cases should be kept.

• Keep the Heart Team active during the COVID-19 pandemic and involved in the reopening phase.

• Apply the Screening Questionnaire of Symptoms and Exposures before performing elective interventional procedures (Appendix A).

• At the beginning of the reopening process, select the patients with the highest potential for benefiting from percutaneous coronary intervention or from structural heart disease intervention (Table 9).

Although controversial, the use of RT-PCR testing for COVID-19 diagnosis in asymptomatic patients admitted for elective procedures can be considered adequate to reduce the risk of hospital transmission. In such cases, the nasopharyngeal/oropharyngeal swab for RT-PCR testing can be collected within the 48 hours preceding the procedure, preferably at the patient's home. This practice facilitates the patients' hospital allocation during admission, rationalizes the specific PPE use, and minimizes the risks of exposing healthcare personnel. If the RT-PCR is not available, we suggest the alternative flowchart (Figure 3).

General Recommendations

• Obtain the patient's informed consent after clarifying the risks and benefits of performing the procedure during the COVID-19 pandemic.

• Elective procedures in symptomatic patients or those with positive RT-PCR for SARS-CoV-2 should be postponed for at least 14 days. In clinical profile C and D patients, the risk-benefit of delaying the procedure until COVID-19 pandemic control should be considered.

• For transcatheter aortic valve implantation, minimalist approach with conscious sedation, when feasible, is recommended, prioritizing shortening the length of hospital stay and reducing the use of TEE.

Preprocedural Recommendations

1. When Routine Pre-admission RT-PCR Testing is Available

• The collection of nasal and oropharyngeal swab for SARS-CoV-2 RT-PCR testing within the 48 hours preceding the procedure is recommended, and preferably at the patient's home.

• All patients should be instructed to keep social distancing and restrict contacts in the 14 days preceding the procedure.

• By use of telephone or electronic contact, trace symptoms and exposure (**Appendix A**) in the 48 hours preceding the procedure.

• If a patient companion is required, apply the Screening Questionnaire of Symptoms and Exposures and ask for RT-PCR testing.

• It the RT-PCR test detects the presence of the virus, wait at least 14 days with symptom improvement for at least 3 days to reschedule the procedure. It is not necessary a new RT-PCR testing to approve the procedure, because the result might remain positive even with non-viable virus.

2. When Pre-admission RT-PCR Testing is Not Available

• All patients should be instructed to keep home isolation and absolute contact restriction in the 14 days preceding the procedure;

• Trace symptoms and exposure risk (**Appendix A**) before the procedure to improve safety.

Procedural Recommendations

All operators must use level 3 PPE (precaution against contact + aerosols).

Postprocedural Recommendations

• Refer patients to the post-anesthesia recovery room according to the triage result (COVID-19 positive or COVID-19 negative areas). If that is not possible, post-anesthesia recovery should happen in the procedure room.

Table 9 – Patients with the highest potential for benefiting from cardiac interventions

Symptomatic coronary artery disease of difficult clinical management
Coronary artery disease and high-risk findings on functional testing
Coronary artery disease and high-risk anatomical findings, such as severe obstruction of the left main coronary artery or of the anterior descending artery proximal third
Symptomatic or asymptomatic severe aortic stenosis with reduced LVEF
Mitral regurgitation in FC III/IV and recent progression, with recent drop in LVEF, or in services with established programs for percutaneous treatment of mitral regurgitation with mitral valve clipping

FC: functional class; LVEF: left ventricular ejection fraction.

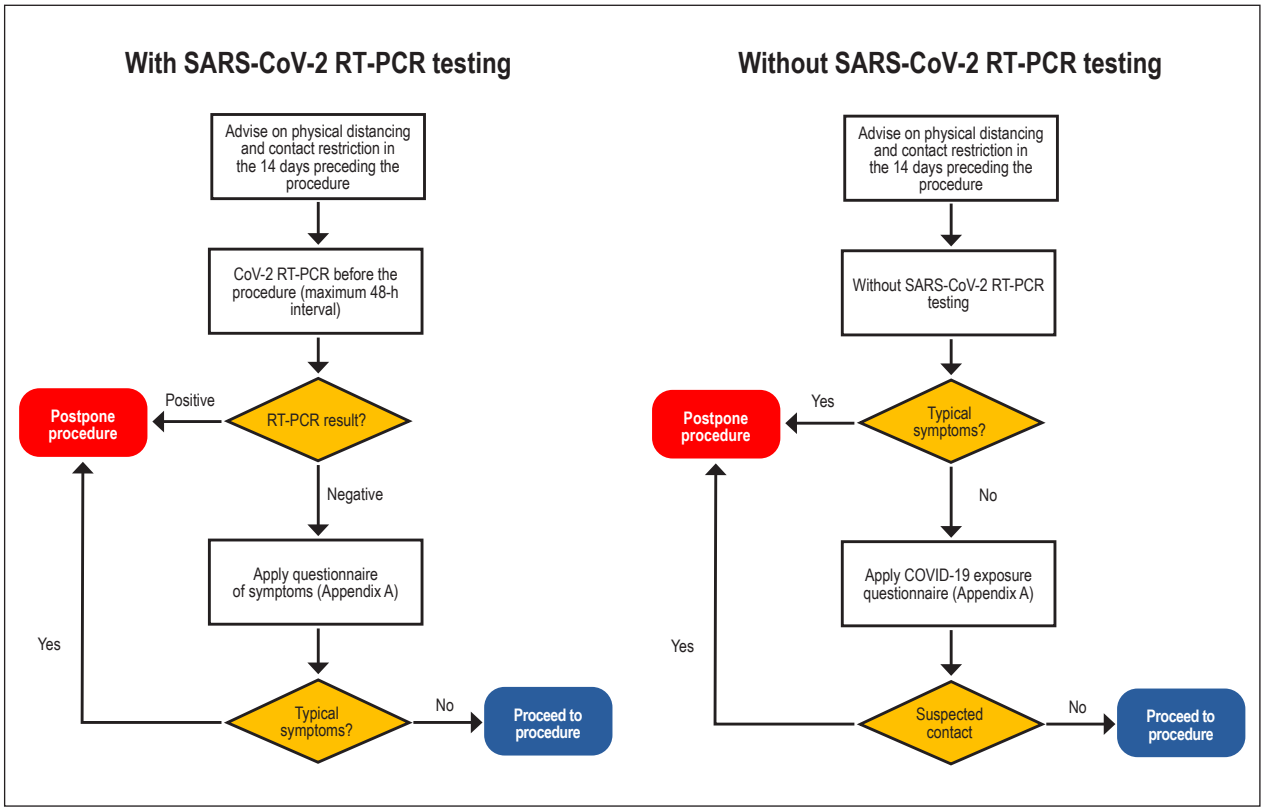

Figure 3 – *Flowchart for managing elective procedures of interventional cardiology and electrophysiology according to SARS-CoV-2 RT-PCR testing availability.*

• Prioritize hospital discharge on the same day, and, if not possible, minimize the length of stay.

• When the intervention or exam is followed by hospital admission, use proper hospital flow and beds reserved for patients without COVID-19.

• After discharge, as an indicator of safety, follow patients up, regarding symptom onset, up to 10 days after the procedure. If the patient develops symptoms, search for the in-hospital contacts of the patient-index.

b. Urgency and Emergency Procedures

With the elevated number of susceptible individuals in the population, the reopening of programs of elective percutaneous interventions will occur concomitantly with admissions related to SARS-CoV-2 infection, which is known to increase the risk for thromboembolic phenomena and to determine multiple cardiac manifestations, such as acute coronary syndromes, myocarditis, type II myocardial infarction and ventricular arrhythmias, in addition to stress cardiomyopathy (Takotsubo syndrome) triggered by the disease itself. Thus, it is essential to maintain a specific flow for the management of suspected or confirmed COVID-19 cases, as well as for the emergency healthcare of patients with acute coronary syndromes and unknown infectious status and no possibility of testing.

General Recommendations

• Reserve one room for confirmed or suspected COVID-19 cases and for emergency patients in services with at least two rooms available.

Preprocedural Recommendations

• Do not delay healthcare for emergency cases, such as ST-elevation acute myocardial infarction (AMI).

• Patients with the pre-hospital diagnosis of ST-elevation AMI via telemedicine and those referred from other units for primary angioplasty or rescue angioplasty should be sent directly to the cath lab, avoiding visit to the emergency unit.

Procedural Recommendations

• Provide level 3 PPE (precaution against contact + aerosols) for all healthcare personnel.

• Maintain the team trained in the techniques to put on and remove the PPE;

• Reduce the number of individuals in the medical and multidisciplinary teams inside the procedure room to the lowest possible.

• Reduce the materials on the stands and check the toolbox before the procedure to avoid opening the door.

• Remove cabinets, whenever possible, or maintain their doors closed during the entire procedure.

• In rooms without negative pressure, avoid opening the door and use the audio communication system for external contact.

• Assign one technologist wearing proper PPE to be outside the procedure room to deliver materials while briefly opening the door.

• Use sedation parsimoniously to prevent airway management.

• Perform rapid sequence orotracheal intubation (OTI), when necessary.

• In patients with progressive impairment of respiratory mechanics, prioritize OTI and avoid using non-invasive ventilation and high-flow nasal cannula.

Postprocedural Recommendations

• At the end of the procedure, direct the patient to the specific zone for confirmed COVID-19 or for patients waiting for SARS-CoV-2 RT-PCR;

• Wait for transportation inside the procedure room to prevent contamination of the post-anesthesia recovery room.

Postprocedural Cleaning

• Remove PPE inside the procedure room;

• Perform final cleaning of the room as usual.

7. Electrophysiological Study

Classification: Invasive contact of airways
Risk: Extremely high

a. Elective Procedures

The general recommendations for reopening elective programs apply to the cath lab invasive procedures. Patient's informed consent should be obtained after clarification of the risks and benefits of undergoing the procedure during the COVID-19 pandemic, and different patients' flows should be observed for elective and urgency/emergency care.

The most urgent tests/interventions (Table 9) and those with the highest prognostic impact should be prioritized to reduce the risk of death and prevent clinical decompensations.

• Elective procedures in symptomatic patients or in those with a recent positive RT-PCR test, even though asymptomatic, should be postponed.

• Although controversial, the use of RT-PCR testing to diagnose COVID-19 in asymptomatic patients admitted for elective electrophysiological study can be considered adequate to reduce the risk of in-hospital transmission (Figure 3).

b. Urgency and Emergency Procedures

In the presence of imminent risk of hemodynamic decompensation or death (Table 10), patients with COVID-19 or unknown infectious status may be admitted for emergency interventions. In these cases, the safety recommendations for the healthcare team apply concomitantly.

The pre-procedural and procedural recommendations are similar to those described for the cath lab.

8. Special Considerations on Heart Transplant Patients

COVID-19 has specific repercussions for patients involved in heart transplant, such as donors and recipients, in the waiting list, and after the transplant. As already known, these patients are at increased risk for both SARS-CoV-2 infection and progression to severe disease because of comorbidities, their constant contact with healthcare units and professionals, in addition to immunosuppression. However, these patients are known for their high adherence to medical recommendations.[20] Thus, targeted prevention and treatment strategies are necessary.[21]

Regarding the donor, non-infected individuals should be chosen, having in mind that many can be asymptomatic/pre-symptomatic/oligosymptomatic carriers and that the current tests have significant limitations. Thus:

• SARS-CoV-2 RT-PCR testing should be performed as soon as organ donation is consented.

• Whenever available, perform chest CT to rule out radiographic findings of suspected infection.

• If the RT-PCR test results positive, the organs should not be used for transplantation.

Regarding in-patients, both in the waiting list and posttransplant management:

• They should be kept in 'non COVID-19' units, being cared for by a dedicated multiprofessional team with no contact with positive cases of SARS-CoV-2 infection.

• In-person outside visits should be limited and not recommended. The communication routine with family should be organized.

Table 10 – Classification of the electrophysiological study procedures during the COVID-19 pandemic[19]

Elective healthcare environment
Electrophysiological study or AF, flutter or nodal ablation in stable outpatients
Electrophysiological study to assess stable tachyarrhythmias
Cardioversion of stable arrhythmias with tolerable symptoms
Left atrial appendage closure in patients on oral anticoagulation
Tilt-table testing
Semi-elective healthcare environment
Ablation of drug-refractory and recurrent ventricular tachycardia
Supraventricular tachycardia determining multiple visits to the emergency unit
AF, flutter or nodal ablation in patients with recurring symptoms
Urgency and emergency healthcare environment
Ablation of ventricular tachycardia due to drug-refractory electrical storm
Wolf-Parkinson-White syndrome or pre-excitation with syncope or cardiovascular arrest
AF, flutter or nodal ablation in patients with significant hemodynamic impairment and drug refractoriness or cardioversion resistance

AF: atrial fibrillation.

Regarding the ambulatory posttransplant management, the following is recommended:

- Limit in-person visits for stable and asymptomatic patients.
- Encourage telemonitoring of the serum levels of immunosuppressants;
- Delay endomyocardial biopsy in stable patients.

Heart transplant recipients, due to their sustained immunosuppression, may present typical (respiratory) and atypical (gastrointestinal) manifestations of SARS-CoV-2 infection. In such cases, the following is recommended:

- Consider reducing the calcineurin inhibitor dose (cyclosporine or tacrolimus).
- Suspend temporarily antiproliferative drugs (mycophenolate or azathioprine).

9. Guidance to Patients with Risk Factors for SARS-CoV-2 Infection and its Clinical Repercussions

Clinical cardiologists play an essential role in the care of patients with SARS-CoV-2 infection, among whom there is a high prevalence of risk factors associated with more severe clinical repercussions. Thus, the proper control of risk factors is essential for continuing the treatment, for the new decision-making, and for guidance on reducing the infection spread.

Patients at Increased risk for Severe SARS-CoV-2 Infection

Table 6 shows the risk factors for the severe COVID-19 forms. These patients should be advised on their condition and the need for continuing their treatment:

- They should neither change nor suspend their medications without talking to their physicians.
- They should maintain a minimum medication supply to one month.
- They should maintain their vaccines updated according to the immunization calendar (especially against influenza and pneumococcal disease).
- They should remain physically active and maintain a healthy lifestyle, as a measure to reduce the risk of COVID-19 complications.[22] The practice of physical exercises according to the recommended safety measures to prevent COVID-19 contamination should be encouraged.
- Fighting against smoking is strongly recommended, even among lower-risk populations, such as young individuals, because of the increased likelihood of complications.[23]
- Never postpone the search for urgent care in case of any warning sign, such as chest pain, dyspnea, changes in speech, gait and/or localized muscular strength, or other condition requiring immediate attention.

These recommendations are aimed at strengthening adherence to treatment and control of cardiovascular risk factors (especially obesity and smoking), a strategy that may add additional value to the reduction in the risk of complications from COVID-19.[24,25]

In addition, patients should be advised on maintaining the measures to reduce the risk for spread, such as:

- To limit physical proximity interactions with other people, whenever possible.
- To take every precaution when interacting with other people:
  - observe the minimum 2.0 m physical distancing.
  - wear a cloth face mask.
- To promote hand hygiene with water and soap or alcohol gel.
- To contact their physician in case of fever, diarrhea or respiratory symptoms.

• In case of suspected COVID-19, contraindicate self-medication and instruct about its risks.

• To avoid activities in which protective measures cannot be taken, such as situations in which social distancing cannot be maintained (gatherings in closed environments, events).

• To avoid getting close to other people who are not taking protective measures.

Post-discharge Care of Cardiac Patients and their Return to the Workplace after SARS-CoV-2 Infection

Studies indicate that up to 20% of the patients have cardiovascular complications, such as arrhythmias, acute coronary syndrome, and myocardial injury during their hospitalization from COVID-19.[21]

These patients have a more severe clinical presentation of COVID-19 and mortality three times higher. In addition, they can face several obstacles in their household setting after discharge. The need for rehabilitation should be emphasized for those with post-discharge functional limitations.

• Physical: several patients will be discharged requiring care because of their respiratory limitations or care in wound/pressure areas. In addition, interventions will be needed to recover both the muscle mass and functional capacity of those with neuromyopathy of the critically-ill patient.

• Psychological and neuropsychological: because of their disease and treatment, recovering patients may develop persistent psychological adversities or even cognitive impairment.

• Socioeconomic: the patients' needs and socioeconomic circumstances have been commonly affected by the COVID-19 pandemic. In addition, the potential impact of the changes during isolation should be considered.

Therefore, patients with severe cardiovascular manifestations of COVID-19 should be reassessed in the first week after hospital discharge regarding cardiovascular symptoms, adherence to medication, and clarification of doubts and difficulties to readapt to routine activities, considering the procedures of rehabilitation described below. In addition, the minimum time to return to work activities should follow the existing guidelines and consider post-discharge functionality and the minimum isolation necessary.

Cardiovascular Rehabilitation

Scientifically established as an important intervention in secondary prevention, cardiovascular rehabilitation is one of the measures with class IA indication by the SBC in several care contexts (coronary artery disease, postoperative period of cardiac surgery, and heart failure), being particularly important after hospital discharge from acute conditions, such as COVID-19.

Currently, when social distancing and mobility restriction measures are required, the implementation of effective models that combine in-person care and remote telemonitoring is urgent. Worldwide, different means of communication have been used in the virtual rehabilitation process (telephone/mobile, apps for smartphone, e-mail, text message, Internet pages, videoconferences). However, the individual risk-benefit assessment of remote healthcare is essential, such as lower intensity in intensive physical training, less social support, remote training standards still being elaborated, and safety concerns with patients at higher risk. The adaptation of cardiopulmonary rehabilitation settings during the COVID-19 pandemic is detailed in Table 11.

10. Safety of Patients and Healthcare Professionals During the COVID-19 Pandemic

Protecting patients and healthcare professionals at all levels should be the major objective in resuming work activities during the COVID-19 pandemic. Studies have shown the high contamination rate among healthcare professionals, in addition to that group's high potential to spread COVID-19, as super transmitters at both the workplace and the community.

Hand hygiene and the proper use of PPE are essential to minimize the contamination risks for healthcare workers by SARS-CoV-2. It is paramount that all healthcare personnel receive training on the proper use of PPE, paying special attention to putting on and removing PPE, which should be standardized to reduce the risk of contamination. All personnel should be trained and show the ability to correctly and safely put on, use, remove, and dispose PPE.[3,26]

Guidance on the specific PPE use should be based on the biological risk the professionals are exposed to during their activities and follow the recommendations:

Table 11 – Recommendations for the adaptation of cardiopulmonary rehabilitation centers for the COVID-19 pandemic

Apply the Screening Questionnaire of Symptoms and Exposures (**Appendix A**) and cancel in-person care in case of a positive answer to any question
The patient and the team must wear surgical masks during the entire length of stay in the rehabilitation center
Maintain the minimum 2.0 m distance, whenever possible, during the use of the rehabilitation equipment (cycle ergometer, treadmill)
Organize individual sessions or reduce the number of patients per session to the minimum possible
Provide systematic disinfection of the material used before and after each activity
Use shorter programs, concentrating effort in the major components of each patient
Replace, whenever possible, in-person sessions with remote assessment and monitoring, instructing patients according to the equipment and using the most suitable means of communication (telephone, text messages, e-mail, videoconference, dedicated platforms and apps)
Promote special strategies for immunocompromised patients, such as those undergoing heart transplantation
Suspend community activities that do not respect the social distancing measures

• Regulation by certifying agencies and Anvisa.

• Proper use, cleaning or periodical disposal, according to technical recommendations.

• Inspection, repair, and replacement according to the manufacturer's instructions.

It is worth emphasizing that, in addition to the team's physical safety, legal, psychological, economic, and information safety should be considered.

a. Physical Safety

To ensure the physical integrity of healthcare professionals who return to their activities is one of the major goals of implementing safety measures. In addition to the continuous training of the whole team, the daily application of the Screening Questionnaire of Symptoms and Exposures to all professionals and the tracing of contacts of confirmed cases, as well as the PPE provision and its rational and systematic use, are essential.

Selection of the Team Upon Return to Work

Services will reopen gradually, thus it is important to start with healthcare professionals at lower risk and to consider adjusting the risk to the workplace the professional is assigned to.

Evidence suggests that younger professionals without risk factors be prioritized to 'close-contact' and 'invasive contact of airways' environments, where the occupational risk for SARS-CoV-2 infection is higher. On the other hand, older or middle-aged professionals with risk factors should be assigned to provide remote healthcare and/or maintain strict physical distancing. The other cases should follow Table 12.

Measures for Transmission Control and Isolation of Suspected Cases

Healthcare professionals who present suggestive symptoms of SARS-CoV-2 infection must be immediately excluded from the workplace. Then, their contacts in the 4 days preceding symptom onset should be traced. Once identified, these contacts should be monitored, instructed to quarantine for 10 days from the last contact, and, when available, undergo nasopharyngeal swab collection for RT-PCR testing.

Criteria for Healthcare Personnel Returning to Work after COVID-19

• Suspected cases

The healthcare professional with suspected COVID-19 (negative RT-PCR or not performed) can return to work after meeting both criteria:

1. At least 3 days (72 hours) have passed since clinical recovery, defined as:

- Resolution of fever without the use of fever-reducing medication.

- Improvement in respiratory symptoms (cough, shortness of breath) AND

2. At least 10 days have passed since symptoms first appeared.

• Confirmed cases

◦ *Symptomatic cases*

The healthcare professional with confirmed COVID-19 (positive RT-PCR) can return to work after meeting both criteria:

1. At least 3 days (72 hours) have passed since clinical recovery, defined as:

- Resolution of fever without the use of fever-reducing medication.

- Improvement in respiratory symptoms (cough, shortness of breath) AND

2. At least 10 days have passed since symptoms first appeared.

◦ *Asymptomatic cases*

The lack of symptoms prevents these individuals from being assessed based on the phase of disease. Thus, if there is confirmation by a positive RT-PCR test in an asymptomatic patient, the criterion for discontinuing quarantine is:

➢ At least 10 days have passed since the date of their first positive RT-PCR test.

For asymptomatic patients confirmed by use of serological tests, there is no clear guidance on their return to work after a positive test. However, considering the workplace safety, the safest strategy should be observed. Thus, we suggest:

Table 12 – Classification of the priorities to consider for the healthcare personnel return

	Young, no risk factor	Middle-aged or young with risk factor*	Elderly or middle-aged with risk factor*
Invasive contact of airways	1	2	3
Close contact	1	2	3
Moderate contact	1	2	2
No contact / Remote	1	1	1

Priority 1 – Return immediately
Priority 2 – Return after all priority 1 healthcare professionals
Priority 3 – Do not return, unless extremely necessary
**The risk factors are listed in Table 4*

➢ For reagent IgM or IgA serology or reagent IgG/IgM – return 10 days after the test.

➢ For reagent IgG serology – no physical distancing is required.

An infection control expert should be consulted to advise on the return to work of individuals who might remain infectious longer than 10 days (immunocompromised conditions).

Medical Residency and Specialization

Interns are an important part of the cardiology programs and services in Brazil. During the COVID-19 pandemic, many of them have been transferred from their imaging internship to the clinical healthcare of patients with COVID-19 at hospitals and intensive care units.

Upon return to their previous activities, beginners should be assigned to sectors where their inexperience does not increase the team's exposure. Education needs to be reviewed, in the search for new learning methods, including learning approaches based on videoconferences and remote training.

b. Legal Safety

Hospitalized patients should sign the informed consent, which should preferably state their awareness about the procedure being performed during the COVID-19 pandemic, with risks inherent in the procedure and the exceptional time. In addition, the daily application of the Screening Questionnaire of Symptoms and Exposures to healthcare professionals and patients should be documented and stored, in case of future need, as should be the written documents about the precautionary measures against transmission used by the healthcare team.

Healthcare Professionals in Hazardous Settings

As previously mentioned in the section *Selection of the team upon return to work*, some professionals will not resume work immediately. In such cases of absence from work (Tables 6 and 12) or during their symptomatic period, isolation and rehabilitation due to SARS-CoV-2 infection, a supportive network between experts is necessary for the possible immediate referral of patients under their care.

c. Psychological Safety

As the COVID-19 pandemic continues, strategies to psychologically support healthcare professionals, mainly those more susceptible to emotional distress, are necessary. The psychological support can include counseling and the development of supportive systems among coworkers. The following are part of the plan:[27,28]

• Monitor constantly the team's wellbeing, especially when prolonged shifts are required or when they are relocated to unknown areas.

• Facilitate access to mental health and psychosocial support services.

• Maintain active search for professionals with psychological impairment and in burnout situations.

• Demand periodic feedback from collaborators.

• Provide updated accurate information to all collaborators.

• Rotate workers from higher physical/emotional stress to lower stress areas and functions.

d. Economic Safety

Currently, the increasing costs with the healthcare to patients with COVID-19, compounded by the reduced income, constitute a financial burden to health organizations both in the public and private sectors. The steering committee must keep the financial planning constantly updated, negotiating public transfers in the Brazilian Unified Health System setting, which is even more overloaded in this COVID-19 pandemic, and insuring according to the revenue forecast in the supplementary health setting. Emphasis should be given to the increase in costs associated with the environmental adjustments, PPE use, and reduction in the capacity of care delivery to ensure patients' physical distancing during their stay in healthcare services.

e. Information Safety

The fight against fake news and the provision of a proper health literature to inform patients are missions of the cardiologist and a multidisciplinary team. The SBC has issued technical reports to guide cardiologists and patients. The World Health Organization and government agencies have shown concern about the "infodemic" (with the spread of fake news) and its impacts on the patients' physical and psychological health.

The healthcare team has the responsibility to be updated and provide patients with clear and objective information based on safe sources to prevent the spread of incorrect, incomplete, misunderstood, or fake information.

11. Appendix A

Screening Questionnaire of Symptoms and Exposures to be applied before elective interventional procedures

Questionnaire of symptoms:

In the last 14 days did you have any of the following symptoms?

Major symptoms (only 1 is enough to raise suspicion):

☐ Fever

☐ Cough

☐ Shortness of breath

☐ Mental confusion

☐ Loss of taste or smell

Minor symptoms (at least 2 are required to raise suspicion):

☐ Fatigue/tiredness

☐ Diarrhea

☐ Runny nose

☐ Nausea and/or vomiting
☐ Sore throat
☐ Headache
☐ Conjunctivitis
☐ Other:_____

Questionnaire of Exposure:

1. In the last 14 days did you have contact, for more than 15 minutes and closer than 2.0 m, with an individual diagnosed with COVID-19 or identified by the doctor as a case of suspected COVID-19?

☐ Yes ☐ No

2. In the last 14 days were you admitted to any health service?

☐ Yes ☐ No

3. If healthcare professional: Have you contacted patients with suspected or confirmed COVID-19 without wearing PPE?

☐ Yes ☐ No

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Erratum

July 2020 Issue, vol. 115 (1), pages 102-108

In the Original Article "Quercetin Ameliorates Lipid and Apolipoprotein Profile in High-Dose Glucocorticoid Treated Rats", with DOI number: https://doi.org/10.36660/abc.20180397, published in the periodical Arquivos Brasileiros de Cardiologia, 115(1):102-108, on page 102, add one more affiliation for the author Ahmad Reza Dehpour. Include the institution: Experimental Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran.

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In the Original Article "Complete Revascularization Versus Treatment of the Culprit Artery Only in ST Elevation Myocardial Infarction: A Multicenter Registry", with DOI: https://doi.org/10.36660/abc.20180346, published in the periodical Arquivos Brasileiros de Cardiologia, 115(2):229-237, on page 229, correct author name Alexandre Tognon to: Alexandre Pereira Tognon and the author Rogério Tumelero to: Rogério Tadeu Tumelero. Remove the institution: Universidade de Passo Fundo, Passo Fundo, RS - Brazil and change to: Associação Hospitalar Beneficente São Vicente de Paulo, Passo Fundo, RS - Brazil from the affiliations of the authors Alexandre Pereira Tognon and Rogério Tadeu Tumelero.

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