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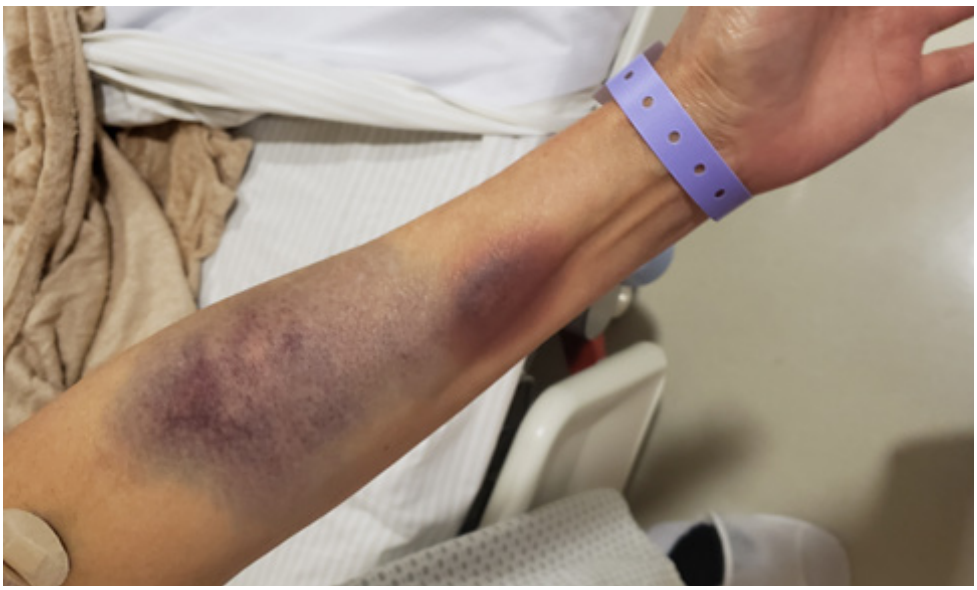

Figure 1 – Spontaneous hematomas in a 62-year-old patient who used acetylsalicylic acid, rivaroxaban and warfarin to protect herself from COVID-19 (however, her PCR and serology tests were both negative). At the Emergence Room, her INR was 26 and the activated partial thromboplastin time ratio was 2. With the reversal of anticoagulation and clinical observation, the patient had no other bleeding complications.. Page 279.

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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COVID-19 and Uncertainty: Lessons from the Frontline for Promoting Shared Decision Making

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COVID-19 has already become the largest and deadliest epidemic of the past hundred years. On a daily basis, healthcare professionals in the frontline are called upon to give answers and make decisions that directly affect the lives of infected patients, and scientists are summoned to the Herculean task of providing "effective medications" in record time for a recently discovered virus with devastating potential mortality. With a hitherto unseen avalanche of information, the debate on how to treat patients with COVID-19 has gone beyond the limits of the technical arena, taking on ideological and political aspects as well.

Science is based on facts. The fact is that we do not currently have an etiological treatment with proven efficacy and safety to combat SARS-CoV-2. At the moment, there are only promises in the pipeline. To exemplify, the most emblematic case of lack of rationality and scientific thinking is the polemic regarding chloroquine/hydroxychloroquine (CQ/HCQ) for treatment of COVID-19. CQ/HCQ is a drug that has been widely and successfully used in patients with malaria and systemic lupus erythematosus. Against COVID-19, the drug inhibits replication of SARS-CoV-2 *in vitro*, and it modulates the inflammatory cascade triggered by the virus.[1] *In vitro* data demonstrate biological plausibility, but plausibility does not mean likelihood that a hypothesis is true. CQ/HCQ was, nevertheless, promoted to the category of "magic bullet" by a publication from France,[2] whose methodology was characterized by high risk of bias and random error, meaning that it could not be defined as "scientific evidence." This notwithstanding, the publication was overestimated, in an ideological manner, by the individuals who were least faithful to the precepts of the liturgy of science. Contaminated by this fallacy, feeling obligated to solve the pandemic magically, even presidents took on the role of drug advertisers, thus helping to viralize pseudoscience and amplify the false information problem.

Even within the medical scientific community, the debate has also become ideological and scarcely rational. One of the claims of CQ/HCQ enthusiasts was that, in a scenario of war, it is necessary to use whatever weapons are available, even without definitive proof of their efficacy and/or clinical safety. Going against the maxim *"Primum Non Nocere,"* they deemed that it was forgivable to do harm, but not to remain inert. On the other side, some embarked on a Manichean debate by emphasizing, also irrationally, observational studies in order to argue that there was proof that it was ineffective. The unwavering defense of CQ/HCQ is seductive, given that there are plausible physiopathological effects, which have been verified in the laboratory, suggesting that the drug is effective. Nevertheless, its clinical efficacy has not been proven in any pathological model of acute viral infection in humans, much less with respect to COVID-19.[3]

The final effect of a drug depends on the result of its positive and negative effects. The results may trigger a final effect that is neutral (futile treatment), positive (effective treatment), or negative (harmful treatment). Before rigorous scientific scrutiny has been applied, it is not possible to predict them. The function of a randomized clinical trial is to prove, with probabilistic accuracy, using statistics, that drug A causes improvement in patients with disease B and that it does not have side effects which would contraindicate prescription.

In an organized scientific ecosystem, prior knowledge provides a basis for future studies through conditional probability. Unlikely hypotheses, which have not been confirmed, when adopted as health policies, lead to unnecessary expenditure of human and economic resources, and they generate false hope in the collective unconscious in addition to, eventually, significant harm.

For physicians who are trained to respond proactively, this uncertainty, in scenarios of collective turmoil, may be extremely disconcerting and, driven by the unconscious desire to resolve their internal conflicts related to medical impotence, they may be betrayed by cognitive biases. Given that the contemporary premise of our vocation is to believe in Medicine based on good science, we need to offer a moment's rest to our minds, which have been troubled by pandemic tsunami so that we may reflect more lucidly, logically, and in a manner enlightened by our creed. The history of biomedical science should have already taught us, as a scientific community, that straying from the paths of formal science can lead us down a "long shortcut." The search for a shortcut, in the heat of despair, can even contribute to deaths that could have been avoided, in the event that the toxic potential of CQ/HCQ, in this scenario, is proven by randomized clinical trials.

Keywords

COVID-19; Coronavirus; Pandemics; Evidence Based Medicine; Bioethics; Clinical Decision Making; Decision Making,Shared; Off Label Use.

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Editorial

From a dogmatic point of view, promoting prescription of drugs before phase III tests should be considered contemporary scientific heresy. Care that is not based on evidence does not necessarily represent good care. The alleged "inertia" of not prescribing a therapy in the absence of supporting evidence is, in most cases, good medical practice. In theory, the pre-test probability of a drug that has never been tested in a determined scenario being effective therein is very remote. Hence the standard of considering experimental clinical trials as the final word. It is not uncommon for hypotheses that are sustained by mechanistic support or observational studies not to be confirmed in randomized trials.

A core principle in science is that the burden of proof lies in demonstrating efficacy, rather than inefficacy; for this reason, we begin with the initial premise of scientific thinking, namely, the null hypothesis must be formally rejected in order to prove the phenomenon. The argument that a therapy is safe alone does not justify implementing an ineffective drug. Proof that a benefit exists is a fundamental condition in order to compare a given drug's positive results with its eventual risks. In the case of CQ/HCQ, we have seen the following situation: The majority of acceptable observational studies have not proven the benefit of the drug.

What, then, will serve as a compass for decision making with so much uncertainty and pandemic pressure, in the absence of evidence? First, it is important to underscore that lack of evidence regarding effect does not mean evidence that there is no effect. To deny a potential benefit categorically does not seem to be the best way, either. It is doubtful whether CQ/HCQ has a priori probability that justifies major scientific effort. Nonetheless, even in cases where there is a reasonable likelihood, the first option would be to commit to the task of selecting patients for allocation into clinical trials. Collective, solidary, and articulated efforts could shorten the duration of this uncertainty.

When this is not possible, it is understandable, in situations of "war," to propose off-label use of medications, when a specific drug that has already been properly registered and approved for scenario A is permitted for scenario B without specific studies, or even compassionate use, when a drug that is still experimental and that has not been registered by any regulatory agency is prescribed for lack of a better option in the belief that it might work. It is necessary to underscore that compassionate use is more an act of mercy than a bet on therapeutic success.

In the heat of this desperate moment, we are experiencing a pandemonium characterized by the unprecedented proliferation of information of the worst quality, with great variability in the prescription practice observed in the frontlines. In the meanwhile, the guidelines and editorials published in the most prestigious scientific journals have categorically stated that we do not yet have effective etiological therapies that are scientifically proven to reduce the mortality of COVID-19.[1] The treatment of viral pneumonia continues, essentially, to be that of support and intervention in the diverse clinical complications that may arise in a minority of patients. To reinvent knowledge, which is substantially well founded, and to abandon the liturgy of modern clinical science appears to be a great retrogression to the Dark Ages.

How, then, shall we make decisions, when uncertainty is the rule? To take an authoritarian or paternalistic stance would not be the wisest path. The current situation in which we find ourselves may perhaps be a unique opportunity to put the principle of patient autonomy into practice, thus enlightening medical decision making.

Historically, patients would entrust decision making to physicians. During the last decades, however, patients have been encouraged to take an active role and to participate in decisions about their health. The *Crossing the Quality Chasm* report, published by the American Institute of Medicine, argues that an active voice should be given to patients in respect to all that will have an impact on their lives. Operationally speaking, this includes transparent information regarding expectations and uncertainties, before shared decision making. Although we understand the complexity of implementing a shared decision-making process during the current situation, the compulsory and indiscriminate prescription of drugs that have no proven efficacy and/or safety for this scenario does not corroborate the values currently put forth. It is noteworthy that the principle of patient autonomy is an attribute that underpins the basis of the Brazilian Unified Health System, since its foundation, and it is in line with precepts of contemporary Bioethics.

Autonomy corresponds to people's capability to decide in accordance with their own values. The basis of autonomy resides in respect for individuals' fundamental rights, considering them as biopsychosocial and spiritual beings endowed with the ability to make their own decisions. During a pandemic, when uncertainty becomes even more evident, the return to this fundamental principle of giving patients a voice in the decision table may serve as a bridge whereby the physician-patient binomial will be able to choose the best path, customized to the expectations of the person who is most interested in positive outcomes, namely, the patient. To take full control of all medical decisions and to deceive ourselves with certainties that do not exist can be a sign of immaturity. It is urgent that we transcend the Hippocratic model, wherein physicians are to apply "regimens for the good of patients, according to their knowledge and reason," leaving no room for their autonomy, to a shared, patient-centered model of care.

The current moment calls for professionals who are up-to-date, confident, and open to transparent dialogue on factual evidence in favor of shared decision making. Separating what is scientific evidence, in the midst of so much clinical pseudoscience, will be the cardinal task. Science is not based on faith, belief, opinion, or authority. On the contrary, doubt and uncertainty are the main reasons behind advances in science. It is indispensable to recognize that the consequences of our decisions are not and cannot be shared. Therefore, medical practices for dealing with COVID-19 require humility in that we recognize the boundaries of current scientific knowledge. Transparent sharing of uncertainties and doubts with patients will make it possible to shine a light on the otherwise excessively cumbersome task of making decisions in this scenario, in which there is still too much darkness. This seems to be a significant opportunity to learn today and to bring important lessons to tomorrow in order to pave the way toward the utopia of "medicine that serves patients".[7]

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Cardiovascular Disease Mortality According to the Brazilian Information System on Mortality and the Global Burden of Disease Study Estimates in Brazil, 2000-2017

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Abstract

Background: The Brazilian Information System on Mortality (SIM) is of vital importance in monitoring the trends of cardiovascular diseases (CVDs) and is aimed at supporting public policies.

Objective: To compare historical series of CVD mortality based on data from the SIM, with and without correction, and from the Brazil Global Burden of Disease (GBD) Study 2017, in the 2000-2017 period.

Methods: Analysis of CVD mortality in Brazil between 2000 and 2017. Three CVD mortality estimates were compared: Crude SIM, Corrected SIM, and GBD 2017. Absolute numbers and age-standardized rates were used to compare the estimates for Brazil, its states and the Federal District.

Results: In the SIM, the total of deaths ranged from 261,000, in 2000, to 359,000, in 2017. In the GBD 2017, the total of deaths ranged from 292,000 to 388,000, for the same years, respectively. A high proportion of the causes of death from CVD corresponded to garbage codes, classified according to the GBD 2017, reaching 42% in 2017. The rates estimated by GBD ranged from 248.8 (1990) to 178.0 (2017) deaths per 100,000 inhabitants. The rates of the Crude SIM and Corrected SIM also showed a reduction for the whole series analyzed, the Crude SIM showing lower rates: 204.9 (1990) and 155.1 (2017) deaths per 100 thousand inhabitants. When analyzing by the states and Federal District, the Crude SIM trends reversed, with an increase in mortality rates in the Northern and Northeastern states.

Conclusion: This study shows the decrease in CVD mortality rates in Brazil in the period analyzed. Conversely, when analyzing by the states and Federal District, the Crude SIM showed an increase in those rates for the Northern and Northeastern states. The use of crude data from the SIM can result in interpretation errors, indicating an increase in rates, due to the increase in death data capture and the improvement in the definition of the underlying causes of death in the past decade, especially in the Northern and Northeastern regions, justifying the use of corrected data in mortality analyses. (Arq Bras Cardiol. 2020; 115(2):152-160)

Keywords: Cardiovascular Diseases/mortality; Data Accuracy/trends; Health Information System/trends; Epidemiology

Introduction

In past years, Brazil has compiled different data sources that constitute the information system on morbidity and mortality and periodic health inquiries, which enable the continuous monitoring of data on mortality, morbidity, and risk factors for cardiovascular diseases (CVDs), and support decision-making processes in health policies.[1,2]

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The Brazilian Information System on Mortality (SIM), which provides data to identify and address death record information, was implanted in 1975, being the first nationwide epidemiological database of the Brazilian Health Ministry.[3] The cornerstone of SIM is the death certificate, which should be completed by the physician caring for the deceased patient. In the absence of that professional, however, the death certificate can be completed by: the substitute physician; the physician from the Death Verification Service – for natural causes of death; or the coroner – for deaths by external causes.[2,3]

All Brazilian municipalities must register their deaths, which results in around 1.3 million deaths reported per year, making SIM one of the major tools to monitor the mortality statistics in Brazil. The SIM coverage has increased in all Brazilian states and Federal District, passing from 86% in 2000 to 98% in 2017; however, some Northern and

Northeastern states maintain coverages lower than 95%.[1-3] In addition, the number of ill-defined causes of death in Brazil has decreased, although it still remains high in some states. Therefore, the analyses of health status based on mortality records should be carried out with corrective methodologies that can minimize the bias caused by ill-defined causes of death, garbage codes (GC), and death underreporting.[4-6]

Since 1990, the Global Burden of Disease (GBD) Study has adopted a methodology that consists in large advances and in a paradigm change in the epidemiological analysis of secondary data, by proposing an integrated focus on diseases and deaths, with robust and standardized methodology of analysis that contemplates the correction of GC, ill-defined causes of death, and death underreporting.[7] The GBD Study provides comprehensive information on 249 causes of death in 195 locations, contemplating countries and some subnational levels, such as Brazil and its 26 states and Federal District. In the GBD Study, the information on causes of death has been collected from vital record systems, mortality surveillance systems, research, hospital records, police records, and verbal autopsies. For Brazil and its 26 states and Federal District, the SIM is the data source on mortality.[7,8] In the GBD Study, several statistical models are used to best estimate the number of deaths per each cause of death according to sex and age. The GBD Study enables comparisons between countries, regions, and subnational data, because the quality of the local mortality data is standardized. In addition, the GBD Study enables the analysis of population trends, because the temporal series data are corrected and standardized, making comparison over time possible.[7-10]

This study was aimed at comparing historical series of CVD mortality based on data from the SIM, with and without correction, and the Brazil GBD Study 2017 estimates.

Methods

This study assessed the historical series of CVD mortality in Brazil from 2000 to 2017. The data source for this study was the SIM, which contains the major information on death records in the whole country. Initially, the proportions of ill-defined causes of death in the SIM were described (Figure 1).

Three estimates of CVD mortality were compared: Crude SIM, Corrected SIM, and Brazil GBD Study 2017. The estimates deriving from the SIM, with and without correction, named Corrected SIM and Crude SIM, respectively, used the definition of CVDs in accordance with the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) chapter IX codes (diseases of the circulatory system - I00-I99). The GBD classification considered initially the following codes: B33.2, G45-G46.8, I01-I01.9, I02.0, I05-I09.9, I11-I11.9, I20-I25.9, I28-I28.8, I30-I31.1, I31.8-I37.8, I38-I41.9, I42.1-I42.8, I43-I43.9, I47-I48.9, I51.0-I51.4, I60-I63.9, I65-I66.9, I67.0-I67.3, I67.5-I67.6, I68.0-I68.2, I69.0-I69.3, I70.2-I70.8, I71-I73.9, I77-I83.9, I86-I89.0, I89.9, I98, and K75.1.

Figure 2 shows the methods for correcting death and population data used to estimate the absolute numbers and mortality rates for the Crude SIM and Corrected SIM, as well as the GBD Study 2017 estimates. The numerator corresponds to the CVDs (I00-I99) registered by the SIM. The estimates

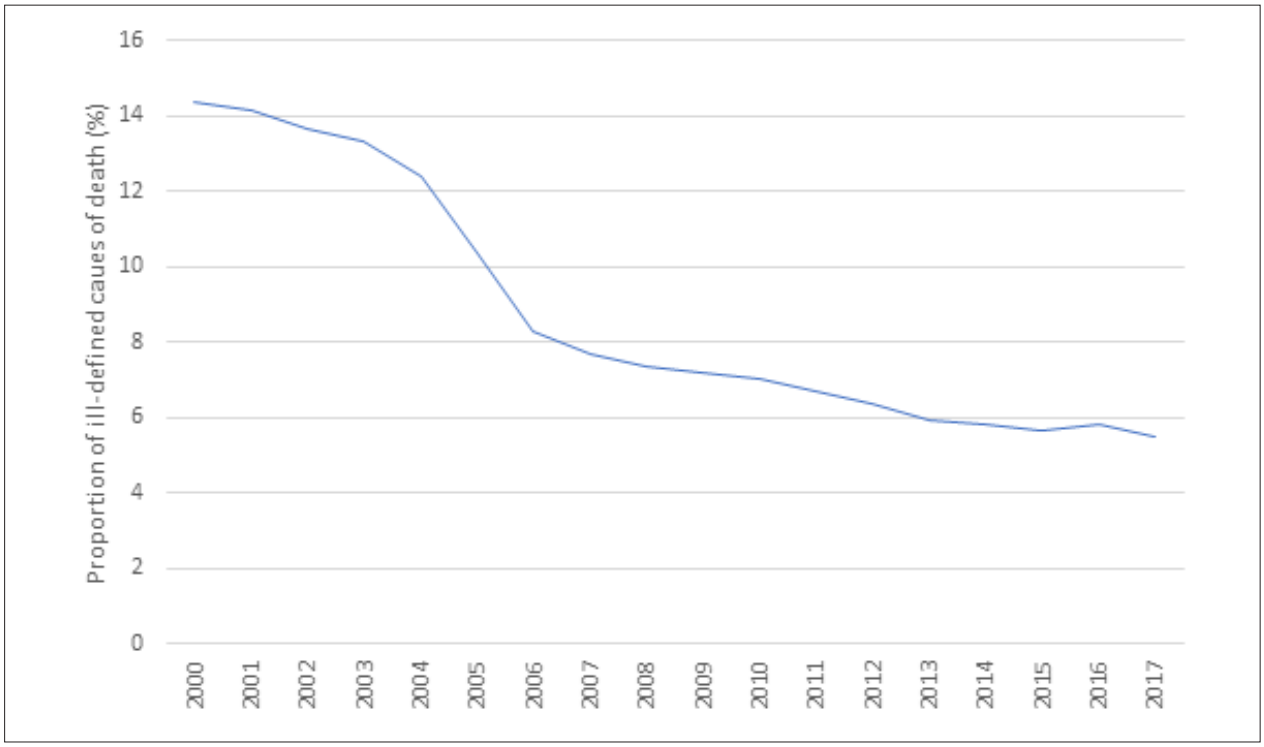

Figure 1 – *Proportion of ill-defined causes of death in the Brazilian Information System on Mortality (SIM), Brazil, 2000 - 2017. Source: SIM.*

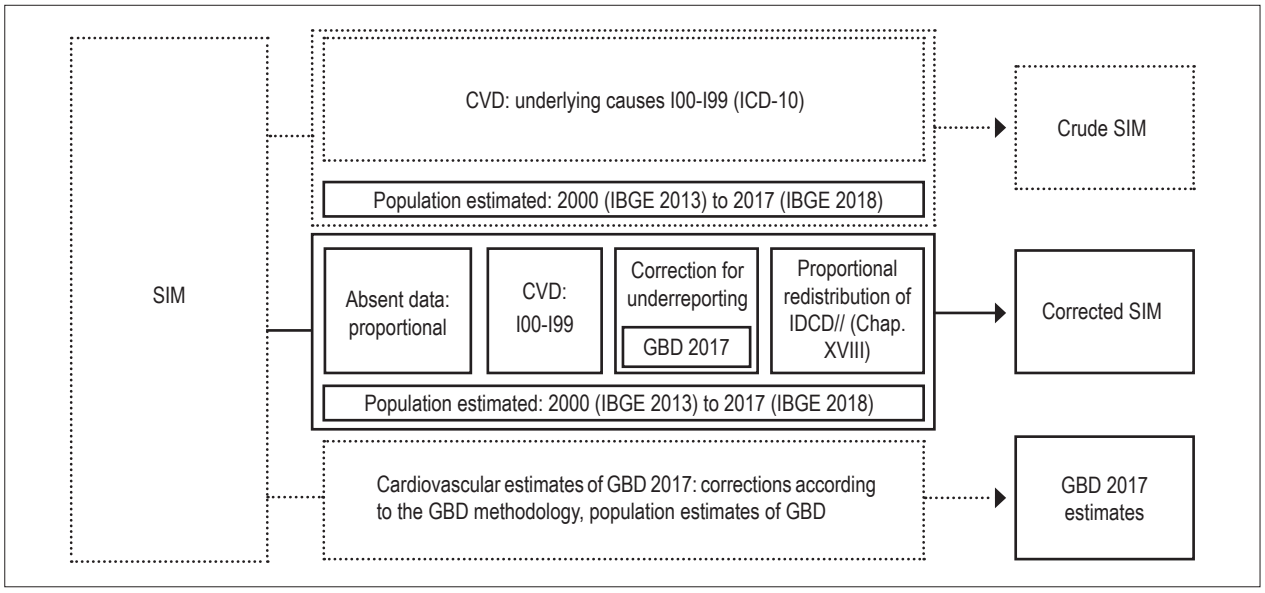

Figure 2 - *Flowchart of the estimates of the Crude and Corrected Information System on Mortality and the Global Burden of Diseases Study, methods for correction and population used, for absolute numbers and mortality rates. CVD: Cardiovascular Diseases; IBGE: Brazilian Institute of Geography and Statistics; SIM: Brazilian Information System on Mortality; GBD: Global Burden of Diseases Study; IDCD: Ill-Defined Causes of Death.*

generated by the Crude SIM were age-standardized, no other correction being applied. The estimates generated by the Corrected SIM were age-standardized and corrected as follows: for underreporting, by using the GBD methodology; for the deaths lacking information on age and sex, by using the proportional redistribution of these deaths; and for the ill-defined causes of death, by using the proportional redistribution of these causes in the groups of cardiovascular causes and the other ICD-10 chapters.[4] The GBD 2017 estimates were extracted from the Institute for Health Metrics and Evaluation (IHME) database, underwent the previously described corrections, such as for underreporting, GC, and ill-defined causes of death, and were detailed in previous publications.[7,8,10]

Data from the Crude SIM and Corrected SIM were compared with the estimates of the GBD Study 2017, which also uses SIM data as a source, both by using the 2000-2017 historical series of the total of deaths and absolute numbers of the diseases listed in the ICD-10 IX chapter, and the age-standardized rates of the three estimates. To calculate the rates in the Crude SIM and the Corrected SIM, the updated population estimates generated by the Brazilian Institute of Geography and Statistics (IBGE) were used as denominator.[11] However, that IBGE estimate only provides data from 2010 onwards; thus, two interpolations were applied: one with data from the year 2000 of the 2013 version made available by IBGE,[12] and another interpolation with data from the year 2010 of the current version made available in 2018.[11] The standard population used to adjust the age-standardized rates, through the direct method, was the world population of the GBD Study.[7] To calculate the rates, the GBD Study considers its own population estimates (Source GBD). All three estimates were analyzed for the ICD-10 chapter IX codes (diseases of the circulatory system - I00-I99) from 2000 to 2017. Figure 2 shows the flowchart used to compare the three estimates, regarding the absolute numbers of deaths and mortality rates for Brazil, its states, and Federal District.

The analyses were performed using Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

Results

Figure 1 shows the proportion of ill-defined causes of death in relation to the total number of deaths in Brazil from 2000 to 2017. That proportion was 14.3% in 2000 and decreased over time, more abruptly from 2005 onward, reaching 5.5% in 2017.

Table 1 shows that a large number of deaths with underlying causes classified as ICD-10 chapter IX codes constituted GC, as by the definition of GC in the GBD Study 2017, and that proportion was 42.1% in 2017. In addition, Table 1 shows that the number of GC decreased slowly over the years, indicating an improvement in the quality of the definition of the ICD-10 chapter IX causes of death. The GBD Study redistributes the GC in its estimates.

The absolute numbers of deaths due to CVD and standardized mortality rates of the Crude SIM, the Corrected SIM, and the GBD Study 2017 estimates were analyzed. Figure 3 depicts the absolute number of deaths due to CVD for the three estimates, with a similar increase for all three methods. The SIM registered approximately 261,000 deaths in 2000, reaching 359,000 deaths in 2017. After data correction, the SIM records ranged from 324,000 in 2000 to 397,000 in 2017. The GBD 2017 estimates increased from 292,000 deaths to 388,000 deaths in those same years.

The CVD mortality rates decreased in the period analyzed (Figure 4). The Crude SIM rates decreased from 211.7 to 155.1 deaths per 100,000 inhabitants, while the Corrected SIM

Table 1 – Total of deaths, absolute numbers and percentages of deaths due to cardiovascular diseases according to the ICD-10 IX chapter codes (I00-I99) and to the definitions of GBD for cardiovascular diseases, and absolute numbers and percentages of garbage codes, in Brazil, 2000 to 2017

Year	Total	I00-I99		Cardiovascular GBD		Garbage codes	
		n	%	n	%	n	%
2000	946,685	260,603	27.5	129,883	49.8	126,803	48.7
2001	961,492	263,417	27.4	130,774	49.6	128,637	48.8
2002	982,807	267,496	27.2	133,160	49.8	130,362	48.7
2003	1,002,340	274,068	27.3	137,413	50.1	132,245	48.3
2004	1,024,073	285,543	27.9	143,811	50.4	137,096	48.0
2005	1,006,827	283,927	28.2	142,656	50.2	136,545	48.1
2006	1,031,691	302,817	29.4	152,017	50.2	145,977	48.2
2007	1,047,824	308,466	29.4	156,253	50.7	147,076	47.7
2008	1,077,007	317,797	29.5	163,255	51.4	149,058	46.9
2009	1,103,088	320,074	29.0	164,036	51.2	150,082	46.9
2010	1,136,947	326,371	28.7	167,974	51.5	152,326	46.7
2011	1,170,498	335,213	28.6	173,397	51.7	155,363	46.3
2012	1,181,166	333,295	28.2	174,750	52.4	152,276	45.7
2013	1,210,474	339,672	28.1	179,200	52.8	153,822	45.3
2014	1,227,039	340,284	27.7	181,223	53.3	152,421	44.8
2015	1,264,175	349,642	27.7	186,570	53.4	156,278	44.7
2016	1,309,774	362,091	27.6	194,987	53.9	159,779	44.1
2017	1,312,664	358,882	27.3	199,872	55.7	150,967	42.1

**Deaths of the cardiovascular chapter not classified as cardiovascular diseases, and garbage codes not presented in the table, mean of 1.8%.*

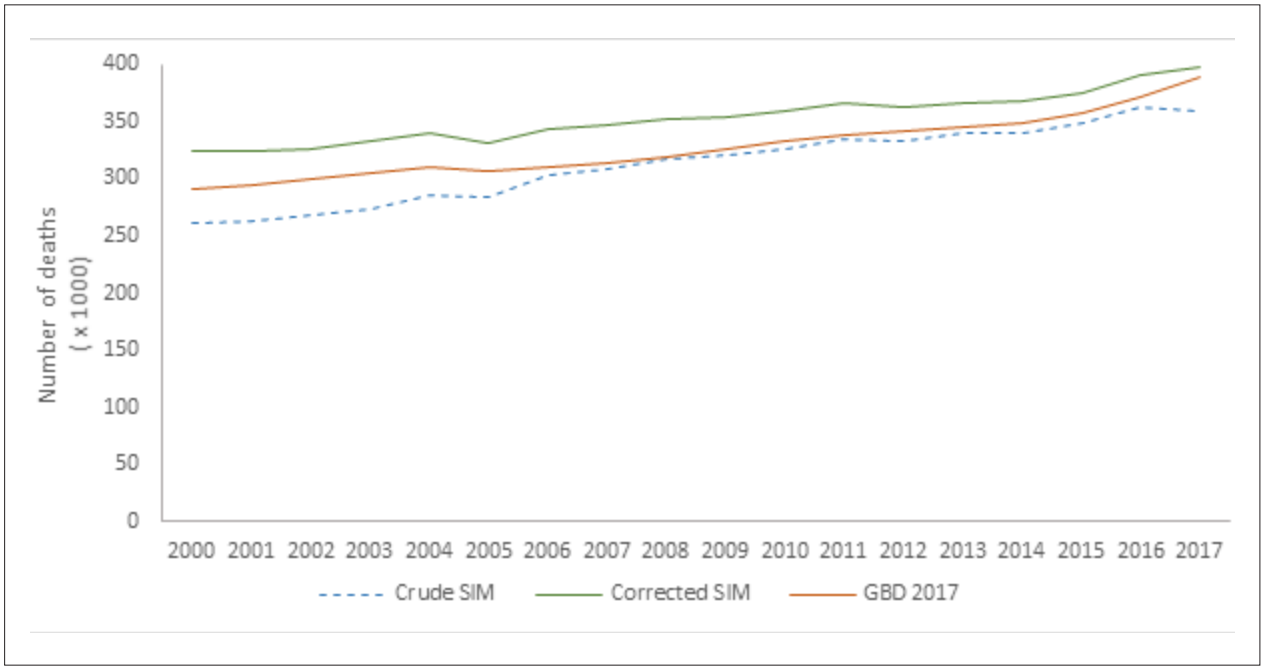

Figure 3 – *Absolute numbers of cardiovascular disease deaths according to the Crude and Corrected SIM and the GBD Study 2017. Brazil, 2000 to 2017. Sources: SIM and Brazil GBD Study 2017.*

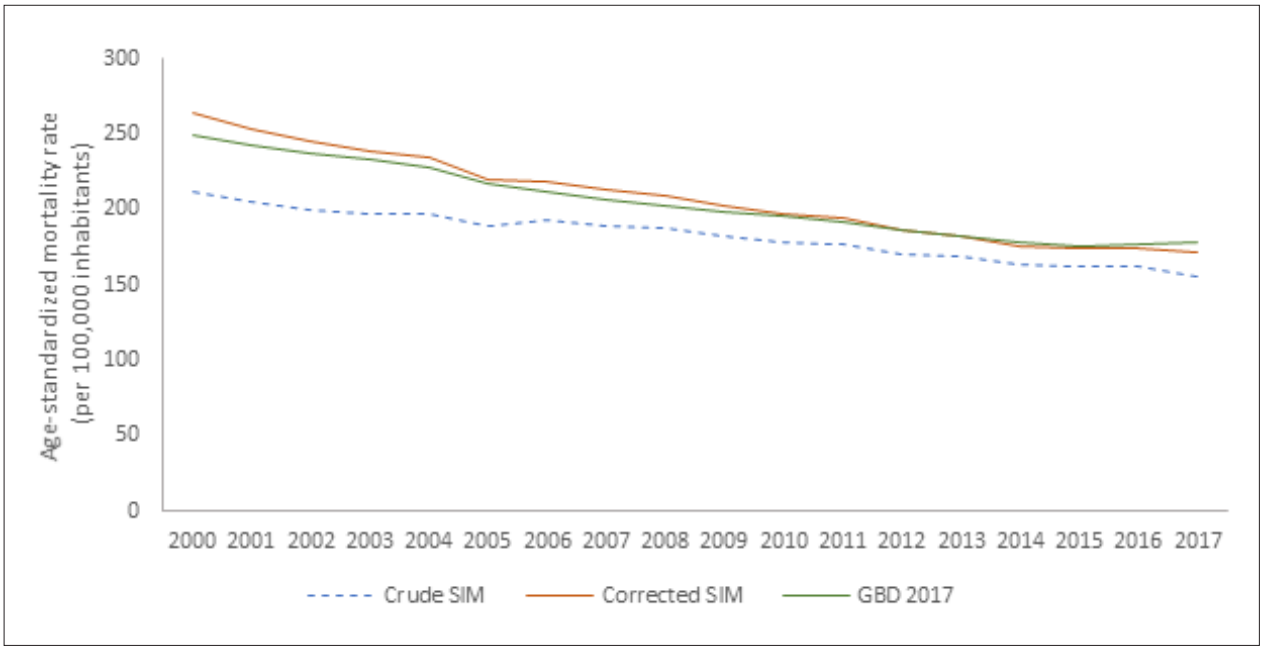

Figure 4 – *Standardized cardiovascular disease mortality rates according to the Crude and Corrected SIM and the GBD Study 2017. Brazil, 2000 to 2017. Sources: SIM and Brazil GBD Study 2017.*

rates decreased from 263.9 to 172.0 deaths per 100,000 inhabitants. The GBD 2017 estimated rates decreased from 248.8 to 178,0 deaths per 100,000 inhabitants. However, it is worth noting that, from 2015 to 2017, the GBD estimated rates increased, and this increase was also observed in the Corrected SIM rates from 2015 to 2016.

When assessing the percentage variations in the standardized CVD mortality rates from 2000 to 2017 by each state and the Federal District, there was a difference in the Crude SIM data, with stabilization in the rates or their increase (of as much as 115%) in most Northern and Northeastern states. That pattern is observed neither in the Corrected SIM data nor in the GBD Study data, whose rates showed a reduction in all Brazilian states and the Federal District (Figure 5, Table 2).

Discussion

This study compares three different methods to estimate the historical series of CVD mortality in Brazil from 2000 to 2017, which decreased, except for the period from 2015 onwards, when there was an increase in the GBD estimated rates and stability in the Corrected SIM rates. The estimates of the Corrected SIM and GBD were similar, especially after 2006, when the quality of the SIM improved. The Crude SIM showed an increase in the rates of the Northern and Northeastern states, while the Corrected SIM and GBD showed a reduction in the rates of all states and the Federal District in the period.

Cardiovascular diseases are the number one cause of death globally[13] and in Brazil,[5,14] corresponding to one third of all deaths. All regions showed a decline in mortality due to chronic non communicable diseases (CNCDs). The CVDs and their complications have a high impact on the loss of productivity in the workplace and in the family income, resulting in a US$ 4.18 billion deficit in the Brazilian economy from 2006 to 2015.[15] Studies conducted in several countries have shown a reduction in the incidence of CVDs and in CVD mortality since the 1960s.[16,17] In Brazil, that reduction occurred later, in the 1990s.[5,14]

Over the years, SIM has been improved, having its coverage increased and the quality of the reports of underlying causes of death in death certificates refined. These advances have resulted from the efforts of the Brazilian Ministry of Health in partnership with states and municipalities to improve death data collection by the SIM. Some examples are the 2005 Project to Reduce Ill-Defined Causes and the Projects to Reduce Regional Inequalities and Child Mortality in the Northeastern states and the 'Legal Amazonia' region.[18] It is worth noting the Project of Active Search for Death Data, which enabled the definition of methodologies to redistribute underreported deaths.[19,20] Those corrections are essential for the accurate interpretation and comparability of historical series in different regions of Brazil.

It is worth noting the important reduction in the percentage of ill-defined causes of death in the SIM, which results from the improvement in the quality of healthcare services and the increase in healthcare coverage, especially the advance of the family healthcare team to inner areas of the country.[5]

In addition, the differences between the Corrected SIM and the GBD Study 2017 can be explained by the percentage of the codes of unspecific causes, named 'garbage code' in the international literature.[8] Although the

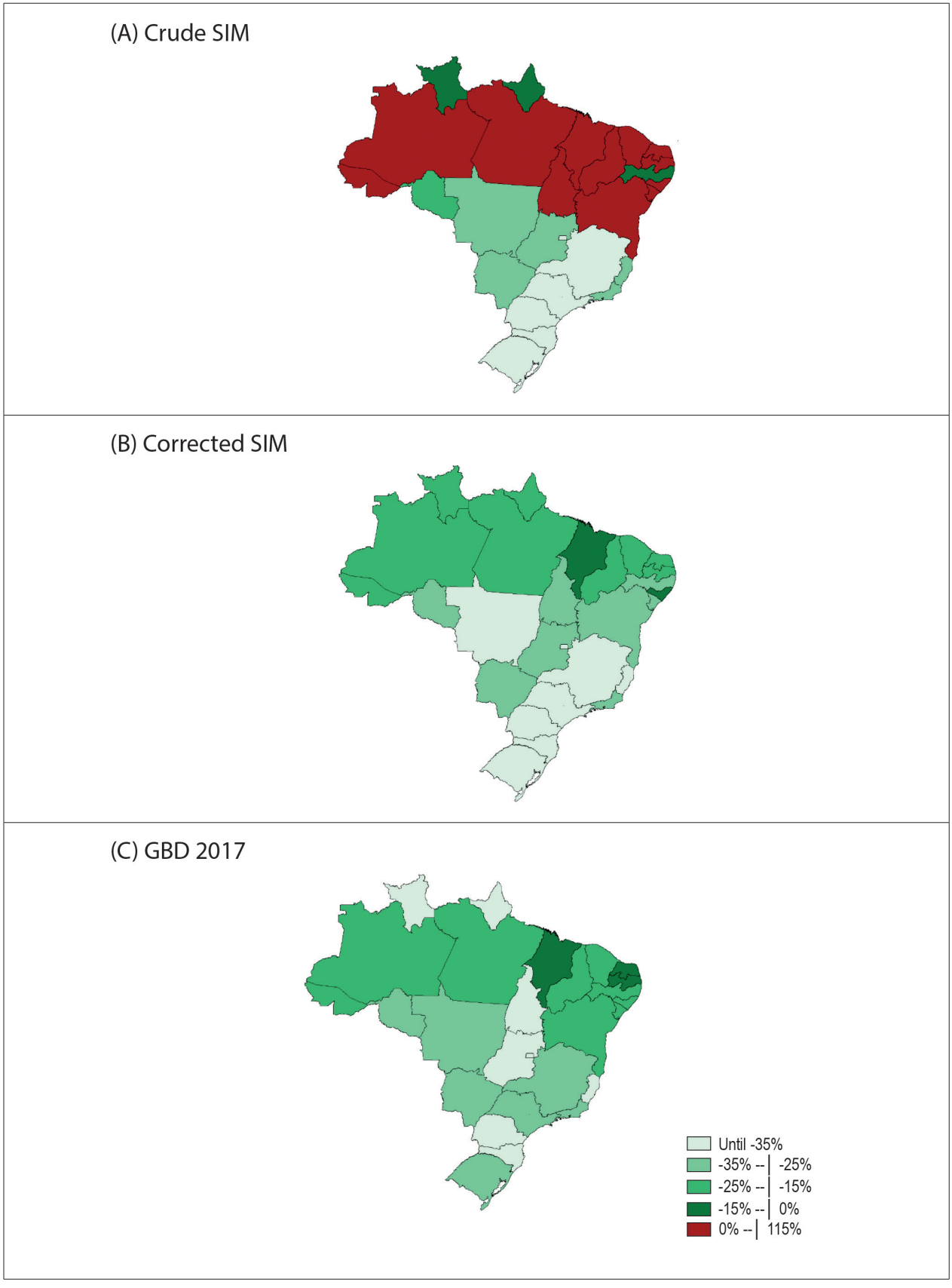

Figure 5 – *Percentage variation of standardized cardiovascular mortality rates from 2000 to 2017. Sources: SIM and Brazil GBD Study 2017.*

Table 2 – Standardized cardiovascular disease mortality rates for Brazil, its states and Federal District, in the years 2000 and 2017, as well as their percentage variations in the period

Location	Crude SIM			Corrected SIM			GBD 2017		
	2000	2017	Variation (%)	2000	2017	Variation (%)	2000	2017	Variation (%)
Acre	122.4	155.4	26.9	199.1	167.6	-15.8	203.9	158.5	-22.3
Alagoas	159.5	210.7	32.1	261.7	225.7	-13.8	253.6	211.9	-16.4
Amapá	149.7	136.1	-9.0	200.9	160.8	-20.0	242.7	157.2	-35.2
Amazonas	124.2	128.6	3.5	188.4	156.0	-17.2	177.5	147.0	-17.1
Bahia	134.8	137.6	2.1	235.6	173.8	-26.2	210.0	162.9	-22.4
Ceará	139.6	158.5	13.6	219.7	165.6	-24.6	194.1	152.4	-21.5
Federal District	233.1	135.6	-41.8	251.2	142.1	-43.4	301.5	175.4	-41.8
Espírito Santo	220.4	156.0	-29.2	278.6	158.6	-43.1	275.8	165.8	-39.9
Goiás	215.5	161.4	-25.1	247.3	166.6	-32.6	252.3	163.9	-35.1
Maranhão	83.5	179.3	114.8	225.5	211.1	-6.4	190.3	184.6	-3.0
Mato Grosso	228.4	152.1	-33.4	258.1	163.7	-36.6	240.2	162.8	-32.2
Mato Grosso do Sul	240.1	165.1	-31.2	270.5	177.0	-34.6	274.6	198.6	-27.7
Minas Gerais	204.6	132.9	-35.1	242.6	146.3	-39.7	228.4	154.5	-32.4
Pará	132.1	156.0	18.1	223.9	182.4	-18.5	200.9	168.6	-16.1
Paraíba	98.2	168.7	71.7	233.3	188.3	-19.3	213.0	190.9	-10.4
Paraná	287.4	152.8	-46.8	306.6	167.8	-45.3	297.0	188.3	-36.6
Pernambuco	206.0	183.2	-11.1	282.0	205.6	-27.1	263.2	214.6	-18.5
Piauí	136.5	190.6	39.6	269.0	201.9	-24.9	227.8	175.1	-23.1
Rio de Janeiro	252.1	168.1	-33.3	292.7	194.9	-33.4	296.0	207.7	-29.8
Rio Grande do Norte	121.9	145.7	19.6	196.6	156.0	-20.7	185.9	159.2	-14.3
Rio Grande do Sul	263.4	138.6	-47.4	277.1	154.6	-44.2	266.2	177.2	-33.4
Rondônia	191.7	157.3	-17.9	251.2	180.3	-28.2	253.0	184.8	-26.9
Roraima	190.5	177.5	-6.8	221.3	187.6	-15.2	305.9	196.3	-35.8
Santa Catarina	237.3	138.6	-41.6	279.9	150.0	-46.4	277.6	170.2	-38.7
São Paulo	264.3	160.3	-39.3	285.6	172.7	-39.5	283.3	185.6	-34.5
Sergipe	141.7	154.0	8.7	234.8	170.2	-27.5	218.6	171.6	-21.5
Tocantins	155.5	186.2	19.8	259.4	193.2	-25.5	294.6	173.9	-41.0
Brazil	211.7	155.1	-26.7	263.9	172.0	-34.8	248.8	178.0	-28.5

rates provided by the Corrected SIM were not corrected by the redistribution of GC, all GBD Study estimates were corrected for death underreporting and redistribution of ill-defined causes and of GC. Thus, the GBD estimated rates differ from those of the other methods that do not use GC redistribution. Some examples of GC causes are as follows: septicemia; cardiac arrest; dehydration; congestive heart failure. They are part of the train of events leading to death, but are not the underlying cause of death.[8] For the GC redistribution, the GBD Study uses algorithms based on medical literature evidence, multiple sources, expert opinions, analysis of multiple causes, and mainly on statistical modelling techniques to define the weight of assigning each GC to the most probable underlying cause of death, called target.[6,8]

The SIM is a consolidated system, which the Brazilian Ministry of Health has been perfecting via processes of validation of internal inconsistencies and improvement in death reporting. However, the classification requires refinement, especially regarding the reduction in GC. When comparing the mortality estimates of the GBD Study with the Crude SIM data, the differences observed are due to age and sex inconsistencies related to causes of death, underreporting, and GC redistribution. The GC redistribution has the greatest influence on the difference

between corrected estimates and crude ones. Level 1 and level 2 GC, those with little specification of the real cause of death, correspond to 12% of the SIM records. When level 3 and level 4 GC are considered to be redistributed in the same group of causes, that is, with better specification of the cause of death, the GC can reach 40%, which can lead to differences in the estimates between the SIM and the GBD.[6,8]

This study indicates that the Crude SIM analyses are biased, especially for the Northern and Northeastern states. Therefore, its adoption is not recommended, especially for the definition of regional policies, because the rates are subject to estimation errors, such as those due to underreporting and excessive proportion of ill-defined causes. Methodological adjustments to coverage and redistribution of ill-defined causes are necessary, even more when it comes to the analysis of historical series, involving a period in which the quality of SIM was impaired.

In 2015, the United Nations Assembly approved the Sustainable Development Goals, representing 17 global challenges to achieve a better and more sustainable future for all. One of the goals is to ensure good health and well-being for all, at all ages. It includes the indicator "a 30% reduction in premature mortality from CNCDs by 2030", whose calculation involves a reduction in CVDs. Reducing CNCDs and CVDs is a global challenge.[21-23]

To meet the goal to prevent and control CNCDs, the World Health Organization has issued a document recommending the adoption of interventions for health promotion, with the implementation of public policies within and across sectors that promote healthy practices, such as healthy diets, low-sodium food products, open public spaces and adequate infrastructure to support physical activity, smoke-free environments, and alcohol advertising regulation.[24] In addition, it is worth noting the importance of investing in primary care and access to medium and high complexity technologies, when necessary, aimed at the whole care of patients with CNCDs.[25]

This study shows an increase (GBD 2017) or stability (Corrected SIM) in the mortality rates due the CVD from 2015 onwards. These data need to be revised because of the short period analyzed. However, other studies have reported worsening of health indicators in Brazil, which has been attributed to the economic crisis, the increase in poverty, and the cuts in health and social policies resulting from the Constitutional Amendment 95/2016 and the freeze on public expenses, health included, for 20 years.[22-25]

This study has limitations. The use of secondary databases can add biases, such as underreporting and inconsistencies in death certificate completion. In addition, the Brazilian population estimates may be subject to errors, as the last available census in Brazil dates back to 2010. Moreover, the GBD estimates might have limitations because of its sources, adjustments, and algorithms used.

Conclusion

This study shows the decline in the CVD mortality rates in the period analyzed, except for the last two years. The comparison of the estimates shows similarities between the Corrected SIM and the GBD Study 2017. However, the use of the Crude SIM data is not recommended, especially for subnational analyses, because it can result in interpretation errors. In this study, the increase in mortality rates might have reflected the improvement in death data capture and in the definition of the underlying causes of death in the past decade, especially in the Northern and Northeastern regions. This justifies the recommendation to always use corrected data for mortality analyses.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Malta DC, Teixeira R, Oliveira GMM, Ribeiro AL; Acquisition of data and Writing of the manuscript: Malta DC, Teixeira R; Statistical analysis: Teixeira R; Obtaining financing: Malta DC, Ribeiro AL.

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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Epidemiology of Cardiovascular Diseases in Brazil: The Truth Hidden in the Numbers

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Short Editorial related to the article: Cardiovascular Disease Mortality According to the Brazilian Information System on Mortality and the Global Burden of Disease Study Estimates in Brazil, 2000-2017

According to the 2030 Agenda of the World Health Organization for Sustainable Development, member states are committed to a 30% reduction in premature mortality from non-communicable diseases, particularly cardiovascular diseases (CVD) (ischemic cardiomyopathy and stroke), cancer, respiratory diseases and diabetes.[1] These conditions account for about 41 million deaths per year, i.e., 71% of deaths worldwide.[2] To direct strategies for to prevent and treat these with these diseases, information from reliable, transparent and reproducible systems is essential. The analysis of mortality trends is key for the effective development of health, social security, investment and other policies.

The Global Burden of Disease (GBD) studies initiative is in line with this agenda, as it aims to improve understanding of diseases through the analysis of data on incidence, prevalence and mortality in a consistent, updated and global manner, both at a regional level and at a national level.[3] Over the past few years, this methodological proposal has brought practical information for reducing these diseases around the world, overcoming challenges regarding methodology, particularly the heterogeneity of records and data from different countries.[4,5] Through data from multiple sources (health records, cohorts and prospective trials, administrative data, verbal analysis and others) and applying complex statistical models, the initiative has provided data by sex, age and country, to more than 310 diseases and conditions, with continuous methodological improvement.[6]

The importance of these new metrics is pointed out in the article by Malta et al.[7] The authors compared historical series of CVD mortality between 2000 and 2017, based on three estimates: gross data from the Mortality Information System (SIM), corrected for ill-defined causes and underreporting, and those applied by the GBD. Over this period, on all databases, there was a reduction in mortality from CVD mortality in Brazil, by 27% in the gross SIM and 28% by the GBD. However, sub-analyses by state have shown how inaccurate the SIM data can be. According to the SIM records, in 12 states, there was an increase in the number of deaths from CVD, while according to the GBD estimates, in all states, there was a reduction in mortality from these diseases. This fact is relevant for the monitoring of prevention and control actions by managers and society. However, a fact to be pointed out is the high percentage, in some states, of death records and ill-defined causes improperly filled out, and, in 2017, 42% are still classified as garbage codes.

The methodology used by the GBD aims to internationally standardize the causes of death, which, in their origin, are established in a single medical record. Due to the wide variability in these aspects, treatment with algorithms and modeling allows a proportion of ill-defined deaths or deaths classified as other causes to be reallocated to more probable causes.[8] A sensitive point of the methodology is the inference for some codes, called "garbage codes". Some are intuitive, like ill-defined causes or symptoms; others are subject to interpretation and discretion. For example, heart failure is understood as an intermediate cause of death, and deaths attributed to this code are reclassified using a regression model considering age, sex and location. The precision and accuracy of these adjustments to each reality is something to be explored. Certainly, the GBD methodology brings us light to unveil the obscure cases of records. However, the dark side exists and needs to be worked on continuously. To rely more on these estimates, we must seek better quality in the original baseline record.[4,8]

Brazil is a country of continental dimensions, with one of the greatest socioeconomic inequalities, a situation that is inevitably related to higher mortality from non-communicable diseases, especially CVD.[9] Population aging, globalization, urbanization with increased obesity and physical inactivity levels are determining factors in these numbers. Fortunately, much has been achieved in the past few decades and we have significantly reduced mortality from these conditions in all states. However, we know that there is much to be done; there are huge inequalities in these numbers, mostly related to factors such as low level of structure and resources in health, and low socioeconomic and cultural level of the population. The most worrying thing is to know that in conditions of scarce resources, the costs of treating CVD end up depleting the existing resources even more, generating a vicious circle of more poverty and delayed growth.

Our challenge is taking this data beyond academia and scientists. How can the estimates of prevalence, incidence

Keywords

Cardiovascular Diseases/mortality; Data Accuracy/trends; Health Information System/trends; Policy Making; Epidemiology.

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and risk factors for cardiovascular diseases be used by managers and politicians in their decision-making efforts?[4,7] The first step, taken by Malta et al.,[7] is to transform existing records into relevant and valid information that can guide objective actions to control CVD. Accepting that local gross records are insufficient for this purpose is extremely relevant. On the other hand, it is essential that these data be used by managers, decision makers, non-governmental organizations and certainly by the medical community, to better understand the diseases of our population and to reassess efforts, identify priority actions to combat and improve cardiovascular health in Brazil.

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Body Adiposity and Apolipoproteins in Children and Adolescents: A Meta-Analysis of Prospective Studies

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Abstract

Background: **Excess Weight and Cardiovascular Diseases are health problems with increasing prevalence among children and adolescents, hence the need to investigate the issues related to them to better deal with the problem.**

Objective: **To investigate the influence of excess adiposity on the levels of apolipoprotein B and A1 in children and adolescents.**

Methods: **A systematic search was conducted in the PubMed, Embase, Lilacs, Web of Science, Ovid and Science direct databases, searching for cohort eligible studies and evaluating their results, methodological quality and risk of bias; combinable studies with good quality and low risk of bias were evaluated by meta-analysis. The summary measure used was the weighted mean difference (WMD) with its respective 95% confidence interval.**

Results: **8 articles attended the eligibility criteria including individuals with age mean varying from 9 to 15.7 years of age. The meta-analysis included 4 articles with a total of 7,974 children and adolescents. It was observed a mean increase of 4,94mg/dL (95%CI: 4,22 to 5,67) in the ApoB levels in individuals with excess of body adiposity. For the ApoA1, we identified a mean reduction of -8,13mg/dL (95%CI: -9,09 to -7,17 mg/dL) in its levels in children and adolescents with higher body adiposity. Beside this, the influence of excess adiposity on the ApoB and ApoA1 levels was higher between adolescents than children.**

Conclusions: **The excess of body adiposity influenced both the reduction of ApoA1 values and the increase of ApoB levels, being these changes more relevant among adolescents. (Arq Bras Cardiol. 2020; 115(2):163-171)**

Keywords: **Child; Adolescent; Obesity; Overweight; Waist Circumference; Apolipoproteins; Meta-Analysis**

Introduction

The growing prevalence of excess body adiposity in children and adolescents is a worldwide health problem.[1,2] According to an editorial published by The Lancet,[3] obese children and adolescents are at increased risk of developing chronic non-communicable diseases (NCDs) in adulthood, such as obesity, heart diseases, type 2 diabetes, stroke; in addition to social and psychological problems, such as lack of self-esteem and stigmatization. Thus, efforts to face the high occurrence of excess body adiposity are justified by the link with the development of cardiovascular disease (CVD), one of the NCDs responsible for the high burden of morbidity around the globe. The factors that contribute to the development of CVD are called cardiometabolic risk factors,[4] and include excess adiposity, high blood glucose, lipid changes (LDL cholesterol and high triglycerides, low HDL cholesterol), high blood pressure, smoking and physical inactivity.

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Excess of adipocytes stimulates cells, cytokines and pro-inflammatory proteins to produce other inflammatory cells, interleukin 6 and tumor necrosis factor alpha (TNFα), which cause inflammation and promote endothelial dysfunction. There is also the action of Apolipoproteins B (ApoB), which adhere to endothelial cells and favor a greater expression of endothelium adhesion molecules, and such effects have a response on the formation of atherosclerotic plaques and other cardiovascular events.[5-9]

Evidence indicates that excess adiposity is strongly correlated with lipid disorders, such as elevated plasma ApoB levels and reduced apolipoprotein A1 (ApoA1).[10,11] Despite this well-established evidence in adults, such knowledge in regard to children and adolescents is still incipient. Therefore, this study aimed to investigate other longitudinal studies that assessed the influence of excess body adiposity on serum levels of ApoB and ApoA1 in children and adolescents.

Method

Identification and Selection of Articles

This is a systematic review with meta-analysis, carried out according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA).[12]

Search Strategies and Eligibility Criteria

Two independent researchers searched the articles in the PubMed, Embase, Lilacs, Web of Science, Ovid and Science Direct databases from December 16, 2016 to July 20, 2017 using descriptors as proposed in the Medical Subject Headings (MESH): exposure (body adiposity and related terms: "obesity" OR "overweight" OR "Abdominal obesity" OR "Central obesity" OR "Waist circumference"), and the outcome (ApoB and ApoA1 levels and related terms: Apolipoprotein OR ApoB OR "Apo B" OR "Apoprotein B"; ApoA OR "ApoA" OR "Apoprotein A"). The descriptors were combined with Boolean operators "or" and "and" in all databases. The search strategy considered the orienting question of investigation, structured by the acronym Population, Exposure, Comparison and Outcome (PECO). Only the terms for the Exposure (E) and Outcome (O) components were defined, in order to avoid unwanted specificity, restricting the selection of studies.

The eligibility criteria for inclusion of an article in the study were: original studies conducted with humans, prospective observational design involving children and adolescents aged between 5 and 19 years old and analysis of the relationship between adiposity and ApoB and ApoA1 levels.

The studies were supposed to provide information on exposure and outcome, with the adoption of mean as a measure of occurrence and respective standard deviation. There were no restrictions as to year, place and language of publication. The selection of articles was based on the information displayed in the heading and abstract, adopting the eligibility criteria available in a standardized form. Duplicates were removed manually. In the following step, the articles that were maintained were read in full.

In case of disagreements, a third reviewer was invited for a consensus meeting. We performed manual search in the reference lists of the selected articles to identify possible studies not included in the electronic search.

Exclusion Criteria

Studies conducted with pregnant women, nursing mothers, individuals with CVD, diabetes mellitus, arterial hypertension and who had undergone bariatric surgery were excluded. The gray literature—defined mainly as abstracts of congresses and conferences, and academic, governmental and industry reports[14]—was included only in the search on Ovid. The authors of the articles that did not report the mean ApoB and ApoA1 serum levels and the standard deviation according to adiposity were contacted via email and, in case of no response, they were kept in the systematic review and excluded from the meta-analysis.

Data Extraction

Two independent reviewers read all the eligible articles in full and listed in a standardized spreadsheet the ones meeting the criteria, taking note of the first author's surname, year of publication, sample size, mean age of participants, sex, and body fat measurement, data on presence or absence of excess adiposity in the end of follow-up, mean and standard deviation of serum ApoB and ApoA1 of participants with and without excess adiposity in the end of follow-up.

Bias risk Assessment

Two independent reviewers assessed the risk of bias according to the Research Triangle Institute Item Bank (RTI – Item bank).[15] This tool is organized into 29 items, aimed at assessing bias in observational studies, of which six of them were applied in this study: Q1 – study design; Q2 – explicit inclusion and exclusion criteria; Q3 – inclusion and exclusion criteria with valid and reliable measures; Q5 – equal recruitment strategy; Q6 – sample size; Q7 – level of detail in the description of the exhibition; and Q14 – exposures assessed using valid and reliable measures. For all questions, answers considered were 1) yes, 2) no or 3) not applicable. A high risk of bias was identified when the study had two or more negative or not applicable answers; and low risk of bias when it presented less than two negative points or not applicable.

Methodological Quality Assessment

Methodological quality was assessed using the criteria proposed in the Newcastle Ottawa[16] scale, which consists of three domains: 1. Selection: in this domain, sample representativeness, determination of exposure and absence of selection bias are identified (article can be scored with up to four stars); 2. Comparability between groups: articles can be scored with up to two stars; 3. Outcome: analysis of outcomes, evidence of exposure, assessment of losses and adequacy of follow-up time (article can be scored with up to three stars), totaling nine stars. For this work, a minimum of six stars was adopted to classify an article with good methodological quality.[17]

Statistical Analysis

Four studies were selected to perform the meta-analysis. According to Higgins & Green,[14] the meta-analysis can be performed by combining two or more different studies. Thus, the descriptive data of the outcome variables according to body adiposity at the end of the follow-up were collected by two independent authors and input in an Excel® spreadsheet.

The simple measure used in the meta-analysis was the difference between the weighted mean (Weighted Mean Difference-WMD) of ApoB and ApoA1 between individuals with and without excess body adiposity, and respective confidence intervals (CI), afterwards put in a forest plot graph. This measure can be used as summary statistics in meta-analyses when the outcome measures in all studies are on the same scale.[14]

To calculate the global WMD, random effects models were used, appropriate for studies with high heterogeneity. This model assumes that studies were conducted differently, forming a random sample of hypothetical population, so there is not one value only that estimates the measure of association, but rather a distribution of values.[18,19]

It is known that heterogeneity is common in observational studies and this influences the measure of association. Thus, the assumption of homogeneity was tested by the Q-Cochran test and the magnitude of heterogeneity was interpreted by the percentage of variation between the studies considered, measured with I^2 statistic (Higgins inconsistency test). An I^2 less than 50% was considered indicative of moderate

heterogeneity.[20] In case of high heterogeneity (I^2 greater than 50%), meta-regression was used.

Considering that less than ten studies were included in the meta-analysis, it was not possible to analyze publication bias with the Egger test and the Funnel plot. However, the comprehensive, sensitive and unrestricted search based on language and year contributed to reduce publication bias.

For all analyses, a p-value less than 5% was adopted as statistically significant. They were performed in the statistical package Stata for Mac version 12 (Stata Corp, College Station, TX, USA), using the command "metan" to obtain the WMD.

Results

Results of the Systematic Review

Selection of Studies

In the systematic search, 7,116 articles were identified, of which 3,978 were duplicated. After reading heading and summary and verifying eligibility, 3,118 articles were excluded. Thus, 20 articles were selected for full reading, being 12 excluded for the following reasons: did not present data on ApoB, ApoA1 according to excess adiposity (three studies); sample composed of individuals with CNCD (hypertension, diabetes, metabolic syndrome or dyslipidemia – nine studies). In total, eight articles were chosen for the systematic review. Four had all the information about exposure and outcomes and were, therefore, included in the meta-analysis (Figure 1).

Study Characteristics

The main characteristics of the eight studies included in the systematic review are described in Table 1. As to origin, one study was carried out in Japan, two in Australia, one in the United States of America, two in England, one in Sweden, and one in Canada, having been published between 2001 and 2016. The sample size ranged from 59 to 7,589 individuals of both sexes, totaling 15,835 individuals, with mean age of 9 to 15.7 years. The minimum follow-up time was 12 months and the maximum was 144 months, periods that are sufficient for the phenomenon to occur.

Risk of Bias

The articles were evaluated using six questions from RTI, with all eight articles considered to be at low risk of bias.

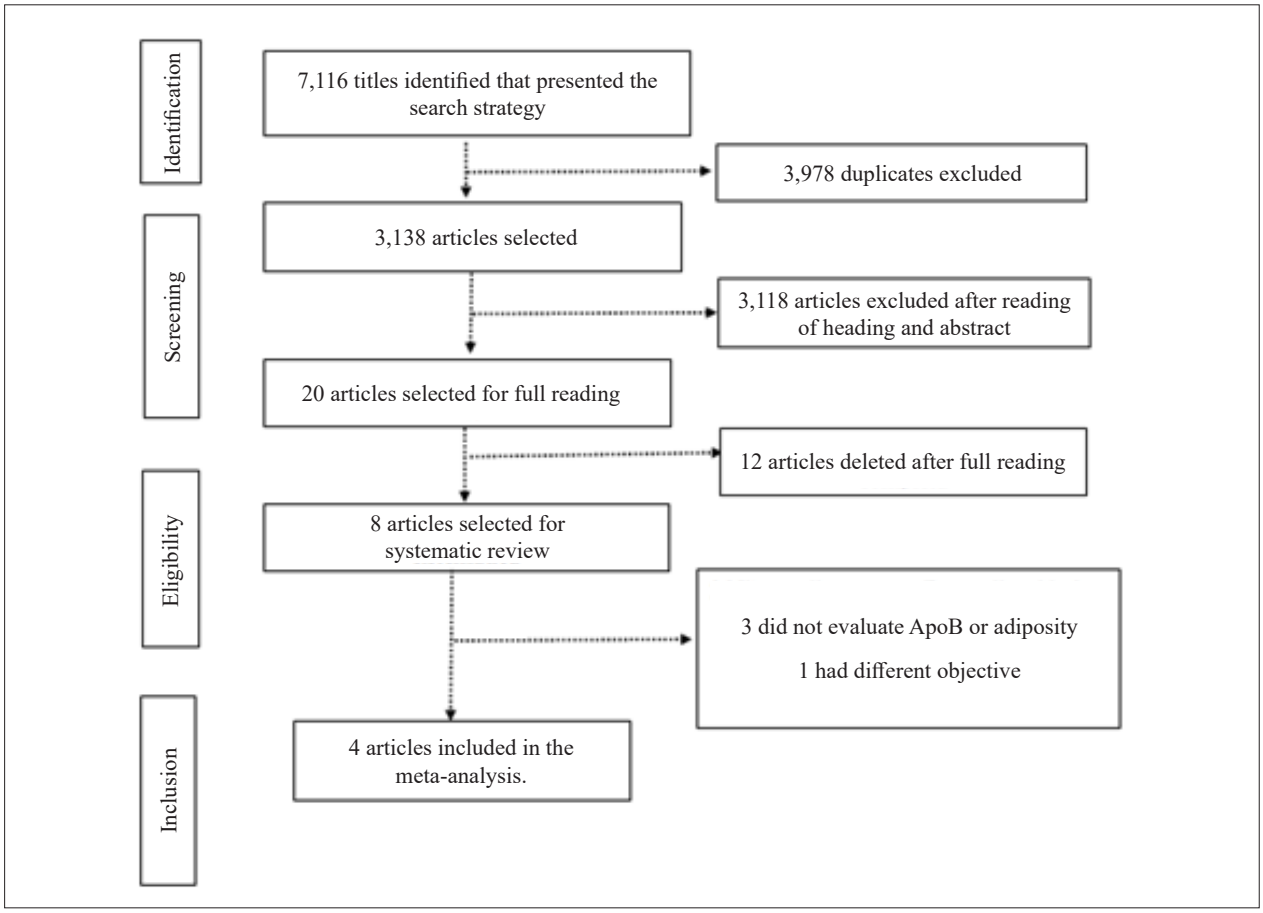

Figure 1 – *Flowchart of the systematic review.*

Table 1 – Main characteristics of studies included in the systematic review *Body Mass Index (BMI); † Dual-energy X-ray absorptiometry (DXA)

Author and year	Country	Mean age	Sample by exposure group		General sample	Follow-up (months)	Adiposity measure
			With excess adiposity	Without excess adiposity			
Falaschetti et al. 2001	England	9.9 years	1,602	5,987	7,589	120	* BMI
Larsson et al. 2010	Sweden	10 years	29	115	144	120	BMI
Benson et al. 2012	USA	12 years	87	75	162	12	BMI
Wilke et al. 2016	Canada	11.7 years	218	412	630	48	BMI and †DXA
Yamazaki 2008	Japan	12 years	19	60	79	144	Adiposity rebound
Bogaert et al. 2003	Australia	8.6 years	-	-	59	12	BMI
Howe et al. 2010	England	9.9 years	-	-	7.033	120	DXA
Mehta et al. 2002	Australia	15.7 years	-	-	139	120	BMI

Source: author.

All studies had adopted a prospective design (Q1), partially presented the inclusion and exclusion criteria (Q2), used valid and reliable measures (Q3), had a high level of detail in the description of the exposure (Q7), used appropriate indicators and valid and reliable means of measure (Q14). Two articles used the strategy of recruiting participants between groups (Q5) and, in six other articles, this item was not applied because there was no separation by groups. Only one article21 did not state the exclusion criteria (Q2).

Methodological Quality Assessment

Among the eight studies included in the systematic review, all showed good methodological quality, reaching eight[21-23] and seven stars.[24-28] The main limitation observed in studies with a score of seven was the lack of description of control factors in terms of comparability of cohorts. The results are shown in Table 2.

Table 2 – Evaluation of methodological quality of the studies included in the systematic review according to the Newcastle Ottawa Scale

Study	Selection	Comparability of cohorts based on design or analysis	Outcome of each study	Total stars
Benson et al. (2012)	4 stars	SP	3 stars	7
Bogaert et al. (2003)	4 stars	1 star	3 stars	8
Falaschetti et al. (2001)	4 stars	SP	3 stars	7
Howe et al. (2010)	4 stars	1 star	3 stars	8
Larsson et al (2010)	4 stars	SP	3 stars	7
Mehta et al (2002)	4 stars	1 star	3 stars	7
Wilke et al. (2016)	4 stars	SP	3 stars	7
Yamazaki (2008)	4 stars	SP	3 stars	7

Results of the Meta-analysis

This meta-analysis included data from 7,974 individuals, whose outcomes are shown in Figures 2 to 5. When assessing the influence of excess body adiposity on serum ApoB values, an average increase of 4.94 mg/dL was observed (95%CI: 4.22 to 5.67 mg/dL) at the levels of this biochemical marker in individuals with excess body adiposity. An average reduction of -8.13 mg/dL (95%CI: -9.09 to -7.17 mg/dL) was identified in the serum levels of ApoA1 in children and adolescents with excess body adiposity (Figures 2 and 3).

Considering the age of the individuals followed up in the original studies, we could carry out a subgroup analysis. According to the results, described in Figure 4, the mean increase in serum ApoB values in individuals with excess body adiposity was greater in the population aged ten years or older (adolescents), when compared to those younger than ten years (WMD 10.60 mg/dL [95%CI: 7.47 to 13.73] and 4.62 mg/dL [95%CI: 3.88 to 5.37], respectively).

Also for ApoA1, excess body adiposity was associated with a greater mean reduction in the serum values of this marker in adolescents aged ten years or older (WMD -10.43 mg/dL [95%CI: -14.35 to -6.51]), compared to children under ten years old (WMD -7.99 mg/dL [95%CI: -8.98 to -6.99]) (Figure 5) .

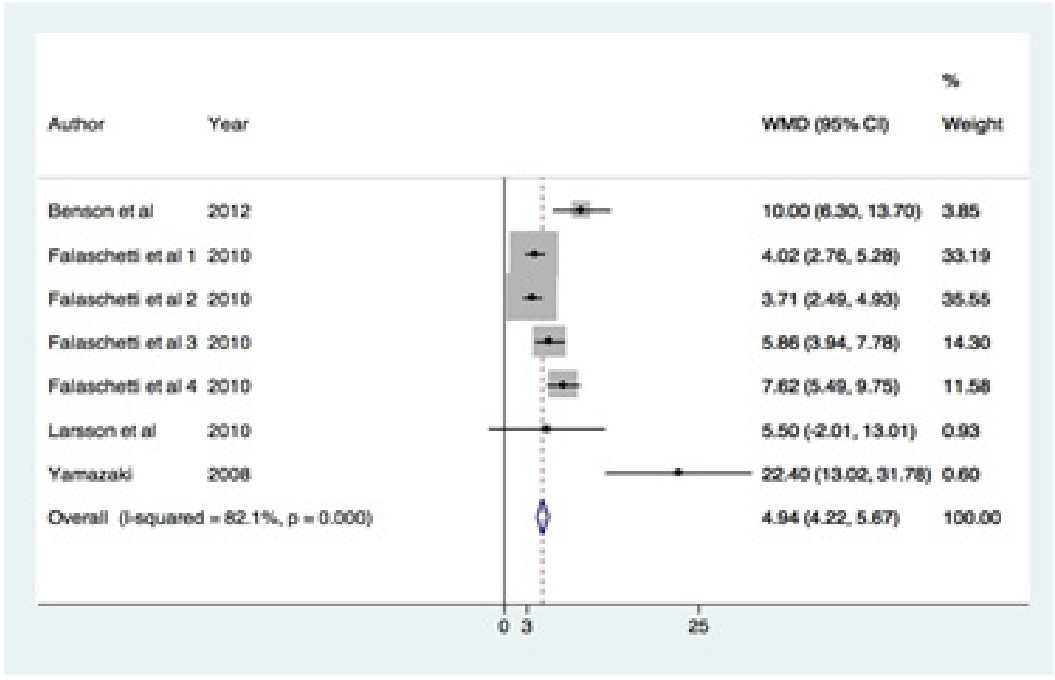

Figure 2 – *Forest plot of the influence of excess body adiposity on the difference of weighted mean of ApoB in children and adolescents. Falaschetti et al. 1 and 3: correspond to overweight and obese boys, respectively. Falaschetti et al. 2 and 4: correspond to overweight and obese girls, respectively.*

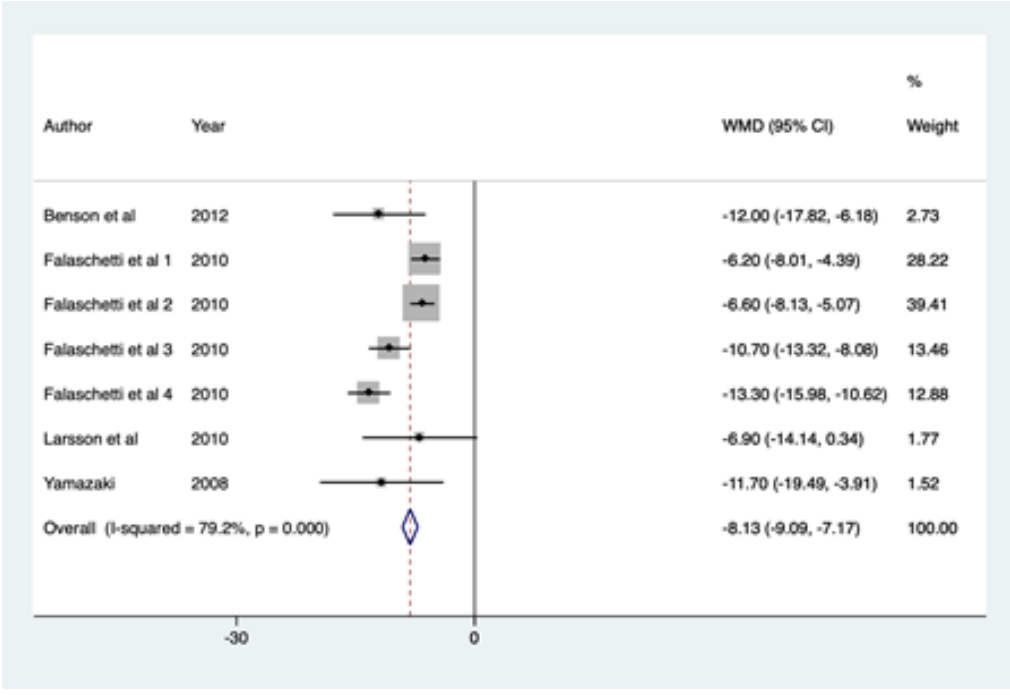

Figure 3 – *Forest plot of the influence of excess body adiposity on the difference of weighted mean of ApoA1 in children and adolescents. Falaschetti et al. 1 and 3: correspond to overweight and obese boys, respectively. Falaschetti et al. 2 and 4: correspond to overweight and obese girls, respectively.*

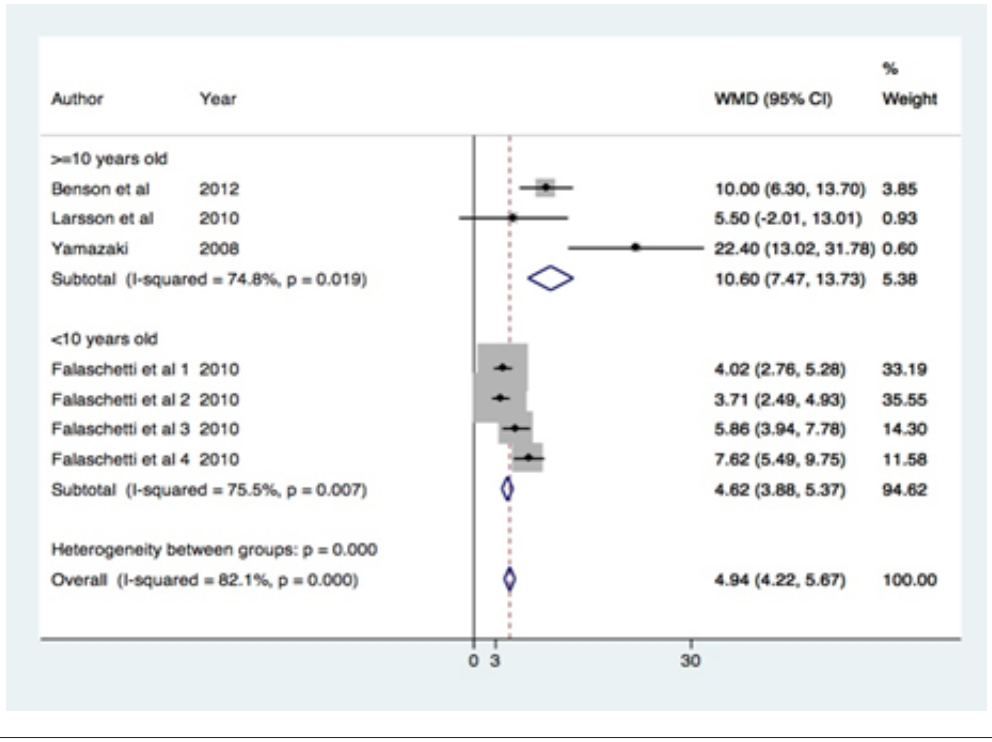

Figure 4 – *Forest plot of the influence of excess body adiposity on the difference from the weighted mean of ApoB, according to the age of children and adolescents. Falaschetti et al. 1 and 3: correspond to overweight and obese boys, respectively. Falaschetti et al. 2 and 4: correspond to overweight and obese girls, respectively.*

Heterogeneity and Meta-regression

The studies had high heterogeneity, with an I^2 greater than 50%. Possible sources of heterogeneity were investigated through meta-regression, including the variables: gender (95%CI -0.76 to 0.71), mean age (95%CI -2.06 to 1.71), mean BMI (95%CI -0.17 to 0.33) and sample size (95%CI: 0.12 to 0.36). None of these covariables could explain the wide heterogeneity between studies (data not shown in table).

Discussion

The results indicated that children and adolescents with excess body adiposity have an inadequate profile of ApoB and ApoA1 markers. These changes were also found to be more pronounced in adolescents than in children. These variations in serum values of apolipoproteins are clinically important and indicate that children and adolescents with excess body adiposity tend to present an inadequate profile of such markers, which can predict higher cardiovascular risk and comorbidities in future life cycles.

Thus, based on the available evidence on the subject and the results of this meta-analysis, the likelihood of a higher cardiometabolic risk in later life cycles should be considered for this population group. Results of some studies have indicated an association between excess body adiposity and increase in atherogenic particles or decrease in non-atherogenic particles in children and adolescents.[29,30] There has also been a higher mean of ApoB in overweight and obese children compared to eutrophic children.[29] This same study[29] found a positive correlation between ApoB, thickness of epicardial adipose tissue and serum triglycerides, placing ApoB as a cardiometabolic marker with a strong correlation with body fat profile.

The persistence and worsening of the risk of ApoB over time has been observed in young adults identified with a more pronounced BMI/Age ratio and greater volume of epicardial fat. The authors observed that this association became more pronounced 12 years after exposure, suggesting that the risk of excess adiposity tends to remain throughout life.[31]

ApoA1 and ApoB are important structural and functional proteins of the HDL and VLDL/LDL lipoprotein particles, respectively. These proteins are essential for the integrity of particles during processing and to lead them to their metabolic destination. When there is a change in the physiological route, the atherogenic particles are directed to organs and systems, compromising their physiological functions, such as the forwarding of VLDL/LDL cholesterol to the artery wall, leading to pathological impairment, as occurs with the etiology of atherosclerosis. Excessive body adiposity is related to a high serum concentration of ApoB. This particle is oxidized on the vessel wall, giving raise to an inflammatory process with local accumulation of macrophages, involving LDL and ApoB residues in the subendothelial space of the vessel, and culminating in endothelial dysfunction, atheroma formation and thickening of the vascular wall.[32,33]

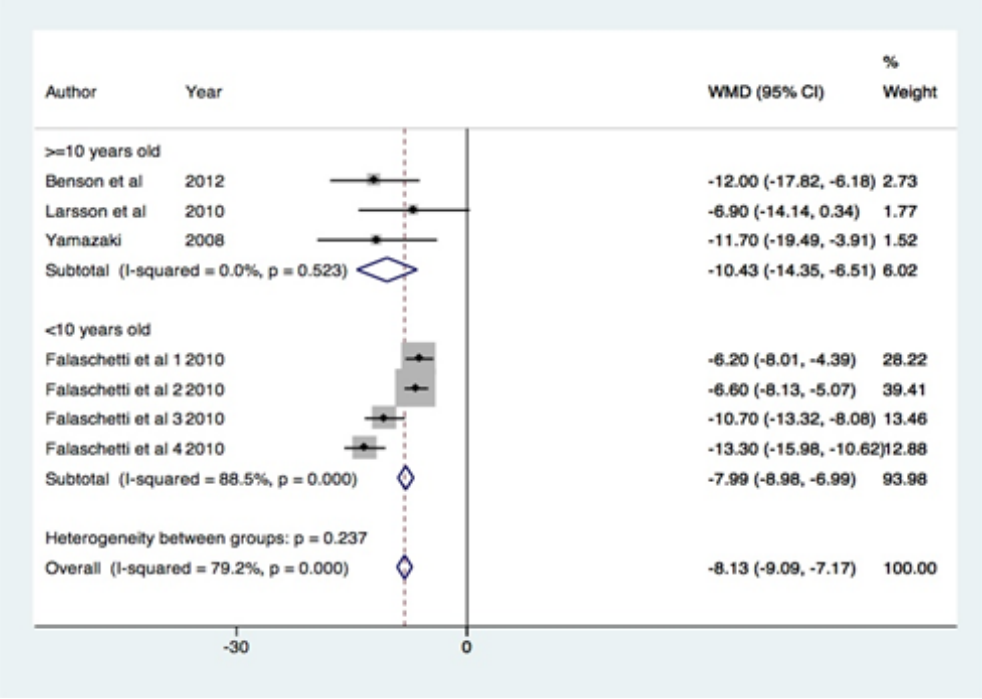

Figure 5 – *Forest plot of the influence of excess body adiposity on the difference of the weighted mean of ApoA1 according to the age of children and adolescents. Falaschetti et al. 1 and 3: correspond to overweight and obese boys, respectively. Falaschetti et al. 2 and 4: correspond to overweight and obese girls, respectively.*

High concentrations of ApoB and LDL are associated with atherosclerosis and stroke in adults.[34] Recent evidence indicates that children and adolescents with high ApoB and low ApoA1 concentrations may show signs of atherosclerosis at earlier ages than those of the same age with normal concentrations of these biochemical parameters.[35]

Scientific evidence highlights that exposure to these risk factors in the first cycles of life can contribute to the development of cardiovascular changes in later periods of life.[31,36]

Applicability of Evidence

It is known that CVDs have a great impact on the population's morbidity and mortality, and therefore require substantial public investment in health care. When determining the robust relationship between excess adiposity and apolipoproteins—investigated in this study—, the results may have important implications from the point of view of formulating policies for the prevention, screening and early detection of subjects at risk, favoring the construction of measures to cope with this health problem.

Potential Biases in the Review Process

Although this investigation was well designed and conducted, it has limitations inherent to meta-analysis studies, especially with regard to the lack of information, in primary studies, on the variables that would allow investigating high heterogeneity between studies. In this study, the influence of the variables age, sex, mean BMI and sample size on the meta-regression was investigated, since only for these there was information available in all studies. It is known that the presence of hypothyroidism can raise ApoB levels,[37,38] an important variable to assess possible causes of heterogeneity; however, none of the studies included in our analysis referred to the presence or absence of this disorder in the individuals evaluated.

The small number of studies addressing this object limited the possibility of analyzing the risk of publication bias by funnel plot. However, some authors question the real usefulness of this instrument for this purpose, considering that the interpretation of its asymmetry is subjective, and there may be errors of interpretation regarding the risk of publication bias. In addition, some effect estimates (OR or mean differences) produced using the funnel plot are naturally correlated with their standard errors, which can produce a false asymmetry and confusion with publication bias.[39]

Many studies had a cross-sectional design, which did not allow the phenomenon of interest to be evaluated, which is naturally longitudinal. Studies with a prospective design, but which measured ApoB and ApoA1 in a single moment, were included under the justification that, in children under nine years old, these changes were not clinically important,[25] a situation that can lead to selection and underreporting bias.

Quality of Evidence

Evidence from 4 studies with 7,974 individuals followed for 12 to 144 months was included in the meta-analysis, enough time for the phenomenon to occur. Despite the limitations, this meta-analysis was well designed, based on the use of appropriate tools to assess the risk of bias, analyzing methodological quality and conducting statistical analyses that allowed investigating possible sources of heterogeneity.

Conclusion

Our findings suggest that excess body adiposity influences the reduction of ApoA1 values and increase in levels of ApoB in children and adolescents, these changes being even more relevant among adolescents. However, considering the low number of longitudinal studies found in this meta-analysis, we suggest further prospective studies that can identify the influence of body adiposity on these important markers of cardiovascular risk in adolescents, considering their negative effects throughout life.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Jesus GS, Costa PRF, Oliveira LPM, Queiroz VAO, Cunha CM, Pereira EM, Oliveira, AM; Acquisition of data: Jesus GS, Oliveira LPM, Queiroz VAO, Cunha CM, Pereira EM, Oliveira, AM; Analysis and interpretation of the data: Jesus GS, Costa PRF, Pereira EM, Oliveira, AM; Statistical analysis: Jesus GS, Costa PRF, Oliveira, AM; Obtaining financing: Jesus GS; Writing of the manuscript: Jesus GS, Costa PRF, Oliveira LPM, Queiroz VAO, Cunha CM, Oliveira, AM.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

This article is part of the thesis of master submitted by Gabriela dos Santos de Jesus, from Universidade Federal da Bahia.

Ethics Approval and Consent to Participate

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

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Obesity, Overweight, Body Adiposity and Cardiovascular Risk in Children and Adolescents

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Short Editorial: Body Adiposity and Apolipoproteins in Children and Adolescents: A Meta-Analysis of Prospective Studies

Obesity and overweight are considered a global public health problem and contribute strongly to several chronic non-communicable diseases (NCDs), including metabolic syndrome, diabetes mellitus (DM), cardiovascular diseases (CVD) and cancer. More than 1.9 billion overweight adults are estimated, representing 39% of the world population, and 13% of obese adults. The World Health Organization estimated, for 2019, more than 38 million overweight or obese children under the age of five. Childhood obesity is associated with higher chances of premature death, increased risk of high blood pressure, DM and cancer. Besides, obese children have early CVD markers, increased risk of fractures, breathing difficulties and insulin resistance.[1]

Obesity, as an independent risk factor for cardiovascular diseases,[2] is related to increased levels of apolipoproteins B (ApoB) and consequent endothelial dysfunction. The presence of obesity and dyslipidemia during childhood reflects the development of cardiovascular morbidities in adulthood.[3]

Excess of body adiposity is related to the presence of dyslipidemia, identified from the increase in the levels of total serum cholesterol and low and high-density lipoproteins. Also, assuming that atherogenic dyslipidemia and atherosclerotic disease can start in childhood and be accompanied by obesity, they must be analyzed as risk factors associated with the presence of coronary heart disease (CAD) in adulthood.[2, 4-6]

High concentrations of ApoB and low concentrations of ApoA1 have been identified as biochemical markers for atherosclerosis even at earlier ages,[7] being associated with waist circumference, adiposity and family history of CAD.[8]

Apolipoproteins A1 and B are essential proteins for the metabolism of lipoprotein particles and their serum levels are recognized as risk predictors for atherosclerotic disease. Evaluation of plasma levels can help to identify increased risk and to adopt early intervention strategies. Therefore, they can add clinical information that goes beyond that obtained by the evaluation of LDL and HDL.[9,10]

In adults, high rates of ApoB are strongly associated with metabolic syndrome and obesity and are better predictors of cardiovascular risk than traditional blood lipid measurements. In the young population, the conventional lipid profile is not a good predictor of CAD in adulthood.[7,10-12]

In the systematic review "Body adiposity and apolipoproteins in children and adolescents: meta-analysis of prospective studies",[13] ApoB was recorded as a cardiometabolic marker associated with body mass among adolescents and children, indicating changes in the profile of apolipoproteins in this population.

The relevance of this study[13] is due not only to the clinical finding, defining relationships between morbidities and biomarkers, but also to the fact that it was aimed at a population of children and adolescents. The findings raise awareness of the need for strategies for collective coping of problems of global magnitude, such as obesity and cardiovascular diseases.

The inclusion of apolipoproteins in the standard evaluation of the lipid profile, such as sensitive biomarkers for risk identification, can be useful as a screening and early detection strategy, in addition to the development of indicators for health monitoring in this population.

Keywords

Child; Adolescent; Hypertension; Diabetes Mellitus; Metabolic Synrome; Overweight; Obesity; Risk Factors; Public Health.

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Blood Pressure Control and Associated Factors in a Real-World Team-Based Care Center

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Abstract

Background: **Although team-based care is recommended for patients with hypertension, results of this intervention in a real-world setting are missing in the literature.**

Objective: **To report the results of a real-world long-term team-based care for hypertensive patients we conducted this study.**

Methods: **Data of hypertensive patients attending a multidisciplinary treatment center located in the Midwest region of Brazil in June 2017 with at least two follow-up visits were retrospectively assessed. Anthropometric, blood pressure (BP), follow-up time, pharmacological treatment, diabetes and lifestyle data were collected from the last visit to the service. BP values < 140 x 90 mmHg in non-diabetics and < 130 x 80 mmHg in diabetics were considered controlled. A logistic regression model was built to identify variables independently associated to BP control. Significance level adopted $p < 0.05$.**

Results: **A total of 1,548 patients were included, with a mean follow-up time of 7.6 ± 7.1 years. Most patients were female (73.6%; n=1,139) with a mean age of 61.8 ±12.8 years. BP control rates in all the sample, and in non-diabetics and diabetics were 68%, 79%, and 37.9%, respectively. Diabetes was inversely associated with BP control (OR 0.16; 95%CI 0.12-0.20; p<0.001) while age ≥ 60 years (OR 1.48; 95%CI 1.15-1.91; p=0.003) and female sex (OR 1.38; 95%CI 1.05-1.82; p=0.020) were directly associated.**

Conclusions: **A BP control rate around 70% was found in patients attending a multidisciplinary team care center for hypertension. Focus on patients with diabetes, younger than 60 years and males should be given to further improve these results. (Arq Bras Cardiol. 2020; 115(2):174-181)**

Keywords: **Hypertension; Blood Pressure/prevention and control; Exercise; Treatment Adherence and Compliance; Sedentarism; Obesity; Life Style.**

Introduction

Hypertension (HTN) is defined as elevated blood pressure (BP) levels based on an average of ≥ two careful readings obtained on ≥ two occasions, or current use of BP-lowering medications.[1,2] Although there is some debate on which thresholds should be used to define HTN, there is no doubt about the burden of HTN as a cardiovascular risk factor and a major cause of disability and death.[3-5]

Elevated BP is the most important treatable risk factor for stroke, atrial fibrillation and heart failure.[5] Reductions in BP are effective to prevent target organ damage, cardiovascular events and death in various clinical conditions involving different BP levels, cardiovascular risk profiles, and comorbidities.[6,7] Despite that, uncontrolled HTN remains a widely prevalent situation worldwide.[8]

Among the strategies aimed to improve BP control, team-based interventions have shown to be highly promising.[9,10] They consist of organizational, patient-centered, multifaceted interventions, led by multidisciplinary teams, aimed at improving the quality of HTB care. HTN team-based care includes patients, patient's primary care providers, and other professionals, such as cardiologists, nurses, pharmacists, physician assistants, dietitians, social workers, community health workers, and others. These workers complement each other by providing process support and sharing responsibilities.[1]

Although team-based care is recommended for patients with HTN by most guidelines,[1,2,11,12] results of this intervention in a real-world setting are missing in the literature. We conducted this study aiming to report the results of a long-term multidisciplinary treatment intervention for patients with HTN, specifically assessing BP control rates and associated factors.

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Methods

Data of all patients with HTN aged 18 years or older, with at least two follow-up visits and attending a multidisciplinary treatment center for HTN in the Central West region of Brazil in June 2017 were retrospectively assessed by convenience.

HTN was defined according to the 7th Brazilian Guidelines on Hypertension: (1) office BP ≥ 140 × 90 mmHg; ambulatory BP monitoring ≥ 130 × 80 mmHg; (3) home BP monitoring ≥ 135 × 85 mmHg.[13] Patients receiving HTN treatment were also considered hypertensive.

The center has been functioning for more than 25 years, dedicated to the treatment of HTN, health professional education and research. Patients with recently diagnosed HTN or those with difficulties to control BP levels are referred to the center and the total number of patients enrolled in the study was 1,701. The multidisciplinary team consists of physicians (general practitioners, cardiologists, endocrinologists and nephrologists), nurses, dietitians, physical therapists, physical educators, psychologists and musical therapists. Aiming to improve treatment compliance and reduce loss of follow-up, the maximum interval between each patient appointment was three months. The maximum interval between two medical visits was six months, and regarding the other healthcare professionals, there was no routine appointments, *i.e.*, the visits were scheduled according to patient's needs determined by clinical examination. Additionally, educational and health promotion activities were performed every two weeks with patients.[14,15] Since beginning of this multidisciplinary service, consultations have been registered in a standardized form. All healthcare professionals directly involved in patients' care were routinely trained to complete this form, ensuring data reliability and reproducibility throughout years.[16,17]

Data collection

Data of the last visit to the service were collected, regardless of the healthcare specialty. Additionally, the dates of patient's first visit registered in medical charts were collected and used to calculate the follow-up time (difference between the first and the last visit to the service), in years.

The following data were collected from the medical records: sex; age: given in years and assessed by the difference between birth date and date of last visit; anthropometric data: weight, height and body mass index (BMI) calculated using the Quetelet formula (BMI = weight in kg/height^2 in meter). Nutritional status was classified according to BMI and following the World Health Organization definitions: non-overweight (BMI < 25kg/m^2); overweight (BMI ≥ 25 kg/m^2 and < 30mg/kg^2) and obese (BMI ≥ 30 mg/kg^2).

BP: a minimum of three BP measurements, with at least 1-min interval, was taken. All measurements were performed after 5 minutes of rest, on the upper limb, with the individual sitting and the arm supported. Appropriate cuffs were used depending on arm diameter. Mean values of the last two measurements were considered for BP control definition. BP measurements were performed with oscillometric devices (OMRON semi-automatic equipment, model HEM-705CP). This routine was adopted in the service to avoid observer bias.

Lifestyle: smoking (current smoker or nonsmoker); alcohol consumption (any alcohol consumption reported during the last visit); leisure physical activity (regular: ≥3 times a week, irregular: <3 times a week and sedentary: no activity).

Diabetes: definition followed the recommendations of the most recent guidelines of the Brazilian Society of Diabetes:[18] (1) symptoms of polyuria, polydipsia, weight loss and casual blood glucose (values obtained at any time of the day regardless of meal times) ≥ 200 mg/dL; (2) fasting blood glucose ≥ 126 mg/dL; diagnosis should be confirmed by repeat testing on another day in case of small blood sugar elevations; (3) 2-hour plasma glucose value after a 75-g oral glucose tolerance test ≥ 200 mg/dL. Diabetes treatment registered in medical records was also considered as diagnosis criteria.

Drug treatment: information whether patient was receiving or not pharmacological HTN treatment and the number of antihypertensive medications.

BP control definitions

Recommendations of the 7th Brazilian Guidelines on hypertension (2016)[19] were adopted (BP values < 140 x 90 mmHg in non-diabetics and < 130 x 80 mmHg in diabetic patients) for analysis of BP control.

Multidisciplinary service

Medical team: assessed symptoms, lifestyle habits and use of medications; performed patients' physical examination; analyzed complementary tests and established patient management (pharmacological and nonpharmacological treatments prescription, complementary tests request, and follow-up visits schedule); referred patients to emergency care or hospitalization if acute clinical decompensation was identified.

Nurses: assessed symptoms, vital signs, lifestyle habits and use of medications; instructed about compliance to both pharmacological and nonpharmacological treatments; defined intervals of visits to the nurse; and referred patients for medical consultation if clinically necessary or to ensure a maximum interval of six months between two medical visits.

Dietitians: emphasized nonpharmacological aspects of care, specifically the diet; collected dietary data; assessed anthropometric data and vital signs. Management was aimed at dietary guidance with emphasis on salt restriction and prescription of diets for patients with specific diagnosis such as diabetes and chronic kidney disease.

Physical educators: developed and assist patients in group physical activities (strength training and aerobic exercise) three times a week and emphasized the importance of regular physical activity.

The other health care professionals did not conduct formal appointments, but rather a series of educational interventions to promote patients' health. Physical therapists conducted periodical meetings previously scheduled or saw with patients at the waiting room and discussed preventive measures for

injuries and falls. Similarly, psychologists and musical therapists acted mainly in the waiting room, providing instructions and interventions aimed at stress reduction and improve the waiting time.

Statistical analysis

Statistical analysis was performed using the software STATA V14 (StataCorp., College Station, Texas, USA). The Kolmogorov-Smirnov test was used and determined that the continuous variables were normally distributed. Continuous variables are presented as mean and standard deviation. Categorical variables are presented as n and %. Unpaired T-test was used to compare continuous variables and the chi-square test to compare categorical ones. A logistic regression model was built to identify variables independently associated to blood pressure control. Diabetes, age ≥ 60 years, female sex, alcohol consumption, smoking, sedentary lifestyle, pharmacological treatment, BMI (kg/m^2) and total follow-up time (years) were used as predictors in the model. The significance level adopted was $p < 0.05$.

Results

A total of 1,548 patients were included, accounting for more than 90% of all patients attending the center (153 were not included due to missing data on the first or last visits). Mean follow-up time was 7.6 (±7.1) years. Most patients were female (73.6%; n=1,139) and the mean age was 61.8 (±12.8) years. Women were more likely to be obese and sedentary, while less likely to consume alcohol and smoke when compared to men. Additionally, lower BP values were found in females when compared to males. Characteristics of the study population, stratified by sex, are presented in Table 1.

Table 1 – Characteristics of the study population stratified by sex (n=1,548), Goiânia, Brazil

Factor	Overall	Male	Female	p-value*
N	1,548 (100%)	409 (26.4%)	1,139 (73.6%)	
Age (years)	61.8 (±12.8)	62.0 (±13.8)	61.8 (±12.4)	0.750
Total follow-up time (years)	7.6 (±7.1)	7.1 (±6.7)	7.8 (±7.2)	0.070
Height (m)	1.58 (±0.09)	1.67 (±0.08)	1.55 (±0.07)	<0.001
Weight (kg)	73.8 (±16.5)	79.2 (±16.5)	71.9 (±16.1)	<0.001
Body mass index (kg/m^2)	29.3 (±5.9)	28.3 (±5.3)	29.7 (±6.0)	<0.001
Nutritional status				
Non-overweight	350 (22.6%)	105 (25.7%)	245 (21.5%)	0.084
Overweight	571 (36.9%)	174 (42.5%)	397 (34.9%)	0.006
Obese	627 (40.5%)	130 (31.8%)	497 (43.6%)	<0.001
First systolic BP (mmHg)	146.3 (±24.0)	148.5 (±24.6)	145.5 (±23.8)	0.030
First diastolic BP (mmHg)	85.5 (±16.0)	87.2 (±15.6)	84.9 (±16.1)	0.014
Second systolic BP (mmHg)	144.5 (±23.1)	146.8 (±23.1)	143.7 (±23.0)	0.018
Second diastolic BP (mmHg)	83.3 (±13.1)	85.0 (±12.9)	82.7 (±13.1)	0.003
Third systolic BP (mmHg)	144.3 (±18.2)	145.1 (±18.4)	144.0 (±18.1)	0.320
Third diastolic BP (mmHg)	83.2 (±10.2)	84.4 (±10.4)	82.8 (±10.1)	0.009
Mean systolic BP (mmHg)†	144.4 (±19.1)	145.9 (±19.4)	143.8 (±18.9)	0.057
Mean diastolic BP (mmHg)†	83.3 (±10.6)	84.7 (±10.7)	82.8 (±10.6)	0.002
Diabetes	412 (26.6%)	113 (27.6%)	299 (26.3%)	0.590
Alcohol consumption	206 (13.3%)	108 (26.4%)	98 (8.6%)	<0.001
Smoking	177 (11.4%)	73 (17.8%)	104 (9.1%)	<0.001
Physical activity				
Sedentary	737 (47.6%)	172 (42.1%)	565 (49.6%)	0.009
Irregular	231 (14.9%)	70 (17.1%)	161 (14.1%)	0.150
Regular	580 (37.5%)	167 (40.8%)	413 (36.3%)	0.100
Pharmacological treatment	1,513 (97.7%)	399 (97.6%)	1,114 (97.8%)	0.770
Number of anti- hypertensive drugs	2.1 (± 0.8)	2.8 (± 0.7)	1.7 (± 0.8)	0.369

*Values given in means (±SD) or n (%). *unpaired t-test to compare continuous variables and chi-square test for comparison of categorical variables; statistically significant at α<0.05. †mean value of second and third readings .*

BP control rate in the study population was 68%, and this value was higher when only non-diabetic patients were considered (79%). On the other hand, assessing exclusively diabetic patients, BP control rate dropped to 37.9%. Figure 1 shows a summary of BP control rates in our study.

Individuals with BP under control were more likely to be females, older, with longer follow-up periods and lower BMI when compared to those with uncontrolled BP. Additionally those with controlled BP were less likely to be obese, diabetic and sedentary in comparison to those without BP controlled. Characteristics of the study population, stratified by BP control, are presented in Table 2.

The multivariable logistic regression model built to identify variables independently associated to BP control in this population showed that diabetes was inversely associated with BP control while age ≥ 60 years and female sex were directly associated (Table 3).

Discussion

We assessed data of more than 1,500 hypertensive patients with regular follow-up in a team-based care center to show the results of this multidisciplinary therapeutic strategy in a real-world setting. All patients included in this study were referred to a center specialized in hypertension treatment and had their treatment fully covered by Brazil's universal health system. Additionally, baseline characteristics of the patients were similar to those reported in the Brazilian Registry of Hypertension,[20] showing the generalizability of the results of the study. Almost 70% of the all patients had their BP controlled, and those results went up to 79% considering only the non-diabetic patients. BP control was inversely associated with diabetes and directly associated with age ≥ 60 years and female sex.

Population studies conducted in Brazil showed that BP control rates varied from 10.1% to 57.6% depending on country region and patient characteristics.[21] None of these studies, however, used data from team-based care centers. Our overall control rate (68%) was higher than those reported in conventional treatments in Brazil. As compared to BP control rates reported in other middle income countries like South Africa (30 and 49%),[22,23] and even in a high-income country like the United States of America (48%),[24] in the current study, we found better results with a team-based intervention.

BP control in patients with HTN and diabetes is challenging; control rates are usually lower than the ones found in hypertensive patients without diabetes.[25] Also, diabetic hypertensive patients are more likely to develop resistant hypertension.[26] Only 37.9% of our diabetic hypertensive patients had their BP under control as opposed to the 79% control rate among the non-diabetic patient. Additionally, diabetes was independently and inversely associated to BP control in this team-based care setting.

Older ages have been associated to BP control in different populations.[22,27] Our results reinforce these findings since we found that age ≥ 60 years was directly associated to BP control. Besides that, the novelty of our findings is the association between older ages and BP control in a team-based care strategy.

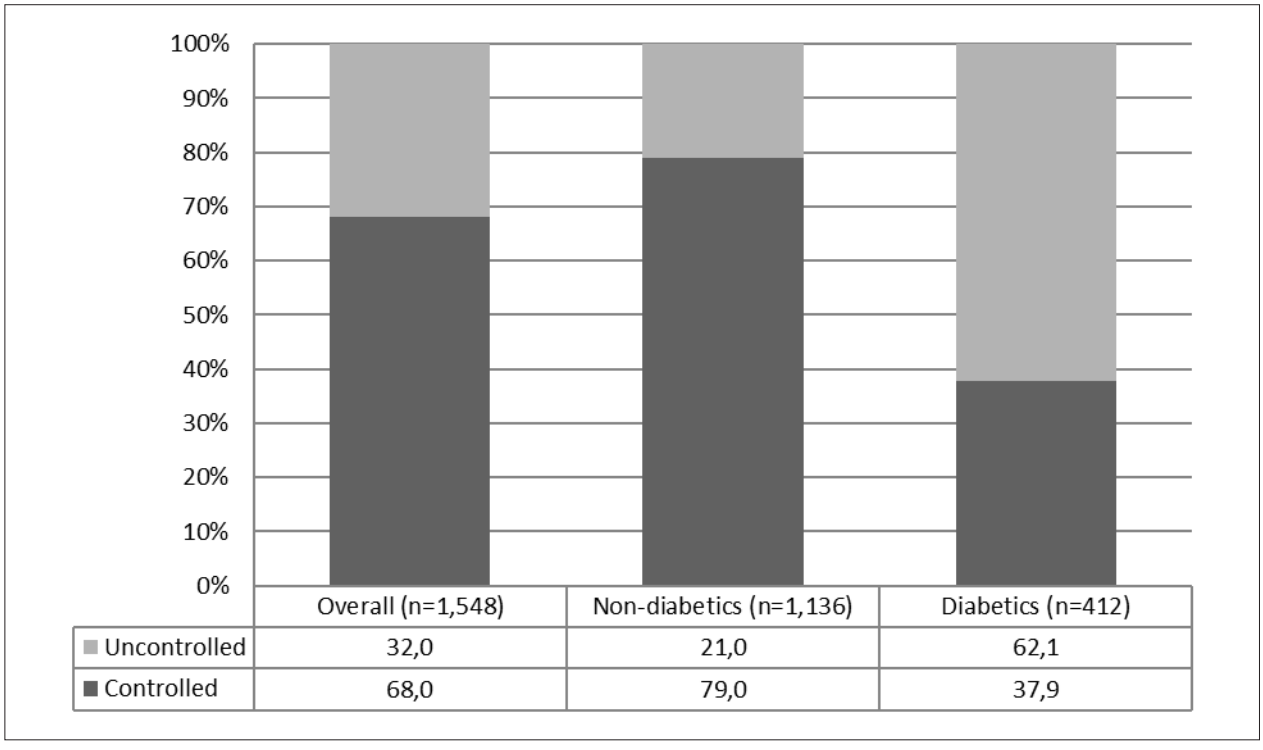

Figure 1 – *Blood pressure control in the overall study population, non-diabetics and diabetics. Goiânia – Brazil. Blood pressure control – BP < 140 x 90 mmHg in non-diabetics and < 130 x 80 mmHg in diabetics.*

Table 2 – Study population characteristics by blood pressure control* (n=1,548). Goiânia – Brazil

Factor	Controlled	Uncontrolled	p-value†
N	1,053	495	
Female sex	793 (75.3%)	346 (69.9%)	0.024
Age (years)	62.8 (±13.1)	59.8 (±11.9)	<0.001
Total follow-up time (years)	8.1 (±7.4)	6.6 (±6.5)	<0.001
Height (m)	1.58 (±0.09)	1.59 (±0.09)	0.059
Weight (kg)	72.4 (±16.6)	76.9 (±15.9)	<0.001
Body mass index (kg/m2)	28.9 (±5.8)	30.4 (±6.0)	<0.001
Nutritional status			
Non-overweight	262 (24.9%)	88 (17.8%)	0.002
Overweight	399 (37.9%)	172 (34.7%)	0.230
Obese	392 (37.2%)	235 (47.5%)	<0.001
First systolic BP (mmHg)	138.8 (19.8)	162.2 (24.4)	<0.001
First diastolic BP (mmHg)	80.6 (14.7)	95.9 (13.4)	<0.001
Second systolic BP (mmHg)	137.0 (18.8)	160.3 (23.4)	<0.001
Second diastolic BP (mmHg)	77.7 (9.9)	95.2 (11.0)	<0.001
Third systolic BP (mmHg)	139.4 (15.8)	154.7 (18.5)	<0.001
Third diastolic BP (mmHg)	79.58 (7.8)	91.3 (10.1)	<0.001
Mean systolic BP (mmHg)‡	138.2 (±15.8)	157.5 (±18.9)	<0.001
Mean diastolic BP (mmHg) ‡	78.6 (±7.7)	93.2 (±9.0)	<0.001
Diabetes	156 (14.8%)	256 (51.7%)	<0.001
Alcohol consumption	130 (12.3%)	76 (15.4%)	0.100
Smoking	119 (11.3%)	58 (11.7%)	0.810
Physical activity			
Sedentary	479 (45.5%)	258 (52.1%)	0.015
Irregular	163 (15.5%)	68 (13.7%)	0.370
Regular	411 (39.0%)	169 (34.1%)	0.064
Pharmacological treatment	1,028 (97.6%)	485 (98.0%)	0.660
Number of anti-hypertensive drugs	3.00 (± 0.81)	2.81 (± 0.76)	0.432

*Values given in means (±SD) or n (%). *Blood pressure control - BP <140 x 90 mmHg in non-diabetics and < 130 x 80 mmHg in diabetics. † unpaired T-test to compare continuous variables and Chi Square test to compare categorical ones; statistically significant at α<0.05. ‡mean value of second and third readings.*

Table 3 – Variables independently associated to blood pressure control (n=1,548). Goiânia – Brazil

Variables	Odds Ratio	[95% Conf.Interval]	p-value
Diabetes	0.15	[0.11-0.20]	<0.001
Age ≥ 60 years	1.45	[1.13-1.90]	0.005
Female sex	1.36	[1.09-1.88]	0.022
Alcohol consumption	0.80	[0.56-1.15]	0.183
Smoking	1.25	[0.80-1.80]	0.330
Sedentary lifestyle	0.78	[0.60-1.02]	0.053
Pharmacological treatment	1.12	[0.50-2.47]	0.741
Body mass index (kg/m2)	0.97	[0.95-1.01]	0.088
Total follow-up time (years)	1.01	[1.00-1.03]	0.098
Number of anti-hypertensive drugs	0.85	[0.68-1.01]	0.320

Sex differences in BP control rates are controversial. While studies have reported that women are more likely than men to have uncontrolled HTN,[28] others have indicated an association between female sex and appropriate hypertension management.[22] In our team-based care center, this is the first time that female sex is directly associated with higher HTN control rates.[16,17]

Randomized controlled trials are often considered the best scientific evidence for ascertaining efficacy and safety of a treatment.[29,30] Once the evidence is available and guidelines recommend treatments, it is important to assess how such interventions perform in a real-world setting. After all, the reality of patient care in a randomized clinical trial is different from usual clinical practice in many ways.[31] In that sense, the positive results shown here, particularly considering that our study was conducted in a public healthcare setting from a country with limited resources, reinforce the relevance of team-based care on hypertension management.

The study design might be a limitation, since we conducted a retrospectively single center study with no control group. Despite that, all medical records are objective, and their completion is exhaustively trained in this center, contributing to reliability of the data. Additionally, although we acknowledge that using a control group would be more appropriate, the positive result found here can foster future studies and help informing the healthcare community about a successful way to manage patients with HTN.

Another potential limitation regards to physical activity assessment. Only planned or formal physical activity – walking, running, cycling, swimming, strength training, etc.), was included in our definition. Therefore, daily physical activities were not considered and our sedentary lifestyle results are probably overestimated.

Costs of implementation and maintenance need to be taken into account when considering a team-based care for hypertension management. Despite that, economic assessment of this intervention in high-income countries showed that team-based care to improve BP is cost-effective.[32] Same assessments need to be conducted in low-to-middle income countries.

Given the positive results of the present study and previous studies involving patients from the same HTN treatment center,[14,16,17,33,34] the format adopted in our service can be a model for other centers handling patients diagnosed with HTN and aiming to implement a team-based strategy.

Conclusion

In the present study, conducted in a real-world setting, the rate of BP control after a team-based approach to hypertensive patients was 70%. Focus on patients with diabetes, younger than 60 years and males should be given to further improve these results.

Author contributions

Conception and design of the research, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Jardim TSV, Souza ALL, Barroso WKS, Jardim PCBV; Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Jardim TSV, Jardim PCBV.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Universidade Federal de Goiás under the protocol number 1822-180. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.z

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Blood Pressure Control: The secret is...Team Work!

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Short Editorial related to the article: Blood Pressure Control and Associated Factors in a Real-World Team-Based Care Center

Hypertension is one of the leading causes of cardiovascular death.[1] Indeed, data from the Heart and Stroke Statistics showed that 45% of the cardiovascular mortality is potentially attributed to hypertension.[1] This worrying scenario has not been changing in the last decades despite the availability of non-pharmacological interventions and the development of several anti-hypertensive classes that effectively contributed to blood pressure (BP) control.[2-5] The reasons for our low effectiveness in controlling BP at the population level are multiple, including the lack of organized public policies regulating salt consumption and increasing awareness, early detection, and effective treatment. Additional challenges include the asymptomatic characteristic of hypertension, therapeutic inertia, among others.[1]

In this edition of the *Arquivos Brasileiros de Cardiologia*, Jardim et al.[6] reported data from a retrospective study exploring a multidisciplinary team strategy in the rate of BP control (set at the traditional <140/90 mmHg). The authors evaluated demographic and clinical data of 1548 hypertensive patients from a specialized hypertension center who have been followed up regularly for 7.6 ± 7.1 years (mean age 62 years, 73.6% women). The multidisciplinary approach described by the authors consisted by the availability of nurses, nutritionists, occupational therapists, physical educators, psychologists and music therapists working in conjunction with the staff physicians (general practitioners, cardiologists, endocrinologists, and nephrologists). The maximal interval for medical outpatient visits was 3 months. According to the patients' needs (determined by the clinical evaluation), the physicians scheduled visits to the professionals mentioned above in a flexible demand. In addition, educational and health promotion activities were performed every two weeks with patients. All this information was recorded on a standardized form. Using this strategy, the authors found that this multidisciplinary team approach was associated with an overall 68% BP control, being more prominent in those aged ≥60 years (OR 1.45; 95% CI [1.13-1.90]), and females (OR 1.36; 95% CI [1.09-1.88]). In contrast, patients with diabetes were associated with a lower probability of reaching the BP target compared to patients without diabetes. Interestingly, no significant differences in the number of anti-hypertensive drugs were observed in the groups who controlled or not BP. This finding suggests that the adherence of this multidisciplinary approach may vary as usually observed with any other intervention.

It is worth mentioning the merit of the related service, whose multidisciplinary practice has been adopted, according to the authors, for over 25 years.[6] The BP control is impressive, considering the current estimates of BP control in Brazil (usually lower than 30% in individual studies).[3] Overall, this investigation's major contribution is that the literature is relatively scarce (particularly from large multicenter observational or randomized studies) in addressing the potential impact of a multidisciplinary team in patients with hypertension. Previous studies involving modest sample sizes suggested the importance of nurses in improving adherence to anti-hypertensive treatments and white coat-effect.[6-11] Similarly, the active approach from pharmacists, physical educators, and nutritionists seem to contribute to improving adherence and BP control.[12,13] However, it is crucial to define if the whole team structure available (and not distinct 'compartments') may contribute to the effectiveness of BP control. In other words, is the whole better than any individual component or the sum of the parts? The study conducted by Jardim et al. was not designed to address this question but highlighted that the fight against hypertension is not based on a single actor. Unfortunately, the lack of a control group (for instance, patients from other centers with no access to an organized multidisciplinary team approach) and the retrospective design prevent any definitive conclusions but pave the way for future investigations in this important research area. Particular attention should be devoted to patients with diabetes. The lower rate of BP control challenging us for extra efforts for this high cardiovascular risk population.

Keywords

Hypertension; Blood Pressure; Prevention and Control; Risk Factors; Patient Care Team/trends; Antihypertensive Agents; Medication Adherence.

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Intermittent Fasting Attenuates Exercise Training-Induced Cardiac Remodeling

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Abstract

Background: The effects of non-pharmacological interventions such as calorie restriction and exercise training on health and prevention of cardiovascular diseases have been investigated in clinical and experimental studies.

Objective: To analyze the influence of intermittent fasting and exercise training on functional fitness, glycemia and cardiac remodeling.

Methods: Wistar rats (n=60) were randomly divided into four groups: control, exercise training (ET), intermittent fasting (IF) and exercise training plus intermittent fasting (ETI). Over 12 weeks, control and ET animals were fed daily a standard commercial diet ad *libitum*, while IF and ETI animals were fed every other day. In addition, the ET and ETI groups were submitted to a running protocol on a treadmill. After this period, functional fitness, nutritional parameters and blood glucose levels were analyzed. In addition to heart morphology, myocardial protein expression of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) was assessed by Western-blot. The results were analyzed using two-way ANOVA and Student-Newman-Keuls test. The level of significance considered was 5%.

Results: Exercise training increased functional fitness in the ET and ETI groups and promoted cardiac fibrosis. The combination of intermittent fasting and exercise training resulted in a smaller area under the blood glucose curve and reduced cardiomyocyte cross-sectional area and interstitial collagen fraction in the ETI group compared to ET. ERK and JNK expression levels were similar among groups (p>0.05).

Conclusions: Intermittent fasting is associated with improved glucose tolerance and attenuates cardiac remodeling induced by exercise training (Arq Bras Cardiol. 2020; 115(2):184-193)

Keywords: Diet; Calorie Restriction; Exercise; Running; Ventricular Remodeling; Glucose; Health Promotion.

Introduction

Classically, calorie restriction is a popular intervention for health improvement, promoting multiple functional benefits and increasing human longevity.[1-4] However, experimental studies have reported controversial changes in cardiovascular parameters in response to calorie restriction, which was found to be associated with contractile dysfunction and myocardial morphological damage.[5-8] Some researchers demonstrated that calorie restriction promoted ultrastructural injuries to cardiac myofibrils and changes in intracellular calcium handling; these responses were related to β-adrenergic system disorders and myocardial contractile dysfunction.[5,7,9] Other morphological changes included ventricular chamber dilation, cardiomyocyte necrosis, interstitial fibrosis and mitochondrial swelling.[10-12]

On the other hand, intermittent fasting (IF) intervention, a model of calorie restriction, was associated with few morphological changes and did not promote myocardial dysfunction after a period of 12 weeks compared to 50% calorie restriction.[11] In this dietary approach, food is available ad *libitum* at intervals alternating with fasting periods, each lasting 12 to 24 hours.[3,4] However, the effects of IF on the heart remain unknown. At the molecular level, the association of mitogen-activated protein kinases (MAPKs), important mediators of cardiac remodeling,[13] has not been studied in calorie restriction models. MAPKs include three main subtypes, extracellular signal-regulated kinase (ERK), c-Jun N-terminal

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kinase (JNK) and p38 kinase (p38K), which regulate the gene transcription of several messengers involved in survival, apoptosis, cell differentiation and cardiac remodeling.[13,14]

Regular exercise training is widely used as a procedure of health promotion and prevention of different cardiovascular conditions.[15,16] However, different experimental studies have reported controversial results, showing that exercise training intervention did not affect or even reduced myocardial performance.[8,9,17-19] Moreover, potential effects of treadmill training on cardiac remodeling in IF models have yet to be clarified. Therefore, the aim of this study was to analyze the influence of IF and exercise training on functional fitness and morphological and molecular parameters of myocardial remodeling. Our initial hypothesis is that exercise training increases functional fitness and attenuates myocardial remodeling induced by IF.

Methods

The experimental protocol was reviewed and approved by the Animal Ethics Committee of the Federal University of Mato Grosso do Sul (CEUA/UFMS; Protocol 615/2014), and was in accordance with the guidelines of the Brazilian Society of Animal Experimentation (COBEA).

Animals and Experimental Design

Male Wistar rats (*Rattus norvegicus albinus*; n=60), aged 30, obtained from the Animal Center of the Federal University of Mato Grosso do Sul (UFMS), Campo Grande/MS, Brazil, were used. The sample size was based on a previous study[16] and considered the probability of exercise refusal and/or escape instinct during the test.[20,21] The animals were randomly divided into four groups: control, intermittent fasting (IF), exercise training (ET) and exercise training plus intermittent fasting (ETI). The control and ET groups were fed daily (*ad libitum*) a standard commercial diet (Nuvilab®, Brazil), while IF and ETI received a similar dietary intervention every other day (intermittent fasting).

Besides nutritional support, animals of the ET and ETI groups were also submitted to a treadmill running protocol (Table 1), according to previous studies.[16,20] Five weekly exercise sessions of physical exercise were held and the experimental period lasted 12 weeks. The animals were kept in cages with two to three experimental units per box at an ambient temperature of 22±2 ºC, humidity of 55±5%, 12-hour light/dark cycle and free access to water.

Determination of Functional Fitness

Functional fitness was analyzed at the end of the experiment using a multistage incremental test, according to previous studies.[21,22] The test was started with a 5-minute warm-up at a speed of 5 m/min. After an interval of 1 min, each animal was submitted to progressive effort at an initial speed of 6 m/min, followed by increments of 3 m/min, lasting 3 min. The protocol was interrupted when the animal had reached exhaustion or when coordination between steps was difficult.[21]

For the evaluation of lactate levels, 25 μl of blood was collected from the animal's tail at rest and after each exercise stage. The blood samples were immediately transferred to Eppendorf tubes containing 50 μl of 1% sodium fluoride (NaF), refrigerated, and stored in a freezer (-20 °C) until the time of analysis. Lactate was measured in an YSI 150 Sport electrochemical analyzer (Yellow Springs Instruments®, Ohio, USA), with standard error of the measurement of ± 2%.

Table 1 – Description of the treadmill exercise protocol

Period	Speed (m/min)	Duration (min)
Week 1–3	10	40–60
Week 4–6	15	40
Week 7–9	18	35
Week 10–12	19	15–25

The results are reported in mmol/L. The anaerobic lactate threshold (LT) was determined by graphically plotting lactate concentrations during the test. The LT was determined from the time of linearity breaking as a function of load increase, obtained by visual inspection. Functional capacity was assessed by the speed at the lactate threshold (SLT), distance covered and blood lactate concentration at the lactate threshold (LacLT) and at exhaustion (LacE), determined during the exercise test. In addition, for a more detailed analysis of lactate kinetics, the relative variation (%) in lactate levels was also obtained from the LacLT and LacE values.

Metabolic Characterization

For analysis of glycemia, the animals were fasted for 8–12 hours and blood samples were collected from the caudal artery to measure glucose at baseline. Next, a 20% glucose solution (Glucose Monohydrate, Merck, São Paulo, Brazil) was administered intraperitoneally at a dosage of 2 g/kg. Blood glucose levels were then evaluated after 15, 30, 60, 90, 120 and 180 minutes.[7,10] Glucose was measured with an Accu-Chek Go glucose meter (Roche Diagnostic Brazil Ltda., São Paulo, Brazil).[23,24]

Nutritional Characterization

Nutritional characterization consisted of the measurement of food intake, calorie intake, and feed efficiency. Food intake was measured daily and calorie intake was calculated from food intake × energy density of the diet.[23] Body weight (BW) was measured once a week using a digital scale. BW gain was obtained as the difference between initial and final BW. To analyze the ability to convert ingested energy into BW, feed efficiency was calculated as the ratio between total BW variation (g) and total calorie intake (kcal).[23,24]

After the experimental period, the animals were fasted for 8 hours and anesthetized by intraperitoneal administration of ketamine hydrochloride (50 mg/kg; Dopalen®, Sespo Indústria e Comércio Ltda — Vetbrands Division, Jacareí/SP, Brazil) and xylazine hydrochloride (10 mg/kg; Anasedan®, Sespo Indústria e Comércio Ltda — Vetbrands Division, Jacareí/SP, Brazil). After euthanasia by decapitation, thoracotomy and median laparotomy were performed in order to remove heart and white adipose tissue from the retroperitoneal and

epididymal compartments.[24] The sum of the two adipose sites in absolute and relative values was considered for the determination of body adiposity.

Characterization of Cardiac Morphology

To assess macroscopic morphology, the atrial and left and right ventricular weights were measured in absolute values and compared to BW and tibia length. Samples of the left ventricle were obtained through a transverse incision 6 mm from the apex. The myocardial fragments were immersed in 10% buffered formaldehyde for 48 hours. Each tissue specimen was then rinsed under running water and stored in 70% ethanol solution for more 48 hours. After the fixation step, the specimens were embedded in paraffin blocks. Histological slides were prepared from 4–7 μm thick tissue cross-sections and stained with hematoxylin/eosin and picrosirius red. For the morphometric analysis of cardiomyocytes, the cardiomyocyte area and the myocardial interstitial collagen fraction were measured as described previously.[23-25]

Hematoxylin/eosin-stained slides were used for the measurement of cardiomyocyte area. At least 100 cardiomyocytes were sampled per animal. Picrosirius red-stained slides were used to determine interstitial collagen fraction. Once the image field was fixed, components of the cardiac tissue were identified according to the highlighted color. Collagen filaments appeared red, while cardiomyocytes appeared yellow. The interstitial collagen fraction corresponds to the percentage of collagen content throughout the tissue specimen. A minimum of 20 fields were used and perivascular regions were disregarded.

For myocardial morphometry, the histological sections were analyzed at a 40-fold magnification with a microscope (LEICA DM LS) coupled to a digital video camera on an IBM microcomputer, equipped with the image analyzer program Image Pro-plus (Media Cybernetics, Silver Spring, Maryland, USA).

Analysis of MAPK Expression

MAPK protein expression levels were determined using Western blot procedures and specific primary antibodies (Santa Cruz Biotechnology Inc., CA, USA): p-JNK (sc-6254), total JNK1/2 (sc -137019), p-ERK1/2 (sc-16982), total ERK 1 (sc-93). The protein levels obtained were normalized to the expression of GAPDH (6C5, sc-32233). The sample preparation methods and electrophoresis conditions have been described previously.[24,26]

Statistical Analysis

The Sigma-Stat software was used for data analysis. Firstly, the results were subjected to normality analysis by the Kolmogorov-Smirnov test. Since the variables had a parametric distribution, measures are presented as mean and standard-deviation and were analyzed using two-way analysis of variance (two-way ANOVA), complemented by the Student-Newman-Keuls comparison test. The cross-sectional area results of cardiomyocytes were divided into categories according to the measurement range using Sturges formula.[27] Absolute and relative proportions were analyzed using the Goodman multiple proportions test.[28] The level of significance was set at 5%.

Results

The results of the functional fitness exercise on a treadmill [total distance (m) and final speed (m/min)] are shown in Figure 1. Exercise groups ET and ETI achieved greater total distance and final speed than control and IF animals. Intermittent fasting did not affect functional fitness ($p>0.05$) (Figures 1A and 1B).

Regarding results of lactate measurements, exercise training exerted a statistically significant effect ($p=0.04$) on LacE (control and IF: 8.16±0.94; ET and ETI: 5.34±0.88 mmol×L^{-1}), without the occurrence of factor interaction. The LT was similar among groups (control: 2.51±1.18; IF: 3.90 ± 0.64; ET: 2.70±0.23; ETI: 3.04±1.33 mmol×L^{-1}). The variation in lactate levels between the inflection point and the end of the test was greater ($p=0.04$) in the sedentary groups (control and IF: 156±19; ET and ETI: 98±18%).

The areas under the glucose tolerance curve are shown in Figure 2. Considering the individual effect of dietary intervention (Figure 2A), intermittent fasting was associated with smaller areas of glycemic response. There were no significant differences in the individual effect of exercise training (Figure 2C). On the other hand, ETI animals showed a smaller area under the glucose curve than ET (Figure 2B). No differences were found for the other statistical comparisons.

With respect to nutritional variables, food consumption and caloric intake were lower in the IF and ETI groups compared to the respective controls. As individual factors, intermittent fasting and exercise training were associated with reduced energy efficiency and lower BW gain. Although BW gain was lower in the IF group compared to control, adiposity levels were similar between the groups (Table 2).

Analysis of cardiac morphology results showed that intermittent fasting *per se* was associated not only with lower atrial weight (0.063±0.002 vs. 0.053±0.002 g; $p=0.006$), but also with reduced left ventricle weight, in absolute terms (0.475±0.011 vs 0.420±0.011 mg; $p<0.001$) and compared to the tibia length. In addition, intermittent fasting reduced heart weight (0.677±0.013 vs. 0.597±0.013 g; $p<0.001$) (Table 2).

Descriptive measurements of myocardial morphometry are shown in Figure 3. The combination of intermittent fasting and exercise training resulted in a significantly smaller cellular area in the ETI group compared to the ET and IF groups (control: 248±46; IF: 255±21; PE: 260±30; PIF: 225±26 μm^2). Considering the frequency distribution of cardiomyocytes, most results were classified within the first two classes, delimited to 327.5 μm^2. However, the ETI group showed a higher proportion of fibers in the 1st class of values (up to 190.1 μm^2) compared to the other groups ($p<0.05$) (Figure 3B).

A statistically significant interaction between intermittent fasting and exercise training was obtained in the interstitial collagen fraction analysis ($p=0.01$). The fraction of interstitial

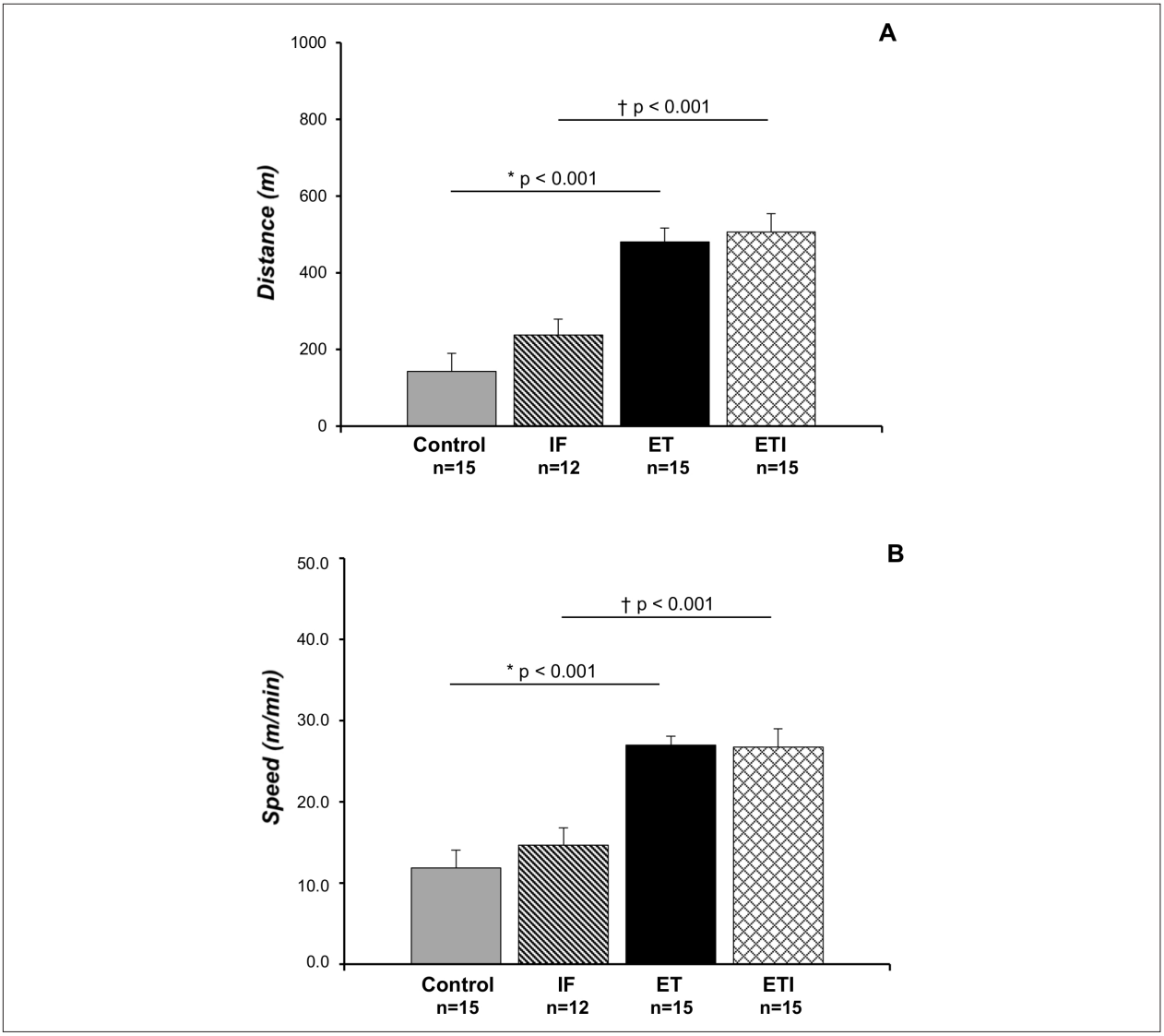

Figure 1 – *Functional fitness measurements expressed as mean ± standard error; (A) distance covered; (B) final speed; Control: sedentary rats receiving the control diet ad libitum; IF: sedentary rats undergoing intermittent fasting; ET: rats exercising and receiving the control diet ad libitum; ETI: rats exercising while intermittent fasting. * p<0.05 vs. control; † p<0.05 vs. IF (two-way ANOVA and Student-Newman-Keuls test).*

collagen was greater in the ET group compared to control (control: 5.32±1.02; IF: 5.25±0.66; ET: 7.31±2.94; ETI: 4.43±0.79%), while ETI exhibited a lower concentration of interstitial collagen than ET (Figure 4A-B).

Tables 3 shows the myocardial expression levels of MAPK-ERK and JNK. No differences were found in the expression of MAPK proteins between the groups (p>0.05).

Discussion

Restrictive dietary interventions are commonly used to reduce susceptibility to chronic diseases, such as obesity, type 2 diabetes, dyslipidemia, hypertension and cardiovascular diseases. In the present study, intermittent fasting was associated with higher food and energy intake on the days the diet was offered, as well as with lower total caloric intake and lower BW measurements. Higher food intake due to intermittent fasting can be explained by changes in satiety.[29,30]

The hypothalamus is an important regulator of body homeostasis and promotes several adjustments, including satiety induction. Changes in the lateral hypothalamus result in aphagia (starvation), whereas alterations in the medial hypothalamus are associated with hyperphagia (increased appetite). As observed here, other studies[11,29] have shown that intermittent fasting increases food intake during feeding days. Likewise, Dorighello et al.[31] demonstrated that intermittent restriction reduced total calorie intake, in agreement with our findings. The period of exercise training did not affect food or calorie intake in the ETI

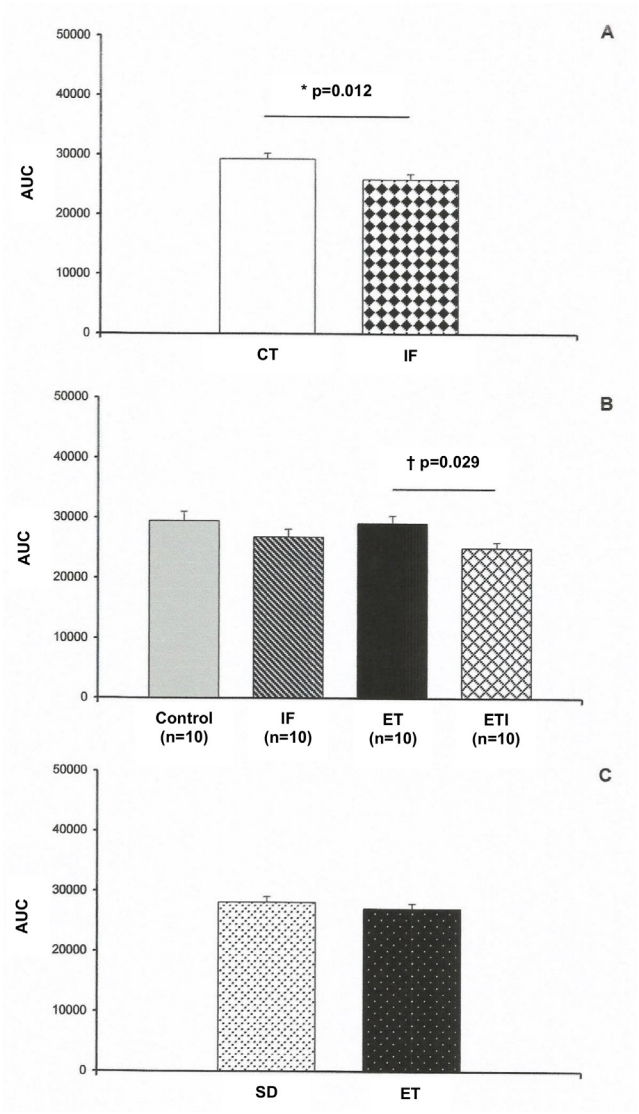

Figure 2 – *Area under the glucose tolerance curve (AUC), according to condition and dietary intervention. (A) Individual effect of intermittent fasting; CT: groups submitted to control diet; IF: groups submitted intermittent fasting; *p<0.05 vs. CT. (B) Combined effect. Control: sedentary rats receiving the control diet ad libitum; IF: sedentary rats undergoing intermittent fasting; ET: rats exercising and receiving the control diet ad libitum; ETI: rats exercising while intermittent fasting; † p<0.05 vs. ET. (C) Individual effect of physical exercise training. SD: sedentary groups; ET: exercised groups Two-way ANOVA and Student-Newman-Keuls test.*

group. Buthani et al.,[32] in a study on humans, showed that trained volunteers, even with increased hunger, did not exhibit a significant increase in food intake.

According to our initial hypothesis, exercise training on a treadmill attenuates metabolic disorders and cardiac remodeling induced by intermittent fasting. In addition to reducing energy efficiency, intermittent fasting modified glucose tolerance, which may be associated with better insulin sensitivity. The fact that insulin promotes lipogenic effects in the adipose tissue[33] may explain why the groups undergoing intermittent fasting did not show significant differences in body adiposity compared to the respective controls (Table 2). Insulin release increases in the presence of greater nutrient availability, such as during the postprandial period. Improvement in insulin sensitivity by adopting an intermittent fasting regime was also found in a recent study on mice.[34]

On the other hand, the combination of intermittent fasting and exercise training reduced body adiposity in the ETI group. Exercise training promotes cardiorespiratory, neural and hormonal adaptations and adjustments.[9,15,16] Within the endocrine context, hormone secretion is also altered by exercise. In the study by Evans et al.,[35] aerobic exercise for 12 months improved insulin sensitivity, with a 19.4% decrease in the area under the oral glucose tolerance curve in older adults. Therefore, the interaction between intermittent fasting and exercise training may have potentiated hormonal effects of insulin metabolism, as supported by the findings obtained for the ET and ETI groups.

Table 2 – Nutritional characteristics and cardiac morphology

	Characteristics	Group				Factor (p-value)		
		Control n=15	IF n=15	ET n=15	ETI n=15	Diet	Exercise	Interaction
Nutritional variables	FC (g/day)	23.30 ± 0.88	17.64 ± 1.00 *	22.88 ± 0.65	17.88 ± 0.77 ‡	<0.001	0.682	0.126
	CI (kcal/day)	84.81 ± 3.20	64.20 ± 3.63 *	83.23 ± 2.38	65.10 ± 2.80 ‡	<0.001	0.665	0.121
	TCI (kcal/day)	7124 ± 269	5393 ± 305 *	6980 ± 192	5468 ± 236 ‡	<0.001	0.602	0.100
	FE (kcal/g)	0.023 ± 0.005	0.019 ± 0.004 *	0.020 ± 0.004	0.017 ± 0.005	0.005	0.050	0.581
	BW (g)	395 ± 46	344 ± 37 *	374 ± 39	349 ± 30	<0.001	0.400	0.202
	BWV (%)	71.0 ± 17.8	42.8 ± 12.0 *	60.5 ± 15.2	37.4 ± 13.6 ‡	<0.001	0.043	0.498
	Adiposity (%)	2.11 ± 0.51	1.91 ± 0.77	1.89 ± 0.72	1.89 ± 0.79	0.584	0.508	0.578
Morphological variables	AW (g)	0.059 ± 0.012	0.052 ± 0.009	0.066 ± 0.013	0.055 ± 0.015 ‡	0.006	0.126	0.422
	RVW (g)	0.134 ± 0.017	0.118 ± 0.034	0.145 ± 0.040	0.130 ± 0.020	0.055	0.143	0.950
	LVW (g)	0.482 ± 0.066	0.404 ± 0.041 *	0.469 ± 0.060	0.436 ± 0.059	<0.001	0.509	0.138
	AW/BW (mg/g)	0.152 ± 0.030	0.152 ± 0.026	0.177 ± 0.036	0.155 ± 0.048	0.247	0.136	0.227
	RVW/BW (mg/g)	0.345 ± 0.033	0.346 ± 0.101	0.380 ± 0.076	0.368 ± 0.063	0.774	0.135	0.737
	LVW/BW (mg/g)	1.24 ± 0.14	1.18 ± 0.10	1.24 ± 0.09	1.23 ± 0.14	0.202	0.437	0.457
	AW/tibia (g/cm)	0.015 ± 0.003	0.013 ± 0.002	0.017 ± 0.003	0.014 ± 0.004 ‡	0.007	0.227	0.328
	RVW/tibia (g/cm)	0.034 ± 0.004	0.030 ± 0.009	0.036 ± 0.009	0.032 ± 0.004	0.065	0.246	0.982
	LVW/tibia (g/cm)	0.121 ± 0.015	0.104 ± 0.009 *	0.117 ± 0.015	0.109 ± 0.015	<0.001	0.892	0.170
	Heart weight (g)	0.674 ± 0.083	0.574 ± 0.063 *	0.680 ± 0.086	0.621 ± 0.058 ‡	<0.001	0.172	0.292

*FC: daily food consumption; CI; daily calorie intake; TCI: total calorie intake; FE: feed efficiency; BW: body weight; BWV: body weight variation; AW: atrial weight; RVW: right ventricle weight; LVW: left ventricle weight; AW/BW: atrial-body weight ratio; RVW/BW: right ventricle-body weight ratio; LVW/BW: left ventricle-body weight ratio; AW/tibia: atrial weight-tibia length ratio; RVW/tibia: right ventricle weight-tibia length ratio; LVW/Tibia: left ventricle weight-tibia length ratio; * p<0.05 vs. Control; ‡ p<0.05 vs. ET (two-way ANOVA and Student-Newman-Keuls test).*

Despite glycemic effects, intermittent fasting did not alter functional fitness. Lactate measurement is one of the parameters most used to estimate aerobic capacity and has been effective to describe functional fitness.[22] The lactate threshold can be defined as the exercise intensity at which the blood lactate concentration suddenly increases.[21,22] In this respect, the running protocol improved functional fitness in the ET and ETI groups, which was supported by lower final lactate values (LacE), less variation in lactate levels and higher speed and distance covered during the final test. Therefore, exercise training was associated with improved aerobic fitness, as previously demonstrated.[16]

Regarding cardiovascular features, exercise training promoted myocardial interstitial remodeling. Intriguingly, intermittent fasting attenuated these exercise-induced effects, as demonstrated by lower values of tissue macro- and microscopic morphometry in the ETI group. Multiple factors stimulate myocardial remodeling, such as nutritional disorders, angiotensin, aldosterone, endothelin, inflammatory cytokines and catecholamines.[36] Morphological and functional changes occur in response to prolonged exercise training in order to improve cardiac performance, including the blood volume pumped and oxygen supply to peripheral muscles recruited during exercise.[21,22] These adaptive alterations induced by exercise training include left ventricular hypertrophy to compensate for hemodynamic demand and interstitial fibrosis.[36,37] Within this context, increased interstitial collagen found in the ETI group may be an indicator of the physiological ventricular remodeling process, although no myocardial hypertrophy was observed. Indeed, some factors can restrict the accuracy of microscopic morphometry, such as tissue sectioning angle and the heterogeneous contractile state of cardiac fibers.[38] These factors may have contributed to the lack of detection of cardiac hypertrophy induced by exercise training.

Intermittent fasting resulted in lower values of macro and microscopic morphology, which were not associated with changes of MAPK protein expression. The phenotypic changes induced by these peptides involve protein synthesis and cell growth, triggering hypertrophy and interstitial fibrosis, which may be associated with myocardial remodeling.[13,14] In addition, MAPK activation is also subordinated to the action of multiple growth factors, such as growth hormone and insulin,[24,33] whose secretion is regulated by nutritional behavior. However, it was not possible to verify association between intermittent fasting and changes in MAPK

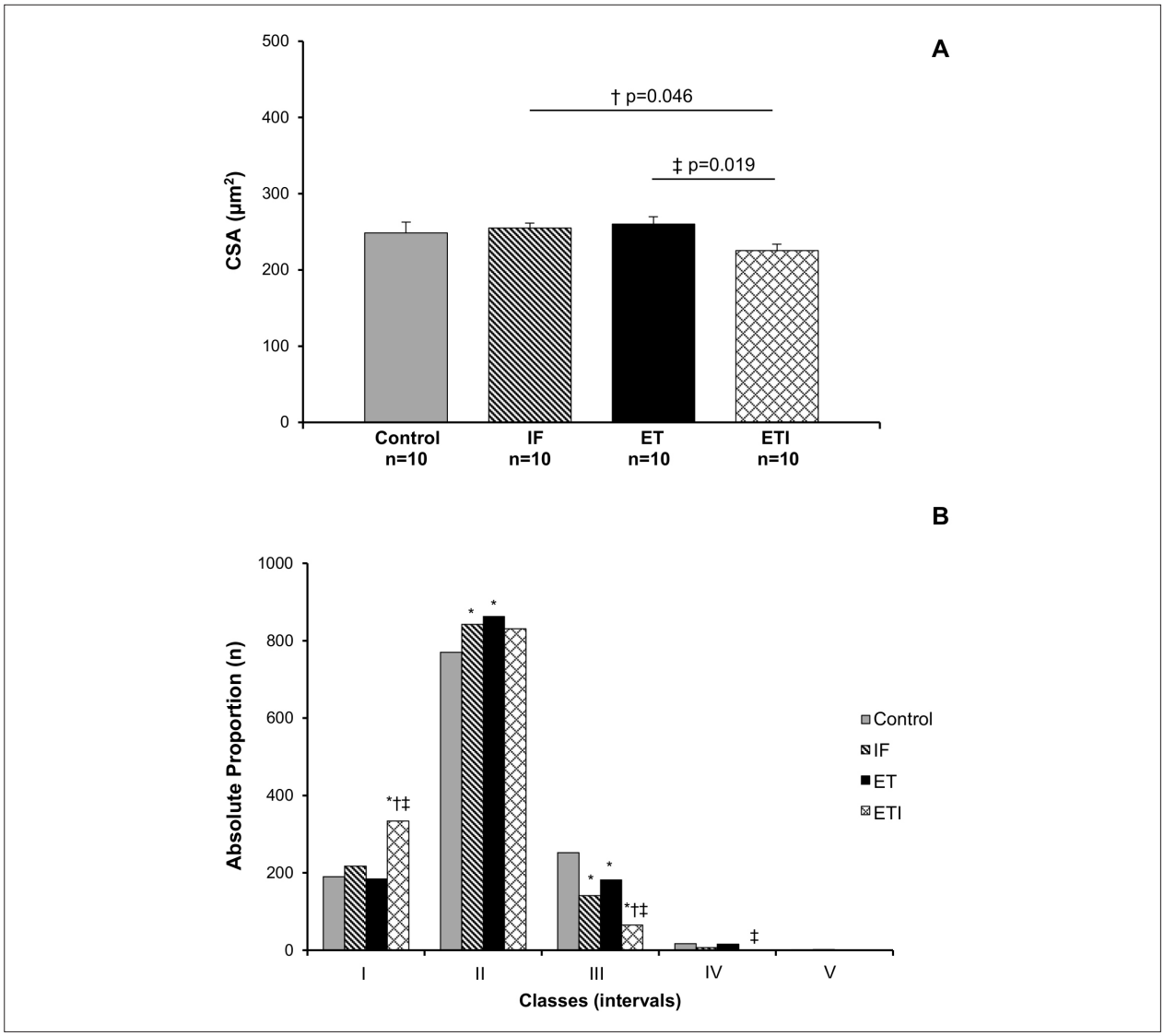

Figure 3 – *(A) Cross-sectional area of the cardiomyocytes (CSA); † p<0.05 versus IF; ‡ p<0.05 vs. ET. Two-way ANOVA and Student-Newman-Keuls test. (B) Frequency distribution of cardiomyocytes according to CSA class. Classes: I (52.7┤ 190.1 µm²), II (190.1┤ 327.6 µm²), III (327.6┤ 465.0 µm²), IV (465.0┤ 602.4 µm²) and V (602.4┤ 739.9 µm²); * p<0.05 vs. Control; † p<0.05 vs. IF; ‡ p<0.05 vs. ET. Goodman test for contrasts within and between multinomial populations. Control, sedentary rats receiving the control diet ad libitum; IF: sedentary rats undergoing intermittent fasting; ET: rats exercising and receiving the control diet ad libitum; ETI: rats exercising while intermittent fasting.*

Table 3 – Protein levels of MAPK isoforms in myocardial tissue

Protein	Group			
	Control n=6	IF n=6	ET n=6	ETI n=6
p-ERK/ERK	1.00 ± 0.52	1.42 ± 1.59	1.08 ± 0.48	1.23 ± 0.78
p-ERK/GAPDH	1.00 ± 0.47	1.18 ± 1.19	0.87 ± 0.41	0.86 ± 0.32
ERK/GAPDH	1.00 ± 0.10	0.99 ± 0.23	0.91 ± 0.16	0.91 ± 0.22
p-JNK/JNK	1.00 ± 0.39	1.00 ± 0.35	1.09 ± 0.61	1.03 ± 0.40
p-JNK/GAPDH	1.00 ± 0.13	1.11 ± 0.26	1.10 ± 0.35	1.15 ± 0.23
JNK/GAPDH	1.00 ± 0.46	1.04 ± 0.42	0.94 ± 0.31	0.96 ± 0.32

Values expressed as mean ± standard deviation. ERK: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase. Two-Way ANOVA (p>0.05).

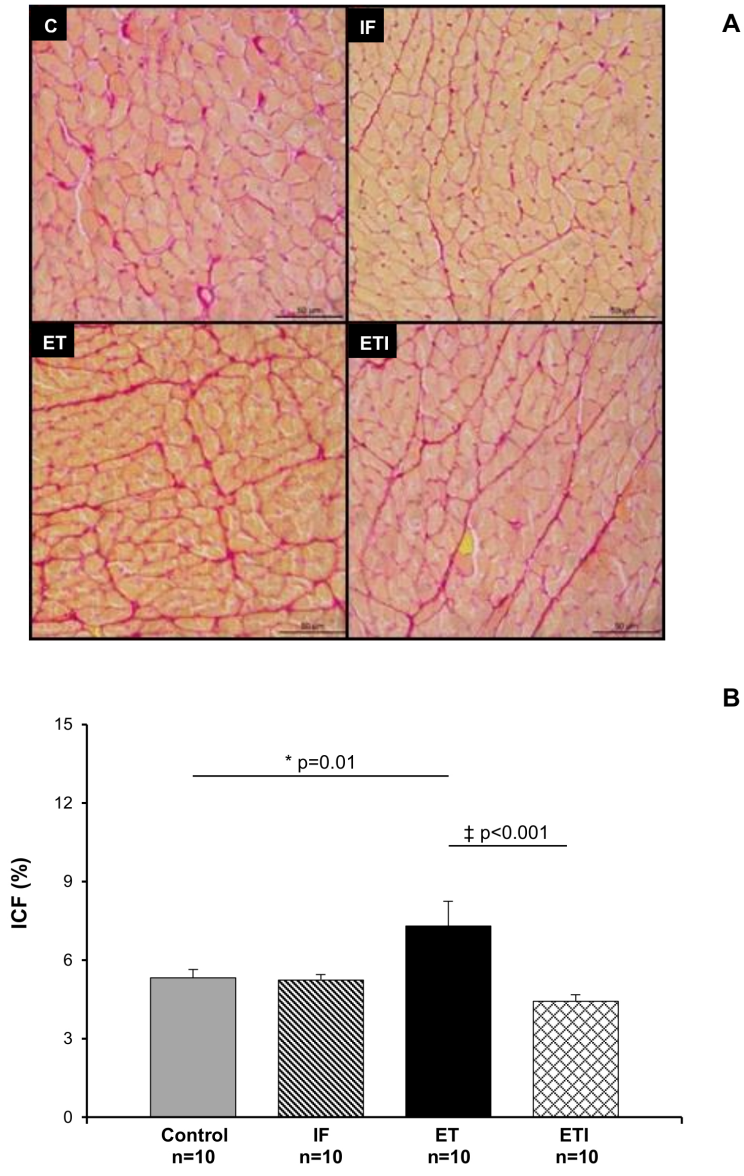

Figure 4 – *(A) Myocardial cross-sections stained with picrosirius red according to group. Control (C), sedentary rats receiving the control diet ad libitum; IF, sedentary rats undergoing intermittent fasting; ET: rats exercising and receiving the control diet ad libitum; ETI: rats exercising while intermittent fasting. (B) Interstitial collagen fraction (ICF); * p<0.05 vs. Control; ‡ p<0.05 vs. ET. Two-way ANOVA and Student-Newman-Keuls test.*

protein expression. In a previous study,[39] intermittent fasting attenuated cardiac hypertrophy and ventricular dilation in infarcted rats, although it did not alter the gene expression of fetal peptides.

The present findings provide evidence of cardiac remodeling induced by exercise training, which was attenuated by intermittent fasting. However, it is not possible to confirm whether the potential effect of dietary restriction is able to reverse pathological processes, such as arterial hypertension and acute myocardial infarction. Likewise, the impact of other experimental models, such as 25 and 50% calorie restriction,[5,7-9] should be further investigated in future studies because they add limitations to the clinical outcomes of the present investigation.

Conclusion

The combination of intermittent fasting and exercise training intervention is associated with improved glucose tolerance. Exercise training alone promotes myocardial interstitial remodeling, which is attenuated by intermittent fasting.

Author Contributions

Conception and design of the research: Basilio PG, Oliveira-Junior SA; Data acquisition: Basilio PG, Oliveira APC, Castro ACF, Carvalho MR, Zagatto AM, Martinez PF, Ota GE; Analysis and interpretation of the data: Zagatto AM, Martinez PF, Okoshi MP, Okoshi K, Reis FA, Oliveira-Junior SA; Statistical analysis: Okoshi K, Oliveira-Junior SA; Obtaining financing: Oliveira-Junior SA; Writing of the manuscript: Basilio PG, Oliveira-Junior SA; Critical revision of the manuscript for intellectual content: Zagatto AM, Martinez PF, Okoshi MP, Okoshi K, Reis FA.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

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Study Association

This article is related to the thesis of master submitted by Priscilla Gois Basílio, from Universidade Federal do Mato Grosso do Sul.

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Intermittent Diet in Exercise-Induced Cardiac Remodeling

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Short Editorial related to the article: Intermittent Fasting Attenuates Exercise Training-Induced Cardiac Remodeling

The article entitled "Intermittent diet regulates physical exercise induced cardiac remodeling" presents relevant information concerning the effects of physical exercise (PE) on cardiac remodeling, functional capacity, nutritional behavior, and glycemic metabolism. The authors also analyzed the expression of proteins related to cellular differentiation and cardiac remodeling, such as extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), to determine the possible molecular mechanisms associated with the effects of intermittent diet and PE. The main findings were that: (1) PE increased functional capacity when isolated or combined with an intermittent diet, (2) prescription of an intermittent diet increased glycemic tolerance during PE programs, (3) intermittent diet was able to reduce cardiac remodeling induced by PE.[1]

It is worth highlighting that this study used an experimental model from *Wistar* rats to mimic an intermittent diet during a long-term PE program (12 weeks).[1] The advantage of animal experiments involving nutritional and physical interventions is the possibility of controlling the confounding variables that can affect the internal validity of the study, such as food intake, lifestyle, and motivation for physical training. In addition, animal models allow for the analysis of morphological, functional, and molecular aspects of cardiac muscle, which enables a more in-depth study of the mechanisms related to the diverse treatments and physical and nutritional interventions. Therefore, the results of this study are highly consistent and relevant for the understanding and improvement of prescribed PE programs, whether when isolated or associated with intermittent diet. The study also reveals a new path for research involving the effects of PE on functional and morphological aspects of cardiac remodeling, and the role intermittent diet in modulating these effects.[1]

Researches aiming to understanding the beneficial effects of isolated PE or the combination of PE with nutritional strategies are fundamental for the prevention and treatment of cardiovascular diseases. This topic has received special attention in recent years, as the World Health Organization indicated approximately 17.2 million deaths from cardiovascular diseases each year, which indicates an important public health issue due to its high costs with treatment and hospital admissions.[2] Risk factor control and the maintenance of healthy lifestyle habits are essential for the prevention and attenuation of cardiovascular complications, highlighting the relevance of studies focusing on PE and nutrition.

In this context, non-pharmacological interventions involving PE and intermittent diet have been advocated for decades to prevent and treat cardiovascular diseases. The benefits of these strategies include improved quality of life, body composition, and cholesterol and triglyceride levels, as well as the prevention of hypertension and atherosclerosis.[3,4] The positive impacts of the combination of an intermittent diet and PE in several health conditions have been shown in experimental and clinical researches.[5-7] However, most studies have evaluated the effects of PE and intermittent diet separately. Thus, the effects of a combination of these treatments are still not completely clear.

A recent study demonstrated the important role of intermittent diet on the reduction of body weight, blood glucose levels, and glycated hemoglobin levels, as well as increasing insulin sensitivity in obese mice.[8] Similarly, aerobic exercise has also been shown to increase muscle expression of glucose transporter type 4 (GLUT-4) in 20 to 70%, both in humans and rodents. This contributes to improving insulin sensitivity and glycemic control.[9] Therefore, it is likely that the combination of PE and intermittent diet could be a more powerful strategy to improve glycemic metabolism. This hypothesis is supported by a recent study that reported greater effects of PE combined with moderate caloric restriction than isolated PE on functional capacity, levels of fatigue and disability, and glycemic control in obese elderly individuals.[10] Similarly, in the article by de Basilio et al.[1] verified improved functional capacity and glycemic metabolism in rats that were submitted to isolated PE or combined with an intermittent diet. These findings reinforce the health benefits from isolated PE and its combination with a caloric-restricted.[1]

Studies aiming to investigate the cellular and molecular mechanisms involved in cardiac remodeling in response to PE and caloric restriction are fundamental to the understanding and application of these strategies in preventive programs and cardiovascular function rehabilitation. The study de Basilio et al.[1] highlights the important evaluation of some mitogen-activated protein kinase (MAPK).[1] Despite not being evaluated in this study, p38 MAPK is one of the most important proteins in the MAPK pathway due to its activity in response to stimuli

Keywords

Intermittent Diet; Heart; Exercise.

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like PE. It can modulate the function of cardiac fibroblasts, extracellular matrix turnover, and paracrine induction of cardiomyocyte hypertrophy.[11] Therefore, future studies are needed to confirm the role of p38 MAPK in cardiac remodeling induced by PE and an influence of intermittent diet.

Myocardial remodeling is regulated through a combination of responses from cardiomyocytes, other cell types, and various mechanosensitive pathways, which can modify the genetic expression and protein synthesis, which cause the functional modifications in the cells.[12] Mechanosensitive stimuli like PE affect cardiomyocytes and fibroblasts leading to alterations in genetic expression and cellular remodeling. Studies have shown the importance of integrins, angiotensin II, calcium, and transforming growth factor beta (TGF-β) regulating the mitogen-activated protein kinase (MAPK) pathway with fibroblasts activation and increased cardiac fibrosis.[12,13]

The effects of caloric restriction on cardiac remodeling have been extensively investigated in animal models with cardiac alterations. It has been demonstrated an improvement in cardiac dysfunction and chronotropic reserves, and regarding molecular aspects, an improvement in sympathetic cardiac innervation and levels of β-adrenergic receptors in rats with myocardial infarction-induced heart failure submitted to intermittent diet.[14] Another study showed that fasting/refeeding cycles resulted in beneficial cardiac effects and reduced myocardial damage due to the caloric restriction in spontaneously hypertensive rats, contributing to reduced cardiovascular risks and morphological damage. In addition, fasting/ refeeding cycles led to slight improvements in the transit of Ca^{2+} and the beta-adrenergic system.[15] Although the study de Basilio et al.[1] did not aim to investigate the effects of isolated PE or combined with caloric restriction diet on Ca^{2+} transport markers, it shows possibilities for future researches on molecular adaptations related to cardiac remodeling induced by PE.[1] We emphasize the importance of testing the findings of this study in other populations associated with health and disease, including groups with overweight, obese, and diabetic subjects such conditions are related to changes in glycemic metabolism.

In conclusion, it is worth highlighting that the article,[1] demonstrates valuable information concerning the effects of isolated PE and the combination of PE with an intermittent diet on morphological and metabolic aspects involved in cardiac remodeling, such contributes to the understanding and enhancement of prevention programs and cardiac rehabilitation.

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Short Editorial

Discrepancy between International Guidelines on the Criteria for Primary Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

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Abstract

Background: **Risk stratification for sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM) is based on different algorithms proposed by the 2011 ACCF/AHA and 2014 ESC guidelines.**

Objective: **To analyze the 2014 ESC model for SCD risk stratification and primary prevention ICD (implantable cardioverter defibrillator) in HCM in comparison to the North American guideline.**

Methods: **An HCM cohort was evaluated and the ESC HCM-Risk SCD score was calculated. Agreement of ICD recommendations criteria between the two guidelines was analyzed with Kappa coefficient. P<0.05 was adopted for the statistical analysis.**

Results: **In 90 consecutive patients followed for 6±3 years, the mean calculated ESC risk score was 3.2±2.5%. The risk predictors that have mainly contributed to the score calculation in the low (1.88% [1.42–2.67]), intermediate (5.17% [4.89–5.70]) and high-risk (7.82% [7.06–9.19]) categories were: maximal left ventricular wall thickness (1.60% [1.25–2.02]; 3.20% [3.18–3.36]; 4.46% [4.07–5.09]), left atrial diameter (0.97% [0.83–1.21]; 1.86% [1.67-2.40]; 2.48% [2.21–3.51]) and age (-0.91% [0.8–1.13]; -1.90% [1.12–2.03]; -2.34% [1.49–2.73]). The European model decreased the ICD recommendations in 32 (36%) patients. Among the 43 (48%) individuals with class IIa recommendation under the 2011 ACCF/AHA guideline, 8 (18%) were downgraded to class IIb and 24 (56%) to class III. Low agreement was found between the two systems: Kappa=0.355 and p=0.0001. In 8 (9%) patients with SCD or appropriate shock, 4 (50%) met class IIa indication with the 2011 ACCF/AHA guideline, but none achieved this class of recommendation with the 2014 ESC model.**

Conclusion: **Low agreement was found between the two strategies. The novel ESC model decreased the ICD recommendations, especially in those with class IIa recommendation, but left unprotected all patients with SCD or appropriate shock. (Arq Bras Cardiol. 2020; 115(2):197-204)**

Keywords: **Cardiomyopathy,Hypertrophic/genetics; Heredity; Death,Sudden, Cardiac; Arrhythmias, Cardiac; Syncope; Defibrillators,Implantable; Cohort Studies**

Introduction

Hypertrophic cardiomyopathy (HCM) represents the most prevalent form of genetic heart disease, affecting one in 200 individuals.[1] Sudden cardiac death (SCD), presently estimated at 0.5 to 1%/year, occurs at any age, although it predominates in young subjects and athletes.[2-4]

The risk stratification for SCD is the basis for the recommendation of implantable cardioverter defibrillator (ICD) in HCM, the only approach considered to be able to modify the disease prognosis.[4-7] There is a consensus about the recommendation in patients with prior cardiac arrest. However, many questions persist regarding primary prevention. Five risk factors identified in longitudinal studies and validated in meta-analyses are recognized as independent predictors of SCD: family history, unexplained syncope, maximal left ventricular wall thickness (MLVWT) ≥30 mm, non-sustained ventricular tachycardia (NSVT) and abnormal blood pressure response to exercise.[5-13] In the 2003 American College of Cardiology (ACC)/ European Society of Cardiology (ESC) Consensus, the ICD recommendation was based on the number of risk markers.[14] The criteria were updated in the 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline, in which modifying factors were included: malignant mutations, late gadolinium enhancement, left ventricular (LV) apical aneurysms and outflow tract obstruction.[15] A novel mathematical and statistical prediction model endorsed by ESC in 2014 and accessible with an online calculator provides an estimate of the absolute risk and five-year mortality rate, applying

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different weights to the former five independent predictors mentioned above, in addition to LV outflow gradient, left atrial diameter and age.[16,17]

The purpose of the study is to analyze the impact of the 2014 ESC model on the SCD risk stratification and the recommendations of ICD primary prevention compared to the previously proposed 2011 ACCF/AHA criteria.

Methods

Patient selection

A cohort of 108 subjects followed at a dedicated HCM outpatient clinic of a tertiary center from March 2007 to March 2018 was retrospectively studied. All patients were submitted to rest electrocardiogram, 24-hour Holter electrocardiogram and echocardiogram. Cardiac magnetic resonance (CMR) imaging was applied to 40 (45%) subjects. Molecular-genetic testing was performed in 18 (20%) patients, whose results were previously published.[18] Diagnosis was established according to the current guidelines[15,17] based on the identification of unexplained LV hypertrophy detected on echocardiogram and/or magnetic resonance imaging by the presence of MLVWT ≥15 mm measured at any segment, with septum/posterior wall ratio ≥1.3 in the absence of chamber dilation or other conditions capable of producing a similar pattern of hypertrophy. Eighteen cases were excluded due to a follow-up period <12 months or previous history of cardiopulmonary arrest, ventricular fibrillation or ventricular tachycardia with hemodynamic impairment. The following outcomes were considered for the analysis: 1. Sudden cardiac death: documented ventricular fibrillation, death one hour from the onset of symptoms or at night without previous clinical worsening; 2. Appropriate ICD shock for ventricular tachycardia or ventricular fibrillation. The study was approved by the Ethics Committee of the institution and performed under the principles of the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Risk stratification for sudden cardiac death

The following predictors were assessed: 1. Age; 2. Family history of SCD in first-degree relatives, <40 years old or at any age with previous diagnosis of the disease; 2. MLVWT measured on echocardiogram; 4. Unexplained syncope within the past 6 months; 5. NSVT defined as three or more successive premature ventricular beats at a heart rate ≥120 beats/min lasting ≤30 s; 6. Abnormal blood pressure response to exercise defined as <25 mmHg rise and/or 10 mmHg drop of maximal systolic blood pressure during peak exercise; 7. Left atrial diameter obtained on M-mode or two-dimensional echocardiogram; 8. Maximum left ventricular outflow tract (LVOT) gradient at rest or with Valsalva maneuver using continuous wave Doppler. The following risk modifiers were considered: 1. LVOT gradient ≥ 30 mmHg; 2. Late gadolinium enhancement on CMR; 3. LV apical aneurysm; 4. Malignant genetic mutations.

The probability of SCD in 5 years was calculated with the ESC HCM-Risk SCD equation as follows:

Probability of SCD in 5 years = $1 - 0.998^{\exp(\text{Prognostic index})}$

Prognostic index = [0.15939858 x maximal wall thickness (mm)] - [0.00294271 x maximal wall thickness^2 (mm^2)] + [0.0259082 x left atrial diameter (mm)] + [0.00446131 x maximal (rest/Valsalva) LVOT gradient (mm Hg)] + [0.4583082 x family history SCD] + [0.82639195 x NSVT] + [0.71650361 x unexplained syncope] - [0.01799934 x age at clinical evaluation (years)].

Recommendations of implantable cardioverter defibrillator therapy

The following criteria for primary prevention ICD were compared:

1. 2011 ACCF/AHA guideline: Class IIa - A family history of SCD in a first-degree relative or MLVWT ≥ 30 mm or unexplained syncope. Class IIa - NSVT or abnormal blood pressure response to exercise associated with other risk factors or modifiers; Class IIb: Isolated NSVT or abnormal blood pressure response to exercise; Class III – absence of the previously mentioned risk factors.

2. 2014 ESC guideline: Class IIa – HCM Risk-SCD ≥6%; Class IIb - <6% and ≥4%; Class III - <4%.

Statistical analysis

Normally distributed continuous variables were expressed as mean±standard deviation and non-normally distributed data presented as median and interquartile ranges (percentile 25 and 85). Continuous variables were tested for normality using the Shapiro-Wilk test. Categorical variables were described as absolute and relative frequencies. Continuous variables were compared with Student's *t* test or one-way analysis of variance (ANOVA), categorical variables with chi-square or Fisher's exact test and differences among categories with standardized adjusted residual analysis. The Kappa coefficient was calculated to determine the agreement between the 2011 ACCF/AHA and the 2014 ESC guidelines for primary prevention ICD. The percentages achieved by each of the risk predictors included in the ESC HCM Risk-SCD score were calculated with the weighted average of the variation of each predictor in the equation over the sum of the variations of these predictors. The estimated survival of the sample was determined using the Kaplan-Meier curve. The sample size was estimated at 70 individuals for an expected Kappa=0.3, considering the occurrence of agreement between the guidelines, Kappa=0 for 90% power and $p<0.05$. SPSS software version 20.0 (SPSS Inc., Chicago, Illinois, USA) was used for the analyses. All comparisons were two-tailed and $p<0.05$ was considered to be statistically significant.

Results

Clinical characteristics

The study population comprised 90 consecutive patients with HCM, mean age 62±12 years, 85 (94%) ≥40 years and 56 (62%) females. The clinical characteristics of the study patients are described in table 1. Along the follow-up period of

6±3 years, 15 (17%) patients received an ICD for SCD primary prevention. Two (2%) patients experienced appropriate shock, 6 (7%) experienced SCD and 6 (7%) had death unrelated to HCM (Table 2).

Five and ten-year SCD or ICD appropriate shock free survival rates were 93% and 92%, respectively, in the period. Five and ten-year all-cause death-free survival in five and ten years was 80%.

ESC HCM risk-SCD score for sudden cardiac death risk stratification

The mean calculated ESC HCM risk-SCD was 3.2±2.5% in the sample and it was estimated as low (<4%) in 67 (75%) patients, intermediate (≥4%–<6%) in 11 (12%) and high (>6%) in 12 (13%). The comparative analysis of SCD markers adopted in the two guidelines between the three risk ranges showed that NSVT [3 (4%) vs. 6 (54%) vs. 8 (67%), p=0.0001], syncope [6 (9%) vs. 3 (27%) vs. 7 (58%), p=0.0001] and increased MLVWT (17±3mm vs. 21±2mm vs. 21±8 mm, p=0.002) were predominant in higher risk. The other predictors do not differ between the groups (Table 3). SCD or appropriate ICD shock rates were similar between low, medium and high-risk patients [6 (8.8%) vs. 2 (18.2%) vs. 0 (0%), p=0.22].

Table 4 presents the percentages achieved by each of the variables included in the ESC HCM Risk-SCD score in the three risk categories. The risk factors that have mainly contributed to the score calculation in the low, intermediate and high-risk levels were MLVWT, left atrial diameter and age. LVOT obstruction, family history of SCD, NSVT and syncope reached lower weights.

Comparison between the 2011 American College of Cardiology Foundation/American Heart Association and the 2014 European Society of Cardiology guidelines

According to the 2011 ACCF/AHA criteria, 43 (48%) patients received class IIa recommendation for ICD, 3 (3%) class IIb and 44 (49%) class III. In the 2014 ESC guideline, 12 (14%) patients received class IIa recommendation for ICD therapy, 11 (12%) class IIb, and 67 (74%) class III. Comparison of the classes of ICD recommendations showed low agreement (Kappa=0.355, p=0.0001) between the two guidelines. The ESC HCM risk-SCD score decreased the ICD recommendations in 32 (36%) patients, maintained in 57 (63%) and provided an additional recommendation in only one (1%). Of the 43 (48%) individuals with class IIa recommendation under the 2011 ACCF/AHA guideline, the ESC risk score decreased the class of recommendation for ICD therapy in 32 (74%) patients, 8 (18%) for class IIb and 24 (56%) for class III. Only 11 (26%) remained in class IIa recommendation. Of the 44 (49%) patients in class III with the 2011 ACCF/AHA guideline, the European model determined an ICD unwarranted in 43 (98%) (Table 5). Figure 1 shows the study summary and its main findings.

The mean calculated ESC risk score was 3±1.7% in the 8 (9%) patients experiencing SCD or appropriate shock. Four (50%) had class IIa recommendation for device implantation with the 2011 ACCF/AHA guideline, but none achieved this class of recommendation with the 2014 ESC model, although 2 (25%) remained in class IIb.

The combination of risk factors that received class IIa recommendation with the 2011 ACCF/AHA strategy was associated with a downgrade in ICD recommendation with

Table 1 – Clinical characteristics of 90 patients with hypertrophic cardiomyopathy

Age (years)	**62±12**
Age >40 years (n, %)	85 (94%)
Female sex (n, %)	56 (62%)
NYHA functional class	
I/II (n, %)	75 (83%)
III/IV (n, %)	15 (17%)
Coronary artery disease (n, %)	11 (12%)
Treatment	
Betablockers (n, %)	70 (78%)
Amiodarone (n, %)	20 (22%)
Verapamil/diltiazem (n, %)	24 (27%)
Echocardiogram	
LA diameter (mm)	44±7
LV diastolic diameter (mm)	43±6
LV systolic diameter (mm)	34±5
Septal diastolic thickness (mm)	19±4
LV posterior wall diastolic thickness (mm)	11±2
Ejection fraction (%)	71±9
E/E´	16±8
LVOT gradient at rest (mmHg)	28±31
LVOT gradient with Valsalva maneuver (mmHg)	36±38
SCD risk factors	
Family history of SCD*	23 (26%)
NSVT*	17 (19%)
Syncope*	16 (18%)
Abnormal BP response to exercise *	9 (10%)
MLVWT >30 mm*	1 (1%)
LVOT gradient ≥30 mmHg †	44 (49%)
LGE on CMR†	11 (12%)
LV apical aneurysm†	0
Malignant mutation†	0
Number of SCD risk factors	
0	42 (47%)
1	32 (35%)
≥2	16 (18%)

**Independent predictors †Modifying factors; NYHA: New York Heart Association; LA: left atrium; LV: left ventricle; LVOT: left ventricular outflow tract; SCD: sudden cardiac death; NSVT: non-sustained ventricular tachycardia; BP: blood pressure; MLVWT: left ventricle maximal wall thickness; LGE: late gadolinium enhancement; CMR; cardiac magnetic resonance.*

Table 2 – Cardiovascular outcomes in 90 patients with hypertrophic cardiomyopathy patients during a 6±3-year follow-up

Heart failure class III/IV	20 (22%)
Atrial fibrillation (n, %)	29 (32%)
Alcohol septal ablation (n, %)	9 (10%)
Surgical myectomy (n, %)	3 (3%)
Dual-chamber pacemaker (n, %)	6 (7%)
ICD implantation (n, %)	15 (17%)
Appropriate ICD shock (n, %)	2 (2%)
Sudden cardiac death (n, %)	6 (7%)
HCM non-related death (n, %)	6 (7%)

ICD: implantable cardioverter defibrillator; HC:= hypertrophic cardiomyopathy.

Table 3 – Distribution of sudden cardiac death predictors in the three risk categories of the 2014 European Society of Cardiology guideline

	ESC HCM Risk-SCD score			p
	<4%	≥4%-<6	≥6%	
	(n=67;75%)	(n=11;12%)	(n=12;13%)	
Age (years)	64±11	60±17	57±13	0.156
Family history of SCD	14(21%)	4(36%)	5(42%)	0.177
Syncope	6(9%)	3(27%)	7(58%)	0.0001
MLVWT ≥30 mm	0	0	1	0.264
NSVT	3(4%)	6(54%)	8(67%)	0.0001
Abnormal BP response to exercise	8(12%)	0	1(8%)	0.595
LGE on CMR	8(12%)	1(9%)	2(17%)	0.822
LVOT ≥30 mmHg	31(46%)	7 (64%)	6(50%)	0.649
Left atrial diameter (mm)	46±7	48±9	48±8	0.545
MLVWT (mm)	17±3	21±2	21±8	0.002
Maximal LVOT gradient (mmHg)	33±42	45±39	40±44	0.77

SCD: sudden cardiac death, MLVWT: maximal left ventricular wall thickness; NSVT: non-sustained ventricular tachycardia; BP: blood pressure; LGE: late gadolinium enhancement; CMR; cardiac magnetic resonance; LVOT: left ventricular outflow tract.

Table 4 – Contribution of sudden cardiac death risk predictors for the ESC HCM Risk-SCD score calculation

	Low risk		Intermediate risk		High risk	
	<4%		≥4% - <6%		≥ 6%	
	Median	p25 - p75	Median	p25 - p75	Median	p25 - p75
ESC HCM Risk-SCD	1.88%	1.42-2.67	5.17%	4.89-5.70	7.82%	7.06-9.19
MLVWT	1.60%	1.25-2.02	3.20%	3.18-3.36	4.46%	4.07-5.09
Left atrial diameter	0.97%	0.83-1.21	1.86%	1.67-2.40	2.48%	2.21-3.51
LVOT gradient	0.03%	0.01-0.24	0.34%	0.15-0.61	0.35%	0.02-1.00
Family history of SCD	0.00%	0.00-0.00	0.00%	0.00-0.70	0.00%	0.00-0.99
NSVT	0.00%	0.00-0.00	1.14%	0.00-1.30	1.64%	0.00-1.96
Syncope	0.00%	0.00-0.00	0.00%	0.00-1.09	1.41%	0.00-1.59
Age	-0.91%	0.8 - 1.13	-1.90%	1.12-2.03	-2.34%	1.49-2.73

ESC: European Society of Cardiology; MLVWT: maximal left ventricular wall thickness; LVOT: left ventricular outflow tract; SCD: sudden cardiac death; NSVT: non-sustained ventricular tachycardia.

Table 5 – Comparison of implantable cardioverter defibrillator recommendations between the 2011 American College of Cardiology Foundation/American Heart Association and the 2014 European Society of Cardiology guidelines

			2014 ESC		
			IIa	IIb	III
		n (%)	12 (14%)	11 (12%)	67 (74%)
2011 ACCF/AHA	IIa	43(48%)	11(26%)	8(18%)	24(56%)
	IIb	3(3%)	0	3(100%)	0
	III	44(49%)	1(2%)	0	43(98%)
			Kappa=0.355, P=0.0001		

ACCF/AHA: American College of Cardiology Foundation/American Heart Association; ESC: European Society of Cardiology.

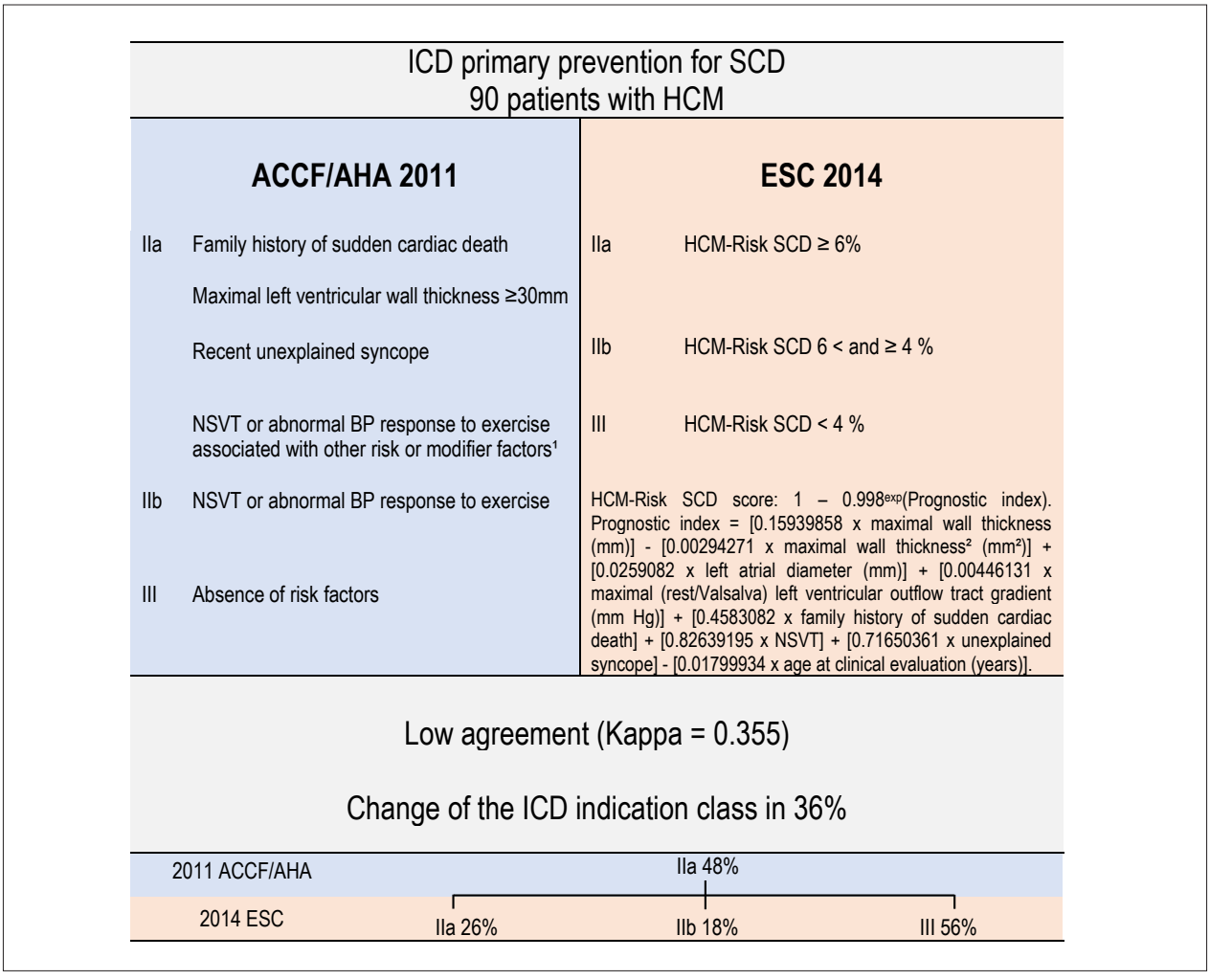

Figure 1 – *Discrepancy between the 2011 ACCF/AHA and the 2014 ESC guidelines on sudden cardiac death primary prevention in hypertrophic cardiomyopathy ICD = implantable cardioverter defibrillator, SCD = sudden cardiac death, HCM = hypertrophic cardiomyopathy, ACCF= American College of Cardiology Foundation, AHA = American Heart Association, ESC = European Society of Cardiology, NSVT = non-sustained ventricular tachycardia, BP = blood pressure; ¹Modifier factors: 1. Left ventricular outflow tract gradient ≥30 mmHg; 2. Late gadolineum enhancement on cardiac magnetic resonance; 3.Left ventricular apical aneurysm; 4. Malignant genetic mutation.*

the 2014 ESC model (p=0.05). Family history of SCD and NSVT associated with LVOT obstruction were the predictors that showed the greatest decrease of ICD class recommendation under the European guideline (Table 6).

Discussion

In this study, for the first time, we compared the SCD primary prevention criteria established by the 2011 ACCF/AHA and the 2014 ESC guidelines in a Brazilian HCM population based on a non-referred outpatient clinical cohort. Our results demonstrate low agreement between the two systems regarding the recommendations for primary prevention ICD. The ESC/HCM Risk-SCD score has lowered the class of implant recommendation over ACCF/AHA in 36% of the patients. Among those in class IIa in the North American guideline, the ESC risk score decreased the class of device recommendation in 74% of the patients, determined an ICD unwarranted in 56% and maintained the recommendation in only 26%. The European risk score has added recommendation in only 1% of the patients. In almost all cases, in which the implantation was not recommended with the North American guideline, the European criteria reassured the decision. The new model has excluded, from class IIa, the 8 (9%) patients experiencing SCD or ICD appropriate shock along the observation period, although 25% of them remained in class IIb.

HCM is an arrhythmogenic heart disease, whose histopathological substrate characterized by hypertrophy, cell disarray, fibrosis and coronary microvascular disease favors the occurrence of lethal ventricular arrhythmias.[5,6,19,20] Risk stratification for SCD is based on observational data obtained in very selected populations. It is considered complex, due to the heterogeneous character of the disease, and imperfect because many deaths occur in the absence of risk predictors.[5-7,21] The limitations offered by the 2003 and 2011 algorithms have been demonstrated in an international registry showing no difference in appropriate shock rates between patients with one, two, three or more predictors.[22] A posterior validation analysis of these criteria reports that the incidence of SCD and appropriate discharge do not differ between patients with none or only one predictor and that the initial algorithms have limited power to discriminate between high and low risk and could result in unnecessary implants.[23]

This study evaluated a HCM cohort with more advanced age and low risk profile: 78% of the patients remained in functional class I/II, 47% presented no risk factors and 35% showed only one. HCM patients aged ≥60 demonstrate reduced morbidity-mortality and SCD rates, even in the presence of risk predictors.[6] Five and ten-year SCD and ICD appropriate shock-free survival rates achieved 93% and 92%, respectively, and only 9% of the patients experienced these events along the period. A multicenter longitudinal study presents similar results and supports that HCM, when conveniently treated, shows reduced mortality in adulthood with a ten-year survival rate similar to that expected in the general population.[3]

The mean calculated ESC HCM risk-SCD score of 3.2±2.5 characterized 75% of the patients as low risk. NSVT, syncope and increased MLVWT were more frequent in high-risk patients compared to others.

In this study, we determine the percentages achieved by each one of the score predictors in the tree risk categories with the purpose of discriminating those that reached more weight in order to justify the low agreement between the two guidelines. We ascertained that the factors that have mainly contributed to the calculation and reached increased values in the low, intermediate and high-risk levels were MLVWT, left atrial diameter and age, the latter with a subtractive effect. These findings may justify the low agreement between the two guidelines, considering that MLVWT as a continuous variable, left atrial diameter and age are not included in the North American strategy. Family history of SCD or syncope, both considered as an ACCF/AHA recommendation for ICD therapy, showed lower contribution to the score calculation.

The combination of risk factors characterized as ACCF/AHA class IIa recommendation for ICD in the sample, mainly family

Table 6 – Sudden cardiac death risk profile in patients with hypertrophic cardiomyopathy in class IIa for implantable cardioverter defibrillator with the 2011 American College of Cardiology Foundation/American Heart Association guideline: restratification with the 2014 European Society of Cardiology model

	2011 ACCF/AHA / 2014 ESC		
	IIa2011/IIa2014	IIa2011/IIb2014	IIa2011/III2014
	n = 11 (26%)	n = 8 (19%)	n = 24 (55%)
Isolated family history of SCD	2 (12%)	2 (12%)	13 (76%)
Isolated syncope	5 (45%)	1 (10%)	5 (45%)
Syncope + family history of SCD	2 (40%)	2 (40%)	1 (20%)
Family history of SCD + MLVWT ≥30mm	1 (100%)	0	0
NSVT + LVOT obstruction	1 (17%)	3 (50%)	2 (33%)
Abnormal BP response + LVOT obstruction + LGE on CMR	0	0	3 (100%)
		P = 0.05	

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; ESC: European Society of Cardiology; SCD: sudden cardiac death; MLVWT: maximal left ventricular wall thickness; NSVT: non-sustained ventricular tachycardia; LVOT: left ventricular outflow tract; BP: blood pressure; LGE: late gadolinium enhancement; CMR: cardiac magnetic resonance.

history of SCD and NSVT added to LVOT obstruction, was associated to a decrease of device recommendations with the ESC risk score, reaching an ICD unwarranted in 55% of the cases. Our results suggest that the downgrade in ICD recommendations provided by the ESC model is mainly related to cases in which the recommendation with the North American guideline is based on the presence of a single predictor associated or not with a modifying risk factor. These findings are justified by the fact that the European model defines primary prevention on the basis of a set of risk factors and not on the presence of a single marker.

The ESC HCM risk-SCD score has been independently validated in the populations of three continents in observational studies mostly showing that the new model contributes to the improvement of risk stratification and clinical decision-making.[24-28] Other studies point out the sensitivity of low score for the recognition of high-risk patients, the capacity to identify cases with an ICD unwarranted and the similar event rates observed in the three risk levels.[29-32] Our study supports these findings demonstrating that the European model decreases the ICD recommendations compared to the North American guideline, leaves all patients with SCD or appropriate shock unprotected and establishes major agreement in cases not requiring implantation. Nevertheless, the metanalysis of six studies conducted with 7,291 patients demonstrates that in most cases, the five-year SCD risk is properly estimated with the ESC score.[33]

The European score settles the stratification for SCD using a rigid statistical model in a complex disease with unpredictable course. Methodological limitations may depend on left atrial evaluation with diameter, LVOT obstruction with Valsalva maneuver, and on exclusion of myocardial ischemia, late gadolinium enhancement and LV apical aneurysm. Although restrictions may be admitted to its performance, particularly in high-risk patients, the European score should be assimilated in clinical practice as a validated tool to guide therapeutic decisions. The assessment of the percentages achieved by the variables in the formula in each case may contribute to the interpretation of results in clinical practice. In the present study, the North American approach would protect a higher number of individuals than the European criteria, although it could result in unnecessary implants and could expose these populations to device complications such as infections and inappropriate shocks.[4,15,17] Prospective studies equally validated in lower risk populations are necessary to identify new predisposing factors that may improve the indications of primary prevention ICD.

Study limitations

The present study is based on the evaluation of a well-documented single-center HCM cohort comprising a less selected and older population. The clinical characteristics and the reduced event rates show the low-risk profile of the study patients, who differ from those included in the majority of the validation cohorts. These aspects may limit our conclusions to populations presenting the same characteristics. However, the study cases are as representative of the disease as those selected in referral centers with higher risk and more prone to complications.

Conclusions

In the study of an older low-risk HCM cohort, we found low agreement between the SCD primary prevention criteria established by the 2011 ACCF/AHA and the 2014 ESC guidelines. The ESC HCM risk-SCD score has decreased the ICD recommendation in the study population, especially in those with class IIa under the North American system and left all patients presenting SCD or appropriate shock in the period unprotected. The major contribution for the score calculation of the risk predictors not included in the 2011 ACCF/AHA strategy may justify in some way the discrepancy between the two guidelines.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: PMattos BP, Scolari FL, Garbin HI; Statistical analysis and Critical revision of the manuscript for intellectual content: Mattos BP, Scolari FL.

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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Which Risk Score Best Assesses Clinical Objectives in Patients with Hypertrophic Cardiomyopathy?

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Short Editorial relatec to the article: Discrepancy between International Guidelines on the Criteria for Primary Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by commonly asymmetric unexplained left ventricular hypertrophy, with greater thickening of the basal interventricular septum. Left ventricular outflow tract obstruction is present at rest in around one third of patients and can be caused in another third. The histological features of HCM include hypertrophy and myocyte disorder, in addition to interstitial fibrosis. Hypertrophy is also often associated with left ventricular diastolic dysfunction.

The first case of HCM was described by Henri Liouville in 1869 in the Gazette Medecine Paris. In 1907, Dr. A. Schmincke, a German pathologist, described two hearts with left ventricular hypertrophy; both were seen in women in their fifth decade of life. Levy and von Glahn, in 1944, from the University of Colombia, in New York, published a series of cases that resembled HCM. In 1949, William Evans, a cardiologist from London, described the familial occurrence of cardiac hypertrophy in a series of patients similar to those described in the article by Levy and von Glahn. Dr. Eugene Braunwald and Dr. Andrew Glenn Morrow published a series of studies where they detailed the clinical and hemodynamic aspects of this disease, allowing the establishment of therapeutic objectives.[1-5]

HCM has a relatively benign course in the majority of patients. However, HCM is also an important cause of sudden death (SD), particularly in adolescents and young adults, with a risk of 0.5 to 2% per year, being the most frequent cause of SD in adolescents.[6,7] The prevention of SD events through a device implantation seem obvious, since the clinical treatment options for the prevention of severe fatal arrhythmia cannot be reliably offered by pharmacological treatment. As a high-cost therapy and one that is not exempt from adverse events (infection and inappropriate shock), it became mandatory to establish which groups would benefit from the indication of therapy with an implanted defibrillator.

Among the SD risk assessment scores to define which patients would have the greatest benefit, the AHA risk calculator published in 2011[8] and the risk calculator for assessing SD by the European Society of Cardiology in 2015 were highlighted.[9] With different methodologies, both proposed to assist the clinician in identifying a group of patients that would have the greatest benefit.

An ideal classification system should be simple, have few criteria, with each criterion being easy to interpret, be reproducible based on existing practice, highly sensitive, with high negative predictive value, capable of reducing risks at the lowest possible cost. Although it meets all the above requirements, we have to consider that the prognostic models are developed to be applied to new patients, who may come from different centers, have different ethnicities, habits, different morbidities and with the most different microbiomes. Therefore, new patients are commonly referred to as different, but similar to the patients who were used to develop the models. When can a new population of patients be considered (sufficiently) similar to the developing population to justify the validation and, possibly, the application of a model? The answer to this question is totally dependent on medical records that can revalidate tools used in our practice.[10]

The present study[11] goes further and prospectively evaluates a cohort of patients using the tools most frequently used at present to validate which of them would be the most accurate in our population, and also identifies the strengths and weaknesses of our capacity to assess and predict future events. The importance of the study goes beyond the topic, since it demonstrates the need to obtain records, allowing the scientific community to be able to revalidate the most distinct clinical scores in our practice, with a huge impact on efficacy (by reducing the occurrence of sudden deaths) as well as efficiency (by allowing us to allocate resources to include patients with the greatest chance of benefit).

Keywords

Cardiomyopathy, Hypertrophic Familial; Safety Management; Discrete Subaortic Stenosis; Defibrillators Implantable; Hypertrophy, Left Ventricular.

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Takotsubo Multicenter Registry (REMUTA) – Clinical Aspects, In-Hospital Outcomes, and Long-Term Mortality

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Abstract

Background: **Takotsubo syndrome (TTS) is an acquired form of cardiomyopathy. National Brazilian data on this condition are scarce. The Takotsubo Multicenter Registry (REMUTA) is the first to include multicenter data on this condition in Brazil.**

Objective: **To describe the clinical characteristics, prognosis, in-hospital treatment, in-hospital mortality, and mortality during 1 year of follow-up.**

Methods: **This is an observational, retrospective registry study including patients admitted to the hospital with diagnosis of TTS and patients admitted for other reasons who developed this condition. Evaluated outcomes included triggering factor, analysis of exams, use of medications, complications, in-hospital mortality, and mortality during 1 year of follow-up. A significance level of 5% was adopted.**

Results: **The registry included 169 patients from 12 centers in the state of Rio de Janeiro, Brazil. Mean age was 70.9 ± 14.1 years, and 90.5% of patients were female; 63% of cases were primary TTS, and 37% were secondary. Troponin I was positive in 92.5% of patients, and median BNP was 395 (176.5; 1725). ST-segment elevation was present in 28% of patients. Median left ventricular ejection fraction was 40 (35; 48)%. We observed invasive mechanical ventilation in 25.7% of cases and shock in 17.4%. Mechanical circulatory support was used in 7.7%. In-hospital mortality was 10.6%, and mortality at 1 year of follow-up was 16.5%. Secondary TTS and cardiogenic shock were independent predictors of mortality.**

Conclusion: **The results of the REMUTA show that TTS is not a benign pathology, as was once thought, especially regarding the secondary TTS group, which has a high rate of complications and mortality. (Arq Bras Cardiol. 2020; 115(2):207-216)**

Keywords: **Cardiomyopathy, Dilated; Cardiomyopathy Takotsubo/mortality; Heart Failure; Stress, Psychological; Chest Pain; Dyspnea; Multicenter Study.**

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Introduction

Takotsubo syndrome (TTS), also known as takotsubo cardiomyopathy or broken-heart syndrome, is a reversible regional dysfunction of the left (LV) and/or right ventricle (RV) in the absence of obstructive coronary disease; a large part of cases are caused by situations of acute stress. It was first described by Sato et al. in 1990, in Japan, with a series of 16 cases that presented clinical characteristics of acute coronary syndrome; all of the patients' coronary arteries were, however, angiographically normal, and they had history of stressful event preceding the chest pain. The name is due to the similarity between the LV during systole and the "takotsubo," which is a trap used in Japan for capturing octopus. In 2006, the American Heart Association classified it in the group of acquired cardiomyopathies, under the name stress-induced cardiomyopathy.

The main manifestations of TTS are chest pain, dyspnea, ischemic ECG changes, slight increase in cardiac enzymes, and impairment of segmental ventricular function, without obstructive coronary disease.[1] Due to the fact that its clinical picture is similar to that of acute coronary syndromes, its main differential diagnosis is acute myocardial infarction (AMI), a clinical condition with high morbidity and mortality, and there are currently no criteria that make it possible to establish a clear distinction between the two pathologies during initial medical care.

Retrospective studies have made it possible to establish the most prevalent characteristics in individuals with TTS, such as female sex (90%), age over 50 years, recent history of physical or emotional stress, acute chest pain, ST-segment elevation (STE) on electrocardiogram (ECG), and increased serum levels of troponin.

In 2016, the European Society of Cardiology (ESC) defined the diagnostic criteria for this syndrome,[1] which were utilized in this registry. Subsequently, in 2018, the ESC updated their diagnostic criteria. Essentially, the modifications were the inclusion of pheochromocytoma as a specific cause of TTS and the possibility of coexisting coronary disease and TTS.

The physiopathology of this syndrome is complex, and it has not yet been fully made clear. Diverse studies indicate excessive release of adrenergic hormones (epinephrine and norepinephrine) secondary to extreme sympathetic activation and the cardiovascular response to this sudden sympathetic activation as the central factors in the physiopathology of the disease.

Complications that result from TTS involve heart failure with reduced ejection fraction, generally below 25%, with apical hypokinesia (80%), moderate to severe mitral regurgitation (15% – 20%), cardiogenic shock (10% – 15%), in-hospital mortality (3% – 5%), and recurrence (5% – 10%).[4,5] Evolution tends to be benign when adequate support is provided early, with reversal of ventricular dysfunction in one to two weeks; reversal may, however, take up to three months.[4]

The REMUTA study is the first multicenter registry conducted in Brazil, involving 12 private centers in the state of Rio de Janeiro. The objectives of this study were to describe the clinical and epidemiological characteristics, complementary exams, prognosis, and in-hospital treatment of patients admitted with TTS and to evaluate in-hospital mortality and mortality during 1 year of follow-up.

(Veja comentário no texto original. A minha sugestão aqui seria "diagnosed")

Methods

Definition of Clinical Subtypes

Primary: Acute cardiac symptoms are the main reason for seeking medical attention.

Secondary: This occurs in patients who were already diagnosed to the hospital for a different, non-cardiac reason; it is a complication of the primary condition or treatment thereof.

Study Design

This is an observational study, with retrospective analysis of medical records. For data on mortality, death certificate records of the state of Rio de Janeiro were evaluated.

Inclusion and Exclusion Criteria

Patients who were admitted to private hospitals with diagnosis of TTS according to the ESC criteria and those who developed TTS while already in the hospital for another reason were included in this study. Patients whose medical records were incomplete regarding data fundamental to analysis were excluded.

Data Collection

Clinical characteristics, laboratory data, chest X-ray, echocardiogram, ECG, cardiac nuclear magnetic resonance, and cardiac catheterization were collected from medical records. Each center coordinator identified patients with TTS in their clinical databases or in the database of the echocardiography or hemodynamics service. Following confirmation that patients met the inclusion criteria, an individual form was filled out with the data previously mentioned. Mortality data was collected from the death database of the Secretary of Health of the state of Rio de Janeiro.

Objectives

To describe the clinical and epidemiological characteristics, complementary exams, prognosis, and in-hospital treatment of patients diagnosed with TTS. To evaluate in-hospital mortality and mortality during one year of follow-up.

Statistical Analysis

Continuous variables were described as mean and standard deviation (SD) or median and interquartile range. We used unpaired Student's t-test or Mann-Whitney test to compare continuous variables and identify univariate predictors of in-hospital mortality. Categorical variables were

described as percentages. The Kolmogorov-Smirnov test was used to test the distribution pattern of numerical variables. We used Fisher's exact or chi-square tests to compare categorical variables and identify univariate predictors of in-hospital mortality. Variables that were significant in univariate analysis were included in multivariate analysis (logistic regression) in order to identify independent predictors of mortality. P-values < 0.05 were considered statistically significant.

Kaplan-Meier curves were constructed to estimate survival, and they were compared using the logrank test. Cox uni- and multivariate analyses were used to identify independent predictors of mortality after hospital discharge.

The statistical program used was SPSS version 15.0.

Ethical Aspects

The study protocol was approved by the Research Ethics Committee of the Casa de Saúde São José, Rio de Janeiro, on November 26, 2017, under certificate (CAAE) number 80206417.5.1001.5664 and opinion number 2.399.599.

Results

A total of 172 patients were identified with the inclusion criteria. After analysis of medical records, 3 patients were excluded, because data fundamental to analysis were not registered in the records. Therefore, analysis included 169 patients who were hospitalized between October 2010 and October 2017, in 12 different centers in the state of Rio de Janeiro.

Average patient age was 70.9 ± 14.1 years and 90.5% of patients were female. The most prevalent symptoms were chest pain (63.6%) and dyspnea (44.6%). History of emotional stress was present in 38.8% of patients. Table 1 shows the clinical variables of the study sample.

In etiological analysis, 63% of cases were primary TTS, and 37% were secondary.

Upon admission, patients presented with clinical stability, as reflected by systolic blood pressure (SBP) 126.73 ± 25.2 (average ± SD) and heart rate 86.30 ± 20 (average ± SD).

Regarding complementary exams, troponin I was positive in 92.5% of patients, with median (interquartile range) of 2.37 (0.63; 4.3) for conventional and 24.3 (0.8; 2650) for ultra-sensitive. Median BNP was 395 (176.5; 1725). STE was present in 28% of patients, while ST segment depression (STD) was present in 11.8%. Table 2 shows the population's main laboratory and ECG characteristics.

All patients underwent coronarography, and non-obstructive coronary disease (< 50%) was present in 24.2% of cases. The other 75.8% had angiographically normal coronary arteries.

Regarding echocardiographic analysis, median left ventricular ejection fraction (LVEF) was 40 (35; 48)% when evaluated by the Simpson method and 48 (40; 62)% when evaluated by the Teichholz method. Complete or partial reversal of LV dysfunction was evaluated, and it was present in 68.2% of cases. Table 3 shows the main echocardiographic variables analyzed, and Figure 1 shows changes in segmental contraction patterns.

Table 1 – Clinical variables of the sample

Variable	REMUTA (N = 169)
Age (mean ± SD)	70.9 ± 14.1
Male sex (%)	9.47
Chest pain (%)	63.6
Dyspnea (%)	44.6
Arterial hypertension (%)	69.7
Diabetes (%)	24.2
Dyslipidemia (%)	37.6
Chronic renal disease (%)	5.4
AF/flutter (%)	21.2
Tobacco use (%)	17.6
Obesity (%)	18.2
Emotional stress (%)	38.8
SBP (mmHg) (average ± SD)	126.73 ± 25.2
DBP (mmHg) (average ± SD)	72.99 ± 15.6
MBP (mmHg) (average ± SD)	90.50 ± 17.8
HR (BPM) (average ± SD)	86.30 ± 20.0
Length of hospital stay (days) (median/IQR)	7.5 (5; 16)

AF: atrial fibrillation; DBP: diastolic blood pressure; HR: heart rate; IQR: interquartile range; MBP: mean blood pressure; SBP: systolic blood pressure; SD: standard deviation.

Table 2 – Laboratory and electrocardiographic variables

Variable (recorded data/total N)	Result
Positive troponin (161/169)(%)	92.5
Positive CK-MB (84/169) (%)	84.7
STE (161/169)(%)	28.0
STD (161/169)(%)	11.8
Complete LBBB (161/169)(%)	7.1
Changes in repolarization (161/169)(%)	52.6
BNP (45/169) (pg/ml)(median/IQR)	395 (176.5; 1725)
Pro-BNP (7/169) (mean ± SD)	4068.57 ± 6121.28
Troponin I (45/169) (median/IQR)	2.37 (0.63; 4.3)
US Troponin I (76/169) (median/IQR)	24.3 (0.8; 2650)

BNP: brain natriuretic peptide; LBBB: left bundle branch block; CK-MB: creatine kinase myocardial band; IQR: interquartile range; SD: standard deviation; STD: ST-segment depression; STE: ST-segment elevation; US: ultra-sensitive.

When analyzing medications used during the hospital stay period, we observed that betablockers (76.2%), antiplatelet agents (60.1%), angiotensin converting enzyme inhibitors or angiotensin receptor blockers (59.5%), anticoagulants (42.6%), and loop diuretics (40.9%) were predominant. Dobutamine (17.7%) and noradrenaline (21.3%) were also used in a relatively large portion of the population (Figure 2).

Table 3 – Echocardiographic variables

Variable (n)	Result
LVEF Teichholz (143) (median/IQR)	48 (40; 62)
LVEF Simpson (87) (median/IQR)	40 (35; 48)
Moderate to severe MR (167) (%)	6.6
LV or RV thrombus (167) (%)	3.0
Pericardial effusion (167) (%)	4.8
LVOT obstruction (166) (%)	4.2
Reversal of LV dysfunction (132) (%)	68.2

LV: left ventricle; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MR: mitral regurgitation; RV: right ventricle

Regarding in-hospital clinical evolution, we observed that 40.5% of patients required non-invasive mechanical ventilation, and 25.7% required invasive mechanical ventilation. Acute pulmonary edema was observed in 24.1% of patients, and circulatory shock was observed in 17.4%. Ventricular arrhythmia was present in 8.5% of patients; cardiorespiratory arrest was present in 12.7%, and mechanical circulatory support was used in 7.7% of cases (Figure 3).

In-hospital mortality was observed to be 10.6%, and mortality after 1 year was 16.5% (Figure 4). Only 1 patient with primary TTS progressed to in-hospital death (0.91%), in contrast with 17 patients in the secondary TTS group (28.3%). Table 4 shows univariate analysis of clinical predictors and complementary exams with their statistical significance.

For the variables with non-normal distribution (troponin, BNP, and ejection fraction), we used the Mann-Whitney test, and only ejection fraction calculated by the Teichholz method showed significant different between the death and survival groups ($p = 0.001$).

In multivariate analysis of predictors of death (forward stepwise logistic regression), we observed that secondary TTS ($p = 0.035$ and OR: 4.5) and cardiogenic shock ($p < 0.001$ and OR: 13.2) were independent predictors of mortality, while the presence of chest pain was a protective factor ($p < 0.011$ and OR: 0.14). Table 5 shows this analysis. The survival curve of these predictors is shown in Figure 5.

Discussion

This study is the first multicenter registry of TTS in Brazil. The most important observations after analysis of data were the following: 1) The majority of clinical and epidemiological characteristics are similar to those in international registries, namely, predominantly elderly women, with chest pain and dyspnea as the most prevalent symptoms; 2) Emotional stress was found in only 38% of cases; 3) We observed an elevated rate of secondary TTS; 4) In-hospital mortality was elevated, as was mortality after 1 year of follow-up, and 5) Secondary TTS and shock were independent predictors of mortality, while chest pain was a protective factor.

In relation to triggering factors, emotional stress was not present in the majority of patients. In the Intertak registry, the largest registry of TTS published to date,[5] the rate was 27.7%, showing that the absence of an emotional factor preceding the clinical manifestation absolutely does not exclude this diagnosis. Furthermore, TTS preceded by physical stress generally has a secondary cause and a worse prognosis.

BNP was shown to be elevated in our population. In the Intertak registry,[5] the average value was 6 times the cutoff limit for the test. These values are greater than those observed in patients with acute coronary syndrome but lower than those of the general population with decompensated heart failure, such as in the BREATHE registry where it was 1075 (518; 1890).

We observed a lower prevalence of STE than the 43.7% seen in the Intertak registry.[5] On the other hand, out study had a higher rate of STD (7.7% in the Intertak registry). A multicenter Japanese registry of TTS showed an elevated rate of STE of approximately 74% and negative T waves in 70% of cases. These data show that typical ischemic changes may be absent in 25% to 70% of cases.

The degree of ventricular dysfunction, as reflected by LVEF, was equal to that observed in the Intertak registry[5] (41% ± 11.8%). The mid-apical pattern was by far the one most found, which is in consonance with the literature. It is noteworthy that, in our registry, the biventricular pattern held third place. This is not well described in other studies on TTS, and it shows that we should pay more attention to the assessment of the RV in this pathology. Non-negligible rates of complications such as moderate to severe mitral regurgitation, pericardial effusion, intra-ventricular thrombus, and left ventricular outflow tract obstruction were observed, showing that ventricular dysfunction is not the only problem and that cardiac involvement may by more complex in some cases. Another point worth underscoring is that practically one third of our patients were discharged from the hospital without an improvement in ventricular function on pre-discharge control echocardiogram. It is worth underlining that, although, by definition, dysfunction ventricular is reversible in TTS, there is no specific time for this improvement. In our sample, median length of hospital stay was 7.5 days. This population should receive closer outpatient follow-up in order to verify if longer ventricular function recovery time has a prognostic impact.

The Swedeheart study, which evaluated 302 patients with TTS, found cardiogenic shock in 5% of cases and cardiac arrest in 3%, while these rates were much lower in our registry. The use of inotropic and diuretic medications was also 7% and 20%, respectively, in the Swedeheart study,[9] which were much lower than the rates observed in our registry, showing, once again, the much greater severity in our cohort. Mortality in the Swedeheart study[9] was 4% in 30 days; in the Japanese registry, it was 6.3% during the in-hospital period, and in the Intertak registry[5] it was 5.6% over 1 year. In addition to the significantly higher mortality in our study, in comparison with international studies, we also observed a high rate of complications such as shock, acute pulmonary edema, need for invasive and non-

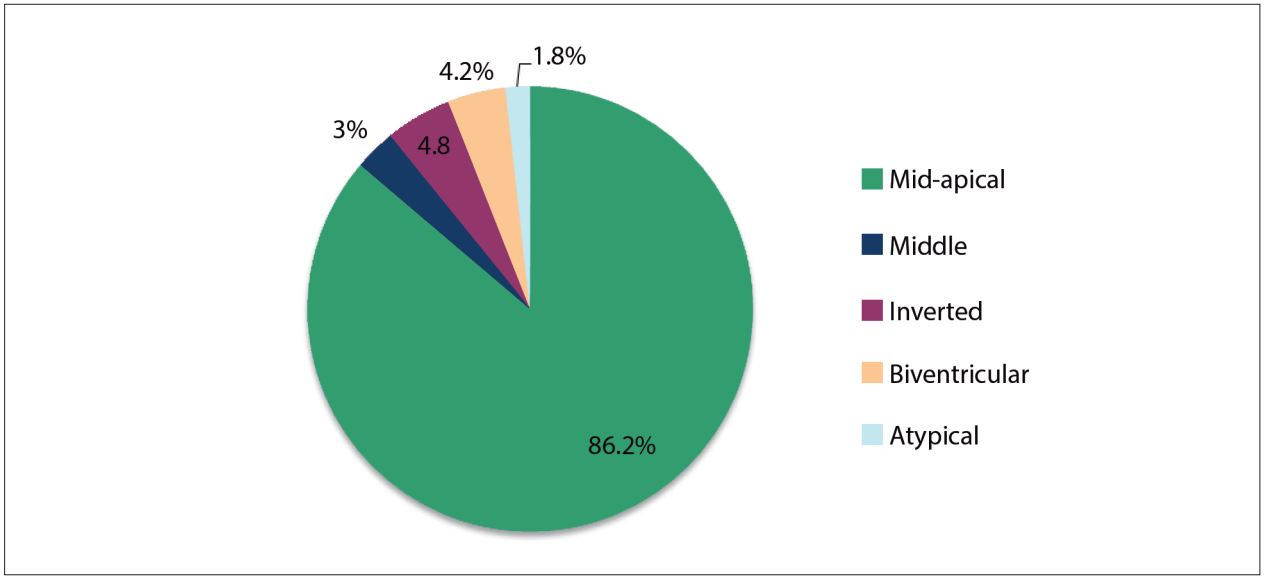

Figure 1 – *Changes in segmental contraction patterns*

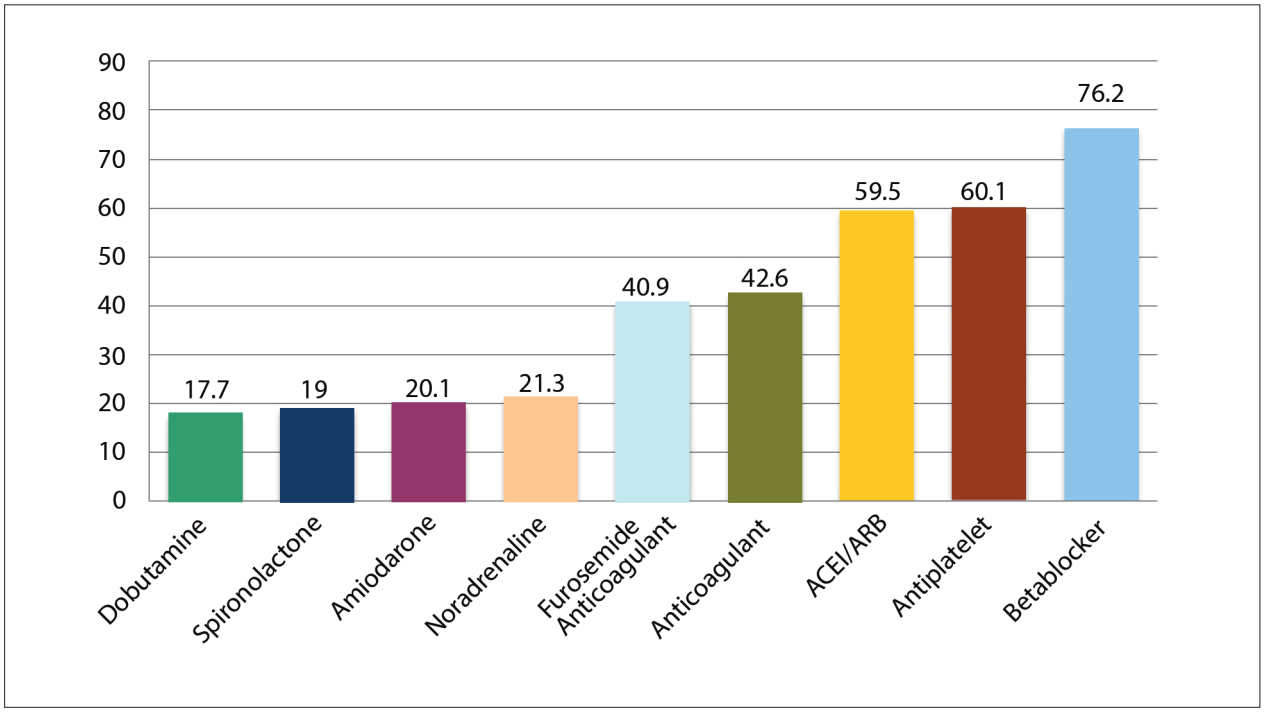

Figure 2 – *Medications used during hospital stay. ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers*

invasive ventilation, and 7.7% use of mechanical circulatory support. Analyzing predictors of mortality in our registry, we found that secondary TTS was largely responsible for this high mortality. These patients who developed TTS within contexts where another disease was the reason for hospitalization appear to have very different characteristics from those with primary TTS. A recently published review article shows that, in secondary TTS, the men-women ratio is much more balanced than in primary TTS, namely 1:1 to 1:3 in secondary TTS, in comparison with 1:9 in primary TTS. Another important difference is that the presence of chest pain in primary TTS is 75%, while it is under 20% in TTS. This corroborates our finding that chest pain was an independent protective factor against mortality. Furthermore, patients with secondary TTS had higher rates of shock (30% – 69% versus 9.9%) and in-hospital

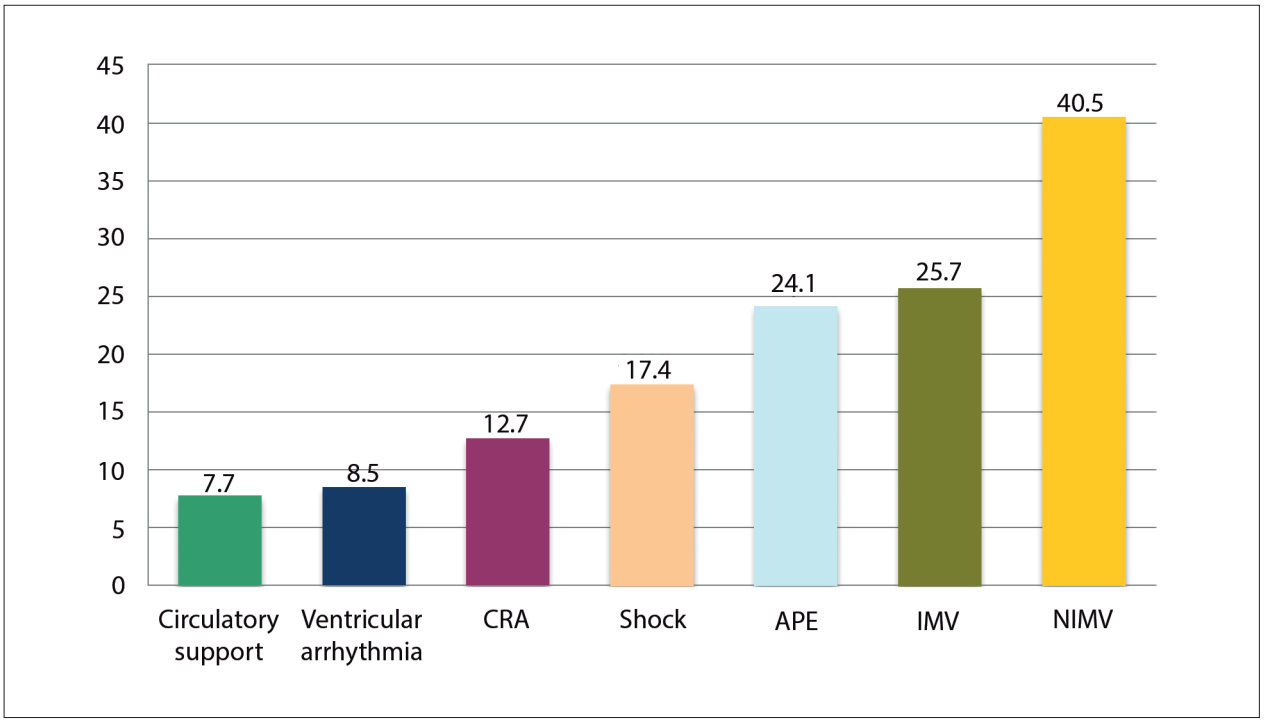

Figure 3 – *In-hospital complications. PCR: APE acute pulmonary edema; CRA: cardiorespiratory arrest; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation.*

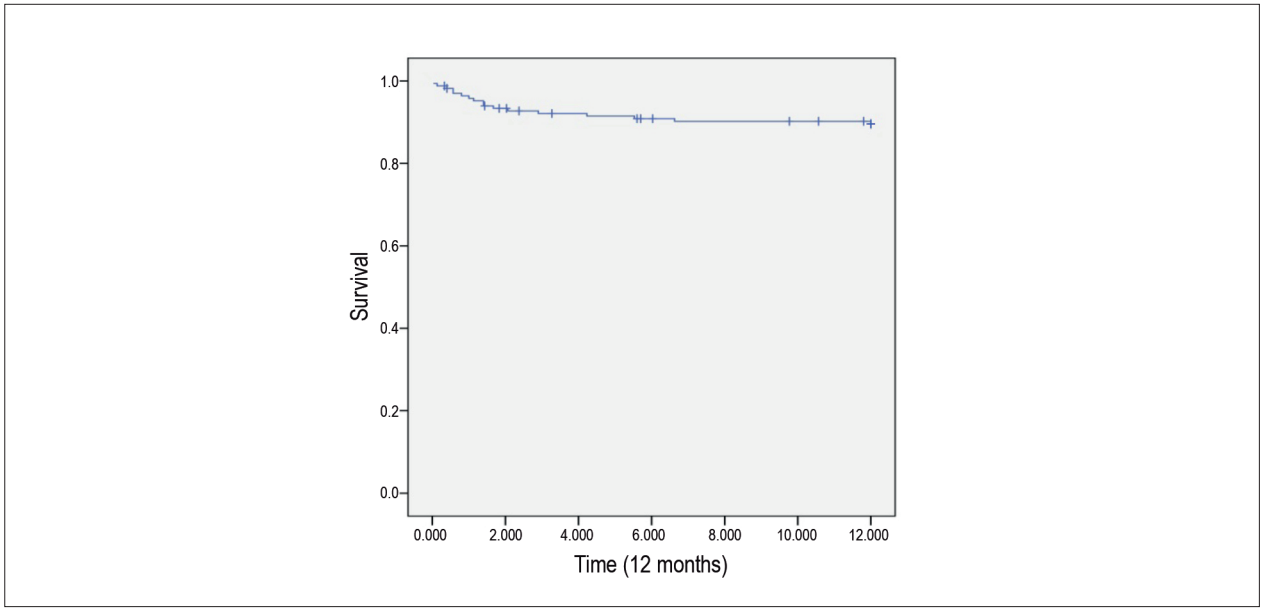

Figure 4 – *Overall 1-year survival.*

mortality (4.1% versus 35% – 50%). In the literature, there is a scarcity of data on secondary TTS, for instance, even simple data on the incidence of this subgroup in registries. A recently published systematic review, involving 54 observational studies with a total of 4,679 patients with TTS evaluating long-term prognosis showed an in-hospital mortality of 2.4%. The yearly rate of mortality during follow-up (median of 28 months with interquartile range of 23 – 34) was 3.5%. Multivariate analysis identified the following 3 predictors of mortality: more advanced age, atypical form of ventricular ballooning, and physical stress. This corroborates our findings, namely, that this is not a

Table 4 – Univariate analysis of clinical predictors and complementary exams

Variable	N	Survival	Death	P value
Age (mean ± SD)	169	70±14	77±14	0.056[δ]
Sex				
Female	153	135	18	
Male	16	16	0	0.22*
Chest pain				
Present	105	100	5	
Absent	60	48	12	0.002[#]
Dyspnea				
Present	74	63	11	
Absent	92	86	6	0.078[#]
Troponin				
Positive	149	134	15	
Negative	12	11	1	1.0*
STE				
Present	45	41	4	
Absent	116	105	11	1.0*
STD				
Present	20	17	3	
Absent	140	128	12	0.4*
Emotional stress				
Present	64	63	1	
Absent	101	85	16	0.003[#]
Secondary takotsubo syndrome				
Present	60	44	16	
Absent	105	104	1	< 0.0001[#]
Biventricular involvement				
Present	7	5	2	
Absent	160	145	15	0.15*
Improved ventricular function				
Present	90	83	7	
Absent	42	34	8	0.77*
Non-invasive mechanical ventilation				
Present	68	55	13	
Absent	100	95	5	0.004[#]
Ventricular arrhythmia				
Present	14	10	4	
Absent	151	138	13	0.041*
Invasive mechanical ventilation				
Present	43	28	15	
Absent	124	121	3	<0.0001*
MBP (mmHg) (mean ± dp)	169	92±17	81±19	0.023[δ]
Cardiogenic shock				
Present	29	19	10	
Absent	138	130	8	<0.0001*
Mechanical circulatory support				
Present	13	8	5	
Absent	155	142	13	0.006*

**Exact Fisher test; [#]Chi-squared test; [δ] Student's t test; MBP: mean blood pressure; SD: standard deviation; STD: ST-segment depression; STE: ST-segment elevation.*

Table 5 – Multivariate analysis of predictors of death

Variable	B	P value	OR	CI (95%)
Chest pain	−1.99	0.011	0.14	0.03-0.6
Secondary takotsubo syndrome	1.5	0.035	4.5	1.1-18
Cardiogenic shock	2.6	0.001	13.2	3.0-59

OR: odds ratio; B: regression constant; CI: confidence interval.

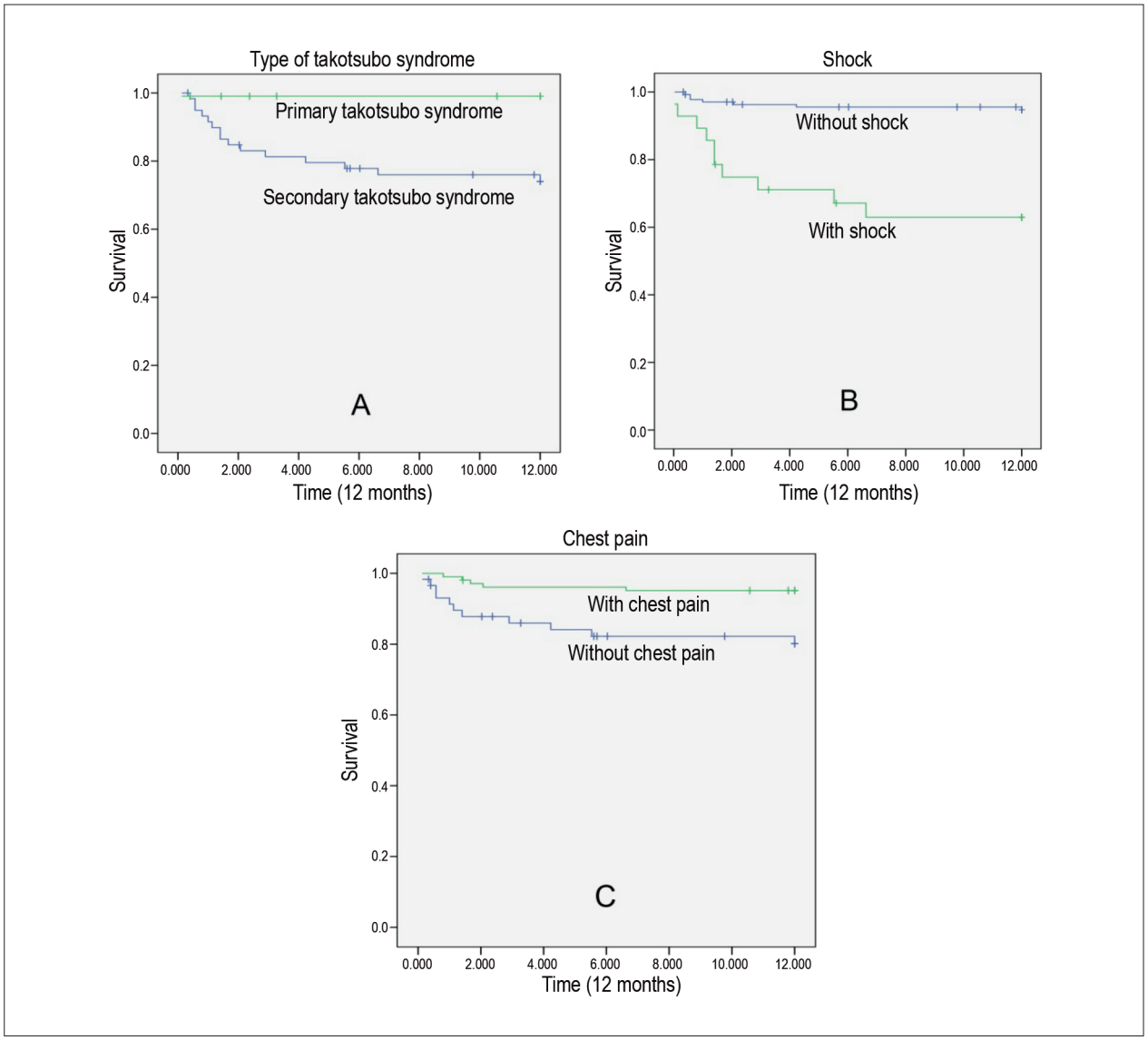

Figure 5 – *Independent predictors of mortality. A: One-year survival according to type of takotsubo syndrome; B: One-year survival according to the presence of shock; C: One-year survival according to the presence of chest pain at admission*

benign pathology and that physical stress, which is closely linked to secondary TTS, is an important prognostic factor. The rate of physical stress in the systematic review[11] and the rate of secondary TTS in our study were very similar, namely 36% and 37%, respectively. Furthermore, in the systematic review, the rate of cardiogenic shock was 19%, which is quite similar to our study, and the rate of malign arrhythmia was 10%. It is worth emphasizing that the systematic review did not include any studies from South America.

Limitations

This registry is a retrospective analysis of medical records. For this reason, some data were missing, especially those from complementary exams, whether due to their absence from medical records or, more likely, because they were not performed. Only 20 patients (11.8%) underwent magnetic resonance (MR), but this is a common characteristic in this type of study, and it reflects clinical practice. In the Japanese registry, only 5.5% of patients underwent MR. Although mortality data during long-term follow-up tend to be quite reliable, we do not have data on post-discharge clinical follow-up.

Conclusion

REMUTA is the first multicenter Brazilian registry of TTS. Its results show that TTS is not a benign pathology, as was once thought, especially in the secondary TTS subgroup which has an elevated rate of complications and mortality. Specific strategies for dealing with this subgroup should be developed with the aim of improving care quality and clinical outcomes for these patients.

Author contributions

Conception and design of the research: Almeida Junior GLG, Mansur Filho J, Xavier SS; Acquisition of data: Almeida Junior GLG, Mansur Filho J, Albuquerque DC, Pontes A, Gouvêa EP, Martins ABB, Nunes NSV, Carestiato LV, Petriz JLF, Santos AMG, Bandeira BS, Abufaiad BEJ, Pacheco LC, Oliveira MS, Filho PEC, Sampaio PPN, Duque GD, Camillis LF, Marques AC, Lourenço Jr. FC, Palazzo JR, Costa CR, Silva BA, Zukowski CN, Garcia RR, Zonis FC, Paula SAM, Ferrari CGF, Rangel BS, Ferreira RM, Mendes BFS, Castro IRC, Souza LGG, Araújo LHD, Giani A; Analysis and interpretation of the data: Almeida Junior GLG, Xavier SS, Martins ABB, Nunes NSV, Carestiato LV, Petriz JLF, Bandeira BS, Sampaio PPN, Duque GD, Marques AC, Lourenço Jr. FC, Palazzo JR, Costa CR, Zukowski CN; Statistical analysis: Almeida Junior GLG, Xavier SS; Writing of the manuscript: Almeida Junior GLG, Martins ABB, Nunes NSV; Critical revision of the manuscript for intellectual content: Mansur Filho J, Albuquerque DC, Xavier SS, Pontes A, Gouvêa EP, Martins ABB, Nunes NSV, Petriz JLF, Bandeira BS, Sampaio PPN, Duque GD, Camillis LF.

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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Takotsubo Syndrome, Does it Exist as a Specific Disease?

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Short Editorial related to the article: Takotsubo Multicenter Registry (REMUTA) – Clinical Aspects, In-Hospital Outcomes, and Long-Term Mortality

The name syndrome combines two Greek roots to describe a condition gathering a group of signs and symptoms existing together in patients. It seems that Avicenna first used it in his 1025 publication "The Canon of Medicine".[1] In genetics, the use of the name syndrome generally assumes that the underlying cause of the disease is known. On the other hand, in medicine, syndrome refers to conditions both with a known and unknown cause.

Historically, associated signs and symptoms found to be of improbable correlation were eventually known to have an underlying cause responsible for all of them. Even after the cause is unraveled, the original word remains, sometimes with the name of the first describer, and this is probably the reason for the existence nowadays of syndromes with identified and unidentified causes.

In this number, *Arquivos Brasileiros de Cardiologia* publishes the article entitled Takotsubo Multicenter Registry (REMUTA) - Clinical aspects, in-hospital outcomes, and long-term mortality.[2] The Takotsubo syndrome was reported initially by Sato et al., in 1990, in Japan, describing 16 cases that shared well-known signs and symptoms: typical chest pain following a stressful event and "angiographically normal" coronary arteries.

The Takotsubo Multicenter Registry (REMUTA) adopted the diagnostic criteria from the task force on Takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology, published in 2016.[3] According to these criteria, if the culprit coronary lesion is identified, the diagnosis of acute coronary syndrome is established, and Takotsubo syndrome is discarded. In the REMUTA registry, all patients performed coronary angiography, and 24.2% of them showed non-obstructive coronary artery disease, defined by the authors as less than 50% obstructions. The remaining 75.8% had, according to the authors, "angiographically normal" coronary arteries. However, there is no reference to the absence of a culprit coronary lesion in the patients studied, a necessary criterion for the diagnosis of Takotsubo syndrome, as stated in the first 2016 consensus, adopted by the REMUTA study.

Keywords

Takotsubo Cardiomyopathy; Ventricular Dysfunction; Coronary Artery Disease; Diagnosis,Differencial; Diagnostic,Imaging.

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Above, the expression "angiographically normal" has quotes, on purpose, for one reason: the definition of angiographically normal coronary arteries is challenging to establish. There are limitations related to the resolution of imaging methods and the well-known concept that even subtle atherosclerotic plaques can trigger coronary thrombosis. Moreover, endothelial dysfunction affecting epicardial coronary arteries or its endocardial ramifications can be responsible for the development of acute coronary syndromes (ACS). Indeed, an International consensus about intracoronary imaging, published in 2019, states that the culprit lesion cannot be identified in 4–10% of the patients with ST-elevation ACS and in >30% of patients non-ST-elevation.[4] Considering all these caveats, even after modifications, the angiographic definition for Takotsubo syndrome does not offer a confident bedside criterion for clinical practice. Maybe for that reason, in 2018, the original definition of Takotsubo syndrome, suggested by Sato et al. was modified again, and the new consensus stated that significant coronary artery disease is not anymore, a contradiction for the diagnosis of Takotsubo syndrome.[5]

In medicine, it is of paramount importance to have health conditions with clear definitions for differential diagnosis, risk stratification, and as reference for future studies in clinical research. This principle paved the way for the establishment of the now central concepts of ST-elevation and non-ST-elevation acute coronary syndromes, for example. At the bedside, modern cardiologists know how to stratify risk and give adequate treatment for both conditions. This is not the case for Takotsubo syndrome that cannot be undoubtedly distinguishable from acute coronary syndromes. As can be seen in Table 1, except for the increased prevalence in postmenopausal women, all other criteria are present in both syndromes, and the differences are based on subjective opinions taken in front of the patient. In the absence of objective criteria, differential diagnosis is challenging, and the patients could be misdiagnosed. Despite considering very important to have a National Registry of a specific disease (and I congratulate the authors for that effort), the reader cannot exclude the possibility that some patients in REMUTA had the diagnosis of ACS instead of Takotsubo Syndrome.

In summary, the correct diagnosis of Taktsubo syndrome often remains elusive. Conversely, recent data showed that magnetic resonance has a promising role in Takotsubo syndrome and could represent, in the future, the cornerstone for the differential diagnosis.[6] Acute coronary syndromes represent today a big and important group of heart diseases, each one with specific characteristics and treatment. Takotsubo syndrome, on the contrary, still lacks a definitive identity. Is it a specific, independent disease or a peculiar presentation of an acute coronary syndrome? As in the Hebrew version of the story of Jonah in the Bible, Takotsubo must swim faster, get stronger and grow; otherwise, it will be swallowed by the giant fish.

Table 1 – Diagnostic criteria comparison chart between Takotsubo and Acute coronary syndromes

Diagnostic criteria	Takotsubo	Acute coronary syndromes
Transient left ventricular dysfunction	+++	+
Emotional/physical trigger	++	+
Neurological disorders as a trigger	++	+
New ECG abnormalities	++	+++
Elevated cardiac biomarkers	+	+++
Discard infection myocarditis	+	+
More frequent in postmenopausal women	+	-
Significant coronary artery disease	+	+++

Figure 1 – *As in the Hebrew version of the story of Jonah in the Bible, Takotsubo must swim faster, get stronger and grow; otherwise, it will be swallowed by the giant fish. Art by Piero de Souza Dias Caramellli.*

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Prognostic Contrast between Anatomical and Clinical Models Regarding Fatal and Non-Fatal Outcomes in Acute Coronary Syndromes

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Abstract

Background: Recurrent ischemic events are mediated by atherosclerotic plaque instability, whereas death after an ischemic event results from gravity of insult and ability of the organism to adapt. The distinct nature of those types of events may respond for different prediction properties of clinical and anatomical information regarding type of outcome.

Objective: To identify prognostic properties of clinical and anatomical data in respect of fatal and non-fatal outcomes of patients hospitalized with acute coronary syndromes (ACS).

Methods: Patients consecutively admitted with ACS who underwent coronary angiography were recruited. The SYNTAX score was utilized as an anatomic model and the GRACE score as a clinical model. The predictive capacity of those scores was separately evaluated for prediction of non-fatal ischemic outcomes (infarction and refractory angina) and cardiovascular death during hospitalization. It was considered as significant a p-value <0,05.

Results: EAmong 365 people, cardiovascular death was observed in 4,4% and incidence of non-fatal ischemic outcomes in 11%. For cardiovascular death, SYNTAX and GRACE score presented similar C-statistic of 0,80 (95% IC: 0,70 – 0,92) and 0,89 (95% IC 0,81 – 0,96), respectively – p = 0,19. As for non-fatal ischemic outcomes, the SYNTAX score presented a moderate predictive value (C-statistic = 0,64; 95%IC 0,55 – 0,73), whereas the GRACE score did not presented association with this type of outcome (C-statistic = 0,50; 95%IC 0,40-0,61) – p = 0,027.

Conclusion: Clinical and anatomic models similarly predict cardiovascular death in ACS. However, recurrence of coronary instability is better predicted by anatomic variables than clinical data. (Arq Bras Cardiol. 2020; [online].ahead print, PP.0-0)

Keywords: Acute Coronary Syndrome/physiopathology; Atherosclerosis; Myocardial Infarction; Mortality; Cardiovascular Diseases/prevention and control; Hospitalization; Prognosis.

Introduction

Multivariate models have been validated as prognostic tools in acute coronary syndromes (ACS), consisting of clinical data,[1] anatomical data[2] or a combination of the two.[3-6] These models have recognized predictive value for recurrent events, but it is not clear whether the prognostic value varies depending on the type of outcome.

Recurrent non-fatal ischemic events represent the phenomenon of atherosclerotic plaque instability, while death after an ischemic event results from the severity of the insult and the resistance of the organism. The different pathophysiological nature of these types of events can cause clinical and anatomical data to have different prognostic capacities depending on the type of outcome. If this is true, the generalization of the prognostic value regarding "cardiovascular outcomes" would be compromised, making it necessary to individualize the prediction of each model for the type of outcome.

This work aims to evaluate and compare the prognostic value of clinical and anatomical data in relation to fatal and non-fatal outcomes in patients with ACS. Thus, a hospital cohort with patients admitted under these conditions was performed, the GRACE score chosen as the representative of the prediction for clinical data and the SYNTAX score used as a predictor based on anatomy.

Metodology

Study Population

Individuals consecutively admitted to the Intensive Cardiovascular Unit of a tertiary hospital between July 2007 and September 2014, with a diagnosis of ACS, were selected. The inclusion criterion was defined by typical or equivalent precordial discomfort and at rest in the last 48 hours, associated

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with at least one of the following characteristics: 1) positive myocardial necrosis marker, defined by troponin T ≥ 0.01 μg / L or troponin I ≥ 0.034 μg / L, which corresponds to values above the 99th percentile;[7,8] 2) ischemic electrocardiographic changes, consisting of T wave inversion (≥ 0.1 mV) or ST segment deviation (≥ 0, 05 mV); 3) documented coronary artery disease, defined by a history of myocardial infarction or previous angiography showing coronary obstruction ≥ 50% of the luminal diameter. In addition, for inclusion in the analysis, patients needed to have undergone a coronary angiography procedure during hospitalization. Those who disagreed with participating in the registry and / or who had previously undergone surgical myocardial revascularization procedures were excluded. The protocol is in accordance with the Declaration of Helsinki, and was released by the Institutional Research Ethics Committees. All patients signed an informed consent form.

Predicative Scores (SYNTAX e GRACE)

The SYNTAX score was calculated by an experienced interventional cardiologist who was blind to the clinical picture and the outcomes. This physician assessed each obstruction of the coronary tree with an obstruction percentage ≥ 50% in vessels with a diameter ≥ 1.5 mm, following the SYNTAX score tutorial[9] and considering various angiographic parameters.

The GRACE score was calculated on patient admission, consisting of eight variables: five of them computed in a semi-quantitative way, that is, different weight for each age group, systolic blood pressure, heart rate, plasma creatinine and Killip class; three of them are computed in a dichotomous way, with the ST segment elevation, elevation of myocardial necrosis marker and cardiac arrest at admission.[10]

Hospital Clinical Outcomes

The scores were tested in relation to the prediction of two types of hospital outcomes with different connotations: (1) non-fatal recurrent coronary outcomes (infarction, re-infarction or refractory angina), which represent the complexity of the coronary instability process; (2) cardiovascular death, which represents the body's inability to adapt to the ischemic myocardial event.

Nonfatal infarction was recorded as a consistent elevation of troponin T or I, above the previously described limits, in patients whose values were negative in the first 24 hours. For patients with infarction on admission, a new peak of CK-MB (≥ 50% of the previous value and above the normal value) was necessary to define a re-infarction. Elevation of necrosis markers related to percutaneous procedure or revascularization surgery were not recorded as a new event. Refractory angina was defined as recurrent chest pain, with at least two episodes, despite the use of nitrate and double product control. Cardiovascular death was defined as sudden death or cardiovascular hospitalization followed by death.

Data Analysis

Categorical variables were expressed as a percentage. Numerical variables were expressed as mean and standard deviation or median and interquartile range in cases of significant leak to normal distribution. The normality of the variables was analyzed using the Kolmogorov-Smirnov statistical test. Numerical variables were compared with the unpaired Student's t-test or Mann-Whitney and categorical with the chi-square test or Fisher's exact test.

Receiver Operating Characteristic (ROC) curves were constructed for the GRACE and SYNTAX score values to predict the outcomes of non-fatal recurrent events and cardiovascular death, with the areas below the curve (C-statistic) compared by the Hanley-McNeil test. Statistical significance was defined by $p < 0.05$. SPSS Statistical Software (version 21.0, SPSS Inc., Chicago, Illinois, USA) and MedCalc Software (version 12.3.0.0, Mariakerke, Belgium) were used for data analysis.

Sample Size Calculation

The sample was sized to offer statistical power for the comparison of SYNTAX C-statistics versus GRACE: to obtain 80% statistical power (one-tailed alpha of 0.05) in detecting 0.05 superiority of C-statistics (for example, 0.65 versus 0.70), it would be necessary to include 192 patients in the analysis.

Results

Sample Description

During the study, 822 patients were included in the register, wherein 370 were submitted to coronarography procedure, while 05 were excluded once they already have previous revascularization surgery. Of the 365 patients analyzed, the media of age was 64 ± 14 years old, 58% were male, 19% of whom had ST-segment elevation myocardial infarction. Coronary Disease with tri-arterial or left main coronary involvement was present in 36% of the sample.

The median of SYNTAX Score was 9 (IQR = 2,5 - 20) and GRACE's 117 (IQR = 90 -144). Analyzing the risk terciles predicted in the SYNTAX Score,[11] 81% of patients had a low value (0 to 22), 10% had an intermediate value (23 to 32) and only 8.5% had high value (≥ 33). Regarding the GRACE score,[10] 44% had low-risk (<109), 28% had intermediate-risk (110 to 139) and 29% had high-risk (≥ 140).

The incidence of cardiovascular death during hospitalization was 4.4% (16 patients) and non-fatal ischemic events were 10.7% (39 patients). Other clinical characteristics are described in Table 1.

Outcome Predictions by Score

For death outcome, SYNTAX and GRACE scores presented discriminatory capacity, with similar c-statistic: 0,80 (95% CI: 0,70 – 0,92) and 0,89 (95% CI 0,81 – 0,96), respectively — p = 0,019 — Figure 1A. When the scores were divided into risk terciles, both scores showed an increase of mortality in the third tercile: respectively, 2,4%, 2,7% and 30% on SYNTAX (P < 0,001) and 0%, 0,9% and 12% on GRACE (p < 0,001) — Figure 2, panel A and B.

Regarding non-fatal recurrent events, SYNTAX score presented a predictor value (C-statistic = 0,64; 95% CI 0,55 -0,73). However, the GRACE score showed no association

Table 1 - Clinical Characteristics and sample outcomes

Clinical Characteristics	
Sample Size	365
Age (years)	64 ± 14
Male	210 (58%)
Ischemia signs in electrocardiogram	166 (46%)
Clinical presentation	
Unstable Angina	98 (27%)
Non-ST-elevation myocardial infarction	196 (54%)
ST-elevation myocardial infarction	71 (19%)
Positive troponin	232 (64%)
Tri-arterial or left main coronary	131 (36%)
Serum creatine (mg/dl)	1,0 ± 0,7
Ejection fraction < 45%	45 (13%)
Killip class > 1	51 (14%)
GRACE Score*	117 (90 – 140)
SYNTAX Score*	9 (2,5 – 20)
Cardiovascular death	16 (4,4%)
Non-fatal recurrent events	39 (11%)

*NSTEMI Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; *: variable exposed as median and interquartile range.*

with this type of outcome (C-statistic = 0,50; 95% CI 0,40 – 0,61) — p=0,027 — Figure 1B. When the scores were divided into risk terciles, SYNTAX showed an increase in outcomes in the upper two terciles (8,4%, 22% and 22%, respectively, p = 0,007). However, GRACE showed no variation (9,6%, 9,3% and 13%, respectively, p = 0,57) — Figure 2, panels C e D.

Clinical Characteristics versus Type of outcome

Patients who evolved to death showed a tendency to higher risk clinical characteristics, compared to survivors. There was a significant difference between the two groups regarding creatinine (3,24 ± 2,6 and 1,15 ± 0,6; p < 0,001), acute left ventricular failure signs (58% and 12%, p < 0,001) and positive troponin (100% and 72%, p = 0,007), with a trend in age difference, ischemic electrocardiogram and blood pressure — Table 2. Nevertheless, there wasn't any difference of those characteristics between patients who evolved with a non-fatal event versus event-free patients — Table 3.

When evaluating the death event, most of those who showed this outcome already had a tri-arterial obstructive disease and/or left main coronary involvement (81%). In the survivors, only 25% had tri-arterial or left main coronary disease, followed by 22% with obstruction of two vessels, 29% with obstruction of one vessel and 24% free of obstructive injury (P ≤ 0,01). On those who showed non-fatal outcomes, the proportion of non-obstructive coronaropathy, one vessel obstruction, two vessels obstruction, tri-arterial/left main coronary were 7,7%, 23%, 26% e 44%, respectively, comparing to 25%, 29%, 21% and 25%, respectively, in free-event individuals (P=0,04)

Discussion

The present study requested a further refinement in risk prediction in patients with acute coronary syndrome (ACS). It was demonstrated how well the clinical paradigm (GRACE) as anatomical (SYTNAX) showed good capacity attributed to death, however only the anatomical model was able to predict recurrent non-fatal events. This demonstration that the scores commonly used in the clinical laboratory of patients with ACS may use a predilection for different outcomes, so far, have not been used in the literature.

It is known that anatomical extension of coronary disease is an independent predictor of plaque progression and recurrent coronary events.[12] When evaluating the same angiographic predictor model used in this cohort, a previous study with optical coherence tomography demonstrated a higher frequency of characteristics compatible with vulnerability of plaque (plaque rich in lipid content, thin-cap fibroatheroma, rupture of plaque in the culprit lesion and multiple broken plaques in the culprit vessel) in patients with ACS with a higher SYNTAX score (≥16) than in tertiles of the low score (<9) and intermediate (between 9 and 16).[13]

Another study carried out in patients with ACS demonstrated that the SYNTAX score is an independent predictor of infarction recurrence, with the best SYNTAX value of 11 to predict this outcome in this population.[14] In addition, the same group demonstrated that the higher the value of SYNTAX after percutaneous intervention, which was called Residual SYNTAX, there was an association with a higher occurrence of fatal and non-fatal outcomes in 30 days and 1 year, with predictive values and discriminatory accuracy similar to the baseline SYNTAX score (pre-treatment).[15] Our study demonstrated that the SYNTAX score is a reasonable predictor of recurrent non-fatal events, in line with the evidence that associates the burden of atherosclerotic disease with this type of outcome.

The GRACE score is a model extensively studied in the prediction of major cardiovascular events in different ACS scenarios.[16-18] Despite this, there is a paucity of data in the literature that assess the predictive accuracy of this score for non-fatal outcomes in isolation. Most studies are associated with combined event prediction (MACE). The clinical variables present in this model reflect the patient's degree of vulnerability to the insult presented in an ACS and, despite predicting anatomical complexity, it does not have a good predictive accuracy, according to data previously demonstrated by our group.[19-21] The current study has not been able to demonstrate an association between the GRACE score and the occurrence of new non-fatal ischemic events.

From a mechanistic point of view, the difference between the findings of these scores can be interpreted through the characteristics of the variables that each one analyzes. The GRACE score uses in its composition variables related to the clinical aspect of the patient and, in a way, is associated with the potential risk of instability in a wide range of patients. However, it is not directly correlated with coronary instability, since due to its composition it is not possible to properly identify the severity of existing lesions. On the other hand, the SYNTAX score, used as the anatomical paradigm, is

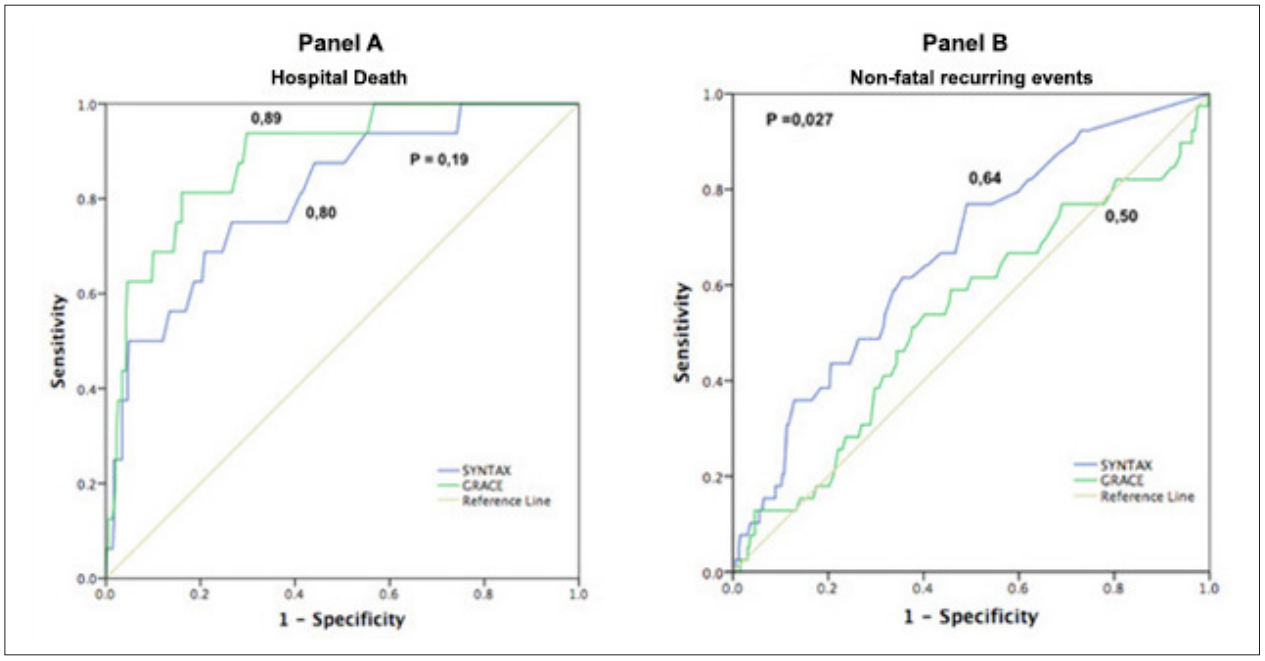

Figure 1 – *C-statistic of cardiovascular death prediction and non-fatal recurrent events, evidencing the accuracy of each score in relation to the type of outcome.*

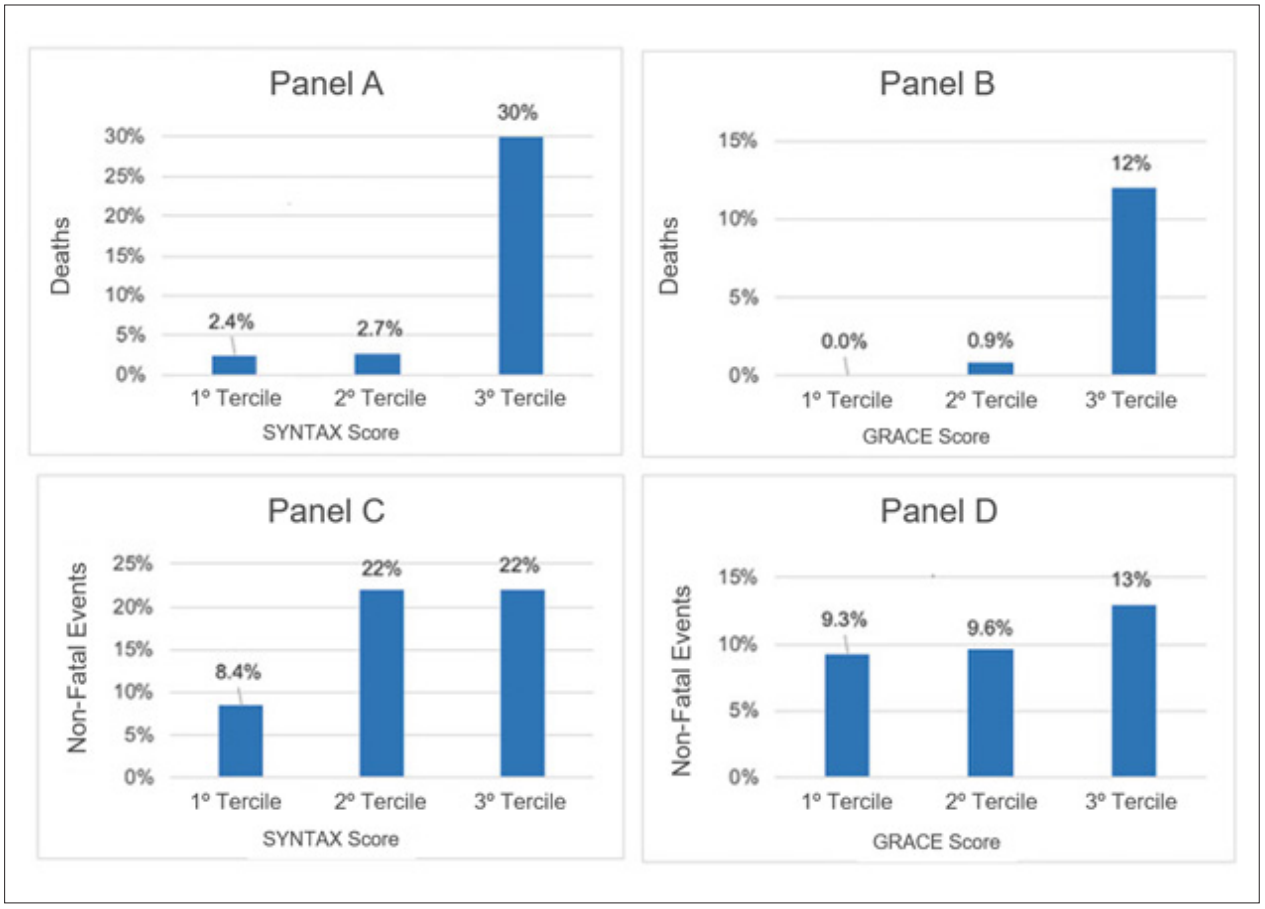

Figure 2 – *Outcome distribution by terciles of the SYNTAX and GRACE scores. A value of p <0.001 was shown in Panel A; p < 0,001 on Panel B; p = 0,007 on Panel C; and p = 0,565 on Panel D.*

Table 2 - Comparing Clinical Characteristics between patients who died versus those who survived the event

Variables	Death	Survival	p value
Sample Size	19	346	
Age	78 ± 10	63 ± 13	< 0,001
Systolic Arterial Hypertension	139 ± 32	153 ± 28	0,06
Heart rate	89 ± 20	79 ± 18	0,03
Creatine	3,24 ± 2,6	1,15 ± 0,6	<0,001
Killip > 1	9 (48%)	42 (12%)	<0,001
Positive Troponin	19 (100%)	248 (72%)	0,007
Ischemic ECG	10 (53%)	116 (34%)	0,08

Table 3 - Comparison of clinical characteristics between patients who presented non-fatal outcome Versus those free of outcomes

	Outcome	No Outcome	p Value
Sample Size	39	346	
Age	68 ± 13	64 ± 13	0.05
Systolic Arterial	159 ± 30	152 ± 28	0.15
Hypertension			
Heart Rate	74 ± 19	80 ± 18	0.06
Creatine	0.9 ± 0.3	1.0 ± 0.7	0.058
Killip > 1	5 (13%)	46 (14%)	0.82
Positive Troponin	30 (77%)	237 (73%)	0.58
Ischemic ECG	16 (41%)	110 (34%)	0.36

based precisely on the severity of existing coronary lesions and manages to fill the gap left by the previous score. In addition, new coronary events (ACS recurrence) potentially influence the prediction of mortality, since infarction causes death. On the other hand, cardiovascular death as an initial event could not influence the occurrence of a subsequent recurrent event. This obvious observation reinforces the logic of our results that when recurrent events are predicted, death is also (SYNTAX score), but the prediction of death due to a cardiac insult does not guarantee prediction of recurrent ischemic events (GRACE score). It is a hypothesis-generating study, which evidenced an eventual need to discriminate the outcomes resulting from an ACS, defining a practical utility for the clinical and anatomical predictive models. The use of combined outcomes has emerged in large registries and clinical trials to address potential limitations of statistical power, however this method establishes the same weight for different outcomes, not distinguishing the relative significance of each one.[22] The practical implications of this study lie in the need to assess, within the clinical-anatomical context, the isolated probability of different outcomes, in addition to recognizing the limited knowledge of clinical data in predicting recurrent coronary events. This could influence the decision-making process for the treatment of patients with ACS, where the initial clinical risk usually dictates the magnitude of the treatment. This study refutes this practice, because in the face of an individual with low GRACE, there would still be the possibility of a high angiographic risk. Thus, a global event prediction, taking into account complementary predictor models and a predilection for different outcomes, is the best way for an adequate risk stratification.

The main limitation of this study is its sample size, which may be subject to type II error. In addition, although we use two scores frequently used in clinical practice, it would still be interesting to have a comparative assessment of the other clinical and anatomical scores for the prediction of different outcomes, from the perspective of the anatomical and clinical paradigms.

Conclusion

In conclusion, the present study indicates that anatomical data contribute to the prediction of recurrent non-fatal events and cardiovascular death in ACS. On the other hand, clinical data are able to predict death, but do not influence the likelihood of non-fatal outcomes.

Author contributions

Conception and design of the research: Viana MS, Correia VCA, Correia LCL; Acquisition of data: Viana MS, Correia VCA, Ferreira FM, Lacerda YF, Bagano GO, Fonseca LL, Kertzman LQ, Melo MV, Noya-Rabelo MM; Analysis and interpretation of the data: Viana MS, Correia VCA, Ferreira FM, Lacerda YF, Bagano GO; Statistical analysis: Viana MS, Correia VCA, Ferreira FM, Lacerda YF, Fonseca LL, Kertzman LQ, Melo MV, Noya-Rabelo MM, Correia LCL; Critical revision of the manuscript for intellectual content: Viana MS, Correia VCA, Ferreira FM, Lacerda YF, Bagano GO, Fonseca LL, Kertzman LQ, Melo MV, Noya-Rabelo MM, Correia LCL.

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Short Editorial: Distinct Prognostic Competence between the Clinical and Anatomical Models in Acute Coronary Syndromes: Comparison by Type of Outcome

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Cardiovascular events, especially acute myocardial infarction, are the main causes of death in Brazil. In some European countries (e.g., France, Portugal, Italy), the 30-day mortality rates due to infarction have declined in recent decades to as low as 3% to 5%. This reflects the organization of healthcare logistics, including pre-hospital care, unified protocols, training, central regulation, and commitment to care.[1] In Brazil, the 30-day mortality rates vary from 3% to 5% in advanced centers and 30% in those where care does not apply the recommended guidelines.[2] This disparity usually reflects a still deficient public healthcare system that lacks diagnostic flowcharts, institutional protocols, central regulation, or professionals who are able to interpret the diagnosis for infarction using an electrocardiogram (ECG). Unfortunately, we still find that many centers lack equipment in emergency sectors (defibrillator, intubation materials, ventilators, electrocardiographs, vasoactive drugs, cardiac monitors, temporary pacemakers, and fibrinolytic drugs) and coronary units, as well as the lack of qualified professionals to provide the best treatment.

The recognition that acute coronary syndromes (ACS) constitute a heterogeneous disease in relation to prognosis was fundamental for the correct identification of individuals at higher risk, who require more intensive intervention.[3] It has been shown that not all patients with ACS belong to high or very high risk categories; there is a considerable percentage consisting of young patients without classic risk factors that can be adequately classified into intermediate or even low risk categories. Thus, it is important to identify those patients at higher risk who need more intensive treatment. Important clinical studies have contributed to the evolution of the approach to patients with ACS.[4-7] Currently, the emerging focus on the involvement of socioeconomic factors in cardiovascular risk has been constantly reported.[8]

Keywords

Cardiovascular Diseases/mortality; Myocardial Infarction; Acute Coronary Syndrome; Public Health; Organizationa and Administration; Diagnostic Equipment; Risk Assessment; Percutaneous Coronary Intervention.

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In this edition, Viana et al.[9] presented a study that compared the predictive capacity of the SYNTAX [10] and GRACE[11] scores for the prediction of non-fatal ischemic outcomes (infarction or refractory angina) and cardiovascular death during hospitalization of patients with ACS. They draw attention to the fact that recurrent non-fatal ischemic events represent the phenomenon of atherosclerotic plaque instability, while death after an ischemic event results from the severity of the insult and the patient's resistance. The different pathophysiological nature of these types of events can cause the clinical and anatomical data to have different prognostic capacities, depending on the type of outcome. If this is true, the generalization of the prognostic value in relation to the "cardiovascular outcomes" would be compromised, making it necessary to individualize the prediction of each model for the type of outcome. Considering the justification of the scarcity of studies of this nature reported in the literature aimed at answering this question, the authors performed a serial study of consecutive cases between 2007 and 2014 in a tertiary hospital in Brazil, with objective of evaluating and comparing the prognostic value of clinical and anatomical data in relation to fatal and non-fatal outcomes in patients with ACS. Patients consecutively admitted with ACS submitted to coronary angiography were recruited. The SYNTAX score was used as an anatomical model and the GRACE score as a clinical model. Of the 365 analyzed patients, the mean age was 64 ± 14 years, with 58% male individuals, 19% of whom had ST-segment elevation myocardial infarction. Coronary heart disease with triple vessel or left main coronary artery disease was present in 36% of the sample.

The median SYNTAX score was 9 (IQR = 2.5–20) and the median GRACE score was 117 (IQR = 90–144). When analyzing the risk tertiles predicted by the SYNTAX score, 81% of the patients had a low value (0 to 22), 10% showed an intermediate value (23 to 32) and only 8.5% had a high value (≥ 33). Regarding the GRACE score, 44% showed low risk (<109), 28% intermediate risk (110 to 139) and 29% high risk (≥ 140). Among the 365 individuals, there was an incidence of 4.4% of hospital death and 11% of non-fatal ischemic outcomes. For cardiovascular death, both scores - SYNTAX and GRACE - showed discriminatory capacity, with similar C-statistics: 0.80 (95% CI: 0.70–0.92) and 0.89 (95% CI 0.81– 0.96), respectively, with p = 0.19. As for non-fatal ischemic outcomes, the SYNTAX score had a predictive value (C-statistic = 0.64; 95% CI 0.55–0.73); however, the GRACE score did not show an association with this type of outcome (C-statistic) = 0.50; 95% CI: 0.40–0.61), with p = 0.027. In conclusion, the authors propose a further refinement in risk prediction in patients with acute coronary syndrome (ACS). Both the clinical paradigm (GRACE) and the anatomical one

(SYNTAX) were shown to have a good predictive capacity for death. However, only the anatomical model was able to predict recurrent non-fatal events. This demonstration that the scores commonly used in the clinical management of patients with ACS may have a predilection for different outcomes has not been described in the literature to date.

Nevertheless, the interpretation of these results should consider the presence of a type β error in this analysis, because of the small number of patients with death events (19 deaths in 365 patients). The non-controlled confounding factors and the uncertainty introduced by a large difference in the third tertile were observed in both scores for the death event. The design of the present study (case series), with a retrospective data collection, represents a partial sample of the population of patients hospitalized for ACS, comprising a subpopulation submitted to coronary angiography, therefore not representing the real scenario of the ACS population treated in this hospital, but a selected subgroup with the best prognosis for which the attending physician indicated the performance of a coronary angiography. Data analysis was performed based on reports, and the imaging data were not obtained by reviewing the images and findings. Finally, a population in different post-ACS evolutionary stages was studied, as the coronary angiography exam was adopted as the reference.

Likewise, we recognize that, despite their usefulness, risk scores tend to overestimate risk,[12] besides presenting limited power of discrimination between high and low risk individuals. They overestimate risk because they are sometimes derived from the general population, and sometimes from specific populations. There is a difficulty in stratifying risk by means of scores, since most events continue to occur in patients considered to be at low or intermediate risk. The limitations of risk scores result from the pathophysiology of ACS itself. Mendelian randomization studies, longitudinal cohort studies with young populations, in addition to autopsy studies, demonstrated that exposure to the risk of atherosclerosis occurs early, varies in intensity throughout life and includes genetic and environmental factors not taken into account in the scores. A single measure of risk factors in the adult individual with ACS fails to quantify the exposure to time-dependent risk. The risk of disease would be expressed more precisely, due to the cumulative exposure to all these risk determinants throughout life.[13]

It is important to note that, in the dynamic process of establishing risk in the patient in which ACS is suspected and / or confirmed, clinical criteria are of paramount importance, managing to identify, without any other resource, the patients at highest risk for the occurrence of death or recurrent ischemic events. Continued clinical evaluation is always essential, whether due to abrupt complications that require rapid changes in conduct or the need for clinical criteria adjusted to the case. The formulation and updating of the evaluation of clinical variables that can predict the risk of adverse results at well-defined points in time are necessary, particularly in terms of cost-effectiveness.

Using only clinical elements, we can define high-risk patients for major cardiac events, both in the short and long term, by the characteristics of their symptoms, their personal history and physical examination. Nevertheless, four variables always seem significant when trying to predict death after ACS. Clinical variables: age, renal dysfunction (expressed by serum creatinine), history of previous AMI, diabetes mellitus - which indicates a global physiological dysfunction characterized by elevated blood glucose - and the left ventricular dysfunction data.

Therefore, in the presence of ACS, in most cases, it is the initial clinical suspicion that provides the offer of the best therapy as well as the prognosis. In the current socio-economic conditions, the evaluation at the patient's arrival at the hospital is the one that ultimately has the greatest possibility of effectiveness along with the disease.

Again, we emphasize that these "scores" should serve as guides, and not as 'strings' for our clinical judgment, with the latter being able to make use of the existing information to choose the best alternative for the patient. Such scores must be open to interpretations and treatment options that may be limited by financial resources. An early diagnosis together with good treatment and cardiac rehabilitation promote good patient recovery.

In our context, changes in the organizational improvement, as well as in patient education, professionals in the emergency department, and coordination with agents in the public or private health system will result in a significant decrease in mortality due to ACS.

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Complete Revascularization Versus Treatment of the Culprit Artery Only in ST Elevation Myocardial Infarction: A Multicenter Registry

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Abstract

Background: Data on the management and prognosis of patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease are limited in Brazil, showing that the available revascularization strategies should be investigated

Objective: To assess the outcomes of complete revascularization versus treatment of the culprit artery only in patients with STEMI and multivessel disease.

Methods: A prospective cohort study was conducted at two medical centers in southern Brazil with a 1-year follow-up after the index procedure. The primary outcome was a composite of cardiac death, reinfarction, or recurrent angina, while the secondary outcome was stroke, nonfatal cardiac arrest, major bleeding, or need for reintervention. The probability of outcomes occurring was compared between the groups using binary logistic regression. A p-value < 0.05 was considered statistically significant.

Results: Eighty-five patients were included. Their mean age was 62±12 years, and 61 (71.8%) were male. Fifty-eight (68.2%) were treated with complete revascularization and 27 (31.8%) with incomplete revascularization. The chance of both the primary and secondary outcomes occurring was significantly greater among patients treated with incomplete revascularization when compared to those treated with complete revascularization (odds ratio [OR] 5.1, 95% confidence interval [CI] 1.6-16.1 vs. OR 5.2, 95% CI 1.2-22.9, respectively), as well as cardiac death (OR 6.4, 95% CI 1.2-35.3).

Conclusion: Registry data from two centers in southern Brazil demonstrate that the complete revascularization strategy is associated with a significant reduction in primary and secondary outcomes in a 1-year follow-up when compared to the incomplete revascularization strategy (Arq Bras Cardiol. 2020; 115(2):229-237)

Keywords: ST Elevation Myocardial Infarction/mortality, Cohort Studies; Hemodynamic; Death Certificates; Angina Pectoris; Stroke; Heart Arrest; Death Certificates; Angina Pectoris; Stroke; Heart Arrest; Percutaneous Coronary Interventions.

Introduction

ST-segment elevation myocardial infarction (STEMI) is an extremely relevant public health issue[1] with a high mortality rate if not properly treated.[2] Approximately 50% of patients present with multivessel coronary artery disease (CAD),[3-4] in which case prognosis is even more unfavorable.[5]

Therapeutic options for this complex group of patients with STEMI and multivessel disease include primary percutaneous coronary intervention (PCI) in the culprit artery and PCI in the other stenoses only for spontaneous ischemia or risk findings in noninvasive tests (incomplete revascularization – IR); multivessel PCI at the time of primary PCI (complete revascularization – CR); primary PCI in the culprit artery and staged approach of the other stenoses (staged CR). Initial studies showed conflicting results.[6] The PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) study, however, led to a paradigm shift as it demonstrated the benefit of multivessel PCI compared to culprit-artery-only PCI.[7] Other trials reinforced the hypothesis that a CR strategy could be beneficial and safe in selected patients with STEMI.[8-10]

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Based on those findings, the American College of Cardiology (ACC) and the American Heart Association (AHA) updated their guidelines in 2015 with recommendations for both CR and staged approach at the time of primary PCI in hemodynamically stable patients.[4] The 2017 European Society of Cardiology (ESC) guideline followed the same path.[11] The 2015 Brazilian Society of Cardiology (SBC) guideline, in turn, finds it reasonable to treat less complex, severe stenosis located in the coronary system linked to the infarct-related vessel.[12] Conversely, the guideline highlights that these patients are more likely to experience new coronary events within 1 year, thus suggesting that severe coronary stenoses that are not directly related to the index procedure should be managed later with a staged approach.[12]

In this study, we aimed to assess real-life outcomes of CR versus treatment of the culprit artery only in patients with STEMI and multivessel disease managed at two hospitals in southern Brazil.

Method

Study Design

A registry study was conducted to evaluate patients with STEMI and multivessel CAD admitted to two medical centers in southern Brazil. Prospective data were collected from October 2015 to March 2016 using hospital admission information. Also, retrospective data were collected from January to September 2015 by reviewing medical records. Primary and secondary outcomes were prospectively assessed by monthly telephone contact for 12 months following hospital discharge for the index event.

Patient Selection

Male and female patients were included if they were aged ≥ 18 years, were admitted to the study centers in the 6-month period, had diagnosis of STEMI treated with primary PCI, and presented with multivessel CAD on coronary angiography – defined as the presence of a lesion ≥ 70% by visual assessment of the angiogram in at least two projections in more than one coronary artery. Patients who were referred to the hospitals for rescue angioplasty after thrombolytic therapy and had multivessel CAD were also eligible.

Patients were excluded if they had undergone previous coronary artery bypass grafting (CABG), had cardiogenic shock at admission, indication for CABG following primary angioplasty, left main coronary artery disease, lesion in the proximal portion of the left anterior descending artery (LAD) or the circumflex artery, or chronic total occlusion of a nonculprit artery (cases which would benefit from CABG at the discretion of the health care team).

Data Collection

Study data were collected using a standardized form for the period of hospitalization for treatment of the acute event, including demographic characteristics, tests performed in the emergency department, coronary angiography results, administered treatment, as well as follow-up data for a 1-year period. All procedures related to patient care were the responsibility of the health care team, with no influence from the researchers. The study was conducted in accordance with Brazilian resolution no. 466/2012 and was approved by the Research Ethics Committees at both institutions. The prospectively enrolled patients signed an informed consent form after the initial test (coronary angiography); for retrospective data collection, the researchers signed a data confidentiality agreement.

Follow-up and Outcomes of Interest

Progression and occurrence of in-hospital outcomes were assessed during hospitalization and, subsequently, via telephone contact and review of medical records. The primary outcome was defined as the occurrence of: (1) death from cardiovascular causes; (2) reinfarction, defined as recurrent ischemic pain (although not mandatory), new ST-segment elevation ≥ 0.1 mV or new Q wave in at least two contiguous leads or abnormal (above the upper limit of normal according to the reference range used by the local laboratory or at least 50% above the value in the previous test) levels of serum markers (troponin or creatine kinase-MB); or (3) recurrent angina, defined as persistent pain, need for sublingual nitrate, or readmission due to recurrent angina.

The secondary outcome was a composite of: (1) stroke; (2) nonfatal cardiac arrest; (3) major bleeding (defined as the need for blood transfusion due to a drop of more than 3 g/dL in the hemoglobin test, and/or hemoglobin level below 10 g/dL, and/or hemodynamic instability, and/or prolonged hospitalization due to major bleeding, and/or hemorrhagic stroke; or (4) need for unplanned percutaneous or surgical reintervention.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22.0 for Windows. Age and time between primary PCI and new procedure were described as mean ± standard deviation. Categorical variables were described as absolute and relative frequency. The distributions of numerical variables were compared between the CR and culprit-artery-only groups using analysis of variance with a single criterion of classification, while those of categorical variables were compared using Pearson's chi-square test with continuity correction or Fisher's exact test whenever appropriate. The chance of primary outcome, secondary outcome, and death from all causes occurring were compared between the groups described above using binary logistic regression. In multivariable analysis, models were compared using the likelihood ratio test. Kaplan-Meier curves for STEMI were calculated for CR and IR. Differences in survival rate were assessed by the log-rank test. Odds ratios were described with their respective 95% confidence intervals. Tests with p-value < 0.05 were considered statistically significant. (Seria cardiovascular causes?)

Results

From January 2015 to March 2016, 248 patients with a diagnosis of STEMI were admitted to the emergency departments at the two study centers; of those, 85 (34.3%) patients had multivessel CAD.

Of the total 85 patients, 58 (68.2%) were treated with CR and 27 (31.8%) were treated with culprit-artery-only revascularization. The mean age was 62±12 years, and 61 (71.8%) participants were male. Inferior infarction occurred in 42 (49.4%) patients, followed by anterior infarction in 37 (43.5%). Seventy-one (83.5%) patients were rated as Killip class I at admission, and 68 (78.8%) had double-vessel disease. The LAD was responsible for 32 (37.6%) infarctions, while the lesion was found to be related to the acute myocardial infarction in 36 (42.4%) patients. Finally, 17 (20.0%) patients had no significant lesions in that artery, as described in Table 1. There was no statistically significant difference between the two revascularization strategies in any of the characteristics that were analyzed, including door-to-balloon time.

Coronary Intervention

Of the 58 patients who were given the CR strategy, 6 (10.3%) were fully treated at the index event – all of them had double-vessel disease, including four patients with the diagonal branch and two patients with the LAD as the nonculprit artery that was treated. Fifty-two patients were treated with staged revascularization of the nonculprit artery – 38 at the initial admission and 14 at a subsequent admission. The mean time between primary PCI and the new procedure was 13±11 days, ranging from 3 to 40 days. Detailed treatment (including PCI and drug therapy) is described in Table 2.

Bare-metal stents were implanted in 76 (89.4%) patients. All patients were given dual antiplatelet therapy and statin

Table 1 – Clinical and demographic characteristics of the study population (n = 85)

		Revascularization strategy			
	Overall	Complete	Incomplete	p
Center				0.43
1	28 (32.9%)	17 (60.7%)	11 (39.3%)	
2	57 (67.1%)	41 (71.9%)	16 (28.1%)	
Age (years)	62±12	62.7±12	60.6±13	0.46
Male	61 (71.8%)	42 (72.4%)	19 (74.0%)	0.99
White	80 (94.1%)	55 (94.8%)	25 (92.6%)	0.99
Previous history				
Hypertension	54 (63.5%)	37 (63.8%)	17 (63.0%)	0.99
Diabetes	22 (25.9%)	14 (24.1%)	8 (29.6%)	0.79
Smoking	26 (30.6%)	21 (36.2%)	5 (18.5%)	0.16
Previous CAD	10 (11.8%)	5 (8.6%)	5 (18.5%)	0.34
AMI location				0.94*
Anterior	37 (43.5%)	26 (44.8%)	11 (40.7%)	
Inferior	42 (49.4%)	28 (48.3%)	14 (51.9%)	
Lateral	6 (7.1%)	4 (6.9%)	2 (7.4%)	
LBBB	4 (4.7%)	2 (3.4%)	2 (7.4%)	0.80*
No. of stenoses				0.87
2	67 (78.8%)	46 (79.3%)	21 (77.8%)	
3	18 (21.1%)	12 (20.7%)	6 (22.2%)	
LAD				0.28
Culprit	32 (37.6%)	22 (37.9%)	10 (37.0%)	
Nonculprit	36 (42.4%)	27 (46.6%)	9 (33.3%)	
No lesion	17 (20.0%)	9 (15.5%)	8 (29.6%)	
LVEF < 50%	41 (48.2%)	25 (43.1%)	16 (59.3%)	0.25
Killip class				0.62*
1	71 (83.5%)	50 (86.2%)	21 (77.8%)	
2	7 (8.2%)	4 (6.9%)	3 (11.1%)	
3	7 (8.2%)	4 (6.9%)	3 (11.1%)	

*Values are mean ± standard deviation or absolute and relative frequency. p: probability value; analysis of variance was used for age; for the others, Pearson's chi-square text or *Fischer's exact test was used. CAD: coronary artery disease; AMI: acute myocardial infarction; LBBB: left bundle branch block; LAD: left anterior descending artery; LVEF: left ventricular ejection fraction.*

Table 2 – Coronary intervention and drug therapy (n = 85)

		Revascularization strategy		
	Overall	Complete	Incomplete	p
Previous thrombolytic therapy	3 (3.5%)	3 (5.2%)	0	0.57*
Stent type				0.30*
Bare-metal	76 (89.4%)	50 (86.2%)	26 (96.3%)	
Drug-eluting	9 (10.6%)	8 (13.8%)	1 (3.7%)	
Glycoprotein IIb/IIIa inhibitors	23 (27.1%)	14 (24.1%)	9 (33.3%)	0.53
Medical therapy within 24 h				
ASA	85 (100%)	58 (100%)	27 (100%)	-
Clopidogrel	85 (100%)	58 (100%)	27 (100%)	-
Statin	85 (100%)	58 (100%)	27 (100%)	-
Beta-blocker	43 (50.6%)	26 (44.8%)	17 (63.0%)	0.19
ACEI/ARB	40 (47.1%)	27 (46.6%)	13 (48.1%)	0.99
Nitrate	30 (35.3%)	20 (34.5%)	10 (37.0%)	0.99
SYNTAX score				0.34*
Low	41 (48.2%)	30 (51.7%)	11 (40.7%)	
Moderate	44 (51.8%)	28 (48.3%)	16 (59.3%)	
High	—	—	—	

*Values are absolute and relative frequency. p: probability value; analysis of variance was used for age; for the others, Pearson's chi-square text or *Fischer's exact test was used. ASA: acetylsalicylic acid; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.*

within 24 hours. Glycoprotein IIb/IIIa inhibitor was used in 23 (27.1%) patients. Regarding the SYNTAX score, 41 (48.2%) patients had a low score, while 44 (51.8%) had a moderate score. No patient had a high SYNTAX score, and there was no statistically significant difference between the two revascularization strategies regarding the distribution of the scores.

Clinical Outcomes

Overall mortality was 8.2%, and 86% of deaths occurred in hospital. The chance of both the primary and secondary outcomes occurring was significantly greater among individuals treated with IR when compared to those treated with CR (OR 5.1, 95% CI 1.6-16.1 vs. OR 5.2, 95% CI 1.2-22.9, respectively). If the chance of cardiac death is analyzed separately, the result was similar (OR 6.4, 95% CI 1.2-35.3), as described in Table 3. Deaths occurred predominantly in hospital, and only one patient died in the late stage of the IR strategy.

In multivariate analysis, as described in Table 4, CR was associated with a decreased chance of both primary and secondary outcomes occurring regardless of sex, age, diabetes, culprit lesion in the LAD, and presence of LAD lesion and ejection fraction < 50%. Also, CR was associated with a decreased chance of the primary outcome occurring regardless of the ventricular wall affected and the extent of CAD. The Kaplan-Meier curves showed a decreased 12-month survival in patients with multivessel disease post-STEMI who underwent IR (p = 0.017) (Figure 1).

Discussion

In this real-world practice registry, we showed that the CR strategy is associated with a significant reduction in hard outcomes in a 1-year follow-up when compared to the IR strategy. Also, the treatment of nonculprit arteries during primary PCI was uncommon, as most patients with multivessel CAD and STEMI were managed with a staged approach within 40 days of the index event.

Multivessel CAD occurs in approximately 40-50% of patients with STEMI[3-4] and is considered a strong independent predictor of mortality.[5] In our study population, the prevalence was about 35%. The natural history of STEMI demonstrates that the occurrence of more generalized pathophysiological derangements has the potential to compromise coronary perfusion beyond the culprit artery distribution and destabilize plaque throughout the coronary vascular bed.[13] The pathological process of STEMI involves the entire coronary tree, and the dynamics of this specific inflammatory process is greater in the first month following the acute event,[14] which may explain an increased mortality rate within 30 days,[15] as seen in the present study. Because these patients have poor prognosis, the role of CR within the context of STEMI should be examined considering the impact of the aforementioned factors on determining whether an aggressive strategy could provide clinical benefit.[13]

Consistent with the still conservative recommendations of contemporary guidelines for real-world clinical practice, several registries demonstrate that the use of multivessel approach ranges from 9% to 24.4%.[16-18] In the ProACS (Portuguese Registry of Acute Coronary Syndromes) registry, for example,

Table 3 – Clinical outcomes according to revascularization strategy (n = 85)

	Revascularization strategy			
	Complete n (%)	Incomplete n (%)	OR (95% CI)	p
Primary outcome (composite)	6 (10.3%)	10 (37.0%)	5.10 (1.6-16.1)	0.005
Cardiac death	2 (3.4%)	5 (18,5%)		
Reinfarction	—	—		
Angina	4 (6.9%)	5 (18.5%)		
Secondary outcome (composite)	3 (5.17%)	6 (22.2%)	5.24 (1.2-22.9)	0.022
Stroke	—	—		
Nonfatal cardiac arrest	2 (3.4%)	—		
Major bleeding	1 (1.7%)	—		
Reintervention	—	6 (22.2%)		

OR: odds ratio; CI: confidence interval.

Table 4 – Independent association between staged revascularization strategy and incidence of primary and secondary outcomes in a 1-year follow-up (n = 85)

	Primary outcome* OR (95% CI)	Secondary outcome† OR (95% CI)
Unadjusted	5.1 (1.6-16.1)	5.2 (1.2-22.9)
Model 2‡	5.2 (1.6-16.5)	5.1 (1.1-23.0)
Model 3§	5.1 (1.6-16.4)	4.9 (1.1-23.1)
Model 4//	5.1 (1.6-16.4)	5.1 (1.1-24.1)
Model 5¶	5.1 (1.6-16.7)	4.3 (0.9-21.0)
Model 6#	4.6 (1.4-15.3)	3.6 (0.7-19.6)
Model 7**	4.7 (1.4-15.7)	2.3 (0.4-14.2)

*OR: odds ratio; CI: confidence interval. *Death, reinfarction, angina; †Stroke, nonfatal cardiac arrest, major bleeding, reintervention. ‡ Adjusted for age and sex. §Model 2 + adjustment for diabetes. //Model 3 + adjustment for culprit lesion in left anterior descending artery (LAD). ¶Model 4 + LAD lesion and ejection fraction < 50%. #Model 5 + infarction location. **Model 6 + number of lesions.*

the rate was 19.2%. In our study, the approach was used in 68.2%. According to some authors, discrepancy between current guidelines and clinical practice results from several factors, including lack of clinical evidence and economic issues involving paying sources and current protocols. The subject is controversial and will only be resolved with a broad international study.[19] Within the context of multivessel treatment, our study showed a predominance of patients with double-vessel disease (78.8%), in agreement with studies such as the PRAMI trial,[7] and patients with less complex lesions, as there were no participants with a high SYNTAX score. Those findings suggest that more severe patients – with triple-vessel disease and a high SYNTAX score – had indication for surgical treatment following primary angioplasty at the study centers.

With regard to drug therapy, all patients were given dual antiplatelet therapy and statins as recommended in STEMI guidelines. There was no difference in the use of glycoprotein IIb/IIIa inhibitors between the groups (around 27.1%), although a large metanalysis concluded that greater benefits are observed in high-risk patients, such as those undergoing CR.[20] Another highlight is the high rate of bare-metal stenting (89.4%), which differs from the results of randomized clinical trials (RCTs).[7-10] This shows a disparity between patients included in RCTs and real-world patients, which reinforces the importance of population registries. Although RCTs use the most widely accepted design for comparing treatments, they have left many important questions unanswered. Careful review of clinical registry information is believed to provide a complementary approach to RCTs, especially because of the potential inclusion of more representative samples of the target population. Furthermore, as RCTs are conducted at centers of excellence, it remains unclear whether their results can be generalized to usual clinical practice. The operator's experience, for example, varies across institutions and may interfere with the results. Registries such as the present study show that even in suboptimal conditions the benefit of CR in patients with multivessel disease remains significant.[21] The SCAAR (Swedish Coronary Angiography and Angioplasty Registry) study followed up from 2006 to 2010 a total of 23,342 patients with multivessel disease who underwent coronary angioplasty with IR and assessed its long-term association with death, new intervention, and myocardial infarction. IR at the time of hospital discharge was associated with a high risk of adverse cardiac events within 1 year, with an adjusted hazard ratio of death and the combination of death/infarction of 1.29 (95% CI 1.12-1.49; p = 0.0005) and 1.42 (95% CI 1.30-1.56; p < 0.0001), respectively.

This study was able to demonstrate a significant benefit of CR in reducing mortality, even when a staged approach was used. CR at the index event was uncommon, being performed only in patients with double-vessel disease, favorable anatomy, and lower severity at admission (Killip class I). Another important finding was the significant benefit regarding repeat revascularization and recurrent angina. In patients with STEMI treated with primary PCI at real-world hospital settings, CR does not increase short- and long-term mortality, proving to be safe when a staged approach is used.[22]

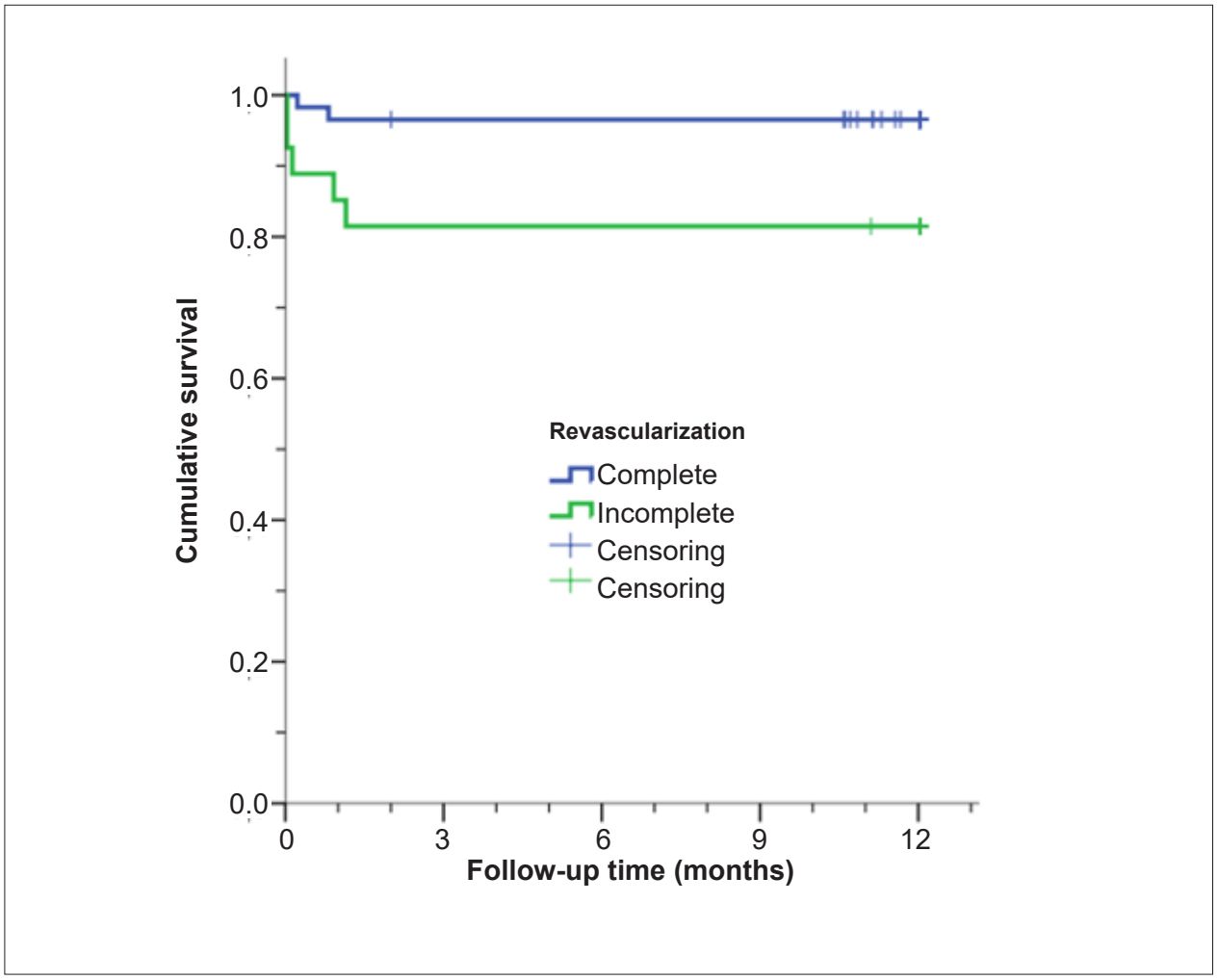

Figure 1 – *Twelve-month survival after complete revascularization (CR) and incomplete revascularization (IR) in patients with acute ST-segment elevation myocardial infarction (STEMI) and multivessel disease. *Log-rank test.*

Although the benefit of a staged strategy following primary PCI has been suggested in several studies including this one, questions remain to be elucidated, such as appropriate timing for staged PCI. In clinical practice, factors such as renal dysfunction, lesion complexity, contrast volume, radiation dose, hemodynamic status, and patient status may influence the decision on optimal timing for revascularization. An electronic survey conducted by the ACC revealed that, although most interventional cardiologists agree to perform CR with a staged approach, their opinions regarding optimal timing for the second PCI vary greatly. Only 22% of respondents performed both first and second interventions at the same hospitalization; most cardiologists recommended waiting at least 15 days for the second procedure.[23]

Despite the evidence and ongoing studies, no study may be able to define a single strategy for patients with STEMI and multivessel CAD. As these patients are heterogeneous, the strategy must be individualized. Undoubtedly, the focus should be on treating the culprit lesion. The decision should ideally be made by a heart team taking anatomical complexity, ventricular function, and patient profile into account in order to reach the best strategy. A complete risk stratification with clinical and angiographic data is crucial for evaluating the patients properly.[24]

The present study has some limitations that should be considered, especially those related to its observational nature. The chance of selection bias cannot be excluded, even though no statistically significant differences were identified regarding the study variables related to the baseline characteristics of patients treated with CR or IR. Also, no change was found in the effect of the strategy on the occurrence of primary outcome due to the factors considered in multivariable analysis, as the intervention strategy was at the operator's discretion. Moreover, this study included a small number of patients from two centers in southern Brazil and may not be representative of settings in other regions and non-public services.

Conclusions

In the present study, we used real-world data from clinical practice at two centers in southern Brazil and found that, in patients with multivessel CAD within the context of STEMI undergoing primary PCI, the CR strategy is associated with a significant reduction in primary and secondary outcomes in a 1-year follow-up when compared to the IR strategy. These data should prompt discussion about current clinical and institutional protocols.

Author Contributions

Conception and design of the research: Cadore JC, Furtado MV, Tumelero R, Tognon A, Krepsky AM, Cadore D, Polanczyk CA; Data acquisition: Cadore JC, Tumelero R, Krepsky AM, Cadore D, Bedin JC, Conte T; Analysis and interpretation of the data: Cadore JC, Furtado MV, Tognon A, Ruschel KB, Polanczyk CA; Statistical analysis: Cadore JC, Tognon A, Polanczyk CA; Writing of the manuscript: Cadore JC, Tognon A, Cadore D; Critical revision of the manuscript for intellectual content: Furtado MV, Ruschel KB, Polanczyk CA.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

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Study Association

This article is part of the thesis of master submitted by Julia Cremona Cadore, from Universidade Federal do Rio Grande do Sul.

Erratum

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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Is Complete Revascularization Truly Superior to Culprit-Lesion-Only PCI in Patients Presenting with ST-segment Elevation Myocardial Infarction?

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Short editorial related to the article: Complete Revascularization Versus Treatment of the Culprit Artery Only in ST Elevation Myocardial Infarction: A Multicenter Registry

Primary percutaneous coronary intervention (PCI) is a standard therapy for patients with acute ST-segment elevation myocardial infarction (STEMI), and its goal is to restore blood flow to the coronary artery that is judged to be causing the myocardial infarction (known as the culprit artery). In up to half of such patients, major stenoses in one or more coronary arteries that are not responsible for the myocardial infarction (nonculprit lesions) may also be seen during the index angiography.[1] Since patients with acute STEMI and multivessel coronary artery disease (CAD) have worse clinical outcomes compared with patients with single-vessel disease, it has been questioned if PCI treatment of all significant nonculprit lesions following primary PCI (complete revascularization) could improve prognosis.

A number of randomized clinical trials (RCT) have addressed this topic by comparing outcomes of patients with STEMI and multivessel CAD who underwent complete revascularization versus treatment of the culprit-lesion-only PCI (incomplete revascularization). Previously, intermediate-sized RCT[2-4] have shown that complete revascularization is safe and reduces the risk of composite outcomes, with results driven predominantly by the decreased risk of subsequent revascularization. Recently, the COMPLETE (Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early Percutaneous Coronary Intervention [PCI] for STEMI) trial,[5] a larger RCT, showed that the risk of the composite outcome death from cardiovascular causes or recurrent myocardial infarction was lower in the complete revascularization group than in the culprit-lesion-only PCI group in patients presenting with STEMI, this benefit been driven by a reduction in new myocardial infarction. Moreover, in the largest meta-analysis of RCT performed to date addressing this topic,[6] complete revascularization was associated with a reduction in cardiovascular mortality compared with culprit-lesion-only PCI in patients with STEMI and multivessel CAD without cardiogenic shock at presentation (odds ratio, 0.69; 95% confidence interval [CI], 0.48-0.99; p=0.05).

Keywords

Coronary Artery Disease; ST Elevation Myocardial Infarction; Myocardial Revascularization; Percutaneous Coronary Intervention.

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However, in order to provide balanced evidence base for clinical decision making, results from observational studies should complement the ones obtained from RCT. Although it is generally accepted that RCT are the "gold standard" for evaluation of medical therapies, these tend to evaluate interventions under ideal conditions among highly selected populations, limiting its provided evidence generalizability to clinical practice.

In this issue of the journal *Arquivos Brasileiros de Cardiologia*, Cadore et al.[7] presents results from an observational study conducted in two Brazilian hospitals comparing complete revascularization vs. culprit-lesion-only PCI in patients with STEMI and multivessel CAD. From a total of 85 patients who had nonculprit lesions with stenosis of at least 70% on visual estimation (72% male, mean age of 62 years), 58 patients (68%) underwent complete revascularization. In the complete revascularization group, the minority of patients (10%) underwent nonculprit lesion PCI during the index PCI procedure for STEMI, while 52 patients (90%) underwent staged revascularization (i.e., PCI during a procedure separate from the index PCI procedure for STEMI), with a mean time between procedures of 13 days. After one year of follow-up, 8% of patients died. Primary composite outcome (cardiovascular mortality, new myocardial infarction, recurrent angina) had occurred in six patients (10%) in the complete revascularization group as compared with ten patients (37%) in the culprit-lesion-only PCI group (odds ratio, 5.1; 95% CI, 1.6 to 16.1; p=0.005). Death due to cardiovascular causes occurred in two patients (3%) who underwent complete revascularization compared to five patients (19%) who underwent culprit-lesion-only PCI (odds ratio, 6.4; 95% CI, 1.2 to 35.3). Stroke, non-fatal cardiac arrest, major bleeding, or subsequent revascularization (the second composite outcome), occurred in three (5%) in the complete revascularization group as compared with six patients (22%) in the culprit-lesion-only PCI group (odds ratio, 5.2; 95% CI, 1.2 to 22.9; p=0.022); however, this difference was not significant after adjusting for potential cofounders.

Although the aforementioned study provides optimistic outcomes favoring complete revascularization, larger observational studies that addressed the discussed issue have shown conflicting results. When analyzing data from the National Cardiovascular Data Registry, Cavender et al.[8] found that the overall in-hospital mortality rates were greater in patients undergoing complete revascularization (7.9% vs. 5.1%, p<0.01), even for patients presenting with cardiogenic shock. Similarly, the analysis of the EUROTRANSFER Registry[9] showed that patients who underwent nonculprit lesion PCI were at higher risk of 30-day and 1-year death compared to patients with culprit-lesion-only PCI, although this difference

in mortality was no longer significant after adjustment for potential covariates. In contrast, Dimitriu-Leen et al.[10] found that the mortality rate at 1 year of follow-up was significantly higher for patients who were treated with incomplete revascularization compared with patients who underwent complete revascularization (9.8% vs 4.3%, respectively, p=0.02). However, after performing multivariate Cox regression analysis, incomplete revascularization was not independently associated with increased all-cause mortality.

In view of the results presented above, could we draw the conclusion that patients presenting with STEMI and multivessel CAD should undergo complete revascularization? Before answering this question, some issues found in the studies addressing this topic should be underscored. First, there is a great heterogeneity in the adopted protocols between both RCT and observational studies that compare complete revascularization vs. culprit-lesion-only PCI, mostly regarding to the timing of nonculprit lesion PCI - during the index PCI procedure or as staged revascularization, and the criteria used to define significant stenosis - 50% or 70% visually determined or guided by fractional flow reserve measurement, which hampers the comparability between the reported results. Second, especially regarding to RCT, it should be taken into account the possibility of publication bias, when studies with statistically significant results have increased likelihood of being published, in this case, favoring complete revascularization. Third, particularly regarding to the published article in this issue of the *Arquivos Brasileiros de Cardiologia* journal, small sample studies are of greater risk of certain types of bias that can significantly alter their findings favoring one or another strategy, and, thus, larger observational studies are further needed to confirm Cadore et al.[7] findings. Moreover, although few studies have shown differences in hard outcomes such as myocardial infarction and cardiovascular death favoring complete revascularization, the majority does not show any difference in all-cause mortality, which might suggest that other causes of death potentially associated with PCI procedures, such as infection, might not have been considered.

Finally, whether to treat nonculprit lesions with PCI in STEMI could be discussed in a larger context, based on the impact of stenting stable lesions. Recent evidence provided by the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial[11] showed that among patients with stable coronary disease who had moderate or severe ischemia, an initial invasive strategy, as compared with an initial conservative strategy, did not reduce the rates of the primary composite outcome death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. Therefore, although patients and clinicians are often more comfortable with revascularization of all suitable coronary stenosis rather than medical therapy, more data from both RCT and observational studies is needed to evaluate if complete revascularization provides additional benefit over culprit-lesion-only PCI in patients with STEMI and multivessel CAD. For now, a reasonable approach should incorporate clinical judgment, and any benefit of revascularization of lesions in nonculprit arteries should be counterbalanced by potential disadvantages of additional PCI procedures.

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Short Editorial

Custodiol®-HTK Solution vs. Cold Blood Cardioplegia for Isolated Coronary Surgery Requiring Prolonged Cross-Clamp Time: A Propensity-Matched Analysis

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Abstract

Background: **Custodiol®-histidine-tryptophan-ketoglutarate (HTK) cardioplegia is widely used.**

Objective: **To compare the outcomes of isolated coronary surgery requiring prolonged cross-clamp time (XCT) in patients receiving a single-dose HTK or multidose cold blood (MCB) cardioplegia.**

Methods: **XCT was ≥120 minutes for 148 consecutive patients undergoing isolated coronary surgery (2009−2016). HTK and MCB cardioplegia were used in 38 and 110 cases, respectively. The two cohorts were compared on baseline characteristics, operative data, and early outcomes. Because risk profile and operative data differed significantly between the two groups, one-to-one propensity score-matched analysis was performed and 34 pairs were generated.**

Results: **While expected operative risk was higher in the HTK than in the MCB cohort (European System for Cardiac Operative Risk Evaluation II, p=0.005), there was no significant intergroup difference regarding in-hospital mortality (p=0.573). Overall (positive) postoperative fluid balance (p=0.003), number of blood transfusions (p=0.017), rates of acute kidney injury (p=0.002) and any major complication (p=0.019) were increased in HTK patients. These results were all confirmed even after propensity matching, though the difference was significant only for fluid balance (p=0.013) and quite significant for blood transfusions (p=0.054). In the HTK cohort, intensive care unit and hospital stay were longer both for overall (p=0.016 and 0.008) and matched patients (p=0.142 and 0.198). In matched patients, peak serum levels of cardiac troponin I were lower in the HTK cohort (p=0.122); serum levels of creatinine were lower in the MCB cohort (p=0.023).**

Conclusion: **For the patients of this study who required prolonged XCT, there was a trend towards poorer outcomes when HTK, rather than MCB cardioplegia, was used. (Arq Bras Cardiol. 2020; 115(2):241-250)**

Keywords: **Myocardial Revascularization/complications; Heart Arrest Induced; Cardioplegic Solutions/thertapeutic use; Myocardial Reperfusion; Postoperative complications; Myocardial Infarction, Stroke; Mortality.**

Introduction

The Custodiol® histidine-tryptophan-ketoglutarate (HTK) solution (Essential Pharma, Newtown, PA, US) is classified as an intracellular, crystalloid cardioplegia because of its low sodium and calcium content.[1] Sodium depletion of the extracellular space causes hyperpolarization of the myocardial cell plasma membrane, inducing cardiac arrest in diastole. A high histidine content buffers the acidosis caused by the accumulation of anaerobic metabolites during the ischemic period; ketoglutarate improves adenosine triphosphate production during reperfusion; tryptophan stabilizes the cell membrane.[2] A single-dose of cardioplegia is claimed to offer myocardial protection for a period of up to three hours.[2,3] Consequently, it is generally used for myocardial protection in complex, adult[4,5] or pediatric cardiac operations[6] and for heart preservation in transplant surgery.[7,8] Actually, safe aortic cross-clamping time (XCT) using Custodiol-HTK cardioplegia has not been established yet. There are also concerns about hyponatremia that follows the rapid administration of the required high volume of this low-sodium cardioplegic solution,[9,10] as well as the adequacy of myocardial protection offered by only a single dose of cardioplegia.[7,8,11] In addition, despite its widespread use, very few clinical studies have compared Custodiol-HTK solution with conventional, blood or crystalloid cardioplegia in coronary bypass surgery.[12]

The aim of this retrospective study was to compare Custodiol-HTK solution with conventional multidose cold blood (MCB) cardioplegia in patients undergoing isolated coronary surgery requiring prolonged XCT. Both myocardial protection and early outcome after surgery were reviewed.

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Methods

Between July 2009 and October 2016, Custodiol-HTK cardioplegia was used in 106 consecutive patients who underwent isolated coronary artery bypass grafting at the Division of Cardiac Surgery of the University Hospital of Trieste, Italy; for 38 (35.8%) of them, XCT was of 120 minutes or longer. The early postoperative outcomes of these 38 patients (HTK cohort) were compared with those of 110 consecutive coronary surgery patients who were operated on in Trieste during the same period, had XCT ≥120 minutes, and received MCB cardioplegia (MCB cohort). Because the two cohorts differed significantly in risk profile and operative data, a propensity-matched analysis was performed as well.

Unless otherwise stated, the definitions and cut-off values of the preoperative variables were those used for the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II).[13] The risk profile of each patient was established preoperatively according to EuroSCORE II. The definitions of postoperative complications were in accordance with the internationally agreed definitions of complications after cardiac surgery.[14] Permanent neurological dysfunction (stroke with focal lesion by computed tomography examination), prolonged (>48 h) invasive ventilation, myocardial infarction, low cardiac output (requiring high doses of inotropic agents, intra-aortic balloon pumping or use of extracorporeal membrane oxygenator), acute kidney injury (with or without renal replacement therapy), multiorgan failure, multiple blood transfusion (three red blood cells units or more), mediastinal re-exploration for bleeding or tamponade, deep sternal wound infection (deep incisional infection or mediastinitis) and sepsis were defined as major complications. In-hospital death and major complications were included in a combined endpoint.

Cardioplegia delivering protocols

Either HTK or MCB cardioplegia was always delivered in both antegrade and retrograde mode at a temperature of ~4°C. Each patient received 20-25 ml of HTK solution per kg of body weight. The pressure of perfusion in aortic root was strictly maintained at 100 mmHg until cardiac arrest, and then at 40–50 mmHg. During the retrograde perfusion, the coronary sinus pressure was 20-25 mmHg. The cumulative perfusion time was 6-8 minutes. When hyponatremia occurred, it was corrected with sodium chloride (3 mEq/ml) solution; systemic hypotension was treated using norepinephrine infusion. Hemodilution was mitigated by removing part of the HTK solution from the aortic root during the retrograde mode.[5,7,8] Conventional (Buckberg) MCB cardioplegia was delivered every 20 minutes, according to standardized protocols.[15]

Blood tests

Blood levels of haemoglobin, creatinine, sodium, potassium and calcium were measured early before surgery and immediately following patient admission in intensive care unit; platelet count and blood coagulation profile before and after surgery were explored as well. Serum levels of creatine kinase, creatine kinase-MB, cardiac troponin I and aspartate aminotransferase were measured during patients' stay in ICU. The values were compared between the HTK and MCB cohorts of propensity-matched patients.

Patients were informed about the study but were not required to provide individual consent, in accordance with the Italian legislation. Although it involves human subjects, this retrospective study was not registered in a publicly accessible database.

Statistical methods

Continuous variables with normal distribution were expressed as mean ± standard deviation and those without normal distribution, as median and the range between the first and the third quartile. Categorical variables were expressed as frequencies and percentages. Statistical comparison of baseline patient characteristics, operative data and postoperative complications was performed using the Chi-square or the Fisher's exact test for categorical variables, and the unpaired Student's *t*-test or the Mann-Whitney *U*-test, for continuous variables. Since the HTK and MCB cohorts significantly differed in risk profile, number of coronary anastomoses, and length of XCT, a multivariable analysis was performed using the backward stepwise logistic regression. The area under the receiver-operating characteristic curve, with a 95% confidence interval (95%CI), was used to represent the regression probabilities. To estimate the probability of a patient being assigned to either one or other group, a propensity score (PS) was calculated in a non-parsimonious way, including the following preoperative patient characteristics: age, sex, hypertension, body mass index, haemoglobin, diabetes on insulin, chronic lung disease, glomerular filtration rate as estimated by the Cockcroft-Gault formula, chronic dialysis, extracardiac arteriopathy, New York Heart Association functional class IV, Canadian Cardiovascular Society class 4 of angina, recent myocardial infarction, left main coronary artery disease, number of diseased coronary vessels, left ventricular ejection fraction, intra-aortic balloon pump use, surgical priority, expected operative risk by EuroSCORE II, number of coronary anastomoses, and length of XCT. One-to-one PS-matching was performed employing the nearest neighbour method and a caliper of 0.2 of the standard deviation of the logit of the PS. To evaluate the balance between the matched groups, the McNemar test for dichotomous variables, the Student's *t*-test for paired samples or the Wilcoxon test for continuous variables, and the analysis of the standardized differences after matching were used. Standardized difference <10% was considered an acceptable imbalance between the treatment groups. The same tests were adopted to test differences in operative data and postoperative complications of matched groups. Two-way analysis of variance was used to observe the interaction between the type of cardioplegia and any major complication for relevant baseline characteristics among PS-matched pairs. All tests were two-sided with the p-value set at 0.05 for statistical significance. Acquisition of the data entries was performed using Microsoft Office Excel, version 2007. Data analyses were performed using the SPSS software package for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Overall series

Although the HTK and MCB cohorts differed significantly in expected operative risk by EuroSCORE II (p=0.005), number of coronary anastomoses (p=0.003) and length of XCT (p=0.031), there was no statistically significant difference regardingt in-hospital mortality (p=0.573). However, overall (positive) postoperative fluid balance (p=0.003), acute kidney injury (p=0.002), number of transfused red blood cells units (p=0.017), and overall major complication rate (p=0.019) were all significantly increased in HTK-patients, who consequently experienced longer in-hospital stays (p=0.008) (Tables 1-3).

PS-matched pairs

A PS was estimated by logistic regression and its area under the receiver-operating characteristic curve was of 0.75 (95 %CI, 0.67–0.81). One-to-one matching resulted in 34 pairs of HTK/MCB patients with similar baseline characteristics, risk profile and operative data, as confirmed by standardized differences being all lower than 10% (Tables 1 and 2). Overall (positive) postoperative fluid balance was significantly higher for HTK than for MCB patients (p=0.013) (Table 2). In the HTK cohort, there was a trend towards a higher number of transfused red blood cells units (p=0.054), an increased risk of acute kidney injury (p=0.150) and any major complication (p=0.128), as well as towards longer intensive care unit (p=0.142) and in-hospital stay (p=0.198) (Table 3). Test for interaction showed that the use of Custodiol-HTK solution in patients with renal impairment could increase the risk of any major complication after surgery (p=0.183; Table 4). Between the two cohorts, there were no significant differences in changes in blood levels of hemoglobin, platelets and electrolytes. Similarly, no significant changes were observed in the coagulation profile between the values immediately before surgery and those immediately following patient admission to ICU, whereas differences in creatinine levels were significant (p=0.023; Fig. 1). Finally, peak serum levels of cardiac troponin I were lower in the HTK than in the MCB cohort, though the difference was not quite significant (p=0.122; Fig. 2).

Discussion

The most relevant finding of this study was that, with respect to conventional MCB cardioplegia, Custodiol-HTK solution did not improve clinical outcomes of a limited series of patients undergoing isolated coronary operations requiring XCT of 120 minutes or longer. In effect, after propensity matching, higher blood levels of creatinine were observed in HTK patients early after surgery, as well as a trend towards a higher number of transfused red blood cells units, an increased risk of acute kidney injury (and renal replacement therapy) and any major complication, and longer intensive care unit and hospital stays. In addition, the test for interaction showed that the use of Custodiol-HTK solution in patients with renal impairment could increase the risk of any major complication after surgery. However, the poorer performance of this intracellular cardioplegia in the difficult subset of patients of the present study was not related to inadequate myocardial protection. Actually, between the HTK and MCB cohorts there were differences neither in the rates of myocardial infarction and low cardiac output nor in the rates of their surrogates, such as prolonged inotropic support, intraoperative and postoperative use of IABP. Besides, the peak levels of cardiac troponin I tended to be lower in HTK than in MCB patients. The increased need for red blood cells units, primarily during surgery, in the HTK cohort was mainly due to hemodilution, associated with administration of large volumes of crystalloid cardioplegia, as required by this method. Despite removing part of the HTK solution from the aortic root during the retrograde mode of delivering, overall (positive) postoperative fluid balance was indeed significantly higher for HTK than MCB patients, even after propensity-matched analysis. In fact, there was neither increased bleeding post-surgery nor any difference on blood coagulation profiles in HTK patients compared with MCB patients. Both hemodilution and the following need for transfusions that occurred in the HTK cohort during operation, as well as the increased positive fluid balance that ensued, could explain both the increased rate of acute kidney injury (and renal replacement therapy) in these patients and the increased risk of any major postoperative complication in HTK patients with renal impairment. Certainly, some systemic metabolic effects might be even involved. For instance, some grade of metabolic acidosis occurs frequently following the use of Custodiol-HTK solution, and must be promptly neutralized.[1-3] However, since no perioperative data on pH or lactacidemia have been reported, this hypothesis could not be confirmed in the study. On the other hand, because the Custodiol-HTK solution is being successfully used to preserve renal function in kidney transplantation surgery[16], direct kidney injury seems unlikely.

Although there was an evident difference in in-hospital mortality between the two study groups (5.6% vs. 1.8%), this difference was not significant (p=0.573), maybe owing to the limited number of study patients. However, there was no difference in in-hospital mortality (p=1.000) after propensity matching, which compensated for difference in expected operative risk in the overall cohort. No increased rate of spontaneous ventricular tachycardia or fibrillation after cross-clamp releasing was recorded. No significantly increased risk of right ventricular dysfunction was reported. No significant benefit derived from using either Custodiol-HTK or MCB cardioplegia for patients with anaemia, unstable angina, recent myocardial infarction or left ventricular dysfunction. The perioperative strict and effective control of hyponatremia, which was obtained in the study patients, could explain the low rate of any transitory neurological dysfunction that occurred in HTK cohort. The lower rate of any transitory neurological dysfunctions observed in HTK patients compared to the MCB group (albeit the difference was not quite significant) was an unexpected result for the present authors.

The role of Custodiol-HTK solution in adult cardiac surgery has not been explored in depth. Generally, the authors who have investigated outcomes following minimally invasive cardiac surgery using Custodiol-HTK solution agreed that avoiding repetitive infusions may reduce the risk for coronary malperfusion due to dislodgement of the endoaortic clamp (if used) and increase the surgeon's comfort during the procedure.[17-20] Almost all of the investigators who have compared Custodiol-HTK with cold blood cardioplegia have

Table 1 – Baseline characteristics of patients and risk profiles*,†

Characteristic	Overall series				PS-matched pairs			
	HTK cohort n=38	MCB cohort n=110	p-Value	Standardized difference	HTK cohort n=34	MCB cohort n=34	p-Value	Standardized difference
Age (years)	66±9.5	66.3±9	0.850		66.1±10	65.3±9.6	0.740	
70–80	12 (31.6)	40 (36.4)		0.001	12 (35.3)	12 (35.3)		0.027
>80	2 (5.3)	5 (4.5)		0.018	2 (5.9)	1 (2.9)		0.010
Female sex	4 (10.5)	11 (10)	1.000	0.057	2 (5.9)	1 (2.9)	1.000	0.001
Hypertension	32 (84.2)	85 (77.3)	0.489	0.007	28 (82.4)	24 (70.6)	0.252	0.000
Body mass index, kg/m^2	28±5.1	27.6±3.7	0.582		28.2±5.1	27.2±3.1	0.318	
>30	10 (26.3)	26 (23.6)		0.008	9 (26.5)	9 (26.5)		0.001
Anaemia‡	18 (47.4)	43 (39.1)	0.371	0.010	16 (47.1)	18 (52.9)	0.624	0.000
Diabetes on insulin	5 (13.1)	7 (6.4)	0.298	0.007	3 (8.8)	5 (14.7)	0.709	0.003
Chronic lung disease	4 (10.5)	8 (7.3)	0.731	0.018	3 (8.8)	3 (8.8)	1.000	0.005
eGFR, ml/min§	75.1±39	83.5±28.4	0.156		74.9±40.9	78.6±26.7	0.659	
50–85	12 (31.6)	44 (40)		0.032	10 (29.4)	13 (38.2)		0.001
≤50	10 (26.3)	11 (10)		0.018	9 (26.5)	6 (17.6)		0.003
Chronic dialysis	2 (5.3)	2 (1.8)	0.573	0.131	2 (5.9)	1 (2.9)	1.000	0.014
Extracardiac arteriopathy	13 (34.2)	27 (24.5)	0.247	0.015	12 (35.3)	10 (29.4)	0.603	0.001
NYHA class IV	2 (5.3)	4 (3.6)	1.000	0.092	2 (5.9)	3 (8.8)	1.000	0.012
CCS class 4	24 (63.2)	52 (47.3)	0.091	0.026	20 (58.8)	18 (52.9)	0.624	0.002
Recent myocardial infarction	7 (18.4)	21 (19.1)	0.920	0.034	6 (17.6)	5 (14.7)	0.740	0.006
Coronary artery disease			0.423				0.606	
Two-vessel	1 (2.6)	9 (8.2)		0.084	1 (2.9)	3 (8.8)		0.004
Three-vessel	37 (97.4)	101 (91.8)		0.008	33 (97.1)	31 (91.2)		0.000
Left main disease	10 (26.3)	43 (39.1)	0.156	0.042	10 (29.4)	10 (29.4)	1.000	0.006
LV ejection fraction, %	52.2±13	54.9 ± 10.1	0.205		52±12.7	52.1±11.4	0.960	
31–50	13 (34.2)	30 (27.3)		0.012	11 (32.4)	13 (38.2)		0.001
<31	2 (5.3)	4 (3.6)		0.060	2 (5.9)	2 (5.9)		0.008
Use of IABP	5 (13.1)	11 (10)	0.762	0.016	3 (8.8)	2 (5.9)	1.000	0.003
Surgical priority			0.275				0.858	
Elective	8 (21.1)	37 (33.6)		0.024	8 (23.5)	10 (29.4)		0.006
Urgent	29 (76.3)	72 (65.5)		0.031	25 (73.5)	23 (67.6)		0.003
Emergency	1 (2.6)	1 (0.9)		-	1 (2.9)	1 (2.9)		-
Expected operative risk (EuroSCORE II), %‖	3.5 (1.6–6.2)	1.7 (1.1–3.9)	0.005		3.3 (1.5–5.8)	3 (1.4–4.8)	0.812	

**Continuous variables were expressed as mean ± SD, or median and the range between the first and the third quartile. Categorical variables were expressed as frequencies and percentages. †Unless otherwise stated, the definitions and cut-off values of the preoperative variables were those used for EuroSCORE II. ‡Defined as haemoglobin <13 g/dl for men and <12 g/dl for women. §The creatinine clearance rate, calculated according to the Cockcroft-Gault formula, was used for approximating the GFR. ‖Ref. 13. CCS: Canadian Cardiovascular Society; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; HYK: histidine-tryptophan-ketoglutarate; IABP: intra-aortic balloon pump; LV: left ventricular; MCB: multidose cold blood; NYHA: New York Heart Association; PS: propensity score; SD: standard deviation.*

Table 2 – Operative data*

Data	Overall series				PS-matched pairs			
	HTK cohort n=38	MCB cohort n=110	p-Value	Standardized difference	HTK cohort n=34	MCB cohort n=34	p-Value	Standardized difference
No. of coronary anastomoses	5.2±1.3	4.6±1	0.003		5.1±1	5.2±1	0.481	
Grafting			0.249				0.510	
Bilateral ITA	30 (78.9)	97 (88.2)			27 (79.4)	30 (88.2)		
Single ITA	8 (21.1)	12 (10.9)			7 (20.6)	4 (11.8)		
SVGs alone	0	1 (0.9)			0	0		
XCT, min	136 (128–148)	130 (124–139)	0.031		137 (128–148)	135.5 (125.5–145.5)	0.971	
120–149	29 (76.3)	97 (88.2)		0.001	26 (76.5)	27 (79.4)		0.000
150–179	8 (21.1)	10 (9.1)		0.022	8 (23.5)	5 (14.7)		0.002
180–209	0	3 (2.7)		0.050	0	2 (5.9)		0.007
>209	1 (2.6)	0		-	0	0		-
Spontaneous VT/VF after cross-clamp releasing	2 (5.3)	12 (10.9)	0.362		0	0	-	
CPB time (min)	234 (217–259)	225 (209–253)	0.193		224.5 (216–252)	234.5 (222–261.5)	0.464	
Length of operation (min)	345 (326–389)	340 (315–369)	0.412		341 (326–378.5)	338 (320–366.5)	0.962	
Total fluid balance/BSA (ml/m^2)	+2900 (2440–3590)	+2440 (2030–3140)	0.003		+2860 (2440–3660)	+2500 (2000–3030)	0.013	

**Continuous variables were expressed as mean ± SD, or median and the range between the first and the third quartile. Categorical variables were expressed as frequencies and percentages. BSA: body surface area; CPB: cardiopulmonary bypass; HYK: histidine-tryptophan-ketoglutarate; ITA: internal thoracic artery; MCB: multidose cold blood; PS: propensity score; SD: standard deviation; SVG: saphenous vein graft; VT/VF: ventricular tachycardia/fibrillation; XCT: cross-clamping time.*

shown similar clinical outcomes for the two options.[5,7,8,17,19] Actually, only few studies have shown some benefits deriving from either one of the two cardioplegic strategies. For example, lower values of cardiac troponin I for XCT >160 minutes have been reported for Custodiol-HTK patients undergoing aortic surgery by Scrascia et al.[4]. Prathanee et al.[12] have stigmatized that using Custodiol-HTK cardioplegia in isolated coronary surgery leads to a significantly increased risk of spontaneous ventricular fibrillation after releasing of the aortic clamp. However, no clinical significance has been given to this fact. Very recently, in a series of 362 patients who underwent (minimally invasive or open) heart valve surgery, Hummel et al.[20] have shown superior outcomes for Custodiol-HTK patients as to blood transfusion, stroke and 30-day hospital readmission from discharge, this translating in an average hospital net savings of about $3,000 per patient. Finally, equivalent outcomes between Custodiol-HTK and cold blood cardioplegia have been shown by Hoyer et al.[11] for 825 pairs of propensity score-matched patients, even though blood cardioplegia seemed to be beneficial in the presence of left ventricular dysfunction.

Because a single-dose of Custodiol-HTK cardioplegia is claimed to offer prolonged myocardial protection,[2,3] during the study period it was generally used, in coronary surgery, for patients with expected long time of surgery (high number of coronary anastomoses, low diameter of the coronary vessels, intramyocardial course, multiple and distal lesions, need for endarterectomy, diffuse coronary calcification, …). This fact may explain both the very long operation times and the high rate (about 36%) of HTK patients who were enrolled in the present study. It should also be emphasized that every proximal anastomosis between the aorta and venous graft was performed during aortic cross-clamping.

The primary limitations of this single-center study were its retrospective nature and the fact that outcomes of a limited series of patients were investigated. Only early outcomes were reviewed and neither late outcomes post-surgery nor coronary angiographic results were explored. Consequently, the results obtained can in no way be considered conclusive and should be verified in larger patient populations by means of randomized controlled trials.

Conclusions

Based on the results of the present study, there was no significant difference in myocardial protection between Custodiol-HTK and MCB cardioplegia. However, outcomes of isolated coronary surgery requiring prolonged XCT seemed to be poorer using Custodiol-HTK solution rather than MCB cardioplegia. Although differences in postoperative fluid balance and renal function seemed to be involved, several variables might have interfered in the outcomes, which

Table 3 – In-hospital outcomes*,†

Complication	Overall series			PS-matched pairs		
	HTK cohort n=38	MCB cohort n=110	p-Value	HTK cohort n=34	MCB cohort n=34	p-Value
In-hospital/30-day death	2 (5.3)	2 (1.8)	0.573	1 (2.9)	0	1.000
Neurological dysfunction (any)	2 (5.3)	8 (7.3)	1.000	2 (5.9)	5 (14.7)	0.427
Transitory‡	1 (2.6)	8 (7.3)	0.448	1 (2.9)	5 (14.7)	0.197
Permanent (stroke)	1 (2.6)	2 (1.8)	1.000	0	1 (2.9)	1.000
Prolonged (>48 h) invasive ventilation	3 (7.9)	6 (5.5)	0.695	2 (5.9)	3 (8.8)	1.000
Atrial fibrillation, new-onset	6 (15.8)	16 (14.5)	0.862	5 (14.7)	4 (11.8)	1.000
Myocardial infarction	0	1 (0.9)	1.000	0	1 (2.9)	1.000
RV dysfunction	4 (10.5)	8 (7.3)	0.731	4 (11.8)	1 (2.9)	0.356
Low cardiac output	6 (15.8)	10 (9.1)	0.362	3 (8.8)	3 (8.8)	1.000
Prolonged (>12 h) inotropic support	23 (60.5)	57 (51.8)	0.354	19 (55.9)	19 (55.9)	1.000
Intra- and postoperative use of IABP	0	9 (8.2)	0.112	0	3 (8.8)	0.239
Acute kidney injury	8 (21.1)	4 (3.6)	0.002	7 (20.6)	2 (5.9)	0.150
Renal replacement therapy	5 (13.2)	0	0.001	4 (11.8)	0	0.114
Multiorgan failure	3 (7.9)	3 (2.7)	0.339	2 (5.9)	1 (2.9)	1.000
48-h Chest tube output/BSA, ml/m2	685 (390–1074.5)	551 (372.5–970)	0.463	616.5 (390–1074.5)	633 (381–953.5)	0.609
No. of transfused RBC units	1.5 (1–3)	1 (0–2)	0.017	2 (1–3)	1 (0–2)	0.054
Multiple blood transfusion (>2 RBC units)	12 (31.6)	19 (17.3)	0.062	11 (32.4)	7 (20.6)	0.271
Massive blood transfusion (>4 RBC units)	5 (13.2)	2 (1.8)	0.012	4 (11.8)	0	0.114
Mediastinal re-exploration	4 (10.5)	6 (5.5)	0.454	3 (8.8)	2 (5.9)	1.000
Deep sternal wound infection	1 (2.6)	4 (3.6)	1.000	0	1 (2.9)	1.000
Sepsis	0	2 (1.8)	1.000	0	1 (2.9)	1.000
Any major complication§	17 (44.7)	27 (24.5)	0.019	15 (44.1)	9 (26.5)	0.128
In-hospital stay (days)	13.5 (10–18)	10 (8–15)	0.008	14 (10–19)	10 (8–15)	0.198
Intensive care unit stay (days)	3 (2–5.5)	2 (1.5–3)	0.016	3 (2–5.5)	2 (1.5–3)	0.142

**Continuous variables were expressed as median and the range between the first and the third quartile. Categorical variables were expressed as frequencies and percentages. †Unless otherwise stated, the definitions of the postoperative complications were in accordance with the internationally agreed definitions of complications after cardiac surgery. ‡Including delayed awakening, manifest psychiatric disorder and seizures. §Including in-hospital death, stroke, prolonged invasive ventilation, myocardial infarction, low cardiac output, acute kidney injury, multiorgan failure, multiple blood transfusion, mediastinal re-exploration, deep sternal wound infection and sepsis. BSA: body surface area; HYK: histidine-tryptophan-ketoglutarate; IABP: intra-aortic balloon pump; MCB: multidose cold blood; PS: propensity score; RBC: red blood cells; RV: right ventricular.*

could depend from a number of aspects related to different surgical teams, adopted surgical techniques, and protocols of perioperative management, as well as from a potential unexplained variability of patients.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Gatti G, Taffarello P, Forti G, Gripari C, Gustin G, Castaldi G, Fiorica I, Pappalardo A; Acquisition of data: Gatti G, Taffarello P, Forti G, Gripari C, Gustin G, Castaldi G, Fiorica I; Statistical analysis: Gatti G; Writing of the manuscript: Gatti G, Taffarello P; Critical revision of the manuscript for intellectual content: Gatti G, Taffarello P, Forti G, Gripari C, Gustin G, Pappalardo A.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

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

Table 4 – Analysis of the rate of any major complication post-surgery* in different subgroups of patients with testing for interaction†

Characteristic	HTK cohort %	MCB cohort %	OR	95% CI	Interaction p-Value
Overall	44.1	26.5	2.19	0.79–6.08	0.132
No anaemia	33.3	25	1.5	0.34–6.7	0.391
Anaemia‡	56.2	27.8	3.34	0.8–13.9	
eGFR >85 ml/min§	33.3	33.3	1.00	0.22–4.56	0.183
eGFR ≤85 ml/min§	52.6	21.1	4.17	1–17.3	
CCS class 1–3	50	31.2	2.2	0.5–9.75	0.970
CCS class 4	40	22.2	2.33	0.56–9.72	
Recent myocardial infarction	46.4	27.6	2.27	0.76–6.85	0.864
No recent myocardial infarction	33.3	20	2	0.13–32	
LV ejection fraction >50%	38.1	26.3	1.72	0.45–6.64	0.522
LV ejection fraction ≤50%	53.8	26.7	3.21	0.66–15.6	

**Including in-hospital death, stroke, prolonged invasive ventilation, myocardial infarction, low cardiac output, acute kidney injury, multiorgan failure, multiple blood transfusion, mediastinal re-exploration, deep sternal wound infection and sepsis. †Unless otherwise stated, the definitions and cut-off values of the preoperative variables were those used for EuroSCORE II. ‡Defined as haemoglobin <13 g/dl for men and <12 g/dl for women. §The creatinine clearance rate, calculated according to the Cockcroft-Gault formula, was used for approximating the GFR. CCS: Canadian Cardiovascular Society; CI: confidence interval; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; HYK=histidine-tryptophan-ketoglutarate; LV: left ventricular; MCB: multidose cold blood; OR: odds ratio.*

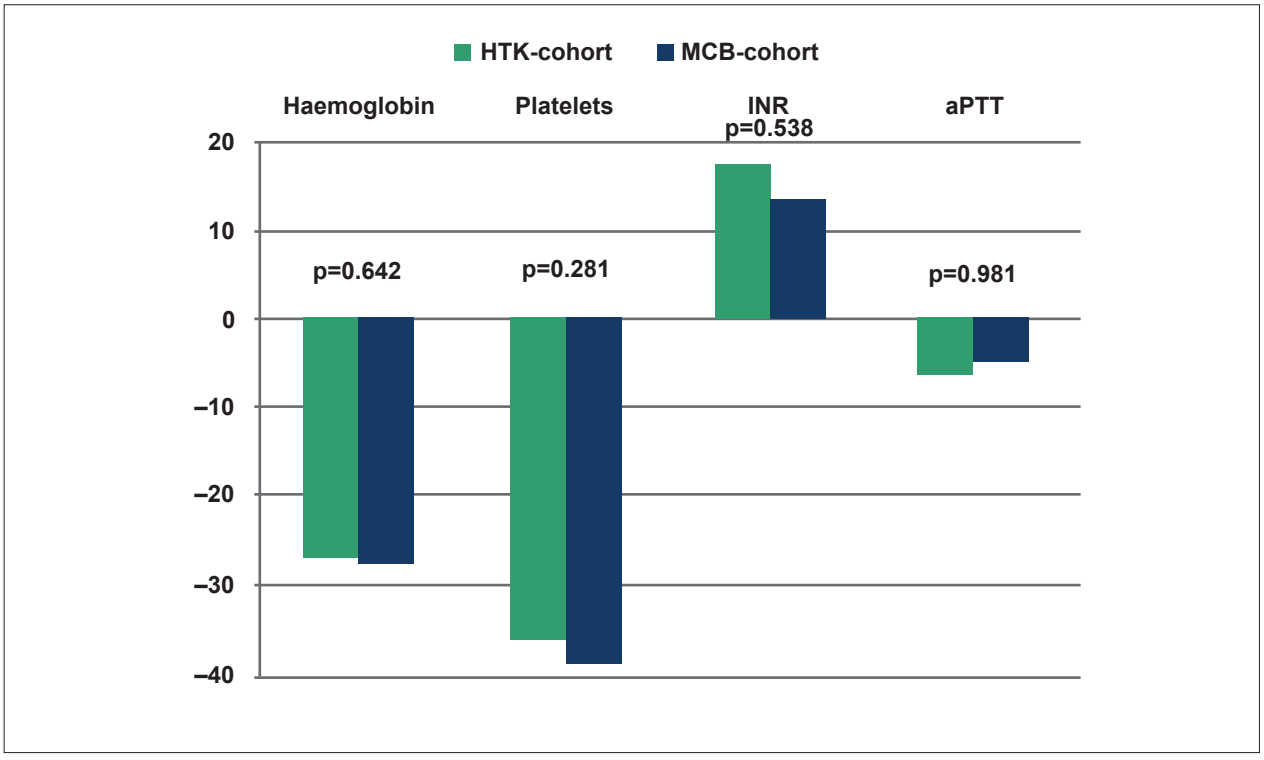

Figure 1A – *HTK vs. MCB-cohort. PS-matched pairs. Differences on changes of blood levels of haemoglobin, platelets, INR and aPTT between the values early before surgery and the values immediately following patient admission to intensive care unit. aPTT: activated partial thromboplastin time; HTK: histidine-tryptophan-ketoglutarate; INR: international normalized ratio; MCB: multidose cold blood; PS: propensity score.*

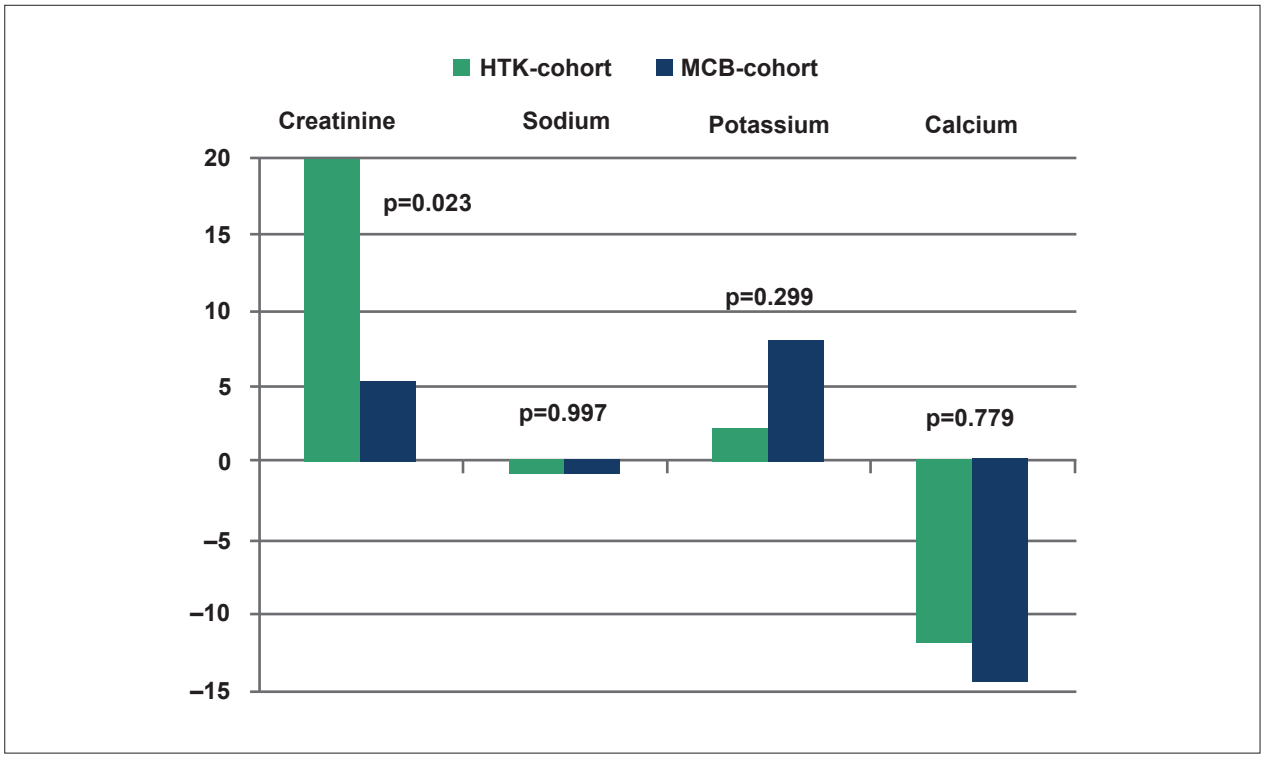

Figure 1B – *HTK vs. MCB cohort. PS-matched pairs. Differences on changes of blood levels of creatinine, sodium, potassium and calcium between the values early before surgery and the values immediately following patient admission to intensive care unit. HTK: histidine-tryptophan-ketoglutarate; MCB: multidose cold blood; PS: propensity score.*

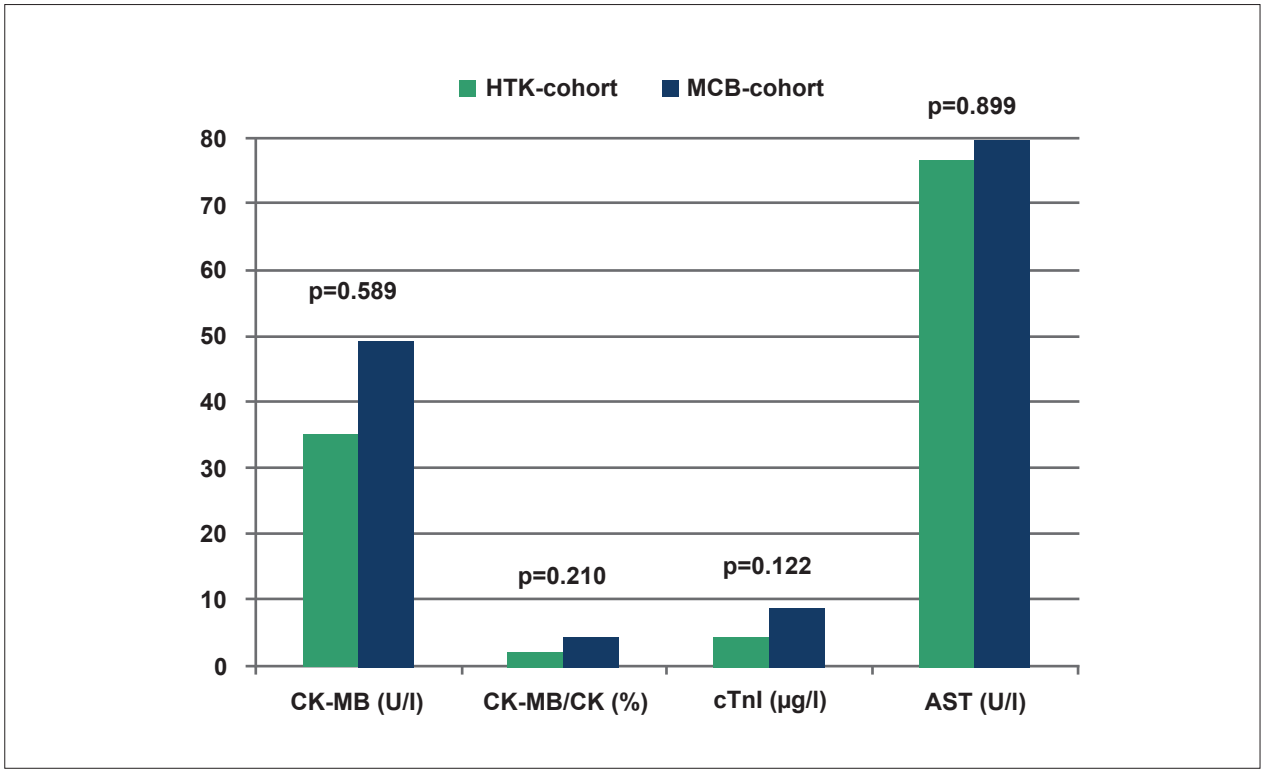

Figure 2 – *HTK vs. MCB cohort. PS-matched pairs. Differences on peak serum levels after surgery of CK-MB, CK-MB/CK, cTnI and AST. AST: aspartate aminotransferase; CK: creatine kinase; CK-MB: creatine kinase-MB; cTnI: cardiac troponin I; HTK: histidine-tryptophan-ketoglutarate; MCB: multidose cold blood; PS: propensity score.*

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Myocardial Protection in Cardiac Surgery - What is the Ideal Method?

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Short Editorial related to the article: Custodiol®-HTK Solution vs. Cold Blood Cardioplegia for Isolated Coronary Surgery Requiring Prolonged Cross-Clamp Time: A Propensity-Matched Analysis

The study of myocardial protection has improved together with cardiac surgery, aiming to prevent intraoperative myocardial injury, which can lead to ventricular dysfunction, arrhythmias, low cardiac output and other complications, often irreversible ones.

Since the first cardiac surgeries with cardiopulmonary bypass (CPB) in 1953 performed by Dr. Gibbon at Massachusetts General Hospital,[1] several methods of myocardial protection have been studied, allowing more extensive cardiac surgeries to be performed, with longer aortic clamping time. In the first surgeries, hypothermia was the method used for myocardial protection, but it showed to be insufficient for longer periods of ischemia.

In 1955, Melrose et al.[2] published in the Lancet a preliminary communication entitled "Elective Cardiac Arrest". The interesting thing is that the Melrose technique used blood as a vehicle for potassium citrate – thus laying the foundations for myocardial protection with blood cardioplegia, using potassium as a depolarizing solution, along the lines of what is done even today. Other agents were subsequently used, such as magnesium, procaine, chelators and calcium blockers, eventually associated among them, with the use of hypothermia or not. Substrates, such as glucose and oxygen, can be provided during the aortic clamping period, to ensure some aerobic metabolism during this period. The addition of other substrates, such as glutamate, aspartate and lactate, as well as ATP or creatine phosphate, precursors to Krebs cycle intermediates, can greatly improve myocardial protection. Several authors such as Buckberg[3] and, in our country, Dr. Braile,[4] have dedicated themselves to studying several possibilities to optimize myocardial protection.

According to several authors, the ideal cardioplegic agent must meet the following requirements:[5]

1. Cardiac arrest: rapid and effective induction of cardiac arrest with a relaxed myocardium and minimum ATP consumption;
2. Myocardial protection: protective effects to delay the irreversible cell damage caused by global ischemia and limit the extent of reperfusion injury;
3. Reversibility: immediate reversal of cardiac arrest with heart rate and contraction force, allowing an early "weaning" from CPB;
4. Low toxicity: short half-life without toxic effects on other systems or apparatus after CPB withdrawal.

Since its introduction, hyperkalemic cardioplegic solutions have become the gold standard in myocardial preservation. The electromechanical arrest of the heart can be achieved by depolarizing the extracellular membrane potential, which reduces the resting potential of ventricular myocytes. After an initial dose, when the electromechanical quiescence is achieved, intermittent doses (every 20 or 30 minutes) are necessary to maintain cardiac arrest and prevent myocardial dysfunction. The association of these solutions with the patient's own blood (blood cardioplegia) has shown a reduction in the levels of cardiac enzymes and reperfusion markers.[3]

The HTK solution (Custodiol®) is a crystalloid solution with a low concentration of sodium and calcium, which acts by causing the hyperpolarization of the myocyte plasma membrane through the depletion of sodium in the extracellular space, inducing cardiac arrest in diastole (unlike conventional cardioplegia – depolarizing). The combination of histidine, tryptophan and ketoglutarate in the formula reduces intracellular acidosis, improves ATP production and stabilizes the membrane, reducing ischemic damage. The HTK solution has been praised as the ideal protection against long-term cardiac surgery, being routinely used in heart transplantation, complex pediatric surgeries, aortic aneurysms and valve reoperations in most centers, as it offers myocardial protection for up to 3 hours with a single infusion of the solution.[6] However, this solution requires specific precautions, such as the management of hypervolemia (20 - 25 mL/kg of the solution infused right after the aortic clamping) and metabolic acidosis, which are usual when using this solution. The discussion about the use of the HTK solution in coronary artery bypass surgery is a relevant one, as it remains the most commonly performed cardiac surgery in Brazil. The work of Gatti et al.[7] has the merit of demonstrating the non-superiority of Custodiol® in relation to the conventional cardioplegic solution, which is significant in our country, since the use of this solution implies in additional costs without benefits in this population.

Even when considering only more complex cases, with multiple anastomoses and aortic clamping time longer than 120 minutes, there was a higher mortality rate in the group that used Custodiol® (5.3% x 1.8%) which was related to other outcomes analyzed, such as greater incidence of renal dysfunction, blood transfusion, intensive care and hospital length of stay, although the difference was not significant

Keywords

Thoracic Surgery; Myocardial Revascularization; Coronary Artery Bypass;Intraoperative Care; Cardioplegic Solutions.

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in the statistical analysis. In the analysis of variables related to the myocardium, the two solutions were shown to be equivalent, with no differences in the rates of infarction, low cardiac output, arrhythmia, inotropic use or in the levels of myocardial necrosis markers (troponin). Some studies have suggested the analysis of ventricular septal function as the best marker to determine postoperative myocardial injury, as the interventricular septum corresponds to 35-40% of the total ventricular muscle mass and is responsible for 80% of the right ventricular function.[8] Reynolds[9] reported that 40% of patients submitted to myocardial revascularization surgery and 60% of patients with valve surgery have paradoxical movement of the interventricular septum in the postoperative period, which denotes some degree of septal damage, often transient, and that is a valuable information that must be obtained by echocardiogram.

Undeniably, Custodiol® has its role in specific situations, where the use of a single dose is technically important, such as in heart transplantations, complex pediatric surgeries and in minimally invasive surgeries, where the infusion of repeated doses of the cardioplegic solution is not possible or is technically more difficult and prone to complications.

Other alternative solutions are still being studied for myocardial protection. In 1995, a new cardioplegic solution was introduced for congenital heart surgery, in a study carried out at the University of Pittsburgh.[10] The solution, patented as "Del Nido's solution", is a mixed depolarizing blood cardioplegia and crystalloid solution that offers safe myocardial protection for up to 90 minutes with a single dose. In addition to containing potassium chloride as a depolarizing agent, the formula also contains magnesium sulphate, mannitol, sodium bicarbonate and lidocaine, and is also being used in long-term cardiac surgeries in adults with excellent results and at low cost, being an alternative to commercially available solutions.

There is no best myocardial protection technique. Despite the wide variety of commercially-available cardioplegic solutions, there is no clear consensus about the ideal composition and techniques for using these solutions. In addition to choosing a solution for each patient, there is the question of the administration route (anterograde, retrograde or combined), in a single or intermittent dose, associated or not with hypothermia and other possibilities. Intermittent clamping (ischemia) without the use of cardioplegic solutions is another myocardial protection technique used by some groups with good results. The surgeons must be able to personalize their choices and choose the most adequate solution or technique for each patient according to the surgical planning, but the cost must also be a factor to be considered in our country, especially in the Public Unified Health System. More expensive solutions should be reserved for specific situations with proven benefit.

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Velocity-Time Integral of Aortic Regurgitation: A Novel Echocardiographic Marker in the Evaluation of Aortic Regurgitation Severity

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Abstract

Background: Echocardiography is essential for the diagnosis and quantification of aortic regurgitation (AR). Velocity-time integral (VTI) of AR flow could be related to AR severity.

Objective: This study aims to assess whether VTI is an echocardiographic marker of AR severity.

Methods: We included all patients with moderate or severe native AR and sinus rhythm who visited our imaging laboratory from January to October 2016. All individuals underwent a complete echocardiogram with AR VTI measurement. The association between VTI and AR severity was analyzed by logistic regression and multivariate regression models. A p-value<0,05 was considered statistically significant.

Results: Among the 62 patients included (68.5±14.9 years old; 64.5%: moderate AR; 35.5%: severe AR), VTI was higher in individuals with moderate AR compared to those with severe AR (2.2±0.5 m vs. 1.9±0.5 m, p=0.01). Patients with severe AR presented greater values of left ventricular end-diastolic diameter (LVEDD) (56.1±7.1 mm vs. 47.3±9.6 mm, p=0.001), left ventricular end-diastolic volume (LVEDV) (171±36.5 mL vs. 106±46.6 mL, p<0.001), effective regurgitant orifice (0.44±0.1 cm² vs. 0.18±0.1 cm², p=0.002), and regurgitant volume (71.3±25.7 mL vs. 42.5±10.9 mL, p=0.05), as well as lower left ventricular ejection fraction (LVEF) (54.1±11.2% vs. 63.2±13.3%, p=0.012). The VTI proved to be a marker of AR severity, irrespective of LVEDD, LVEDV, and LVEF (odds ratio 0.160, p=0.032) and of heart rate and diastolic blood pressure (DBP) (odds ratio 0.232, p=0.044).

Conclusions: The VTI of AR flow was inversely associated with AR severity regardless of left ventricular diameter and volume, heart rate, DBP, and LVEF. VTI could be a marker of AR severity in patients with native AR and sinus rhythm. (Arq Bras Cardiol. 2020; 115(2):253-260)

Keywords: Heart Failure; Aortic Valve Insufficiency/diagnosis,imaging; Echocardiography, Doppler/methods.

Introduction

Aortic regurgitation (AR) is one of the most common valvular disorders in the developed world.[1] Typical management of the condition involves a combination of clinical signs and symptoms and data collection through complementary testing. Echocardiography is a key tool for the diagnosis and quantification of AR,[2] and its proper interpretation requires an approach integrating qualitative, semiquantitative, and quantitative measures and parameters.[3,4] However, these parameters are not exempt from limitations.[3]

Velocity-time integral (VTI) is defined as the area measured below the Doppler velocity curve at any given point. In the case of AR, its value corresponds to the diastolic pressure gradient between the aorta and the left ventricle (LV).[5] In patients with AR, the VTI is multiplied by the aortic effective regurgitant orifice (ERO) to calculate the regurgitant volume (RV) (RV=EROxVTI).[2,6,7] This parameter has demonstrated its effectiveness in determining AR severity, even though the ERO value is calculated using the proximal isovelocity surface area (PISA) method, which is known to have inherent limitations in patients with AR.[3,8,9] Additionally, taking into account the aforementioned equation, patients with severe AR typically have larger RV[2] and ERO values,[7,10] but there is no evidence of the behavior of VTI in relation to AR severity.

Furthermore, patients with severe AR usually present increased end-diastolic pressure in the LV[11] as well as reduced diastolic blood pressure (DBP).[12,13] These pressure changes can

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pathophysiologically decrease VTI by reducing the pressure gradient between the aorta and LV. This study aimed to determine whether VTI is an echocardiographic marker of AR severity.

Methods

Study design and population

This retrospective cross-sectional observational study was performed over ten months (from January to October 2016). All patients with AR who visited our cardiac imaging laboratory during this period were eligible to participate. Patients had to exhibit moderate to severe AR in a native (non-prosthetic) valve as well as sign an informed consent form to be included in the study. We excluded patients with atrial fibrillation or evidence of any type of arrhythmia, multiple or eccentric jets of AR. The study complied with the declaration of Helsinki and was approved by the ethics committee of our local research panel.

Baseline Characteristics of the Population

We gathered the following demographic and clinical information from all study participants: age, gender, history of arterial hypertension, dyslipidemia, diabetes mellitus, and smoking habits. Any type of antihypertensive, hypolipidemic, or antiarrhythmic drugs that the subjects were taking at the time of their inclusion in the study was also recorded. During the echocardiogram, the height and weight of each patient were collected, and three arterial blood pressure measurements were taken after 5 minutes of rest, using an M6 Comfort HEM-7221-E8 (Omron Healthcare, Kyoto, Japan) blood pressure monitor – validated through Dabl®Educational Trust and British Hypertension Society protocols –, following the European Society of Hypertension/European Society of Cardiology (ESH/ESC) recommendations.[14] The final arterial blood pressure was the average of the second and third values. Heart rate (HR) was determined at the moment of the measurement of the VTI of AR. All patients also had a blood test performed immediately after collection to determine the plasma creatinine level and calculate the glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease – Epidemiology Collaboration) formula.[15] The blood test analyzer used was a PE Chemistry (Roche Diagnostics, Manheim, Germany).

Echocardiographic Variables

Echocardiograms were performed on all subjects with an Acuson Siemens SC2000 ultrasound system. We used the Simpson's biplane method to obtain standard measurements, images, and clips, including left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular ejection fraction (LVEF), in accordance with recommendations from the American Society of Echocardiography.[16] Both thickness and diameter were determined in M-mode with proper alignment whenever possible; otherwise, measurements were made in 2D. The measurement of the VTI of AR flow was taken using continuous Doppler readings from the view with the best alignment with the regurgitant jet, mainly the apical 5-chamber view (Figure 1) or the parasternal long-axis view in cases of vertical regurgitant jet. Given that HR behaves as a temporal determinant of aortic VTI, the VTI index (VTIi) was calculated in addition to the absolute VTI value by dividing VTI by HR (VTIi=VTI/HR). The morphology of aortic valves was examined from the parasternal short-axis view. The systolic diameters of the right and left ventricular outflow tract were also measured. Pressure half-time (PHT) was calculated using the apical 5-chamber view. The vena contracta (VC) was estimated with color Doppler in two orthogonal planes, according to the recommendations.[16] ERO was calculated based on the PISA method.[10,17] To that end, images of the regurgitant flow were obtained using the best possible view for the alignment of the convergent flow. When zoomed in at this view, the color Doppler scale was optimized until the isovelocity hemisphere could be adequately differentiated. The PISA radius was measured between the first aliasing circumference relative to the center of the hemisphere in protodiastole, at the exact moment that the regurgitant flow reaches its maximum velocity. The RV was defined as the ERO x VTI product. Additionally, whenever possible, the RV was also determined quantitatively by estimating the aortic and pulmonary systolic volume.[18] The flow reversal in the thoracic aorta was established using Pulse Doppler in the proximal end of the descending aorta through the suprasternal view. Holodiastolic flow with end-diastolic velocity >20 cm/s was considered a positive flow reversal. Finally, following a comprehensive and integrative analysis of the different structural, qualitative Doppler and the semiquantitative parameters obtained and taking into account the latest recommendations,[3,6] two experienced echocardiographers separately quantified the AR. A third experienced echocardiographer assessed and conclusively quantified the AR in case of discordance between the two first cardiologists.

Statistical Analysis

We tested all variables for normal distribution using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean±standard deviation (SD), and those with skewed distribution as median [interquartile range (IQR)]. Categorical variables were expressed as percentages. Correlations were studied through Spearman's or Pearson's method, as appropriate. Inter-rater variability for AR severity quantification was determined by the intraclass correlation coefficient and Bland-Altman plots.[19] Reliability analyses using kappa statistics (κ) defined the consistency between the two echocardiographers regarding AR severity (moderate or severe). Baseline differences between moderate or severe AR patients were assessed by unpaired Student's *t*-test or Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables. Logistic regression analysis evaluated the association between each baseline variable and severe AR. Multivariate logistic regression models determined the variables independently associated with severe AR. The variables included were those with $p<0.05$ in the univariate analysis, excluding RV, ERO, and

VC, as they were not available for all patients and could cause overfitting. Model performance for predicting severe AR was evaluated by calibration (Hosmer-Lemeshow statistic) and discrimination (C-index) measures, both internally validated using the bootstrap resampling technique. The association between the VTI of AR and its severity was explored through multivariate analysis regardless of HR and DBP. We evaluated the relationship between VTIi and AR severity with a new logistic regression analysis. Confidence intervals (95%CI) were provided when appropriate. All probability values were 2-sided, and p-value<0.05 was statistically significant. Statistical analysis was performed using the SPSS software, v.18.0 (SPSS Inc., Chicago, Illinois).

Results

The original sample consisted of 65 patients with moderate or severe native AR in sinus rhythm. Proper Doppler alignment of the regurgitant jet could not be obtained for three patients, who showed very eccentric jets, and were thus excluded. Out of the remaining 62 participants, 40 (64.5%) presented moderate AR, and 22 (35.5%) had severe AR. Acute AR was diagnosed in 4 patients (6.5% of the sample). The consistency among the quantification determined by the two echocardiographers was κ=0.83. All patients included were Caucasian. Table 1 presents the baseline characteristics of the sample.

As shown in Table 2, the VTI of the aortic regurgitant flow was higher in patients with moderate AR than in those with severe AR. The VTI range was 2.05 m [1.53–3.58 m] in the moderate AR group and 1.88 m [0.96–2.84 m] in the severe AR group. We found a significant and inverse correlation between VTI and HR [Pearson's correlation coefficient (r_p)=-0.408, p=0.001]. Patients with severe AR presented lower LVEF, higher LVEDD and LVESD, as well as a larger ERO, RV, and VC. However, the proper measurement of these parameters was only possible in 62.9% of the sample for ERO, 67.7% for RV, and 72.6% for VC. We underline that we identified no statistically significant association between AR severity and PHT, even though we detected a trend for it.

In the bivariate analysis (Table 3), VTI was inversely associated with AR severity. Besides, the classic severity variables related to the size and function of the left ventricle were associated with AR severity. In the multivariate analysis, the VTI value acted as a marker of AR severity regardless of LVEDD, left ventricular end-diastolic volume (LVEDV),

Table 1 – Baseline characteristics

Characteristic	Total (n=62)	Moderate AR (n=40)	Severe AR (n=22)	p-value
Age (years)	68.5±14.9	68.6±14.2	66.1±15.5	0.299
Male	33 (53.2)	20 (50)	13 (59.1)	0.492
BMI (kg/m²)	27.5±4.7	26.5±4	29.4±5.9	0.340
SBP (mmHg)	135.6±17.8	133.6±16.7	139.4±19.8	0.213
DBP (mmHg)	62.2±15.5	63.2±12.7	59.8±19.8	0.373
Heart rate	66.8±11.3	65.8±10.6	68.5±12.4	0.382
Arterial hypertension	45 (72.6)	29 (72.5)	16 (72.7)	0.985
Diabetes mellitus	11 (17.7)	8 (20)	3 (16.6)	0.530
Dyslipidemia	30 (48.4)	20 (50)	10 (45.5)	0.732
Active smokers	10 (16.1)	6 (15)	4 (18.2)	0.744
eGFR (mL/kg/1.73 m²)	77.3 [40.3]	86.6 [42.3]	72.9 [34.6]	0.408
Hemoglobin	13.2±1.8	13.3±1.8	13.2±2	0.893
Beta-blockers	29 (46.8)	17 (42.5)	12 (54.5)	0.363
ACE inhibitors	19 (30.6)	11 (27.5)	8 (36.4)	0.469
ARA	16 (25.8)	13 (32.5)	3 (13.6)	0.104
DHP CCB	2 (3.2)	2 (5)	0 (0)	0.286
Non-DHP CCB	10 (16.1)	4 (10)	6 (27.3)	0.145
Amiodarone	2 (3.2)	1 (2.5)	1 (4.5)	1
Diuretics	31 (50)	17 (42.5)	14 (63.6)	0.111
Statins	26 (41.9)	19 (47.5)	7 (31.8)	0.231
Previous hospital admission for HF	16 (25.8)	9 (22.5)	7 (31.8)	0.422

ACE: angiotensin-converting enzyme; AR: aortic regurgitation; ARA: angiotensin receptor antagonists; BMI: body mass index; CCB: calcium channel blockers; DBP: diastolic blood pressure; DHP: dihydropyridine; eGFR: estimated glomerular filtration rate; HF: heart failure; SBP: systolic blood pressure.
Continuous variables with normal distribution are expressed as mean±standard deviation, those with skewed distribution as median [interquartile range], and categorical variables as n (percentage).

Table 2 – Values of echocardiographic parameters

Parameter	Total (n=62)	Moderate AR (n=40)	Severe AR (n=22)	p-value
AR VTI (m)	2.1±0.5	2.2±0.5	1.9±0.5	0.010
AR VTIi (VTI/heart rate)	0.033±0.012	0.036±0.013	0.028±0.01	0.024
Aortic PHT (ms)	397.3±110.1	434.2±127	367.5±86.2	0.062
Vena contracta (mm)	6±1.5	5.5±1.5	7.1±1.2	0.035
ERO (cm^2)	0.31±0.2	0.18±0.1	0.44±0.1	0.002
Regurgitant volume (mL)	56.9±24	42.5±10.9	71.3±25.7	0.05
Thoracic aorta flow reversal	33 (53.2)	12 (30.8)	21 (95.5)	<0.001
IV septum thickness (mm)	13.1±3.6	12.5±3.5	13.8±3.5	0.460
Posterior wall thickness (mm)	10.6±2.8	10.3±2.7	11±3.1	0.383
LVEDD (mm)	50.5±9	47.3±9.6	56.1±7.1	0.001
LVESD (mm)	31±11.4	26.9±12.3	38.4±8.1	<0.001
LVEDV (mL)	131.9±54.3	106±46.6	171±36.5	<0.001
LVESV (mL)	53.6±36.1	39.9±32.2	78.7±27.5	<0.001
LVEF (%)	59.7±13.2	63.2±13.3	54.1±11.2	0.012
AR peak velocity (m/s)	4.2±0.51	4.3±0.5	4.1±0.52	0.344
Aortic systolic peak velocity (m/s)	2.7±1.2	2.8±1.4	2.7±0.9	0.791
Bicuspid aortic valve	5 (8.1)	3 (4.8)	2 (3.2)	0.826
Elevated LV filling pressure	26 (41.9)	16 (42.1)	10 (50)	0.566
Severe mitral regurgitation	2 (3.2)	2 (5)	0 (0)	0.286
Severe mitral stenosis	1 (1.6)	1 (2.5)	0 (0)	0.455
Severe aortic stenosis	8 (12.9)	6 (15)	2 (9.1)	0.507

AR: aortic regurgitation; ERO: effective regurgitant orifice; IV: interventricular; LV: left ventricle; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVESD: left ventricular end-systolic diameter LVESV: left ventricular end-systolic volume; PHT: pressure half-time; VTI: velocity-time integral; VTIi; velocity-time integral index. Continuous variables with normal distribution are expressed as mean±standard deviation and categorical variables as n (percentage).

Table 3 – Bivariate logistic regression model (dependent variable: severe aortic regurgitation)

	Odds ratio	95%CI	p-value
AR VTI	0.198	0.053–0.748	0.017
AR VTIi	<0.001	<0.001–0.005	0.033
LVEF	0.941	0.895–0.989	0.017
LVEDD	1.144	1.047–1.249	0.003
LVESD	1.119	1.044–1.199	0.001
LVEDV	1.032	1.015–1.049	<0.001
LVESV	1.034	1.013–1.057	0.002

95%CI: 95% confidence interval; AR VTI: velocity-time integral of aortic regurgitation; AR VTIi: velocity-time integral index of aortic regurgitation; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume.

Table 4 – Multivariate logistic regression model (dependent variable: severe aortic regurgitation)

	Odds ratio	95%CI	p-value
AR VTI	0.160	0.030–0.856	0.032
LVEF	1.005	0.933–1.082	0.895
LVEDD	1.049	0.934–1.178	0.419
LVEDV	1.030	1.009–1.052	0.005
	Odds ratio	**95%CI**	**p-value**
AR VTIi	<0.001	<0.001–<0.001	0.019
LVEF	1.007	0.932–1.089	0.859
LVEDD	1.063	0.939–1.204	0.333
LVEDV	1.032	1.010–1.055	0.005

95%CI: 95% confidence interval; AR VTI: velocity-time integral of aortic regurgitation; AR VTIi: velocity-time integral index of aortic regurgitation; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction.

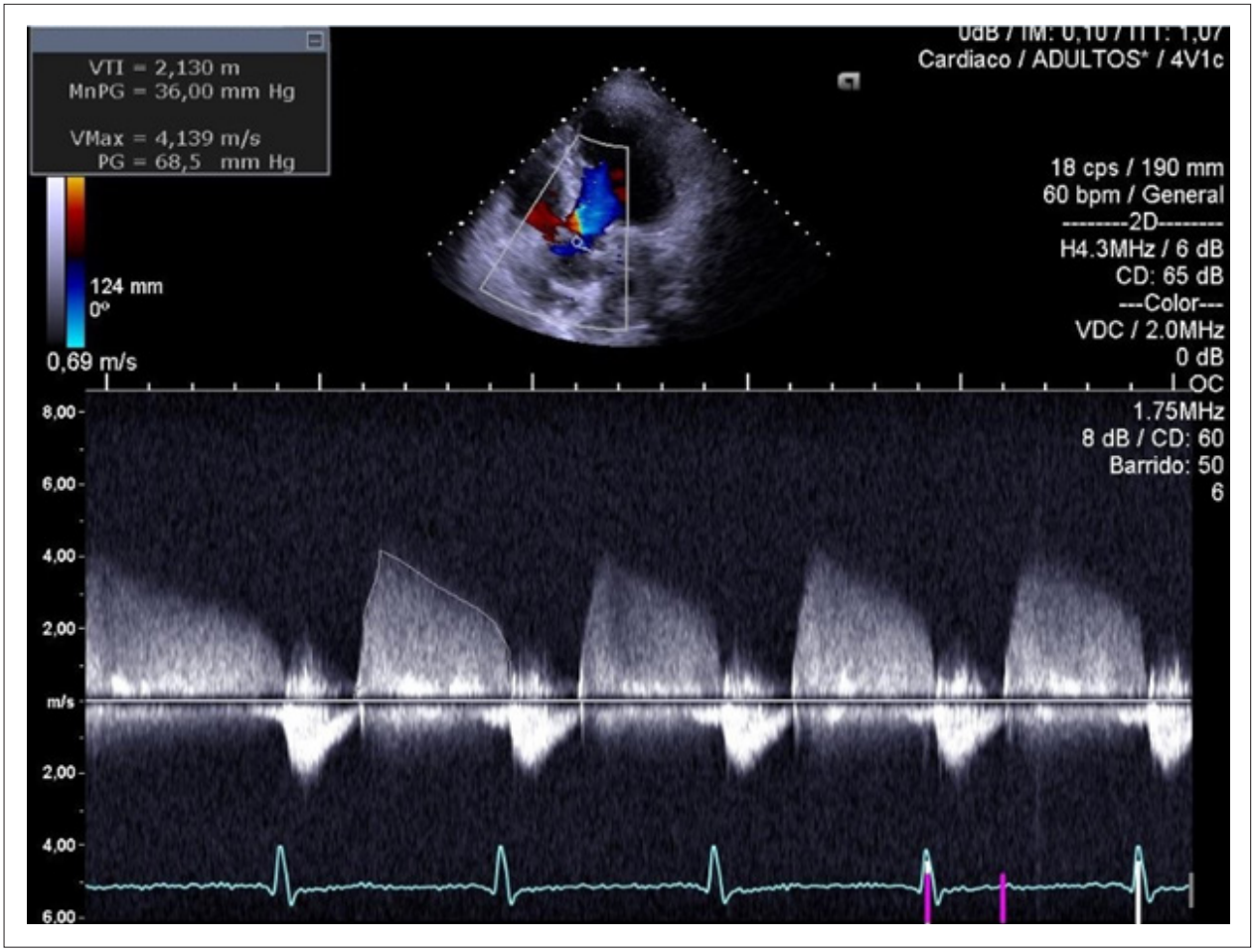

Figure 1 – *Measurement of the velocity-time integral of aortic regurgitation flow from the apical 5-chamber view. MnPG: mean pressure gradient; PG: maximum pressure gradient; Vmax: maximum aortic regurgitant flow velocity; VTI: velocity-time integral of aortic regurgitation.*

and LVEF (Table 4). LVESD and left ventricular end-systolic volume were excluded from the multivariate analysis due to collinearity with LVEDD (r_p=0.905, p<0.001) and LVEDV (r_p=0.871, p<0.001), respectively. We also excluded ERO, RV, and VC from the multivariate analysis as they could not be obtained for all patients due to poor ultrasound window or difficulty in measuring. This model showed greater discrimination (Statistic C=0.837, 95%CI 0.728–0.947) and an accurate calibration (Hosmer-Lemeshow χ^2=2.30, p=0.970).

On the other hand, since HR and DBP could pathophysiologically influence the VTI measurement (DBP as a determinant of velocity, and HR of time), the association between VTI and AR severity was assessed adjusting for HR and DBP. VTI was also inversely related to AR severity, irrespective of these factors (OR 0.232, 95%CI 0.056–0.961, p=0.044). Finally, the VTIi of AR also showed an inverse association with AR severity (Table 3) and acted as a marker of AR severity, regardless of LVEDD, LVEDV, and LVEF in the multivariate analysis (Table 4). Additionally, this variable was also related to AR severity, irrespective of DBP (OR<0.001, 95%CI <0.001–0.001, p=0.029).

Discussion

This study suggests that the VTI of AR can be used as a marker of severity in patients with significant AR, considering that estimating severity through echocardiography is a difficult process involving the integration of several different tests and parameters.[2-4,20]

Effectively, ERO by the PISA method works as a parameter for the stratification of AR severity,[3,7] and an indirect relationship can be found between ERO and VTI (ERO=RV/VTI).[3,10] More severe AR presents a larger ERO and RV, but the behavior of VTI is unknown. In this study, the VTI of the aortic regurgitant flow was inversely associated with AR severity. The scientific evidence available corroborating this relationship is scarce. Zarauza et al.[21] published a study that assessed the value of VTI of AR, amongst other parameters, in a sample of 43 patients with moderate to severe AR.[21] Their findings were similar to ours (severe AR VTI: 1.8±0.7 m vs. 1.9±0.5 m; moderate AR VTI: 2.2±0.8 m vs. 2.2±0.5 m, respectively). However, in the study by Zarauza et al.,[21] the differences between VTI in severe and moderate AR did not reach statistical relevance. The difference in sample size for patients with moderate AR

(15 vs. 40) could explain the lack of a significant result. To the best of our knowledge, no other study has assessed the value of VTI as an indicator of AR severity.

A remarkable aspect of the present study is the direct association between AR severity and end-diastolic and end-systolic diameters and volumes, in addition to the inverse relationship to LVEF. These findings are consistent with available scientific evidence, which supports the predictive role of left ventricular diameter and ventricular function as markers of advanced AR and negative prognoses.[11,22-24] In our opinion, this aspect reflects an appropriate and rigorous methodology for measuring these parameters. This study found that the relationship between VTI and AR severity did not depend on echocardiographic variables, such as left ventricular diameters, volumes, or ejection fraction. This result could potentially support the use of VTI as an indicator in most echocardiographic scenarios involving AR and sinus rhythm.

Despite being echocardiographic methods recommended for determining the severity of significant AR,[3,25,26] the calculations necessary to estimate VC, RV, and, as we previously mentioned, ERO obtained by PISA present several limitations.3,8,9,17 In fact, this study could not evaluate whether the VTI value was associated with severe AR, regardless of ERO, RV, or VC, as the percentage of patients from whom this data could be obtained was not enough to perform a valid multivariate analysis. In contrast, VTI could not be estimated in only 3 of the 65 patients of this study due to improper alignment of the AR jet. Thus, VTI has proven to be a reproducible parameter that can be easily obtained and examined in most patients and could provide valuable information for the stratification of AR severity.

We also emphasize that although PHT was obtained for all patients who had their VTI calculated, we found no significant differences between individuals with moderate and severe AR, which prevented the inclusion of this parameter in the multivariate analysis. Therefore, we could not assess the additional value of VTI with respect to PHT. Current clinical guidelines suggest that the usefulness of PHT is low in cases of chronic AR,[2,3] and the sample of the present work consists mainly of chronic AR patients. The low rate of acute AR in the present study (6.5%) precluded a feasible statistical evaluation of the acute AR cohort. This issue could explain the lack of differences in the PHT values between the moderate and severe AR groups.

Our results also suggest that the association between lower VTI and severe AR does not seem to be significantly affected by hemodynamic variables, such as HR and DBP. If other studies supported this relationship behavior, the use of VTI could reach a wide variety of patients. However, we consider that the relationship between VTI and AR severity could not be significantly changed by these hemodynamic variables due to a lack of extreme values. We highlight that we found a tendency for lower DBP in patients with severe AR and that we excluded patients with atrial fibrillation. Thus, since HR is a temporal determinant for the VTI of AR, we also calculated the VTI indexed by HR to normalize the VTI value and further study its relationship to AR severity. Additionally, HR correlated significantly and inversely with AR VTI. The relationship between this new variable and AR severity was not only maintained but proved to be stronger and independent of LVEDD and LVEF (OR<0.001, p=0.031). In other studies, such as the one by Zarauza et al.,[21] VTI was normalized using the diastolic length.[21] However, there are few levels of consistency throughout the indexing of VTI in terms of HR. We believe that these findings support the pathophysiological hypothesis that a smaller VTI is associated with a more severe AR, regardless of the HR.

Our study presents several limitations. First, this is a single-center study that did not analyze patients with AR and atrial fibrillation or prosthetic valves, and thus the value of the aortic VTI in those subpopulations is unknown. Second, the VTI was obtained by Doppler imaging, and, therefore, it is subject to the limitations of this technique. Additionally, our analyses only included patients with moderate or severe AR in an attempt to avoid a potential underestimation in the VTI measurement of low-density mild regurgitant jets; thus, the usefulness of VTI in determining the severity of mild AR remains unclear. ERO, RV, and VC could not be obtained for all patients, partially due to the retrospective nature of the present paper, preventing the assessment of the VTI value with respect to these parameters in predicting severe AR in a multivariate analysis. No other exploration techniques, such as transesophageal echocardiogram, 3D ultrasound, or cardiac magnetic resonance, were performed to study the AR severity or the mechanism of regurgitation in depth.[27,28] Moreover, the lack of a gold standard method precluded a more accurate assessment of the VTI value. Otherwise, the ranges of the VTI values obtained made inaccurate the calculation of a valid cut-off point. Thus, the small number of patients included prevented a cross-sectional validation of the VTI measured, making it difficult to reach solid conclusions. Lastly, we performed no clinical follow-up of the sample, making it impossible to know whether the VTI value has any prognostic or clinical implications.

Conclusions

The VTI of AR is an easily obtainable and reproducible ultrasound parameter that seems to be associated with AR severity. Further studies are necessary to evaluate whether this parameter is capable of providing additional diagnostic and prognostic information for patients with AR, and whether it is useful in other clinical scenarios, such as atrial fibrillation and in individuals with prosthetic valves.

Author Contributions

Conception and design of the research and Writing of the manuscript: Abellán-Huerta J, Bonaque-González JC; Data acquisition: Abellán-Huerta J, Rubio-Patón R, García-Gómez J, Egea-Beneyto S, Soto-Ruiz M; Analysis and interpretation of the data: Consuegra-Sánchez L, Castillo-Moreno JA; Critical revision of the manuscript for intellectual content: Soria-Arcos F, Ramos-Martín JL, Castillo-Moreno JA.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

Sources of Funding

There was no external funding source for this study.

Study Association

This study is not associated with any thesis or dissertation.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Comisión Investigación Área II SMS under the protocol number 2015-068. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Original Article

Assessment of Aortic Valve Regurgitation by Echocardiography: Basic and New Concepts

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Short Editoral related to the article: Velocity-Time Integral of Aortic Regurgitation: A Novel Echocardiographic Marker in the Evaluation of Aortic Regurgitation Severity

Echocardiography remains the gold standard for the diagnosis and grading of valvular heart diseases,[1] despite the development of other imaging modalities. Aortic valve regurgitation (AR) is a common valvular disorder,[2] which can also be one of the most challenging to accurately quantify. Echocardiography helps in assessing the severity of AR utilizing multiple two-dimensional, three-dimensional and color Doppler techniques, but most importantly, offers a unique opportunity for hemodynamic evaluation, which is extremely important when grading the severity of AR.

In the article entitled: "Velocity-time integral of aortic regurgitation: a novel echocardiographic marker in the evaluation of aortic regurgitation severity", the authors tested, as a proof of concept, the correlation between AR velocity-time integral (VTI) and the severity of aortic valve regurgitation in a multivariate analysis and showed the inverse correlation between AR VTI and AR severity, regardless of left ventricular diameter, volume, heart rate, diastolic blood pressure or left ventricular ejection fraction. They also showed that AR VTI is an easily obtainable and reproducible method to assess AR severity when compared to other commonly used methods, such as Proximal Isovelocity Surface Area (PISA). This study introduces an interesting and promising concept that will add to confidence level when assessing AR severity. It also makes physiological sense, as patients with severe AR will have a smaller diastolic gradient between the aorta and the left ventricle (higher left ventricular end diastolic pressure and lower diastolic blood pressure), which will theoretically result in a smaller AR VTI value due to rapid equalization of pressure between the aorta and the left ventricle.

It is worth noting, however, that there are a few limitations to this study. First, there is a lack of a gold standard for the assessment of AR severity other than an "expert opinion". Second, the severe AR group is probably consisted of two separate groups: the acute severe AR group and the chronic severe AR group. It is important to distinguish between these two groups as chronic, well compensated, severe AR is likely to be hemodynamically similar to moderate AR with a larger AR VTI value, when compared to those with acute severe AR. The lack of association between AR severity and pressure half time in this study supports the fact that the severe AR group is probably a mix of patients with variable chronicity. Third, some AR jets will be very challenging to sample by continuous wave Doppler, given their eccentricity. This is mainly notable in patients with bicuspid or unicuspid aortic valves, which tend to have very eccentric regurgitant jets. Finally, a clinical follow-up to assess survival, need for aortic valve surgery or other adverse events based of AR VTI value will be needed to verify the utility of the concept.

Conclusion

Introducing new concepts or techniques that can help grading AR severity is a valuable resource. AR VTI is a promising concept that is physiologically sound and appears reproducible. Larger clinical trials will be needed to further assess its role and, more importantly, its prognostic value and correlation with clinical outcomes.

It is imperative, however, to keep in mind that it is very unlikely that we will find a single echocardiographic marker that will be a gold standard when assessing AR severity. The echocardiographist has to keep an open mind and integrate all available data to come to a final conclusion. This includes the following:[1]

1- Clinical data (wide pulse pressure, heart rate, symptoms)

2- Two-dimensional and three-dimensional evaluation of the aortic valve (valve anatomy assessing for number of leaflets, perforations, vegetation, cusp prolapse etc...) and cardiac chambers (LV and RV size and function, LA size)

3- Color Doppler (Vena Contracta,[4] jet width compared to LVOT width, PISA[5] evaluation when feasible and 3D color Doppler quantification[6])

4- Spectral Doppler (Jet signal density, pressure half time, AR VTI, LVOT VTI, aortic valve VTI, mitral inflow pattern, right ventricular systolic pressure estimation etc…).

However, as with other valve lesions, echocardiographists and trainees should refrain from diagnosing AR severity based on color Doppler alone, even if it is tempting to do so initially. Assessing the hemodynamic consequences of AR should be a key component of the evaluation. For example, diagnosing severe AR in the setting of a normal left ventricular end diastolic size, without diastolic flow reversal in the descending thoracic or abdominal aorta, or with a normal pulse pressure is unlikely to be accurate and should be reassessed.

Keywords

Aortic Valve Insufficiency; Aortic Regurgitation; Blood Fow Velocity; Diagnostic, Imaging; Echocardiography; Echocardiography, Doppler; Echocardiography, Three-Dimensional.

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Furthermore, utilizing other modalities to assess AR severity might be needed when echocardiographic and clinical data are inconclusive or contradictory. Cardiac Magnetic Resonance Imaging (MRI) has an important and promising role in assessing AR severity, especially with eccentric jets or peri-prosthetic valvular leaks. It helps assess the regurgitant fraction utilizing phase-contrast imaging and left and right ventricular size and function with good accuracy.[7] Cardiac Computed Tomography (CT) can also be helpful to identify peri-prosthetic leaks and guide surgical and percutaneous procedures.[8] Finally, a well-performed aortogram carried out in the catheterization laboratory can be very valuable, when other testing modalities are inconclusive.

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Review Article

Serum Levels of BDNF in Cardiovascular Protection and in Response to Exercise

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Abstract

Cardiovascular disease (CVD) is currently the leading cause of death in Brazil and worldwide. In 2016, CVD accounted for more than 17 million deaths, representing 31% of all deaths globally. Molecular and genetic mechanisms may be involved in vascular protection and should be considered in new therapeutic approaches. In this sense, recent studies have reported that brain-derived neurotrophic factor (BDNF) is reduced in individuals predisposed to develop CVD, and that aerobic physical training increases the amounts of circulating BDNF. BDNF is a neurotrophin found at high concentrations in the hippocampus and cerebral cortex and is considered a key molecule for the maintenance of synaptic plasticity and survival of neuronal cells. In addition to neuronal plasticity, BDNF is also important in vascular function, promoting angiogenesis through the regulation of reactive oxygen species (ROS). However, a variant of the BDNF gene in humans, the Val66Met polymorphism (substitution of the amino acid valine for a methionine at position 66 of the codon), occurring in 20-30% of the Caucasian population, may affect plasma BDNF concentrations and its activity in all peripheral tissues containing tyrosine kinase B receptors (TrkB), such as the endothelium. Thus, we will present a discussion about the role of serum BDNF levels in cardiovascular protection, Val66Met genetic variant in vascular reactivity and the effect of physical exercise.

Introduction

The main causes of death from noncommunicable diseases are cardiovascular diseases (CVD). Across the world, CVD deaths increased 12.5% between 2005 and 2015, reaching 17.9 million deaths.[1] In Brazil, CVD mortality accounted for 28% of all deaths in the last five years, accounting for 38% of all deaths in the productive age range (18 to 65 years).[2]

Keywords

Cardiovascular Diseases/mortality; BDNF; Brain-Derived Neurotrophic Factor; Endothelium Vascular; Nerve Growth Factors; Neuronal Plasticity; Polymorphism; Exercise.

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The most relevant CVD in terms of public health are heart (coronary artery disease and heart failure) and cerebrovascular diseases. Risk factors for CVD are well known (among them, obesity, dyslipidemia, diabetes and sedentary lifestyle). However, its molecular basis is complex and is linked to a wide range of biological pathways, including lipid and glucose metabolism, inflammation, vascular repair and angiogenesis.

The main etiology of CVD is atherosclerosis, a complex chronic inflammatory process of the arterial wall that involves the recruitment and activation of cells in the lesion of the intima layer. This endothelial cell activation by inflammatory cytokines and oxidized lipoproteins, followed by increased adhesion of circulating blood monocytes to the endothelium and migration of vascular smooth muscle cells into the developing neointimal layer, leads to the development of the atherosclerotic plaque, progressively obstructing the vascular lumen and reducing blood flow.[3] In addition, atherosclerosis occurs in endothelial dysfunction, characterized by reduced bioavailability of nitric oxide (NO) on the wall of blood vessels.[4]

Endothelial dysfunction is a marker of cardiovascular risk and is present in CVD such as hypertension, coronary artery disease and chronic heart failure.[5] Several factors have been associated with the endothelium-dependent blood flow modulation, such as the bioavailability of L-arginine, tetrahydrobiopterin (BH4), LDL-cholesterol and vascular endothelial growth factor (VEGF) levels, among others.[4]

Although the brain-derived neurotrophic factor (BDNF) is directly related to the health of neurons,[6] translational and clinical experimental studies have demonstrated their strong association with the vascular system. In fact, initially neurotrophins had their actions identified basically in the development and maturation of the nervous system. However, since the late 1990s, strong evidence has emerged in the literature that neurotrophins are implicated in important cardiovascular functions.[7] More recently, an important study has demonstrated the association of circulating BDNF to the vascular system, specifically angiogenesis, through the regulation of reactive oxygen species (ROS).[8] Thus, in addition to the nervous system function, accumulated evidence suggests that BDNF is also important for the cardiovascular system.

Because of the association between BDNF and angiogenesis, increased vasodilation and tissue perfusion, this neurotrophin is another important link between lifestyle and vascular health, with repercussions on brain structure and cognitive function in older adults.[9] A lifestyle that includes cognitive engagement, regular exercise, and a healthy diet is a key strategy to maintain brain health during the aging process.[9]

In this context, several studies have shown that exercise is one of the main factors in increasing serum BDNF levels[10-12]

and that increasing BDNF levels is the key element that links exercise to cognitive benefits.[13] However, variations in the levels of circulating BDNF, including its increase in response to physical training,[12] can be explained by a genetic variant of BDNF, a functional single-nucleotide polymorphism (SNP), responsible for the substitution of the amino acid Valine to Methionine at position 66 of the codon. The Val66Met polymorphism, a condition that occurs in 20-30% of the Caucasian population,[14-16] impairs both regulated secretion and intracellular traffic of BDNF.[14,17] These new findings have opened a new field of research in cardiovascular and therapeutic medicine.

Brain-Derived Neurotrophic Factor (BDNF)

BDNF is the most expressed neurotrophin in the central nervous system, found at high concentrations in the hippocampus and cerebral cortex. It is a key molecule involved in the maintenance of synaptic plasticity and synaptogenesis of the hippocampus, a site of memory acquisition and consolidation.[18,19] The altered production and secretion of BDNF have been demonstrated in several neurodegenerative disorders , such as Alzheimer's and Parkinson's disease.[20-22] In cognitively normal individuals, the concentration of BDNF in the cerebrospinal fluid decreases throughout life in the absence of dementia, and a lower concentration of BDNF in the cerebrospinal fluid was strongly associated with impaired memory and lower executive function.[23] Current knowledge points to the fact that abnormal cognition is associated with BDNF decrease in the hippocampus, which is a determining factor in the impairment of factors such as learning skills, depression, mood, anxiety disorders and schizophrenia.[24]

While BDNF promotes neuronal survival and enhances synaptic plasticity by activating its tyrosine kinase receptor B (TrkB), its precursor, proBDNF, acts antagonistically, resulting in cell apoptosis when interacting with the p75 receptor of neurotrophins (p75NTR). This important function demonstrates that both are involved in different physiological functions.[25,26]

The BDNF is produced presynaptically in the cell bodies of the sensory neurons projected in the dorsal horn, whereas in the hippocampus it is produced predominantly by the postsynaptic dendrites.[22,27,28] Peripherally, serum BDNF is found in blood plasma platelets and consists of vascular endothelial cells and peripheral mononuclear blood cells.[29,30] Its therapeutic potential is characterized by its ability to freely cross the blood-brain barrier in both directions via high saturation capacity of the carrier system.[22,30,31] In the peripheral nervous system, BDNF still plays an additional role, acting on axonal regeneration. It is worth mentioning that the BDNF gene and its TrkB receptor are expressed not only in the brain, but also in other parts of the body, such as the heart, lungs and endothelial tissue, [26,32,33] demonstrating its function in other organs and tissues of the body.

The BDNF gene is located on the short arm (p) of chromosome 11 (11p13) and comprises 11 exons and 9 functional promoters.[34]

A naturally-occurring functional polymorphism in the human BDNF gene at nucleotide 196 (G/A) encodes a substitution of amino acid valine to methionine at position 66 (Val66Met or Met66Met), which besides resulting in lower production and circulating amounts of BDNF,[14] has been associated with greater susceptibility to neurodegenerative disorders. Functionally, the Met66Met and Val66Met polymorphisms cause impairments in the intracellular traffic and in regulated secretion in neurons.[14,17]

In fact, the inheritance of this polymorphism has been associated with poor cognitive performance in healthy elderly individuals[35] and memory impairment of individuals.[14] Additionally, the Val66Met polymorphism leads to 4 to 11% lower hippocampal volume observed by magnetic resonance imaging in healthy adults.[23]

BNDF and Cardiovascular Function

The link between heart disease and cognitive impairment has been reported in the literature.[36,37] Some authors believe that the mechanism of "cardiogenic dementia" involves chronic cerebral hypoperfusion caused by the reduction in cardiac output due to various cardiovascular diseases.[38,39] Although the association between cognitive disorders and cardiovascular risk factors is a complex one and possibly mediated by different mechanisms, the presence of clinically manifest or silent cerebral microvascular changes are involved. In addition, a recent study[24] provided new insights into the potential molecular mechanism by which heart disease induces brain dysfunction. These authors, studying a transgenic mouse model that has specific microRNA-1-2 (miR-1-2) cardiac overexpression, have observed that cardiac overexpression of miR-1 also induced behavioral abnormalities that are associated with the negative regulation of BDNF expression in the hippocampus. A broader understanding of how heart disease affects cognitive function may lead to new therapeutic strategies.

The importance of circulating levels of BDNF in cardiovascular protection was evident in the prospective cohort study of the Framingham Heart Study (FHS).[40] To evaluate a potentially causal association between the levels of BDNF and CVD, a Mendelian randomization analysis was performed using the goals of the CARDIoGRAM (Coronary Artery Disease Genome-Wide Replication and Meta-Analysis) study. In this study, conducted with a large community-based sample, the researchers observed that higher levels of BDNF are associated with a lower risk of cardiovascular events and death, regardless of the standard risk factors, including low-grade inflammation markers, body mass index (BMI), physical activity and depression.[40]

In fact, an important role of BDNF in the cardiovascular system is the promotion of vascular angiogenesis and increase in capillary density.[41] Studies have shown that BDNF acts on endothelial cells promoting neovascularization in response to hypoxic stimuli via the Akt pathway.[42-44]

The first evidence of BDNF involvement in the angiogenesis process came from the study by Donovan et al.[45] about the development of the embryonic myocardium, in which it was shown that the overexpression of BDNF is associated with an increase in capillary density. Recently, an elegant experimental study demonstrated for the first time that BDNF promotes the formation of angiogenic tubes through the generation of ROS

derived from NADPH oxidase (NOX) by TrkB receptor signal transduction, probably via Akt activation , resulting in the migration of endothelial cells.[8] The study suggests that: TrkB ⇒ NADPH oxidase 2 (Nox2) ⇒ ROS ⇒ Phosphoinositide 3-kinase (PI3K)/Akt. [8]

In fact, BDNF has been consistently implicated in the angiogenesis and maintenance of vascular integrity. Specifically in the endothelium, besides the binding of BDNF to its high affinity receptor TrkB,[25,46] there is also the expression of the p75 receptor, of which binding to the pro-BDNF has been related to vascular smooth muscle apoptosis.[47,48] Considering the conjugated localization of BDNF-TrkB and pro-BDNF-p75 in the endothelium and due to the antagonistic physiological action between BDNF and pro-BDNF, it is important to take into account the balance between plasticity/survival and apoptosis in peripheral blood flow through the BDNF/pro-BDNF ratio.

More recently, the link between this neurotrophic and cardiovascular protection was evidenced in the study by Okada et al,[49] conducted with conditional BDNF-knockout mice, in which BDNF expression was systemically reduced. In this study, the authors demonstrated that a mechanism mediated by the Central Nervous System is involved in the regulation of cardiac function after myocardial infarction. Ischemic insults are transmitted from the heart to the Central Nervous System through afferent cardiac fibers after the myocardial infarction, thereby increasing BDNF neuronal expression. An increase in circulating BDNF promotes the survival of cardiomyocytes and is associated with increased expression of pro-angiogenic factors. Comparatively, knockout animals had greater myocardial damage after the experimental infarction compared to wild-type mice.[49]

In this context, the Val66Met polymorphism can affect serum concentrations of BDNF and, consequently, influence the activity of tissues containing TrkB receptors, be they neurons or even peripheral tissues, such as vascular endothelial cells.

BDNF and Cognitive Effects of Exercise

There is much evidence that physical exercise, especially aerobic exercise, has a beneficial effect on cognitive domains, particularly on executive and memory functions and reduces hippocampal atrophy in late adulthood, with BDNF being heavily involved.[11,50-57]

Epidemiological and intervention studies reinforce the idea of using physical activity as a strategy to increase neuroplasticity in pathological conditions.[58] Several studies have shown that exercise not only causes structural changes in the brain, but also protects against aging-related cognitive decline.[57,59]

Physical exercise activates molecular and cellular cascades that promote neuronal plasticity and neurogenesis, inducing expression of the gene encoding BDNF.[10,60] Peripheral concentrations of BDNF increase in both acute and chronic aerobic exercise, and the magnitude of this increase seems to be dependent on exercise intensity.[61]

In addition, greater cognitive benefits are obtained when the duration of the program and the exercise session are longer, individuals are older, with greater benefits for women than for men.[56] The difference between genders regarding BDNF levels in cerebrospinal fluid in favor of women may be due to hormonal effects,[23] since estrogen receptors are located in cells expressing BDNF and its TrkB receptor, so that estrogen regulates the expression of BDNF.[62]

Interestingly, this benefit of exercise occurs even in young adult men. This was evidenced in a cohort study of young Swedish men enlisted in military service at age 18 (n=1,221,727),[50] in which a significant positive association was found between cardiovascular fitness and cognitive performance after adjusting for relevant confounders.

Largely, the benefits of exercise on the production of BDNF and neuronal plasticity are related to increased cerebral and muscle vascularization. In fact, in a recent review[63] the authors have shown that the cognitive benefits of good cardiovascular fitness are related to increased cerebral circulation and angiogenesis. This important adaptation allows increased flow and upregulation of neurotrophins in the neurogenic niche of the hippocampus, a phenomenon that occurs even after acute exercise sessions.[63]

Specifically, studies on the acute and chronic effects of exercise on serum BDNF concentration still yield controversial results. For example, in a study comparing the chronic and acute effects of physical exercise on the serum concentrations of BDNF, it was demonstrated that a single exercise session was able to induce a transient increase in BDNF levels, but the same results were not achieved after a longer period of training.[64] On the other hand, in another study where the sample was submitted to 6 months of training, a trend in an increase in serum BDNF concentration was found, in addition to an improvement in cognitive function.[65] A similar result was found in a longitudinal study with the elderly, which resulted in an increase in the volume of hippocampal parts and, according to the authors, this fact is related to the increase in BDNF levels.[51]

These apparently controversial results may be dependent on the duration of the exercise benefits, specifically on post-exercise BDNF plasma levels, i.e., whether they occur soon after a single session of acute exercise, after a session of a regular exercise program (showing changes in BDNF release after repeated exercise sessions) or changes in resting BDNF levels after a regular exercise program.[66] Indeed, this was evidenced in the recent meta-analysis on the effects of exercise on serum BDNF,[66] which concluded that regular exercise intensified the effect of an exercise session on BDNF levels (Hedges' g =0.59; P=0.02). However, the results indicated a lower effect of regular exercise on resting BDNF levels (Hedges' g =0.27; P=0.005). There is reliable evidence from human studies indicating that each exercise episode results in a BDNF dose response and that the magnitude of this response can be increased over time through regular exercise.[66]

There is a large body of evidence that demonstrates that exercise works on several powerful neuroprotective pathways that can converge to promote continued brain health into senescence. These benefits occur either in response to acute activities or in regular practice and occur both in response to high-intensity exercises and in moderate-intensity aerobic exercises, increasing levels of circulating neurotrophic factors and neurotransmission, exerting beneficial effects on mood and cognitive functions in individuals of all ages.

BDNF and Cardiovascular Effects of Exercise

In the cardiovascular system, BDNF is involved, at least in part, in vascular endothelial benefits. In addition, a recent study found that active older men have significantly higher plasma BDNF levels compared to their inactive peers. In this study, BDNF correlated with VO_2max (R=0.765, p<0.001). Additionally, there was an inverse correlation between BDNF and the atherogenic index (TC / HDL), hsCRP and oxLDL. These findings demonstrate that a higher level of cardiorespiratory fitness is associated with a higher level of circulating BDNF, which in turn is related to lower cardiovascular risk.[67]

However, it is possible that polymorphisms may influence the beneficial effects of exercise. We have recently observed that peripheral vascular reactivity and serum BDNF responses to physical training are impaired by the BDNF Val66Met polymorphism, a responsiveness that is associated with serum BDNF concentrations in healthy individuals.[12]

Considering all of the above, the importance of physical exercise in promoting brain and cardiovascular health is gaining recognition, whether in the physiological condition of the brain aging process or in individuals affected by the early stages of neurodegeneration. In fact, the various animal and human studies suggest that physical activity may reduce the risk of cognitive decline, and therefore, an active lifestyle may be considered a preventive strategy for brain health deterioration, just as it occurs with cardiovascular dysfunction.

Undoubtedly, with increasing longevity, long-term preventive approaches, with an emphasis on promoting positive health habits that delay cognitive decline and its progression, are increasingly important. It is worth remembering that in addition to modulating the internal brain environment, the regular practice of physical exercise acts directly on the cardiovascular, immune and metabolic systems, playing an essential role in a healthy lifestyle.

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Conception and design of the research: Trombetta IC, Lemos Jr. JR; Writing of the manuscript: Trombetta IC, DeMoura JR, Alves CR, Carbonari-Brito R, Cepeda FX, Lemos Jr. JR; Critical revision of the manuscript for intellectual content: Trombetta IC, Lemos Jr. JR.

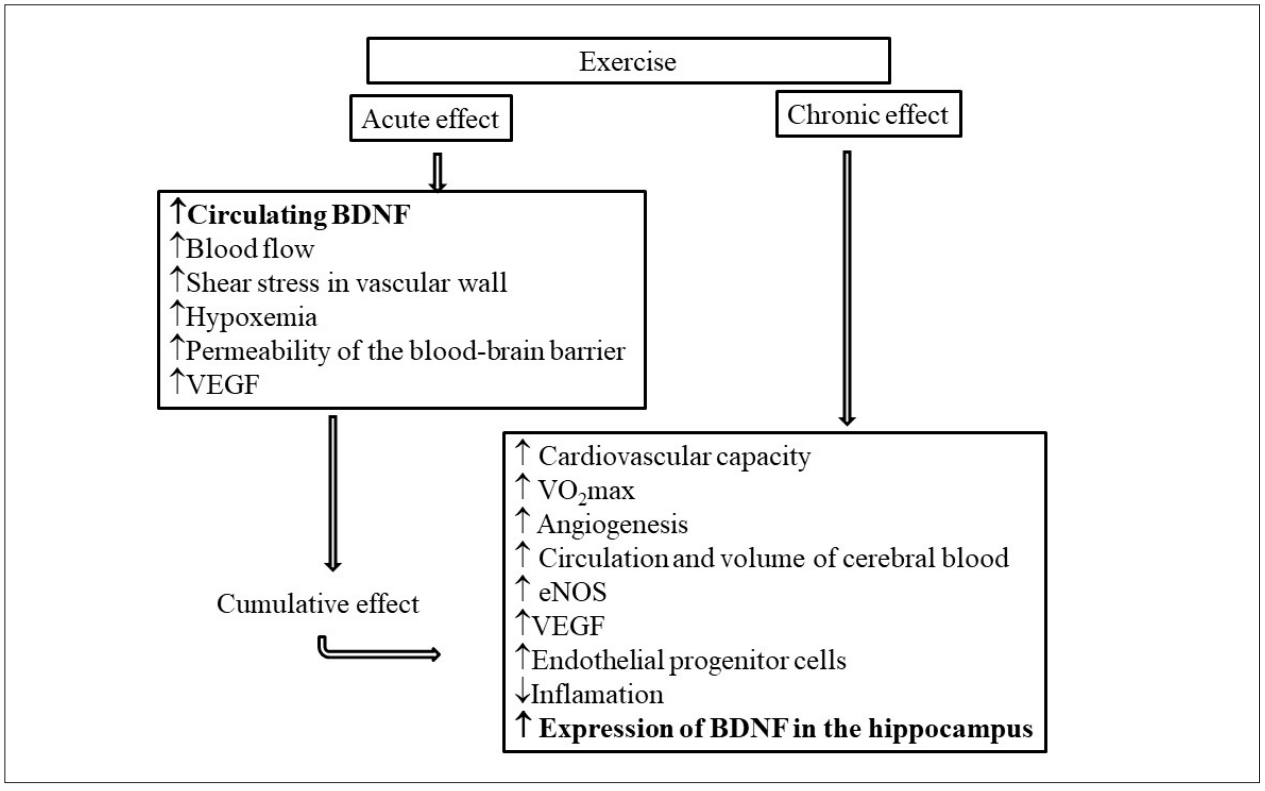

Figure 1 – *Acute and chronic effect of physical exercise on cardiovascular aspects related to BDNF (Adapted from Stimpson et al, 2018).*

Potential Conflict of Interest

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

Study Association

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

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Pharmacological Treatment of Hypertension: From the Golden Trio to the Octet

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The treatment of hypertension comprises numerous pharmacological options, which may hinder patient management standardization, thus contributing to therapeutic failure.[1] However, in more recent years, several studies and guidelines from diverse hypertension and cardiology societies have suggested preferential pharmacological classes to treat hypertension.[2-6] Based on this evidence, the present report aims to propose a simple and practical pharmacological treatment algorithm that can be applied to patients ranging from stage 1 to refractory hypertension cases (Figure 1).

Hypertension treatment combines lifestyle changes (including salt intake reduction, weight control, physical activity performance , alcohol intake moderation, and smoking cessation), discontinuation of substances that may increase blood pressure (BP), and sequential addition of antihypertensive medications.[2-4,7,8] According to current hypertension guidelines, antihypertensive classes that should be preferentially initiated for the treatment of hypertensive patients include the so-called *golden trio*:[9] a renin-angiotensin system inhibitor (RASI) (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker), a calcium-channel blocker (CCB) or a thiazide-type/thiazide-like diuretic (THIAZ).[2-4] In most hypertensive patients, treatment initiation usually includes the combination of two pharmacological classes, an approach that aims to optimize BP control efficiency and predictability. Conversely, monotherapy has been recommended for stage 1 hypertensive patients with low cardiovascular risk, pre-hypertensive patients and frail elderly patients.[2,4] The usual preferred dual combinations comprise a RASI plus a CCB or a RASI plus a THIAZ,[4] although in patients with high cardiovascular risk the combination of RASI plus CCB seems to be superior to the combination of RASI plus THIAZ in reducing adverse cardiovascular events.[10] If BP control is not achieved with two pharmacological classes, the use of three drugs should be instituted, preferentially comprising the *golden trio* components. When these three drugs are used, but BP control is not achieved and hydrochlorothiazide is the prescribed THIAZ, this latter drug should be substituted by a long-acting THIAZ (chlortalidone or indapamide).[1,11] In addition, a loop diuretic, such as furosemide, should replace the THIAZ if glomerular filtration rate is <30 mL/min.[11]

Beta-blockers (βB), which were considered a preferential initial class for hypertension treatment in the past,[12,13] have not been recommended as a first-choice class to treat hypertension according to more recent guidelines. Therefore, βB have been indicated as monotherapy or in combination with other classes when there are specific indications, such as angina, post-myocardial infarction, heart failure, arrhythmia or heart rate control.[2-4]

The inadequate control of BP with the use of three drug classes should be confirmed by ambulatory or home BP monitoring, after excluding causes of pseudo-resistant hypertension (mainly poor medication adherence and inadequate dosage).[1,11,14] Patients with uncontrolled BP using maximal dosages of three or more antihypertensive classes, including RASI, CCB and THIAZ, and in which pseudo-resistance was ruled out, are considered as having resistant hypertension, whereas those who have controlled BP while taking four antihypertensive classes, including RASI, CCB and THIAZ, are considered as having controlled resistant hypertension. Patients with uncontrolled BP using maximal dosages of five or more antihypertensive classes, including a long-acting THIAZ and spironolactone, are considered as having refractory hypertension. It is noteworthy that patients with resistant or refractory hypertension should undergo further investigation of end-organ damage and investigation/treatment of secondary causes of hypertension.

Growing evidence has suggested that, in the absence of BP control with optimized and concomitant use of RASI, CCB and THIAZ, the fourth antihypertensive class to be instituted should be an aldosterone antagonist, particularly low-dose spironolactone (25-50 mg/day), as demonstrated in several studies and meta-analyses.[5,15-17] However, spironolactone may not be tolerated by some patients, due to its anti-androgenic

Keywords

Hypertension; Antihypertensive Agents; Drug Therapy; Life Style; Exercise; Weight Loss; Medication Adherence.

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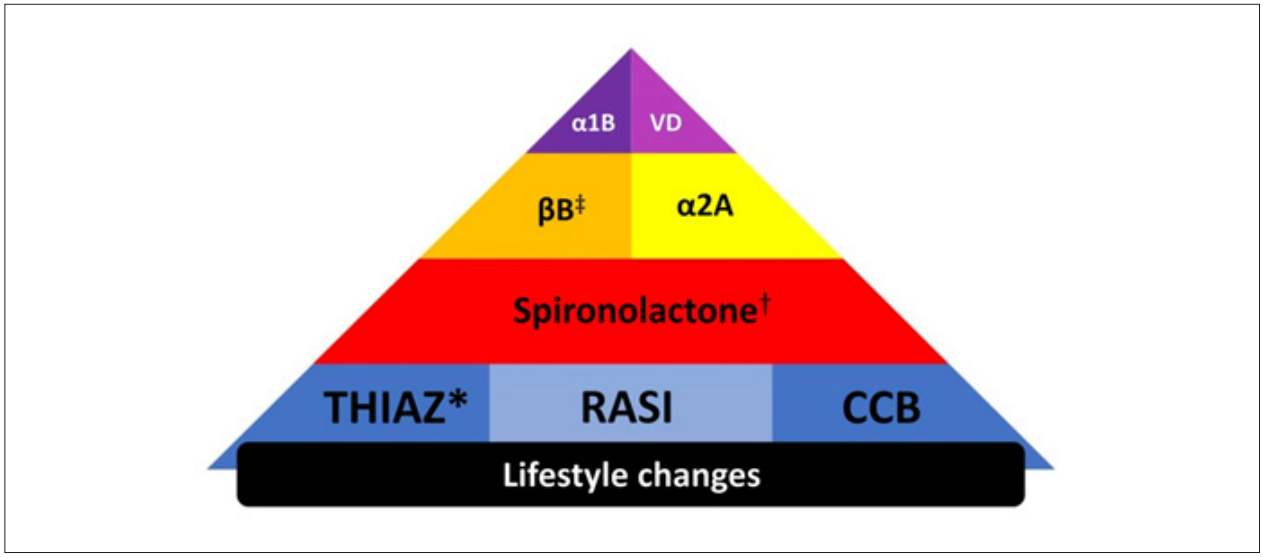

Figure 1 – *Structured octet for the treatment of hypertension.*
*THIAZ: thiazide-type/thiazide-like diuretic; RASI: renin angiotensin system inhibitor; CCB: calcium-channel blocker; βB: Beta-blocker; α2A: central alpha-2 agonist; α1B: alpha-1 adrenergic blocker; VD: direct vasodilator. *When BP control is not achieved with THIAZ, RASI and CCB, and the THIAZ is hydrochlorothiazide, substitute this latter drug by a long-acting THIAZ (chlortalidone or indapamide). If glomerular filtration rate <30 mL/min, substitute THIAZ by a loop diuretic, such as furosemide. †If spironolactone is not tolerated, particularly due to anti-androgenic side effects, consider substituting this drug by amiloride. ‡βB is indicated as the first choice for the initial treatment when there are specific indications, such as angina, post-myocardial infarction, heart failure, arrhythmia or heart rate control.*

side effects, resulting in gynecomastia or breast tenderness, impotence in men, and menstrual irregularities in women. In this regard, the results of the PATHWAY-2 trial suggested that 10-20 mg/day of amiloride, a potassium-sparing diuretic, is as effective as spironolactone in reducing BP in resistant hypertensive patients, thus constituting an alternative to spironolactone in the treatment of resistant hypertension.[15] However, it should be noted that amiloride, as an isolated formulation and at the aforementioned dosage, is not currently available in Brazil.

The ReHOT study compared the effects of spironolactone *versus* a central alpha-2 agonist (clonidine) in resistant hypertensive patients. Although there were no differences in the primary endpoint (BP control during office and ambulatory BP monitoring) achieved by spironolactone or clonidine, results of the secondary analysis showed greater 24-hour BP reduction with spironolactone, reinforcing the use of spironolactone as the fourth preferential drug for the treatment of resistant hypertension.[6] However, BP reductions achieved by clonidine were also substantial, which may establish this drug as a good option to be added to spironolactone when BP control has not been attained.

The PATHWAY-2 trial also investigated the BP effects of a βB (bisoprolol) or an alpha-1 adrenergic blocker (doxazosin) as alternative medications to spironolactone. These drugs were not as effective as spironolactone, but significantly reduced BP *versus* placebo when added to baseline antihypertensive medications in resistant hypertensive patients.[5] Therefore, a βB or an alpha-1 adrenergic blocker should be added subsequently to spironolactone in patients with uncontrolled BP. However, because the ALLHAT study showed that doxazosin was markedly inferior to chlortalidone in preventing cardiovascular events, particularly heart failure,[18] we suggest that an alpha-1 adrenergic blocker should be one of the last antihypertensive classes to be added to the treatment of patients with resistant hypertension.

Few studies have evaluated the impact of direct vasodilators, such as hydralazine or minoxidil, in the treatment of resistant hypertension. In addition, this antihypertensive class may cause marked fluid retention and tachycardia, and therefore should be considered as one of last choices in the treatment of resistant hypertension.[11]

In summary, based on the abovementioned data, we propose a structured octet for the pharmacological treatment of hypertension (Figure 1). Lifestyle changes and components of the *golden trio* (RASI, CCB and THIAZ) comprise the bottom of the treatment algorithm. Spironolactone should be preferentially used as the fourth antihypertensive class when there is no adequate BP control with the latter medications. Then, central alpha-2 agonists and βB may be added, while direct vasodilators and alpha-1 adrenergic blockers should be considered as the last options to be instituted for hypertension treatment.

Author Contributions

Conception and design of the research: Feitosa ADM, Mota-Gomes M, Passarelli Júnior O, Barroso WKS, Miranda RD, Barbosa ECD, Brandão AA, Nadruz W; Writing of the manuscript: Feitosa ADM, Nadruz W; Critical revision of the manuscript for intellectual content: Mota-Gomes M, Passarelli Júnior O, Barroso WKS, Miranda RD, Barbosa ECD, Brandão AA.

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Myocardial Injury Biomarkers and Cardiac Complications Associated with Mortality in Patients with COVID-19

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Abstract

Background: SARS-CoV-2 is an emerging RNA virus associated with a severe acute respiratory disease known as COVID-19. Although COVID-19 is predominantly a pulmonary disease, some patients have severe cardiovascular damage. We performed a quantitative evidence synthesis of clinical data, myocardial injury biomarkers, and cardiac complications associated with in-hospital death in patients with COVID-19.

Methods: We searched the databases PubMed, Embase, and Google Scholar to identify studies comparing clinical data, myocardial injury biomarkers, and cardiac complications between non-survivors and survivors of COVID-19. Effect sizes were reported as mean difference or standardized mean difference for continuous variables and risk ratio for dichotomous variables with 95% confidence intervals. A random effects model was used to pool the results.

Results: Six retrospective studies reporting data from 1,141 patients (832 survivors and 309 non-survivors) were included. We found that underlying cardiovascular conditions; elevation of high-sensitivity cardiac troponin I, N-terminal pro-B-type natriuretic peptide, and creatine kinase-MB; and cardiac complications were associated with increased risk of death for patients with SARS-CoV-2 infection.

Conclusions: The confirmation that underlying cardiovascular conditions, elevation of myocardial injury biomarkers during COVID-19 infection, and acute cardiovascular decompensation are predictors for mortality in SARS-CoV-2 infection must encourage new research to clarify potential mechanisms and test appropriate treatments. (Arq Bras Cardiol. 2020; 115(2):273-277)

Keywords: Coronavirus; COVID-19; SARS-CoV-2; Mortality.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that leads to an emerging infectious disease with remarkable pulmonary involvement, known as COVID-19. In addition to the hypothesis that cardiac patients are more susceptible to COVID-19 infection via ACE2 receptor dysregulation, preliminary individual reports have shown that patients with previous cardiovascular disease are at a higher risk of adverse outcomes. Moreover, patients who present any clinical or biological marker of acute cardiac involvement during COVID-19 infection are less likely to survive.[1]

Although acute cardiac involvement, whether clinical or revealed by biomarkers, has been described as a common condition among patients hospitalized with COVID-19, and it is associated with a higher risk of in-hospital death,[2] current available evidence is based on individual studies with potentially overlapping data.[3] Therefore, a synthesis of evidence can help confirm these findings. In this study, we performed a quantitative evidence synthesis of clinical data, myocardial injury biomarkers, and cardiac complications associated with in-hospital death in patients with COVID-19.

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Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[4] Given the urgent need for this review, PROSPERO registration was not sought.

We searched the databases PubMed, Embase, and Google Scholar to identify studies comparing clinical data, myocardial injury biomarkers, and cardiac complications between non-survivors and survivors of COVID-19. We included only studies with clinical data that provided, at least, concentrations of high-sensitivity cardiac troponin I (hs-cTnI). Patients were considered to have acute myocardial injury if serum levels of hs-cTnI were above the 99th percentile upper reference limit (URL). Heart failure was defined when the serum level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) exceeded the normal range and in the presence of associated symptoms, such as dyspnea, orthopnea, and lower extremity edema. Arrhythmia was defined as rapid ventricular tachycardia lasting more than 30 seconds, inducing

hemodynamic instability and/or ventricular fibrillation, and clinically significant bradycardia on electrocardiography. We excluded publications with potentially overlapping reports based on data collection and setting and studies from which data extraction was not possible. In the event of potentially overlapping data, we selected the study with the most complete information.

Reports were screened in two stages, screening of titles and abstracts followed by the retrieval and screening of full-text articles. Searches were performed from January 1, 2020 to April 14, 2020, without language restrictions. The reference lists of all eligible studies and reviews were also evaluated to identify additional studies for inclusion. The following search terms were used: "COVID-19", "SARS-CoV-2", and "coronavirus". All COVID-19 reports, irrespective of cardiovascular topic, were reviewed.

Data from publications were extracted by two authors and crosschecked for accuracy. Our outcome of interest was in-hospital death. Clinical data (age, sex, and existing comorbidities), myocardial injury biomarkers (hs-cTnI, NT-proBNP, and creatine kinase-MB [CK-MB]), and cardiac complications (acute cardiac injury, heart failure, and arrhythmias) were considered independent variables.

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) was used to grade the quality of each study. This tool is composed of 14 items that evaluate the representativeness and selection of the sample, description and measurement of exposure, follow-up of participants, and treatment of confounding factors. The findings were discussed qualitatively. Disagreements were resolved by discussion.

Effect sizes were reported as mean difference (MD) or standardized mean difference (SMD) for continuous variables and risk ratio (RR) for dichotomous variables with 95% confidence intervals (CI). To calculate MD and SMD, means and standard deviations (SD) of myocardial injury biomarkers were obtained for each study. If the means and SD were not directly reported in the publication, indirect methods of extracting estimates were used.[5,6] When data were not presented in tables or in the text and the authors could not be reached, data were extracted using WebPlotDigitizer graph digitization software (available at http://arohatgi.info/WebPlotDigitizer). Not all studies reported data on all predictor variables, and the pooled analysis was estimated from the data available for each variable.

A random effects model was used to pool the results, and 2-tailed $p < 0.05$ was used to determine significance. Cohen's classification was used to interpret magnitude of the effect size for myocardial injury biomarkers. SMD > 0.8 was considered a large effect size. Statistical heterogeneity was quantified by the I^2 index, and potential for publication bias was analyzed for hs-cTnI using Egger's regression test and visual inspection of funnel plots. Because of the small number of studies reporting data for NT-proBNP and CK-MB, analysis of publication bias was not performed. Analyses were conducted using Review Manager 5.3 (Cochrane IMS, Copenhagen, Denmark).

Results

After screening 8,091 titles and abstracts, 31 full-text articles were assessed for eligibility and 25 studies were excluded, seven of which were due to potentially overlapping data. Six retrospective studies[1,7-11] were included, providing data from 1,141 patients (633 male and 508 female) with confirmed SARS-CoV-2 infection, 832 survivors and 309 non-survivors. Details of included studies are shown in Table 1.

The risk of bias of the studies is showed in e-Table 1 in the supplemental digital content. All studies had clear objectives and eligibility criteria, recruited subjects from the same population, and described the definitions of exposure factors and outcomes. However, studies have not been able to determine whether the sample size was representative for

Table 1 - Characteristics of included studies and clinical data of patients with COVID-19, including in-hospital deaths

Authors	Design	Setting	Data collection	Sample size	Age*	Sex		In-hospital deaths	Survivors
						Male	Female		
Zhou et al, 2020[1]	Retrospective cohort	Jinyintan Hospital and Wuhan Pulmonary Hospital	Dec 29, 2019 to Jan 31, 2020	191	56.3 (15.6)	119	72	54	137
Cao et al, 2020[7]	Retrospective cohort	Zhongnan Hospital of Wuhan University	Jan 3, 2020 to Feb 1, 2020	102	52.7 (22.2)	53	49	17	85
Chen et al, 2020[8]	Retrospective cohort	Tongji Medical College of Wuhan	Jan 13, 2020 to Feb 28, 2020	274	58.7 (19.3)	171	103	113	161
Guo et al, 2020[9]	Retrospective cohort	Seventh Hospital of Wuhan	Jan 23, 2020 to Feb 23, 2020	187	58.5 (14.7)	91	96	43	144
Wang et al, 2020[10]	Retrospective cohort	Renmin Hospital of Wuhan University	Jan 1, 2020 to Feb 6, 2020	339	70.0 (8.2)	166	173	65	274
Zhang et al, 2020[11]	Retrospective cohort	Wuhan No.1 Hospital	Dec 25, 2019 to Feb 15, 2020	48	70.6 (13.4)	33	15	17	31

Data reported in mean and standard deviation.

the population. In addition, none of the studies performed analysis for adjustment of confounding factors.

Results of meta-analysis showed differences in age between groups. Non-survivors of COVID-19 were older compared to survivors (MD = 14.3 years, 95% CI 9.2 to 19.4). Male sex (RR = 1.3, 95% CI 1.2 to 1.4), the presence of existing hypertension (RR = 1.7, 95% CI 1.2 to 2.4), and cardiovascular disease (RR = 3.3, 95% CI 1.4 to 7.8) were also associated with increased risk of mortality.

The meta-analysis of myocardial injury biomarkers showed a large increase in hs-cTnI (SMD = 1.0, 95% CI 0.8 to 1.2), NT-proBNP (SMD = 1.1, 95% CI 0.7 to 1.4), and CK-MB (SMD = 1.0, 95% CI 0.2 to 1.8) in non-survivor patients. Elevated hs-cTnI values above the 99th percentile URL were associated with 8-fold increase in the risk of in-hospital death (RR = 8.0, 95% CI 2.2 to 28.5). No evidence of substantial publication bias was observed for hs-cTnI. Cardiac complications, including acute cardiac injury (RR = 8.9, 95% CI 4.2 to 19.3), heart failure (RR = 5.1, 95% CI 2.5 to 10.7), and arrhythmias (RR= 4.9, 95% CI 1.2 to 10.9) were found to be risk factors for COVID-19 related death. Comparisons of clinical data, myocardial injury biomarkers, and cardiac complications between non-survivors and survivors of COVID-19 are displayed in Table 2. Forest plots and funnel plots are shown in the supplemental digital content (e-Figures 1 – 3).

Discussion

Surveillance of cardiovascular events associated with COVID-19 seems very warranted.[12] This study confirms and better quantifies the association between myocardial injury biomarkers and/or acute cardiac complications with in-hospital death in patients with COVID-19. However, it remains unclear whether acute cardiac involvement is primarily provoked by SARS-CoV-2 or whether it is a multifactorial non-specific cardiac involvement of a severe systemic infection.[13] It has been proposed that SARS-CoV-2 may lead to cardiac injury via multiple mechanisms including direct viral invasion of cardiomyocytes and subsequent myocarditis, since viral particles have been identified in myocardial cells.[14] However, changes in cTnI over time and the absence of typical signs on echocardiography and ECG in patients with COVID-19 have suggested that myocardial injury in patients with COVID-19 is more likely related to systemic consequences of disease.[15]

Other plausible mechanisms that have been suggested to explain troponin elevation in this scenario include type 1 and, mainly, type 2 myocardial infarction due to acute respiratory distress syndrome, sepsis, cytokine storm, and even Takotsubo syndrome.[16] Therefore, SARS-CoV-2 infection may either induce new cardiac injuries and/or act as a precipitating factor to worsen underlying cardiovascular diseases and lead to death.

In this meta-analysis, we analyzed well-established biomarkers for myocardial injury diagnosis and outcome prediction. Elevation of hs-cTnI, NT-proBNP, and CK-MB were associated with increased risk of death in patients with SARS-CoV-2 infection.

Management of patients with myocardial injury biomarkers and acute cardiovascular decompensation is primarily based on supportive care and individualized approach to better guide treatment. Unfortunately, we do not have evidence to

Table 2 - Comparison of clinical data, myocardial injury biomarkers, and cardiac complications between non-survivors and survivors of COVID-19

Parameter	MD (95% CI) between non-survivors and survivors	SMD (95% CI) between non-survivors and survivors	RR (95% CI)	p value	I^2
Clinical					
Age, years	14.3 (9.2 to 19.4)	-	-	< 0.001	88%
Male	-	-	1.3 (1.2 to 1.4)	< 0.001	0%
Comorbidities					
Hypertension	-	-	1.7 (1.2 to 2.4)	0.001	74%
Cardiovascular disease	-	-	3.3 (1.4 to 7.7)	0.005	70%
Myocardial injury biomarkers					
hs-cTnI	-	1.0 (0.8 to 1.2)	-	< 0.001	42%
hs-cTnI (> 99th percentile)	-	-	8.0 (2.2 to 28.5)	0.001	93%
NT-proBNP	-	1.1 (0.7 to 1.4)	-	< 0.001	50%
CK-MB	-	1.0 (0.2 to 1.8)	-	0.010	81%
Cardiac complications					
Acute cardiac injury	-	-	8.9 (4.2 to 19.1)	< 0.001	79%
Heart failure	-	-	5.1 (2.5 to 10.7)	< 0.001	75%
Arrhythmias	-	-	4.9 (1.2 to 19.0)	0.020	85%

MD: mean difference; SMD: standardized mean difference; RR: risk ratio; CI: confidence interval. Positive results for SMD indicate increased levels of biomarkers in non-survivor patients.

guide the proper use of antiplatelet agents, anticoagulants, β-blockers, ACE inhibitors, and statins in this critical scenario, and we must adapt the current knowledge.[17] For instance, it has recently been suggested that renin-angiotensin-aldosterone system inhibitors could be deleterious or beneficial for patients with COVID-19,[18] but we lack definitive evidence for this decision.

The findings of this study should be treated with caution. Its main limitations include the following: (1) Studies are limited to a single region and this has reduced our ability to verify possible population variability; (2) there was a moderate to high between-study heterogeneity, and (3) studies did not perform analysis for adjustment of confounding factors and their results were based on standard univariate models.

Conclusions

This meta-analysis confirms that underlying cardiovascular conditions, elevation of myocardial injury biomarkers during COVID-19 infection, and acute cardiovascular decompensation are predictors for mortality in SARS-CoV-2 infection. Further studies are needed to clarify potential mechanisms of cardiovascular injury and test appropriate treatments.

Author contributions

Conception and design of the research: Martins-Filho PR, Santos VS; Data acquisition and Statistical analysis: Martins-Filho PR; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Martins-Filho PR, Barreto-Filho JAS, Santos VS.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

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Ethics approval and consent to participate

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

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The Other Side of the Coin: Risks of Media Discussions of Scientific Medical Data During the COVID-19 Pandemic

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The COVID-19 declared by the WHO in March 2020 has brought about a series of changes in the population's daily life. Social isolation measures, quarantine, and lockdown have been implemented in diverse countries around the world. The elevated number of cases, currently close to 4 million worldwide,[1] with more than 250,000 deaths due to the disease, has led to great interest in pathology; on account of this, a revolution has occurred in the production and publication of medical data. Numerous scientific articles evaluating all aspects of COVID-19, from epidemiology to clinical presentation and potential therapeutic options, have become available to the medical community.[2] In a little over 4 months, more than 10,000 articles have been published on this topic, and, in a never-before-seen manner, the leading medical journals have made them available in real time, free of charge.

This speed of production and this immense quantity of available data do not come without a price. Many of these articles were not submitted to adequate review of methodology; much less were they evaluated by their peers or refined over time. The need to understand COVID-19 and to search for better alternative therapies has led to an avalanche of questionable studies. The chaff has been mixed with the wheat, and medical recommendations have started to change at frightening speeds. Data with higher degrees of reliability and evidence, derived from randomized, placebo-controlled studies, are now considered too time-consuming. Case series and expert opinions have begun to guide clinical conduct, with a direct impact on clinical management of patients. Instead of indicating solutions, the flood of studies has become a problem and begun to cause confusion regarding clinical practice for managing patients with COVID-19.

Let us take the evaluation of anticoagulation in patients with COVID-19 as an example. Rather consistent data from the literature have suggested that there is a vascular pathology in the lungs of patients with severe respiratory conditions in COVID-19. A high incidence of thrombosis has been identified in this population, greater than in other similarly severe clinical situations, even under adequate prophylactic anticoagulation.[3] Thrombi have been identified in pulmonary circulation, in small vessels that are not identifiable on conventional angiography.[4] Increased D-dimer has shown an impact on mortality of patients with COVID-19, suggesting that patients with more severe thrombotic conditions in their microcirculation have worse prognosis.[5] Finally, evaluation of pulmonary mechanics of patients with respiratory failure due to COVID-19 has demonstrated that pulmonary compliance was not as reduced as expected in this population. There was, however, a surprising increase in pulmonary shunt fraction in this population, indicating that much of the hypoxemia was not due to changes in ventilation (as expected in other forms of acute respiratory distress syndrome), but rather to changes in pulmonary circulation.[6]

Accordingly, if there is a thrombotic pathology of the pulmonary circulation in a severe disease, it would intuitively make sense to use anticoagulants to treat this condition and potentially improve hypoxemia and the gas exchange. Case series and retrospective studies have demonstrated that there would be a potentially tangible clinical benefit to this conduct.[7] However, adequate dosages, the best agents to use, and the coagulation intensity cannot be defined by these types of studies. Only prospective randomized controlled studies can provide the evidence that is necessary in order to treat patients safely, by accurately defining these questions. In the meantime, while these studies have not been completed and data are not yet available, several consensuses have made very different and, at times, contradictory recommendations regarding the best way to promote anticoagulation in patients with COVID-19 (be it prophylactic, therapeutic, or via "alterative regimens").[8-10] Multiple orientations often end up causing confusion and insecurity on the part of physicians, and caution is fundamental when interpreting this information.

There is, moreover, a third component which, during the COVID-19 pandemic, stands between medical information, physicians' interpretation thereof, and communication with a patient, namely, journalistic media. The population's growing interest in information about COVID-19 has led to intense coverage on the part of the press, regarding all aspects of the disease, including therapeutic advances. However, information communicated directly from a scientific article to the population by journalists, as a rule, requires interpretation, criticism, and risk assessment. The benefit of taking this information in may be outweighed by the risk that this information, without criticism, may induce, in the event that it results in clinical conduct.

Keywords

Coronavirus; COVID-19; Pandemics; Quarantine; Social Isolation; Respiratory Diseases; Communicable Diseases; Diagnostic, Differencial; Information Technology/trends; Social Media.

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Consider the following example: A 62-year-old female patient was admitted to the emergency room with large spontaneous hematomas throughout her body (Figure 1). Fifteen days prior, she had onset of hyaline rhinorrhea, without fever or myalgia. Fearing COVID-19, the patient sought information about pathology, and she came across some data in the media about a potential treatment with anticoagulants. She subsequently attempted to protect herself from COVID-19 using diverse anticoagulants concomitantly. Of her own accord, she began taking rivaroxaban, warfarin, and acetylsalicylic acid. Just in case, she had also taken hydroxychloroquine and azithromycin (also influenced by data from journalistic media, which mentioned studies on the potential benefits of these therapies.[11]) Upon admission, she presented hemoglobin 12, international normalized ratio 26, and activated partial thromboplastin time ratio 2. She was hospitalized, and anticoagulation was reversed. She underwent both PCR and serology for SARS-CoV-2 (which causes COVID-19), both of which were negative. In this manner, this patient, who had never had COVID-19, might have died due to complications from therapies which are still being evaluated for treating a disease which she never had. COVID-19 was identified only 5 months ago. Notwithstanding its severity and the high number of victims, time and experience are still necessary, in respect to both clinical management [12] and interpretation of scientific data produced in unprecedented quantities and speeds. The democratization of information is fundamental, and the press is doing an excellent job in this role. Raw technical information, however, without the necessary refinement provided by clinical experience, may have very harmful consequences if it is carelessly absorbed by a population that is fragile due to concerns about this disease. Access to information provided by the media is fundamental in order for patients to participate actively in their treatment. These treatments, however, should always be guided by the professionals who are most qualified to conduct them, namely physicians.

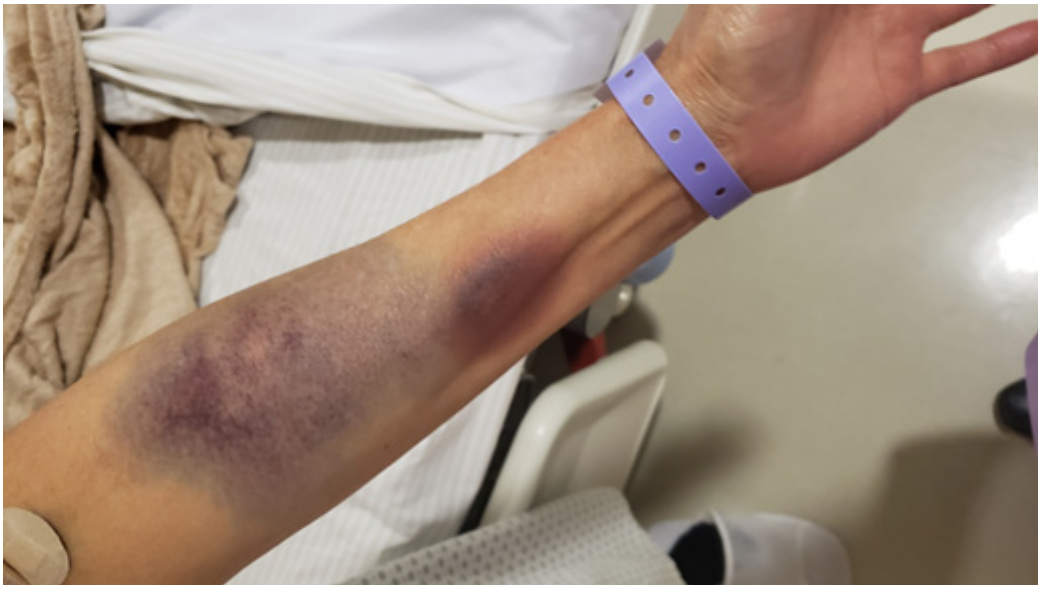

Figure 1 – *Spontaneous hematomas in a 62-year-old patient who used acetylsalicylic acid, rivaroxaban and warfarin to protect herself from COVID-19 (however, her PCR and serology tests were both negative). At the Emergence Room, her INR was 26 and the activated partial thromboplastin time ratio was 2. With the reversal of anticoagulation and clinical observation, the patient had no other bleeding complications.*

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Circulatory System Diseases in Patients with COVID-19: Description of Clinical and Epidemiological Profile of 197 Deaths

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Dear Editor,

On December 31, 2019, China notified the World Health Organization (WHO) of an outbreak of pneumonia in the city of Wuhan, capital of the Hubei province. A few days later, the causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified.[1]

The disease, named coronavirus disease 2019 (COVID-19), rapidly spread throughout countries worldwide, and, on March 11, 2020, the WHO declared a global pandemic.[1] In Brazil, the first case was confirmed on February 26, and the first death occurred on March 17, in São Paulo. On April 9, Brazil had a total of 155,000 confirmed cases and 10,000 deaths from the disease.[2]

Recent studies have already indicated the following double relationship between the circulatory system and COVID-19:[3-5] i. The virus may cause cardiovascular changes, such as arrhythmias, acute cardiac injury, myocarditis, and others, and ii. The presence of circulatory system diseases increases the risk of worsening and mortality due to the disease. This relationship has been cause for concern on the part of clinical physicians and scientists. Based on this assumption, this study aimed to describe the clinical and epidemiological profile of deaths due to COVID-19 in patients who had prior circulatory system diseases.

This is a cross-sectional observational study involving 197 patients who died from COVID-19 in Pernambuco, all of whom had at least one prior circulatory system disease. The following were analyzed: sex, age range, signs/symptoms, comorbidities and risk factors, and time from first symptoms to death. Data were obtained from the state's COVID-19 monitoring webpage (https://dados.seplag.pe.gov.br/apps/corona.html) on May 7, 2020. After collection, the database underwent adjustment of variables for subsequent analysis. In this study, only descriptive statistics (absolute frequency, relative frequency, mean, and standard deviation) were used, with the assistance of SPSS software, version 24.0 (IBM Corporation). Given that this study used public domain data, Research Ethics Committee approval was waived.

On May 7, 2020, the state of Pernambuco had registered 9,325 cases and 749 deaths due to COVID-19. Of these deaths, 293 (39.11%) had the field "comorbidities" filled out (12 stated that the patients had no comorbidities, and 281 cited the comorbidities). Of the 281 comorbidities reported, 197 presented at least one circulatory system disease, accounting for 70.10% of individuals with reported comorbidities and 26.30% of all deaths.

Predominance was observed in women (53.3%; n = 105) and patients 50 years or older (92.3%; n = 182). The following four signs/symptoms had frequency above 50%: dyspnea (80.7%; n = 159), cough (72.1%; n = 142), fever (67.0%; n = 132), and oxygen saturation < 95% (58.9%; n = 116) (Table 1).

With respect to the presence of comorbidities, 78.7% (n = 155) had two or more, at least one of which was related to the circulatory system. Systemic arterial hypertension was observed in 82.7% (n = 163) of individuals, and non-specified heart disease was observed in 25.9% (n = 51) (Table 1).

In addition to involvement of the circulatory system, the most common diseases and risk factors in the study population were diabetes mellitus (53.8%; n = 106), obesity (11.2%; n = 22), chronic renal disease (10.7%; n = 21), prior stroke (8.1%; n = 16), tobacco use (7.6%; n = 15), chronic obstructive pulmonary disease (4.6%; n = 9), and cancer (4.1%; n = 8). Average time from onset of symptoms to death was 9.7 ± 7.8 days. It is worth underscoring that, for 10 of the 197 patients included in this study, it was not possible to calculate time from onset of symptoms to death (Table 1).

The profile shown in this study is in agreement with that observed in other parts of the world.[3-5] Nonetheless, the following three aspects warrant attention: i. the elevated proportion of individuals with multiple comorbidities (78.7% had two or more diseases/baseline risk factors), ii. the wide variety of diseases/risk factors observed, and iii. the clinical status in which individuals arrived at the hospital (compromised respiratory function).

The sum of comorbidities/risk factors in a single person may elevate the risk of mortality from COVID-19, although there are still not any precise estimates of these risks. In a study involving 416 hospitalized patients with COVID-19, carried out in a hospital in Wuhan, China, 44 (10.6%) and 22 (5.3%) had coronary heart disease and cerebrovascular disease, respectively. The also observed other comorbidities, such as chronic heart failure (4.1%; n = 17), chronic renal failure (3.4%; n = 14), chronic

Keyword

Coronavirus-19/complications; Fever; Severe Acute Respiratory Syndrome; Dyspnea; Respiration Disorders; Risk Factors; Hypertension; Diabetes Mellitus.

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Letter to the Editor

Table 1 - Clinical and epidemiological characteristics of patients with circulatory system diseases who died from COVID-19 in Pernambuco. Pernambuco, Brazil, 2020 (n = 197)

Variable	n	%
Sex		
Female	105	53.3
Male	92	46.7
Age (years)		
20-29	2	1.0
30-39	3	1.5
40-49	10	5.2
50-59	26	13.2
60-69	53	26.9
70-79	58	29.4
80+	45	22.8
Signs/symptoms		
Fever	132	67.0
Dyspnea	159	80.7
Cough	142	72.1
Oxygen saturation < 95%	116	58.9
Sore throat	12	6.1
Asthenia	9	4.6
Diarrhea	9	4.6
Nausea/vomiting	7	3.6
Headache	3	1.5
Myalgia	3	1.5
Weight loss	2	1.0
Abdominal pain	1	0.5
Runny nose	1	0.5
Constipation	1	0.5
Number of comorbidities		
Only one	42	21.3
Two	81	41.1
Three or more	74	37.6
Cardiovascular and hematological system		
Systemic arterial hypertension	163	82.7
Unspecified heart disease	51	25.9
Chronic venous insufficiency	5	2.5
Coronary artery disease	4	2.0
Thrombosis	3	1.5
Arrhythmia	2	1.0
Chagas disease	1	0.5
Anemia	1	0.5
Endocrine/metabolic system		
Diabetes mellitus	106	53.8
Obesity	22	11.2
Dyslipidemia	2	1.0
Hypothyroidism	1	0.5
Respiratory system		
Tobacco use	15	7.6
Chronic obstructive pulmonary disease	9	4.6
Pneumonia	2	1.0
Tuberculosis	1	0.5
Asthma	1	0.5
Neurological disease		
Stroke (prior event)	16	8.1
Unspecified mental disease	5	2.5
Unspecified neurological disease	4	2.0
Alzheimer's	4	2.0
Myasthenia	1	0.5
Other conditions/risk factors		
Chronic renal disease	21	10.7
Cancer	8	4.1
Alcoholism	5	2.5
Unspecified dermatological disease	3	1.5
Liver disease	2	1.0
Amputated limb	3	1.5
Other conditions with only one reported case (HIV, pancreatitis, prior transplant, osteoporosis, bedridden).	1	0.5
Time from onset of symptoms to death (average and standard deviation, in days)	**9.7 ± 7.8**	

obstructive pulmonary disease (2.9%; n = 12), and cancer (2.2%; n = 9), which were also observed in our study. Mortality was higher in individuals with heart injury (51.2% in the group with injury vs. 4.5% in the group without injury), and preexisting diseases were factors associated with higher mortality.[4]

The association between several comorbidities/risk factors may explain the compromised respiratory condition upon admission, with dyspnea and oxygen saturation < 95%, which indicates severely compromised pulmonary function in these patients. The close functional relationship between the cardiovascular (doubly affected by the baseline disease and by SARS-CoV-2 infection) and pulmonary systems (accentuated pulmonary injury) should be prioritized during the process of caring for patients with COVID-19 who have circulatory system disease.[3-5]

Finally, we underline the need to adopt and/or strengthen mechanisms that reduce contamination of individuals with circulatory system diseases by COVID-19. For those who are already contaminated, early diagnosis and monitoring of clinical picture should be rigorously followed, in order to avoid worsening and death in these individuals.

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Position Statement of the Brazilian Society of Cardiology Department of Exercise Testing, Sports Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation (DERC/SBC) on Activities Within its Scope of Practice During the COVID-19 Pandemic

Development: Brazilian Society of Cardiology Department of Exercise Testing, Sports Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation

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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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Declaration of potential conflict of interests of authors/collaborators of the Position Statement of the Brazilian Society of Cardiology Department of Exercise Testing, Sports Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation (DERC/SBC) on Activities Within its Scope of Practice During the COVID-19 Pandemic
If, within the last 3 years, the author/collaborator of the statement:

Names of statement collaborators	Participated in clinical and/or experimental studies sponsored by pharmaceutical or equipment companies related to this statement	Spoke at events or activities sponsored by industry related to this statement	Was (is) a member of a board of advisors or a board of directors of a pharmaceutical or equipment industry	Participated in normative committees of scientific research sponsored by industry	Received personal or institutional funding from industry	Wrote scientific papers in journals sponsored by industry	Owns stocks in industry
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Nabil Ghorayeb	No	No	No	No	No	No	No
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William Azem Chalela	No	No	No	No	No	No	No

Content

1. General Rules

- The Brazilian Society of Cardiology Department of Exercise Testing, Sports Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation (DERC) is closely monitoring the COVID-19 pandemic and its consequences, and is aligned with the Brazilian Medical Association (AMB) regarding the position statements issued by its specialized departments and affiliate societies.
- It recognizes that containment of the pandemic is a core strategy.
- This document provides an up-to-date overview of recommendations to minimize risks to both patients and clinicians during this pandemic period.
- Given the dynamics of the pandemic, any of these recommendations may be updated if and as new facts and scientific evidence arise.
- All preventive measures advised by the Ministry of Health and the World Health Organization (WHO) should be systematically incorporated into high-quality care for patients with cardiovascular diseases, as they are considered to be at high risk.
- Any and all procedures must follow recommended standards for disinfection, use of personal protective equipment (PPE), and contact precautions.
- Any discontinuation, continuation, or interruption of activities inherent to the SBC/DERC scope of practice must comply with the provisions of local health authorities or the bylaws of the health facilities where they are conducted.
- At this time, compensation for treadmill exercise tests (TMETs), cardiopulmonary exercise tests (CPETs), nuclear cardiology procedures, and cardiopulmonary rehabilitation cannot be reduced as a result of any measures taken in the fight against the pandemic, unless otherwise instructed by the AMB Permanent Technical Committee on the Hierarchical Brazilian Classification of Medical Procedures.

2. Treadmill Exercise Test and Cardiopulmonary Exercise Test

- Careful assessment of respiratory symptoms and complaints and other acute infectious conditions should begin when the patient calls to schedule the test. The appointment may then be confirmed or discouraged, so as to avoid unnecessary movement of patients where social distancing measures are in place. Patients should come alone, except for children (under 18) and those otherwise incapable.[1,2]
- Patient who have already contracted COVID-19 and have recovered, if asymptomatic and clinically stable, should postpone TMET and CPET for at least 30 days after recovery. Even patients recovered from COVID-19 must follow the recommendations and procedures described herein.
- Considering the potential risk for generation of contaminants during TMET and CPET, we recommend that the number of tests be reduced as much as possible—optimally, one test per hour per ergometer.
- Once the appointment has been confirmed, instruct patients to come already wearing appropriate clothing and footwear, as they will not be allowed to use changing rooms at the clinic or hospital.
- Upon arrival, reassess the patient for signs and symptoms of COVID-19 by interview or completion of a specific epidemiological questionnaire. Measure body temperature and provide a surgical mask at the entrance to the facility. Receptionists and other secretarial staff must wear a face mask and gloves at all times, as well as maintain a safe distance from patients.[3,4]
- As usual, all patients must sign an informed consent form. This is mandatory.

However, it is suggested that additional considerations be included in the form due to the ongoing pandemic, namely: it is impossible to accurately specify the quantitative risk of contracting the coronavirus during a TMET or CPET, but:

- All possible preventive measures will be undertaken to minimize contamination.
- The risk of contracting an infection during a TMET or CPET is probably higher compared to that of the same test performed once the pandemic is over.
- The physician in charge of the test must adequately contextualize the indications for the test and, in case COVID-19 or any other acute respiratory syndrome is suspected (history of fever, cough, nasal discharge, weakness, tachycardia, cyanosis, abnormal pulmonary auscultation), inform the attending physician and discontinue the test.

- An order for a TMET or CPET must be preceded by a thorough physical examination of the patient to determine whether the test is truly indicated. Thus, such tests cannot be ordered or requested via telemedicine.[5]
- Examination rooms should be large and well-ventilated. Natural ventilation is preferred; common climate-control systems (fans and HVAC) should be avoided due to the potential for environmental dispersal of contaminants. [6]
- It is well established that TMET and CPET pose a theoretical risk of contamination for the performing clinician and team. The physician and auxiliary staff (technicians, paramedics, nurses) are advised to wear a respirator (FFP2/N95-equivalent filtration efficiency or higher), goggles, and procedure gloves throughout the test. Staff are to remain at least 2 meters away from the patient for as long as possible. Institutional recommendations and the advice of municipal and state health departments should be followed.
- Patients must wear an FFP1-equivalent medical mask (such as a surgical mask) upon entering the testing area of the facility. Patients must wash their hands with soap and water and apply hand sanitizer (containing at least 70% alcohol) before contact with any equipment or any other surface in the examination room.
- In the clinic and hospital setting, before the test begins, staff are to confirm that potentially contaminating devices and surfaces have been properly cleaned and sanitized. Institutional protocols should incorporate the recommendations of health authorities regarding these procedures and must be followed.[6]

If a test is to be performed in an office setting or at a clinic that has no environmental services protocols in place, the following actions are recommended:

- Clean the ECG cables with a 70% alcohol wipe.
- Clean and perform high-level disinfection for transmissible pathogens of the ergometer support bar, treadmill mat, cycle ergometer saddle, sphygmomanometer cuff, stethoscope, and other high-touch surfaces using one or more of the following recommended products:[1,7]
- Active chlorine-based (0.5% sodium hypochlorite solution).
- Quaternary ammonium ("quat")-based (final concentration no higher than 0.8%).
- Accelerated hydrogen peroxide-based (concentration no higher than 0.5%).
- Alcohol-based (concentration no lower than 70%) or alcohol plus a quaternary ammonium ("quat") compound.
- Disposable materials—especially monitoring electrodes—are preferred when performing TMET and CPET. Dispose of all materials properly and in an appropriate container.
- In case of CPET, the physician in charge of the test must confirm there is capacity to sterilize the entire system effectively, including the expired gases circuit and analyzer, and that institutional protocols which incorporate the recommendations of health authorities are followed.
- The physician in charge of the test is to assess and update the crash cart/trolley and all other emergency equipment so as to ensure it is adapted to the latest recommendations for resuscitation and treatment of complications during the COVID-19 pandemic.[8,9]
- Facilities which offer TMET and CPET are to update their protocols for patient transfer in the event of complications and emergencies in concert with the availability and guidelines of insurers, health management organizations, and local emergency medical services.[10]
- Professionals (including the physician and auxiliary staff) with a suspected or confirmed diagnosis of COVID-19 are to be relieved of their duties and follow current recommendations for treatment and self-isolation.[6]
- The usual criteria for selection of ergometers and exercise protocols, the classic diagnostic and prognostic criteria for TMET and CPET, and the conventional pre- and post-test probabilities still apply. We suggest that the test report describe the behavior of the QT interval during exertion and at the fourth minute of recovery. [11,12]
- At the present time, it is reasonable to consider postponing TMET and CPET whenever the test is unlikely to have a direct impact on care or clinical outcome in the following months.[3]

3. Cardiopulmonary and Metabolic Rehabilitation

The COVID-19 pandemic has had a profound impact on health services, including cardiopulmonary and metabolic rehabilitation (CPMR) services, which play a fundamental role in the clinical management of patients with cardiovascular, pulmonary, and metabolic diseases, providing significant reductions in hospitalization and overall mortality rates.[13-17]

However, to date, isolation and social distancing have been the cornerstone of COVID-19 control, especially for patients at higher risk of hospitalization, respiratory complications, and mortality—precisely those with indications for CPMR programs.[18,19] Therefore, in line with the recommendations of global and national health authorities, CMR services involving face-to-face activities have been suspended due to the risk of contagion.

Within the context of COVID-19, considering that CPMR is essential for the process of recovery of functional capacity of patients with heart failure[17,20] or after cardiovascular events and interventions, and that the time to initiation of an exercise program after hospital discharge can influence functional recovery, disease management, and mortality rates, we believe that home-based CPMR programs—delivered at a distance with the support of digital technologies—should be prioritized. Such programs have been adopted to good effect by many services in Brazil and elsewhere.[17,21]

Home-based exercises should follow the usual recommendations for conventional CPMR. The exercise prescription should be individualized and based on prior evaluation whenever possible.[17,21] For safety purposes, it is recommended that the scale of perceived exertion be used during physical exercise, which should be of light and/or moderate intensity at most. At the present time, we suggest that high-intensity, exhausting exercises with a very high rating of perceived exertion be avoided.

It bears stressing that, given the nationwide heterogeneity of the epidemiological curve of COVID-19 and regional differences in the incidence of new cases, hospitalization rates, and infrastructure (such as the occupancy rate of public and private hospitals), different recommendations may be relevant to different locations. Therefore, these should always follow the guidance of health organizations and authorities.[22]

Once there is clear evidence that the pandemic is being brought under control and social isolation measures are lifted by health authorities, conventional CPMR services (i.e., including face-to-face activities) will be able to resume their activities, gradually and with strict observance of the relevant precautions for the protection of patients and providers alike. As activities are gradually resumed, the following recommendations will apply:

- Patients, their chaperones, and staff members with flu-like symptoms or a history of contact with confirmed or suspected cases in the preceding 14 days are to self-isolate for however long is recommended by health organizations and local health authorities.[23]
- Noncontact (infrared) temperature screening of patients upon arrival is advised.
- Face coverings, hand sanitizer, and frequent handwashing with soap and water are mandatory for patients and all others who attend exercise facilities. Staff members are to follow the recommendations of health regulatory agencies, trade unions, and relevant professional boards/trade associations regarding the use of PPE.
- Spray bottles containing 70% alcohol and disposable paper towels are to be made available for disinfection of exercise equipment before and after individual use. Shared use of equipment (weight machines, weight benches, free weights, etc.) should be avoided.
- To promote increased air circulation, keep doors and windows open whenever possible.
- Reduce the number of patients allowed in the facility simultaneously, so as to allow greater distancing between them.
- Implement predefined working hours, with a strictly controlled duration of and intervals between sessions, to overlap between groups and allow disinfection of the environment and equipment.

Note: to provide a measure of legal protection to facilities that offer CPMR, it is recommended that a letter of referral for rehabilitation be obtained from the patient's attending physician, as well as written informed consent from patients themselves.

4. Nuclear Cardiology

During the pandemic, nuclear cardiology services are advised to limit their activities to urgent studies in symptomatic patients, in which the test result has the potential to change immediate management or affect the patient's short-term prognosis. It is also essential that scans be performed on inpatients and emergency department patients requiring urgent assessment, as this can guide management, shorten hospital stay, and thus free up hospital capacity.[3,24]

4.1. Adaptation of Nuclear Cardiology Practices During the COVID-19 Pandemic

4.1.1. General Considerations When Scheduling a Nuclear Cardiology Scan[24,25]

- Increase the interval between scans to avoid crowding.
- When scheduling, ask if the patient has any signs or symptoms suggestive of possible COVID-19 infection (fever, cough, dyspnea, unusual fatigue, myalgia, diarrhea, anosmia, hyposmia, dysgeusia, or ageusia). If so, the appointment should preferably be postponed.
- Ask if the patient has been exposed to a confirmed or suspected case in the preceding 2 weeks. If so, the scan should preferably be postponed.
- Patients should be contacted the day before the scan to ensure they are not experiencing any suspicious signs or symptoms. If so, the scan should be rescheduled if possible.
- Patients should be instructed to come in for the scan alone. Patients who absolutely require a companion or chaperone should come with only one person, ideally someone with no relevant risk factors (such as diabetes, unstable heart disease, arrhythmias, age >65 years, etc.).
- Ask that patients and their chaperones come in already wearing PPE (face coverings at the very least). Alternatively, the facility should consider providing PPE to be worn for the entire time patients are at the nuclear medicine department.

4.1.2. Considerations Upon Patient Arrival at the Facility[24-26]

- Upon arrival at the nuclear cardiology lab, reassess the patient for the presence of signs, symptoms, or potential exposure to COVID-19, by interview or completion of a specific epidemiological questionnaire.
- Given the risk of transmission by asymptomatic carriers, patient care staff in the waiting room and all other non-medical staff in the laboratory are to wear a mask at all times.
- Instruct patients and their chaperones to wear face coverings while in the nuclear medicine department.
- Facilities must ensure that waiting rooms have easy access to hand washing stations and/or hand sanitizer.
- Enforce a distance of at least 2 meters between individuals, so as to avoid crowding in waiting rooms and other facilities. Instruct all those who attend to follow distancing rules, respiratory etiquette, and frequent hand washing and/or application of hand sanitizer.
- In facilities offering modalities other than just nuclear cardiology, interactions between inpatients and outpatients should be avoided, as should any contact between outpatients and patients with cancer or other immunocompromised patients.

4.1.3. Considerations During the Scan[24-26]

A) Regarding staff and the environment

- General principles of PPE use apply throughout the scan.

- Minimize the number of staff members in contact with the patient.
- Minimize patient–staff contact time.
- Highlight importance of frequent hand hygiene.
- If the patient has suspicious symptoms, all staff members in contact with the patient must wear full PPE (respirator, eye protection, apron, and gloves) and provide a mask to the patient.
- In patients with confirmed active COVID-19, scans should be performed only if absolutely necessary. Check local infection control policies and consider scheduling these patients as the last scan of the day. Use a separate scanner if possible. After the scan, complete terminal cleaning of the room and all equipment is to be performed.
- The scanner gantry, bed, gurney, treadmill, sphygmomanometer, stethoscope, and infusion pumps are to be cleaned after each scan by personnel wearing appropriate PPE.
- Regular cleaning of high-touch surfaces (including door handles, tables and desks, computers, keyboards, telephone receivers, and dictation equipment) by personnel wearing appropriate PPE is mandatory.

***B) Selection of scan protocol*[24]**

- Choose the shortest protocol.
- Consider one-day imaging protocols.

***C) Selection of stress protocol*[24]**

- As the SARS-CoV-2 virus is spread by droplets, procedures which generate droplets or aerosols are considered to pose the greatest risk. Therefore, pharmacological stress tests are preferred to exercise tests.
- If an exercise test is considered absolutely necessary, the staff must wear appropriate PPE (preferably, an N95/FFP2 respirator) and keep their distance from the patient except if providing direct care or while injecting the tracer. Follow the guidelines of this position statement regarding TMET.
- Use of automated blood pressure cuffs in lieu of sphygmomanometers requiring operator intervention should be considered.

***D) Interpretation of test results*[24-26]**

- Avoid the presence of several physicians and/or interns in the same location if possible.
- In scans requiring computed tomography (CT)-based attenuation correction, CT images must be interpreted in the context of pulmonary findings possibly indicative of COVID-19.

5. Sports Cardiology

5.1. Physical Activity and Sports During the COVID-19 Pandemic

Regular physical activity is essential for the promotion of health and correction of risk factors for cardiovascular diseases. A sedentary lifestyle worsens the natural history of chronic degenerative diseases and increases mortality. Both while lockdown measures are in place and once restrictions on mobility have been lifted, the following guidance applies for physical activity at home, in gyms and health clubs, and outdoors, as well as for participation in sports in general.[27]

5.2. Physical Activity at Home

Broadly, the following guidelines are to be followed:[27]

- Exercise in a well-ventilated place; keep doors and windows open whenever possible.
- If more than one person will exercise in the same room, keep a minimum distance of 2 meters between them (i.e., one person per 4 m^2).
- Preferably, physical activities should be practiced individually. To increase safety, stick to those exercises which you already used to performing.
- Wash hands and exercise equipment very well with soap and water or hand sanitizer (70% alcohol-based) during physical activities.
- Use disposable towels or individual fabric towels, laundering them after every use.
- Do not overexert yourself while training; follow your physician's advice.
- Stop exercising at once if any of the following symptoms appear: fatigue, chest or back pain, dizziness, palpitations, muscle pain, fever, nausea, vomiting, diarrhea, or flu-like symptoms.
- Sedentary individuals and those who have not trained for a long time should limit themselves to light physical activity only.

5.3. Outdoor Physical Activity

Follow the guidelines of local health authorities regarding restrictions on outdoor physical activity.[27] Even where restrictions have already been lifted, individual, isolated exercise is recommended, as described above. Always bear in mind that, as of yet, there is still no specific treatment for the virus, and some precautionary measures must continue to be followed.

There are not many validated standards for specific recommendations regarding the practice of outdoor activities during a pandemic. Only one Belgian–Dutch study suggested that a distance of 2 meters is ineffective in preventing the spread of the virus during such activities. Instead, the authors suggest:

1. A distance of 4 to 5 meters between people walking behind one another.
2. A distance of 10 meters when jogging or cycling slowly.
3. A distance of 20 meters when cycling quickly.

It bears stressing that the aforementioned measures and suggested behaviors are subject to constant change as the pandemic evolves.[28-30]

5.4. Physical Activity in Gyms and Fitness Clubs

- Hand sanitizer (70% alcohol-based) and face masks should be provided for use by members and staff in all areas (front desk, weight rooms, free weights, classrooms, swimming pool, changing rooms, etc.).

- Active temperature screening at the front door is recommended.
- All rooms should undergo 30 minutes of general cleaning and disinfection once or twice a day.
- Cleaning kits, containing single-use paper towels for immediate disposal and a specific product for disinfection of equipment (mats, dumbbells, weight machines, etc.), should be placed at strategic points in the weight training and free weight areas.
- Limit the number of members in the gym at any one time and the space allocated to each member. In free-weight areas, classrooms, and other shared spaces (e.g., training areas, locker rooms), occupancy should be limited to one person per 4 m^2.
- Use of contiguous machines should not be allowed (i.e., if one machine is in use, the next one over should be out of service).
- Water cooler privileges should be limited to refilling of individual bottles.
- Home and building gyms, once cleared to reopen by the health authorities, should set aside exclusive hours for residents of the same apartment or unit. Proper cleaning after use is mandatory.[29]

5.5. I've Been Diagnosed with COVID-19 – When Can I Resume Physical Activities?

Whichever regular physical activity is desired, clearance for practice is contingent upon negative PCR and clinical reassessment. Before resuming any physical activity, regardless of intensity, a pre-exercise assessment is mandatory to diagnose potential sequelae of COVID-19.[30-34]

5.6. Assessment of Athletes Who Have Contracted COVID-19

- Athletes with asymptomatic infection and confirmed presence of antibodies (positive serology).
- Athletes with a history of mild COVID-19-related illness (not requiring hospitalization), confirmed or suspected.
- Athletes with a history of moderate-to-severe COVID-19-related illness (requiring hospitalization), confirmed or suspected.
- Athletes with a history of COVID-19 infection (regardless of severity) with evidence of myocardial injury, confirmed by one or more of the following: in-hospital ECG changes, elevation of troponin or natriuretic peptide levels, arrhythmia, or impairment of heart function.

Pre-exercise assessment with ECG and additional tests (as guided by the initial assessment) is mandatory. Whenever possible, confront with findings of previous tests, with a view to screening for persistent or de novo post-infectious symptoms.

Athletes who exhibited cardiac abnormalities during COVID-19 infection will require serial cardiac imaging before resuming their regular activities, and should resume these activities only gradually. In addition, all patients with cardiac involvement must be followed by a specialist.

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In the "Position Statement of the Brazilian Society of Cardiology Department of Exercise Testing, Sports Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation (DERC/SBC) on Activities Within its Scope of Practice During the COVID-19 Pandemic", with DOI number: https://doi.org/10.36660/abc.20200797, published in the journal *Arquivos Brasileiros de Cardiologia,* 115(2):284-291, on page 290, where you read:

"Whichever regular physical activity is desired, clearance for practice is contingent upon negative PCR and clinical reassessment."

The correct is:

"For people previously diagnosed with symptomatic Covid-19 who remain asymptomatic after recovery, a new test is not recommended within the next 3 months after the onset date of infection, and release for physical activity will depend on clinical evaluation."

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Position Statement on the Use of Antiplatelet Agents and Anticoagulants in Patients Infected with the New Coronavirus (COVID-19) – 2020

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

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Content

1. Introduction

The new coronavirus (SARS-CoV-2) pandemic has led to debate about the best treatment for the disease and its complications. Recent publications have shown that cardiovascular disease is among the main risk factors for disease progression, including high blood pressure and diabetes mellitus.[1-6]

It has been demonstrated that patients infected with the new coronavirus (COVID-19) have distinct activation of prothrombotic mechanisms, including a greater likelihood of thrombotic events. Acute coronary syndrome (ACS) with or without ST-elevation can occur in patients with COVID-19, although the actual incidence is still uncertain.[7-10] Thus, several issues related to using antiplatelet agents and anticoagulants in patients with suspected or confirmed COVID-19 infection remain uncertain. The following recommendations are valid for the most diverse clinical situations, such as atrial fibrillation, acute coronary syndrome, chronic coronary artery disease, percutaneous coronary intervention, post-cardiac surgery, ischemic stroke, and venous thromboembolism, and should be applied on a case-by-case basis.

2. Pathophysiology

2.1. Mechanism of Cellular Entry

The functional receptor and gateway of the SARS-CoV-2 virus is angiotensin-converting enzyme 2. This carboxypeptidase has the opposite effect of angiotensin-converting enzyme 1, i.e., it increases the degradation of angiotensin 2 and thus has a vasodilating effect. In addition to being present in lung parenchyma, angiotensin-converting enzyme 2 is also distributed throughout the cardiovascular system, kidneys and heart. It is known that angiotensin-converting enzyme 2 has a certain role in ventricular function. Severe left ventricular dysfunction occurred in animal models that reduced the expression of angiotensin-converting enzyme 2. Apparently, infection with the new coronavirus can promote downregulation of these receptors, which could lead to myocardial injury and lung injury.[1,2,11] Despite this possible association, an observational study of 8,910 patients infected with SARS-Cov-2 found no increase in mortality among patients using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[12] Thus, these medications should not be discontinued in patients who used them prior to infection.

2.2. Myocardial Injury

Several studies, mainly Chinese, have demonstrated the impact of myocardial injury on the progression and severity of COVID-19. Chinese data indicate the presence of myocardial injury in approximately 20 to 30% of hospitalized patients, as well as in 40% of those who died. There are data showing that elevations in some markers, such as troponin and D-dimer, are associated with worse prognosis, intensive care unit hospitalization, mechanical ventilation, and death.[2,13,14]

The mechanism of myocardial injury is still not well established. In addition to the direct effect of the virus, there is myocardial stress induced by respiratory failure and hypoxemia, including supply and demand imbalances, as well as the indirect action of systemic inflammatory response on myocardial tissue and endothelial function.[14-19]

Data on the effects of myocardial inflammation is also insufficient. It is not clear whether COVID-19-induced myocarditis produces heart failure with reduced ejection fraction. There have been anatomopathological findings of lymphocytic myocarditis, even in patients with preserved ejection fraction and signs of ventricular hypertrophy.[14-19]

2.3. Association with Acute Coronary Syndrome

The increased risk of ACS in patients with COVID-19 can be explained by increased thrombotic activity, evidenced by the frequent elevation of D-dimer and thrombocytopenia. There is also an increase in coronary events in direct association with viral respiratory infection. Factors related to inflammatory activity (e.g., endothelial dysfunction, platelet activation, macrophage activation, liver dysfunction, tissue factor expression and cytokine release) can increase the risk of atherosclerotic plaque instability. More recent studies have also identified high levels of antiphospholipid antibodies in patients with COVID-19, although it is not known whether this is related to disease severity.[5,7-10,15,20]

At the beginning of the infection phase, platelet inhibition can reduce the formation of intravascular fibrin and thrombus. Thus, the use of pre- but not post-admission acetylsalicylic acid was found to be associated with a lower risk of respiratory failure and mortality in patients with community-acquired pneumonia. Despite the fact that all $P2Y_{12}$ inhibitors reduce platelet and leukocyte aggregates and platelet-derived proinflammatory cytokines, ticagrelor, which is orally administered, is unique in having an additional well-documented target of inhibition: equilibrative nucleoside transporter 1, which contributes to the inhibition of cellular adenosine uptake. Therefore, ticagrelor has more potent anti-inflammatory properties, although it has not been tested in COVID-19.[7]

It should be pointed out that in view of the high incidence of myocardial injury due to the virus and the indirect effects of infection, non-ischemic disease must be considered in an

ACS diagnosis, even in the presence of electrocardiographic changes. A case series was published[21] of 18 patients in New York hospitals with COVID-19 and ST-segment elevation suggestive of acute myocardial infarction, including four with diffuse ST-segment elevation and 14 with focal ST-segment elevation. Of these patients, 50% had coronary angiography and 33% had no obstructive coronary disease. In all, 44% of the patients were diagnosed with acute myocardial infarction. Thus, even in patients with ST-segment elevation, differential diagnoses must be considered due to the heterogeneous clinical picture. However, regardless of the etiology, mortality was 72%. Therapeutic decision making and invasive stratification strategies should consider the clinical condition, the findings of complementary tests, the team's experience, and the availability of the hemodynamics laboratory.[14,16] In two other studies, a lower incidence of ACS was found in northern California compared to the same period the previous year, while a higher incidence of out-of-hospital cardiac arrest was found in Italy. This suggests a lower demand for emergency services by the population.[22,23]

In addition to all these factors, the effects of social isolation have raised enormous concern. Most people have drastically reduced physical activity. In addition, diets can become inadequate due to higher carbohydrate intake. Such lifestyle changes may contribute to thrombotic events, including stroke and ACS.[24]

2.4. Thromboembolic Mechanism

Patients infected with COVID-19 are likely to have an increased risk of venous thromboembolism (VTE). Although a large case series has not yet been published, there are reports of abnormal coagulation parameters in hospitalized patients with severe COVID-19.[25-27]

A recent case series of 106 COVID-19 patients who underwent pulmonary arteriography found that 30% had VTE. Patients with COVID-19 and pulmonary embolism had higher levels of D-dimer than those without an embolism ($p < 0.001$), in addition to a greater need for intensive care (75% vs. 32%, $p < 0.001$). A D-dimer level > 2,660 μg/L showed 100% sensitivity and 67% specificity for pulmonary embolism.[28]

D-dimer levels have been associated with higher mortality rates and seem to progressively increase with infection severity. The phase of the disease in which acute respiratory distress syndrome develops and the radiological pattern worsens is marked by a significant increase in D-dimer levels, which is observed in the most severe cases of myocardial injury and disseminated intravascular coagulation. The systemic inflammatory response in infected patients can result in endothelial injury with a consequent increase in thrombin production and a reduction in endogenous fibrinolysis. This prothrombotic state is called sepsis-induced coagulopathy and precedes disseminated intravascular coagulation. The various mechanisms involved in sepsis-induced coagulopathy act simultaneously, culminating in a prohemostatic state. Apparently, inflammatory cytokines are the most important mediator of this clotting disorder during sepsis.[29]

A cross-interaction has been demonstrated between inflammation and coagulation, with inflammation inducing coagulation activation and coagulation accentuating inflammatory activity. Platelets play a central role in the development of coagulation abnormalities in sepsis and can be activated directly by pro-inflammatory mediators, such as platelet activating factor, as well as through thrombin. Platelet activation can also stimulate fibrin formation by an alternative mechanism. The expression of P-selectin in the platelet membrane not only induces the adhesion of platelets to leukocytes and endothelial cells but also increases the expression of tissue factor in monocytes. Under normal circumstances, coagulation activation is controlled by three important physiological anticoagulant pathways: the antithrombin system, the activated protein C system, and the tissue factor pathway inhibitor. In sepsis, all three pathways become dysfunctional. In the midst of this imbalance in the coagulation system, endogenous fibrinolysis is greatly reduced.[29]

In a Chinese retrospective cohort study, elevated D-dimer levels (> 1 g/L) were strongly associated with hospital death. In another study comparing COVID-19 survivors and non-survivors, non-survivors had significantly higher levels of D-dimer and fibrin degradation products, and 71.4% of non-survivors met the clinical criteria for disseminated intravascular coagulation during the course of disease. In addition to disseminated intravascular coagulation, critically ill patients who have experienced prolonged immobilization are at high risk of VTE. Vascular inflammation can also contribute to a state of hypercoagulation and endothelial dysfunction in such patients. In seriously ill patients with COVID-19 who clinically deteriorate, as evidenced by hypoxia or hemodynamic instability, thromboembolic disease should be considered.[25-27]

3. Drug Interactions and Cardiovascular Pro-/Antithrombotic Effects

So far, there is no specific treatment for COVID-19 infection, and a variety of therapeutic regimens have been used in severe cases in a hospital environment, although the efficacy and safety of many are still being investigated. Since these drugs can be used in specific situations, it is worth considering their side effects on the cardiovascular system and possible drug interactions with other therapies frequently used in cardiac patients.

3.1. Antiretrovirals

Ribavirin and remdesivir block RNA polymerase, while lopinavir-ritonavir inhibits viral replication. Ribavirin-induced cardiotoxicity has not been reported. However, lopinavir-ritonavir prolongs the QT and PR intervals, especially in patients who already have long QT intervals or are using other medications that interact with the QT interval.

Both ribavirin and lopinavir-ritonavir enhance the anticoagulant effect, modifying the action of warfarin (mainly ribavirin) and new anticoagulants such as apixaban and rivaroxaban (mainly lopinavir-ritonavir).[30-32] In another study, an association of dabigatran and antivirals in hospitalized COVID-19 patients resulted in increased in serum plasma levels, requiring medication withdrawal in more than half of the patients.[31]

Lopinavir-ritonavir may also influence the activity of $P2Y_{12}$ inhibitors by inhibiting CYP3A4, which reduces the serum level of active metabolites of clopidogrel and increases the activity of ticagrelor. Therefore, due to the high risk of bleeding, the concomitant use of ticagrelor and lopinavir-ritonavir is discouraged.[11]

There is also evidence that using clopidogrel during treatment with lopinavir-ritonavir may result in an insufficient antiplatelet effect, although this has not been observed with prasugrel, which makes it the ideal medication.[32] In the presence of contraindications for prasugrel (e.g., previous stroke, advanced age, low body mass index, and increased risk of bleeding), clopidogrel is indicated, and platelet activity should be evaluated.[30,32]

Remdesivir, an antiretroviral under investigation for use with COVID-19, was used during the Ebola epidemic. Despite its promise, in a randomized, double-blind, multicenter study, it did not result in better mortality outcomes than placebo. Although there was a trend toward symptom reductions, it was not significant.[33] No cardiotoxicity or other important drug interactions have been reported for this drug.[30,32]

3.2. Hydroxychloroquine and Chloroquine

Hydroxychloroquine and chloroquine are frequently used in patients with malaria and other systemic inflammatory diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Apparently, they can block viral entry into cells, in addition to stimulating immunomodulation, attenuating the production of cytokines, and inhibiting autophagy and lysosomal activity in the host. They may also have antithrombotic properties, especially against antiphospholipid antibodies.[5,34,35]

These drugs have been used in previous SARS and MERS epidemics, and there is evidence of their efficacy. A Chinese study of 100 patients with COVID-19 found that chloroquine was associated with radiological improvement, increased viral clearance, and decreased disease progression. Despite its promising results, the study had several limitations and can be interpreted in different ways.[5,34,35] In other observational studies, hydroxychloroquine, associated or not with azithromycin, did not result in favorable outcomes. No decrease was found in mortality or intubation time, and no difference in seroconversion was found in patients with mild to moderate disease.[36-38] Several studies are ongoing about the impact of hydroxychloroquine and/or chloroquine.

Although generally well tolerated, chloroquine and hydroxychloroquine can have serious side effects, such as prolonging the QT interval and inducing hypoglycemia, retinopathy and neuropsychiatric disorders. However, no interaction with antiplatelet agents or anticoagulants has been reported.[5,34,35]

3.3. Corticosteroids

Methylprednisolone is another medication that can be considered during severe cases of COVID-19 and acute respiratory distress syndrome. Although it is known to cause water retention, hydrolytic changes and hypertension, interaction with antiplatelets or anticoagulants has not been reported.[35]

3.4. Heparins

A Chinese study[39] of 449 hospitalized COVID-19 patients found that a prescription strategy of enoxaparin 40-60 mg/day or unfractionated heparin 10,000-15,000 U/day resulted in 28-day mortality benefits in two subgroups. In one of these groups, which consisted of patients with criteria for sepsis-induced coagulopathy > 4 (increased prothrombin time, decreased platelet count, and increased SOFA-Score), there was a difference of 40% vs. 64.2% ($p = 0.029$). The other subgroup, which consisted of patients with > 6 times the normal D-dimer concentration, there was a difference of 32.8% vs. 52.4% ($p = 0.017$). This demonstrates that chemical prophylaxis for VTE or full anticoagulation therapy should be considered on a case-by-case basis in all hospitalized patients with COVID-19, and a careful search should be made for thrombotic events.[26,27,31,39-41]

3.5. Immunoglobulins and Anti-IL6 Antibodies

Immunoglobulin use depends on two mechanisms: viral neutralization and immunomodulation. One intriguing application of viral neutralization is convalescent serum or plasma. Since this therapy has pleiotropic effects that result in suppressed inflammation, this therapy can potentially alleviate disease severity in the hyperinflammatory phase. More robust evidence is needed to confirm these findings. Likewise, it may be that COVID-19 patients with a cytokine storm can benefit from monoclonal antibodies targeting interleukin-6 receptor, since it has been successful in mitigating inflammation in transplanted patients. Although this could be reflected in the patient's thrombotic state, there is still no concrete evidence about it.[15]

Although anti-interleukin-6 receptor antibodies increase CYP3A4 expression, there are no dose-adjustment recommendations regarding patients using antiplatelet agents or anticoagulants.[5]

4. Recommendations

4.1. Anticoagulants

The decision to prescribe low molecular weight heparin or prophylactic unfractionated heparin for VTE or as full anticoagulation therapy should be made on a case-by-case basis, and should always be considered in hospitalized high-risk VTE patients.[5,29,39-43]

Based on expert consensus and the results of a few retrospective studies, when anticoagulation is not contraindicated, anticoagulant therapy can be considered for use in patients with severe COVID-19 and signs of sepsis-induced coagulopathy and/or very high D-dimer levels in association with other biomarkers that denote severity. This strategy requires the use of strict institutional protocols that allow for surveillance and rapid intervention when complications arise.[29]

It is possible that anticoagulant therapy is more beneficial when initiated in the pre-thrombotic phase than in advanced cases, when the risk of bleeding is greater. When opting for anticoagulation, it would seem reasonable to use low molecular weight heparin as the drug of choice in stable patients with normal creatinine clearance (subcutaneous dose of 1 mg/kg every 12 hours). In case of shock or creatinine clearance below 50 mL/min/m^2, unfractionated intravenous heparin (18 IU/kg/h) is preferable, targeting an activated partial thromboplastin time between 1.5 and 1.8. However, there is no evidence to support the wide use of heparin in therapeutic doses for COVID-19. Figure 1 illustrates a suggested assessment and therapeutic strategy for this group of patients based on current evidence.[29]

The European Society of Cardiology recommended full anticoagulation in all patients with signs of severity, e.g., respiratory rate > 24 bpm, arterial oxygen saturation $< 90\%$, high C-reactive

protein, high or rising D-dimer levels, and high fibrinogen levels. With respect to D-dimer levels, the recommendation is full anticoagulation when > 3,000 ng/mL, chemical prophylaxis alone when < 500 ng/mL, and 40 mg enoxaparin every 12 hours when between 500 and 3,000 ng/mL.[42]

Prophylaxis for thromboembolism, which should be continued after hospital discharge, must also be individualized with either low molecular weight heparin or new anticoagulants, assessing the risk/benefit of thrombotic events vs. bleeding (Figure 2).

Although there is no specific evidence regarding COVID-19, it is reasonable to consider individualizing the risk stratification of thromboembolic and hemorrhagic events and extending drug prophylaxis for up to 45 days in patients with reduced mobility, cancer, previous VTE, high D-dimer levels (i.e., > 2 times the upper limit of normal).[5]

Regarding patients who have been using anticoagulants for any reason, the medication should be continued whenever possible. However, if the patient is hospitalized for COVID-19-associated pneumonia, continuation must be determined on a case-by-case basis. Since there may be changes in the pharmacokinetics of medications, renal failure, liver failure, thrombocytopenia, and disseminated intravascular coagulation in critically ill patients, parenteral anticoagulation with low molecular weight heparin or unfractionated heparin is preferable if there are no contraindications.[5,7,26,27,31,39,40]

There is an interaction between lopinavir-ritonavir and oral anticoagulants. It is not advisable to administer rivaroxaban and edoxaban concomitantly. In patients using warfarin, apixaban doses should be reduced and there should more frequent monitoring of prothrombin time. Thus, in patients who have been using oral anticoagulants and must continue using them after admission, it is advisable to administer low molecular weight heparin in the parenteral form. It should be remembered that if patients evolve to blood dyscrasia or disseminated intravascular coagulation, the risk of bleeding must be considered when continuing these medications, since they are suspended in almost all cases.[32]

4.2. Antiplatelet Agents

Patients who use antiplatelet agents for chronic coronary disease should continue taking them. In hospitalized patients on dual antiplatelet therapy, the prescription should be individualized (Figure 3).[5,7,40]

Given the high risk of bleeding in patients after percutaneous coronary intervention (PCI) complicated by COVID-19, a shorter duration of dual antiplatelet therapy (DAPT) may be beneficial in this population in addition to the preferential use of clopidogrel in those at high risk of bleeding, although the risk of stent thrombosis vs. bleeding should always be considered. To counterbalance the increased risk of bleeding associated with DAPT, more recent studies have provided evidence in favor of early withdrawal of acetylsalicylic acid after PCI, which mainly reduces bleeding rates. Among patients on DAPT, continuing the $P2Y_{12}$ inhibitor in monotherapy (preferably ticagrelor) may be a reasonable strategy when a PCI was performed more than 3 months ago. Due to a lack of evidence, DAPT should not be discontinued for those who received a PCI less than 3 months ago.[5,7]

If the patient requires antivirals, there is an interaction between lopinavir-ritonavir and clopidogrel and ticagrelor, and these medications should be avoided or platelet activity evaluated. Prasugrel can be administered with caution, unless there are contraindications. Interactions with intravenous antiplatelet agents such as cangrelor have not been reported.[11,30,32]

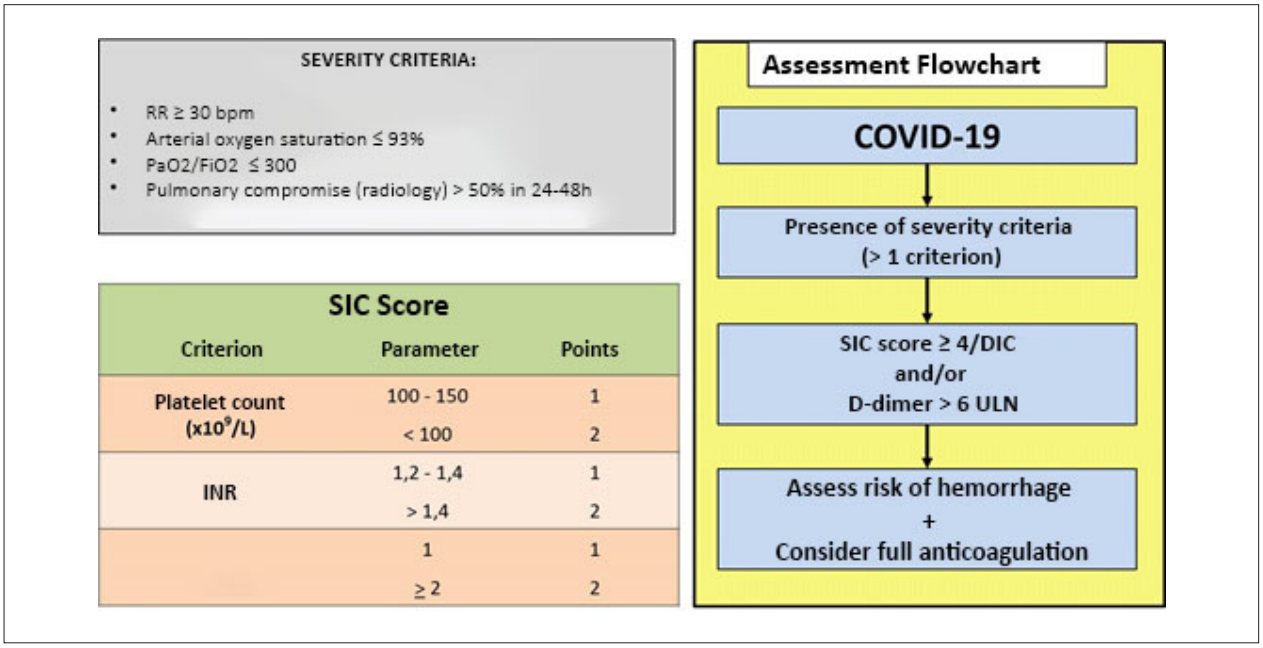

Figure 1 – *Management suggestion and flowchart for assessing anticoagulant therapy in critically ill patients with COVID-19.*
RR: respiratory rate; SIC: sepsis-induced coagulopathy; INR: international normalized ratio; SOFA: sequential organ failure assessment; DIC: disseminated intravascular coagulation; ULN: upper limit of normal.

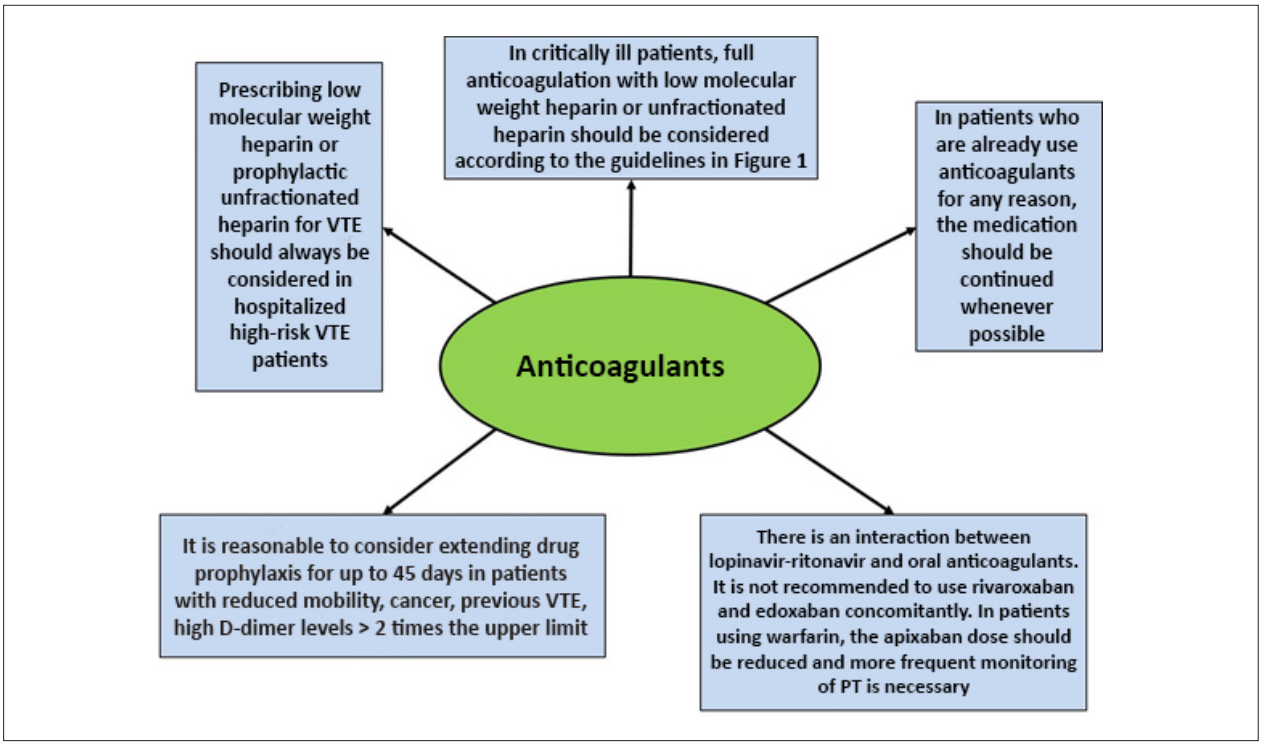

Figure 2 – *Recommendations regarding the use of anticoagulants in patients with COVID-19. VTE: venous thromboembolism; TP: prothrombin time.*

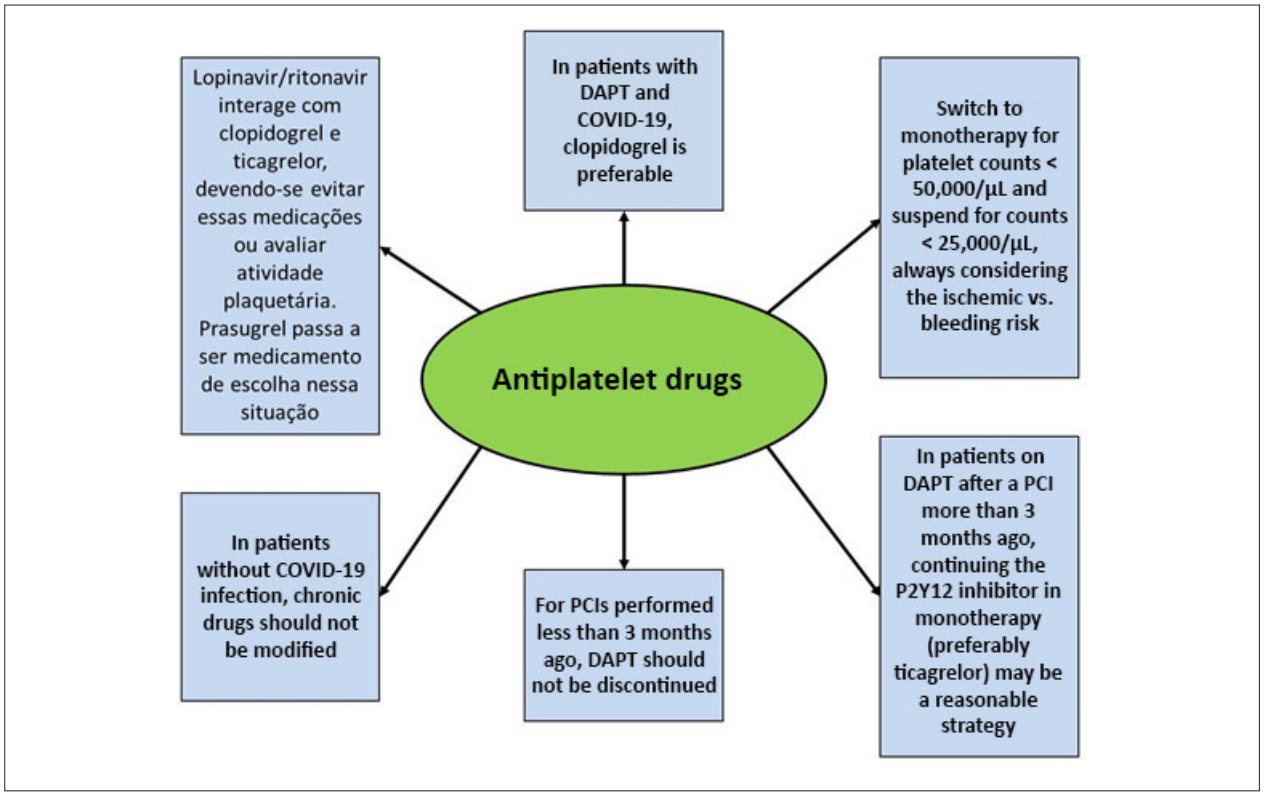

Figure 3 – *Recommendations regarding the use of antiplatelet agents in patients with COVID-19. PCI: percutaneous coronary intervention; DAPT: double antiplatelet therapy.*

Expert consensus recommends taking proactive measures or even discontinuing all antiplatelet therapy in patients with platelet counts < 100,000/μL and < 50,000/μL, respectively.[7] There is, however, a more current recommendation that suggests switching to monotherapy if the count is < 50,000/μL and suspending therapy if the count is < 25,000/μL, always considering ischemic risk vs. bleeding risk.[5]

4.3. Thrombolytics

Both the American Heart Association and the European Society of Cardiology indicate the use of thrombolysis as the first option in suspected/confirmed COVID-19 patients with acute myocardial infarction and ST-segment elevation, both in centers without hemodynamic services and in those with hemodynamic services that have not made adequate preparations to avoid contaminating the team.[5,7,44-47]

So far, there is no contraindication for using thrombolytics in this context, and their use should be based on the usual contraindications and should be individualized in situations of electrical or hemodynamic instability, disseminated intravascular coagulation, thrombocytopenia, bleeding and renal or hepatic failure.[48]

It should be pointed out that differential diagnoses of ST-segment elevation should always be considered, such as myopericarditis, for which thrombolysis should be avoided.[5]

5. Final Considerations

Evidence about the interaction of COVID-19 with coagulation and platelet activation systems is still early. There is strong evidence that this pathway could be an important therapeutic target. However, more robust studies are still needed to determine the real importance of prothrombotic mechanisms and the best therapy for this group of patients.

Table 1 – General recommendations about COVID-19/antiplatelet agents and anticoagulants

Indication	Class of recommendation	Level of evidence
Drug association between antithrombotic therapies and medications used in the treatment of COVID-19		
In patients using lopinavir-ritonavir, prasugrel should be the antiplatelet agent of choice	IIB	B
In patients using lopinavir-ritonavir, if prasugrel is contraindicated, clopidogrel should be used	IIB	B
In patients using lopinavir-ritonavir, if clopidogrel is used, platelet activity should be monitored	IIB	B
Ticagrelor should be discouraged in patients using lopinavir-ritonavir	IIB	B
In patients who are already using anticoagulants and will be using lopinavir-ritonavir, the anticoagulant must be replaced with the parenteral form (heparins)	IIA	B
In patients who are already using anticoagulants, avoid associating rivaroxaban or edoxaban with lopinavir-ritonavir	III	B
In patients who are already using anticoagulants with warfarin (and must continue this medication) and lopinavir-ritonavir, prothrombin time should be evaluated more frequently.	IIA	B
Remdesivir has no significant drug interaction with antiplatelet agents and anticoagulants	IIA	B
Corticosteroids have no significant drug interaction with antiplatelet agents and anticoagulants	IIA	B
Immunoglobulins and anti-interleukin-6 antibodies have no significant drug interaction with antiplatelet agents and anticoagulants	IIB	B
Hydroxychloroquine and chloroquine have no significant drug interaction with antiplatelet agents and anticoagulants	IIB	B
In patients using hydroxychloroquine or chloroquine, the QT interval should be monitored	IA	B
The use of anticoagulants in patients with COVID-19		
Chemical prophylaxis for thromboembolic events should be performed for all inpatients	IIA	B
Full anticoagulation should be considered in special cases after assessing the risk/benefits, e.g., using the sepsis-induced coagulopathy score or D-dimer >6 normal	IIB	B
In patients who are already using anticoagulants, the medication should be continued whenever possible	IIA	B
Consider extending chemical prophylaxis for thromboembolic events up to 45 days after discharge for at-risk patients	IIB	B
The use of antiplatelet agents in patients with COVID-19		
The medication patients with chronic coronary disease should be continued	IIA	C
In patients using dual antiplatelet therapy post-angioplasty (with a PCI more than 3 months ago) monotherapy may be considered, as long as the risk of bleeding and stent thrombosis is considered.	IIA	B

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Erratum

In the Original Article "Experience in a Brazilian Center with Crioablation for Electric Isolation of the Pulmonary Veins in Paroxysmal and Persistent Atrial Fibrillation – Preliminary Results in Brazil" with DOI number: https://doi.org/10.36660/abc.20200320, published in the periodical Arquivos Brasileiros de Cardiologia, correct the word in the English title Crioablation para Cryoablation. Correct the name of the author Eduardo Barbosa for Eduardo C. Barbosa. Change the DOI number to DOI: https://doi.org/10.36660/abc.20190307.

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