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EDITORIAL

Open Science and the Role of Cardiology Journals in the COVID-19 Pandemic

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"It is not the strongest of the species that survives,
not the most intelligent that survives.
It is the one that is the most adaptable to change."
— Charles Darwin

In July 2020, Brazil has the world's second highest Covid-19 death toll. The COVID-19 pandemic is spreading fast in America. Since the first case of COVID-19 was confirmed, it took 114 days in Brazil (February 26-June 19) and 98 days in the USA (January 21-April 29) for the number of cases to reach more than 1,000,000. Parallel to the rapid growth of COVID-19 cases, there has been a progression in the number of scientific publications. Until June 2020, more than 25,800 papers about COVID-19 were published in PubMed (17,800 open access - 69%). This volume of scientific publications is unprecedent. The Journal of the American Medical Association (JAMA), for example, received more than 11,000 submissions from January 1 to June 1, 2020, compared with approximately 4,000 submissions during the same period in 2019.[1] The International Journal of Cardiovascular Sciences is facing a similar situation with more than doubled manuscripts submitted. Our aim is to discuss the importance of Open Science during the COVID-19 pandemic and the role of cardiology journals in this special moment.

COVID-19 is a new disease and many of its aspects are still obscure. What is known about SARS-CoV-2 transmission, incubation, and environmental stability? What are the risk factors for the disease? What is the best evidence-based therapy? What is the real importance of asymptomatic and presymptomatic virus shedding in SARS- CoV-2 transmission? How long neutralizing antibodies persist following infection, and do they confer immunity to reinfection? These and many other key questions are still unanswered.[2] There is a great need for fast and efficient publication of information, but at the same time all efforts must be made to assure quality, and avoid biases and limitations.[3]

Research reports submitted to the IJCS are initially reviewed by the editor-in-chief, then by the associate editor, and finally by reviewers. For manuscripts that need revisions, the entire peer review process takes no less than 60 days. As a task force of the IJCS editors and reviewers, COVID-19 manuscripts are under fast track to reduce the time to response to the authors to 15 days and accelerate the time from submission to publication, and importantly, of reliable data. Our first fast-track paper about COVID-19 was published in April covering the cardiovascular consequences of SARS-CoV-2 infection.[4] In a two-month period, this article was cited in two papers and the preprint was downloaded more than 400 times. The second fast-track paper was an editorial proposing a framework to fight against fake medical news, which can even aggravate the effects of the COVID-19 pandemic.[5] Many articles on COVID-19 are about to be published in the IJCS. What is the impact of this acceleration in the publication process? Horbach studied the duration of publication process in medical journals and found that, compared to prior pandemic, turnaround times have decreased on average by 49% during the pandemic, and publication process became nearly twice as fast for Covid-19 related articles.[6]

Peer review is essential in science and editors must assure scientific rigor in methodological issues and solid statistical analyses.[1] Scientific misconduct (fabrication,

Keywords

COVID-19; Coronavirus; Pandemics; Scientific Publications; Peer Review; Ethical Review; Open Access Publishing.

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falsification, and plagiarism) is directly related to the urge to publish more[7] and has affected prestigious medical journals since the beginning of the pandemic. The New England Journal of Medicine and The Lancet are among the oldest, most respected and most influential medical journals in the world. Both journals had important COVID-19 papers [8,9] retracted due to data fabrication. Most of the time, reviewers do not examine the raw data of the studies they review. One of the multiple benefits of Open Science is that research data can be checked by anyone who accesses the data repository, thereby reducing the likelihood of scientific misconduct.[10]

What is the role of cardiology journals during COVID-19 pandemic? First, they must adapt to the urgent needs of fast peer review and editorial evaluation. Second, cardiology journals must ensure scientific rigor and research integrity. Third, they must focus on the cardiac aspects of COVID-19 because the cardiology community needs reliable resources of specific information related to their practice, such as the influence of previous heart conditions, safe cardiological practices, cardiac effects of COVID-19 therapy, typical cardiac manifestations of COVID-19, the effects of quarantine on the cardiovascular system and many other emerging issues. Fourth, and finally, non-COVID-19 cardiac research must not be forgotten. All cardiac diseases and their consequences still exist, and many unmet needs of non-COVID-19 cardiac diseases must be pursued. Science must provide answers for these and many other questions. Cardiology journals must accomplish their mission and provide their readers with comprehensive knowledge on cardiovascular sciences in the best way possible.

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International Journal of Cardiovascular Sciences. 2020; 33(4):307-317

ORIGINAL ARTICLE

The Role of Patent Foramen Ovale Closure in the Secondary Prevention of Cryptogenic Stroke: a Meta-Analysis Report

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Abstract

Background: Patent foramen ovale (PFO) closure has been compared to medical therapy for secondary prevention of recurrent cryptogenic stroke.

Objectives: To produce an updated meta-analysis including only data from the primary analyses of clinical trials and to evaluate the role of PFO closure in the secondary prevention of recurrent stroke.

Methods: Search in Medline (PubMed) and in ISI Web of Knowledge. Parameters under analysis and meta-analyses were: stroke, transient ischemic attack (TIA) and atrial fibrillation (AF). Comprehensive Meta-analysis Software V.2.0 (Biostat) was used. Random-effects analyses were carried out. A level of significance of 5% was used.

Results: In this study six, randomized trials enrolling 3,750 patients were included. Unlike other published meta-analyses on the same topic, in this case, only clinical trial data, and not follow-up data, were used. PFO closure, as compared with medical therapy alone, demonstrated superiority in reducing the rate of recurrent stroke (risk ratio with PFO closure vs. medical therapy, 0.37; 95% confidence interval [CI], 0.17 to 0.78; p = 0.01). PFO closure did not offer a significant benefit in prevention of TIA (risk ratio with PFO closure vs. medical therapy, 0.96; 95% CI, 0.64 to 1.44; p = 0.85). Among patients assigned to closure group, an increased risk of atrial fibrillation was seen (risk ratio with PFO closure vs. medical therapy, 4.64; 95% CI, 2.38 to 9.01; p < 0.01).

Conclusions: In patients with cryptogenic stroke who had a patent foramen ovale, a protective effect of closure was seen concerning the risk of recurrent stroke, but not regarding the prevention of TIA. (Int J Cardiovasc Sci. 2020; 33(4):307-317)

Keywords: Foramen Ovale Patent/Diagnosis; Stroke; Isquemic Attack, Transient; Atrial Fibrillation; Risk Factors; Stroke/Prevention and control.

Introduction

Stroke remains one of the most important causes of death and morbidity worldwide.[1] Between 20% and 30% of ischemic strokes have no identifiable cause after exclusion of all potential causes, and they are denominated cryptogenic strokes.[2] Forty to fifty percent of patients who suffer a cryptogenic stroke also have a patent foramen ovale (PFO). This association suggests that some cryptogenic strokes, particularly in younger patients, may be due to paradoxical embolism, which consists in the passage of a thrombus from the venous to the atrial system through a patent foramen ovale.[3,4]

The options to implement secondary prevention of recurrent stroke for patients with a patent foramen ovale who have had a cryptogenic stroke have been the administration of antithrombotic medications or percutaneous closure of PFO. However, it was not initially clear whether percutaneous closure is superior to medical therapy.[5,6] The results of early studies gave

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no room for excessive optimism. These relatively modest results have been attributed to the choice of closure device, off-protocol closure device use within the medical therapy arms, patient selection criteria and slow enrolment,[1,3,5,7,8] among other reasons.

In the years 2017 and 2018, three new clinical trials were published, which demonstrated that percutaneous PFO closure, as compared with medical therapy, does reduce the risk of recurrent stroke.[6,9,10] Some of these results, impressive as they are, have been obtained by the selective inclusion of patients with high-risk PFO features, including the size of the patent foramen ovale, or the presence of an atrial septal aneurysm, making PFO closure particularly persuasive in these patients. However, restricting device closure entirely to patients with high-risk characteristics of PFO may be too conservative.[11]

Concerning the clinical trials currently published, several meta-analyses were carried out,[12-19] but all of them include data from a follow-up study[2] rather than the original clinical trial data, that is, data that the authors themselves considered to be exploratory.

The purpose of the present study was to produce an updated meta-analysis including only data from the primary analyses of clinical trials evaluating the role of PFO closure in the secondary prevention of recurrent stroke, since several texts previously published contained data from both original clinical trials and a follow up study.

Methods

Search strategy

The study started with a search on Medline (PubMed) database, using the query "patent foramen ovale" AND "stroke" AND "closure" with the filter "clinical trial". The search took place on July 2018, and no articles were excluded based on publication date. The search yielded 40 articles. A further search was carried out in a second database, ISI Web of Knowledge, using the same query, with the filter "article", on December 2018, yielding 840 articles (Figure 1, supplementary file 1). Additional studies were found after searching the references of previous review articles and other relevant sources, including articles related to the topic in question as well as articles citing the selected articles.

Inclusion criteria

Only human studies were included, and only interventional studies comparing PFO closure with medical therapy were considered within the scope of this review.

Exclusion criteria

The following were excluded: mechanistic studies, animal studies, studies of PFO physiology, case reports, editorials, review papers, study protocols, non-randomized studies, duplicate studies (if found), systematic reviews and/or meta-analyses, sub-group analyses of included studies, follow-up data of included studies, cost analyses or surveys, comparison between medical treatments, comparison between closure devices, studies on PFO closure only, guidelines, genetic and pathological studies.

Statistical analysis

We aimed at presenting an overview of clinical trials evaluating interventional studies comparing PFO closure with medical therapy. The meta-analysis was carried out by using the Comprehensive Meta-analysis Software V.2.0 (Biostat, New Jersey, USA). Random-effects analyses were carried out, given the considerable heterogeneity of some of the data. The parameters chosen for analysis and also for the meta-analyses were: stroke, transient ischemic attack and atrial fibrillation. Risk ratios were calculated. A level of significance of 5% was used. Results were reviewed by a biostatistician (CS).

Quality assessment of studies and data extraction

Study quality and eligibility were independently assessed by two researchers. Different opinions regarding the relevance of articles were solved by consensus between the authors. Global article quality assessment was carried out according to the method used by Haffar and colleagues (supplementary file 2).[20]

Results

A total of six articles were identified and selected for further study.[3,5,6,8-10] Interobserver agreement was 100%. Between 2012 and 2018, six randomized controlled trials (RCTs) comparing closure of PFO with medical

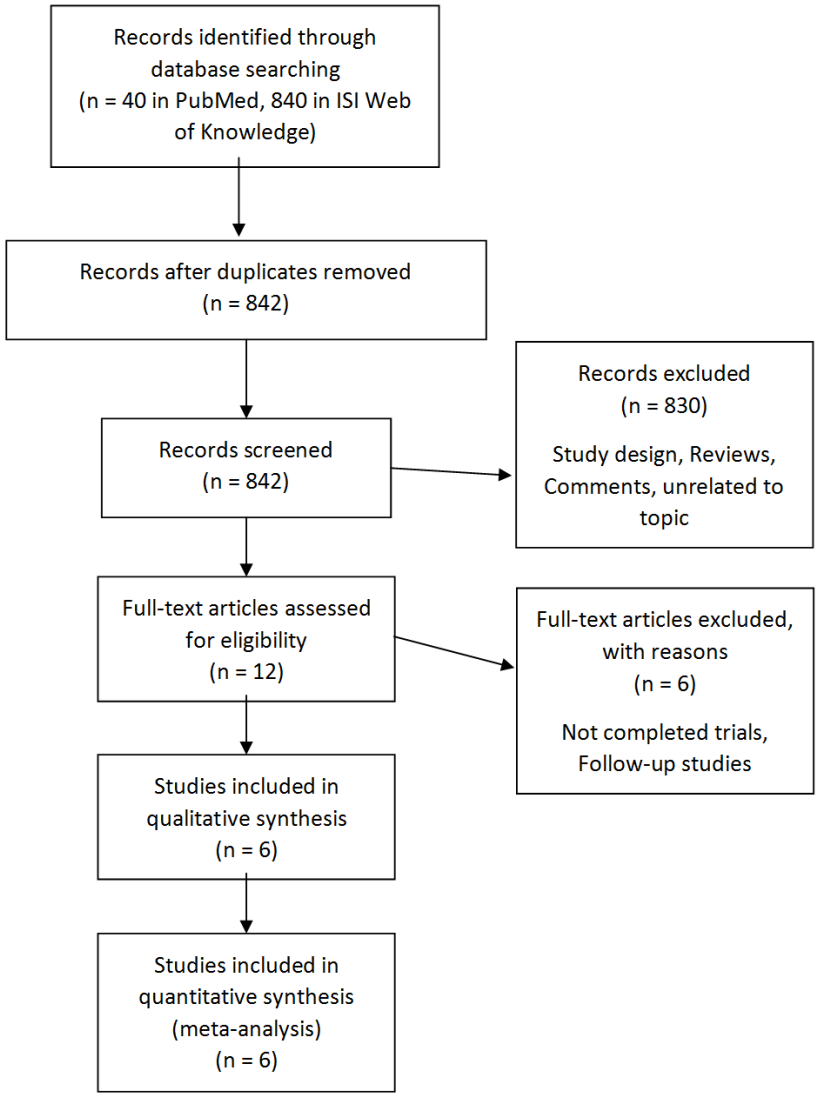

Figure 1 - Flow Diagram of Studies selection.

therapy alone for secondary prevention of patients with cryptogenic stroke and patent foramen ovale were published. These studies involved a total of 3,750 patients who were randomly assigned to either closure with the percutaneous device (closure group) or medical therapy alone (medical-therapy group). Concerning the acronyms, CLOSURE 1 denotes "Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale", RESPECT "Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment", PC trial "Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale (PFO) using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism", CLOSE "Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence", REDUCE "GORE HELEX Septal Occluder / GORE CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO) - The Gore REDUCE Clinical Study", DEFENSE PFO "Device Closure Versus

Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale"). The main aspects of the selected studies are shown in Table 1. In the closure group, device implantation was performed soon after randomization and, after the procedure, all patients were given antithrombotic therapy at the discretion of the site investigator, but always in accordance with the guideline recommendations. The mean follow-up duration varied between RCTs from 2 to 5.3 years.

The data of patients enrolled in each RCT are listed in Table 2. After randomization, a total of 1,889 patients were assigned to closure arm and 1,671 patients were assigned

Table 1 - The main aspects of selected studies

	Total number of patients	Inclusion criteria	Device and additional therapy	Medical therapy	Follow-up duration (years)	Primary outcomes	Level of significance adopted
CLOSURE 1 (2012)	909	1. 18 to 60 y of age 2. PFO documented on TE 3. CS or TIA within the previous 6 mo	STARFLex Septal Closure System + clopidogrel 75 mg/day, 6 months, + aspirin, 81 or 325 mg/day, 2 years	Aspirin or warfarin or both	2	A composite of stroke or TIA < 2 y and death (death for any cause < 30 d or death for neurologic causes between 31 d and 2 y)	5%
RESPECT (2013)	980	1. 18 to 60 y of age 2. PFO documented on TE 3. CS within the previous 270 d	Amplatzer PFO Occluder + 81 to 325 mg of aspirin plus clopidogrel for 1 month, followed by aspirin monotherapy for 5 months	Aspirin or clopidogrel or aspirin + ER-dipyridamole or warfarin	Mean: 2.6 ± 2.0	A composite of ischemic stroke or early death after randomization	5%
PC TRIAL (2013)	414	1. < 60 y of age 2. PFO documented on TE 3. CS, TIA with cerebral ischemic lesion, or PTE	Amplatzer PFO Occluder + 100-325 mg/day aspirin for at least 5 to 6 months + either 250-500 mg/d ticlopidine or 75-150 mg/day clopidogrel for 1 to 6 months	Antiplatelet therapy or oral anticoagulation	Mean: 4.1[a] 4.0[b]	A composite of death, nonfatal stroke, TIA or peripheral embolism	5%
CLOSE (2017)	663	1. 16 to 60 y of age 2. PFO with atrial septal aneurysm or large interatrial shunt 3. CS within the previous 6 mo	One randomization arm: any of eleven different devices + dual antiplatelet therapy (75 mg of aspirin plus 75 mg of clopidogrel per day) for 3 months, followed by single antiplatelet therapy throughout the remainder of the trial	Two further randomization arms: antiplatelet therapy alone (antiplatelet-only group), or oral anticoagulation (anticoagulation group). Antiplatelet regimen: aspirin, clopidogrel, or aspirin combined with ER-dipyridamole. Patients with contraindications to anticoagulants or to PFO closure were randomly assigned to the alternative noncontraindicated treatment or to antiplatelet therapy	Mean: 5.3 ± 2.0	Fatal or nonfatal stroke.	5%

Cont. Table 1 - The main aspects of selected studies

	Total number of patients	Inclusion criteria	Device and additional therapy	Medical therapy	Follow-up duration (years)	Primary outcomes	Level of significance adopted
REDUCE (2017)	664	1.18 to 59 y of age 2. PFO documented on TE 3.CS within the previous 180 days	Helex Septal Occluder or Cardioform Septal Occluder + Antiplatelet therapy as in the medical therapy arm + clopidogrel at the time of the procedure and for 3 days	75-325 mg/day aspirin or 50-100 mg/day Aspirin + 225-400 mg/day dipyridamole or 75 mg/day clopidogrel	Mean: 3.2	Two coprimary end points of clinical ischemic stroke and new brain infarction	5%
DEFENSE PFO (2018)	120	1. High-risk PFO - PFO with atrial septal aneurysm, hypermobility (phasic septal excursion into either atrium ≥ 10 mm), or PFO size (maximum separation of the septum primum from the secundum) ≥ 2 mm 2. CS within the previous 6 mo	Amplatzer PFO Occluder + dual antiplatelet regimen (aspirin 100 mg/day in combination with clopidogrel 75 mg/day) for at least 6 months; anticoagulation therapy allowed as alternative	Aspirin or aspirin + clopidogrel or aspirin + cilostazol or warfarin	Median: 2.8	Composite of stroke, vascular death, or major bleeding	5%

A: closure group; B: medical therapy group; PFO: patent foramen ovale; TE: transesophageal echocardiography; CS: cryptogenic ischemic stroke; TIA: transient ischemic attack; PTE: peripheral thromboembolic event; D: days; Mo: month; Y: years; ER: extended-release; Aspirin: acetylsalicylic acid. For acronyms see text.

to medical therapy arm. The mean age was 46 years in both groups. Furthermore, dropouts were observed in each study and similar rate of serious adverse events were seen between the two treatment arms. Efficacy and safety endpoints are illustrated in Table 3.

The clinical endpoints under evaluation in the present report were: stroke, transient ischemic attack and incidence of atrial fibrillation during the follow-up period.

When compared to medical treatment only, PFO closure significantly reduced the rate of recurrent stroke (risk ratio, 0.37; 95% confidence interval [CI], 0.17 to 0.78; p = 0.01; I squared 51.12; Figure 2).

However, PFO closure did not offer any significant benefit in the prevention of TIA (risk ratio, 0.96; 95% CI, 0.64 to 1.44; p = 0.85; I squared 0.00; Figure 3).

Each study demonstrated a relatively low frequency of device and procedure-related complications. PFO closure increased the risk of atrial fibrillation (risk ratio with PFO closure, 4.64; 95% CI, 2.38 to 9.01; p < 0.01; I squared 3.84, Figure 4). Importantly, in most cases, AF was periprocedural.

Table 2 - Data concerning number of patients, mean age, dropouts and serious adverse events of patients enrolled in each study. For acronyms see text

	Number of patients		Mean age (years)		Dropouts (number of patients)		Serious adverse events (%)	
	Closure	Control	Closure	Control	Closure	Control	Closure	Control
CLOSURE 1	447	462	46.3 ± 9.6	45.7 ± 9.1	69	87	16.9	16.6
RESPECT	499	481	45.7 ± 9.7	46.2 ± 10.0	46	83	23.0	21.6
PC TRIAL	204	210	44.3 ± 10.2	44.6 ± 10.1	31	42	21.1	17.6
CLOSE	238	235	42.9 ± 10.1	43.8 ± 10.5	21	12	35.7	33.2
REDUCE	441	223	45.4 ± 9.3	44.8 ± 9.6	39	33	23.1	27.8
DEFENSE PFO	60	60	49 ± 15	54 ± 12	-	-	-	-

Table 3 - Data concerning stroke, transient ischemic attack (TIA) and atrial fibrillation (AF), in patients involved in trials comparing closure of patent foramen ovale versus medical therapy (total number of patients in brackets). For acronyms see text

	Stroke		TIA		AF	
	Closure	Control	Closure	Control	Closure	Control
CLOSURE 1	12 (447)	13 (462)	13 (447)	17 (462)	23 (402)	3 (458)
RESPECT	9 (499)	16 (481)	6 (499)	4 (481)	3 (499)	3 (481)
PC TRIAL	1 (204)	5 (210)	5 (204)	7 (210)	6 (204)	2 (210)
CLOSE	0 (238)	14 (235)	8 (238)	8 (235)	11 (238)	2 (235)
REDUCE	6 (441)	12 (223)	21 (441)	8 (223)	29 (441)	1 (223)
DEFENSE PFO	0 (60)	5 (60)	0 (60)	1 (60)	2 (60)	0 (60)

Data on risk difference and annualized risk difference concerning the three outcomes under evaluation are presented in supplementary file 2.

Discussion

Controversy has persisted after the first reports were published on whether PFO closure reduces the risk of recurrent stroke for patients with cryptogenic stroke and documented PFO, when compared with medical therapy. Since 2012, six randomized controlled trials were published with the aim of comparing these two forms of secondary prevention.[3,5,6,8-10] In the present updated meta-analysis, transcatheter PFO closure in cryptogenic strokes was shown to be superior to medical therapy in reducing recurrent stroke, although the risk of TIA was similar between the two groups. We also confirmed that patients who underwent transcatheter closure were more likely to develop transient atrial fibrillation as compared with the medical-therapy group. Our findings are in line with the results of recent meta-analyses,[12-19] However, the present study includes data of the RESPECT trial published in 2013, as opposed to recent meta-analyses, which selected the RESPECT long-term results, published in 2017, and therefore are not the primary results of a controlled trial, but rather a follow-up study.

All six studies included young to middle-age patients with PFO documented on transesophageal echocardiography (TE) and cryptogenic stroke, usually in the six months prior to randomization.

Three randomized controlled trials (RCTs) conducted earlier, which were published in 2012 and 2013, failed

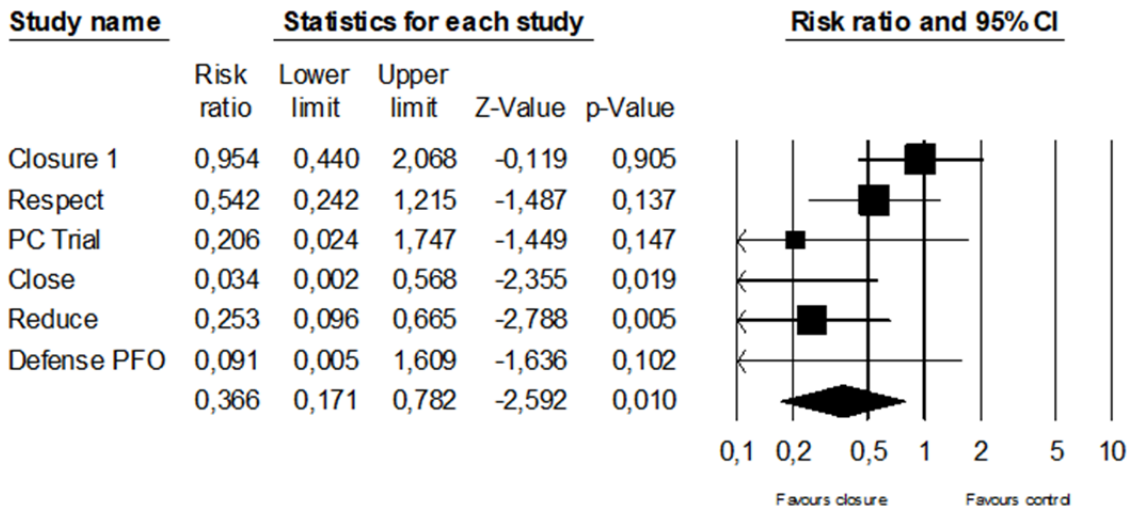

Figure 2 - Risk Ratios for recurrent stroke in six major trials.
CI: confidence interval. For references and trial acronyms, see text.

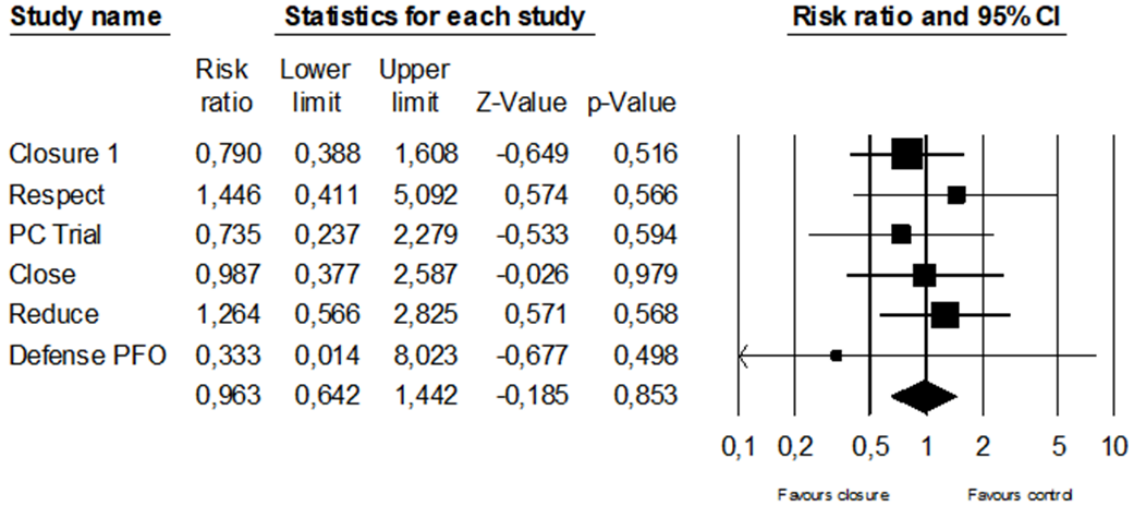

Figure 3 - Risk Ratios for transient ischemic attack in six major trials.
CI: confidence interval. For references and trial acronyms, see text.

to show superiority of PFO closure over medical treatment to decrease stroke recurrence or TIA.[3,5,8] These relatively modest results have been attributed to several limitations, including choice of the closure device, off-protocol closure device use within the medical therapy arms, patient selection criteria, low sample size, slow enrolment, short duration of follow-up,[1,3,5,8] among other factors. Although in the first trials, PFO closure did not show greater benefit than medical therapy alone, more recent studies did observe its superiority.[6,9,10]

The REDUCE trial had a smaller number of patients with uncontrolled vascular risk factors than previous trials with less rigorous exclusion criteria. For instance, the CLOSE and DEFENSE-PFO trials only included

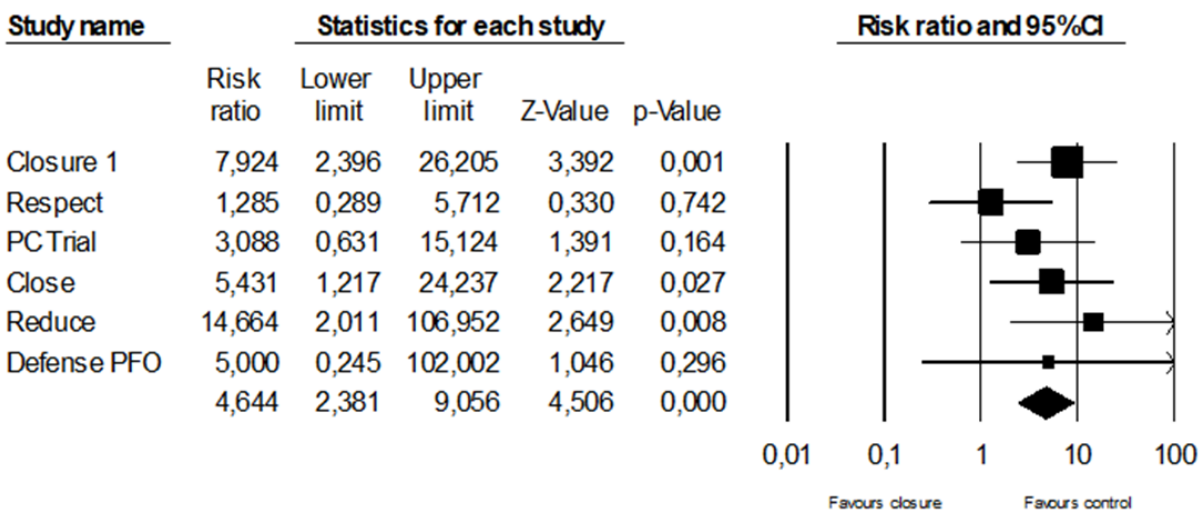

Figure 4 - Risk Ratios for atrial fibrillation in six major trials.
CI: confidence interval. For references and trial acronyms, see text.

patients with high-risk anatomic PFO features. Therefore, better and stricter patient selection in more recent RCTs may have increased the probability of having a stroke due to PFO and consequently may have increased the likelihood that PFO closure would be effective.

Patent foramen ovale presumably provides an anatomic substrate for paradoxical embolism, which may be the cause of most of the cryptogenic strokes.[21] Our findings confirm that PFO closure significantly decreased the rate of recurrent ischemic stroke. The risk of TIA, however, was unaltered, pointing in the direction of a different pathophysiology of TIA in this setting (possibly unrelated to paradoxical embolism) and the potential misclassification of non-ischemic events as TIA. Each study demonstrated low frequency of device and procedure-related complications but a significant increase of AF in the interventional group was seen, which could in theory increase the risk of recurrent stroke. However, most cases of atrial fibrillation occurred early after the procedure with no recurrence during follow-up.

The key to an appropriate treatment strategy could be to detect which patients may derive more benefit from PFO closure. Recent studies have shown some characteristics that increase the potential benefit for the patient, but more studies are needed to clarify this issue.[22] The decision to choose a given type of treatment should be multidisciplinary and shared with the patient, considering the preferences of each person.

The major sources of data heterogeneity are presented in Table 1 – differences in inclusion criteria, in device used, in medical therapy, and in mean follow-up. Patients requiring long-term anticoagulation therapy were mostly excluded from the clinical trials. Thus, the population of patients under anticoagulation therapy does not seem to have a proven benefit with PFO closure for the time being.

Limitations

The studies included were all open label and not double blind, which might impact the results with differential evaluation of suspected events and unequal referral of those events to the adjudication committees. As stated above, there was non-uniformity in the follow-up period, patients' characteristics, inclusion criteria and closure device used between the studies included. TIA was only a primary endpoint in two of the clinical trials, namely, PC trial and CLOSURE I trial.

Preference of some patients and physicians prompted a differential dropout of studies and crossovers between the two treatment groups that may have biased the trials results. Thus, PFO closure was not performed in all patients initially assigned and not all patients who underwent the procedure had a successful closure.

If residual shunts persisted, this might mask the real efficacy of PFO closure in the prevention of recurrent strokes. Similarly, some patients of medical group underwent PFO closure with devices approved by the Food and Drug Administration (FDA) for other indications (off-label use).

In the medical therapy groups, there was lack of standardization in the type and doses of the medical therapy used in each site and the use of anticoagulant treatment was more frequent as compared with the closure group. In addition, discontinuation of antithrombotic treatment was allowed after PFO closure in many trials, which may have increased the risk of non-PFO-related stroke in these studies. Finally, the definitions used for reporting atrial fibrillation varied among trials and may not be directly comparable.

Conclusions

At the present stage, patent foramen ovale closure seems to be superior to medical treatment in reducing recurrent stroke in patients with cryptogenic stroke. Comparable risks of TIA for both strategies have been seen in the studies published so far. Furthermore, even though a significantly higher risk of new-onset atrial fibrillation was seen with closure, studies suggested that it was usually periprocedural. These findings suggest that PFO closure is a better strategy for secondary prevention of recurrent stroke in patients with a cryptogenic stroke and patent foramen ovale.

Author contributions

Conception and design of the research: all authors. Acquisition of data: SPPP, AN. Analysis and interpretation of the data: all authors. Statistical analysis: JPLN, CS. Writing of the manuscript: all authors. Critical revision of the manuscript for intellectual content: all authors

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 study is associated with the master thesis of the first author.

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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Supplementary file 1

Search strategy:

1. Medline (PubMed) database - query "patent foramen ovale" AND "stroke" AND "closure" with the filter "clinical trial".
2. ISI Web of Knowledge - query "patent foramen ovale" AND "stroke" AND "closure" with the filter "article".

Supplementary file 2

Study	Did the patient(s) represent the whole case(s) of the medical center	Was the diagnosis correctly made	Were other important diagnosis excluded	Were all important data cited in the report	Was the outcome correctly ascertained	Global quality assessment
CLOSURE 1	Yes	Yes	Yes	Yes	Yes	Good
RESPECT	Yes	Yes	Yes	Yes	Yes	Good
PC TRIAL	Yes	Yes	Yes	Yes	Yes	Good
CLOSE	Yes	Yes	Yes	Yes	Yes	Good
REDUCE	Yes	Yes	Yes	Yes	Yes	Good
DEFENSE PFO	Yes	Yes	Yes	No	Yes	Moderate

Article quality assessment according to the method used by Haffar et al. For acronyms and complete references see text.

EDITORIAL

To Close or not to Close PFOs in Cryptogenic Stroke, an Evolving Question

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Editorial related to the article: The Role of Patent Foramen Ovale Closure in the Secondary Prevention of Cryptogenic

A matter of intense debate in the last decades, the ideal strategy for secondary prevention in patients with cryptogenic stroke and patent foramen ovale (PFO) is not yet clearly defined. PFOs are prevalent in the general population and can be found in up to 40% of patients with cryptogenic stroke.[1] Although in some cases of cryptogenic stroke PFO might be just an innocent bystander, paradoxical embolism is a well-known potential causative mechanism, especially in patients with concomitant deep venous thrombosis, whereby PFO closure may represent an effective measure to avoid recurrences.[2] Even among patients with PFO, phenotypical heterogeneity may also determine percutaneous treatment suitability and directly impact on results, whereas the presence of large shunts, atrial septal aneurysm or associated complex septal defects must also be taken into account.

In the past years, several evidence-based guidelines and expert consensus on the management of patients with PFO and prevention of recurrent stroke have been published by international scientific societies, including a position paper sponsored by the European Association of Percutaneous Cardiovascular Interventions (EAPCI), with the participation of eight European scientific societies.[3] A recent guideline by the American Academy of Neurology (AAN) was published online last April.[4]

This issue of the International Journal of Cardiovascular Sciences presents the results of an interesting study entitled "The Role of Patent Foramen Ovale Closure in the Secondary Prevention of Cryptogenic Stroke: a Meta-Analysis Report", authored by Pereira and coworkers.[5] This study sheds new light on the discussion of this important topic, adding relevant information about the results of different management strategies for secondary prevention of stroke in patients with PFO. The authors included data from six randomized clinical trials with a total of 3,750 patients. Unlike other meta-analyses published so far, they considered only original clinical trial data, a difference that provides more reliability to the obtained results. Interestingly, there was a significant lower incidence of stroke in patients submitted to PFO closure compared with those who received medical treatment alone (risk ratio [RR] = 0.37; 95% confidence interval [0.17 to 0.78]; p = 0.01), in accordance with recent findings of the CLOSE and DEFENSE-PFO trials,[6,7] which recruited only PFO patients with high-risk anatomic features.

It is important to emphasize that ischemic stroke may be caused by a variety of heterogeneous mechanisms, and adequate secondary prevention must focus on the correct target population. Not every PFO is deemed for closure and not every PFO anatomy is amenable to percutaneous closure, but once the procedure is correctly indicated, it is of paramount importance to assemble a multidisciplinary team in charge of choosing the correct device and minimizing complications.[8] Diagnosing PFO is not always a simple matter. Many factors can contribute for a non-diagnostic study and yield false positive results, such as intrapulmonary shunts or false negative diagnoses due to an inadequate Valsalva maneuver or a redundant Eustachian valve, which may prevent the contrast solution from reaching the atrial septum. Therefore, in order to achieve the best results, it is crucial to follow a stepwise approach with transthoracic echo (TTE), transcranial Doppler (TCD)

Keywords

Patent Foramen Ovale; Secondary Prevention; Stroke/prevention and control; Risk Factors; Atrial Fibrillation.

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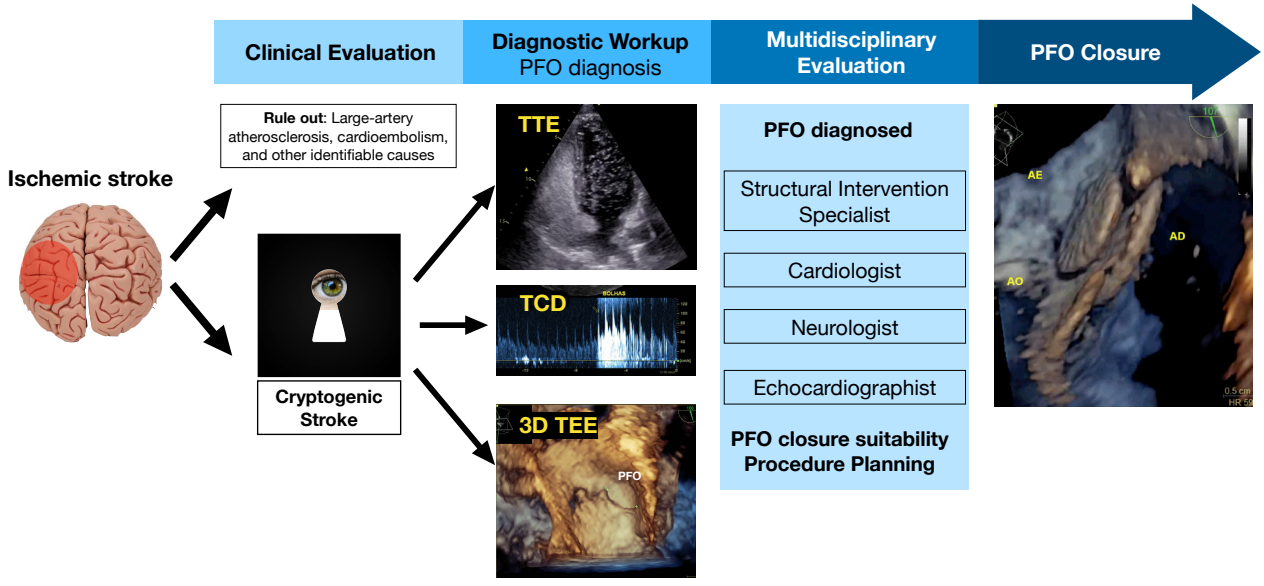

Figure 1 – Flowchart of PFO closure in cryptogenic stroke. PFO = patent foramen ovale, TTE = Transthoracic echocardiogram, TCD = transcranial Doppler, 3D TEE = three-dimensional transesophageal echocardiogram

and transesophageal study (TEE) using agitated saline solution with adequately performed Valsalva maneuver throughout the steps. TTE will test the quality of contrast arrival and Valsava maneuver will be diagnostic in most cases. TCD will help quantify the shunt by means of a more precise bubble count, and TEE will define the anatomy for interventional planning (Figure 1). Large shunts and high-risk anatomic PFO are well-depicted by three-dimensional echocardiogram, allowing for a better periprocedural guidance and the achievement of optimal results.

In younger patients, who face a longer period of recurrent stroke risk, and in patients with contraindications to long-term anticoagulation, the benefits of transcatheter therapy is less debatable, and contemporary devices have promoted a reduction in the incidence of complications, even though not negligible[8]. Since the publication by Kutty et al.,[9] when available evidence pointed to uncertainty regarding the potential benefits of PFO closure compared to medical treatment alone, some well conducted studies have broken this paradigm, such as the one carried out by Wahl et al.,[10] They enrolled 308 consecutive patients to either undergo PFO closure (n = 150) or maintain medical therapy (n = 158), and demonstrated a significant reduction in the composite endpoint of stroke, transient ischemic attack (TIA) and peripheral embolism in the PFO closure group (11% vs 21%, hazard ratio = 0.43; 95% CI = 0.20–0.94; P = 0.033). Since then, new evidence has emerged and data from new studies, using new devices, and well-designed patient selection, have allowed for the establishment of very solid recommendations for this treatment option in selected patients, as stated in the recently updated AAN guidelines[3]. In the present paper, Pereira and cols[4] also highlight the increased risk of atrial fibrillation in patients undergoing PFO closure (RR for PFO closure, 4.64; 95% CI, 2.38 to 9.01; $p < 0.01$), which reinforces the need for adequate selection, as well as careful balance of risk and benefits when indicating this procedure. The choice for intervention should preferably contemplate centers with large expertise and low rates of procedural complications.

In summary, the present study refines the existing evidence for additional risk reduction of PFO closure vs medical treatment alone, through the analysis of less biased data derived from the original clinical trials, as clearly stated by the authors[4]. Considering that many patients are particularly young and may benefit from a long-lasting risk reduction promoted by the intervention, these findings acquire even greater importance. The constant pursue for updated data as science moves forward is invaluable, in light of newer and refined transcatheter techniques and the development of new anticoagulant drugs.

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International Journal of Cardiovascular Sciences. 2020; 33(4):321-328

ORIGINAL ARTICLE

Electrocardiographic Abnormalities in Hypertension Models

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Abstract

Background: Hypertensive condition can lead to abnormalities in heart structure and electrical activity. The electrocardiogram (ECG) is a recording of the electrical activity of the heart and widely used to diagnose and detect heart problem.

Objective: We conducted a comparative ECG analysis between two hypertension models (L-NAME and SHR) and their controls (Wistar and Wistar-Kyoto) at six and 15th week of age.

Methods: Blood pressure was measured at the end of the 15th week, and electrocardiography was performed at six and 15 weeks of age in anaesthetized rats. Data normality was confirmed by Kolmogorov-Smirnov test followed by unpaired Student's t-test and the Mann-Whitney for parametric and non-parametric data, respectively. Results are expressed as mean ± SD. The accepted level of significance was set at $p < 0.05$.

Results: L-NAME exhibited prolongation of JT and QT intervals and SHR showed a decrease in heart rate when compared to Wistar-Kyoto and L-NAME. Wistar-Kyoto exhibited short PR interval with increased QRS complex, and only QT prolongation at 15 weeks compared to Wistar.

Conclusions: All the hypertension models used in this study featured an increase in blood pressure. However, while SHR showed cardiac dysfunction, L-NAME exhibited changes in ventricular performance. These results may guide future studies on different types and models of hypertension. (Int J Cardiovasc Sci. 2020; 33(4):321-328)

Keywords: Rats; Hypertension; Blood Pressure; Electrocardiography/methods; NG-Nitroarginine Methil Éster/adverse effects; Rats, Inbred (SHR).

Introduction

Prolonged exposure to stressors can lead to changes in the adaptive systems and consequently increased circulating levels of cortisol and adrenaline.[1-3] This imbalance can result in several types of diseases, including cardiovascular diseases, which are the leading cause of death in the world.[4] The development of hypertension may be associated with sympathetic overactivity, however the underlying mechanisms that surround the pathogenesis of hypertensive disease are complex and challenging, encouraging researchers to elucidate these mechanisms.[5-7]

Animal models are critical to advancements in medical research and provide valuable information regarding many aspects of the disease.[8-10] Classically, there are two well established models of sympathetic overactivity: the NG-monomethyl-L-arginine methyl ester (L-NAME)-induced hypertension and the spontaneously hypertensive rats (SHR).[10]

Hypertensive condition can lead to abnormalities in cardiac structure, and consequent dysfunction in cardiac electrical activity.[11,12] The electrocardiogram (ECG) is a recording of the electrical activity of the heart and widely used to diagnose and detect heart problems.[13] This test shows typical upward and downward

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deflections (waves) that reflect the alternate contraction of the atria and the ventricles.[14] The first wave, P, is due to atrial contraction and its prolongation has been associated with hypertension caused by endothelial dysfunction and interatrial conduction delay.[12,15] The Q, R, S complex indicates ventricular depolarization.[12] The duration of the QRS interval and the amplitude of the waves separately are related to mortality in hypertension.[16,17] The final wave, named T, represents the repolarization of the ventricles and its correlation with the QRS complex (QT-interval). It is an important marker of ventricular activity and has been shown to have clinical utility.[12,18] In the present study, we aimed to conduct a comparative ECG analysis between two hypertension models (L-NAME and SHR) and their controls (Wistar and Wistar-Kyoto).

Methods

Animals

Studies were conducted with adult, male, six and 15-week-old Wistar (HanUnib:WH), Wistar-Kyoto (NTacUnib:WKY) and SHR (SHR/NTacUnib) rats (*Rattus norvegicus*). All animals were provided by the Multidisciplinary Center for Biological Research (CEMIB - UNICAMP). The rats were housed in collective cages (3 rats per cage) at 22°C on a 12 h light-dark cycle (lights on at 06:30 a.m.) with ad libitum access to standard chow (Labina Purina®) and filtered water. All animal housing, animal care and experimental procedures, and sample size were approved by the Ethics Committee on Animal Experimentation (CEUA) of the Institute of Biology of Unicamp in Campinas, Brazil (no. 2615-1), in accordance with the NIH guidelines. The animals were divided into four groups: control Wistar (WIS, n = 6), induced hypertension (L-NAME, n = 6), control Wistar Kyoto (WKY, n = 6), and genetic hypertension (SHR, n = 6). For the L-NAME group, we inhibited nitric oxide synthesis by administration of L-NAME (Enzo Life Sciences International, Inc.5120 Butler Pike, Plymouth Meeting, PA 19462) 40 mg/kg/day, for 5 weeks in the drinking water, started at the 10th week of life of WIS.[19] Water was changed three times a week, with correction in dose/weight. The rats were anesthetized with tiletamine 29 mg kg^{-1} and zolazepam 29 mg kg^{-1}, i.p. (Zoletil 50® - Virbac Laboratories, Carros, France); and xylazine 12.88 mg kg^{-1}, i.p. (Anasedan® - Sespo Ind. e Com. Ltda, Paulínia/SP, Brazil).

Blood Pressure

Blood pressure monitoring was performed at the end of the 15th week under anaesthesia. Blood catheterization was performed by insertion of a cannula (PE 50) into the right carotid artery of anesthetized animals, attached to a strain-gauge pressure transducer that was connected to a MLS370 amplifier/7 blood pressure Module (ADInstruments - Australia), and to the data acquisition system PowerLab 8/30. For analysis of the results, we used the Software LabChart Pro (ADInstruments - Australia).[20]

Electrocardiography

Electrocardiography was performed in anesthetized rats in the supine position during spontaneous breathing. Recordings were performed at 6 and 15 weeks of age, using hypodermic needle electrodes, with computerized electrocardiography (MLS360/7 ECG Analysis Module, ADInstruments, Australia), for five minutes.[21]

Statistical Methods

Data are presented as mean ± SD. Normality of data distribution was confirmed by Kolmogorov-Smirnov test and then we performed unpaired Student's t-test for parametric and the Mann-Whitney test for nonparametric data. All statistical analysis was performed with Graph Pad Prism version 7.00 for Windows (Graph Pad Software, San Diego, California, USA). The accepted level of significance was $p < 0.05$.

Results

Blood pressure

L-NAME and SHR 15-week-old rats exhibited increased systolic blood pressure, diastolic blood pressure, mean diastolic pressure and mean pressure when compared to their respective controls, WIS and WKY rats. There were no differences in systolic blood pressure, diastolic blood pressure, mean diastolic pressure and mean pressure between hypertensive rats (L-NAME vs. SHR) and control groups (WIS vs. WKY). Peak time was higher in SHR when compared with WKY but was not different when compared with L-NAME. No difference was observed in this parameter in control rats. There were no differences in pulse pressure, ejection and non-ejection time and cycle duration between the study groups (Table 1).

Table 1 - Evaluation of blood pressure in hypertensive (L-NAME and SHR) and normotensive (WIS and WKY) rats at 15 weeks of age

	WIS	L-NAME	WKY	SHR
Systolic pressure	118.8 ± 16.53	156.4 ± 30.35*	119.5 ± 11.64	139.4 ± 12.84*
Diastolic pressure	96.28 ± 20.05	133.6 ± 31.35*	95.85 ± 16.58	114.6 ± 13.85*
Pulse pressure	22.54 ± 10.44	22.83 ± 4.91	23.61 ± 5.23	24.86 ± 5.56
Mean pressure	106.9 ± 22.58	145.2 ± 30.28*	107.1 ± 15.57	127.1 ± 12.88*
Ejection time (s)	0.0608 ± 0.0083	0.0736 ± 0.0385	0.0616 ± 0.0092	0.0690 ± 0.0220
Non-ejection time (s)	0.0777 ± 0.0123	0.0897 ± 0.0196	0.0811 ± 0.0122	0.0895 ± 0.0268
Cycle duration (s)	0.1389 ± 0.0187	0.1496 ± 0.0245	0.1421 ± 0.0208	0.1555 ± 0.0246
Time to peak (s)	0.0309 ± 0.0115	0.0399 ± 0.0076	0.0230 ± 0.0060	0.0405 ± 0.0100*
Mean diastolic pressure	102.9 ± 24.64	141.4 ± 29.89*	103.0 ± 16.16	128.2 ± 7.81*

*Blood pressure parameters of Wistar (WIS), Wistar-Kyoto (WKY), NG-monomethyl-L-arginine methyl ester (L-NAME)-induced hypertension, and spontaneously hypertensive rats (SHR) at six and 15 weeks of age. Data are presented as mean ± SD. *p < 0.05 compared to controls (WIS vs. L-NAME; WKY vs. SHR), n = 6.*

Electrocardiographic (ECG) analysis:

The six-week-old L-NAME rats showed no ECG changes compared with WIS. However, the 15-week-old L-NAME rats exhibited increase in QT, QTc and JT intervals when compared to their controls, suggesting impaired ventricular conduction after the intervention (Figure 1, Table 2).

SHR at six weeks of age showed a decrease in heart rate (HR) and an increase in the RR interval when compared with WKY. At this age, SHR also exhibited changes in atrial electrical conduction, such as increased PR interval and P-wave duration. Changes in ventricular function were also observed, with a decrease of QT and QTc intervals, increase in Q wave amplitude and decrease in R and S waves' amplitudes. By visual analysis, the ECG revealed a delay in atrial conduction and shortening in ventricular conduction compared with six-week-old WKY (Figure 1, Table 2).

The 15-week-old SHR continued to exhibit lower HR and increased RR and PR interval than WKY, indicating an impairment of atrial conduction with increase in P-wave duration. These rats failed to show a decrease in QT, QTc, JT and P wave amplitude when compared to WKY, probably due to a failure in ventricular conduction at 15 weeks of life, and a decrease in S wave amplitude at six weeks. Ventricular extrasystole followed by compensatory pauses may characterize impaired ventricular conduction in the SHR when compared with WKY (Figure 1, Table 2).

Regarding the differences between hypertension models used in this study, our results showed that six-week-old SHR exhibited several changes when compared to L-NAME rats, such as a decrease in HR, increase in RR and PR intervals and duration, increased P wave amplitude, as well as a reduction of QT interval, QTc and JT. At 15 weeks of age, SHR exhibited higher RR interval and P amplitude than L-NAME, an increase in P wave amplitude and shorter JT interval when compared to L-NAME (Figure 1, Table 2).

Analysis between the control rats demonstrated that six-week-old WKY had a reduction in PR interval and an increase in QRS interval when compared with WIS. At 15 weeks of age, WKY showed an increase in the QT interval when compared with the WIS (Figure 1, Table 2).

Discussion

In both hypertension models, the animals showed higher systolic, diastolic and mean pressure values at 15 weeks. Ribeiro et al.,[22] identified progressive increase in blood pressure in L-NAME rats after 4-6 weeks of life, reaching 164 ± 6 mmHg when compared with 108 ± 3 mmHg in controls. SHR rats developed hypertension at 4–6 weeks of age without any type of intervention and

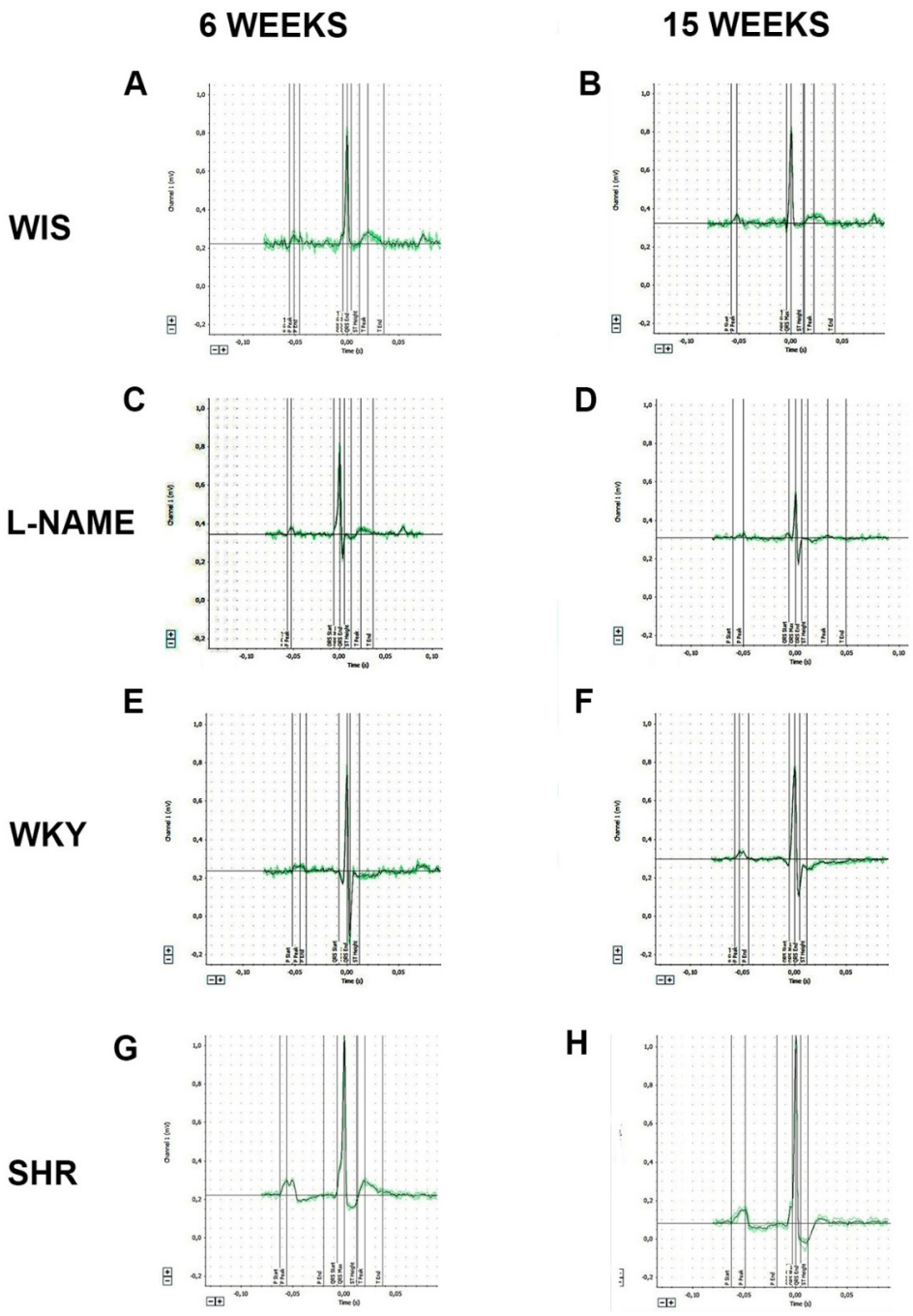

Figure 1 - Electrocardiographic tracing records.
A) WIS at six weeks; B) WIS at 15 weeks; C) L-NAME at six weeks; D) L-NAME at 15 weeks; E) WKY at six weeks; F) WKY at 15 weeks; G) SHR at six weeks; H) SHR at 15 weeks. WIS: Wistar; WKY: Wistar-Kyoto; L-NAME: NG-monomethyl-L-arginine methyl ester (L-NAME)-induced hypertension; SHR: spontaneously hypertensive rats.

exhibited an increased cardiac output with normal total peripheral resistance.[9] The development of hypertension in SHR progressively promoted structural changes in the heart, which were associated with progressive cardiac hypertrophy.[9] Our results corroborate those reported by Anishchenko et al.,[23] showing an increase in systolic and

Table 2 - Electrocardiographic parameters of hypertensive rats and its controls at six and 15 weeks of age

	Six weeks old				15 weeks old			
	WIS	L-NAME	WKY	SHR	WIS	L-NAME	WKY	SHR
Heart rate (BPM)	478.4 ± 16.55	467.4 ± 34.70	462.8 ± 38.37	325.8 ± 74.09*#	427.4 ± 61.26	420.2 ± 31.12	426.7 ± 33.58	351.7 ± 94.33*
RR interval (s)	0.1256 ± 0.0044	0.1291 ± 0.0101	0.1312 ± 0.0128	0.1916 ± 0.0378*#	0.1433 ± 0.0239	0.1445 ± 0.0118	0.1416 ± 0.0122	0.1831 ± 0.0508*#
PR interval (s)	0.0507 ± 0.0051	0.0484 ± 0.0045	0.0463 ± 0.0017#	0.0534 ± 0.0031*#	0.0495 ± 0.0031	0.0502 ± 0.0035	0.0484 ± 0.0034	0.0533 ± 0.0048*
P duration (s)	0.0162 ± 0.0045	0.0137 ± 0.0041	0.0153 ± 0.0039	0.0256 ± 0.0088*#	0.0168 ± 0.0035	0.0159 ± 0.0044	0.0163 ± 0.0031	0.0202 ± 0.0047*
QRS interval (s)	0.0119 ± 0.0032	0.0177 ± 0.0049	0.0199 ± 0.0058#	0.0170 ± 0.0052	0.0144 ± 0.0030	0.0161 ± 0.0047	0.0162 ± 0.0062	0.0210 ± 0.0204
Qt interval (s)	0.0471 ± 0.0141	0.0530 ± 0.0146	0.0596 ± 0.0180	0.0394 ± 0.0070*#	0.0409 ± 0.0063	0.0569 ± 0.0149*	0.0524 ± 0.0139#	0.0425 ± 0.0207
QTc (s)	0.1333 ± 0.0405	0.1484 ± 0.0438	0.1664 ± 0.0547	0.0909 ± 0.0154*#	0.1094 ± 0.0205	0.1495 ± 0.0383*	0.1398 ± 0.0373	0.1042 ± 0.0603
T peak T end Interval (s)	0.0123 ± 0.0057	0.0149 ± 0.0062	0.0122 ± 0.0058	0.0139 ± 0.0040	0.0135 ± 0.0050	0.0237 ± 0.0177	0.0159 ± 0.0093	0.0119 ± 0.0067
JT interval (s)	0.0341 ± 0.0127	0.0344 ± 0.0086	0.0351 ± 0.0124	0.0223 ± 0.0072#	0.0250 ± 0.0089	0.0399 ± 0.0147*	0.0315 ± 0.0162	0.0197 ± 0.0070#
P amplitude (mV)	0.0376 ± 0.0046	0.0315 ± 0.0238	0.0448 ± 0.0220	0.0460 ± 0.0139#	0.0261 ± 0.0153	0.0173 ± 0.0229	0.0309 ± 0.0188	0.0487 ± 0.0178*#
Q amplitude (mV)	0.0053 ± 0.0158	-0.0029 ± 0.0231	-0.0240 ± 0.0251	0.0023 ± 0.0105*	-0.0092 ± 0.0218	-0.0074 ± 0.0476	-0.0079 ± 0.0101	-0.0089 ± 0.0720
R amplitude (mV)	0.5448 ± 0.0828	0.5287 ± 0.1936	0.5883 ± 0.0970	0.4031 ± 0.2295*	0.4134 ± 0.1117	0.3163 ± 0.1301	0.4149 ± 0.0924	0.4884 ± 0.2930
S amplitude (mV)	-0.1097 ± 0.1176	-0.1440 ± 0.1016	-0.1876 ± 0.1374	-0.0486 ± 0.0530*	-0.0883 ± 0.1175	-0.1300 ± 0.1048	-0.1692 ± 0.0786	-0.0320 ± 0.1019*
T amplitude (mV)	0.02443 ± 0.0481	0.0646 ± 0.0364	0.0243 ± 0.0264	0.0070 ± 0.0736	0.0104 ± 0.0502	0.0169 ± 0.0626	0.0105 ± 0.0234	-0.0310 ± 0.1202
ST Height	-0.0131 ± 0.0317	0.0094 ± 0.0329	-0.0267 ± 0.0074	-0.0412 ± 0.0343	-0.0156 ± 0.0380	-0.0202 ± 0.0224	-0.0387 ± 0.0237	-0.0468 ± 0.1094
First beat	1,251 ± 87.17	1,208 ± 72.64	1,172 ± 98.40	830.6 ± 178.1	1,097 ± 161.3	1,055 ± 97.52	1,082 ± 86.60	893.7 ± 246.8
Last beat	1,254 ± 87.17	1,211 ± 72.64	1,175 ± 98.40	833.6 ± 178.1	1,100 ± 161.3	1,058 ± 97.52	1,085 ± 86.60	896.7 ± 246.8

*Electrocardiographic parameters of Wistar (WIS), Wistar-Kyoto (WKY), NG-monomethyl-L-arginine methyl ester (L-NAME)-induced hypertension, and spontaneously hypertensive rats (SHR) rats at six and 15 weeks of age. Data are presented as mean ± SD. *p < 0.05 compared to control (WIS vs. L-NAME; WKY vs. SHR); #p < 0.05 WIS vs. WKY; and L-NAME vs. SHR, n = 6.*

diastolic blood pressure in SHR compared with WKY at six weeks of life.[23] There are no data comparing ECG measures between WIS and WKY rats in the literature.

SHR showed a decrease in HR when compared to WKY and L-NAME. A possible interpretation of this data is the involvement of cyclic adenosine monophosphate (cAMP), which may be less available due to increased depletion induced by phosphodiesterase 3A (PDE3A). PDE3A is considered the main cAMP regulator in cardiomyocytes and an important regulator of cardiac contractility.[24-26] Increased expression of PDE3A results in reduced availability of cAMP and

changes in the cyclic nucleotide balance, with a direct relationship with many diseases, including hypertension.[27] The availability of cAMP is also linked to hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels, where beta-adrenergic stimulation activates adenylate cyclase, resulting in an increase in cAMP synthesis.[28] Increased cAMP raises the membrane potential, leading to higher depolarization rate, and subsequent increase in heart rate, acting as a second messenger in the modulation of HCN channels.[29] This could be a possible explanation for the cardiac abnormalities found in WKY. However, studies in the literature that explain these effects are scarce and technical limitations avoid us to validate this hypothesis, so further studies are needed to confirm it.

El-Mosallamy et al.,[30] demonstrated that L-NAME rats exhibited increase in RR interval, longer duration of the P wave and ST-segment elevation. However, in our results, the treatment with L-NAME induced an increase in QT, QTc and JT intervals at 15 weeks. Prolongation of QT and JT intervals are considered an indication of ventricular arrhythmia, the major cause of sudden death in hypertension.[12,31] The RR interval may change with dysregulation of the atrial electrical activity, and ceases to be constant in irregular heartbeats.[32] SHR showed increased RR interval, resulting in bradycardia. This change may be related to the ventricular extrasystole observed in this strain.[33]

The PR interval corresponds to the period that electrical signals are delayed at the atrioventricular (AV) node, before it travels through the ventricular branches to induce cardiac depolarization and may be prolonged during AV nodal dysfunction.[34] Therefore, increased PR interval is also linked to bradycardia.[32] We found a failure in atrial conduction in SHR rats, which are consistent with the studies by Hazari et al.,[35,36] that showed prolongation of PR interval in SHR compared with WKY.

In addition to the atrial conduction delay, SHR also showed impaired ventricular conduction, with a decrease in QT and QTc, and shortening of QT at six weeks of life. These results are commonly related to electrolyte disorders such as hyperkalemia.[37] Hazari et al.,[35] described that 12-week-old SHR have prolongation of the interval QT, JT and QTc. In our study, six-week-old SHR exhibited shorter duration of QT, JT and QTc intervals, which was probably related to hyperkalemia.[38-40] The ECG confirmed that SHR, beyond the electrical conduction failure, show T-wave inversion, which may lead to ischemic heart failure with advanced hypertension. Animal restraining, restraint-stress and difficulties with placing the electrodes in the same position in different rats are significant limitations of the method.

Conclusion

The present study shows that cardiac function is different in SHR compared with L-NAME rats. While SHR showed cardiac dysfunction, L-NAME exhibited changes in ventricular performance. Although decreased levels of PDE3A may have contributed to the changes observed in WKY, it was not sufficient to cause hypertension in this strain. Thus, all the hypertension models used in this study featured an increase in blood pressure, but each with its distinct adaptive mechanism. These results can serve as a basis for future studies on different types and models of hypertension.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis master submitted by Ana Gabriela Conceição-Vertamatti, from *Universidade de Campinas*.

Ethics approval and consent to participate

This study was approved by the Committee for Ethics in Animal Experimentation (CEUA) under the protocol number 2615-1. 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.

Author contributions

Conception and design of the research: Grassi-Kassisse DM. Acquisition of data: Conceição-Vertamatti AG, Borghi F, Ishizu LY, Costa GT, Ramos LA, Areas MA. Analysis and interpretation of the data: Conceição-

Vertamatti AG, Borghi F, Ramos LA, Areas MA, Grassi-Kassisse DM. Statistical analysis: Conceição-Vertamatti AG, Borghi F, Grassi-Kassisse DM. Obtaining financing: Grassi-Kassisse DM. Writing of the manuscript: Conceição-Vertamatti AG, Borghi F, Ishizu LY, Costa GT, Grassi-Kassisse DM. Critical revision of the manuscript for intellectual content: Conceição-Vertamatti AG, Borghi F, Areas MA, Grassi-Kassisse DM.

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EDITORIAL

Relevance of Animal Models and Echocardiogram for Hypertensive Disease Studies

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Editorial related to the article: Electrocardiographic Abnormalities in Hypertension Models

Hypertension is the main risk factor for the development of cardiovascular diseases, such as cerebrovascular and ischemic heart diseases, as well as for premature death worldwide. The prevalence of this condition was about 30% in low-, middle- and high-income countries in 2010. Cardiovascular pharmacotherapy and lifestyle changes constitute important measures to manage cardiovascular diseases, and the reduction of blood pressure is a fundamental strategy to prevent and treat them. Systemic arterial hypertension is a clinical multifactorial condition. The underlying mechanisms of hypertensive disease are complex, which is why it is essential to elucidate them.[1] Many animal models of hypertension can serve this purpose, most of which were developed considering the probable causes of this condition, such as high salt intake and renin-angiotensin-aldosterone system overactivity. It is important that each model exploit a single pathway to hypertension development.[2]

Spontaneously hypertensive rats (SHR) are genetically modified animals commonly chosen for several studies, including antihypertensive drugs screening. They provide an inexpensive experimental model and have a hypertensive phenotype similar to human patients. There are also endocrine models of hypertension, including the administration of deoxycorticosterone acetate (plus salt) and N-ω-nitro-L-arginine methyl- ester (L-NAME). According to the literature, both SHR and L-NAME models are related to sympathetic overactivity.[2,3]

A hypertensive condition can affect cardiac electrical activity and, since electrocardiogram (ECG) techniques involve the recording of the heart's electrical activity, it seems to be a useful tool to evaluate high blood pressure-related cardiac impairment. These findings may explain the greater occurrence of arrhythmias and sudden death among hypertensive patients. ECG is considered a simple and inexpensive technique, being widely performed to diagnose cardiovascular diseases.[4,5]

The manuscript published by Conceição-Vertamatti et al.,[6] in the International Journal of Cardiovascular Sciences, proposes a comparative analysis encompassing two different experimental models of hypertension (endocrine/genetic) and their respective controls. Thus, the animals were divided into four experimental groups (6 animals/group): Wistar rats treated and untreated with L-NAME, Wistar-Kyoto rats and SHR. In brief, L-NAME treatment (40 mg / kg / day in drinking water) was performed between postnatal weeks 10 and 15. All assays were conducted under anesthesia. The four experimental groups were submitted to ECG recording, both at postnatal weeks 6 and 15, while non-invasive blood pressure measurements were carried out only at the end of the experimental period. Data normality was confirmed (Kolmogorov-Smirnov test) followed by unpaired Student's t-test or the Mann-Whitney.

The authors observed higher systolic, diastolic, mean and mean diastolic pressures in L-NAME and SHR groups compared to their respective controls (Wistar and Wistar-Kyoto rats). In addition, SHR also presented higher time- to-peak values than Wystar-Kyoto rats. According to Conceição-Vertamatti et al.,[6] these data are in agreement with the literature and validate the experimental models of hypertension used. No differences were observed between controls or hypertensive groups regarding the hemodynamic parameters.

Several differences were noticed between SHR and Wistar-Kyoto rats regarding the ECG parameters,

Keywords

Hypertension/complications; Blood Pressure; Cardiovascular Diseases/mortality; Electrocardiography/methods; Rats; Animal Models.

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especially at postnatal week 6. This pattern was not observed when comparing Wistar with L-NAME rats, which presented few differences, only at postnatal week 15. The highest parameters found for the L-NAME group were corrected QT, QT and JT intervals, which suggests changes in ventricular repolarization. SHR presented higher RR/PR intervals, S/P/Q amplitudes and P duration, while corrected QT/QT/JT intervals, R amplitude and heart rate were decreased. ECG parameters were not distinguished between controls, although differences were noticed when comparing SHR and L-NAME groups. Because L-NAME treatment began at postnatal week 10, it is important to highlight the differences between them, observed only at postnatal week 15 (increased RR interval and P amplitude, decreased JT interval for SHR). These findings altogether suggest that SHR developed cardiac dysfunction, whereas L-NAME rats presented alterations in ventricular performance. Thus, depending on the experimental model, the adaptive mechanisms triggered by hypertension may be distinct.[6]

Previous researches have included these two hypertensive experimental models and the evaluation of ECG tracings. Scridon et al.,[7] reported unprovoked atrial tachyarrhythmias in aging spontaneously hypertensive rats correlating them with changes in the autonomic nervous system. Abdel-Rahman et al.,[8] in their turn, described differences between L-NAME and Wistar rats regarding the ECG parameters similarly to Conceição-Vertamatti et al.,[6] However, the latter authors highlighted the fact that none of them compared two different models of hypertension with each other on this matter.

Although of great importance, the manuscript published by Conceição-Vertamatti et al.,[6] presents a few limitations that must be briefly discussed. More accurate data could be obtained with a different strategy for oral administration of L-NAME, rather than the drinking-water approach. It is important to consider that the authors kept three rats in the same cage, so the gavage method should be preferred. In addition, since the authors performed multiple comparisons, one-way ANOVA and Kruskal-Wallis tests should also be preferred for the statistical analysis. Moreover, it would be interesting if the authors had included females in their study, since the literature describes that sex-related differences are observed in the progression of cardiovascular disease and survival.[9]

Studies are required to test strategies for hypertension prevention and control, especially among low-income populations. Therefore, studies that allow for a better understanding of the hypertensive pathology are very welcome.

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ORIGINAL ARTICLE

Clinical and Epidemiological Profiles of Patients Admitted to a Pediatric Cardiac Intensive Care Unit

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Abstract

Background: Congenital and acquired heart diseases are important causes of morbidity and mortality in children. In critical congenital heart defects, when treatment is not adequate, clinical manifestations may lead to death in the neonatal period.

Objective: To establish the clinical and epidemiological profile of patients admitted to the pediatric cardiac intensive care unit (UTI) in a tertiary hospital.

Methods: This was a cross-sectional study conducted from January 2013 to December 2014, based on analysis of patients' medical records. The study sample was composed of 307 children and adolescents with congenial and acquired heart diseases. The score Risk Adjustement for Congenital Heart Surgery 1 (RACHS-1) was used for categorization of the various surgical procedures. Descriptive statistics were calculated using the Satistical Package for Social Sciences (SPSS). Categorical variables were compared using the Pearson's chi-square test, considering a level of significance of 5%.

Results: There was a predominance of patients aged between 28 days and one year (44%). Congenital heart diseases (91.9%) prevailed over acquired heart diseases (8.1%). Extracorporeal circulation was used in 138 patients who underwent surgical procedures, lasting from 12 to 261 minutes. Most patients (88.9%) were discharged from the ICU and 11.1% died. Using the score RACHS-1, corrective cardiac surgery was performed in 75.8% and paliative surgery in 24.2% of the patients.

Conclusions: Patients aged between 28 days to one year, with cyanotic congenital heart disease, undergoing cardiac surgery with extracorporeal circulation duration longer than 120 minutes are at a higher risk of death. (Int J Cardiovasc Sci. 2020; 33(4):331-336)

Keywords: Heart Defects, Congenital/Surgery; Epidemiology; Intensive Care Units, Pediatric; Heart Septal Defects/Surgery; Heart Septal Defects, Ventricular/Surgery.

Introduction

During embryonic period, cardiac chambers are formed from the cardiac tube division, and interaction of cardiovascular system is defined. During this process, some diseases may appear and progress to death or abnormalities, many of them soon after birth.[1] Congenital heart diseases are described as defects in the structure of the heart that is present at birth, caused by failure of heart formation after conception or between the eight and tenth week of gestation.[2]

Congenital heart diseases can be classified according to pulmonary flow. Obstructive acyanotic heart defects with normal flow include coarctation of the aorta, interrupted aortic arch, aortic stenosis, mitral stenosis and pulmonary stenosis. Acyanotic heart defects with pulmonary hyperflow and left-to-right shunt include interventricular communication (IVC), interatrial communication (IAC),

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persistent arterial channel (PAC), atrioventricular septal defect (AVSD) and aorta-pulmonary window. Cyanotic congenital heart defects include decreased pulmonary flow and obstructive diseases with right-to-left shunt: tetralogy of Fallot, tricuspid atresia, pulmonary atresia with or without IVC, transposition of the great arteries (TGA) with pulmonary stenosis (PS), Enstein anomaly, TGA without IVC, hypoplastic left heart syndrome (HLHS), total anomalous pulmonary venous return (TAPVR), and complex heart diseases with PS. Cyanotic cardiac defects with normal flow and parallel circulation include TGA with IVC and common arterial trunk, mitral atresia, and complex heart diseases without PS are classified as cyanotic cardiac defects with pulmonary hyperflow and arteriovenous malformations.[3]

Fetal echocardiography is an imaging test that has been used for the diagnosis of cardiac malformations. However, this test is not performed in all pregnant women, and complex heart diseases related to the arterial channel may not be detected by obstetric ultrasound.[4] In this regard, pulse oximetry has been recommended by the American College of Cardiology and the American Academy of Pediatrics since 2009 as the screening method for critical congenital heart diseases.[5,6]

In Brazil, it is estimated that 28 thousand new cases of congenital heart diseases are diagnoses per year.[7] Eighty percent of children with cardiac problems at birth will need some type of intervention.[2] Considering the number of surgical interventions required and the number of procedures actually performed, there has been a deficit of 65%, especially in the North and Northeast regions, with deficits of 93.5% and 77.4%, respectively.[8]

Rheumatic carditis, the most common complication of rheumatic fever, is one of the most common heart diseases acquired during childhood in the world, and has been considered the main cause of heart disease among children in developing and developed countries.[9-13]

The objective of the present study was to determine clinical and epidemiological profile of patients admitted to a pediatric cardiac intensive care unit (ICU) of a tertiary hospital in Salvador city, Brazil. This could be used as a basis by tertiary care units to adapt to these conditions and for the development of governmental policies aimed at improving the health of children and adolescents with heart diseases.

Methods

This was a retrospective, cross-sectional study, based on analysis of medical records of patients admitted to a pediatric cardiac ICU of a tertiary hospital in Salvador, Brazil, during the period from January 2013 to December 2014.

A total of 367 medical records of patients aged between 0 and 15 years, with diagnosis of congenital and acquired heart diseases, were included. Sixty medical records had incomplete admission or discharge forms and were excluded.

Data were collected from the medical records using a specific form that included personal data (age, sex, nutritional status calculated by Z-score), place of origin, clinical and surgical diagnosis, treatment, time of extracorporeal circulation (ECC) and length of stay at the ICU.

Patients with congenital heart diseases undergoing surgical intervention were classified using the Risk Adjusted Classification for Congenital Heart Surgery 1 (RACHS-1), which is an adjusted risk score for surgeries in congenital heart diseases, developed by Jenkins et al.[14] This instrument allows categorization of several surgical procedures that have similar hospital mortality into six levels.

This study was approved by the ethics committee of the *Hospital Ana Nery de Salvador/Bahia*.

Statistical analysis

The variables of the study (age, sex, nutritional status, place of origin, diagnosis, time of ECC, treatment and hospital mortality) were presented in RACHS-1 categories and expressed as numbers and percentages. For the variables: length of hospitalization, time of ECC and age, mean and standard deviation were also calculated. Results were described in tables.

All data were inserted into a database constructed using the Epidata 3.1 software and then transferred to the SPSS software version 20. To determine possible factors associated with hospital mortality, we used the Pearson's chi-square Test. Adjusted association measures (odds ratio) were obtained by logistic regression model, and the level of statistical significance was set at 5%.

Results

A total of 367 patients were admitted to the pediatric cardiac ICU during January 2013 and December 2014, and 307 were included in the study (Table 1). Distribution of the types of treatment by congenital heart diseases is described in Table 2.

Table 1 - Distribution of 307 patients admitted to a pediatric cardiac intensive care unit by demographic and nutritional profile and heart disease (2013-2014)

	Total	
	n	%
Sex		
Female	146	47.6
Male	161	52.4
Origin		
Capital	108	35.2
Countryside	199	64.8
Age (mean 3.10 ± 4.10)		
< 28 days	26	8.5
> 28 days -1 year	135	44
> 1-5 years	48	15.6
> 5 - 10 years	35	11.4
> 10 years	63	20.5
Total	307	100
Nutritional status		
Underweight (Z-score < -3)	104	33.9
Wasting (Z-score ≥ -3 and < -2)	61	19.9
Normal (Z-score ≥ -2 and < +1)	108	35.1
Overweight (Z-score ≥ +1 and < +3)	34	11.1
Diagnosis of heart disease		
Acquired	25	8.1
Rheumatic	25	
Congenital	282	91.9
Acyanotic	151	
Cyanotic	131	

Table 2 - Frequency of therapeutic treatments for acquired and congenital heart diseases in 307 patients admitted to a pediatric cardiac intensive care unit (2013-2014)

Heart diseases	n
Acquired	
Clinical	9 (35%)
Surgery	13 (52%)
Mitral valve replacement	5 (38.5%)
Double valve replacement*	3 (23%)
Mitral valve repair	5 (38.5%)
Percutaneous	3 (12%)
Mitral valvuloplasty	2 (66.7%)
Aortic valvuloplasty	1 (33.3%)
Congenital	
Clinical	74 (26.2%)
Surgery	190 (67.4%)
Total repair	144 (75.8%)
Palliative repair	46 (24.2%)
Percutaneous	18 (6.4%)
Pulmonary valvuloplasty	14 (77.8%)
Aortic valvuloplasty	1 (5.6%)
Balloon atrioseptostomy	3 (16.7%)

(*) mitral and aortic.

The most common diagnoses of acyanotic heart defects were IVC (24.5%), followed by total AVSD (19.9%), PAC and IAC (13.2% each), coarctation of the aorta (11.9%), partial AVSD (7.3%), pulmonary valve stenosis (PVS) (4.6%), aortic stenosis (4%), and double outlet right ventricle (DORV) + subaortic IVC (1.3%). Among the cyanotic congenital heart defects, the most common was tetralogy of Fallot (30%), followed by tricuspid atresia (17.6%), complex heart diseases (15.3%), pulmonary atresia (9.9%), TGA (9.2%), DORV + PS (6.1%), TAPVR (6.1%), single ventricle and truncus arteriosus (2.3% each) and Enstein anomaly (0.8%).

Among children and adolescents with complications of surgical repair (n = 94), 64.3% had hemodynamic complications, 33.3% had infection, 27.2% coagulation disturbances, 14% arrythmias, 6.5% renal complications, 6.5% procedural complications, and 3,2% neurological complications.

ECC was used in 138 patients; duration of ECC was < 90 minutes in 52.2%, 90-120 minutes in 21%, and > 120 minutes in 26.8%. Mean time of ECC was 95.2 ± 53.7 minutes, varying from 12 to 261 minutes.

Mean length of stay at the ICU was 9.7 ± 16.4 days, varying from one to 181 days. ICU length of stay was < 7 days for 73.3% of patients, 8-15 days for 15.3% and > 15 days for 11.4%.

Of 307 patients, 11.1% died and 88.9% were discharged from the ICU. Cardiogenic shock was the cause of 61.8% of deaths, followed by septic shock (35.5%) and coagulation disturbances (2.9%).

A robust association was found between age and death (p = 0.001) (Table 3). The type of heart disease (p = 0.004) and the use of ECC were also associated with hospital mortality; however, after logistic modelling, only age (adjusted OR = 2.706; p = 0.001) and diagnosis of congenital heart diseases (adjusted OR = 0.363; p = 0.001) were associated with hospital mortality. Bivariate analysis was not performed for acquired heart diseases, as they constituted only one category, which made the crossing of data impossible.

The RACHS-1, adjusted for congenital heart diseases, was used in 190 patients. In category 1 (21.1%), the most frequent were PAC (43.6%) and IAC (41%) surgical treatments. In category 2 (50%), the total surgical repair of tetralogy of Fallot (35.7%) was the most common procedure. In category 3 (44.9%), the systemic-to-pulmonary shunt (modified Blalock-Taussig shunt) was the most common procedure (33.7%), and in category 4 (13%), Rastelli operation (30.8%) was the main procedure. No intervention was classified as category 5 or 6.

The highest percentage of deaths (38.5%) occurred in category 4, as described in Table 4.

Table 3 - Frequency of deaths in patients admitted to a pediatric cardiac intensive care unit by age, sex, nutritional profile (Z-score), diagnosis, treatment and extracorporeal circulation time (2013-2014)

Category	Deaths (n = 34)		p*
	Yes n (%)	No n (%)	
Age (n = 307)			
< 28 days	7 (20.6%)	19 (7.0%)	0.001
> 28 days and ≤ 1 year	21 (61.8%)	114 (41.8%)	
> 1 year ≤ 5 years	5 (14.7%)	43 (15.8%)	
> 5 years	1 (2.9%)	97 (31.9%)	
Sex (n = 307)			
Female	15 (44.1%)	131 (48.0%)	0.670
Male	19 (55.9%)	142 (52.0%)	
BMI for age (Z score) (n = 307)			
Underweight	13 (38.2%)	95 (34.8%)	0.542
Wasting	5 (14.7%)	56 (20.5%)	
Normal	14 (41.2%)	90 (33.0%)	
Overweight	2 (5.9%)	32 (11.7%)	
Diagnosis (n = 307)			
Acquired heart disease	2 (5.9%)	23 (8.4%)	0.609
Congenital heart disease	32 (94.1%)	250 (91.6%)	
Congenital heart disease (n = 282)			
Acyanotic	10 (31.2%)	141(56.4%)	0.007
Cyanotic	22 (68.8%)	109 (43.6%)	
Treatment (n = 307)			
Acquired heart disease (n = 25)			
Clinical	1 (50%)	8 (34.8%)	0.145
Surgical	0 (0%)	13 (56.5%)	
Percutaneous	1 (50%)	2 (8.7%)	
Congenital heart disease (n = 282)			
Clinical	11 (34.4%)	63 (25.2%)	0.441
Surgical	20 (62.5%)	170 (68.0%)	
Percutaneous	1 (3.1%)	17 (6.8%)	
ECC time (n = 138)			
< 90 minutes	4 (23.5%)	68 (56.2%)	0.018
90 - 120 minutes	4 (23.5%)	25 (20.7%)	
> 120 minutes	9 (52.9%)	28 (23.1%)	

BMI: body mass index; ECC: extracorporeal circulation; (*) Pearson's chi-square test; p-values < 0.05 were considered statistically significant.

Discussion

The present study evidenced a high prevalence of children coming from the countryside of Bahia state. This is probably due to a lack of specialized services in pediatric cardiology for an early diagnosis and treatment of these patients in the cities of origin. Previous studies corroborate this finding.[15-19] The predominance of men and infants younger than one year was also similar to previous studies.[15,16,19-22]

In developed countries, Kawasaki disease is the main cause of acquired heart disease, notably in Japan and in the USA, with incidence varying from 3 to 112 per 100,000 children younger than five years old.[9] In underdeveloped and developing countries, rheumatic carditis is the main cause of acquired heart disease, as in Brazil.[10-12] In the present study, acquired heart disease accounted for 8.1%, with rheumatic heart disease as the main cause. Similar results were reported by Miyague et al.[23]

In the study population, heart valve lesions accounted for 52% of rheumatic heart diseases treated surgically,

Table 4 - Distribution of hospital mortality in 20 patients admitted to a pediatric cardiac intensive care unit by RACHS-1 score categories (2013-2014)

RACHS-1	Observed mortality n (%)	Expected mortality (%)*
Category 1	2 (5.1)	0.4
Category 2	2 (4)	3.8
Category 3	11 (13.3)	9.5
Category 4	5 (38.5)	19.4

(*) Jenkins et al., 2002.

35% of the cases treated clinically and 12% of those undergoing percutaneous procedures. Valvuloplasty and mitral valve replacement accounted for most of the procedures. According to Muller,[10] the mitral valve is affected in most cases of rheumatic carditis, while aortic valve lesions are present in approximately 30% of the cases. In our study, 23% of patients with rheumatic heart disease treated surgically underwent double valve replacement. No case of pulmonary or tricuspid valve disease was reported, corroborating the findings of this author[10] who described that lesions related to these both valves have transient anatomic features in the acute phase, corresponding to an estimated 5% of the cases.

The most common diagnosis among acyanotic heart defects was IVC (24.7%), similar to previously reported by Aragao et al., (21%)[17] and Miyague et al., (30.5%).[23] These same authors reported the prevalence of 7.7% and 19.1% for IAC and 18% and 17% for PAC, respectively. We found a prevalence of 13.2% of these conditions. Tetralogy of Fallot was the most frequent cyanotic congenital heart disease (32.1%), corroborating the studies by Miyague et al. (9.9%),[23] Borges et al. (8.1%)[16] and Aragao et al. (14%),[18] but contrasting with the findings of Nina et al.,[21] describing the presence of this anatomical malformation in only 4% of the patients.

With respect to mortality rate in the study group (11.1%), 0.65% of deaths were related to acquired heart diseases, mostly (10.35%) congenital heart defects. This is similar to that reported by Guitti[15] (10%) and lower than the percentage reported by Nina et al. (17.2%).

Regarding the RACHS-1 score, although 44.9% of the patients were classified in category 3, mainly those undergoing palliative surgeries (33.7%) related to the systemic-to-pulmonary shunt (modified Blalock-Taussig shunt), the highest mortality was found in category 4 (38.5%) followed by category 3 (13.3%). In agreement with Jenkins et al.,[14] the higher the risk category, the higher the mortality. Similar findings were reported in national and international studies.[19,21,22,24]

In our study group, mortality predictors were infants aged between 28 days and one year (61.8% of deaths, p = 0.001), diagnosis of cyanotic congenital heart disease (68.8% of deaths, p = 0.007) and time of extracorporeal circulation greater than 120 minutes (52.9%, p = 0.018).

Comparisons of these findings with other tertiary care centers would provide information that may serve as a basis for a more detailed knowledge of these patients' profile, and development of indicators to guide the prediction of technological support and reassessment of processes, contributing to the performance in these centers.

Limitations of these studies were those expected and inherent to cross-sectional designed studies, particularly those related to data collection. There were no electronic medical records, which made it difficult to identify some clinical variables, such as age, body weight and medical history of the patients. The scarcity of the literature on the application of the RACHS-1 was another limitation.

Conclusion

Congenital heart diseases were more prevalent than acquired heart diseases. Surgical treatment was the main reason of admission of the children to the pediatric cardiac ICU. Total repair surgeries were more prevalent than palliative surgeries. Hemodynamic complications were more commonly seen in patients undergoing surgical interventions. In this study, patients with cyanotic congenital heart diseases, aged between 28 days and one year, undergoing surgical treatment, with extracorporeal circulation duration longer than 120 minutes are at higher risk of death. Although most patients were classified as risk category 3 in the RACHS-1 score, the highest mortality rate was associated with risk category 4.

Author contributions

Conception and design of the research: Guimarães JR. Acquisition of data: Guimarães JR. Analysis and interpretation of the data: Guimarães ICB. Statistical analysis: Guimarães JR. Writing of the manuscript:

Guimarães JR, Guimarães ICB. Critical revision of the manuscript for intellectual content: Guimarães ICB.

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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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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EDITORIAL

Risk Factors for Mortality in Pediatric Cardiac Intensive Care Unit

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Editorial related to the article: Clinical and Epidemiological Profiles of Patients Admitted to a Pediatric Cardiac Intensive Care Unit

Congenital heart defect commonly requires care in pediatric intensive care unit (PICU). They are a heterogeneous group of disorders with an annual incidence of 25,757 new cases in Brazil, 12 cases per 1,000 inhabitants[1]. In this paper, Guimarães et al.,[2] published a cross-sectional study to describe the epidemiology of patients admitted to PICU from a tertiary hospital in Brazil. In this editorial, we review recent progress in understanding the risk factors for mortality in PICU. The editorial was produced by searching Pubmed and Scielo, using the terms "PICU", "RACHS", "CHD", and "mortality".

Congenital heart defects (CHD) are serious and common conditions that have a significant impact on morbidity, mortality and healthcare costs in both children and adults.[3] It is estimated that at least 32,000 infants in the United States will be affected each year by CHD.[3] Of these, approximately 25%, or 2.4 per 1,000 live births require invasive treatment in the first year of life. While advances in treatment in the last decades have decreased infant mortality, they have also led to an increase in the number of children and adults with CHD.[4] Despite these advances and developments in interventional and surgical techniques, heart disease in children remains an important cause of morbidity and mortality.[5]

Although acquired defects contribute to hospitalizations in PICU, congenital diseases are more prevalent. In developed countries, Kawasaki disease is the main cause of acquired heart disease in children younger than five years old. In underdeveloped and developing countries, such as Brazil, rheumatic carditis is the main cause of acquired heart disease. In the series Guimarães et al.,[2] acquired heart disease accounted for 8.1%, with rheumatic heart disease being the main cause. The most common diagnoses of acyanotic heart defects were interventricular communication (24.5%), followed by total atrioventricular septal defect (19.9%), persistent arterial channel and interatrial communication (13.2% each) and coarctation of the aorta (11.9%). Among the cyanotic congenital heart defects, the most common was tetralogy of Fallot (30%), followed by tricuspid atresia (17.6%), complex heart diseases (15.3%), pulmonary atresia (9.9%), transposition of the great arteries (9.2%), complex heart diseases with PS (6.1%), total anomalous pulmonary venous return (6.1%), single ventricle and truncus arteriosus (2.3% each) and Einstein anomaly (0.8%). These data coincide with those published by several authors. Like other authors, Guimaraes, et al.,[2] used the risk stratification of patients admitted to the PICU: the RACHS score. The RACHS-1 score is a simple model that can be easily applied because it requires little data. Despite having some shortcomings as low individual predictive power and disability of classification of all cardiac procedures,[6] it has been widely used to compare mortality among services and to evaluate the evolution of the quality of care provided. Because it is a good predictor of mortality, it has been widely used to compare mortality among services and to evaluate the evolution of the quality of care provided.[7] However, the RACHS-1 score does not address individual and structural factors of a service that can directly affect surgical outcomes.[6]

In open heart surgery, due to cardiomyopathy pulmonary bypass (CPB), which has different effects on different organs of the body, it is more likely to develop complications during or after surgery.[8] Almost 400 thousand open heart surgery using pump cardiovascular (CPB) are performed worldwide, out of which about 6% in children.[9] To better prevent these complications and improve the prognosis of action, identification of mechanisms, incidence and risk factors play a major role.[10]

Keywords

Heart Defects Congenital/mortality; Risk Factors; Mordity; Intensive Care Units; Hospitalization; Heart Septal Defects, Ventricular; Aortic Coarctation; Arterial Switch Operation.

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In a recent single-centered study with a total of 2,308 paediatric patients submitted to cardiac surgery with cardiopulmonary bypass support, Xien Zeng et al.,[11] noted that 677 (29.3%) of the surgeries resulted in postoperative complications and 1.631 (70.7%) did not. The mean surgical age was 22 (±30) months, and 1,151 (49.9%) patients were male. The risk factors evaluated for 2,308 patients stratified by postoperative complication revealed that patients who underwent surgery and experienced postoperative complications were significantly younger, lighter and shorter. Lower blood oxygen saturation levels before and after surgery were also associated with postoperative complication. Moreover, a longer surgical time, CPB, aortic cross-clamping time and particularly delayed sternal closure were associated with complications. Therefore, the right incision thoracotomy will definitely reduce the risk of complications compared to the median sternal incision. Importantly, an emergent operation was a risk factor for complications. Certainly, patients with multiple heart defects who undergo multiple procedures in the same visit will have a higher risk of complications.[11] Cavalcante CT et al., [12] carried out a retrospective analysis of 3,071 patients, from January 2003 to December 2014, and noted that mortality also varied during the twelve years of records, with significant decrease despite an increase in the number of procedures, ranging from 13.3% (171/1288) to 10.4% (191/1889) in the period II (P=0.014). Mortality in the last three years was 9% (2012-2014). When they evaluated the deaths according to RACHS-1 category, they found that the more complex the procedure, the higher the mortality rate is (P=0.0001), however when analyzing the association between RACHS-1 score and mortality in the two periods separately, was noted a decrease in mortality category in recent years, with the exception of category 6.[12]

Another study analyzed a total of 325 patients: 271 with cardiopulmonary bypass and 54 without cardiopulmonary bypass. Of the 325 patients, 141 (43%) had complications (95% confidence interval, 38%-49%). Of the 325 patients, 82 (25%) developed cardiac and 120 (37%) developed extracardiac complications. The evidence from logistic regression analysis was insufficient to suggest a relationship between CPB support and the incidence of cardiac or extracardiac complications after adjusting for age, gender, previous sternotomy, and RACHS-1 levels. For patients receiving CPB, longer CPB times, higher RACHS-1 levels, and a lower temperature with CPB were associated with a greater number of cardiac complications.[13]

A reduction in postoperative complications to improve outcomes in both adults and children undergoing a variety of surgical procedures has been a general focus for many researchers. In this study cohort, the overall mortality rate of patients with complications was 5.5% and the corresponding value in all patients was 1.6%. Furthermore, the postoperative length of hospital stay, length of cardiac intensive care unit stay and mechanical ventilation duration were significantly longer for patients who experienced postoperative complications, compared to patients without complications. The ability to predict complications prior to it will really help clinicians improve the care process by optimizing critical care resources for high-risk patients.[11]

Identifying and correcting complications early might change the relationship of complication development and mortality; thus, the downstream effects of a given complication might differ from institution to the next, depending on the infrastructure. The associations between complications and outcome might be most important in establishing patterns to target early recognition and preventive treatment.

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ORIGINAL ARTICLE

Waist Circumference Above 80 cm Predicts Increased Systolic Blood Pressure in Healthy Young Adult Women

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Abstract

Background: Among anthropometric measures for assessing adiposity-related risk, waist circumference (WC) is simple and fast to perform. Cut-off values for WC proposed by the International Diabetes Federation (IDF), and the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATP III) are categorized by gender and are not age-specific.

Objective: To analyze the association between WC and cardiometabolic risk factors in adult women.

Methods: A total of 164 healthy adult women were grouped by WC according to IDF and NCEP-ATP III cutoff values. Continuous variables were described as mean ± standard deviation or median (interquartile range). The Shapiro-Wilk test was used to assess the normality of data. Variables were analyzed by unpaired Student's t-test, Mann-Whitney U and Kruskal-Wallis tests. The correlation of WC categories with systolic (SBP) and diastolic (DBP) blood pressure, fasting blood glucose, high-density lipoprotein cholesterol (HDL-c), and triglycerides were examined by Spearman's rho correlation coefficient and linear regression analysis. A p value < 0.05 was considered statistically significant.

Results: Increased WC showed a significant correlation with SBP, DBP, glucose, HDL-c, and triglycerides. In bivariate linear regression, approximately 63.0 % of the variability of SBP (≥ 130 mmHg) among the age group 20-40 years was predicted by increased WC according to both criteria.

Conclusion: A WC above 80 cm in women aged 20-40 years strongly predicted variability in SBP, calling attention to the importance of measuring WC for the monitoring and prevention of cardiovascular and metabolic diseases in women in this age group. (Int J Cardiovasc Sci. 2020; 33(4):340-347)

Keywords: Body Weight and Measures; Anthropometry/instrumentation; Young Adult; Women,; Abdominal Circumference; Blood Pressure; Risk Factors.

Introduction

For a long time, several studies have indicated a correlation of waist circumference (WC) with abdominal (subcutaneous and intra-abdominal) fat mass[1,2] and accumulation of visceral adipose tissue.[3,4] Subsequent studies have confirmed that WC, a simple measurement, is the best surrogate marker of visceral adiposity.[5,6] In fact, a panel promoted by the Association for Weight Management and Obesity Prevention (NAASO), the Obesity Society, the American Society for Nutrition, and the American Diabetes Association has encouraged the use of WC in clinical practice.[7]

It has become evident that WC is more linked to cardiovascular risk factors than body mass index (BMI). A survey assessing 168,000 primary care patients across 63 countries[8] has demonstrated that BMI, and particularly WC, are strongly associated with cardiovascular disease

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and diabetes mellitus. Similarly, a recent population-based Australian survey with 4,487 women aged 20-69 years has concluded that central obesity measures (mainly WC) are more strongly correlated with cardiovascular risk when compared with measures of general obesity like BMI.[9]

In addition to WC, blood pressure, fasting glucose, HDL-cholesterol, and triglyceride levels have become important allies in clinical practice due to the increasing prevalence of metabolic disorders, such as overweight, obesity, and hypertension. All these risk factors are present in metabolic syndrome (MS), which has become a concern for many health organizations.

Following the World Health Organization (WHO)'s recommendations, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) and the International Diabetes Federation (IDF) have emphasized the importance of fat in the etiology of MS, and WC is a crucial component of MS definition.

In addition, it is interesting to note that the cut-off values for WC proposed by the IDF and NCEP-ATPIII are categorized by gender but are not age-specific, although changes in WC with age have been reported for many years.[10]

To address this issue, this study aimed to investigate the relationship between WC and individual components of cardiometabolic diseases and to assess the ability of WC to predict cardiometabolic risk factors across age groups in adult women.

Methods

This observacional, cross-sectional study was approved by the Research Ethics Commitee of the Federal University of Goiás with protocol number 784.446/2014. The cohort comprised 164 women aged 20-78 years, who responded to an invitation to participate in physical exercise program for women's health, promoted by the university and the municipal administration of the city of Santo Antônio de Goiás (Goiás, Brazil).

A sample size of 164 participants was calculated considering a number of 850 women in this age range (online data published by the *Instituto Brasileiro de Geografia e Estatística*, IBGE[11]), with a margin of error of 7% and confidence interval of 95%. When the sample was divided into age groups, the margin of error increased to 15%.

The exclusion criteria comprised women younger than 19 years, pregnant women, and women with a diagnosis of infectious or contagious disease, neurological or cognitive deficit, cardiac disease, or hypertension.

Anthropometric and blood pressure measurements

All WC measurements were performed by the same researcher using a flexible, inelastic tape placed directly on the skin, with the participant in a standing position and with abdominal muscles relaxed. WC was measured by placing the measuring tape around the abdomen at a midpoint between the top of the iliac crest and the lowest rib. Blood pressure measurements at rest were obtained with a sphygmomanometer by the same researcher with the patient in the sitting position. Two measurements were obtained from each patient, and average of both measurements was used in the analysis.

Biochemical analysis

Fasting blood was collected before breakfast for measurement of glucose, HDL-cholesterol, and triglycerides. Eight milliliters of blood was collected by venipuncture and aliquoted in two Vacutainer® tubes with EDTA (Vacuplast CRAL, São Paulo/Brazil). Samples were conditioned in a refrigerated thermal box and transported in less than one hour to our laboratory to separate plasma by centrifugation. Levels of glucose were measured by the glucose oxidase (GOD) -Trinder and of HDL-cholesterol and triglycerides by glycerol phosphate oxidase (GPO) –Trinder commercial colorimetric methods using an automated analyzer (LabMax 240).

International Diabetes Federation and National Cholesterol Education Program Adult Treatment Panel III cut-off values

Both IDF[12] and NCEP-ATPIII[13] adopt similar cut-off values for all MS components, with the exception of WC. In order to include both WC cut-off values in our analysis, we divided the participants into two groups: "increased WC," defined by WC ≥ 80 cm (IDF) or > 88 cm (NCEP-ATPIII); and "normal WC," defined by WC levels below those mentioned above. Other values considered to be "altered" for the purpose of this study included SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, fasting glucose ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL, and HDL-cholesterol < 50 mg/dL according to both IDF and NCEP-ATPIII criteria.

Statistical analysis

Continuous variables with normal distribution are presented as mean ± standard deviation (SD) and as median and interquartile range (IQR) when data followed a non-normal distribution. Initially, participants were

distributed into two WC categories according to the IDF and NCEP-ATPIII cut-off values. The Shapiro-Wilk test was used to assess the normality of all dependent variables (age, WC, SBP, DBP, serum glucose, HDL-cholesterol, and triglycerides) distributed into the WC categories and age groups. Comparison of data between WC categories were made by unpaired Student's *t* test (with Levene's test for equality of variance) and the Mann-Whitney U-test for data with normal and non-normal distribution, respectively. Values between age groups were compared with Kruskal-Wallis test.

For correlation and regression analyses, WC was the independent variable and SBP, DBP, glucose, HDL-cholesterol, and triglycerides the dependent variables. The strength of the association between WC (categorized as normal or increased) and the variables SBP, DBP, serum glucose, HDL-cholesterol, and triglycerides was measured by Spearman's rho (ϱ) correlation coefficient. The size of the correlation coefficient was interpreted according to Mukaka[14] in which the correlation between 0.00 and 0.30 was considered as negligible, 0.30 and 0.50 as low, 0.50 and 0.70 as moderate, 0.70 and 0.90 as high, and 0.90 and 1.00 as very high.

Participants were divided into three age groups: < 40, 40-50, and > 50 years, and correlations between WC and other variables were also assessed according to these groups. Simple and hierarchical linear regression analysis was used to examine the relationship between increased WC and cardiometabolic risk factors, and to estimate the explained variance (R square, *R2*) of these risk factors by WC. First, on simple linear regression analysis, the anthropometric measure (normal and increased WC) was included as an independent variable, and then each variable (SBP, DBP, serum glucose, HDL-cholesterol, and triglycerides) was tested as a dependent variable. All data related to cardiometabolic risk factors were also divided into normal and altered groups according to the IDF and NCEP-ATPIII criteria. On regression studies, all variables were log transformed to meet the requirements of the analysis. A p value < 0.05 was considered statistically significant.

Results

The study included 164 participants with a median age of 44.0 years [IQR13.75]. Median [IQR] of WC, SBP, DBP, glucose, HDL-c and triglycerides in the overall cohort was 94.2 [IQR18.5]cm, 127.0 [IQR 20] mm Hg, 81.0 [IQR 14] mm Hg, 86.0 [IQR 18] mg/dL, 48.0 [IQR 13] mg/dL and 117.5 [IQR 68.5] mg/dL, respectively.

Results of the median or mean ± SD of age, SBP, DBP, glucose, HDL-c and triglycerides values were compared according to WC categories defined by IDF and NCEP-ATP III criteria (Table 1). Compared with normal WC participants, the group with increased WC was older, and showed higher levels of WC, SBP and DBP (all p < 0.05). In contrast, levels of glucose, HDL-cholesterol,

Table 1 - Distribution of clinical characteristics of women´s participants (n = 164) by WC categories according to IDF and NCEP-ATPIII cutoff points

	IDF		NCEP-ATPIII	
	WC < 80 cm n = 26	WC ≥ 80 cm n = 138	WC ≤ 88 cm n = 53	WC > 88 cm n = 111
Age (years)	35.11 ± 10.5	44.6 ± 10.1*	39.7 ± 10.8	44.7 ± 10.3*
WC (cm)	73.3 ± 4.4	100.4 ± 14.3*	79.3 ± 7.0	104.1 ± 13.5*
SBP (mmHg)	116.0 ± 10.7	128.7 ± 15.3#	120.4 ± 15.2	129.7 ± 14.4#
DBP (mmHg)	74.7 ± 8.4	84.9 ± 11.0*	77.3 ± 9.4	86.1 ± 10.9*
Glucose (mg/dL)	93.1 ± 57.3	90.7 ± 40.0#	88.9 ± 42.1	92.1 ± 43.5
HDL-c (mg/dL)	49,2 ± 9.4	49.2 ± 11.2*	50.6 ± 9.0	48.5 ± 11.6
Triglycerides (mg/dL)	111.4 ± 51.6	130.4 ± 74.5*	115.2 ± 47.1	133.2 ± 80.3

*Data are expressed as mean ± SD. WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-c: high density lipoprotein-cholesterol. # p < 0.05, compared with normal WC (Student´s t test), assuming equal variances. * p < 0.05, compared with normal WC (Mann-Whitney U test).*

and triglycerides showed no difference between the two categories of WC defined by both criteria.

Values of age, SBP, DBP, fasting glucose, HDL-c and triglycerides values in the overall cohort was distributed by age group (Table 2). Significant changes were observed between the three age groups in WC (p = 0.036), SBP (p < 0.001) and DBP (p = 0.011).

Table 3 shows the correlation coefficients of the studied variables with each WC category according to the IDF and NCEP-ATPIII cut-off values. For participants with increased WC, the analysis showed that the WC categorized by IDF criteria had low correlation with DBP (ϱ = 0.425, p = 0.000) and a negligible correlation with SBP, HDL-cholesterol (ϱ = 0.285, p < 0.01; ϱ = -0.270, p < 0.001, respectively). As for the WC defined by the IDF criteria, we observed a low correlation with SBP, DBP (ϱ = 0.315, p = 0.001; and ϱ = 0.442, p = 0.000, respectively) and a negligible correlation with HDL-cholesterol and triglycerides (ϱ = -0.227, p = 0.017; and ϱ = 0.225, p = 0.018, respectively), by the NCEP-ATPIII criterion.

Bivariate regression analysis showed that for both criteria, IDF and NCEP-ATPIII, only the variability of SBP, DBP, and HDL-cholesterol levels could be explained by increased WC (Table 4). Among them, DBP showed the highest percentage of variability in the age group > 50 years (27% and 30.5%, respectively). A total of 22.7% and 18.4% in the SBP variability was explained by increased WC in participants aged < 40 years, while 9.8% and 8.5% of the variability in HDL-cholesterol levels was explained by increased WC among participants aged 40-50 years.

Table 2 - Distribution and comparison of clinical characteristics between age groups

	Age groups			
	< 40 yrs n = 54	40-50 yrs n = 69	> 50 yrs n = 41	p-value[a]
WC (cm)	91.9 ± 16.7	97.7 ± 17.9	99.0 ± 12.8	0.036
SBP (mmHg)	120.9 ± 13.14	126.4 ± 15.3	134.7 ± 14.9	< 0.001
DBP (mmHg)	80.6 ± 10.6	82.7 ± 10.6	87.7 ± 11.9	0.011
Glucose (mg/dL)	96.8 ± 61.3	88.9 ± 20.7	86.9 ± 41.6	0.077
HDL-c (mg/dL)	47.9 ± 8.5	48.9 ± 10.3	51.3 ± 14.0	0.562
Triglycerides (mg/dL)	126.7 ± 62.3	117.8 ± 63.3	144.5 ± 92.1	0.162

[a]*Kruskal Wallis test.*

Table 3 - Spearman´s rho correlation coefficients (ϱ) between increased waist circumference according to the IDF and NCEP-ATPIII criteria and blood pressure, fasting glucose, lipoprotein levels and triglycerides values

	Total n = 164		IDF				NCEP-ATPIII			
			WC < 80 cm n = 26		WC ≥ 80 cm n = 138		WC ≤ 88 cm n = 53		WC > 88 cm n = 111	
	ϱ	p-value	ϱ	p-value	ϱ	p-value	ϱ	p-value	ϱ	p-value
SBP (mmHg)	0.411	0.000	0.520	0.006	0.285	0.001	0.406	0.003	0.315	0.001
DBP (mmHg)	0.506	0.000	0.411	0.037	0.425	0.000	0.406	0.003	0.442	0.000
Glucose (mg/dL)	0.184	0.018	0.011	0.957	0.183	0.032	0.09	0.524	0.224	0.018
HDL-c (mg/dL)	-0.213	0.006	0.026	0.901	-0.270	0.001	0.215	0.122	-0.227	0.017
Triglycerides (mg/dL)	0.172	0.028	-0.031	0.879	0.164	0.056	0.059	0.676	0.225	0.018

Table 4 - Bivariate linear regression analysis

Variables	IDF					
	< 40 yrs		40-50 yrs		> 50 yrs	
	R^2	p-value	R^2	p-value	R^2	p-value
SBP	0.227	0.002	0.096	0.016	0.009	0.553
SBP ≥ 130 mmHg	0.638	0.002	0.002	0.826	0.000	0.921
DBP	0.227	0.003	0.147	0.002	0.270	0.001
DBP ≥ 85 mmHg	0.057	0.393	0.145	0.061	0.361	0.003
HDL	0.076	0.093	0.098	0.015	0.054	0.150
HDL-cholesterol < 50 mg/dL	0.031	0.554	0.17	0.014	0.059	0.274
	NCEP-ATPIII					
	< 40 yrs		40-50 yrs		> 50 yrs	
	R^2	p-value	R^2	p-value	R^2	p-value
SBP	0.184	0.023	0.080	0.044	0.084	0.107
SBP ≥ 130 mmHg	0.630	0.011	0.000	0.980	0.063	0.286
DBP	0.212	0.014	0.124	0.011	0.305	0.001
DBP ≥ 85mmHg	0.263	0.025	0.079	0.163	0.359	0.005
HDL	0.028	0.391	0.085	0.038	0.048	0.228
HDL-cholesterol < 50 mg/dL	0.077	0.471	0.180	0.031	0.023	0.525

When dependent variables were categorized according to the cut-off value of each criterion, the percentage of variability of the risk factor in the altered category, explained by increased WC, was always greater than the variability of the non-categorized variable (as observed in Table 4). Thus, increased WC (≥ 80 cm by the IDF or > 88 cm by the NCE-ATPIII) correlated only with three health risk factors – SBP, DBP, and HDL-cholesterol. Increased WC explained 63.8% and 63% of the variability of increased SBP (in women aged < 40 years), 36.1% and 35.9% of that of increased DBP (in women > 50 years), and 17% and 18% of that of altered HDL-c (in women aged 40-50 years), respectively for IDF and NCEP-ATPIII.

Discussion

The women participating in the present study were grouped according to categories of WC based on cut-off values determined by the IDF and NCEP-ATPIII criteria. The purpose of this distribution was to assess the association of WC categories with the following health risk factors: age and levels of SBP, DBP, HDL-cholesterol, fasting glucose, and triglycerides.

The prevalence of increased WC categorized according to the IDF criteria (≥ 80 cm) was superior to that of increased WC categorized according to the NCEP-ATPIII criteria (> 88 cm): 84% *versus* 68%, respectively. This was already expected, considering the lower cut-off recommended by the IDF compared with the NCEP-ATPIII. Considering that the WC is a crucial criteria for the diagnosis of MS, the higher prevalence of increased WC found in this population of women is concerning.

We also observed that median SBP, DBP, and WC values increased significantly with age. These results are aligned with data from the literature that show a continuous increase in SBP between the ages of 30 and 84 years and over. Although DBP values have a varying pattern with aging, they also increased until the fifth decade.[15] In contrast, increases in WC with increasing age are more difficult to evaluate, since this evaluation require longitudinal studies and repeated measures

analysis, which are uncommon in cross-sectional studies.[16] A 5-year longitudinal cohort study including Australian adults reported an increase in mean WC of 0.46 cm/year.[17] In our study, we observed that, in addition to the increase in mean WC with increasing age, mean WC values were above the normal values in all groups (for both IDF and NCEP-ATPIII criteria), corroborating the high prevalence of increased WC in our study.

In the association analysis, we showed a significant correlation between WC and all risk factors evaluated. The same was also observed with increased WC.

Several studies have reported a relationship between WC and risk factors for cardiovascular disease. A classic study, conducted with 70 women aged 23-50 years, reported that WC correlates moderately with plasma triglycerides and HDL-cholesterol levels and weakly with fasting glucose levels (blood pressure was not evaluated in the study).[4] Significant correlations between WC and cardiovascular risk factors (HDL-cholesterol, total cholesterol, SBC, and DBP) have also been reported in subjects aged 20-59 years.[3]

Some authors have reported correlations of WC with indicators of MS. Shen et al.,[18] evaluated 1,010 healthy men and women and found weak but significant correlations between WC and each MS component (SBP, DBP, and serum levels of glucose, TG, HDL-cholesterol, and insulin). Another population-based study published in 2002 by Zhu et al.,[19] including 9,019 American men and women found that WC correlated weakly but significantly with SBP, DBP, and levels of serum LDL-cholesterol, HDL-cholesterol, and plasma glucose.

A substantial limitation of all the studies mentioned above was the lack of WC categorization, as done in our study. Only a few authors have assessed individuals grouped into normal and increased WC categories. For example, Elbassuoni[20] reported an association of increased WC with cardiovascular risk factors (SBP, DBP, fasting glucose, triglycerides, and HDL-cholesterol) among 68 pre-menopausal women with a mean age of 32 years. Also, using previous data from a large cohort representative of the US population (US Department of Health and Human Services, National Center) and gender-specific WC cut-off points according to the NIH guidelines, Janssen et al.,[21] showed that the health risks associated with increased WC (> 102 cm for men and > 88 cm for women) in men were limited to overweight individuals, but in women, the risks affected those with normal weight, overweight, and class 1 obesity. This finding emphasizes the importance of incorporating WC measurements into clinical practice.

Considering that in the present study the cut-off values for WC in both IDF and NCEP-ATPIII criteria showed correlations with SBP, DBP, and HLD-cholesterol levels, WC values ≥ 80 cm (which would also include those above 88 cm), could potentially be included as a regular measurement in clinical practice.

On regression analysis, we found that increased WC could explain the variability of high SBP (> 60%), high DBP (> 35%) and low HDL-cholesterol levels (≥ 17%) among young adult women. To the best of our knowledge, this is the first study to report such finding.

In 2010, Stevens et al.,[16] pointed out that the inclusion of separate cut-off values by gender was appropriate and that the same is not adequate for age, since the inclusion of age-specific WC cut-off values in adults would require an examination of disease risk and use of different cut-off values for different age groups, compromising the simplicity of this useful health risk indicator.

Limitations of the present study include the small sample size, which does not allow inference of a causal relationship. Future studies with greater sample size should be conducted to confirm our findings.

The results from our study, if confirmed in a larger cohort, emphasize the importance of categorizing WC values by age groups and indicate that two simple measurements – blood pressure and WC – should be performed in young adult women in preventive health programs.

Conclusions

This study showed an association of WC ≥ 80 cm with SBP, DBP, and HDL-cholesterol levels in adult women and is in line with population-based studies aimed at simplifying the identification of health risk factors in daily practice. Additionally, the detection of SBP ≥ 130 mmHg and WC ≥ 80 cm in a young adult women patient should trigger further investigation of health risks factors, particularly cardiometabolic ones.

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Author contributions

Conception and design of the research: Silva GRA, Silva MS, Guillo LA. Acquisition of data: Silva GRA. Analysis and interpretation of the data: Silva GRA, Silva MS, Guillo LA. Statistical analysis: Silva GRA, Guillo LA. Obtaining financing: Silva MS. Writing of the manuscript: Silva GRA, Guillo LA. Critical revision of the manuscript for intellectual content: Silva MS, Guillo LA.

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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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Federal de Goiás* under the protocol number 784.446/2014. 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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EDITORIAL

"Simplicity is the ultimate sophistication" (Leonardo Da Vinci)

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Editorial related to the article: Waist Circumference Above 80 cm Predicts Increased Systolic Blood Pressure in Healthy Young Adult Women

Although scientists are developing many complex tools for the detection and prevention of diseases, simple measures are still proven to be valid. For example, body mass index (BMI) have been criticized for not considering lean body mass. However, recent studies have shown that a high BMI is associated with cardiometabolic risks, even in the presence of high levels of lean body mass.[1] Therefore, with a weight scale and a stadiometer, we can say many important things. Based on the article by Silva et al.,[2] we can add another tool to the toolbox: a measure tape. The authors show that waist circumference is associated with blood pressure, glucose, and lipid levels. In some cases, waist circumference explained more than 60% of the variability of a risk factor. Important to say that many of these parameters underlie some of the more prevalent diseases and most common causes of death, like hypertension, diabetes, and cancer.

It has been long known that excess fat is associated with health problems; however, it has been found that not all fats are the same. Central fat is more associated with health risks than gluteofemoral fat,[3] which is largely explained by the endocrine characteristics of visceral fat, mediated by adypocitokines.[4]

Most health professionals, or even researchers, do not have access to sophisticated methods capable of analyzing body composition or visceral fat. A few have the means to study the mechanism of the association between visceral fat and health parameters. However, a measure tape is easily accessible and used. The study by Silva et al. is particularly interesting and extremely useful because it reinforces that simple and inexpensive measures are valuable tools to track health risks and elaborate strategies to prevent potential problems.

More than five centuries later, Da Vinci was proven to be right once again.

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Keywords

Body Weight and Measures; Abdominal Circumference Anthropometry /instrumentation; Young Adult; Women; Blood Pressure; Risk Factors.

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ORIGINAL ARTICLE

Determinants of Arterial Stiffness and Vascular Aging in the Older Adult

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Abstract

Background: Arterial stiffness (AS) is recognized as an important and independent risk factor for cardiovascular diseases (CVD).

Objective: This study was aimed at identifying the main determinants of AS in the elderly.

Design and Methods: This was an observational, cross-sectional study of elderly participants. Blood pressure (BP) and parameters of arterial function were measured using a validated device. Clinical and demographic data, global cardiovascular risk, health-related quality of life, dietary profile and cognition data were evaluated. Blood samples were collected for biochemical profiling of the participants. Handgrip strength test was performed. Student's t-test and the χ^2 or Fisher exact tests were used for between-group comparisons as adequate. Correlational analysis was performed with the Pearson correlation coefficients and linear regression analysis. A two-tailed $p < 0.05$ was considered significant.

Results: Fifty-four participants (81.8 ± 8.8 years; 65-94 years) were included in the study. Central BP was 132.7 ± 23.7 mmHg and 51.5 ± 15.7 mmHg, respectively, for aortic systolic and pulse pressures. Mean pulse wave velocity (PWV) was 12.9 ± 2.1 m/s and augmentation index 30.1 ± 12.9%. The proportion of participants with abnormal AS (increased PWV) was 27.8%. Participants with abnormal AS had higher brachial and central BP, higher BMI and higher abdominal fat. Functionality and nutritional status were worse in participants with abnormal AS. Regression analysis indicated age, brachial and central BP and vascular resistance as main determinants of AS.

Conclusions: Abnormal AS is a common finding in the elderly and is highly associated with hypertension, functional decline and impairment of kidney function. (Int J Cardiovasc Sci. 2020; 33(4):349-356)

Keywords: Vascular Stiffness; Hypertension; Pulse Wave Analysis; Cardiovascular Diseases; Comorbidity; Risk Factors.

Introduction

Population aging is a major challenge for the upcoming decades, as the estimated share of European people aged 65 years or over will increase up to 30% by 2060.[1] Aging, particularly arterial aging,[2] is associated with increased comorbidity; cardiovascular diseases (CVD) account for most of health problems of the elderly and are the leading cause of death and disability.[3] Also, older adults are at higher absolute cardiovascular risk.[4]

Cardiovascular risk assessment has been mainly focused on standard variables such as age, gender, concomitant diseases, blood pressure (BP), cholesterol, and smoking habits, among others. However, other risk factors have emerged, as is the case of arterial stiffness (AS), which is an increasingly recognized risk factor for CVD.[5,6] In addition to invasive methods, AS can be measured using non-invasive devices. For example, the Mobil-O-Graph is an oscillometric device that calculates central pressures and velocities from the analysis of the brachial pulse pressure wave velocity and was validated in comparison with non-invasive[7-10] and invasive[11,12] methods.

Central arteries stiffen with age, which affects its buffering function and the normal ventricular-arterial coupling, and consequently reduces the hemodynamic effectiveness of the heart. This causes an increase in

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the pulse wave velocity (PWV) and an earlier return of the reflected waves, leading to an increase of both systolic blood (SBP) and pulse pressure (PP). Therefore, aging-related hypertension (HT) is characterized by a significant increase in SBP and no change or even a decrease in diastolic blood pressure (DBP), and the predominant phenotype in elderly people is thus isolated systolic hypertension (ISH).[13] In addition, it is also known that the arterial stiffening process is accelerated by HT.[14]

Frailty has also been linked with CVD in the elderly, and cardiovascular risk factors, in turn, predict frailty.[15] Handgrip strength (HGS) has been proved to be a reliable indicator[16] of frailty,[17] and therefore, an indicator of functional decline.

AS is influenced by several factors, such as age, BP, metabolic profile, genetics, medication, body composition, lifestyle, among others.[5,6] Although these factors have been widely studied in the general population and in particular clinical settings, such as HT, diabetes, dyslipidemia and chronic kidney disease, little evidence exists concerning the elderly population. Therefore, the aim of this study was to identify the main determinants of AS in the elderly.

Methods

Study design, population and ethical considerations

This was a cross-sectional, observational, study of participants enrolled in the AGA@4life project. The aim of the AGA@4life project is to evaluate the effects of different interventions (psychological, physical and nutritional therapy) on the promotion of an active and healthy aging. This preliminary analysis aims at identifying the main determinants of baseline AS of the elderly enrolled in the project. The study population was recruited from a day care center in Portugal (*Associação para a Defesa do Idoso e da Criança - ADIC*, Vilarinho, Portugal). People aged above 65 years, of both genders, physically autonomous and with no prior history of cerebrovascular or neurological disorders were invited to participate in the study. The study enrolled 54 elderly volunteers aged between 65 and 94 years, who agreed to participate, i.e., by convenience sampling.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Polytechnic Institute of Coimbra. Anonymity and confidentiality of the collected data were assured. The study was conducted for scientific purposes only, and thus, there's no conflict of interest to be declared. All participants signed an informed consent prior to the study.

Blood pressure and arterial stiffness

AS was obtained by pulse wave analysis (PWA) using the AGEDIO device (IEM, Stolberg, Germany), which uses the Mobil-O-Graph validated technology for recording brachial blood pressure (bBP) and performing PWA.[7-10] Oscillometric measurement of bBP provides brachial SBP (bSBP) and brachial DBP, mean arterial pressure (MAP) and pulse pressure (PP), as well as heart rate (HR). Immediately after the measurement of bBP, the cuff is reinflated at diastolic phase for approximately 10 seconds, while continuously recording brachial pulse waves with a high-fidelity pressure sensor.[7-10] Brachial SBP and bDBP are used for calibrating the pulse waveforms. Afterwards, the device's software (HMS, version 5.1) applies a generalized transfer function, the ARCSolver algorithm, to reconstruct the aortic pulse waveforms.[7-10] Wave separation analysis is implemented by decomposition of the aortic pulse waveform into forward (incident) and backward (reflected) pulse waves. These data together with aortic characteristic impedance, age and gender allow the estimation of oscillometric PWV. After quality check, the main parameters derived from the PWA are obtained, including: PWV, which is estimated from the reconstructed aortic pulse waveform, taking into consideration the characteristic impedance and age, and assuming a three-element Windkessel model;[9] the augmentation pressure (AP), the augmentation index (AIx) and the heart-rate adjusted augmentation index (AIx@75), all of them measures of the augmentation component of the aortic SBP, dependent on the timing of the reflected wave; total vascular resistance (TVR), also derived from the ARCSolver algorithm. Increased AS was classified considering the reference values for PWV, i.e., two standard-deviations (SDs) above the reference PWV values, adjusted for age and gender.[5]

Overall procedure

Participants were enrolled in the study in January 2018. During February and March 2018, multidisciplinary diagnostic evaluation of each participant was performed at baseline, comprising the analysis of relevant demographic and clinical information, including comorbidities, ongoing treatments, diet, physical activity,

cardiovascular risk profile and history of falls. The HGS was measured in the dominant hand using a Jamar hydraulic hand dynamometer (measured in Kg/f), with participant seated with shoulder adducted, elbow flexed 90º and forearm in neutral position.[18,19] Individuals were instructed to exert maximal grip strength for five seconds, only once.

The Portuguese version of the physical exercise self-efficacy questionnaire was used to evaluate the individual's self-confidence regarding the practice of physical activities.[20] Diet profile was evaluated with the Portuguese version of the mini nutritional assessment.[20] Cognitive function was evaluated at baseline using the Cambridge Neuropsychological Test Automated Battery (CANTAB - Cambridge Cognition, Cambridge, UK) platform.[21,22] AS and brachial and central BP were also measured, and blood samples were collected for biochemical analysis.

Statistical Analysis

Data were compiled in Excel 2016 (Microsoft Office, Redmond, WA), checked for quality, and then imported into SPSS Statistics version 24 (IBM, Armonk, NY) for statistical analysis. Post-hoc statistical power was checked with the GPower software version 3.1.9.2 (Universität Kiel, Germany) providing a power coefficient > 0.9 for a medium effect size. The distribution of variables was tested for normality by Kolmogorov-Smirnov's test, and the homogeneity of variances was addressed with the Levene's test. Variables with a non-normal distribution were log-transformed. A simple descriptive statistic method was applied for demographic and clinical characterization. Data are presented as mean ± SD for continuous variables, and as frequency (%) for categorical variables. Comparisons between independent groups were performed with Student's t test for continuous variables, and with the χ^2 or Fisher's exact tests for categorical data. For between-group comparisons, adjustments to age and/or gender were made. Pearson correlation coefficients (r) was calculated with AS (PWV) as the dependent variable. Univariable and multivariable linear regression analysis were also performed with AS (PWV) as the dependent variable and adjusting to age and gender in the multivariable model. Assumptions for linear regression were previously checked, including the presence of a linear relationship, normal distribution and homoscedasticity of errors, as well as independence of the observations. A two-tailed $p < 0.05$ was considered significant.

Results

The study enrolled 54 participants (70% women), with a mean age of 81.8 ± 8.8 years (range: 65-94 years). About 5% of the participants were smokers and 5% were former smokers. Twenty percent of the participants had family history of cardiovascular disease. Hypertension was observed in 80% of the participants, and 64% were under anti-hypertensive treatment. Dyslipidemia accounted for 60% of the participants, with 48% medicated with statins, and diabetes was identified in 26% of the participants, all of them medicated accordingly. Main characteristics are presented in Table 1.

Mean PWV was 12.9 ± 2.1 m/s. Significant differences were observed between genders, with males presenting higher BP and PWV. The proportion of participants

Table 1 - Demographic and clinical characteristics of the study population (n = 54)

	Mean ± SD
Age (years)	81.8 ± 8.8
Body mass index (Kg/m²)	26.9 ± 4.3
Systolic BP (mmHg)	146.8 ± 37.7
Diastolic BP (mmHg)	79.7 ± 75.8
Heart rate (bpm)	68.2 ± 10.9
Aortic systolic BP (mmHg)	132.7 ± 23.7
Aortic pulse pressure (mmHg)	51.5 ± 15.7
AIx@75 (%)	30.1 ± 12.9
Cardiac output (L/m)	4.8 ± 1.1
Haematocrit (SI)	39.7 ± 5.2
Total Cholesterol (mg/dL)	181.8 ± 39.0
HDL Cholesterol (mg/dL)	42.7 ± 8.5
LDL Cholesterol (mg/dL)	128.5 ± 36.2
Triglycerides (mg/dL)	140.6 ± 51.8
Glycemia (mg/dL)	114.7 ± 56.4
Creatinine (mg/dL)	0.8 ± 0.2
C-reactive protein (mg(dL)	0.4 ± 0.6
Microalbuminuria (mg/L)	42.7 ± 82.5
Haemoglobin A1c (%)	5.3 ± 1.7
Pulse wave velocity (m/s)	12.9 ± 2.1

BP: blood pressure; AIx@75 : augmentation index corrected for heart rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

with abnormal PWV, according to the reference values adjusted for age,[5] was 27.8% (n = 15). Participants with abnormal PWV were significantly older, had significantly higher brachial and central BPs, higher Aix@75 and higher vascular resistance, lower HGS and worse nutritional status (Table 2).

Univariable linear regression with PWV as dependent variable detected a significant association with age, gender, BP, vascular resistance, creatinine and HGS (Table 3). In multivariable analysis (adjusted for age and gender), BP (particularly the PP component), vascular resistance and handgrip maintained a significant association with PWV.

Also, the presence of hypertension was significantly associated with PWV. PWV increased exponentially with age, as depicted in Figure 1, which occurred in a similar manner in men and women; however, a steeper increase was observed in hypertensive participants, indicating a shift in the expected trend of arterial ageing, where hypertension accelerates the rate of AS with age.

Pulse wave velocity was also significantly and inversely correlated with HGS (Figure 2; Pearson r = -0.512; p = 0.001).

Discussion

Considering the current evidence recognising AS, and particularly PWV, as a strong and independent determinant of cardiovascular risk,[6] we performed a study aimed at identifying the main determinants of AS in the very old, identifying the factors that may accelerate arterial ageing and, thereby potential routes for preventive actions targeting the maintenance of vascular health. The study enrolled 54 participants with mean age

Table 2 - Comparative profiles of the participants as a function of the presence of abnormal arterial stiffness (aortic pulse wave velocity)

	Normal PWV (n = 39)	Abnormal PWV (n = 15)	p-value
Age, years	78.8 ± 8.2	88.7 ± 1.3	< 0.001
Females, %	66.0	80.0	0.693
BMI, Kg/m²	27.0 ± 4.3	26.4 ± 4.5	0.705
Brachial SBP, mmHg	137.0 ± 35.0	175.3 ± 31.6	0.004
Brachial DBP, mmHg	79.4 ± 17.8	83.7 ± 1.2	0.368
Brachial PP, mmHg	63.4 ± 18.8	91.6 ± 29.4	0.001
Heart rate, bpm	69.7 ± 11.7	64.0 ± 7.2	0.162
Total cholesterol, mg/dL	180.5 ± 40.8	185.9 ± 34.6	0.741
HDL cholesterol, mg/dL	43.0 ± 8.6	42.0 ± 9.2	0.762
Creatinine, mg/dL	0.8 ± 0.2	0.9 ± 0.3	0.070
Hypertension, %	70.0	100.0	0.050
Aortic SBP, mmHg	127.0 ± 21.7	150.9 ± 20.8	0.004
Aortic PP, mmHg	46.8 ± 12.8	65.3 ± 15.9	0.001
AIx@75, %	28.0 ± 13.8	36.5 ± 7.4	0.020
Vascular resistance	1.3 ± 0.2	1.7 ± 0.4	0.006
Handgrip strength, Kg/f	17.5 ± 8.1	12.1 ± 4.8	0.020
Mini nutritional assessment, score	23.5 ± 7.1	19.7 ± 4.1	0.040
PWV, m/s	12.1 ± 1.7	15.6 ± 0.9	< 0.001

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; HDL: high-density lipoprotein; AIx@75: augmentation index corrected to heart rate; PWV: pulse wave velocity.

Table 3 - Univariable and multivariable linear regression analysis with pulse wave velocity as dependent variable

	Univariable			Multivariable*		
Variable	β	CI	p-value	β	CI	p-value
Age, years	0.213	0.171; 0.255	< 0.001	-	-	-
Gender	1.554	0.091; 3.016	0.038	-	-	-
BMI, Kg/m²	0.036	-0.103; 0.203	0.669	0.046	-0.044; 0.136	0.308
Brachial SBP, mmHg	0.020	0.002; 0.038	0.027	0.021	0.015; 0.028	< 0.001
Brachial DBP, mmHg	0.001	-0.045; 0.047	0.961	0.035	0.013; 0.057	0.002
Brachial MAP, mmHg	0.037	0.004; 0.075	0.031	0.043	0.031; 0.054	< 0.001
Brachial PP, mmHg	0.053	0.029; 0.076	< 0.001	0.037	0.028; 0.047	< 0.001
Heart rate, bpm	-0.046	-0.111; 0.018	0.155	0.004	-0.034; 0.041	0.848
Aortic SBP, mmHg	0.037	0.010; 0.065	0.010	0.039	0.030; 0.047	< 0.001
Aortic PP, mmHg	0.082	0.045; 0.120	< 0.001	0.057	0.041; 0.072	< 0.001
AIx@75	0.053	0.001; 0.106	0.050	0.022	-0.010; 0.053	0.167
Vascular resistance	3.701	1.876; 5.526	< 0.001	2.039	1.035; 3.043	< 0.001
Total cholesterol, mg/dL	0.005	-0.015; 0.025	0.621	-0.001	-0.012; 0.010	0.801
HDL cholesterol, mg/dL	-0.014	-0.106; 0.078	0.762	-0.008	-0.058; 0.041	0.731
Triglycerides, mg/dL	0.008	-0.007; 0.023	0.261	0.004	-0.005; 1.219	0.620
Glycaemia, mg/dL	0.015	0.002; 0.028	0.025	-0.001	-0.010; 0.007	0.745
Creatinine, mg/dL	3.777	0.320; 7.233	0.033	1.684	-0.268; 3.636	0.088
Microalbuminuria, mg/L	0.009	0.001; 0.018	0.071	-0.001	-0.007; 0.004	0.611
Hangrip strength, Kg/f	-0.114	-0.180; -0.047	0.001	-0.049	-0.097; -0.001	0.046
MNA, score	-0.071	-0.297; 0.155	0.526	-0.008	-0.128; 0.113	0.895

** adjusted for age and gender; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; AIx@75: augmentation index corrected to heart rate; HDL: high density lipoproteins; MNA: mini nutritional assessment.*

of 81.8 ± 8.8 year. From these, 80% had HT, which, *per se*, is an important CVD risk factor, and even more considering that only 64% of these hypertensive participants were under anti-hypertensive treatment.

As expected, the results showed age as a strong determinant of PWV and BP, and a significant proportion of participants (28%) had abnormal AS, according to the expected values for age and gender.[5] This clearly reveals the interplay of chronological ageing with other contributing factors for the progression of AS through the lifespan, and particularly in the old and very old.[23] The dependence of AS on age relates to the decrease in arterial compliance due to a decreased ratio of elastin to collagen, resulting from an enhanced degradation of elastin and accumulation of stiffer collagen in the arterial media layer.[13,14]

On the other hand, there is an intrinsic, two-sided relationship between AS and BP. Our study showed that abnormal values of PWV were significantly related with HT, and that increases in both brachial and central systolic and PPs were associated with higher PWV. The increase in the stiffness of central arteries, mostly in older individuals, also contributes to an earlier arrival of the reflected component of the pulse wave, illustrated in the univariable regression analysis with a significant association between PWV and the AIx@75. This would cause an increase in the SBP and no change, or even a decrease in DBP, paving the way to increased

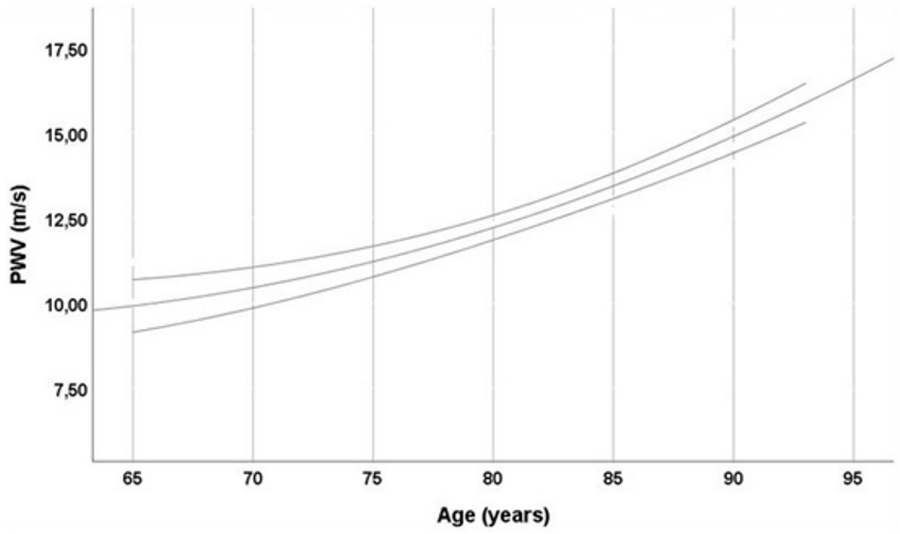

Figure 1 - Aortic pulse wave velocity increase with age.

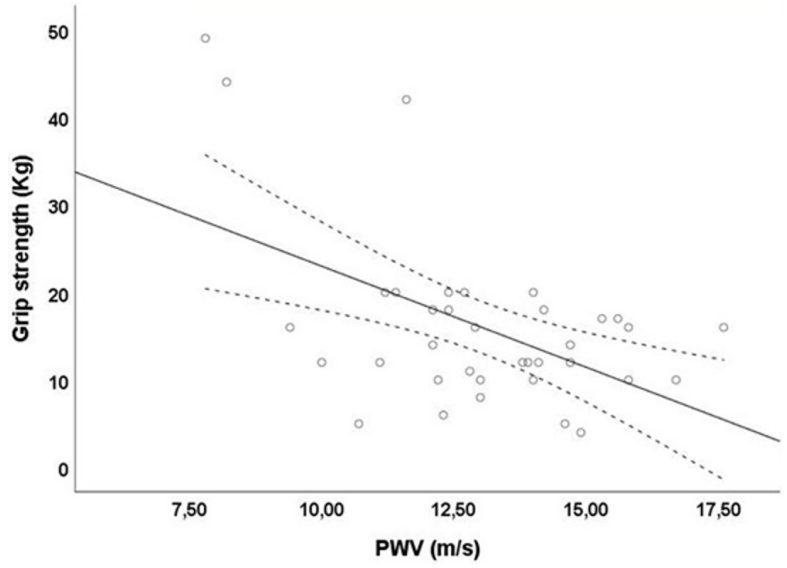

Figure 2 - Aortic pulse wave velocity and handgrip strength.

pulsatility and increased PP.[24] These hemodynamic adaptations serve the basis for ISH, which is the most prevailing HT phenotype in the very old.[5] Conversely, HT has been proved to cause arterial damage that may accelerate AS.[2,14,23,24] This was also supported by the strong association of BP and vascular resistance with AS demonstrated in the present study.

In addition to the expected association of AS with hemodynamic parameters, a significant association of AS was found with kidney function and overall health parameters. In fact, there was an association of AS with creatinine values, with participants with abnormal AS showing higher mean creatinine levels and worse kidney function, which is in line with previous evidence

demonstrating an independent association between PWV and kidney function.[25,26] Also, frailty represents a state of greater physiological vulnerability, which further affects the interaction between risk factors, disease progression and the phenotypic expressions of CVD.[15,17]

The HGS test has been acknowledged as one important marker of frailty and degree of sarcopenia in the elderly.[17] In the present study, we found a significant inverse association of PWV with HGS, with participants with abnormal AS showing significantly lower scores in the HGS test, and thus, greater frailty and worse overall health. This association was also documented in a population analysis derived from the Framingham Heart Study,[15] which corroborates AS as a biomarker that may express the cumulative exposure to risk factors through the lifespan and adaptations of some aspects of biological ageing (abnormal AS) whose course is dissociated from the expected chronological ageing.[27-29]

The present study has limitations that should be considered. The use of a single-point method for assessing arterial properties is a limitation that must be acknowledged[30] despite its previous validation.[7-12] The size of the cohort is limited, even though the post-hoc statistical power analysis provided evidence in favor of its adequacy for the analytical procedures used. The results refer to one single measurement per participant, therefore considerations about age-dependent trends must be taken with caution.

As a future challenge, we seek to explore tailored interventions to improve functionality and overall quality of life, evaluating whether personalized interventions, such as exercise programs, nutritional counselling and drug adherence programs are effective for preventing and/or treating AS and restoring vascular health in the elderly.

Highlights

- Abnormal arterial stiffness is a common finding in older adults and is strongly associated with isolated systolic hypertension.
- Abnormal arterial stiffness is a form of accelerated vascular ageing that is associated with a worse overall cardiovascular risk profile.
- Frailty and impaired kidney function are strongly associated with arterial stiffness.
- The identification of the main determinants of arterial stiffness in the elder may be instrumental for the design of tailored and effective intervention programs.

Author contributions

Conception and design of the research: Pereira T. Acquisition of data: Pereira T, Costa T. Analysis and interpretation of the data: Pereira T, Costa T. Statistical analysis: Pereira T, Costa T. Obtaining financing: Pereira T. Writing of the manuscript: Pereira T, Costa T. Critical revision of the manuscript for intellectual content: Pereira T, Costa T.

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 Polytechnic Intitute Of Coimba under the protocol number 8/2018. 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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EDITORIAL

Vascular Aging and Arterial Stiffness in Older Adults

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Editorial related to the article: Determinants of Arterial Stiffness and Vascular Aging in the Older Adult

Deaths from cardiovascular disease, according to the WHO, are projected to reach around 14 million by 2030. The global population is aging at an accelerated rate and the prevalence of arterial hypertension (AH) increases with advancing age.[1] Aging is the common denominator in several cardiovascular diseases. Arterial stiffness and increased pulse wave velocity (PWV), as well as central systolic pressure are major predictors of cardiovascular events. (Figure 1) [2]

Arterial stiffness reflects the true arterial wall damage of risk factors, and it increases with aging. On the other hand, mean blood pressure (MBP), glycemia and lipids are circulating markers whose values fluctuate along the follow-up of patients. Thus, measuring circulating biomarkers at a certain time may give only a snapshot and not the whole history of arterial wall damage. As shown in Figure 2, the gray zone before the time at measurement, when the risk assessment of a hypothetical patient is done, represents a period of life when circulating biomarkers may present altered values and, consequently, aggression to the vascular wall, interchanged with periods of good control of circulating biomarkers. This indicates that, most often, the physician does not know the amount of exposure to CV risk factors that a patient presents throughout life. Because risk scores perform a cross-sectional analysis of a single moment, they may not be able to quantify the overall cardiovascular and residual risks of each patient. However, the evaluation of arterial stiffness expresses the sum of all the aggressions caused by circulating markers on the arterial wall over time and, for this reason, it expresses more accurately the future risk of a CV event or death.[2] (Figure 2)

Further assessment and stratification of risk, in addition to the biomarkers already established, such as blood pressure (BP), blood glucose, cholesterol and carotid intima-media thickness, must provide a better and cost-effective risk prediction. Therefore, a study investigated whether a 1 m/s increase in PWV was associated with a 7% increased risk of a cardiovascular event for a 60 year old man.[3]

In addition, the altered behavior of central hemodynamic parameters, such as central systolic blood pressure (cSBP) and the (heart rate-corrected) augmentation index (AI), is influenced by arterial stiffness and plays a crucial role in the interface between the traditional cardiovascular continuum vascular and aging continuum, which represents the current view of the pathophysiology of cardiovascular diseases.[4-6]

In addition to cardiovascular impairment, another concern related to aging is cognition. A review showed that arterial stiffness severity was positively correlated with cognitive impairment. The mechanisms may be associated with greater arterial pulsatility, damaging the cerebral microcirculation, which causes various phenomena associated with cerebral small vessel diseases. It may also be associated with reductions in white matter and gray matter integrity, medial temporal lobe atrophy and Aβ protein deposition.[7]

Emerging evidence suggests that frailty is a risk factor for CVD. Individuals are considered frail if they present at least three out of these five items: unintentional weight loss of ≥10 lbs within a year, self-reported exhaustion, weakness as measured by grip strength, slow walking speed, and decreased physical activity. High frailty levels are associated with increased stiffness.[8]

Keywords

Cardiovascular Diseases/mortality; Hypertension; Vascular stiffness; Risk factors; Biomarkers; Blood Pressure; Aged; Frailty; Pulse Wave Analyses.

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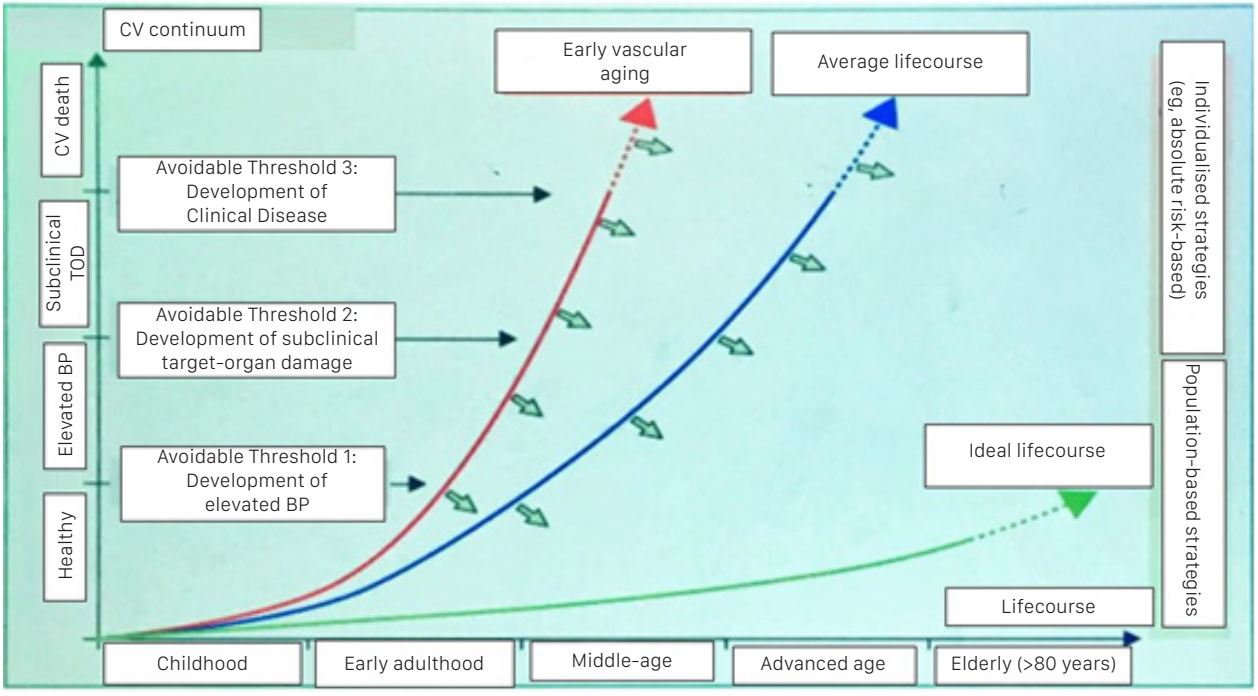

Figure 1 – Ideal lifecourse and vascular aging (Adapted from Nilsson et al Early Vascular Aging and Prevention)[2]
CV: cardiovascular; TOD: target organ damage; BP: blood pressure.

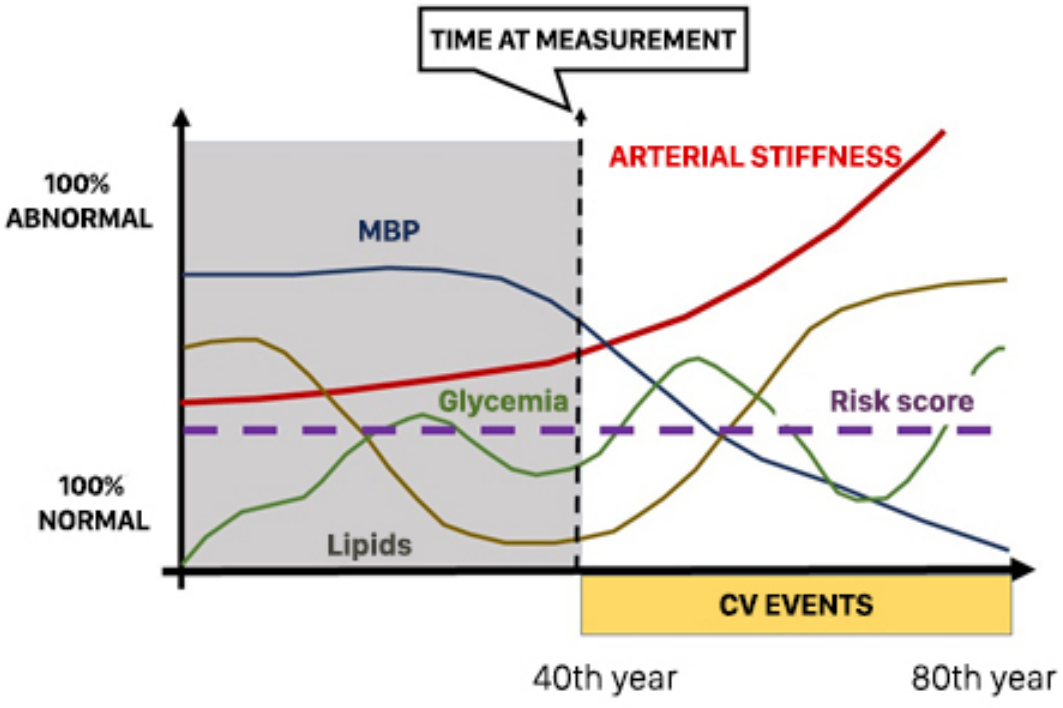

Figure 2 – Vascular Aging (Adapted from Nilsson et al Early Vascular Aging and Prevention). Mean BP (MBP); Cardiovascular (CV) events[2].

The article published in this issue was a cross-sectional, observational study of participants enrolled in the AGA@4life project, developed to evaluate the effects of several interventions (psychological, physical and nutritional therapy). The aim of the preliminary analysis was to identify the main determinants of arterial stiffness in the very old, identifying the factors that may accelerate arterial ageing and potential routes for preventive actions targeting the maintenance of vascular health. The study enrolled 54 elderly aged between 65 and 94 years from a day care center, in Vilarinho, Portugal.[9]

Arterial stiffness was obtained by an oscillometric method that uses the Mobil-O-Graph, a method validated in previous studies. Hypertension was observed in the large majority of the participants (80%) which, in its isolated form, is an important cardiovascular risk factor; however, only 64% were under treatment. Aging was seen as a determinant factor for PWV and blood pressure, and there was an intrinsic relationship between PWV and blood pressure. The study also showed an association between PWV and renal function, as well as frailty.

Most of the knowledge on accelerated vascular aging has been acquired from the general population, not including the most advanced age group. Therefore, researches on arterial stiffness in the elderly, such as the one carried out by the AGA@4life project,[9] are important to develop adequate and useful intervention programs for a better cardiovascular protection of this group.

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ORIGINAL ARTICLE

Influence of Family History of Diabetes on Cardiac Autonomic Dysfunction of Adolescents

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Abstract

Background: To evaluate cardiac autonomic modulation of adolescents with a family history of diabetic parents.

Objective: This study aims to evaluate the influence of a family history of diabetes on cardiac autonomic modulation.

Methods: This is an analytical and cross-sectional study on adolescents between 11 and 18 years of age, of both genders, who were divided into group with a family history of diabetes and a control group without a family history of diabetes. The study protocol consisted of the analysis of heart rate variability, blood pressure, anthropometric measurements, and body composition. Also, by using questionnaires, level of physical activity, sexual maturation, and sleep quality were evaluated. Normality of data distribution was tested using the Kolmogorov-Smirnov test. Then, statistical significance was evaluated using the Student's t-test, and the Hedges'g teste was used for calculation of the effect size. The level of significance adopted in the statistical analysis was 5%.

Results: When the group of individuals with a family history of diabetes was compared with the control group, statistically significant differences were observed in the variables the standard deviation of the NN time series interval (SDNN) (43.9 ± 2.2 vs. 53.5 ± 2.6 ms), the square root of the quadratic differences (RMSSD) (41.9 ± 3.3 vs. 52.4 ± 3.2 ms), standard deviation of beat-to-beat instantaneous variability (SD1) (29.7 ± 2.3 vs. 37.1 ± 2.3 ms), long-term standard deviation of continuous RR intervals (SD2) (. 54.1 ± 2.6 vs. 66.66 ± 3.5 ms), and in low frequency (LF) (496.0 ± 49.5 vs. 728 ± 71.6 ms^2) and high frequency (HF) (1050.0 ± 120.4 vs. 737.4 ± 98.5 ms^2) in the frequency domain.

Conclusions: Global autonomic modulation is decreased in adolescents with a family history of diabetes. We also observed a decrease in vagal activity in this group. So, sympathetic autonomic modulation is predominant in this population. (Int J Cardiovasc Sci. 2020; 33(4):360-367)

Keywords: Diabetes/heredity; Diabetes/Epidemiology; Adolescent; Body Weight; Body Mass Index, cardiac Autonomic System.

Introduction

Among the most common non-communicable chronic diseases worldwide, diabetes mellitus (DM) stands out because it affects more than 340 million people in the world.[1] According to Irigoyen et al.,[2] DM has reached epidemic proportions due to factors such as increased life expectancy, high prevalence of obesity and sedentary lifestyle.[2]

The main risk factors for the pathogenesis of DM are related to family history and lifestyle, such as impaired fasting blood glucose, reduced glucose tolerance, gestational diabetes, birth weight greater than 4 kg, sedentary lifestyle, dyslipidemia (triglycerides

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> 250 mg/dl and HDL < 35 mg/dl), severe obesity, polycystic ovary syndrome, age ≥ 45 years, moderate cardiovascular risk, and hypertension (> 140/90 mmHg or antihypertensive use in adults).[3] Thus, DM can be associated with different types of complications like autonomic dysfunctions in adult diabetic patients or their relatives with the disease. However, the prevalence of children and adolescents in pre-diabetic states or even with risk factors for type 2 DM is still unknown.[4]

Additionally, one of the complications of DM is its relationship with autonomic imbalance associated and cardiovascular risk, due to its effects on the blood pressure regulatory system.[5,6] Thus, quantification of parasympathetic and sympathetic cardiac autonomic modulation is fundamental as indicator of cardiovascular function,[7] because the autonomic nervous system plays a relevant role in the maintenance of cardiac homeostasis. Therefore, evaluation of heart rate variability (HRV) allows a sensitive and anticipated indication of the individual's health impairment.[6]

Studies show that a decrease in HRV promoted by a reduction in vagal activity has been associated with adverse events in normal individuals and patients with chronic diseases, and consequent increased risk of morbidity and mortality.[8,9] Thus, this study aims to evaluate the influence of a family history of diabetes on cardiac autonomic modulation.

Materials and Methods

Sample

This study is part of a large Brazilian national project called Systemic Arterial Hypertension in Children and Adolescents (HASCA in Portuguese), which aims to monitor and study the development of hypertension in the early stages of life of the Brazilian population. HASCA is a national multicenter study based on nine Brazilian cities (Sao Luis, Pelotas, Sao Paulo, Aracaju, Porto Velho, Porto Alegre, Belo Horizonte, Rio de Janeiro, and Vitoria).

The sample consisted of 69 adolescent volunteers aged 11 to 18 years, selected by convenience, with 46 participants without a family history of diabetes (controls) and 23 with a family history of diabetes (FHD). Participants of this study were students from a state public school (Rio Anil Integrated Center - CINTRA) in São Luís, Brazil, which was randomly chosen by a simple draw among public schools.

To participate in the study, individuals should be present at all stages of data collection, which consisted of: (1) public call for the study and explanation about the project; (2) signature of the informed consent form by the parent or guardian of the child or adolescent, and signature of the informed consent form by the child or adolescent participating in the project; (3) assessment of anthropometric measurements and sexual maturation, administration of sleep quality questionnaires and physical activity level, and collection of capillary blood glucose and hemodynamic data. Subjects who were absent in any of the phases of the study, patients who reported to have any disease that may affect blood pressure (cardiovascular disease, chronic arterial hypertension, vasovagal syncope), and those using any medication to control blood pressure were excluded.

The study was approved by the research ethics committee of the *Universidade Federal do Maranhão* approval number 1378142 in accordance with the 466/12 resolution of the Brazilian National Health Council of the Ministry of Health.

Body mass index

For measurement of body weight, a Filizola® scale with a capacity of 150 kg and a sensitivity of 0.1 kg, previously calibrated, was used. Volunteer were wearing light clothes and not wearing any accessories (e.g. bracelet, watches, ring). Height was measured using a Trena EST 23® compact stadiometer (2.10 m height), attached to the scale. The patient's head was positioned in the horizontal plane; the patient was barefoot, arms hanging loosely at their sides and heels straight, touching the stadiometer.[10] From these measurements, the Body Mass Index (BMI) was calculated, obtained by the ratio of weight (kg) by height squared,[11] to assess the nutritional status of participants.

Waist circumference

Waist circumference (WC) was measured using an inelastic measuring tape at the edge of the iliac crest, with participant in expiration.12 WC was classified according to the criteria and cutoffs proposed by Fernández et al.,[13] 2004: < p10 (low) > p10 and < p75 (adequate); > p75 and < p90 (high) > p90 (very high).[13]

Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Scale, a self-administered questionnaire that assesses sleep quality over the past month, was applied.

The PSQI identifies and separates people into the following groups – good sleep (overall score ≤ 4 indicates), poor sleep (score ≥ 5) sleep disorders (scores ≥ 10).[14]

Heart rate variability

HRV was recorded with a 12-lead electrocardiogram (WinCardio 6.1.1) and the 600 Hz electrocardiogram signal (Micromed Biotechnology Ltda) in the supine position for 10 minutes at rest, with spontaneous and normal respiratory rate (between 9 and 22 breaths per minute).

The indices were evaluated with Kubios VFC Analysis software, version 2.0 (Kubios, Finland).

Time-domain variability

RR interval time series were analyzed in 5-minute sections with a 50% overlap. Two competent observers analyzed the data using the Kubios HRV® software with automatic filter (Kuopio, Finland), the same used in the HRV analysis. Then, a multi-parameter HRV analysis was performed for the iRR time series. HRV parameters included mean normal-to-normal (NN) [mean NN (ms)] intervals, the standard deviation of the NN time series interval (SDNN), and the square root of the quadratic differences. NN intervals (RMSSD), the pNN50, as well as SD1 (standard deviation of beat-to-beat instantaneous variability) nonlinear analysis, SD2 (long-term standard deviation of continuous RR intervals; nu: normalized units; ms: milliseconds; ms^2: squared milliseconds) nonlinear analysis, and total variance.

Frequency domain variability (Spectral Analysis)

Frequency domain HRV measurements were characterized by the Fast Fourier Transform (FFT), in 5-minute segments, 50% overlap, 4 hz interpolation, divided into very low frequency (VLF 0 to 0.04 Hz), low frequency (LF 0.04-0.15 Hz) and high-frequency (HF, 0.15-0.4 Hz) components. The sympathovagal balance was calculated by the ratio of LF to HF components and expressed in absolute values (ms^2) and normalized units (NU).

Blood pressure

For blood pressure measurements, two validated, automated blood pressure monitors were used (Omron® HEM-711 and OMROM® 905). The protocols used for analysis of blood pressure data followed the most recent guidelines of the Seventh Brazilian Guidelines on Hypertension[15] and the Fourth Report on the Diagnosis, Evaluation, and Treatment of Hypertension in Children and Adolescents,[15] including an age-appropriate cuff according to height percentiles.[15]

Volunteers were considered with altered blood pressure when the values reached the 95% percentile, taking into account height, age and gender, according to the fourth report on Diagnosis, Assessment and Treatment of Hypertension in Children and Adolescents[9] and Brazilian Hypertension Guidelines.[16]

Assessment of physical activity

Level and practice of physical activity were assessed using the International Physical Activity Questionnaire (IPAQ) - short version.[17] The questions related to the activities performed in the week prior to the questionnaire administration.

Sexual maturation

The stage of sexual maturation was assessed according to the criteria proposed by Tanner.[18] Girls and boys were assessed by female evaluators and male evaluators, respectively, to avoid embarrassment.

Blood glucose test

Postprandial capillary blood glucose was measured using a calibrated portable glucometer (ON CALL PLUS), using their respective reagent strips to ensure their accuracy.

Statistical analysis

First, data were submitted to the Kolmogorov-Smirnov normality test. Then, the one-tailed, unpaired Student's t-test was used to analyze differences between the groups (FHD and Control). The size effect was calculated according to the Hedges'g method in which indices greater than 0.8 showed high clinical relevance. The level of significance adopted in the statistical analyses was 5%. Data are shown as mean and standard deviation. Statistica® 5.0 software was used for data analysis.

Results

The anthropometric and metabolic variables of the Control group and the FHD group are presented in Table 1. When compared with the Control group, the FHD group showed no statistically significant differences in body composition, age, height, weight, systolic blood pressure (SBP), diastolic blood pressure

(DBP), waist circumference (WC), body fat percentage, body mass index, glycemia, sexual maturation index or sleep quality. Nonetheless, although WC was not statistically different between the groups, the size of the effect showed high clinical relevance when comparing the groups.

The HRV of the Control and the FHD groups are shown in Figure 1 and Table 2. No statistically significant differences were observed between the groups in the time domain variables RR average, pNN50 (%) and total variance (ms²), but differences were observed in SDNN, RMSSD, SD1, and SD2. The variables LF (ms²) and HF (ms²), in the frequency domain, also showed statistical differences. The other frequency domain variables in normalized units – LF (nu) and HF (nu) – and the LF/HF balance did not show significant differences. However, it is important to highlight that both LF/HF and the total variance (ms²) showed to have a significant clinical impact when the effect size was evaluated.

Discussion

The main finding of this study was a decrease in vagal activity in children of diabetic parents before the manifestation of any change in glycemia, suggesting an impairment in cardiac autonomic modulation.

These results can be observed in the HRV of the participants, which does not corroborate the study by Rocha et al.,[8] which compared the autonomic function of individuals aged 18 to 49 years, with and without a family history of type 2 DM (DM2) in the absence of glucose intolerance. In this study, the authors observed differences in BMI, serum lipids, leptin, and C-reactive protein, in addition to similar autonomic parameters between the groups. In contrast, our results indicated earlier changes in HRV, which, in turn, corroborate the study by Iellamo et al.,[19] which showed that these changes occur primarily in individuals with diabetic parents.

Anthropometric indices, sexual maturation, Pittsburgh's sleep quality, SBP, DBP, blood glucose and physical activity level were not significantly different between the groups, showing that they were not determining factors to changes in the HRV. However, WC showed a high effect, a result that corroborates studies that relate abdominal fat accumulation with the increase of WC as an important risk factor for the development of DM2.[20, 21]

In addition, it was possible to notice a reduction in HRV in individuals with a family history of diabetes, with worse cardiac autonomic modulation, resulting in greater sympathetic activity.[22-24] This suggests that altered autonomic function would precede the onset of glycemic dysfunction, which corroborates the study by

Table 1 - Body composition of adolescents without a family history of diabetes (controls) and adolescents with a family history of diabetes (FHD)

	Controls (n = 46)	FHD (n = 23)	*p*	Effect size
Age (years)	16.41 ± 1.33	16.16 ± 1.8	0.52	0.16
Height (cm)	163.3 ± 1.173	159.9 ± 1.717	0.10	2.47
Weight (kg)	57.00 ± 1.617	53.97 ± 2.085	0.26	1.69
Waist circumference (cm)	72.4 ± 1.160	70.29 ± 1.462	0.27	1.66
Body fat (%)	26.79 ± 1.374	26.07 ± 1.465	0.74	0.51
Body mass index (kg/m²)	21.33 ± 0.518	21.02 ± 0.612	0.71	0.56
Systolic blood pressure (mmHg)	112.45 ± 2.332	113.54 ± 1.542	0.75	0.51
Diastolic blood pressure (mmHg)	65.16 ± 1.102	67.24 ± 1.595	0.28	1.61
Glycemia	87.15 ± 11.216	83.31 ± 10.725	0.35	0.34
Sexual maturation index	2.92 ± 0.611	2.89 ± 0.311	0.63	0.05
Pittsburgh	1.54 ± 0.658	1.47 ± 0.611	0.65	0.10
IPAQ	1.34 ± 0.487	1.62 ± 0.517	0.21	0.56

IPAQ: International Physical Activity Questionnaire; data presented as mean ± standard error; Student's t-test. Controls vs FHD ($p < 0.05$). The size effect was calculated according to the Hedges'g method.

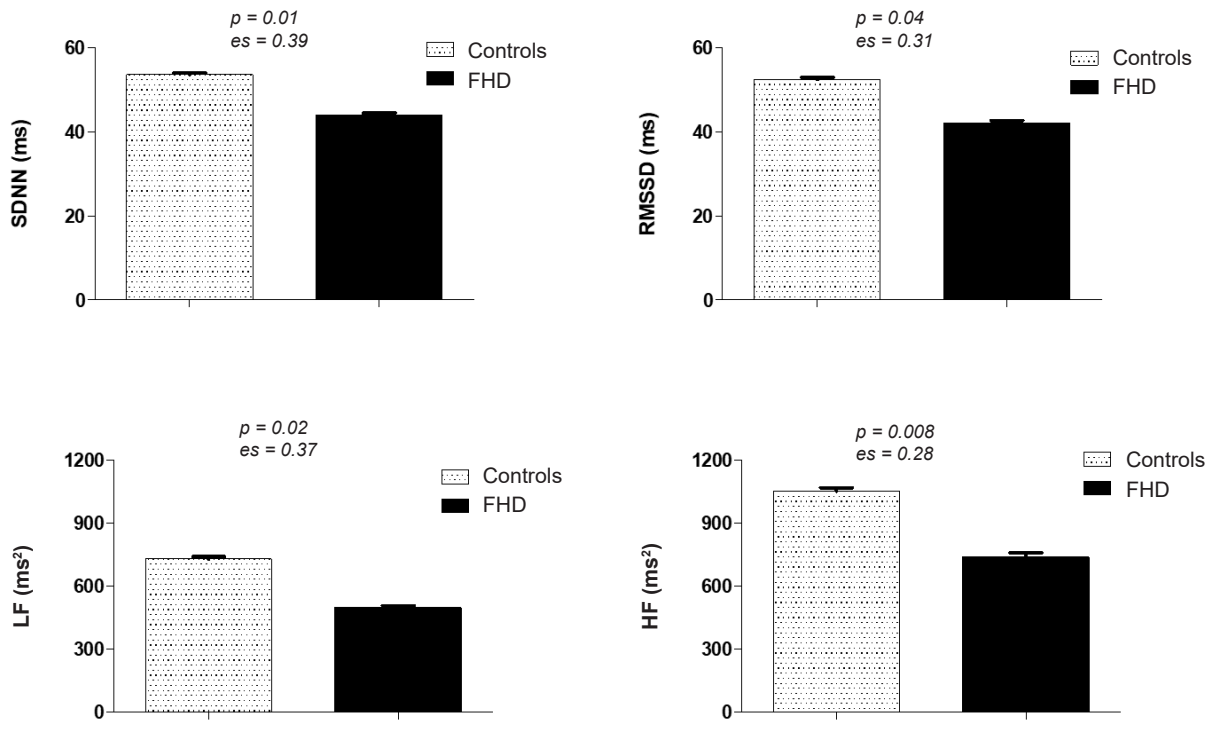

Figure 1 - Cardiac autonomic dysfunction in adolescents with and without a family history of type 2 diabetes mellitus.
SDNN: standard deviation of all NN intervals; RMSSD: root mean square of successive differences of NN intervals (ms); LF: low frequency; HF: high frequency. One-tailed, unpaired Student's t-test. Control vs. family history of diabetes ($p < 0,05$); es: effect size.

Table 2 - Variability analysis of heart rate in adolescents without a family history of diabetes (controls) and adolescents with a family history of diabetes (FHD)

	Controls (n = 46)	FHD (n = 23)	*p*	Effect size
Time domain				
Total variance (ms²)	1649.31 ± 1154.67	1532.4 ± 1154.60	0.6614	0.10
Mean RR (ms)	823.7 ± 19.85	767.2 ± 20.69	0.0724	2.80
pNN50 (%)	32.67 ± 3.083	24.00 ± 3.327	0.0784	2.73
Non-linear				
SD1 (ms)	37.14 ± 2.334	29.73 ± 2.348	0.0439	3.16
SD2 (ms)	66.66 ± 3.545	54.14 ± 2.623	0.0186	3.82
Frequency domain				
LF (nu)	45.17 ± 2.465	43.27 ± 2.681	0.6250	0.74
HF (nu)	54.83 ± 2.465	56.73 ± 2.681	0.6250	0.74
LF/HF	1.039 ± 0.1156	0.8844 ± 0.1111	0.3867	1.35

pNN50: percentage of adjacent NN intervals differing by more than 50 milliseconds; SD1: standard deviation of the variation in the beat-to-beat interval; SD2: standard deviation of continuous or long-term variability of RR intervals; nu: normalized units; ms: milliseconds; ms²: milliseconds squared; LF: low-frequency component; HF: high-frequency component; data presented as mean ± standard error; Student's t-test. Controls vs FHD ($p < 0.05$). The size effect was calculated according to the Hedges'g method.

Fiorentini et al.,[25] with 75 individuals with a mean age of 47.71 years, divided into a group with a family history of DM2 and insulin resistance, a group of descendants with a family history without insulin resistance and a control group. The authors identified that changes related to the reduction in autonomic system function were associated with a family history of diabetes.[25]

The results in this study showed changes in cardiac autonomic modulation suggestive of lower vagal activity, which was also noted in the study by Kardelen et al.[26] in children with an average age of 12 years and insulin dependence.

The time-domain RMSSD (ms^2) and SDNN variables confirmed a lower cardiac autonomic modulation in children of diabetic parents found in the analysis of adjacent RR intervals,[27] reflecting a decrease in vagal activity.[28] Therefore, a significant decrease in RMSSD and SDNN is indicative of a reduction in vagal tone and greater modulation of the cardiac sympathetic autonomic nervous system as shown in adolescents in the family history of diabetes group, corroborating previous studies.[26,29,30]

Analysis of the frequency domain revealed that HF (ms^2) and LF (ms^2) indices are lower in children of diabetics, corroborating the studies by Chen et al.[31] and Malik et al.,[32] including DM2 children aged from eight to 12 years, showing a decrease in the LF (ms^2), HF (ms^2) components, as well as in total variance. Although our study did not show significant differences in total variance, this parameter showed a high effect size, indicating important clinical representativeness.

The LF/HF ratio, a marker of autonomic imbalance, was lower in children with parents with DM2. This is different from the study by Fiorentini et al.,[25] which identified changes in LF/HF ratio indicating lower vagal activity in 70 Caucasian individuals, mean age of 47 years, descended from parents with DM2. The failure to identify autonomic imbalance in the present study may be related to the age range of the groups in our study, since autonomic nervous system disorders in insulin-resistant patients are closely related to longer exposure to the disorder.[33,34] However, it is important to emphasize that the LF/HF balance showed a strong effect, supporting it as an important marker of clinical changes in cardiac autonomic modulation in adolescents with a family history of diabetes.

The SD1 and SD2 values indicated a lower vagal activity in the FHD group, which corroborates the findings of Kaminski et al.[35] who evaluated the sympathovagal activity in adult individuals. However, their sample comprised individuals aged 11 to 18 years incomplete, which makes the findings important evidence for a better understanding and early identification of an association of cardiac autonomic dysfunction with a genetic factor in the etiology of this condition.

First-degree relatives of individuals with DM2 are known to have two to six times greater risk of developing the disease compared with individuals with no family history of diabetes.[36] In this case, the genetic component is a determining factor, where the possibility of individuals with a family history of diabetes is five to ten times higher for the development of the disease than the general population.[37]

In terms of clinical and scientific relevance of the findings, some points need to be highlighted. First, in the studies reviewed, there was little scientific evidence, since HRV in adolescents with a family history of diabetes has been poorly studied and deserves further investigation. Our findings may be used in subclinical detection of autonomic dysfunctions, definition of the risk level, and in early diagnosis of hemodynamic and autonomic changes in offspring of individuals with DM. This would reduce overall mortality and the risk of the development of DM2, metabolic complications and other noncommunicable chronic diseases.

In interpreting these results, some limitations need to be considered. The study allowed verifying the existence of a family history of diabetes among participants, however, it was not possible to determine the type of DM in the parents; also, insulin and lipid levels of these individuals were not assessed, which could have provided relevant clinical information and should be explored in future studies.

Conclusion

Global autonomic modulation is decreased in adolescents with a family history of diabetes. It was also observed a vagal activity decrease (RMSSD and SD1 indices), indicating that a sympathetic modulation is predominant in this population.

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Author contributions

Conception and design of the research: Mostarda CT. Acquisition of data: Dias-Filho CAA; Soares-Junior NJ; Sena CS; Andrade RM; Vieira ASM; Pinto LM. Analysis and interpretation of the data: Dias CJ; Ferreira AC. Statistical analysis: Carvalho WRG; Soares-Junior NJ. Writing of the manuscript: Dias-Filho CAA; Ferreira AC. Critical revision of the manuscript for intellectual content: Mostarda CT; Brito-Monzani JO; Dias CJ.

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 *Universidade Federal do Maranhão* under the protocol number 1.378.174/2015. 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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EDITORIAL

Identification of Preclinical Markers Related to Hereditary Diseases: Expanding the Horizons of the Study of Cardiac Autonomic Modulation

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Editorial related to the article: Influence of Family History of Diabetes on Cardiac Autonomic Dysfunction of Adolescents

The Autonomic Nervous System (ANS) consists of two opposite pathways (sympathetic and parasympathetic) that have action both on the atrial and ventricular myocardium, as well as on atrioventricular and sinus nodes, thus exerting influence on the variation of heart rate (HR). The increase in HR is a consequence of the greater action of the sympathetic pathway and the lower parasympathetic activity (vagal inhibition), while its reduction basically depends on predominance of vagal activity. The influence of ANS on the heart is dependent on information that departs, among others, from baroceptors, chemoreceptors, changes in the respiratory system, vasomotor system, renin-angiotensin-aldosterone system and thermoregulatory system.

The discovery of the relationship between ANS and mortality from cardiovascular diseases has led to several studies, which have proven the existence of reduced parasympathetic and increased sympathetic activity in several pathologies of the cardiovascular system. These findings made it necessary to develop quantitative markers of cardiac autonomic activity, and heart rate variability (HRV) is the most promising autonomic marker[1]. Historically, their clinical interest arose in 1965, when Hon and Lee demonstrated a well-defined clinical application of HRV in the area of fetal distress monitoring. In 1977, Wolf et al.,[2] showed an association between low HRV and higher risk of mortality after acute myocardial infarction and Kleiger et al.,[3] in 1987, confirmed that HRV was a potent and independent predictor of mortality after acute myocardial infarction. In 1996, in an age-stratified cross-sectional study, Barbosa et al.,[4] reported >18 % per decade reduction in HRV in healthy adults and >25 % per decade reduction in subjects two years post-myocardial infarction with persevered left ventricular systolic function.[5] Additionally, the authors observed that aging related HRV decrease was mainly related to reduction in spontaneous vagal activity. In 2002, Nunes studied HRV variability in preschool healthy children, defining normality ranges for HRV variables in this population.[6]

HRV represents the spontaneous and continuous variation of cardiac interbeat interval. Therefore, HRV comprises the oscillations between the RR intervals of heartbeat, which reflect the changes resulting from the action of the ANS on the behavior of HR. HRV's analyses, from linear methods, can be performed as a function of two parameters: time domain (analysis of records deriving from times greater than 10 minutes, expressed in milliseconds, through variation of the duration of intervals between normal QRS complexes resulting from sinus depolarization and its mathematical indices) and frequency domain (records of wave intensity verified in time intervals of up to 4 minutes and it's unit is determined by Hertz).

In the time domain, SDNN and SDNNi are indexes taken through individual RR intervals and represent sympathetic and parasympathetic activities, while rMSSD and pNN50 are obtained through adjacent RR intervals and reflect parasympathetic activity. The parameters obtained by the frequency domain are: HF (High Frequency): values between 0,15 a 0,4Hz, related to respiratory activity and it is an indication

Keywords

Autonomic Nervous System/complications; Diabetes Mellitus/complications; Autonomic Denervation; Genetic Diseases, Inborn; Adolescent.

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of vagus influence on the heart; LF (Low Frequency): associated with baroreceptor reflex with values between 0.04 and 0.15Hz, resulting from the joint action of the parasympathetic and sympathetic components on the heart, with predominance of sympathetic; LF/HF ratio is calculated and provide sympathetic / parasympathetic balance. The limitation of implementation this technique includes the presence of all no sinus rhythm, heart transplant, pacemaker activity and the presence of atrioventricular block.

The measurement of HRV is extremely important for clinical understanding of physiological variables, since the increase in HRV indicates good physiological adaptation, while the reduction has been pointed out as a predictor of diseases or the occurrence of adverse events in patients with previous diseases. Numerous conditions have been described as responsible for measurable autonomic changes through HRV, such as: several heart diseases, nervous anorexia, epilepsy, asthma, anxiety disorders, obesity, hypertension and diabetes mellitus.

Diabetes mellitus (DM) is a global health epidemic thought to be affecting 415 million people worldwide, with a further 318 million suffering with glucose intolerance and at increased risk of developing the disease. Type II DM is a multifactorial polygenic inheritance form of diabetes, comprising about 90% all DM cases. About 75% may manifest sustained elevated blood glucose levels as early as in the fifth decade of life. Cardiac autonomic neuropathy (CAN) is a common underdiagnosed complication of DM.[7] Interestingly, subtle autonomic neurologic deficits have also been documented earlier in the course of diabetes and during the prediabetic period in subjects with impaired glucose tolerance in comparison with healthy individuals. The impact of CAN on patients with DM can be devastating, and it has been shown that impaired autonomic system can be associated with increased mortality, cardiovascular disease (CVD), chronic kidney disease (CKD), and morbidity in DM. CAN has several risk factors that are common to other diabetes-related vascular complications, such as: glycemic control, diabetes duration and CVD risk factors. Besides that, several genes have been linked to the development and progression of diabetic polyneuropathy and CAN, among which are TCF9L2, APOE, and ACE.[8]

CAN, usually, only becomes symptomatic in the later stages of the disease and the vagus nerve is usually the first nerve to be affected, resulting in symptoms of sympathetic predominance. Subclinical CAN is initially limited to baroreceptor abnormalities and reduction in HRV, but as the disease progresses, cardiac involvement becomes more evident and symptomatic with resting tachycardia, reduced exercise tolerance, orthostatic hypotension, QT prolongation, silent ischemia, cardiomyopathy and CKD.[6]

Early determination of CAN is vital to the success of therapeutic input, as it has been suggested that cardiovascular denervation may be reversible if diagnosed soon after onset, through a combination of nonpharmacological and pharmacological approaches, including lifestyle modification, intensive glycemic control, and treating underlying risk factors, such as hyperlipidemia and hypertension.[9]

Dias-Filho et al.[10], conducted a Brazilian multicenter study to evaluate cardiac autonomic modulation of adolescents with a family history of diabetic parents. They selected 69 teenagers from state public schools, aged 11 to 18 years, 23 with family history of diabetes. The authors managed to investigate nonmetabolic traits of early putative phenotypic expression of diabetes, specifically on the autonomic modulation of the heart. They have found that teenagers with parental history of diabetes, as compared to those with no such familial history, showed slight but significant overall reduction in heart rate variability, with a particular effect on the vagal limb of heart rate modulation.

The study protocol consisted of the analysis of heart rate variability, blood pressure, anthropometric measurements, and body composition. They also used questionnaires to evaluate level of physical activity, sexual maturation, and sleep quality and all variables were paired with no significant difference between the 2 groups. When the group of individuals with a family history of diabetes was compared with the control group, statistically significant differences were observed in SDNN (43.9 ± 2.2 vs. 53.5 ± 2.6 ms), RMSSD (41.9 ± 3.3 vs. 52.4 ± 3.2 ms), SD1 (29.7 ± 2.3 vs. 37.1 ± 2.3 ms), SD2 (54.1 ± 2.6 vs. 66.66 ± 3.5 ms), and LF (496.0 ± 49.5 vs. 728 ± 71.6 ms^2) and HF (1050.0 ± 120.4 vs. 737.4 ± 98.5 ms^2). They concluded that global autonomic modulation is decreased in adolescents with a family history of diabetes.

These important findings suggest an early decrease in vagal tone in adolescents with diabetic parents, suggesting that the sympathetic / vagal imbalance in this population could be an earlier mark of disease and might be considered to optimize non-pharmacological measures that would prevent the development of diabetes in the future.

Some considerations, however, deserve to be highlighted. It is important to stress that present findings do not allow one to infer the presence of disease or dysfunction in healthy teenager population. All variables showed results within expected normal limits, although significant differences were found between groups. The paired data table of adolescent populations in the study does not inform whether there was also a pairing regarding gender, since it is known that sex can influence HRV. In 2006, Rajendra Acharya et al.,[11] observed that HRV is lower with age and that variation is greater in women, particularly during and preceding the menstrual period. It is also necessary when analyzing HRV in a population, that all variables that might affect it in some way should be controlled. In addition to gender, variables such as major or minor component of REM sleep, presence or absence of sleep apnea, would be more useful than just the sleep quality questionnaire, which, in addition to being flawed, does not report relevant sleep data that can influence HRV. Finally, due to the small sample size, these findings must be confirmed later.

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ORIGINAL ARTICLE

Treatment Eligibility and Therapeutic Responses of an Ecuadorian Population at High Cardiovascular Risk Based on the ATP III Guidelines

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Abstract

Background: The Adult Treatment Panel III (ATPIII) guidelines aim to reduce cardiovascular morbidity and mortality. In Ecuador, 20% of people have high LDL cholesterol levels, and 39% have high triglyceride levels.

Objective: To analyze lipid-lowering regimens in Ecuadorian patients and determine the achievement rate of the ATPIII goals for lipid profile.

Methods: Using a retrospective analysis, 385 subjects older than 30 years, who received pharmacological treatment for dyslipidemia for at least three months was randomly selected from institutions at two large cities in Ecuador. Data were collected from patients' medical records and analyzed by chi-square test or paired t-test; p-values less than 0.05 were considered significant.

Results: Baseline total cholesterol values were above 200 mg/dL in 75% of subjects, LDL-c values above 129 mg/dL in 83% of subjects and triglycerides values above 150 mg/dL in 79% of subjects. Most (n = 253, 95.8%) patients at very high cardiovascular risk were taking statins, 50% of them atorvastatin. Considering the ATPIII guidelines' goals, only 24 subjects (19%) at high CV risk achieved an LDL-c < 100 mg/dl, while a significantly lower percentage (p = 0.04) of patients at very high risk reached an LDL-c < 70mg/dl (11%; n = 30).

Conclusion: These data indicate a low rate of compliance with the ATPIII guidelines, independent of the medication used or duration of the treatment. This may be attributed to the prescription of low doses of medication and a therapy targeting isolated lipid fractions rather than a complete lipid profile. (Int J Cardiovasc Sci. 2020; 33(4):371-376)

Keywords: Cardiovascular Diseases/prevention and control; Cholesterol; Triglicerides; Sedentarism; Tabaquism; Lifestyle; Dyslipidemia; Patient Compliance.

Introduction

The development of noncommunicable chronic diseases is associated with smoking, sedentary lifestyle and nutritional factors, and their detrimental effects can be reduced by a healthy lifestyle.[1,2] In Ecuador, health care of patients with diabetes mellitus, dyslipidemia, and hypertension accounts for the majority of physician-patient appointments and hospital discharge in the last twenty years.[3] Recently, the National Health and Nutrition Survey (Encuesta Nacional de Salud y Nutrición - ENSANUT) presented by the Ecuadorian

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Ministry of Public Health showed that dyslipidemia is present in 19.9% of people below 60 years old while hypertriglyceridemia reaches 38.7% nationwide.[4]

For more than a decade, treatment of dyslipidemia by the medical community has been based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines (ATP III and subsequent updates).[5] This approach relied heavily on the Framingham Heart Risk Score as a predictor of 10-year risk of coronary heart disease (CHD) events, specifically myocardial infarction and CHD-related death. Moreover, ATPIII provides therapy guidelines for low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (non-HDL-c) established based on patients' predicted risk and related comorbidities. In general, these guidelines recommend aggressive treatment of LDL-c of patients at higher risk, with specific LDL-c targets for each risk category.[5]

Since the late 1980s, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors ('statins') has been used as the primary treatment of hypercholesterolemia. A pooled analysis of the Cholesterol Treatment Trialists' Collaboration (CTTC) showed that every 1 mmol/L (38.67 mg/ dL) reduction in LDL-c with statin therapy was associated with a reduction in any major cardiovascular event by 21% to 28%.[6]

The present study analyzes different lipid-lowering regimens in Ecuadorian patients at high and very high cardiovascular risk, to determine if ATPIII guidelines achieve their treatment goals.

Materials and methods

This was a retrospective study approved by the institutional review board of the *Universidad San Francisco de Quito* (2015-044IN). A sample of patients' medical records was calculated (5% precision, 95% confidence interval and 50% variability) and obtained from six hospitals in the two main cities of Ecuador assuming a rate of 2:1 between public and private institutions. In Quito city, the hospitals that participated in the study "Hospital de Especialidades Eugenio Espejo" (public hospital, run by the Ministry of Public Health), "Hospital Carlos Andrade Marín" (public hospital, run by the social security administration), and "Hospital de Los Valles" (private hospital). In Guayaquil, the hospitals included were "Hospital Luis Vernaza" (public hospital, run by the *Junta Beneficencia* – Charity Board), "Hospital Teodoro Maldonado Carbo" (public hospital, run by the social security administration), and "Clinica Kennedy" (private hospital).

Medical records of subjects that met the following criteria were included in our analysis: (a) subjects that attended an internal medicine, cardiology or endocrinology outpatient clinics, (b) subjects older than 30 years (c) patients with a diagnosis of dyslipidemia evidenced by laboratory tests (d) subjects undergoing pharmacological treatment at one of the mentioned hospitals for at least three months. Subjects that met the above criteria were selected per institution using a random number generator (www.random.org) and data from the medical records were collected using forms specially designed for this study.

According to the ATP III algorithm, subjects are placed in one of three risk categories: (1) established CHD and CHD risk equivalents, (2) multiple (2+) risk factors, and (3) zero to one (0–1) risk factor. CHD risk equivalents include noncoronary forms of clinical atherosclerotic disease, diabetes, and multiple (2+) CHD risk factors with 10-year risk for CHD > 20%. Subjects with CHD or CHD risk equivalents can be categorized as high risk. The goal for LDL-lowering therapy in high-risk patients is an LDL-c level < 100 mg/dL. According to ATP III, for a baseline or on-treatment LDL-c < 100 mg/dL, no further LDL-lowering therapy is recommended. For all high-risk patients with LDL-c levels > 100 mg/dL, LDL-lowering dietary therapy should be initiated.[5]

Other factors that place subjects in the category of very high risk are the presence of established CVD plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides > 200 mg/dL plus non-HDL-C > 130 mg/dL with low HDL-C [< 40 mg/dL]), and (4) patients with acute coronary syndromes.[5]

Statistical analysis

Continuous variables with a normal distribution, assessed by the Shapiro-Wilk test, were described as mean and standard deviation while categorical variables were presented as frequencies. Data were analyzed using the SPSS, using the chi-square test for categorical variables and the paired t-test for the continuous variables. A p-value less than 0.05 was considered as significant.

Results

A total of 385 patients were recruited, with an average age of 59.8 ± 13.2 years; 46% (n = 178) were male and 68% of them were at a very high risk of cardiovascular disease.

Analysis of baseline lipid profile showed total cholesterol levels higher than the desirable (< 200 mg/dL) in 75% of subjects and LDL-c near optimal/above optimal (129 mg/dL) in 83% of subjects. HDL cholesterol was lower than 40 mg/dL in 43% of patients, and triglycerides were above normal (< 150 mg/dL) in 79% of patients. There were no differences in lipid values between subjects at high or very high cardiovascular risk (Table 1).

Very high cardiovascular risk was significantly more frequent in women (57%; p = 0.02). Treatment resulted in a significant reduction of total and LDL cholesterol as well as triglycerides both in high and very high-risk subjects (Table 1).

However, the response rate to treatment ranged from 50% to 75%, with no difference between high and very high-risk subjects (Figure 1). Interestingly, all three parameters (total-c, LDL-c, and triglycerides) were seen to lower in 40% and 47% in high and very high-risk patients, respectively, with no statistical difference between the groups. Finally, improvement in the lipid profile – total-c, LDL-c and triglyceride reductions plus HDL-c increase – was evidenced in only 21% and 28%, respectively, with no statistical difference between the groups.

Regarding the LDL-c goal attainment (NCEP-ATP III therapy guidelines), only 24 (19%) high-risk subjects achieved an LDL-c < 100 mg/dL, while a significantly lower percentage (p = 0.04) of subjects at very high cardiovascular risk reached an LDL-c < 70mg/dL (11%; n = 30). Additionally, ATP III goals were attained in a larger percentage by men (20.7%) than women (12.6%), although this difference was not statistically significant.

The most common pharmacological treatment was statin-based therapy, i.e. simvastatin at an initial dose of 20 mg in 35% (n = 68) of patients, or atorvastatin at an initial dose of 40mg in 56% (n = 110) of the subjects. Ezetimibe alone or in combination with simvastatin was used in 11 subjects (5.6%). Lastly, fibrates, i.e. gemfibrozil (600 mg) or fenofibrate (160 mg) was the treatment prescribed to only 3% (n = 5) of the patients.

In very-high risk patients, statins were used in 95.8% of the cases (n = 253) and in those, atorvastatin corresponded to 50%, simvastatin 34.8% and rosuvastatin 11% (Table 2).

The 30 patients who reached the ATP III LDL-c goal were prescribed high doses of statins either alone or in combination.

Discussion

A reduction of lipid values – total-c, LDL cholesterol and/or triglycerides – in patients at high and very high cardiovascular risk was 56% and 53%, respectively. Therefore, we conclude that regardless of the treatment option or its duration, approximately half of the patients did not show an improvement in lipid profile.

It was not surprising that pharmacological treatment for dyslipidemia was mainly based on statins and particularly on atorvastatin. What is surprising is that low doses have been prescribed for high-risk patients, even though it is known that the success rate of such

Table 1 - Lipid values (mg/dL) in Ecuadorian subjects categorized by cardiovascular risk before and after pharmacological treatment for dyslipidemia

	Age	%Female	Total-c	LDL-c	Triglycerides	HDL-c
High risk (n = 125)	54.1 ± 14.3	48.0	235 ± 60	151 ± 62	271 ± 195	49 ± 26
			212 ± 55	135 ± 52	204 ± 156	48 ± 26
			0.018	0.03	0.003	0.76
Very high risk (n = 264)	62.6 ± 11.7	57.2	228 ± 54	140 ± 50	268 ± 285	43 ± 13
			197 ± 51	123 ± 45	208 ± 152	44 ± 13
			< 0.0001	< 0.0001	0.003	0.37

Total-c: total cholesterol; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.

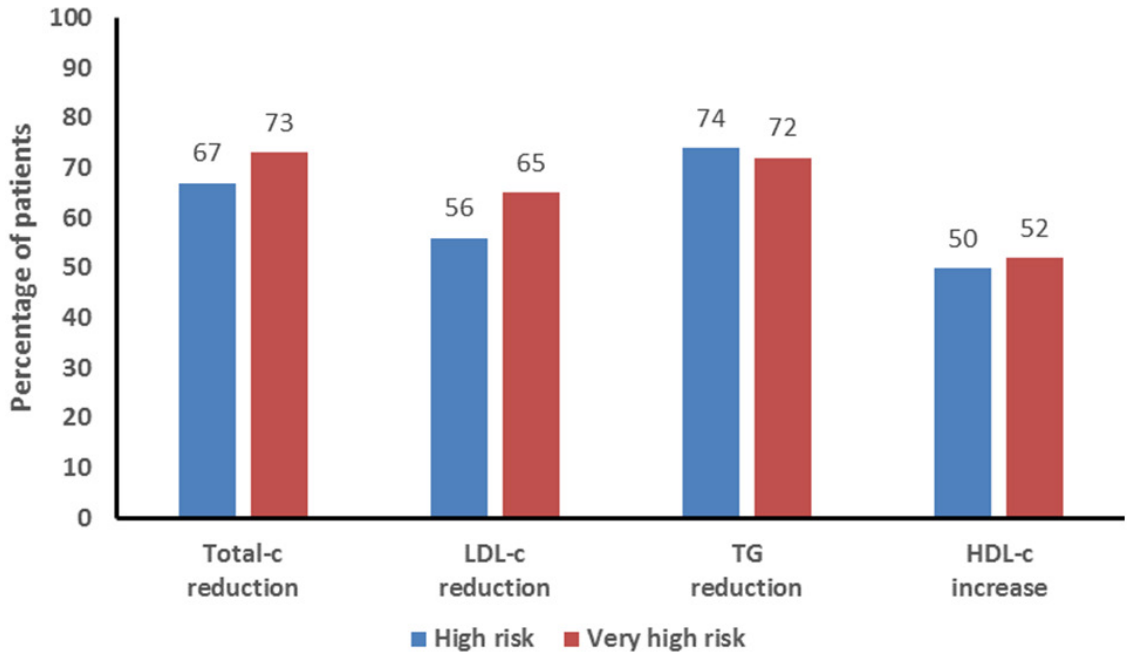

Figure 1 - Response rate (improvement of lipid profile) in Ecuadorian patients after treatment for dyslipidemia.
Total-C: total cholesterol; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.

doses is low.[7] It is also to be noted that fibrates have been prescribed to high-risk patients, given that recent trials have shown that these medications have failed to achieve a statistically significant reduction in lipid levels and, when combined with statins, have shown an increase in side effects.[8]

Moreover, the use of ezetimibe, particularly in association with statins, was found to be reduced. This may be explained by the fact that ezetimibe is not included in the National Essential Medicines List, which is a mandatory reference in public institutions. In private institutions, however, we could not find a clear explanation other than a misinterpretation of ATP III therapeutic goals by physicians.

In 2013, a new set of recommendations for the management of dyslipidemia were released by the American College of Cardiology (ACC) in collaboration with the American Heart Association (AHA). These guidelines refer to overall atherosclerotic cardiovascular disease and differ significantly from the previous ATP III guidelines by the fact that LDL-c and non-HDL-c goals were completely abolished.[9] In addition, ATP III and subsequent updates state that the decrease in the lipid profile solely is not enough to reduce cardiovascular risk.[10]

Our analysis shows that the achievement of ATPIII treatment goals by patients at high risk was no different between statin therapies, i.e. 22% atorvastatin at 40 mg, 18.2% simvastatin at 40 mg and 18.8% rosuvastatin at 20 mg. Atorvastatin in higher doses allowed an additional 15% while no increase was found with higher doses of simvastatin or rosuvastatin. In patients at very high-risk, the ATPIII LDL-C goals were achieved by 18.4% of patients taking atorvastatin at 40 mg, 7.6% of patients taking simvastatin and 3.6% of patients taking rosuvastatin. The use of higher doses did not result in a difference in success rates for LDL-c goal achievement.

We also analyzed our results based on the 2013 ACC/AHA guidelines as reference, and found that although 94% of the patients required a high-intensity statin therapy (atorvastatin at 40/80 mg or rosuvastatin at 20/40 mg), only 35.4% of patients actually received it, and from these, only 10.7% reached the expected goal of 50% reduction LDL-c.[9]

Our results are comparable to those reported in a study conducted in Mexico, which showed that therapeutic

Table 2 - Distribution of pharmacological therapy for dyslipidemia in Ecuadorian patients at very high cardiovascular risk (n = 253)

	10 mg	20 mg	40 mg	80 mg
Atorvastatin (n = 132)	2 (0.8%)	23 (9.1%)	78 (30.8%)	29 (11.5%)
Simvastatin (n = 92)	2 (0.8%)	47 (18.6%)	39 (15.4%)	4 (1.6%)
Rosuvastatin (n = 29)	9 (3.5%)	8 (3.2%)	12 (4.7%)	--
	100 mg	**160 mg**	**300 mg**	**600 mg**
Gemfibrozil (n = 26)	--	--	1 (1.9%)	25 (46.3%)
Fenofibrate (n = 28)	1 (1.9%)	2 (3.7%)	2 (3.7%)	23 (42.6%)
	10 mg			
Ezetimibe (n = 6)	6 (75.0%)			
Ezetimibe 10 mg + simvastatin (n = 2)	2 (25.0%)			

goals were attained by 29% of subjects taking initial dose of statin therapy and and after statin dosage adjustment 42% of the subjects reach the goal at the end of the study. ATPIII therapy goals were better attained in groups at a lower risk.[11]

As we described in the preliminary analysis of the results, previously published by our group,[12] physicians are probably not evaluating the total lipid profile when selecting and monitoring the therapy. Evidence of this is: a) nearly half of the subjects had a total cholesterol reduction and showed a 60% reduction in triglycerides; b) all three parameters (total-c, LDL-c and triglycerides) were reduced in almost 43% of the subjects; and c) 70% of the study population had mixed hyperlipidemia.

In this sense, although it may be appropriate to adhere to treatment guidelines that recommend addressing LDL-C levels as the first step, it is important to deeper evaluate and treat these patients.[13]

Adherence to treatment is an important factor that affects the success of reaching the proposed target and is highly dependent on educational and motivational interventions.[14] Previous studies on adherence to statin treatment showed that in longer periods of time (6 months), around 50-60% patients continue on treatment.[15,16] Treatment adherence was not considered in the present study, but we previously reported that one out of four patients (25%) stated to have forgotten at least one dose of their treatment, regardless of disease and duration of treatment.[17]

Although the retrospective design of the study and the lack of a stratified sampling constitute limitations to the analysis of the results, we conclude that there is a very low rate of ATP III therapy goal achievement among patients with dyslipidemia categorized as high and very high cardiovascular risk, independently of the treatment option or its duration. This can be attributed to the prescription of low doses of statins and to potential confounders like the simplistic evaluation of isolated lipid fractions rather than the complete lipid profile.

Author contributions

Conception and design of the research: Hernández I, Estrella A, Salazar J, Duarte Y, Torres E, López C, Terán S, Mendoza A, Terán E. Acquisition of data: Salazar J, Duarte Y, Torres E, López C, Terán S, Mendoza A. Analysis and interpretation of the data: Hernández I, Estrella A, Salazar J, Duarte Y, Torres E, López C, Terán S, Terán E. Statistical analysis: Terán S, Mendoza A, Terán E. Obtaining financing: Estrella A. Writing of the manuscript: Hernández I, Estrella A, Terán E. Critical revision of the manuscript for intellectual content: Hernández I, Estrella A, Salazar J, Duarte Y, Torres E, López C, Terán S, Mendoza A, Terán E.

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 USFQ under the protocol number 2015-044IN. 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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EDITORIAL

Are we Improving Adherence to Cardiovascular Guidelines?

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Editorial related to the article: Treatment Eligibility and Therapeutic Responses of an Ecuadorian Population at High Cardiovascular Risk Based on the ATP III Guidelines

Chronic noncommunicable diseases (NCDs) comprise the world's leading group of causes of death, accounting for premature deaths, loss of quality of life, and adverse economic and social impacts. They represent about 70% of global deaths, close to 38 million deaths annually, significantly exceeding deaths from external causes and infectious diseases, such as COVID-19. Almost 45% of the deaths, more than 17 million, occur as a result of cardiovascular disease (CVD).[1] The same happens in Brazil, where 72% of the deaths are due to NCDs, and about 30%, to CVD.[1]

Dyslipidemia is a significant risk factor for CVD, particularly coronary artery disease (CAD) and stroke. Prospective and long-term epidemiological studies have shown that individuals with healthier lifestyles and fewer risk factors for CAD could improve their life expectancy by decreasing cardiovascular morbidity and mortality.[2] The Framingham Offspring Study, which followed 3501 participants from 1987 to 2011, has demonstrated that low levels of high-density lipoprotein (HDL) or high levels of low-density lipoprotein (LDL) and triglycerides, alone or in any combination, are associated with increased risk for CVDs.[3] Therefore, intervention measures are necessary to reduce morbidity and mortality, as well as the cost of hospitalization due to those diseases. In addition, improving the quality of life and health of the population is essential.

Lifestyle changes, such as the adoption of a healthy diet and physical activity, can favorably affect plasma lipid concentrations. However, many patients need medication to achieve their therapeutic goals.[2] In recent years, lipid-lowering therapy, in particular statins, has been one of the most used interventions for primary and secondary prevention of atherosclerotic cardiovascular diseases, since studies have shown their efficacy in reducing both future events and CVD mortality.[4,5]

In this sense, to identify individuals at risk for CVD, guidelines have been developed, recommending the use of lipid-lowering therapy for the prevention/treatment of those diseases. The National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) used the Framingham score to assess the risk of CAD for ten years. The NCEP-ATP III classified individuals into three categories, high risk (> 20%), moderate risk (10-20%) and low risk (<10%), suggesting the use of lipid-lowering therapy to reduce LDL (<100 mg/dl) in patients at high risk for CAD, whose LDL concentrations are ≥130 mg/dl. The HDL targets were considered secondary objectives in patients with high levels of triglycerides (> 200 mg/dl).[6]

An observational and retrospective study, evaluating the adherence of internal medicine residents in Worcester, Massachusetts, to the NCEP-ATP III guidelines for the treatment of patients with dyslipidemia, has shown better adherence to drug therapy (44% - 77%) and changes in lifestyle (44% - 83%) as compared to the recommendations for follow-up (22% - 31%), evidencing the difficulties of adherence over time.[7]

The American College of Cardiology (ACC) and the American Heart Association (AHA) developed in 2013 a guideline on cardiovascular risk assessment and hypercholesterolemia management. The guideline established new perspectives on LDL treatment goals, using a new tool to assess cardiovascular risk, the pooled cohort equations (PCE). The guideline suggested the use of statin to individuals aged 40 to 75 years, without

Keywords

Cardiovascular Diseases/complications, Mortality; Cardiovascular Diseases/prevention and control; COVID-19; Dyslipidemias; Triglycerides; Life Style; Tabagism; Hydroxymethylglutaryl-CoA Reductase Inhibition/therapeutic use; Patient Compliance.

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a diagnosis of clinical atherosclerotic cardiovascular disease or diabetes mellitus, with LDL-c between 70 mg/dl and 189 mg/dl and cardiovascular risk by PCE ≥ 7.5% in 10 years.[8] In 2018, a new AHA/ACC cholesterol guideline was published, proposing the categorization of cardiovascular risk and recommending the start of statin therapy for individuals at intermediate or high risk and considering those at borderline risk in certain circumstances. The use of ezetimibe and PCSK9 inhibitors was also suggested for those with severe primary hypercholesterolemia.[9]

In the current edition of the *International Journal of Cardiovascular Sciences*, Hernandez et al.,[10] have analyzed lipid-lowering regimens in Ecuadorian patients to assess whether the therapy targets of the NCEP-ATP III guidelines were achieved. Those authors carried out a retrospective analysis with 385 patients (46% men; mean age, 59.8 ± 13.2 years). They observed that 68% of the patients had a very high risk for CAD, and most of them (n=253; 95,8%) were on atorvastatin (50%), simvastatin (34,8%), and rosuvastatin (11%). Regarding the targets of the NCEP-ATP III guidelines, the authors observed that only 24 individuals (19%) with high cardiovascular risk reached LDL-c <100 mg/dl, while 30 individuals (11%) with very high risk reached LDL-c <70 mg/dl. The results were also analyzed based on the 2013 ACC/AHA guidelines, and only 10.7% of the patients receiving high-intensity statins reached the target of a 50% reduction in LDL cholesterol.

Few studies have described the impact of guidelines on clinical practice. Yu et al.,[11] have assessed the achievement of statin-use goals, as well as LDL-c levels before and after the 2013 ACC/AHA guidelines in 1938 patients with CAD. Those authors have reported that the proportion of patients achieving LDL-c goals ranged from 51% to 56% for the 70-mg/dl target and from 77% to 85% for the 100-mg/dl target, remaining unchanged in the comparison cohorts.[10]

The authors have attributed those results to the prescription of low doses of drugs and to therapies aimed at isolated lipid fractions. Other factors, however, must be considered, such as the knowledge of healthcare professionals about the guidelines and adherence to the treatment proposed, which includes both drug therapy and changes in lifestyle.

In this sense, the guidelines are consistent in recommending to all individuals, regardless of their level of risk, changes in lifestyle, such as the following: adoption of a healthy eating pattern, which emphasizes the intake of fruits, vegetables, whole grains and healthy sources of protein, and limits the consumption of ultra-processed foods; maintenance of body weight; regular physical exercise; and smoking cessation. Those measures are the basis of any intervention to reduce the risk of CVD.[6,8,9,11]

Considering the multifactorial nature of CVDs, it is necessary to implement a multidisciplinary approach to the set of risk factors responsible for their occurrence, morbidity, and mortality, with guidelines that contemplate these premises. This relates directly to the success of the proposed recommendations. Thus, the successful treatment of dyslipidemias will not only depend on the degree of cardiovascular risk and lipid profile, as assessed by the authors. It also depends on interventions that promote greater knowledge about the recommendations among all involved with the care, as well as on a more comprehensive scope of non-pharmacological population measures, which will have direct implications for cardiovascular outcome.[12,13]

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ORIGINAL ARTICLE

Performance of a Hematological Scoring System in Predicting All-Cause Mortality in Patients with Acute Myocardial Infarction

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Abstract

Background: The presence of nucleated red blood cells (NRBCs) and increases in mean platelet volume (MPV) and neutrophil to lymphocyte ratio (NLR) in peripheral circulation are associated with poorer prognosis in patients with acute coronary disease.

Objective: We developed a scoring system for in-hospital surveillance of all-cause mortality using hematological laboratory parameters in patients with acute myocardial infarction (AMI).

Methods: Patients admitted for AMI were recruited in this prospective study. Exclusion criteria were age younger than 18 years, glucocorticoid therapy, cancer or hematological diseases and readmissions. NRBCs, MPV and NLR were measured during hospitalization. The scoring system was developed in three steps: first, the magnitude of the association of clinical and laboratory parameters with in-hospital mortality was measured by odds ratio (OR), second, a multivariate logistic regression model was conducted with all variables significantly ($p < 0.05$) associated with the outcome, and third, a β-coefficient was estimated by multivariate logistic regression with hematological parameters with a $p < 0.05$.

Results: A total of 466 patients (mean age were 64.2 ± 12.8 years, 61.6% male) were included in this study. A hematological scoring system ranging from 0 to 49, where higher values were associated with higher risk of in-hospital death. The best performance was registered for a cut-off value of 26 with sensitivity of 89.1% and specificity of 67.2%, positive predictive value of 26.8% (95% CI: 0.204 – 0.332) and negative predictive value of 97.9% (95% CI: 0.962 – 0.996). The area under the curve for the scoring system was 0.868 (95% CI: 0.818 – 0.918).

Conclusions: Here we propose a hematological scoring system for surveillance tool during hospitalization of patients with acute myocardial infarction. Based on total blood count parameters, the instrument can evaluate inflammation and hypoxemia due to in-hospital complications and, consequently, predict in-hospital mortality. (Int J Cardiovasc Sci. 2020; 33(4):380-388)

Keywords: Myocardial Infarction; Coronary Artery Diseases; Severity of Illness Index; Mortality; Scoring System; Nucleated Red Blood Cells; Mean Platelet Volume; Neutrophil to Lymphocyte Ratio.

Introduction

Acute myocardial infarction (AMI) is the main cause of death in the world and the prevalence is rising in developing countries.[1] According to previous studies, the mortality has been declining in higher-income countries, and it has generally been attributed to greater use of preventive measures, adherence to current guidelines and revascularization procedures.[1,2] A recent paper, published by our research group, showed that the

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presence of nucleated red blood cells (NRBCs), and increases in the neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) in peripheral blood of patients hospitalized with AMI are associated with a poorer prognosis.[3]

The bone marrow is responsible for producing blood cells (red blood cells, leucocytes and platelets), by a process called hematopoiesis, which originates from a single progenitor cell called the stem cell. Pluripotent stem cells, existing in small amounts in the bone marrow, can reproduce when necessary and lead to differentiation processes in different hematological cell lines.[4] Growth inducers promote multiplication but not differentiation of the stem cells. This is the function of another group of proteins, called differentiation inducers, which are controlled by factors external to the bone marrow. For example, in case of red blood cells, exposure to low oxygen concentrations over a long period results in the induction of growth, differentiation and increased production of red blood cells. This stimulus to the bone marrow is produced by erythropoietin, a glycoprotein primarily (90%) produced in the kidneys, but also in the liver, in response to hypoxemia. Prior studies have shown that severe hypoxemia and infection are the main cause of synthesis of NRBCs, and increases in NLR and MPV in peripheral blood, when hematological diseases, cancer, congestive heart failure, acute and chronic anemias are excluded.[5-13]

The aim of this study was to propose a scoring system for these hematological variables. Actual and reproductive variability of these hematological biomarkers during hospitalization of these patients could be a predictor of all-cause mortality and help the medical team in diagnostic and therapeutic decision.

Materials and methods

Ethics Statement

This study is part of the project (Neutrophil to Lymphocyte Ratio, Mean Platelet Volume and Erythroblast as prognostic biomarkers in patients with AMI) approved by the Ethics Committee of the Hospital Complex HUOC/PROCAPE of the University of Pernambuco under number CAAE: 51802115.7.0000.5192 (Brazil Platform). The research was conducted according to the principles of the Declaration of Helsinki.

Study Design

The present study proposes a scoring system based on β-coefficient values estimated by multivariate logistic regression model adjusted for NRBC, MPV and NLR in patients hospitalized with AMI. In logistic model, these coefficients are obtained using the method of maximum likelihood and they represent the probabilistic change in one variable when all others are fixed. The coefficient β of each variable was multiplied by 10 to optimize the rounding. Subsequently, accuracy parameters were calculated.

All patients included in the study were followed up by researchers from hospital admission to discharge. Management of these patients was established based on well-defined protocols for primary angioplasty, myocardial revascularization surgery or clinical treatment. Data on clinical course and laboratory tests of the patients were obtained daily from electronic medical records by the authors of the study.

Study Population

All consecutive patients admitted with AMI to PROCAPE, a tertiary teaching hospital with 250 beds, referral for emergency cardiac care, between January 1, 2016 and September 30, 2016 were included. We excluded patients younger than 18 years, on glucocorticoid therapy, patients with cancer or hematological diseases, and those readmitted after hospital discharge. All patients signed an informed consent form to participate in the study.

Definition of terms and study variables

The diagnosis of AMI was established based on clinical, electrocardiographic and laboratory (troponin) criteria.[2,3] As for electrocardiography, myocardial infarction can be divided into ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (non-STEMI).[2,3] With respect to the KILLIP and TIMI Risk scores, patients were classified into low risk (KILLIP I to II and TIMI Risk 0 to 3) and high risk (KILLIP III to IV and TIMI Risk 4 to 7). Potential risk factors associated with AMI such as demographic characteristics (age, gender), systemic arterial hypertension (blood pressure ≥ 140 x 90 mmHg), diabetes mellitus (plasma glucose above 126 mg/dL), smoking habit (yes or no), sedentary lifestyle (regular practice of physical exercise or not), kidney disease (creatinine above 1.3 mg/dL) and

depression (use of medicine or not) were adjusted for the statistical model.[3]

For patients' stratification according to the Killip classification, the following categories were used: I – normal, II – heart failure, III - acute lung edema, IV – cardiogenic shock.[14] The TIMI Risk score to non-STEMI is based on 7 variables – age ≥ 65 years, ≥ 3 risk factors for coronary artery disease, previous cardiac catheterization (stenosis > 50%), electrocardiography (ST-segment depression ≥ 0.5 mm), anginal symptoms, use of acetylsalicylic acid (ASA) in the last 7 days, and elevated troponin levels.[15]

Complete blood count parameters including NRBCs, leukocytes, neutrophils, lymphocyte, platelet, MPV were measured using a Sysmex XE-2100 blood analyzer (Sysmex, Kobe, Japan). A positive NRBC was defined as any value above zero; cut-off level for high MPV was ≥ 10.4 fL, and NRL was calculate by dividing the neutrophil count by the lymphocyte count, with a high cut-off level of ≥ 3.7, as previously described.[5-7] Blood samples were collected between 24 and 48 hours after admission.

Statistical analysis

The scoring system was developed in three steps (Figure 1). Multiple linear and multivariate logistic analysis of hematological variables and cardiovascular risk factors were used to identify independent predictors of mortality. In the first step, the magnitude of association of clinical and laboratory parameters with in-hospital mortality were measured by odds ratio (OR), whose statistical significance was estimated by likelihood ratio (Pearson chi-squared test) and represented by p-value. In the second step, the multivariate logistic regression model was conducted with all variables with a p value < 0.05 and the outcomes remained in the model. In the third step, another adjusted logistic regression was calculated, with hematological parameters with $p < 0.05$ and a coefficient β (strength of association between variables). A score was attributed to each variable, which was the coefficient β of each variable multiplied by 10, for the sake of rounding off. To analyze the accuracy of the scoring system, a receiver operating characteristic (ROC) curve was constructed, and sensitivity, specificity, positive and negative predictive values, positive (LR+) and negative (LR-) likelihood ratios, with their respective confidence intervals, were calculated.

Continuous variables were expressed as mean ± standard deviation (normal distribution) or median (without normal distribution) and categorical variables were expressed as absolute or percent values, as appropriate. The association of higher levels of NRBC, MPV and NLR with clinical and laboratory characteristics of the patients were assessed using Pearson Chi-squared test or Mann-Whitney U test. Regression analysis was performed for the variables identified as statistically significant in univariate analysis. The abilities of NRBC, MPV and NLR to distinguish patients with AMI from low or high risk of in-hospital death were evaluated using ROC curve analysis. The overall agreement between the hematological scoring system and Killip / TIMI Risk scores was assessed using Kappa coefficient. Statistical analyses were conducted using the Statistical Program for Social Sciences (SPSS), version 10.0 for Windows.

Results

A total of 466 patients (mean age 64.2 ± 12.8 years, 61.6% male) were included in this study. Total mortality was 11.8% (55 patients): 43/326 (13.2%) STEMI and 12/140 (8.6%) non-STEMI. Clinical characteristics related to in-hospital mortality among patients with AMI are described in Table 1.

The presence of NRBCs in the sample was detected in 9.1% (42 patients), 27 (5.8%) with levels > 200/μL. Mean MPV value was 10.9 ± 0.9 fL and the mean NLR value was 3.71 (2.38; 5.72). The association of in-hospital mortality with the presence of NRBCs and increases in MPV and NLR in peripheral blood is shown in Table 1. We used the univariate model to assess which clinical and laboratory factors were associated with in-hospital mortality among patients with AMI (Table 1).

To identify independent predictor variables associated with in-hospital mortality, we performed a multivariate analysis model (Table 2). After adjustment, the points assigned to each hematological variable of the scoring system proposed and respective coefficients β are detailed in Table 3. The hematological scoring system proposed had a scale ranging from 0 to 49, where higher values were associated with higher risk of in-hospital death. The better performance was registered for a cut-off value of 26 with sensitivity of 89.1% and specificity of 67.2%, positive predictive value of 26.8% (95% CI: 0.204 – 0.332) and negative predictive value of 97.9% (95% CI: 0.962 – 0.996) (Table 4). The area under the curve for the scoring system was 0.868 (95% CI: 0.818 – 0.918) (Figure 2). A score ≥ 26 points in the scoring system proposed showed an agreement of 82.1% with

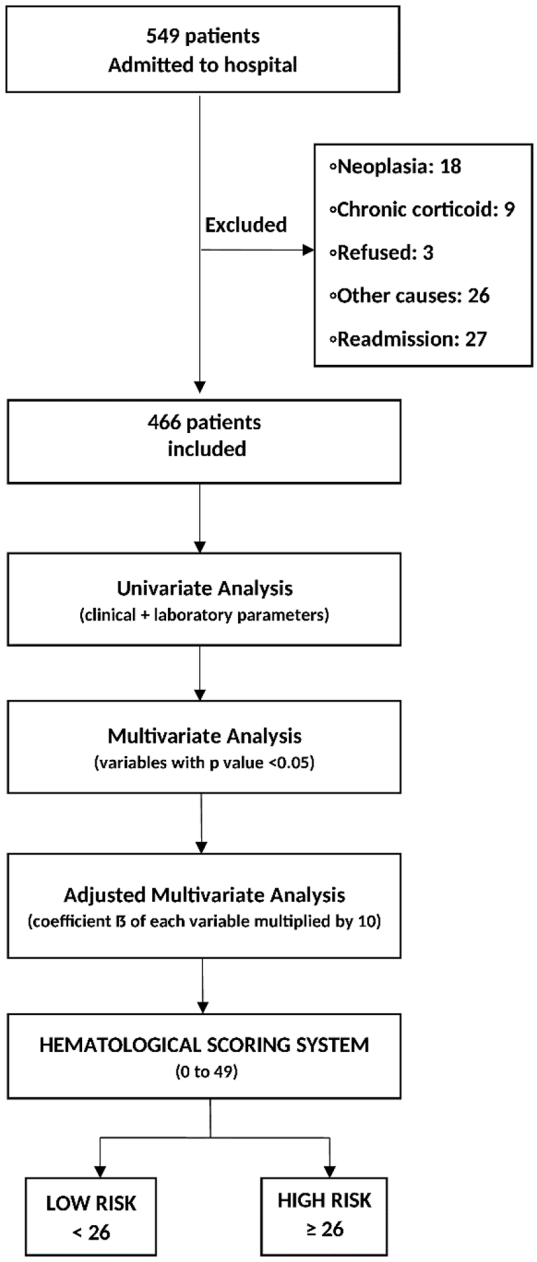

Figure 1 - Algorithm of the selection of the study population and development of the hematological scoring system.

KILLIP score III and IV (kappa coefficient = 0.141; 61.5% overall agreement) (Table 5) and a score < 26 showed an agreement of 81% with TIMI Risk score 0 to 3 (kappa coefficient = 0.162; 50.7% overall agreement) (Table 6).

Discussion

NRBCs, MPV, and NLR are independent predictors of all-cause mortality in AMI patients.[3] These hematological parameters are directly associated with severity of systemic inflammation and hypoxemia, and these two mechanisms are directly implicated in the pathophysiology of organic dysfunction. An intense inflammatory response is activated in the early step of cardiac ischemic injury. However, other conditions including sepsis and shock may occur during hospitalization. In this study, we propose a scoring system with these hematological parameters

Table 1 - Clinical and laboratory characteristics related to in-hospital mortality among patients with acute myocardial infarction by logistic regression

Factors	OR	CI (95%)	p-value
Age[a]			
< 65 years	1.0	-	-
≥ 65 years	3.58	1.89 - 6.77	< 0.001
Sex[a]			
Female	1.0	-	-
Male	1.01	0.57 - 1.80	0.970
Skin color[a]			
White	1.0	-	-
Brown	0.80	0.43 - 1.50	0.485
Black	0.44	0.17 - 1.15	0.094
Classification of AMI			
Non-STEMI	1.0	-	-
STEMI	1.62	0.83 - 3.18	0.160
Risk factors			
Systemic arterial hypertension	1.88	0.92 - 3.84	0.085
Diabetes mellitus	1.75	0.99 - 3.08	0.053
Kidney disease	1.15	0.43 - 3.07	0.787
Family history of coronary heart disease	0.27	0.14 - 0.55	< 0.001
Dyslipidemia	0.76	0.42 - 1.39	0.375
Depression	0.14	0.02 - 1.01	0.051
Smoking	0.78	0.43 - 1.39	0.400
Sedentary lifestyle	1.47	0.83 - 2.59	0.187
Laboratory measures			
Erythrocyte[b]	0.18	0.11 - 0.32	< 0.001
Hemoglobin[b]	0.65	0.55 - 0.76	< 0.001
Leukocytes[c]			
≤ 10,5	1.0	-	-
> 10.5	5.52	2.71 - 11.3	< 0.001
CRP[c]			
≤ 36,7	1.0	-	-
> 36.7	7.98	3.44 - 18.5	< 0.001
IG%[c]			
≤ 0.3	1.0	-	-
> 0.3	11.7	4.88 - 27.9	< 0.001
TNT[c]			
≤ 1.87	1.0	-	-
> 1.87	2.23	1.23 - 4.05	0.008
RDW SD[c]			
≤ 43.2	1.0	-	-
> 43.2	4.34	2.22 - 8.48	< 0.001
RDW CV[c]			
≤ 13.5	1.0	-	-
≥ 13.5	4.22	2.16 - 8.23	< 0.001
NLR			
< 3.7	1.0	-	-
≥ 3.7	16.0	5.67 - 45.0	< 0.001
NRBC			
Absence (0)	1.0	-	-
Presence (≥ 1)	33.9	15.8 - 72.8	< 0.001
MPV			
< 10,4	1.0	-	-
≥ 10.4	3.32	1.46 - 7.55	0.004

[a] per 100 person-day of hospitalization; [b] Decreased risk with the increase of one unit of the laboratory marker; [c] Risk for values above the median; OR: Odds Ratio; CI: confidence interval; CRP: c-reactive protein; IG: immature granulocyte; TNT: troponin T; RDW SD: red cell distribution width measured as standard deviation; RDW CV: red blood cell distribution width as coefficient of variation; NLR: neutrophil to lymphocyte ratio; NRBC: nucleated red blood cell; MPV: mean platelet volume.

to be used for clinical surveillance during patients' hospitalization.

In the last five decades, due to scientific advances and the advent of automated counting of peripheral blood cells in a safe and reliable way, the complete blood cell count has become an important clinical tool to detect variations in hematopoietic response to existing injury. Thus, these variables reflect not only ischemia and its hemodynamic repercussions, but also inflammatory processes (infectious or not) during hospitalization that may contribute to increased mortality of AMI patients, thereby complementing the risk stratification scores currently used in the clinical practice.

In the present study, we demonstrated that the presence of NRBCs (OR 33.9, 95% CI: 15.8 - 72.8, p < 0.001), increases in MPV (OR 3.32, 95% CI: 1.46 - 7.55, p = 0.004) and NLR (OR 16.0, 95% CI: 5.67 - 45.0, p < 0.001) in peripheral blood was associated

Table 2 - Multivariate analysis of factors related to in-hospital mortality among patients with acute myocardial infarction by logistic regression

Factors	OR	CI (95%)	p-value	Adjusted OR	CI (95%)	p-value
Age						
< 65 years	1.0	-	-	1.0	-	-
≥ 65 years	3.58	1.89 - 6.77	< 0.001	2.94	1.25 - 6.96	0.014
Erythrocytes[a]	0.18	0.11 - 0.32	< 0.001	0.36	0.17 - 0.76	0.006
Leukocytes[b]						
≤ 10.5	1.0	-		1.0	-	-
> 10.5	5.52	2.71 - 11.3	< 0.001	3.83	1.48 - 9.91	0.006
Platelet[b]						
≤ 231	1.0	-		1.0	-	-
> 231	9.44	2.94 - 30.3	< 0.001	9.02	1.71 - 47.4	0.009
NLR						
< 3.7	1.0	-	-	1.0	-	-
≥ 3.7	16.0	5.67 - 45.0	< 0.001	4.28	1.30 - 14.1	0.017
NRBC						
Absence (0)	1.0	-		1.0	-	-
Presence(> 1)	33.9	15.8 - 72.8	<0.001	10.1	4.06 - 24.9	< 0.001
MPV						
< 10.4	1.0	-		1.0	-	-
≥ 10.4	3.32	1.46 - 7.55	0.004	2.99	1.05 - 8.55	0.041

[a] Decreased risk with the increase of one unit of the laboratory marker; [b] Risk for values above the median; OR: Odds Ratio; CI: confidence interval; NLR: neutrophil to lymphocyte ratio; NRBC: nucleated red blood cell; MPV: mean platelet volume.

Table 3 - In-hospital mortality score among patients with acute myocardial infarction by logistic regression

Factors	Adjusted OR	CI (95%)	p-value	Coefficient β of logistic regression	Score* (β x 10)
NLR					
< 3.7	1.0	-	-		0
≥ 3.7	4.28	1.30 - 14.1	0.017	1.455	15
NRBC					
Absence (0)	1.0	-	-		0
Presence (> 1)	10.1	4.06 - 24.9	< 0.001	2.308	23
MPV					
< 10,4	1.0	-	-	-	0
≥ 10.4	2.99	1.05 - 8.55	0.041	1.095	11

** Variation of points from 0 to 49 points; * The higher the score, the higher the risk of intrahospital death; OR: Odds Ratio; CI: confidence interval; NLR: neutrophil to lymphocyte ratio; NRBC: nucleated red blood cell; MPV: mean platelet volume.*

with poorer prognosis. The scoring system with these three variables, after adjusted multivariate analysis and a cut-off of 26 points, showed a sensitivity of 89.1%, specificity of 67.2%, negative predictive value of 97.9% and positive predictive value of 26.8%. Thus, with these cut-off points on a scale of 0 to 49 points, patients can be categorized into two groups: low and high risk of death, with an accuracy of 86.8% (area under the ROC curve). The main purpose of this hematological scoring system is to promote better clinical surveillance during hospitalization based on these laboratory variables. In addition, results of the score showed an agreement with patients' clinical data, as the lower risk in-hospital mortality was associated with lower score values. This hematological scoring system had a negative predictive value of 97.9%.

Table 4 - Sensitivity, specificity, positive predictive value and negative predictive value of the scoring system proposed using a cut-off of 26

Proposed scale of points	In-hospital Mortality	
	Yes	No
≥ 26 points	49	134
< 26 points	6	274
Validation measures	**Percentage value**	**CI (95%)**
Sensitivity	89.1%	0.809 – 0.973
Specificity	67.2%	0.626 – 0.717
Positive predictive value	26.8%	0.204 – 0.332
Negative predictive value	97.9%	0.962 – 0.996
C Statistic	86.8%	0.818 – 0.918

CI: confidence interval.

Table 5 - Relationship between the hematological scoring system and the KILLIP score in predicting mortality among patients with into ST-segment elevation myocardial infarction

Scale of points	KILLIP		Total
	I and II	III and IV	
≥ 26 points	120 (40.3%)	23 (82.1%)	143
< 26 points	178 (59.7%)	5 (17.9%)	183
Total	298	28	326

Kappa coefficient = 0.141 (61.5% overall agreement).

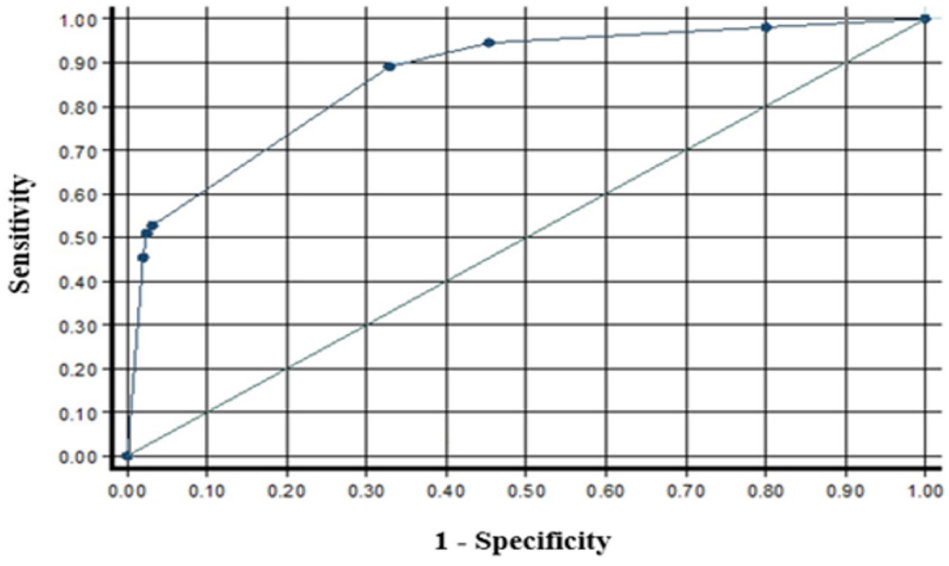

Figure 2 - ROC curve for the scoring system in predicting mortality. Area under the ROC curve = 0.868 (95% CI 0.818 - 0.918).

Table 6 - Relationship between the hematological scoring system and the TIMI RISK score in predicting mortality among patients with non-ST-segment elevation myocardial infarction

Scale of points	TIMI RISK		Total
	0 to 3	4 to 7	
≥ 26 points	8 (19.0 %)	35 (35.7%)	43
< 26 points	34 (81.0 %)	63 (64.3%)	97
Total	42	98	140

Kappa coefficient = 0.162 (50.7% overall agreement).

Patients with non-STEMI and STEMI were also classified as low risk (TIMI RISK 0 to 3 and Killip I and II) and high risk (TIMI RISK 4 to 7 and Killip III and IV), respectively, which facilitated the comparison with the hematological scoring system. In our sample, 70% of the patients had STEMI and 82.1% of these at high risk of mortality (Killip III and IV) had a score ≥ 26 points in the scoring system proposed. Also, 81% of the patients with non-STEMI at low risk of mortality (TIMI RISK 0 to 3) had a score < 26 points in the scoring system. Therefore, this new hematological scoring system could complement these extensively used risk scores in AMI patients. As mentioned before, the main purpose of this hematological scoring system is to improve clinical surveillance during hospitalization based on these laboratory variables, which would be of help in therapeutic decision making.

This hematological scoring system is dynamic, and changes in the risk profile may reflect the response to a treatment proposed. In this study, the instrument showed an 89.1% probability of identifying the outcome among those who died in this population. However, the hematological scoring system had a low positive predictive value (26.8%), probably due to the effective treatment employed. In this sample, 70% of these patients had STEMI and of these 43.9% had ≥ 26 points in the scoring system, and 30.7% of patients with non-STEMI had ≥ 26 points in the scoring system. In the present study, total mortality was 11.8% (55 patients): 43/326 (13.2%) STEMI and 12/140 (8.6%) non-STEMI.

Few studies have evaluated the performance of a scoring system including laboratory variables as a prognostic marker in AMI. Yanishi et al.,[16] developed a simple stratification model using white blood cell count, hemoglobin, C-reactive protein, creatinine and blood sugar levels for predicting in-hospital mortality in STEMI (ROC curve of the derivation and validation in laboratory model of 0.81 and 0.74 respectively, $p < 0.01$). A recent study by Ibrahim et al.,[17] proposed a scoring system using clinical variables (male sex and previous percutaneous coronary intervention) and four biomarkers (midkine, adiponectin, apolipoprotein C-I, and kidney injury molecule-1) to predict with high accuracy the presence of obstructive coronary artery disease and mortality. In this study, elevated scores were predictive of ≥ 70% stenosis in all subjects (OR: 9.74; $p < 0.01$). At optimal cut-off, the score had 77% sensitivity, 84% specificity, and a positive predictive value of 90% for ≥ 70% stenosis. In another recent publication, Gerber et al.,[18] demonstrated the importance of risk stratification for informed decision in clinical care.

The present study has some limitations. First, patients were selected in a single center. Second, heparin could inhibit platelet aggregation, but not platelet size. However, we increased the sample size, and used standardized and predetermined protocol to minimize possible bias.

Conclusions

The proposed hematological scoring system is a surveillance tool based on laboratory data, shown to be associated with in-hospital mortality in AMI patients. This simple and low-cost tool can be used to assess inflammation and hypoxemia caused by in-hospital complications using complete blood count parameters measured by an automated method. In addition, the scoring system is easy to use and interpret by all the multidisciplinary team members and can be calculated in the laboratory.

Further studies would help to confirm the usefulness and importance of this scoring system based on hematological laboratory parameters for clinical surveillance of inpatients with AMI.

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Author contributions

Conception and design of the research: Monteiro Júnior JGM, Torres DOC Silva MCFC. Acquisition of

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REVIEW ARTICLE

The Role of ^{18}F-FDG PET/CT in Cardiac Sarcoidosis

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Cardiac sarcoidosis (CS) is a rare and potentially fatal condition, characterized by the presence of non-necrotizing granulomatous inflammation and concomitant fibrosis. A variety of clinical manifestation has been described, such as conduction disorders, ventricular arrythmias, congestive heart failure and sudden cardiac death, making a prompt diagnosis and early treatment desirable. Endomyocardial biopsy is the gold-standard diagnostic test, but has a low sensitivity due to the multifocal aspect of the disease. Advanced imaging modalities, such as cardiac magnetic resonance and positron emission tomography (PET) with 18F-fluorodeoxyglucose are now part of the diagnostic criteria and also assist in determining treatment response. However, the interpretation of those studies can be challenging and needs to be made by specialists, as the misdiagnosis could be harmful for the patient. This article describes the pathophysiology of CS and advanced imaging modalities (with a major focus on PET) that should be considered for diagnostic approach and therapy monitoring. Also, newer clinical trials evaluating treatment strategies are described.

Introduction

Systemic sarcoidosis (SS) was first described more than a century ago by the Norwegian dermatologist Caesar Boeck. He correlated skin nodules with epithelioid cells with large nuclei and giant cells as "multiple benign sarcoid of the skin", for their resemblance with sarcoma.[1] Today, the cause of the disease remains unknown, but evidence points toward immunological response to an unidentified antigenic trigger in individuals with genetic susceptibility.[2] The estimation of the prevalence of SS in the population varies in the literature also depending on the type of study: epidemiologic, autopsy or imaging.

Some previous data showed prevalence as high as 100-330 cases per 100,000 inhabitants.[3,4] Environmental factors have been attributed to those differences, including sex, age and ethnicity,[5] showing a predisposition for environmental and genetic factors. The reported incidence is similar across sex in North American population but greater in females in Scandinavian and Japanese populations,[6,7] but more likely to be chronic and fatal in black Americans.[8] The disease usually develops before the age of 50 years, with a peak incidence at 20 to 39 years old,[9,10] and is very uncommon under the age or 15 or older than 70.[2] Symptomatic cardiac sarcoidosis (CS) has been reported in 2-5% of the patients with the systemic form.[11-13] However, with the advance of new cardiac imaging techniques, cases of asymptomatic (clinically silent) cardiac involvement have been diagnosed.[14] The disease has been reported in at least 20% of the autopsies and imaging report in the United States to as much as 50% in Japan.[7,15]

Keywords

Cardiomyopathies; Sarcoidosis; Heart Failure; Metabolism Disorders; Sudden Cardiac Death; Diagnostic, Imaging; Magnetic Resonance Imaging/diagnostic; Positron Emission Tomography Computed Tomography/diagnostic.

Pathophysiology

The presence of non-necrotizing granulomatous inflammation is the major characteristic of CS and is sometimes associated with fibrosis. Histologic proof of non-necrotizing granuloma differentiates CS from

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lymphocytic or viral myocarditis and from tuberculosis with necrotizing granulomas. Although frequent in the lungs, sarcoidosis may affect any organ. In addition, any part of the heart can be involved, particularly the basal septum, the lateral wall, the papillary muscle and the right ventricle. In an autopsy study of post-mortem diagnosis of CS, the scar was more frequently located in the interventricular septum, posterior left ventricle, right and anterior left ventricle and lateral left ventricle (in descending order of frequency).[16] Although a positive endomyocardial biopsy (EMB) is definitive for the diagnosis of CS, its sensitivity is around 30% due to the patchy involvement of the myocardium.[17]

Clinical features

CS has different types of manifestations, including clinically silent form, sudden cardiac death, conduction disturbances, ventricular arrhythmias and heart failure.[5,18-21] Other rare findings can be pericardial effusion or coronary involvement.[13,22] CS is the most malignant manifestation of sarcoidosis and 25% of the deaths are related to the cardiac form.[5] The extent of left systolic dysfunction has been pointed as the most significant independent predictor of mortality. Patients with severe left ventricular (LV) dysfunction with left ventricular ejection fraction (LVEF)< 30% at the time of presentation had a 10-y survival rate >80% in Japanese studies.[23] Also, the 10-year transplantation-free cardiac survival was 83% in a large population-based cohort.[6]

Diagnosis

The diagnosis of sarcoidosis requires three elements: 1) compatible clinical and radiographic manifestations; 2) exclusion of other diseases that may present similarly and 3) histopathologic detection of noncaseating granulomas. Multiple criteria have been proposed for diagnosing CS but the most commonly used are those by the Japanese Ministry of Health and Welfare (JMHW), revised in 2017[24] and those by the Heart Rhythm Society (HRS) published in 2014[25] (**Tables 1 and 2**). Their basic difference is that the revised 2006 criteria did not mandate positive biopsies (either cardiac or extracardiac) for the clinical diagnosis of CS. Due to its patchy and mid-myocardial involvement, EMB has an elevated number of false-negative and there is an ongoing debate whether positive histology is required for the diagnosis.[26] New imaging techniques – positron emission tomography (PET), cardiac magnetic resonance imaging (MRI), electrocardiography, and electroanatomic voltage mapping – can increase the sensitivity of the EMB.[27] The JMHW defines the presence of myocardial Gallium-67 uptake, a SPECT tracer, as a major criterion, due to its high specificity (despite its low sensitivity). However, this radiotracer causes a high radiation exposure to the patient (high half-life of 78h) and has a lower resolution than the PET. Cardiac MRI, perfusion studies and echocardiography findings are considered minor criteria. Both 18F-fluorodeoxyglucose (18F-FDG) PET and Gallium-67 are diagnostic but have also the potential role for monitoring disease activity and therapy response. The A Case Control Etiology of Sarcoidosis Study (ACCESS) is a sarcoidosis organ assessment instrument that categorizes SS clinical manifestations as: a) highly probable, as at least 90% likelihood of sarcoidosis causing this manifestation; b) probable: 50-90% likelihood of sarcoidosis causing this manifestation of c) possible: <50% of likelihood of sarcoidosis causing this manifestation. This instrument was developed by expert opinion and is useful for clinicians and researchers in establishing criteria for sarcoidosis organ involvement.[28]

Diagnostic imaging tools

Echocardiography

Traditionally, transthoracic echocardiography is the initial imaging modality in patients with suspected CS, as for all types of cardiomyopathy. LV systolic and diastolic function can be easily assessed, as well as LV geometry, volumes, right ventricular (RV) performance and myocardial thinning or thickening. Echocardiography is able to identify some of the CS diagnostic criteria such as depressed LVEF, basal thinning of the interventricular septum and structural or wall motion abnormality. It is important to know that echocardiography is very operator-dependent, and despite a high specificity and a positive predictive value up to 92%,[29] its sensitivity is reduced, and a normal study cannot rule out the presence of CS.

SPECT

SPECT studies with 99m-Tc-perfusion agents or 201-Tl are other diagnostic tools to evaluate the presence of scar at rest, as microvascular compression or fibrogranulomatous replacement of the myocardium

Table 1 – Heart Rhythm Society diagnostic criteria for cardiac sarcoidosis

Histologic diagnosis from myocardial tissue
Noncaseating granuloma on endomyocardial biopsy with no alternative cause identified
Clinical diagnosis
Probable diagnosis of cardia sarcoidosis exists if there is histologic diagnosis of extra-cardiac sarcoidosis and one or more of the following is present:
Cardiomyopathy or atrioventricular block responsive to immunosuppressive treatment Unexplained reduced LVEF (<40%) Unexplained ventricular tachycardia Mobitz II second- or third-degree heart block Patchy ^{18}F-FDG uptake on cardiac PET consistent with cardiac sarcoidosis Late gadolinium enhancement on cardiac MRI consistent with cardiac sarcoidosis Cardiac gallium-67 uptake *and* Exclusion of other causes of cardiac manifestations

LVEF: left ventricular ejection fraction; PET: positron emission tomography; MRI: magnetic resonance imaging. Adapted from Blankstein et al.[58]

Table 2 – 2017 Revised Japanese criteria for cardiac sarcoidosis

1. Major criteria
1. (a) High-grade atrioventricular block (including complete atrioventricular block) or fatal ventricular arrhythmia (e.g., sustained ventricular tachycardia and ventricular fibrillation) 2. (b) Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening) 3. (c) Left ventricular contractile dysfunction (left ventricular ejection fraction less than 50%) 4. (d) Gallium-67 citrate scintigraphy or ^{18}F-FDG PET reveals abnormally high tracer accumulation in the heart 5. (e) Gadolinium-enhanced MRI reveals delayed contrast enhancement of the myocardium
2. Minor criteria
6. (f) Abnormal ECG findings: Ventricular arrhythmias (nonsustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q waves 7. (g) Perfusion defects on myocardial perfusion scintigraphy (SPECT) 8. (h) Endomyocardial biopsy: monocyte infiltration and moderate or severe myocardial interstitial fibrosis

PET: positron emission tomography; MRI: magnetic cardiac imaging; ECG: electrocardiogram; SPECT: single-photon emission computed tomography Adapted from Terasaki F, Yoshinaga K. New guidelines for diagnosis of cardiac sarcoidosis in Japan. Ann Nucl Cardiol. 2017; 3(1):42-45.

can lead to a perfusion defect. Usually, those defects do not follow the typical vascular distribution of coronary disease, unless when very extensive. Another finding described in some rest-stress perfusion studies is the reverse distribution.[30,31] It happens when a perfusion defect at rest improves on stress imaging and it is probably related to a focal reversible microvascular constriction in coronary arterioles around granulomas, however not specific to CS. SPECT imaging can be used together with 18F-FDG PET to evaluate the presence of active inflammation and its relation with scar.

Despite being less sensitive than 18F-FDG PET and exposing the patient to a higher amount of radiation, gallium-67 scintigraphy using both planar imaging and SPECT is still used in CS, especially in areas with limited access to PET equipment. Gallium-67 citrate is produced in a cyclotron and has the advantage of being more available as its longer half-life can

facilitate its distribution to distant services at reduced cost. Granulomas with giant cells are exquisitely avid for this radiotracer uptake (**Figure 1**) and a positive gallium-67 scintigraphy is considered as a major criterion for the diagnosis of CS by the consensus of specialists of the HRS.[25]

MRI

As an advanced cardiac imaging modality, besides giving detailed assessment of biventricular function, CMR has the capacity to detect myocardial edema, perfusion abnormalities and to evaluate the presence and size of scar. The addition of T2 weighted imaging and T2 mapping give CMR the capacity to detect edema and inflammation and some have suggested could be an alternative to 18F-FDG PET(32) (**Figure 2**). The use of gadolinium, an extracellular contrast agent, is recommended to evaluate the presence of myocardial scar as it demonstrates slower washout from areas of fibrosis and inflammation compared to normal myocardium. The pattern of late gadolinium enhancement (LGE) findings follows the same pathophysiological distribution of the areas of fibrosis,[33,34] with sometimes an extension into the RV insertion points.[35] CMR has the capacity to distinguish subcentimeter lesions and to differentiate between subepicardium, midmyocardium and subendocardium, due to its excellent in-plane spatial resolution. This distribution is helpful in recognizing CS, however it is not entirely specific and similar findings can be seen in other pathologies. CS have a tendency to spare the subendocardium, which is a common finding in ischemic cardiomyopathy with prior infarct.[35,36] CMR sensitivity for CS approaches 75-100% and its specificity 76-78%.[33,37] The prognostic capacity of LGE was studied in a previous study that analyzed 155 patients with systemic sarcoidosis who underwent CMR for workup of CS involvement.[12] The median follow-up time was 2.6 years and the primary end-points were death, aborted sudden cardiac death and appropriate implantable cardioverter defibrillator (ICD) discharge. They found the presence of LGE in 25.5% of the patients with a hazard ratio of 31.6 for the primary end-points and 33.9 for any event. Regarding the patients with no LGE, no one had an adverse event (except for one patient who died from pulmonary infection). Those findings suggested that in patients with SS, scar indicated by LGE was the best independent predictor of potentially lethal events, stronger than LVEF and end-diastolic volume with a very high negative predictive value for adverse outcomes, including arrhythmic events. Ise et al.,[38] described in 43 consecutive LGE-positive patients that the presence of large-extent LGE (≥20% of left ventricular mass) correlated with absence of functional LV recovery following steroid therapy and higher risk of cardiac mortality, hospitalization for heart failure and life-threatening arrhythmias.[38]

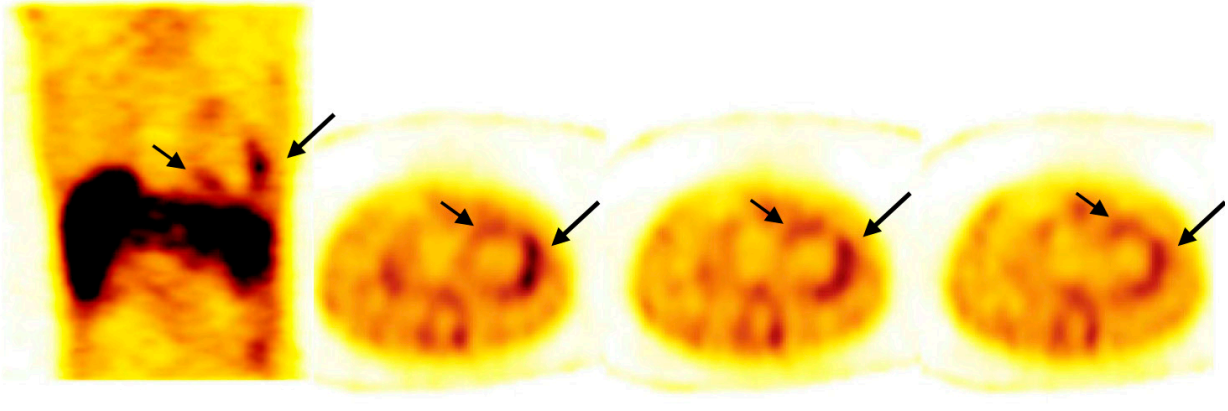


Figure 1 – Gallium-67 SPECT of a 36-year-old female patient with newly-diagnosed left ventricular systolic dysfunction. Coronal and axial sections demonstrate accumulation of the radiotracer in the left ventricular lateral wall (long arrow) and in the interventricular septum (short arrow); endomyocardial biopsy confirmed the presence of granulomas of giant non-caseous cells compatible with active sarcoidosis. After steroid therapy systolic function improved and the follow-up scintigraphy was negative

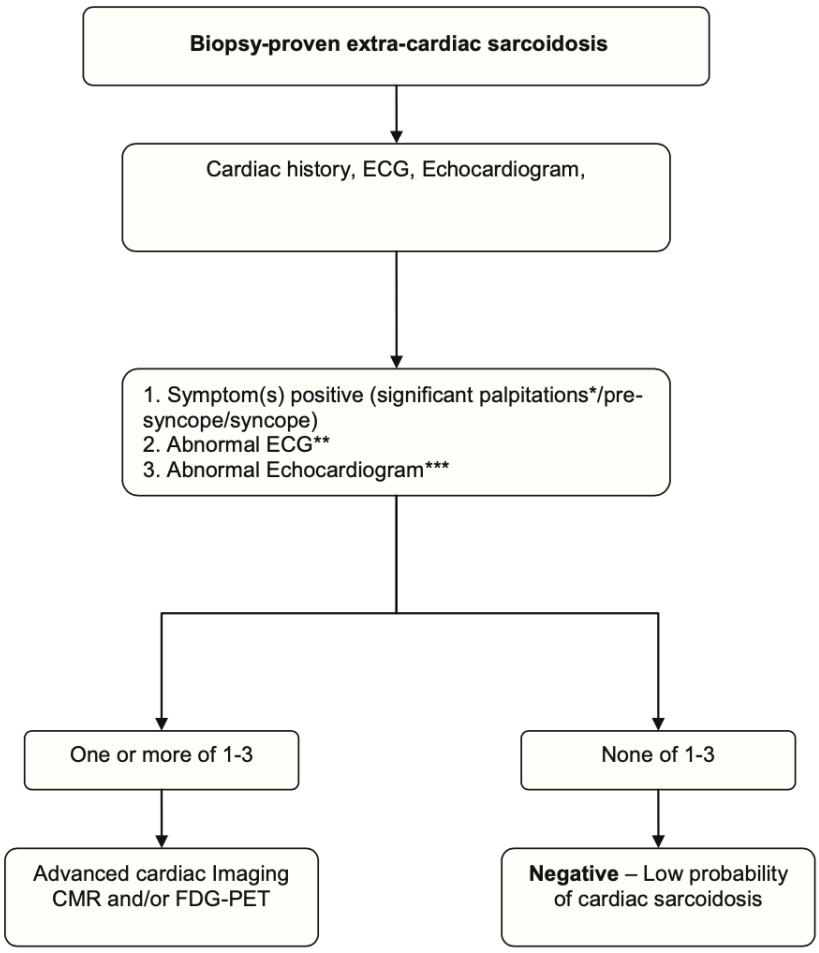


Figure 2 – Suggested algorithm for the investigation of patients with biopsy-proven extracardiac sarcoidosis; *palpitations were defined as prominent patient complaint lasting > two weeks
** abnormal electrocardiogram (ECG) defined as complete left or right bundle branch block and/or presence of unexplained pathological Q waves in two or more leads and/or sustained second or third degree atrioventricular block and/or sustained or non-sustained ventricular tachycardia**
*** abnormal echocardiogram defined as regional wall motion abnormality and/or wall aneurysm and/or basal septum thinning and/or left ventricular ejection fraction < 40%**
CMR: cardiovascular magnetic resonance; ECG: electrocardiogram; FDG-PET: 18F-fluorodeoxyglucose-positron emission tomography; *reproduced with permission from Birnie et al.*[25]

CMR has some benefits compared with PET imaging, as there is no exposure to ionizing radiation and no need for patient preparation such as specific diet before the image acquisition. CMR is useful when the diagnosis is complex in order to rule out other types of cardiomyopathies and/or infiltrative diseases. However, CMR imaging is limited in patients with recently implanted pacemakers or other metallic devices and gadolinium is contra-indicated in patients with advanced renal disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2).[39]

PET for CS

18F-FDG is a glucose analog used in PET imaging to evaluate myocardial inflammation.[40,41] Myocardial cells use a mixture of free fatty acids and glucose for energy production under normal resting conditions. When preferentially switched to free fatty acid substrate, the presence of 18F-FDG uptake can indicate an inflammatory lesion. Inflammatory cells such as macrophages and lymphocytes utilize glucose as their primary energy source.[42,43] 18F-FDG follows the

pathway of glucose crossing the cellular membrane via glucose transporter (GLUT 1 and 3) and being phosphorylated by hexokinase inside the cell, where it gets trapped, and can be detected by PET imaging.[44,45] To improve the specificity in identifying pathological glucose uptake, background physiologic myocardial glucose metabolism must be suppressed; to accomplish this, the patient needs to undergo a specific preparation including dietary manipulation with a high-fat, low-carbohydrate diet, prolonged fasting, intravenous heparin or a combination of these approaches as described in the Joint SNMMI-ASNC Expert Consensus Document on the Role of ^{18}F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring.[46] 18F-FDG PET imaging is commonly performed concurrently with a PET or SPECT myocardial perfusion scan.[47] The combination of both perfusion defects and 18F-FDG uptake in multiple areas following a non-coronary distribution makes the diagnosis more likely. Youssef et al.,[48] in a meta-analysis, collected data from 164 patients and showed that PET had a pooled sensitivity of 89% and a pooled specificity of 83% in diagnosing CS.[48] A recent meta-analysis by Kim et al.,[49] had similar results, with a pooled sensitivity of 84% and a pooled specificity of 83%. The specificity increases with the correlation with extra-cardiac findings, seen in a 18F-FDG whole-body imaging, such as positive mediastinal and/or hilar lymphadenopathy. However, the presence of 18F-FDG uptake in a mismatch pattern with perfusion defect can also be seen in the presence of hibernating myocardium, and a careful differentiation must be made in patients with known ischemic cardiomyopathies.[32] It is important to keep in mind that 18F-FDG uptake is related to active inflammation within the myocardium, and the absence of uptake cannot rule out the presence of CS.[46]

Indications for cardiac PET

Diagnosis

In the absence of histologic confirmation, PET is useful to investigate suspected CS; however, the diagnosis should not be based on PET findings alone but in combination with other methods including ECG, Holter and echocardiography. Some clinical scenarios in which cardiac PET may be useful have been previously described:[46] 1) patients with histologic evidence of extra-cardiac sarcoidosis with an abnormal screening for CS, such as left bundle branch block or unexplained pathologic Q waves on ECG, regional wall motion abnormalities, wall aneurysm, basal septal thinning or LVEF </=50%, sustained or non-sustained ventricular tachycardia, LGE on MRI, unexplained palpitations or syncope; 2) patients with new onset of conduction disease, unexplained by other diagnosis, normally found in younger patients (<60 years old) with second or third degree atrioventricular block; or 3) patients with idiopathic sustained ventricular tachycardia.

Monitoring response to therapy

PET imaging is useful in monitoring patients who undergo immunosuppressive therapy as it has the capacity to quantify inflammatory state before and after treatment using the standardized uptake value (SUV), and therefore assess treatment response.[50] It can help in important decisions such as the duration or the intensity of the medication used and choosing the more appropriate immunosuppressive therapy.-

Patterns of uptake – visual interpretation

18F-FDG PET is normally acquired as a whole-body imaging and commonly uses computed tomography (CT) for attenuation-correction and anatomy correlation, and thereby has to be visualized using standard views (short-axis, sagittal and coronal views).[46] It is important to have an adequate alignment between PET and CT and to correlate the findings with the non-corrected images, in order to rule-out artifacts due to partial volume. There should also be a dedicated cardiac acquisition, normally visualized using the traditional cardiac imaging display, to compare with the perfusion imaging (PET or SPECT). Both images are generally normalized to the maximum counts per pixel of the image. The use of gated imaging can also add information such as LV volume, wall motion and systolic function. Both perfusion and 18F-FDG images should be interpreted simultaneously. A normal study should show a complete absence of 18F-FDG uptake in the myocardium and an absence of perfusion defect.[40] Another physiological or non-specific pattern is a focal and homogeneous 18F-FDG uptake in the lateral wall, without any perfusion defect.[46] Diffuse uptake is a non-specific finding and can be seen in both normal controls and patients with sarcoidosis.[40]

Inflammation should be considered in the presence of focal or diffuse 18F-FDG uptake[40] (**Table 3**).

Table 3 – Positron emission tomography (PET) interpretation of the perfusion and metabolism findings

	PET findings			
Perfusion	Normal	Normal	Abnormal (perfusion defect)	Abnormal (perfusion defect)
Metabolism	Normal (negative) Diffuse / lateral wall uptake (non-specific)	Focal increase	Focal increase Multiple areas	Normal (negative)
Interpretation	Normal	Early disease Inflammation No scar	Mismatch pattern Scar and inflammation	Scar and no active inflammation

Adapted from Blankstein et al.[58]

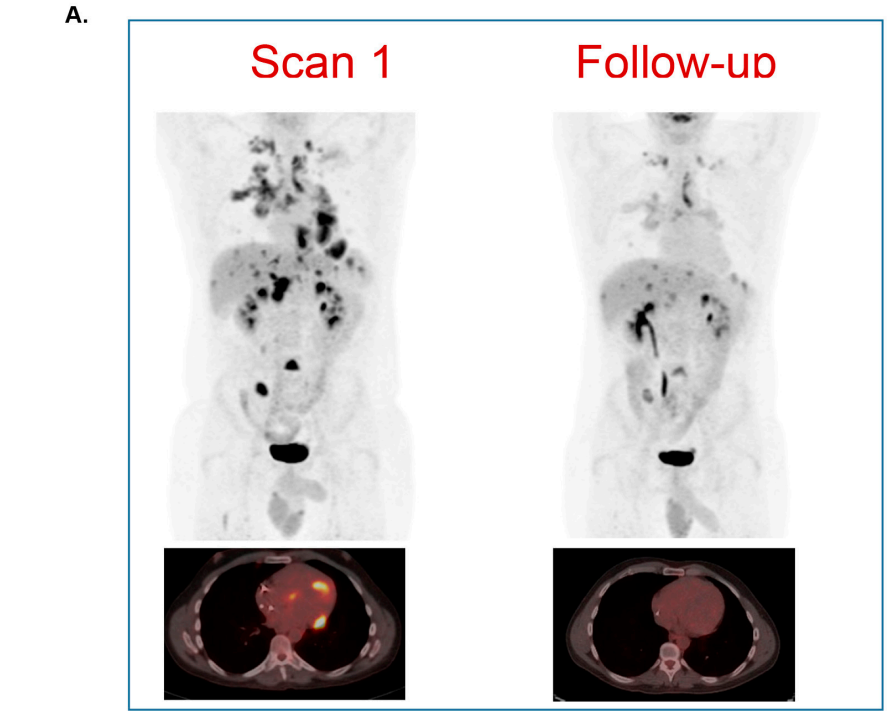
Resting perfusion defects can be due to compression of the microvasculature by inflammation, with a mismatch between.[46] In the later phases of the disease, scarring/fibrosis can be seen, in addition to a matching pattern with rest perfusion defect and no 18F-FDG uptake. However, not all patients with CS develop scarring. When multiple focal areas of FDG uptake, involving the basal antero-septum, basal inferior and basal lateral walls are present, CS should be considered. Some areas of scar with no inflammation (match) can coexist with areas of scar with inflammation (mismatch). The combination of both findings (mismatch) has been associated with the worst outcome,[51,52] as well as the presence of RV uptake.

Challenges with FDG PET

The diagnose of CS with 18F-FDG is often a challenge. Patients can have comorbidities such as ischemic cardiomyopathy that can make the diagnosis even more difficult. Scar can be seen in both diseases and the presence of hibernating myocardium can mimic areas of inflammation due to CS. The same can happen in patients with active myocarditis or systemic rheumatologic conditions with cardiac involvement. Studies of patients with ICD leads have to be interpreted carefully using both attenuation-corrected and non-attenuation-corrected images as false 18F-FDG uptake can be seen near the leads due to partial-volume artifact and misinterpreted as positive. One of the greatest challenges with 18F-FDG is the adequate preparation for the test, since a poor adherence to the diet may lead to diffuse 18F-FDG uptake, making the study uninterpretable. Moreover, up to 25% of the patients do not respond to any of the strategies to reduced myocardial uptake leading to a high rate of false-positives or inconclusive results.[32,53] Therefore, 18F-FDG PET studies for CS should be conducted in experienced centers, with qualified physicians, since false-positive studies could be harmful to immunosuppressed patients. **Figures 3** and **4** illustrate two different cases before and after therapy.

Prognosis

Cardiac PET can help in the diagnosis and assessment of treatment response in CS. Given the risk of sudden cardiac death and the potential side effects of ICD, some studies have tried to identify how cardiac PET findings could be related to adverse cardiac events in a population with CS. Blankstein et al.,[52] studied 118 patients who underwent PET with 18F-FDG and Rb-82 to assess inflammation and perfusion defect, and categorized them according to the imaging findings as (a) normal; (b) positive perfusion defect or glucose uptake; or (c) positive perfusion defect and glucose uptake.[52] They followed the patient for an average of 1.5 year to identify the outcomes of death and sustained ventricular tachycardia (VT). Among the patients, 47 (40%) had normal and 71 (60%) abnormal cardiac PET findings. During the follow-up, there were 31 (26%) adverse events, with 27 VT and 8 deaths. Cardiac PET was able to predict adverse event with the presence of both perfusion defect and abnormal FDG (findings present in 29% of the patients), with a hazard ratio of 3.9 ($p<0.01$). However, based on current knowledge, PET cannot rule in or out the need for ICD in CS patients.



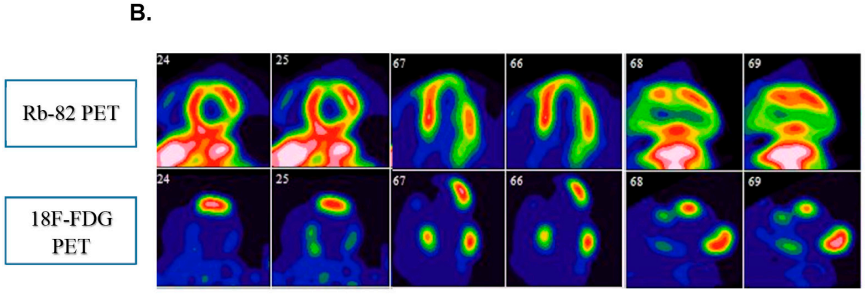


Figure 3 – A. *18F-fluorodeoxyglucose-positron emission tomography (18F-FDG PET) whole body and fused PET/Computed tomography of the heart at baseline and follow-up of a 39-year-old male presenting with episodic complete heart block and sinus node dysfunction. The patient had dual chamber cardioverter defibrillator implantation and was diagnosed with cardiac and systemic sarcoidosis. Treatment with low-dose prednisone and methotrexate was initiated.* **Scan 1**. *Whole-body findings: cluster of FDG-avid, tiny nodules in the right lung (SUVmax=6.94), bilateral hilar adenopathy (SUVmax=6.4), bilateral supraclavicular lymph node, multiple foci of increased FDG activity in the liver and spleen and prominent lymph node in the porta hepatis. Cardiac findings: four areas of increased FDG uptake correlating with regions of reduced myocardial perfusion on rest imaging (basal inferolateral wall, basal inferoseptal wall, basal to mid-anterior wall, apical lateral wall and apex). Follow-up of seven months afterwards (***Scan 2***): Whole-body: Interval reduction in the degree of metabolic activity of all the previous findings. Cardiac findings: no active inflammatory process in the myocardium. Regions of scar in the mid-anterior wall, mid-to- apical inferolateral wall and apex.*
B. *Baseline study with rubidium-82 (top line) and 18F-FDG (bottom line) in short axis, horizontal long axis and vertical long axis, showing the perfusion-metabolism mismatch pattern in the basal inferolateral wall, basal inferoseptal wall, basal to mid-anterior wall, apical lateral wall and apex*

PET imaging has proven to be useful in predicting treatment response, not only by reduction of inflammation but also by improvement of LV function. Osborne et al.[54] evaluated the relationship between the reduction in myocardial inflammation measured by FDG uptake and the improvement in LV ejection fraction.[54] They assessed 23 patients with serial PET scans (median of four per patient) and quantified the maximum SUV and volume of tissue with inflammation to assess the extension and intensity of FDG uptake for each study performed. The median time between the first and the last scan was two years. Most of the patients (91%) were treated with corticosteroids, and 83% had ICDs. There was a significant inverse linear relationship between maximum SUV and ejection fraction (EF) with an expected increase in EF of 7.9% per SUV reduction of 10g/mL by longitudinal regression model (p=.008). On the volume-based analysis, EF increased 2.1% per 100 cm^3 decrease in volume of

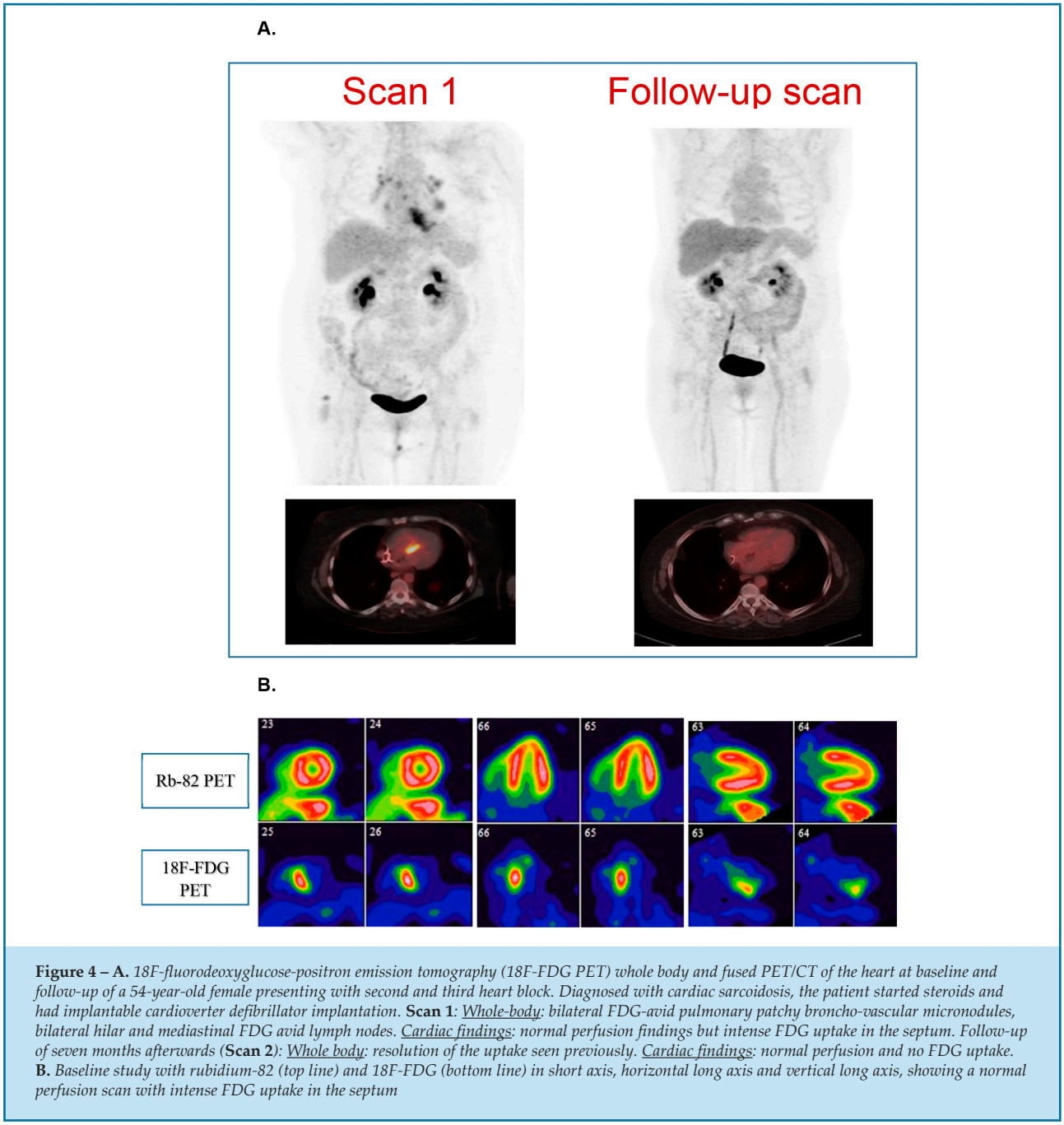


Figure 4 – A. *18F-fluorodeoxyglucose-positron emission tomography (18F-FDG PET) whole body and fused PET/CT of the heart at baseline and follow-up of a 54-year-old female presenting with second and third heart block. Diagnosed with cardiac sarcoidosis, the patient started steroids and had implantable cardioverter defibrillator implantation.* **Scan 1**: *Whole-body: bilateral FDG-avid pulmonary patchy broncho-vascular micronodules, bilateral hilar and mediastinal FDG avid lymph nodes. Cardiac findings: normal perfusion findings but intense FDG uptake in the septum. Follow-up of seven months afterwards (***Scan 2***): Whole body: resolution of the uptake seen previously. Cardiac findings: normal perfusion and no FDG uptake.* **B.** *Baseline study with rubidium-82 (top line) and 18F-FDG (bottom line) in short axis, horizontal long axis and vertical long axis, showing a normal perfusion scan with intense FDG uptake in the septum*

inflamed tissue using a threshold of 2.7g/mL, and when using a threshold of 4.1g/mL, there was an increase in EF of 3.8% per 100cm^3 decrease. These findings showed a correlation between the reduction of the intensity and extension of 18F-FDG uptake due to myocardial inflammation in patients with CS and improvement in LVEF. Based on this small study, serial PET scanning could be useful in guiding the immunosuppressive therapy, preventing the development of heart failure in patients with CS. **Table 4** summarizes the use of 18F-FDG PET in the management of CS.

PET/MRI

The combination of PET with MRI in a single acquisition is now possible with the use of advanced hybrid cameras. Despite the elevated price of the equipment, hybrid scanners can offer great benefit

Table 4 – Use of 18F-FDG PET in the management of Cardiac Sarcoidosis

Indication	Significant findings	Technical aspects	References
Diagnosis	Normal or decreased perfusion in the involved region of the myocardium, with increased 18F-FDG uptake	Inadequate preparation can severely impair the accuracy for the diagnosis of CS	58
Prognosis	Perfusion defect or focal 18F-FDG uptake in left ventricle, increased uptake in right ventricle, extensive and severe uptake in the myocardium	Up to 25% of qualitative 18F-FDG PET exams may not be reproducible (90-120 minutes of 18F-FDG uptake improves reproducibility)	42, 52, 59
Assessment of Treatment Response	Decreased or resolved 18F-FDG uptake in the myocardium can support the decision to wean prednisone	Increased costs and radiation exposure. Limit to 3-4 scans in a year. Caution should be taken concerning the effect of steroid on false-positive 18F-FDG-PET results	60
Diagnosis of extra-cardiac sarcoid disease activity or findings to guide a biopsy from an extracardiac location of 18F-FDG uptake	18F-FDG avid lymph nodes or other accessible area to guided biopsy can provide a definitive diagnosis or exclude malignancy in uncertain cases	The whole body 18F-FDG PET as well as the CT transmission (on hybrid scanners) images need to be reviewed and reported in conjunction with a physician credentialed to supervise and interpret body PET/CT	47

CS: cardiac sarcoidosis; PET: positron emission tomography; CT: computed tomography; 18F-FDG: 18F-fluorodeoxyglucose

because of the reduced cost of personnel and reduced risk of complications.[55] For the patient, it would mean a single visit to the imaging department, and less time spent in the hospital. The MRI would play the role of the CT for attenuation correction, anatomic reference and evaluation of extracardiac findings and will add value of tissue characterization, mainly for scar and edema.[56] The combination of both imaging techniques improves spatial relationship between the findings of scar and inflammation, making it useful to patient's management and understanding of the phases of the disease (mismatching, scarring or inflammation alone).

CHASM CS-RCT

Due to the lack of previous clinical trials to evaluate treatment strategies in CS, the Cardiac Sarcoidosis Multi-Center Randomized Controlled Trial (CHASM CS-RCT; NCT-03593759) is an ongoing multicenter randomized controlled trial aiming to evaluate the optimal initial treatment strategy for patient with active CS.[57] The inclusion criteria are: patients with clinically manifest CS with at least one finding such as advanced conduction system disease, significant node dysfunction, non-sustained or sustained ventricular arrythmia, LV dysfunction or RV dysfunction. The primary hypothesis is that a low dose prednisone/ methotrexate combination will have non-inferior efficacy to standard dose prednisone and will result in a significantly better quality of life due to less side-effects when compared to the standard therapy. The subject are randomized in a 1:1 ratio to high dose prednisone (0.5mg/kg/day for six months, with maximum dose of 30mg/day) or to prednisone 20mg/day for one month, 10mg/day for one month, then 5mg/day for one month, followed by discontinuation of prednisone and initiation of methotrexate 15-20mg once weekly for six months. This study uses PET imaging (perfusion and metabolism with FDG) to evaluate the presence of scar and inflammation. Showing the non-inferiority of the low-dose steroid will be enough to guide therapy toward a highly-effective treatment with less adverse effects and better quality of life for the patient.

Conclusion

CS can be difficult to diagnose and often requires multiple tools to reach timely diagnosis. Cardiac MR and FDG PET are advanced imaging techniques that can be used a complementary fashion for diagnosis,

monitoring treatment response and progression over time. Those modalities demonstrate distinct distribution and patterns of the disease at different stages, such as perfusion defects due to fibrosis, FDG uptake or elevation of T2 signal caused by inflammation as well as impairment of the ventricular function. Prospective randomized controlled trials as CHASM CS-RCT are needed to validate not only the role of imaging in diagnosis but also in order to assess therapy management to guide the best treatment for each individual, taking into consideration not only the response but also patient's quality of life.

Author contributions

Conception and design of the research: Wiefels C. Writing of the manuscript: Wiefels C, Lamai O, Kandolin R, Birnie D, Leung, E, Mesquita CT, Beanlands R. Critical revision of the manuscript for intellectual content: Wiefels C, Lamai O, Kandolin R, Birnie D, Leung, E, Mesquita CT, Beanlands R.

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Study Association

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Ethics approval and consent to participate

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

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VIEWPOINT

Should Physical Activity Be Considered Essential During the COVID-19 Pandemic?

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Introduction

The novel coronavirus (COVID-19) disease, considered a pandemic by the World Health Organization (WHO),[1] which until April 13, 2020, had 1,776,867 confirmed cases with 111,828 deaths worldwide, led the Ministry of Health of Brazil[2] to prepare a manual with several actions to prevent the spread of the disease. Among these actions, social distancing is recommended, instructing people to remain at home. In addition, many heads of state and municipal executive power across Brazil have issued decrees proposing the closure of several spaces, including gyms, clinics, clubs, and other public and private spaces for physical activity. These actions caused the Brazilian population to have difficulties to continue the practice of physical activity.

On the other hand, since the beginning of the pandemic, some studies have been published in different parts of the world, calling attention to the importance of continuing to practice physical activity. For example, in the city of Wuhan in China, the initial epicenter of the disease, people were recommended to practice physical activity even at home.[3] In a recent study focused on elderly people, outdoor physical activity and also exercising at home were suggested as therapy to combat the physical and mental consequences of quarantine due to the Covid-19 pandemic.[4] In addition, according to a recent position of the American College of Sports Medicine,[5] people should continue to stay physically active while at home during the pandemic.

Keywords

Pandemics; Coronavirus; COVID-19; Physical Activity; Exercise; Sedentarism; Leisure Activities; Psychological Phenomena.

In line with these publications, legal provisions published in countries such as the United Kingdom[6] and France[7] recognized the practice of physical activities in open environments as an essential activity during the quarantine period.

It should also be noted that the literature is consistent in showing the various benefits provided by physical activity for health, especially for the cardiovascular, metabolic[8] and immune[9] systems, as well as for mental health.[10]

Therefore, it seems clear that the practice of physical activity both at home and in open environments should be considered as an essential activity during the COVID-19 pandemic in any legal statement issued by government agencies. The objective of this point of view is to describe the evidence for this.

Studies that highlight the importance of staying physically active during the Covid-19 pandemic

The first study was published in the city of Wuhan in China,[3] the initial epicenter of the disease, where people were recommended to practice physical exercises even at home. The authors recommended that strengthening exercises, balance activities and stretching exercises or a combination of them should be performed. They also recommended walking around the house, lifting and transporting groceries, going up/down stairs, and doing squats, sit-ups and push-ups. In addition, Tai Chi Chuan and Yoga exercises have also been suggested. Physical activity could be done with the aid of technological resources, such as exercise videos and online professional guidance.

Subsequently, a study by researchers from Spain and the USA,[4] with focus on the elderly, emphasized the importance of outdoor physical activities or exercises

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done at home as therapy to fight against the physical and mental consequences of Covid-19 quarantine. The authors suggested a multicomponent exercise program, including aerobic, resistance, balance, coordination, and mobility training exercises both in outdoor environments and in community homes.

In addition, a recent point of view[11] suggested the maintenance of physical activity in open environments or indoors during the period of the COVID-19 pandemic. The authors also called attention to the reduction of sedentary behavior, that is, the time we spend sitting, lying down, or reclining, except for the hours of sleep during the day.

Position of the American College of Sports Medicine

In a recent position of the American College of Sports Medicine,[5] it was suggested the practice of outdoor and indoor physical activities, which could positively modulate the immune function. The outdoor activities, suggested by this entity, were walking or running around the neighborhood, using a local park to be active, taking a bike ride in nature, and also doing gardening and lawn work, and playing active games with the family. The authors recommended that people should always avoid crowded spaces and wash their hands when get home. As indoor physical activities, the American College of Sports Medicine suggested to put on some music and walk quickly around the house, go up down the stairs 2-3 times a day, dance, jump rope, follow an exercise video, and use cardio machines at home.

Legal determinations in European countries during the pandemic

In recent legal determinations published in countrieslike the United Kingdom and France, the practice of physical activities in open environments was recognizedas an essential activity during the quarantine period. In case of the United Kingdom,[6] people were instructed to leave home for one of the four reasons: purchases of basic necessities, such as food and medicines, which should be as infrequently as possible; practicing one type of exercise a day, for example, running, walking or cycling (alone or with members of your family); any medical need; to help a vulnerable person; and go to work, but only when it cannot be done at home.

With regard to France,[7] circulation is allowed upon presentation of a completed, dated and signed form, justifying the reason for leaving. Among the permitted activities, physical activity was considered essential, as explained in the document: short journeys, limited to one hour per day and within a radius of 1 kilometer from home, related either to individual's physical activity (excluding collective sporting practices or involving any proximity to other people), either to a walk with people who live in the same household, or to fill the needs of pets.

Importance of physical activity and its benefits for the cardiovascular, metabolic, and immune systems and mental health

The benefits of physical activity to cardiovascular and metabolic health have been widely and long reported in the literature. Physical activity has an inverse association with blood pressure levels,[12] diabetes,[13] lipid changes,[14] risk of coronary artery disease,[15] and risk of cardiovascular events,[16] acting as an important protective factor for different cardiometabolic disorders. In addition, more recently, the importance of reducing sedentary behavior has also been discussed as an important approach to maximize the benefits of physical activity in preventing cardiometabolic disorders.[17]

Regarding the immune system, physical activity, especially at moderate intensity and duration, can favor immune responses and improve resistance of the body. On the other hand, high-intensity and prolonged exercise can cause immunosuppression and therefore should be avoided during the COVID-19 pandemic.[9]

A recent publication[18] by Italian researchers presents lessons learned from studies on influenza and physical activity in obese patients and suggests that the findings may be considered for COVID-19. The authors emphasize the positive effects on immunomodulation provided by the practice of light- to moderate-intensity physical exercise.[18] In the same line of reasoning, in a study carried out in the USA, it was observed that physical exercise acts as a preventive agent against viral influenza infection, both in obese and non-obese rats.[19]

As for mental health, several studies have shown that the practice of physical activity can bring important benefits for the prevention of depression,[10] anxiety, Burnout syndrome and perceived stress.[20] Thus, physical activity becomes an important ally for the management of these health problems that affect the population, especially during the COVID-19 pandemic.[4]

Conclusion

Considering the benefits of physical activity to the cardiovascular, metabolic, and immune systems, and for mental health, we suggest that any legal determination that may be published by municipal, state or federal agencies consider outdoor physical activities as an essential practice. It must be emphasized that the exercises must be practiced individually or at most with people who live in the same household, avoiding groups or clusters of people together and respecting the safe distance suggested by health entities. Also, especially for elderly people, it is suggested to stay physically active while at home, preferably with online guidance from physical educators. Sedentary behavior should also be reduced, that is, the time we sit, lie down or recline, and time spent in front of the television, computer and the like. Finally, if you feel comfortable and safer, it is suggested to wear masks during walking, running, or cycling.

Author Contributions

Conception and design of the research: Pitanga FJG. Critical revision of the manuscript for intellectual content: Pitanga FJG, Beck CC, Pitango CPS.

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 graduation program.

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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VIEWPOINT

Challenges in Pharmacological Management of Cardiovascular Diseases in Covid-19: do Benefits Outweigh Risks?

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Introduction

Cardiovascular diseases (CVD) are the main cause not only of global mortality but also of reduced quality of life. They cover ischemic heart disease, stroke, heart failure, peripheral artery disease, and various other heart and vascular conditions. In 2017, CVDs caused about 17.8 million deaths worldwide, corresponding to 330 million years of life lost and another 35.6 million years of life with disabilities. Almost 80% of deaths occur in low- and middle-income countries, such as Brazil, where the occurrence of CVDs and their risk factors are on the rise as a result of an ongoing epidemiological transition.[1] In low-income countries CVDs greatly affect working-age populations, and the total economic loss resulting from this group of diseases is high, representing 2% of Gross Domestic Product. In addition, the disability caused by CVDs has economic consequences at multiple levels: individual, family, economic agents, public institutions, government, and society as a whole.[2]

Recent studies also show that chronic conditions, such as CVD, increase the risk of aggravation and death associated with the new coronavirus 2019 disease (COVID-19), whose outbreak was characterized as a pandemic by the World Health Organization (WHO) in March 2020. The new coronavirus is a betacoronavirus called SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus 2), phylogenetically identical to other coronaviruses capable of determining acute respiratory distress syndrome (ARDS), which is responsible for numerous deaths. The most common symptoms of COVID-19 include fever, cough, dyspnea, myalgia, fatigue, diarrhea, sore throat, chest pain, confusion, and lethargy. Acute and chronic cardiovascular complications have also been observed in the course of COVID-19, being attributed to several mechanisms, such as relative ischemia, systemic inflammation mediated by pathogens, with increased levels of several biomarkers. In this context, studies point to the relevance not only of chronic conditions, such as hypertension, but also of the age and immunological status of the host, characterizing a complex, multifactorial, and bidirectional model that can comprehend the drugs used to treat these pathologies.[3]

It is important to note that there is no vaccine for prophylaxis, nor specific drug therapy for the treatment of COVID-19. The repositioning of medications such as chloroquine, hydroxychloroquine, and some antivirals has been considered for the treatment of this disease.[4] However, the clinical effectiveness of this approach has not yet been adequately proven. In addition, the literature points out that the combination of lopinavir / ritonavir antivirals alters cardiac conduction, with prolongation of the QT interval and atrioventricular block.[5] This change in heart rate is also seen in the use of chloroquine / hydroxychloroquine, which can contribute to the development of cardiomyopathy in patients with rheumatic diseases.[4] These cardiotoxic effects are particularly uninteresting in patients with CVDs, such as those using β-blockers, with which these drugs may have a pharmacodynamic drug interaction with regard to atrioventricular conduction.

Lifestyle changes and cardiovascular pharmacotherapy play a truly important role in the management of CVDs across their spectrum. Drug therapy has

Keywords

Cardiovascular Diseases/mortality; Coronavirus/complications; COVID-19/complications; Pandemics; SARS Severe Acute Respiratory Syndrome; Dyspnea; Fever; Anticoagulants.

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proven to be a life-saving or life-prolonging tool in some cases, as well as to improve the quality of life in others, as a result of its role in improving debilitating symptoms.[6] The reduction of blood pressure using one or more drugs in association is fundamental for the prevention and treatment of CVDs. Globally, 62% of cerebrovascular diseases and 49% of ischemic heart diseases were attributed to suboptimal blood pressure control. Similarly, the development of drugs to control serum lipid levels has had an important impact on the prevention and treatment of these diseases. Statins can reduce the risk of cardiovascular events by 20%, and the benefits of therapy increase with their duration. In addition, antiplatelet drugs, such as low-dose acetyl salicylic acid, play an important role in preventing ischemic heart disease and stroke. As the mechanism of action of the main pharmacotherapeutic options for the prevention of CVDs (antihypertensives, hypolipemiants and antiplatelet agents) are independent, fixed dose combinations of these substances are adopted.[7]

Although the different classes of antihypertensive drugs have similar efficacy for preventing the vascular results of interest, the literature points that β-blockers appear to be inferior to others for the prevention of major cardiovascular events, such as stroke and renal failure. In the case of heart failure prevention, while diuretics appear to be superior, calcium channel blockers are inferior; however, for stroke prevention they are superior. The combination of these agents with angiotensin-converting enzyme inhibitors (ACEI) has proven to be more effective in preventing CVDs than the ACEI-diuretic association.[8] However, the benefit not only of ACE inhibitors but also of angiotensin receptor blockers (ARB) in the course of COVID-19 is controversial.[3] In view of the above, the aim of the present review was to analyze the risk-benefit ratio of cardiovascular pharmacotherapy in patients with COVID-19.

Methods

The electronic databases LILACS, MEDLINE and SCOPUS were consulted, crossing the term COVID-19 with the different CVDs individually, as well as with the different pharmacological groups associated with the treatment of these pathologies, without delimiting the time for the research that was conducted in April 2020. Figure 1 illustrates the selection process of the researched studies and the number of publications found at each stage.

A total of 84 results were found, from which articles that were not available in English and / or Portuguese were excluded. Studies were also discarded after reading the titles and abstracts, as well as after reading the full text. After screening, 15 articles were selected because they showed a direct relationship with the subject of the present study.

Results and Discussion

Antithrombotic and Statins

Antithrombotics include anticoagulants, antiplatelet agents, and fibrinolytics. These agents are prescribed in several situations related to hemostasis disorders that favor the formation of thrombi. Anticoagulants can be for oral use, such as warfarin and xabans, or for parenteral use, such as high and low molecular weight heparins (LMWHs). [9,10]

Statins are drugs used to treat dyslipidemia, reducing the risk of cardiovascular disease.[7] These agents, as well as antiplatelet inhibitors of P2Y12 activity (clopidogrel and ticagrelor) and oral anticoagulants, present pharmacokinetic interactions with lopinavir / ritonavir, antiviral agents evaluated in prospective studies, as well as ribavirin and remdesivir, leading to the need for revision of the therapeutic regimen to avoid toxicity if used in combination. The literature also points to an interesting anti-inflammatory effect of statins to mitigate the course of COVID-19.[11]

Anticoagulant therapy with heparins, mainly with LMWHs, such as enoxaparin, seems to be associated with a better prognosis in patients with severe COVID-19 provided they meet the criteria for sepsis-induced coagulopathy or with markedly high D-dimer levels. All of this is due to the risk of disseminated intravascular coagulation and venous thromboembolism.[9,10] Although COVID-19 is characterized by hyperfibrinolysis, studies that attempt to restore fibrinolytic function have not been reported.[12]

The literature points to an association between viral load and the severity of COVID-19 so that individuals with a higher viral load can develop severe acute lung injury, requiring hospitalization in an intensive care unit with poor prognosis. Mortality of patients developing ARDS is 49%. Many patients with COVID-19 develop multiple organ failure. The main causes of death are ARDS, septic shock with multiple

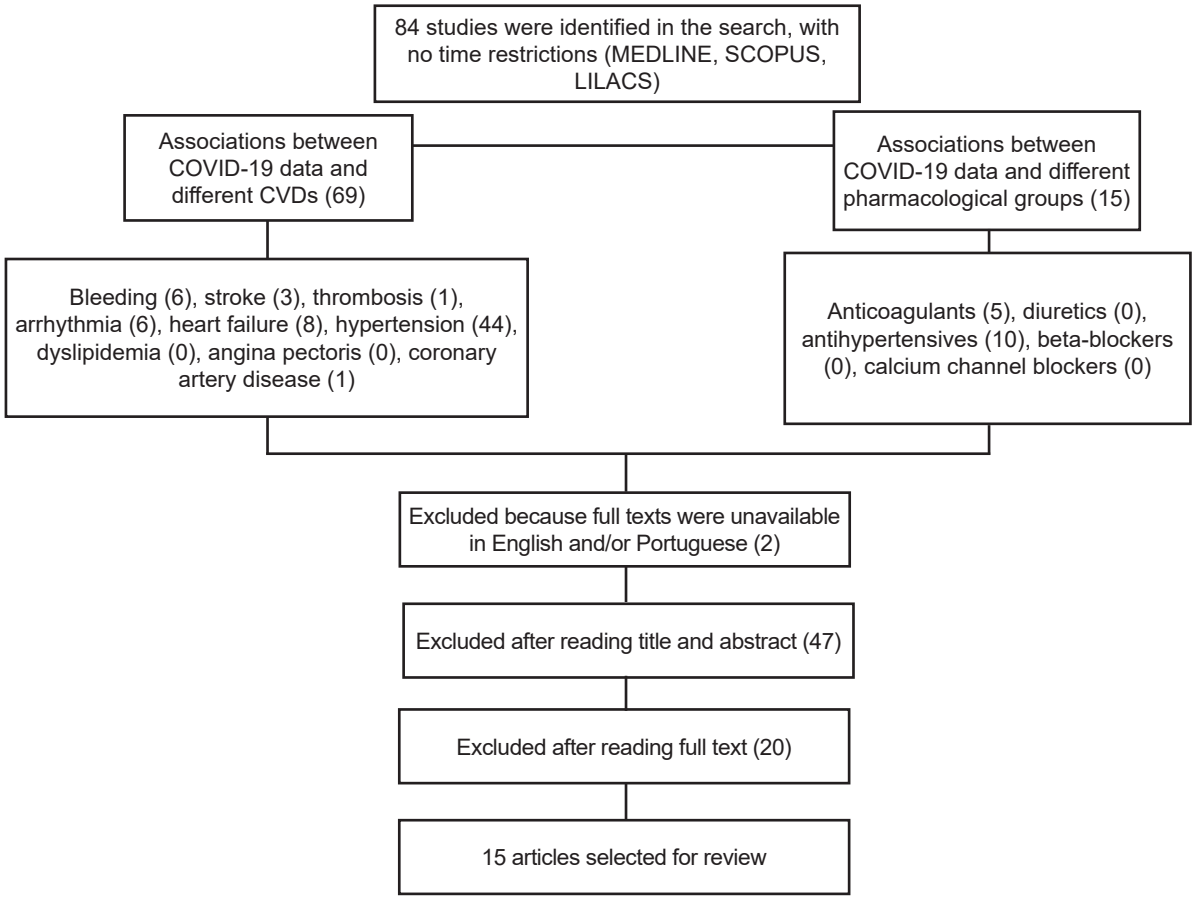

Figure 1 – Flowchart of the selection process of the searched studies. The number of articles in each stage is indicated in parentheses.

organ failure, disseminated intravascular hemorrhage/coagulopathy, acute hepatic/renal heart injury and secondary bacterial infections. Consistent with clinical observations, the lungs are the organs that suffer the most damage, followed by moderate injury to heart, liver, kidney, and brain. Patients with high plasma/plasminogen levels and pre-existing conditions seem to present a mechanism that contributes to increase the susceptibility to infection and fatality by the new coronavirus. Therefore, targeting hyperfibrinolysis with antiplasmin compounds (broad spectrum or specific) may prove to be a promising strategy to improve the clinical outcome of patients with comorbidities. Clinical trials with several protease inhibitors are being conducted in China; however, there are no suitable animal models of COVID-19 with underlying medical conditions to test new therapeutic agents.[10]

In the fibrinolysis process, plasmin generates soluble D-dimer and D-monomer from the proteolytic cleavage of fibrin. The activity of this enzyme can be detected in bronchial-alveolar lavage (BAL), including in healthy individuals. However, significantly increased levels of D-dimer and D-monomer are found in patients with ARDS, who also have a higher expression of α2-antiplasmin, a specific plasmin inhibitor. Thus, while the fibrinolytic activity decreases by half, the level of D-dimer increases, showing a nonproportional change between the level of expression and activity of plasmin and antiplasmin in favor of fibrin degradation in ARDS patients. In addition, the literature points to a prominent reduction in platelets in individuals with COVID-19. Therefore, in this context, the idea that the administration of antiproteases can be beneficial is reinforced. On the other hand, based on laboratory and pathological results, hypercoagulation occurs, as evidenced by the presence of microthrombi along the blood vessels of multiple organs. It is not known whether fragmented hemorrhage coexists with areas

infected with the new coronavirus.[10] The best prognosis for LMWH therapy in severe cases of COVID-19 is attributed to the uncoordinated coexistence of hyperproteolysis and hypercoagulation.

The endothelial cell dysfunction induced by coronavirus infection results in increased production of thrombin, which generates a hypercoagulable state. Moreover, hypoxia found in severe COVID-19 may stimulate thrombosis, not only increasing blood viscosity, but also a signaling pathway dependent on the hypoxia-inducible transcription factor. The anti-inflammatory effect of LMWH can also add benefit to its use. In China, a dose considered prophylactic (Table 1) was used, with hemorrhagic complications being uncommon and generally mild. However, it is important to consider whether a higher dose of LMWH could be convenient in non-Asian patients with severe COVID-19. Since the decline in platelet count and the prolongation of prothrombin time correlate with increased mortality and hypofibrinogenemia is not common in sepsis, the criteria for sepsis-induced coagulopathy are important to guide anticoagulant therapy, as well as high levels of D-dimer, which acts as an indirect marker of coagulation activation, even because the activation of coagulation contributes to the compartmentalization of pathogens, reducing their invasion. Anticoagulation in patients without significant coagulopathy is associated with a potential risk.[9] Therefore, anticoagulant therapy performed mainly with LMWH appears to be associated with a better prognosis in severe cases of COVID-19 in patients who clearly meet sepsis-induced coagulopathy criteria or have significantly high levels of D-dimer.[9]

Table 1 – Therapeutic regimen recommended for the control of ARDS in patients with COVID-19

Drug	Dosage
Unfractionated heparin [9]	10000-15000 U/day
Enoxaparin[9]	40-60 mg every 24h
Acetazolamide[21]	250mg every 12h
Nifedipine[21]	30mg every 12h (prolonged release)
Sildenafil[21]	20-50mg every 8h
Tadalafil[21]	10mg every 12h

Drugs that Modulate the Renin-Angiotensin-Aldosterone System

The Renin-Angiotensin-Aldosterone System (RAAS) plays a crucial role in the homeostasis of blood volume, and consequently, of systemic blood pressure. Its actions are mediated by Angiotensin II (Ang II) via the AT1 and AT2 receptors, which in vascular smooth muscle generate vasoconstriction and vasodilation, respectively. The cleavage of Angiotensin I (Ang I) by ACE accounts for the formation of Ang II. On the other hand, the homologous ACE2 enzyme converts Ang I to Ang 1-9, which is an inactive metabolite, and Ang II to Ang 1-7, a peptide that can act via the MAS receptor (MasR) playing an anti-inflammatory, antifibrotic and vasodilator role. ACE2 is expressed in several tissues such as heart, lung, kidney, spleen, liver, brain, among others, presenting about 40% homology to ACE (figure 2). The affinity of Ang II for its binding site in the ACE2 enzyme is 400 times greater than the affinity of this same peptide for the binding site in ACE.[13,14]

It is known that ACE2 participates in the process of cell invasion by the SARS virus, in which the S protein (Spike) present in the virion binds to this transmembrane enzyme, promoting its internalization via endocytosis with the virus. This interaction configures an important and limiting process in its replication cycle. In addition, with endocytosis and consequent decrease in the density of this enzyme in the tissue membrane, there is a decrease in the degradation of the Ang II substrate by the former and consequently the formation of Ang 1-7 product, which favors the process of pulmonary fibrosis. Studies show that the mechanism adopted by the new coronavirus is similar, corroborating the clinical findings that ARDS is highly prevalent in COVID-19.[14,15] Furthermore, in silico studies have shown that, due to mutations, this virus has a greater affinity for ACE2 than other SARS, which may be related to a greater dynamics of infection by the new coronavirus.[15]

Atri et al.,[11] also described that the expression of ACE2 is encoded on the X chromosomes, which may explain the sexual differences pointed out in the epidemiology of COVID-19, which seems to affect more males than females.[11]

In the pathophysiology of heart failure, changes in the density of ACE2 and the increase of its expression in the heart are also identified, which may reflect a compensatory effect in the face of cardiac remodeling and hypertrophy, favoring the increase in the local concentration of Ang 1-7. Thus, the deleterious effects

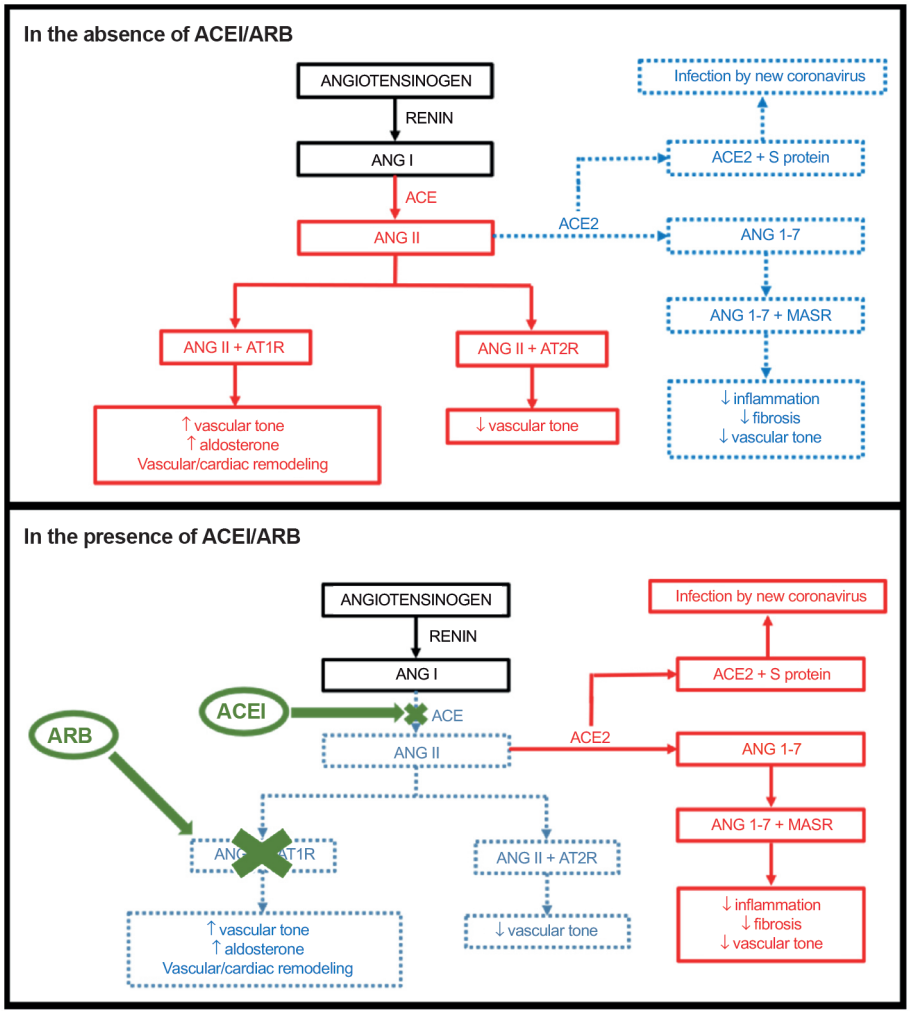

Figure 2 – Schematic representation of the renin-angiotensin-aldosterone system in two different situations: in the absence and in the presence of pharmacological interventions using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II AT1 receptor blockers (ARBs). For each situation there is a highlighted axis (red) and a faded axis (blue). Angiotensinogen is produced in the liver as a renin (enzyme secreted by the kidney) substrate and generates angiotensin I (ANG I), an inactive peptide. Through the action of angiotensin-converting enzyme (ACE), ANG I is converted into angiotensin II (ANG II), which determines its effects by binding to its receptors AT1 (AT1R) and AT2 (AT2R). The action of angiotensin-converting enzyme 2 (ACE2) on ANG II leads to the production of angiotensin 1-7 (ANG 1-7), which determines various effects by binding to Mas receptors (MASR). Also, ACE2 is able to bind to S protein in the virion, favoring cell invasion by the new coronavirus.[13,14]

of COVID-19 on the cardiovascular system may also involve reducing the availability of ACE2 in the heart. It was observed that the coronavirus increases myocardial inflammation, causing cardiac dysfunction possibly due to a decrease in the cardioprotective effects associated with the ACE2-Ang1-7-MasR axis.[17] Lippi et al., in their meta-analysis, demonstrated that cardiac Troponin I concentrations were significantly increased in patients infected with the new coronavirus, showing possible cardiac injury.[18] In turn, Guan et al., observed that 13.7% of 1099 patients with COVID-19 had increased Creatine-Kinase, and 37.2%, a high concentration of lactate dehydrogenase.[19] In addition, cardiac injury is further supported by a decrease in oxygen supply due to pulmonary insufficiency.[17]

In view of this, it is worth discussing the use of drugs that negatively modulate the RAAS and can simultaneously increase the expression of ACE2 during the course of COVID-19. The expression / activity relationship of ACE2 regarding the use of ARB and ACEI is still unclear. However, studies in different experimental models (healthy rats, with acute

myocardial infarction or with heart failure) indicate that drugs belonging to these therapeutic classes, such as enalapril and lisinopril, would be able to increase the gene expression of ACE2 in the heart. Losartan, on the other hand, showed an increase in protein expression and enzyme activity in healthy hearts.[13,20] The literature also points that other therapeutic classes encompassing drugs such as spironolactone, ibuprofen, thiazolidinediones, atorvastatin, and fluvastatin also modulate positively the activity and / or protein expression of this enzyme in some tissues.[15,20]

ACEI / ARB are therapeutic classes widely used by the hypertensive population, as well as indicated for patients with heart failure, and, according to the literature, their actions on ACE2 are indirect. The mechanism of action of ACE inhibitors, such as lisinopril, encompasses their ability to bind to ACE, inhibiting its activity and, therefore, the formation of Ang II. ARBs, like losartan, are AT1 receptor antagonists, binding to this pharmacological receptor and preventing its activation by Ang II. Thus, both classes are able to decrease vasoconstriction mediated by this active peptide and blood volume, justifying the antihypertensive effect, as well as reducing the cardiac remodeling observed in heart failure and apparently predisposing patients to infection with the new coronavirus, although the latter association is still uncertain (figure 2).[17] As Ibuprofen also increases the expression of ACE2, the WHO (World Health Organization) requested caution and the suspension, when possible, of the use of this non-steroidal anti-inflammatory as an analgesic and antipyretic for the treatment of disease symptoms. However, it should be noted that there is greater evidence of RAAS and Ang II activity, to the detriment of Ang 1-7, in patients infected with the new coronavirus due to ACE2 endocytosis, which is then correlated to viral load and pulmonary damage. From this perspective, intervention with ARB and ACE inhibitors in patients with COVID-19 and CVD could then be positive, due to the fact that the decrease in overactivation of RAAS and the favoring of the ACE2 pathway, with higher production of Ang 1-7, have the additional potential to mitigate lung injury.[20] Thus, there is a duality associated with the negative modulation of RAAS and the consequent increase in the expression of ACE2 in the course of COVID-19: the possible facilitation of host infection by the new coronavirus versus the attenuation of the deleterious effects of the disease by increasing the availability of Ang 1-7.

Therefore, the use of camostat, a protease inhibitor approved for the treatment of chronic pancreatitis, can increase the safety of drugs that increase ACE2 expression. This substance seems to inhibit the TMPRSS2 transmembrane protease present in the host cell membrane that favors the access of the viral genome to the cellular machinery for replication via S protein - ACE2 interaction. A randomized, placebo-controlled study is being conducted to verify the effects of this agent in COVID-19.[11]

Figure 2 illustrates the RAAS, in the absence or in the presence of pharmacological interventions covering ACEI and ARB, as well as its point of intersection with the infection by the new coronavirus.

Other Cardiovascular Drugs

The review by Solaimanzadeh, published on March 20, 2020, points to the benefit of using other drugs with action on the cardiovascular system such as nifedipine, a calcium channel blocker used as an antihypertensive and anti-anginal agent, acetazolamide, an example of a diuretic inhibitor of carbonic anhydrase, used in acute mountain sickness, in edematous conditions and in glaucoma, as well as phosphodiesterase inhibitors commonly prescribed for erectile dysfunction, such as sildenafil and tadalafil, in patients with COVID-19. This is because all these drugs are useful in the treatment of high-altitude pulmonary edema (HAPE). Both conditions exhibit a reduced proportion of partial arterial oxygen pressure to fractional inspired oxygen, with concomitant hypoxia and tachypnea, reduced levels of carbon dioxide and the presence of irregular infiltrates in the lung fields. Likewise, elevated levels of fibrinogen in both conditions are likely to be an epiphenomenon of edema formation rather than activation of clotting. Thus, both COVID-19 and HAPE converge to ARDS. Acetazolamide is then useful as it potently reduces hypoxic pulmonary vasoconstriction, improves minute ventilation, and expired vital capacity, as does nifedipine and phosphodiesterase inhibitors, which are also drugs that reduce pulmonary pressure.[21]

Table 1 shows the dosage of cardiovascular drugs that may be useful for patients with ARDS in the course of COVID-19.

Final Considerations

To date, there is no evidence on the risk-benefit ratio of the use of most cardiovascular drugs in patients with COVID-19. The evidence that points to benefits is particularly related to the improvement of ARDS and not to the treatment of CVD per se. The use of antiplatelet drugs seems to be inadvisable, not only due to the pharmacokinetic drug interaction with lopinavir / ritonavir, an association that may prove to be effective in the treatment of COVID-19, as also observed for statins, but also because it may lead to reduced levels of platelets and bleeding. Due to the pharmacodynamic drug interaction with these promising antivirals, β-blockers may also be inadvisable.

In order to especially mitigate ARDS, the use of nifedipine, acetazolamide, phosphodiesterase inhibitors, and LMWH seems to be recommended, provided that, in the case of the latter, eligibility criteria are clear.

Many experts warn that discontinuing antihypertensive pharmacotherapy is a dangerous choice and the clinical benefit associated with the use of ACEI / ARB in patients with heart failure is also widely described. As the literature points to the dual effect of these agents in patients with COVID-19 by promoting ACE2 overload in tissues such as the lungs, favoring virus infection, but also reducing the severity of lung injury, perhaps the risk-benefit ratio may suggest the maintenance of pharmacotherapy with these agents for patients with CVD during the course of COVID-19. In this context, it may also be interesting to maintain statins in dyslipidemic patients who do not use the lopinavir / ritonavir association.

In view of all these considerations, it is important to point out that it is mandatory that the health team remains attentive to the clinical manifestations because the studies associated to the disease caused by the new coronavirus still include a relatively small number of individuals, with much to be elucidated about the polynomial COVID-19-ARDS-CVD-cardiovascular pharmacotherapy.

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Conception and design of the research: Pedro SS, Scaramello CBV. Acquisition of data: Scaramello CBV. Writing of the manuscript: Pedro SS, Scaramello CBV. Critical revision of the manuscript for intellectual content: Brito FCF, Scaramello CBV.

Potential Conflict of Interest

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

Ethics Approval and Consent to Participate

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

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VIEWPOINT

Heart Failure with Preserved Ejection Fraction and COVID-19: a Pernicious Relationship

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Introduction

The ongoing pandemic of Severe Acute Respiratory Virus-2 (SARS-CoV2) infection was first recognized in China in 2019 and brought significant health and economic threats around the world. On January 31, 2020, the World Health Organization (WHO) declared the disease caused by SARS-CoV2 an international public health emergency and on March 11, 2020, the WHO declared it a pandemic.[1,2] Three months after the initial WHO declaration, there are more than 5 million confirmed cases worldwide and 300,000 deaths. In Brazil, in the same time interval, there were more than 850,000 cases and 43,000 deaths, with an upward trend.[3]

The epidemiological and clinical severity of the pandemic by COVID-19 was initially supported by 4 alarming elements: (a) respiratory transmission with a high infectivity rate; (b) high lethality in specific subgroups; (c) high demand for intensive care and mechanical ventilation; and (d) no effective vaccine or specific treatment. Given the magnitude of the problem and the scarcity of resources, there was a recommendation for hospitalizing critically ill patients and providing them with supportive treatment and, above all, mitigation via social isolation aimed at flattening out the epidemic curve.[4-12]

COVID-19 and cardiovascular diseases

Among the various clinical manifestations of COVID-19, cardiovascular complications are one of the most significant and with a potential risk of mortality. COVID-19 may present with respiratory failure secondary to pneumonia; acute respiratory distress syndrome; and severe cardiac injury characterized by high troponin and heart failure (HF). This presentation is associated with increased mortality.

The COVID-19 pandemic imposes a double burden on people with cardiovascular disease (CVD). About 40% of patients hospitalized with COVID-19 have CVD with a worse clinical outcome. Many of the most severe manifestations, such as myocardial injury, can occur between 8 and 14 days after the onset of symptoms. Several observational studies from Chinese and European series have identified advanced age and the presence of comorbidities, such as diabetes, hypertension, atherosclerotic coronary disease (CAD), and chronic obstructive pulmonary disease (COPD), as predictors of progression to severe illnesses, with higher lethality.

The increase in the frequency of adverse cardiovascular events after the resolution of COVID-19, similar to other viral infections such as influenza, may also play a role in mortatily of patients with. COVID-19. Thus, understanding the relationship between the immune response of the viral host and the cardiovascular system will be extremely important in the care and treatment of patients with COVID-19.[13] Several mechanisms are related to cardiac injury in patients with COVID-19, such as direct viral myocardial injury, microvascular injury, stress cardiomyopathy (Takotsubo), acute coronary syndrome, myocardial injury due to an imbalance in oxygen supply and demand, and systemic inflammatory response with myocardial injury.[14] This could be specially deleterious in patients with HF with preserved ejection fraction (HFpEF), in whom baseline diseases such as diabetes and hypertension are prevalent (Figure 1).

Keywords

Cardiovascular Diseases/complications; Heart Failure/complications; Stroke Volume; Coronavirus; COVID-19; Pandemics; Mortality; Pneumonia.

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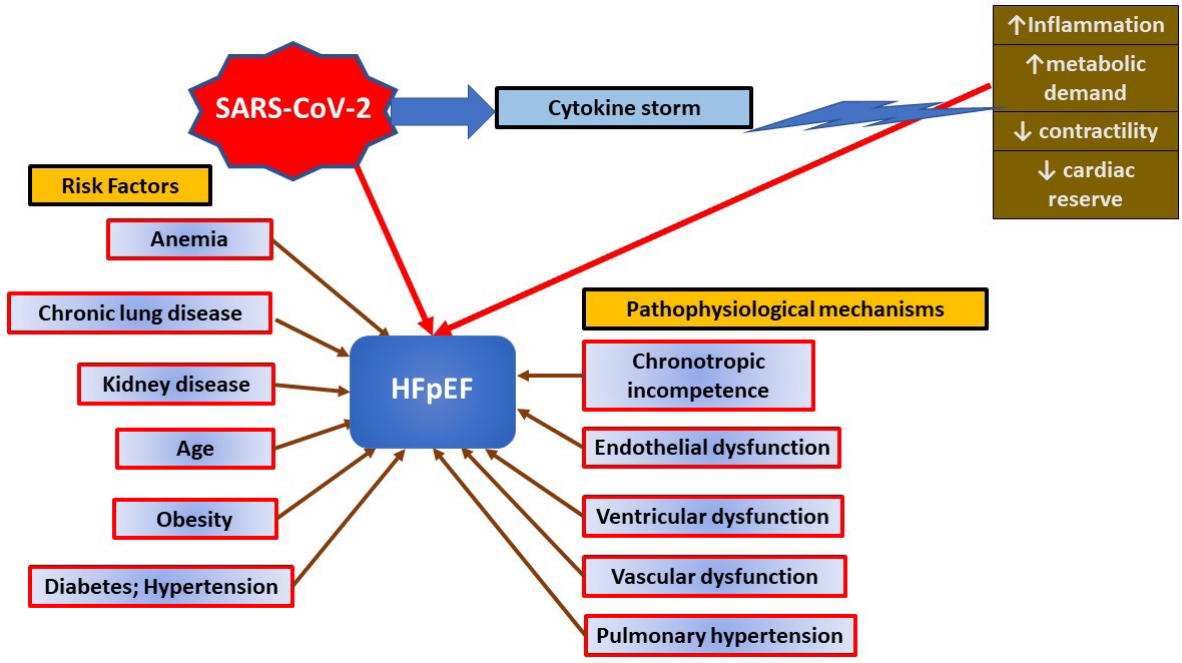

Figure 1 – Pathophysiological mechanisms of myocardial injury in COVID-19 and its relationship with HFpEF and comorbidities.

COVID-19 and Heart Failure

HF is associated with high morbidity and mortality with high costs for the health system and represents the final phenotype of many cardiovascular disorders. In recent decades, the incidence of HF has remained stable, however the prevalence has increased over time, mainly in relation to HFpEF, probably due to the longer survival of patients secondary to the available therapeutic resources. A study conducted in the population served by the Family Medical Program in Niterói, state of Rio de Janeiro, showed a prevalence of HF of 9.3%, of which 59% had the HFpEF phenotype, assessed in individuals aged 45 years or over.[15]

In general, patients with HFpEF are older, women, and diagnosed with hypertension. The prevalence of other risk factors varies according to the criteria used in the methodology to define and select patients with HFpEF[16,17] (figure 2). Biomarkers with a prognostic impact on CVD can be valuable in this high risk subgroup. Hospitalized patients should have their levels of natriuretic peptides, D-dimer, and troponin monitored. Troponin, in particular, can be an ally in the early detection of cardiac complications.[18] Small elevations (2 to 3 times above the cutoff), may be due to pre-existing diseases. However, high elevations (> 5 times above the cutoff) may be the result of severe respiratory failure, tachycardia, hypoxia, or shock, due to COVID-19, or indicate direct myocardial injury as seen in myocarditis, Takotsubo syndrome, or even type 1 acute myocardial infarction, triggered by COVID-19.[19] The measurement of these biomarkers in an outpatient setting has not been studied, but it could be useful for monitoring signs of severity in this high risk group, along with O2 saturation.

Metabolic diseases, COVID-19, and HFpEF

In the metabolic context, obesity and dysglycemia are common comorbidities in HFpEF. Obesity determines hemodynamic overload, left ventricular and atrial remodeling, in addition to activation of the renin-angiotensin-aldosterone system, a mechanism directly involved in the pathophysiology of COVID-19. Furthermore, obesity stimulates the sympathetic nervous system, natriuretic peptides, Adiponectine-induced inflammatory diseases and oxidative stress. This altered milieu results in different degrees of myocardial and vascular functional impairment, usually without significant systolic ventricular dysfunction, but with a typical phenotypic manifestation of HFpEF.[20]

Recent data show that people with obesity may also experience more symptoms of COVID-19 and are more

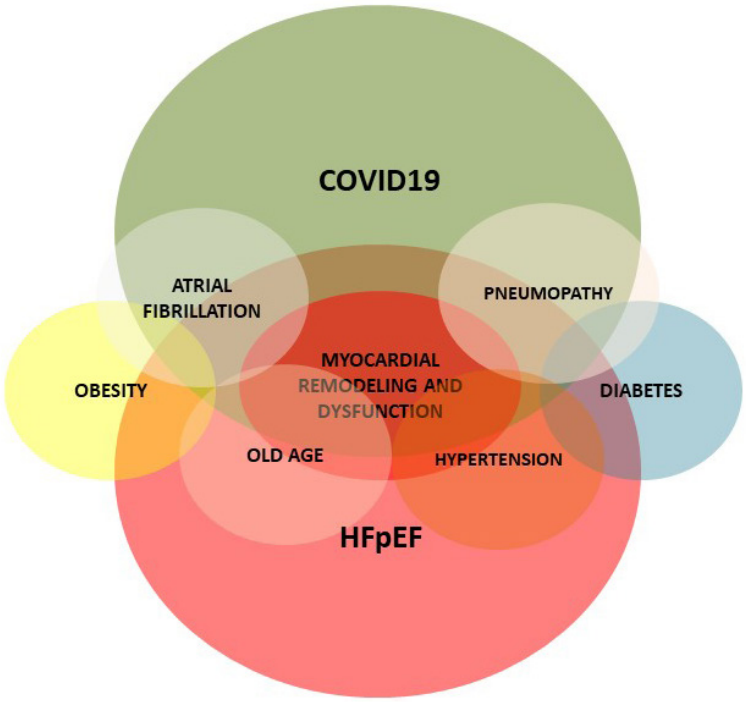

Figure 2 – Comorbidities: overlaping risk factos for COVID-19 and HFpEF.

likely to need intensive treatment. A retrospective cohort study found that patients with severe obesity defined by a body mass index (BMI) >40kg/m2 who contracted COVID-19 in France were more likely to have mechanical ventilation, regardless of the presence of advanced age, hypertension, or diabetes.[7,8]

The position of the European Association for the Study of Obesity on COVID-19 shows concern about the possibility of weight gain in quarantined patients and recommends caloric control in the diet, as well as good glycemic control in those who are also diabetic, as a method of try to reduce the risk and severity of infection.[21]

Diabetes plays a central role in the interaction of HFpEF and COVID-19. Diabetes is a primary risk factor for the development of severe pneumonia and sepsis due to viral infections in general. In parallel, glycemic dysregulation associated with insulin resistance is associated with progressive changes in cardiac structure and function that result in myocardial remodeling and left ventricular systolic and diastolic dysfunction. More specifically, diabetes can determine diabetic cardiomyopathy, and may be associated with HF manifestations and higher frequency of clinical complications resulting from this syndrome.[22] The occurrence of the association of diabetes with structural heart disease typical of HFpEF is, therefore, a first explanation for the increased susceptibility of diabetic patients to complications in COVID-19. Another possibility may be associated with innate defects of immunity, affecting the cellular immune response mediated by viral aggression.[23]

When affected by COVID-19, diabetic patients experience exacerbated hyperglycemia, especially in older individuals.[24] Acute hyperglycemia has been associated with the activation of the angiotensin-converting enzyme 2 (ACE-2), which is the receptor for the coronavirus spike protein. Coronavirus infection reduces the expression of ACE2, inducing cell damage, hyperinflammation, and respiratory failure.[25] In addition, the virus has the potential to damage pancreatic beta cells, which can determine insulin deficiency and frequent cases of severe diabetic ketoacidosis on hospital admission.[23]

The COVID-19 event in diabetic patients, therefore, affected even the recommendations for drug treatment of type II diabetes. A group of drugs strongly indicated for the treatment in the context of high cardiovascular risk, frequent in HFpEF, are the Sodium-Glucose-Cotransporter 2 (SGLT2) inhibitors. Initial reports associated these drugs with an increased risk of developing ketosis in insulinopenic patients (type I

diabetes and some type II diabetes). In this scenario, a recent positioning of the Brazilian Societies of Diabetes, Endocrinology and Metabology, and Cardiology defined safety recommendations for the use of these drugs. In summary, the document does not recommend the use of SGLT2 inhibitors in patients with type I diabetes; suggests suspension in patients with type 2 diabetes, prone or not to ketosis, who are simultaneously using insulin, in case of symptomatic infection by the Coronavirus; does not recommend SGLT2 inhibitors for patients without diabetes or with pre-diabetes to reduce cardiovascular risk, and also does not recommend the use of SGLT2 inhibitors in hospitalized patients due to the increased risk of dehydration.[26] The content of these recommendations is based on the principle of patient safety in the COVID-19 pandemic scenario. Therefore, it does not seem relevant to discuss the potential withdrawal of the benefits of SGLT2 inhibitors to such patients with diabetes and HFpEF in the medium and long term.

Cardiovascular Disease and Prognosis in COVID-19

Preliminary data from the COVID-19 case series suggested that hypertension correlates with worse results (23.2%) compared to other metabolic disorders. It was postulated that this observation was correlated with the use of ACE inhibitors or angiotensin receptor blockers (ARB) instead of hypertension itself. This supposed correlation was rapidly disseminated among medical communities, which encouraged the hasty withdrawl of the use of these drugs in patients with COVID-19.[14]

This worsening seems to be related to the endocytosis of SARS-CoV2, which is mediated by the ACE-2 receptor and is fundamental in the viral life cycle. There are conflicting data on the effect of inhibitors of the renin-angiotensin-aldosterone system, including ACE inhibitors and ARB, on ACE2 activity in various human tissues and the resulting susceptibility to SARS-CoV2 infection. All available data are insufficient to recommend discontinuation of ACE inhibitors or ARBs in individuals with an existing indication for therapy with these drugs, and the main medical societies strongly recommended continuation of treatment. An open randomized study is underway to examine the effect of prophylactic withdrawal from ACE inhibitors or ARBs in individuals with COVID-19.[14]

Although the ACE-2 receptor may allow SARS-CoV2 to enter cells, its free circulation forms could then inactivate the virus, interrupting coupling to membrane ACE-2 receptors and the consequent entry into pulmonary endothelial cells. However, the circulating plasma level of ACE-2 may be insufficient to protect the ACE-2 receptors connected to the SARS-CoV2 coupling membrane. In addition to circulating soluble ACE-2, it was observed that mineralocorticoid receptor antagonists such as spironolactone, with a well-studied safety and risk profile, increase the expression of soluble ECA-2 in the plasma by 3 to 5 times.[27-29]

Three recent studies, with a large number of patients, evaluated the risk of using ACE inhibitors or ARBs in patients with COVID-19. A study that evaluated a potential harmful effect of ACE inhibitors and ARBs in 8910 patients hospitalized with COVID-19 showed that there was no potential harmful association between the use of ACE inhibitors or ARBs with hospital death in this clinical context.[30] Another study that evaluated 6272 patients with severe SARS-CoV-2 infection, where the use of ACE inhibitors and ARBs was more frequent in patients with Covid-19 than in the control group, showed no association between the use of ACE inhibitors or ARBs with a severe or fatal COVID-19 course.[31] Finally, Reynolds HR et al.,[32] evaluating in 12 594 patients the relationship between treatment with ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, and thiazide diuretics and the potential risk of these drugs in patients with COVID-19 showed that there was no substantial increase in relation to the association of these 5 common classes of antihypertensive drugs with the risk of developing severe conditions in patients who tested positive for COVID-19.[32]

The benefits of spironolactone in patients with HFpEF were assessed in the TOPCAT study, which showed a reduction in the number of hospital admissions for HF.[33] In patients with hypertension, spironolactone is widely used, being indicated as the fourth medication in the treatment of resistant arterial hypertension.[34]

More recently, a hypothesis has suggested that inhibition of the angiotensin 1 receptor (AT1R) may provide benefits to patients with COVID-19. AT1R antagonists are widely used in hypertensive patients and increase the cardiac expression of ACE2 in rats and the urinary concentration of ACE2. Therefore, a higher expression of ACE2 after chronic therapy with angiotensin receptor blockers can protect patients with COVID-19 from acute lung injury. In this scenario, the role of neprilisin (NEP) and its sacubitrile

inhibitor should also be reviewed. Recently, Zhang et al.[35] demonstrated that sacubitril / valsartan reduced the concentration of pro-inflammatory cytokines and the neutrophil count, while increasing the lymphocyte count more than valsartan alone or placebo in patients with acute HF. This evidence supports the biological plausibility of the early administration of sacubitril / valsartan in patients with COVID-19, in order to maximize the anti-inflammatory effects of sacubitril and contain the effect of Angiotensin I in the lungs.[36] It should be noted, however, that there has been no clinical studies evaluating cardiovascular outcomes that support this practice.

Therapeutics for COVID-19 and Cardiovascular Disease

HFpEF patients with multiple comorbidities are at high risk of death in the case of SARS-CoV2 infection, therefore it is imperative that preventive measures be taken. To date, there is no vaccine to prevent COVID-19. The best prevention is to avoid exposure to the virus. The usual preventive measures that can reduce the risk of exposure include: wearing face masks; regular hand washing with soap or disinfection with hand sanitizer containing at least 70% alcohol; avoiding contact with infected people, keeping an adequate distance; and refraining from touching the eyes, nose and mouth with unwashed hands.[37] In addition, patients with HFpEF should be vaccinated against pneumococcal pneumonia and influenza.

Social isolation to prevent COVID-19 does not necessarily mean the adoption of a sedentary lifestyle. Patients with HFpEF in functional class II and III benefit from regular aerobic exercise to improve their functional capacity and diastolic function.[35] Whenever possible and within the precautions of respiratory contamination, exercise should be maintained.

HFpEF patients use polypharmacy to control comorbidities such as angiotensin-converting enzyme (ACEI) inhibitors, diuretics, statins, oral hypoglycemic agents, and some medications that can reduce hospitalization due to HF decompensation, such as spironolactone, candesartan, nebivolol and sacubitril / valsartan, in female patients and with a left ventricular ejection fraction of less than 57%, as evidenced in the PARAGON-HF Study.[38,39] Such prior medications must be maintained in the pandemic and in the eventual contamination by the virus.

The antiviral properties of chloroquine (CQ) were previously observed in HIV and other viruses. It has been postulated that CQ and Hydroxychloroquine (HCQ) inhibit endosomal maturation, a process by which endosomes are translocated from the cell to central hubs. In addition, CQ could prevent the viral replication of SARS-CoV1 in vitro. A follow-up study demonstrated comparable effectiveness of HCQ, a less toxic derivative, and suggested that the mechanism of decreased endosomal maturation did indeed apply to SARS-CoV2 infection in vitro. So far, the role of HCQ in COVID-19 has only been evaluated in non-blind, non-randomized, and low-quality studies. At the time of writing this article, CQ and HCQ have clinical off-label use authorized by the Federal Council of Medicine. There are ongoing clinical trials which assess the in vivo outcome of this hypothetical property. In addition, CQ and HCQ prolong the QT interval, which increases the risk of a pro-arrhythmic effect. Significant caution should therefore be taken when initiating these agents in patients with a QTc interval >500ms, in those with congenital long QT syndrome, with structural heart disease, or under concomitant use of other QT interval prolonging agents.[14] In fact, a recently published observational study with more than 96 000 patients hospitalized for COVID-19 showed an increased risk of death with HCQ and CQ when used alone or in association with a macrolide.[40]

Chloroquine and Hydroxychloroquine cardiomyopathy

There are case reports which relate the use of CQ and HCQ with the onset of diastolic and systolic ventricular dysfunction, dilated cardiomyopathy, pulmonary hypertension secondary to left ventricular dysfunction, atrioventricular blocks, and ventricular tachyarrhythmias. In most cases, reversibility is observed after drug withdrawal. Diagnostic confirmation is given by the presence of cytoplasmic curvilinear bodies on electron microscopy of the cardiac muscle added to the clinical history of using CQ or HCQ, and the absence of other factors.[41-44] A possible genetic predisposition is speculated such as the polymorphism of α-galactosidase A, the genetic basis of Fabry's disease. Both CQ / HCQ cardiomyopathy and Fabry disease have clinical and histological similarities.[45]

Pandemic and Delayed Care for Patients with Decompensated HF

The evidence that the hospital can be a place where the infection can be contracted has dramatically reduced the access of non-COVID-19 patients to emergency care and emergency services, as well as elective hospital activities not related to COVID-19. The need to reorganize hospital activities to treat patients who suffer from severe forms of COVID-19 requires us to learn the safe treatment of patients who stay at home with milder forms of COVID-19, and the need to keep more vulnerable individuals, such as those with HFpEF, out of hospital. The flexible use of tools such as telemedicine, for integration and not as an alternative to traditional care, adapted to the needs of clinical, family and social health contexts, could allow the creation of personalized, effective, and efficient management programs for the care of these patients,[46] as recommended in the II Brazilian Directive on Telemedicine in Cardiology of the Brazilian Society of Cardiology.[47]

Final considerations

HFpEF is multifactorial and has a pathophysiological relationship with multiple comorbidities such as hypertension, diabetes, obesity, atrial fibrillation, advanced age, and atherosclerosis. The systemic inflammatory state is a common link between these elements. COVID-19 has a well-defined etiological agent; however, its morbidity and lethality vary with the host. The intense systemic inflammatory response also seems to be the link that explains the worsening of the clinical condition. Comorbidities have emerged as predictors of poor prognosis in SARS-CoV2 infection since the beginning of its description, and in both HFpEF and COVID-19, they constitute the pernicious and disastrous element. If they are in pairs - HFpEF and COVID-19 - maximum alert, double care.

Author contributions

Conception and design of the research: Mesquita ET; Jorge AJL; Villacorta Junior H; Danzmann LC; Martins WA. Writing of the manuscript Mesquita ET; Jorge AJL; Villacorta Junior H; Danzmann LC; Martins WA. Critical revision of the manuscript for intellectual content : Mesquita ET; Jorge AJL; Villacorta Junior H; Danzmann LC; Martins WA.

Potential Conflict of Interest

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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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CASE REPORT

Entrapment of Broken Guidewire in the Coronary Artery: A Rare Percutaneous Coronary Intervention Complication Requiring Urgent Revascularization

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Introduction

Entrapment and fracture of the coronary guidewire is a rare complication of percutaneous coronary interventions (PCIs). The incidence of such complication in PCI is reported to be between 0.2 and 0.8%.[1,2] Despite technical improvements and development of more flexible and high-quality guidewires, the incidence of these complications is increasing.[3]

There are many management strategies for entrapped guidewires reported in the literature. In a report including 67 patients, surgery was performed in 43.4%, percutaneous interventions were performed in 41.8% and conservative therapies were chosen for 14.9% of the patients.[4]

Herein, we reported a case of broken and entrapped guidewire in a coronary vessel during PCI which was removed by open heart surgery.

Case report

A 53-year old male patient was referred to our center with the diagnosis of non-ST elevated myocardial infarction (NSTEMI). He had a history of chest pain which lasted for approximately six hours. He had chronic coronary artery disease and had been using acetylsalicylic acid (ASA) and metoprolol for seven years. He also had a history of PCI performed in another health center two years before. Coronary angiography and PCI were planned for the patient after primary evaluation in the emergency room. Laboratory results showed a troponin T level of 0.166 ng/mL, total cholesterol of 213 mg/dL and low-density lipoprotein (LDL) of 150 mg/dL. There was no sign of myocardial ischemia in the electrocardiogram (ECG). The left ventricular ejection fraction (LVEF) was 60% and concentric left ventricle hypertrophy was observed by echocardiograph.

A diagnostic coronary angiography revealed a plaque in the middle segment of the left anterior descending (LAD) artery, and PCI was then performed. A 182 cm x 0.014" floppy guidewire was introduced into the LAD artery and another guidewire of the same size was introduced into the diagonal artery for prevention of the diagonal artery occlusion through the right femoral arterial access sheath. A coronary stent (Coroflex® ISAR NEO 3.0 mm X 16 mm, B. BRAUN, Germany) was implanted into the lesion in the middle segment of the LAD artery at 16 atm pressure. Unfortunately, the distal piece of the guidewire in the diagonal artery broke and was entrapped in the coronary artery (Figure 1). Although the remaining piece of the guidewire was easily removed, the piece entrapped in the coronary artery could not be removed with the loop snare or an angioplasty balloon (3.5 x 15 mm, NC Boston Scientific). After failure of these measures, an urgent coronary bypass operation was planned. The patient had no chest pain or arrhythmias during or after the PCI procedure.

After preparation for the coronary artery bypass graft surgery (CABG), the patient was transferred to the operating room. Cardiopulmonary bypass was initiated after standard median sternotomy and cavoatrial cannulation. The left internal mammary artery (LIMA) graft and the saphenous vein graft (SVG) were harvested. The coronary arteries were exposed. The retained piece of guidewire in the coronary artery could not be removed

Keywords

Coronary Artery Disease; Myocardial Infarction; Angiography, Coronary; Percutaneous Coronary Intervention/complications, Device Removal; Myocardial Revascularization.

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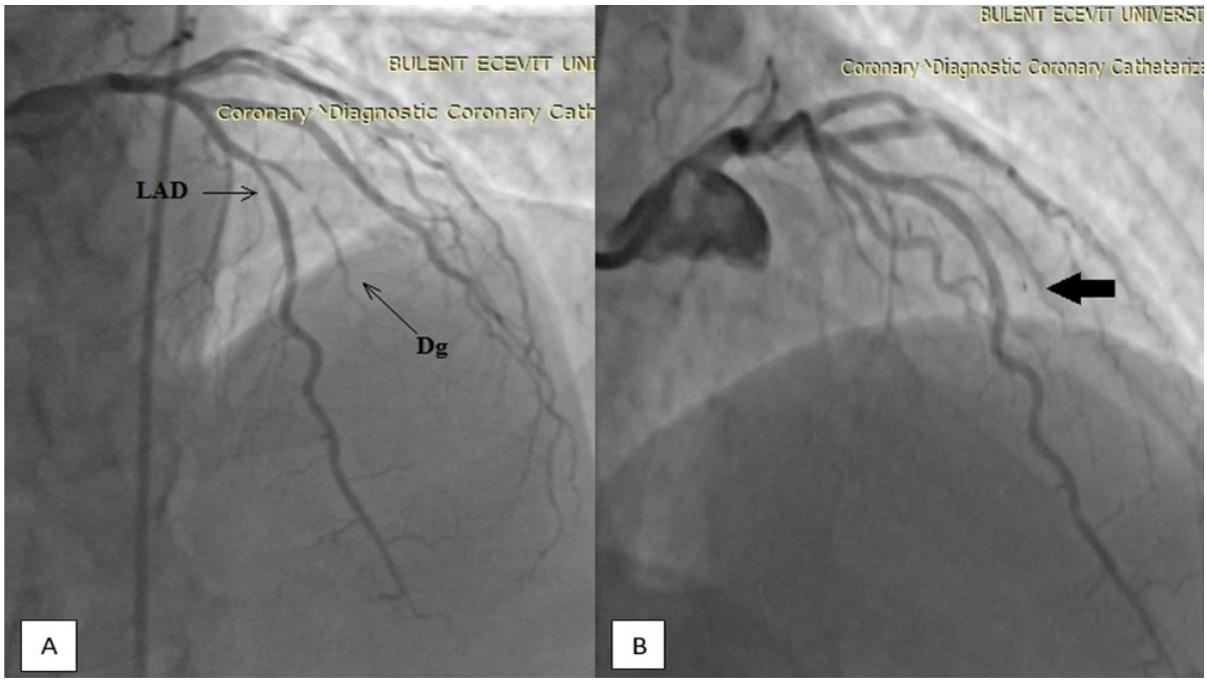

Figure 1 - A) Lesions of the LAD and diagonal arteries (arrows); B) The stuck guidewire in the diagonal coronary artery (arrow).

by arteriotomy of the diagonal artery. Then aortotomy was performed and the 12 cm piece of guidewire was successfully retrieved (Figure 2). Then an aorta-LAD artery to the LIMA graft bypass and an aorta-diagonal artery to the SVG bypass were performed. There were no complications in the postoperative period and the patient was discharged after four days.

Discussion

Complex and bifurcation lesions of the coronary arteries, multiple usages of the same guidewire lead to structural deterioration of the wire, which increases the risk of guidewire entrapment in the coronary vessel.[3] Over-rotation or entrapment of the distal tip of the guidewire in a coronary vessel can also lead to the wire fracture.[3]

The guidewire fragments retained in the coronary artery can cause arterial embolism, thrombosis, dissection, and rupture of the vessels.[3] Treatment options of entrapped guidewire are percutaneous intervention techniques, conservative therapies, and open surgery.[1,4] Percutaneous intervention techniques are recommended as the treatment of choice. The most commonly used percutaneous technique in this complication is the snare loop and its modifications. Small pieces of guidewire can remain in the distal segments of the coronary arteries or in chronically occluded or thrombosed vessels if they do not cause any adverse effects. If percutaneous techniques fail and signs of ischemia are observed, then the patient should be urgently transferred to open surgery.[3] Surgical treatment consists of removal of the retained piece of guidewire and revascularization of the affected coronary arteries.[5]

In the present case, guidewire entrapment was probably caused use of a reused guidewire, which was entrapped in a calcified coronary plaque and broke in the femoral region after forceful attempts to remove it. The distal part of the guidewire extended to the ascending aorta from the diagonal artery. Urgent surgery was preferred in this case after failure of percutaneous intervention techniques and because the conventional method was not applicable.

Conclusion

The number of studies about surgical removal of fractured guidewire entrapped in a coronary artery is

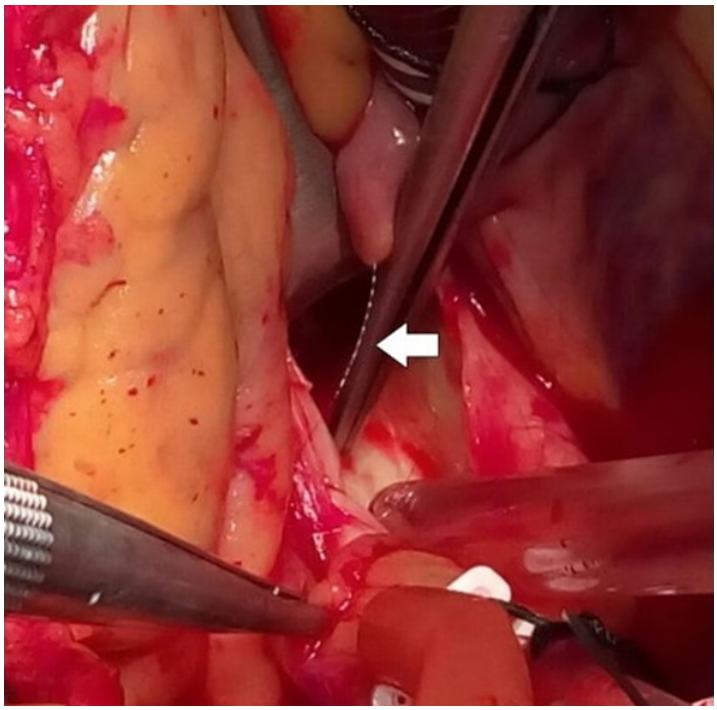

Figure 2 - Intraoperative image of the guidewire piece in the aorta.

very limited in the literature. The most recommended treatment is the urgent surgical removal of the extraneous material from the coronary circulation. We believe that new percutaneous techniques should be developed for the treatment of calcified plaques to reduce the risk of guidewire entrapment.

Author contributions

Conception and design of the research: Coskun E; Acquisition of data: Coskun E, Tekin A; Analysis and interpretation of the data: Altınay L; Statistical analysis: Altınay L, Coskun E; Obtaining financing: No; Writing of the manuscript: Coskun E, Altınay L; Critical revision of the manuscript for intellectual content: Tutun U; Supervision / as the major investigador: Coskun E, Altınay L, Tutun U.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

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

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CASE REPORT

Congenital Heart Disease Revealing Familial 22q11 Deletion Syndrome

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Abstract

Congenital heart defects are the most common birth defects and the leading cause of mortality in the first year of life. It is well known that the 22q11 deletion syndrome (22q11DS) is the most common microdeletion syndrome in humans and that congenial heart diseases (CHDs) are one of the most common phenotypic manifestations. However, it should be noted that the 22q11 deletion was also found in a significant number of patients with isolated CHD. The 22q11DS phenotype may include cardiovascular anomalies, palatal abnormalities, nasal voice, immune deficiency, endocrine dysfunctions, a varying degree of cognitive deficits and intellectual disabilities, velopharyngeal insufficiency, and characteristic craniofacial dysmorphism. This condition affects about 1 in 4,000 live births, making 22q11DS the most common microdeletion syndrome in humans. Here we describe the cases of three children who were referred to the clinical hospital center with the diagnosis of CHD, but with no direct signs of 22q11DS. Investigation of familial data led us to suspect that the mothers could be carriers of 22q11DS. The multiplex ligation-dependent probe amplification (MLPA) testing confirmed that the patients and mothers exhibited 3 Mb 22q11 deletions, which justified the clinical signs in the mothers and the CHD in children. In the presence of a few characteristics that are common of a spectrum of some known syndromes, a familial examination can provide clues to a definitive diagnosis, as well as to the prevention of diseases and genetic counseling of these patients.

Keywords

Congenital Heart Disease/genetics; Face/abnormalities/genetics; DiGeorge Syndrome/genetics; Chromosomes, Human, Pair 22/genetics; Chromosome Deletion.

Introduction

Congenital heart defects (CHDs) are the most common group of birth defects in humans that arise during cardiac embryogenesis and differ in morphology, physiology, and clinical outcome. They occur in about 1% of all live births irrespective of ethnic backgrounds, socioeconomic conditions, and geographic barriers.[1] The causes of CHDs are multiple, and typically categorized in genetic and nongenetic factors. Nongenetic factors include teratogenic exposures during pregnancy and epigenetic alterations. Identifiable genetic etiologies are reported to be as high as 40% in syndromic CHD, including single gene disorders, chromosomal anomalies, and copy number variations (CNV).[2]

The 22q11.2 deletion syndrome (22q11DS; Online Mendelian Inheritance in Man #602054) is the most frequent microdeletion syndrome, and is one of the most common genetic causes of CHD, responsible for 1.5% to 5% of all CHD at birth.[3] This genetic disorder affects pharyngeal and neurobehavioral development, and causes congenital heart defects, velopharyngeal insufficiency, hypoparathyroidism, thymic aplasia or hypoplasia, craniofacial dysmorphism, learning difficulties, and psychiatric disorders.[1] Combination of these signs differ from patient to patient, resulting in a large number of phenotypes ranging from normal to severely handicapped individuals.[2] The frequency of clinical signs was previously reported by our group in a study involving 179 patients with 22q11DS confirmed by genetic tests (Table 1). Usually, 15–20% of the CHDs are conotruncal heart defects (CTDs). CTDs are more commonly associated with 22q11DS and comprise

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structural malformations that are similar to ventricular outflow tract defects. These include the Tetralogy of Fallot (TOF), pulmonary atresia with ventricular septal defect (PA-VSD), a double outlet right ventricle, transposition of the great arteries, persistent truncus arteriosus, and an interrupted aortic arch.[3] Low-copy repeats (LCRs) of 22q11 have been suggested to mediate a non-allelic homologous recombination, resulting in 22q rearrangement. An unequal crossover between the LCRs usually results in a 3 mebabase (Mb) deletion in one copy of chromosome 22, and a reciprocal and similarly sized duplication in the other one.[4] A microscopic deletion at 22q11 occurs in approximately 1 out every 4,000 live births. Different deletion genotypes have been delineated to this condition: a predominant 3-Mb deletion accounting for 90% of the cases, a 1.5–2-Mb deletion in 8%, and atypical smaller deletions in 2%. Phenotypic variability has been attributed to the presence or absence of genes in the breaking points, and CNVs depending on the size of the deletion.[5] Familial cases of 22q11DS present a higher frequency of uncommon 1.5–2 Mb deletions;[6] patients with this deletion have symptoms that are indistinguishable from those seen in patients with larger deletions, indicating that this region may be fundamental to the phenotype.[7-10] Here we describe the cases of three children who were referred to our hospital with diagnoses of heart disease and no signs of 22q11DS, which turned out to be familial cases of 22q11DS.

Table 1 - Frequency of clinical features in patients with 22q11.2DS

Clinical features	Frequency
Abnormal ears	45%
Hypoplastic alae nasi	29.40%
Long face	41%
High nasal bridge	19.60%
Broad nasal root/nose	24%
Micro/retrognathia	47.70%
Epicanthic folds	19%
Malar flattening	32%
Long digits	68.30%
Narrow palpebral fissures	73.20%
Hypoplastic face	34%
Speech delay	76.40%
Learning disabilities	75%
Behavioral disturbances	72.50%
Palatal abnormality	66.00%
Congenital heart disease	64.60%
Ventricular septal defect	35.8%
Atrial septal defect	28.3%
Tetralogy of Fallot	20.0%
Pulmonary atresia/stenosis	11.3%
Persistent truncus arteriosus	5.6%

Clinical reports

This study was approved by the ethics committee of the Federal University of Goiás in Goiania, Brazil. Written informed consent were obtained from all family members included in the study.

Proband 1 was a 16-month-old girl born via cesarean section at term. The parents were nonconsanguineous, including a 23-year-old gravida 1, para 1 (G1P1) mother and a 27-year-old father. Her birth weight was 3,280 g (25–50th percentile), length was 46 cm (3rd percentile), and occipital frontal head circumference (OFC) was 35 cm (> 50th percentile). A clinical examination at the age of 16 months showed a round face, narrow forehead, TOF, and normal development. Clinical examination of the mother revealed a long face, mid-face hypoplasia, retrognathia, slender hands and digits, long toes, hypernasal speech, a speech delay, and a learning disability. The clinical examination of her grandmother showed epicanthic folds, retrognathia, normal development, and a surgically corrected cleft palate. Further information from the family also revealed an individual who died at birth due to heart disease (Figure 1A1). Pictures of this family were not allowed for publication.

Proband 2 was a 19-month-old boy who was born via cesarean section at term. The parents were nonconsanguineous, including a 26-year-old G1P1 mother and a 29-year-old father. His birth weight was 3,360 g (25–50th percentile), length was 47 cm (3rd percentile), and OFC was 35 cm (> 50th percentile). Clinical examination at 19 months of age showed interventricular communication and normal development, with no further clinical features. Clinical examination of his mother revealed a long face, small mouth, dysmorphic

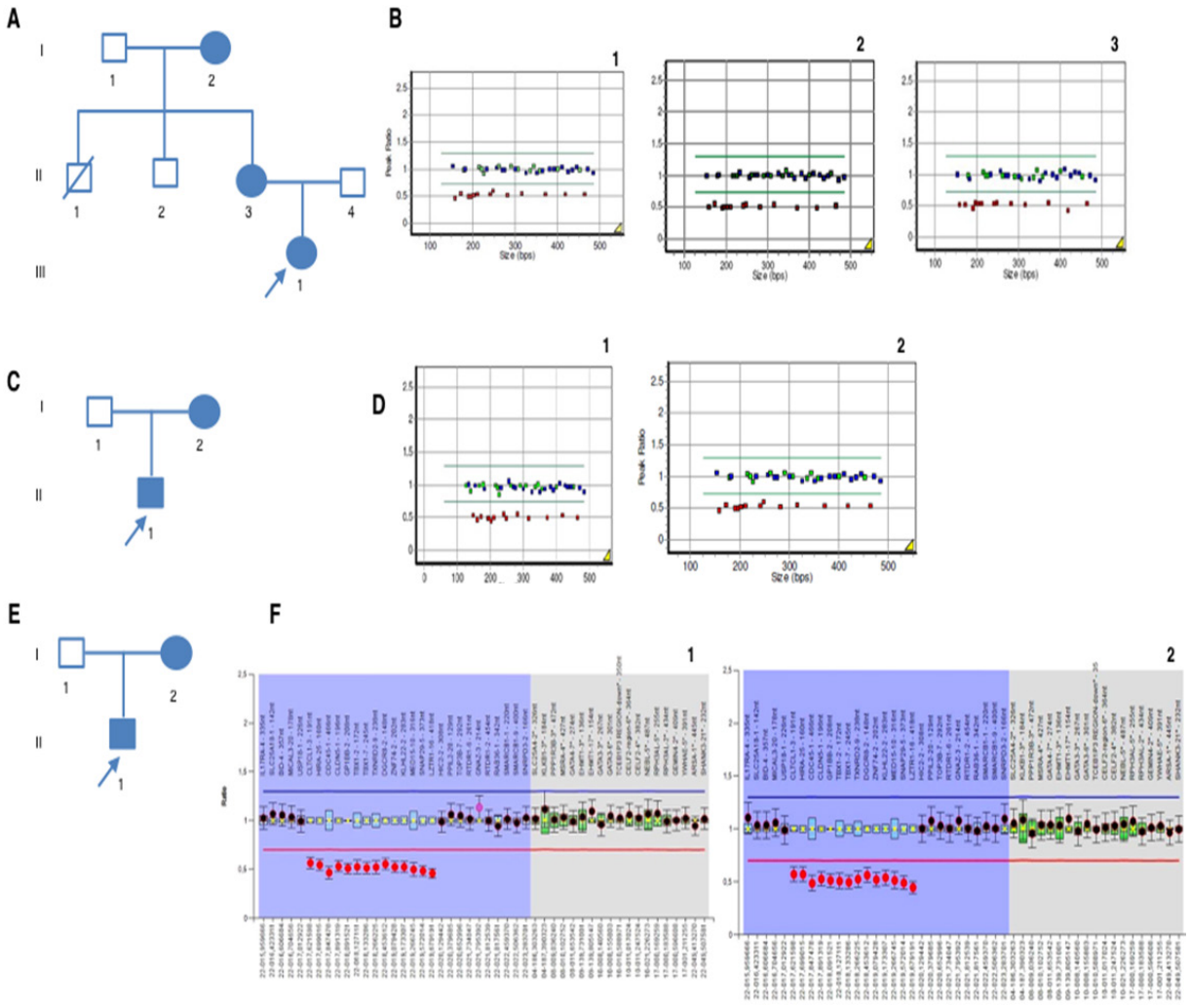

Figure 1 - A. Proband 1' family pedigree. Individuals 1 and 3 presented 3 Mb deletions at 22q11 without congenital heart defects (CHDs). Individual 4 is the proband and presented a 3 Mb deletion at 22q11 with a CHD. Individual 2 had a CHD and died at birth, with no further information. B. Results of multiplex ligation-dependent probe amplification (MLPA) of the proband 1's family showing a deletion from the LCR22-A to LCR22-D in the child (1), mother (2), and grandmother (3). C. Proband 2's family pedigree. Individuals 1 and 2 presented 3 Mb deletions at 22q11, but only individual 2 had a CHD. D. The MLPA results of the proband 2's family showed a deletion from the LCR22-A to LCR22-D in the child (1) and mother (2). E. Proband 3's family pedigree. Individuals 1 and 2 presented 3 Mb deletions at 22q11, both had CHDs. F. The MLPA results of the family of the proband 3 showed a deletion from the LCR22-A to LCR22-D in the child (1) and mother (2).

ears, and learning disability; clinical examination of his father was normal.

Proband 3 was a 2-year-old boy who was born via cesarean section at term. The parents were nonconsanguineous, including a 31-year-old G1P1 mother and a 30-year-old father. His birth weight was 3,120 g (25–50th percentile), length was 46 cm (3rd percentile), and OFC was 36 cm (> 50th percentile). His clinical examination at 25 months of age showed pulmonary atresia with interatrial communication and a short stature. Clinical examination of his mother showed upslanting palpebral fissures, a prominent nose, and speech delay. Clinical examination of the father was normal.

Methods

Multiplex ligation-dependent probe amplification (MLPA) was performed on DNA from peripheral blood

lymphocytes, extracted using the Puregene Blood Core Kit C (Qiagen Sciences Inc., Germantown, MD, USA). The SALSA MLPA probemix P250 DiGeorge syndrome test kit (MRC-Holland BV, Amsterdam, Netherlands) was used to determine the copy number changes in the 22q11.2 region. The MLPA was performed following the manufacturer's instructions, and all runs included DNA from three normal controls to calibrate the unknown samples. The reaction products were detected using an ABI-3500 Genetic Analyzer (Applied Biosystems Inc., Foster City, CA, USA). To size the polymerase chain reaction (PCR) products and obtain the peak areas, we used the GeneMapper Software (Applied Biosystems Inc.). These data were exported into the GeneMarker software (Softgenetics LLC, State College, PA, USA) or Coffalyser.Net software (MRC-Holland BV) for analysis.

Results

The MLPA results of the proband 1's family showed a deletion of 3 Mb extending from LCR22-A to LCR22-D in the patient, mother, and grandmother. The MLPA results of the probands 2 and 3's families showed a deletion of 3 Mb extending from LCR22-A to LCR22-D in the patient and mother. Figure 1 shows the family pedigrees of probands 1, 2, and 3, as well as the MLPA results of these families.

Discussion

CHDs often occur in association with other malformations and as a feature of well-defined genetic syndromes. Frequently, heart defect is one of the first signs of a genetic disorder that may result in an important medical problem in early childhood.[11] The 22q11 chromosomal region deletion is considered the second most common cause of CHDs after Down syndrome,[12] and cardiovascular manifestations of the 22q11 deletion are highly variable.[13] According to the literature, the del22q11.2 is usually sporadic, with prevalence of familial cases ranging from 6% to 28% of patients with this disorder.[8-10] In the present work, we reported three familial cases of individuals who presented the same 3 Mb deletion in the 22q11 region. Approximately 87% of the patients with 22q11DS have a common 3 Mb deletion region, known as the "common" deleted region (CDR), which includes at least 48 known genes. Smaller deletions may occur more frequently in familial cases than in non-familial cases with del22q11.2.[6] It has been hypothesized that individuals with the small deletion may have a milder phenotype, and a better chance to produce offspring.[13] However, molecular analysis of the 22q11.2 region in our families revealed the presence of 3 Mb deletion in an individual that we had considered as having a mild phenotype. Once familial cases are relatively less frequent, it is difficult to affirm that the size of the deletion is related to familial cases or to the phenotype. The expected 90% frequency of the 3 Mb deletion was observed in the families studied. They presented a clinical variability ranging from the typical characteristics of a 22q11 deletion, as observed in the mother, to only a CHD, as observed in the child.

In the present familial reports, we observed that the affected parent was the mother. Devriendt et al.,[6] reported that the affected parent of all index patients was also the mother. They concluded that this was compatible with the previous hypothesis that this preference for maternal inheritance in familial cases could be due to either decreased fertility[13,14] or decreased reproductive success[13-15] in the affected males, with respect to the affected females. However, Matsuoka et al.,[16] suggested that there was no relationship between fertility and del22q11.2. Although the three families has been investigated to fertility, it is possible that there is a preference for maternal inheritance in familial cases, as pointed out by several authors.[13,14]

The role of the 22q11 region genes in nonsyndromic CHDs is unclear. A mutational analysis of the TBX1 gene, which maps to the 22q11 chromosomal region commonly deleted in patients with DiGeorge/velocardiofacial syndrome, failed to detect the pathogenetic mutations in nonsyndromic individuals with the specific conotruncal defect subtypes commonly found in del22.[17,18] In the present study, based on the clinical features of the probands, we would not suspect 22q11DS, because the main clinical characteristic was CHD, which was the reason why these children were referred to our clinic. The presence of some of the characteristics of 22q11DS were observed in the mothers (we did not have permission to publish the images of the families), which encouraged us to investigate the presence of the deletion in these individuals. The region in the patients reported here encompasses the TBX1 gene, which can be considered the causative agent, and the differences existing between the mother's and child's phenotypes could be attributed to the presence or absence of genes in the breaking points, plus copy number variations in the rest of the genome.[5] Moreover, the possibility that

this intrafamilial phenotype variability may be related to an unknown molecular mechanism or stochastic factors cannot be denied.[19]

Even though the 22q11DS is considered a relatively common chromosomal abnormality, it is still an underdiagnosed condition in the general population, even more so in developing countries and diverse populations, and in many cases the 22q11DS is secondary to a CHD.[20] In many countries, this conditions have not been systematically recognized by pediatricians, neonatologists and cardiologists, particularly in the first year of life.[21]

The prevalence of 22q11.2DS in patients with CHD has been estimated in attempt to establish a screening for this condition in CHD patients, with or without other features of the syndrome.2,13 In the present study, we investigated three probands that presented CHDs and we identified some of the clinical signs in the mothers, which led us to confirm the presence of 22q11 familial deletions.

The 22q11DS is a constitutional disease with a broad spectrum of phenotypes. Thus, if a child is initially evaluated for CHD, it is probable that other clinical signs will appear throughout the course of the disease. Therefore, the early diagnosis of the syndrome allows a better prognosis and treatment of these patients. It is of note, however, that the presence of microdeletion does not imply the occurrence of postoperative complications.

In the presence of a few or even unique features, as in CHD, within the spectrum of some known syndromes, a familial examination could provide definitive clues for a diagnosis, as well as to prevention and genetic counseling of patients.

Author contributions

Conception and design of the research: Santos MVPF, Ribeiro-Bicudo LA. Acquisition of data: Santos MVPF, Gamba BF, Empke SLL, Alves CC. Analysis and interpretation of the data: Santos MVPF. Gamba BF. Writing of the manuscript : Santos MVPF, Gamba BF, Bérgamo NA. Critical revision of the manuscript for intellectual content: Ribeiro-Bicudo LA.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Bruno Faulin Gamba, from *Universidade Federal de Goiás*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CONEP under the protocol number 1.966.673. 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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CASE REPORT

The Association between Covid-19 and ST Elevation Myocardial Infarction: Variable Clinical Presentations on a Case Report Series

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Introduction

The current global pandemic caused by the new coronavirus (COVID-19) already reaches 185 countries with approximately 3 million infected people and more than 200 thousand deaths.[1,2] With continental dimensions and an elevated socioeconomic disparity, Brazil, by the beginning of May, presents with increasing infection rates and mortality close to 8%. The numbers may be higher considering the lack of adequate testing of the population and healthcare professionals.[3]

According to the World Health Organization (WHO), cardiovascular diseases represent the leading cause of deaths around the world.[1]. Recent reports confirmed that patients with cardiovascular comorbidities are at a higher risk to develop the most severe form of the COVID-19. [4-6] The association between these two pathologies can lead to high morbidity and mortality rates and has been the object of continuous efforts by the medical community. In this sense the management of Acute Coronary Syndrome (ACS) has undergone changes in both diagnosis and treatment since the beginning of the pandemic.[7-10] Another aggravating factor regarding the approach of ACS during this period is the multiple clinical presentations and differential diagnosis associated with COVID-19, such as myopericarditis, pulmonary embolism and arrhythmia.[4-6]

Keywords

Coronavirus; COVID-19; Pandemics; ST Elevation Myocardial Infarction; Morbidity and Mortality; Acute Coronary Syndrome; Diabetes Mellitus; Hypertension; Chest Pain; Severe Acute Respiratory Syndrome.

We report a series of three cases of ST-elevation myocardial infarction (STEMI) that represent the impact of COVID-19 in the management of ACS and the main protocol adaptations in the largest private hospital group in Brazil (Rede D'OR São Luiz). This report was approved by the responsible Ethics Committee and the Informed Consent Form was not required.

Case 1

We report the case of a 71-year-old male with systemic arterial hypertension (in use of angiotensin II receptor blocker), insulin dependent diabetes mellitus and dyslipidemia referred to the cardiovascular emergency unit due to oppressive chest pain initiated in the previous 24 hours, which worsened within the next 2 hours. He denied flu-like symptoms and reported fear of going to a hospital due to the risk of contamination by SARS-CoV-2.

At admission, vital signs were stable and physical examination revealed no significant changes. The electrocardiogram (ECG) showed ST-Elevation at inferior leads and ST depression in V2-V4 (Figure 1).

According to the institutional protocol, the patient was treated with Aspirin 300 mg, Ticagrelor 180 mg, Atorvastatin 80 mg and was immediately sent to the Cardiac Catheterization Laboratory (CCL). A total obstruction in the proximal segment of the right coronary artery (RCA) associated with a large amount

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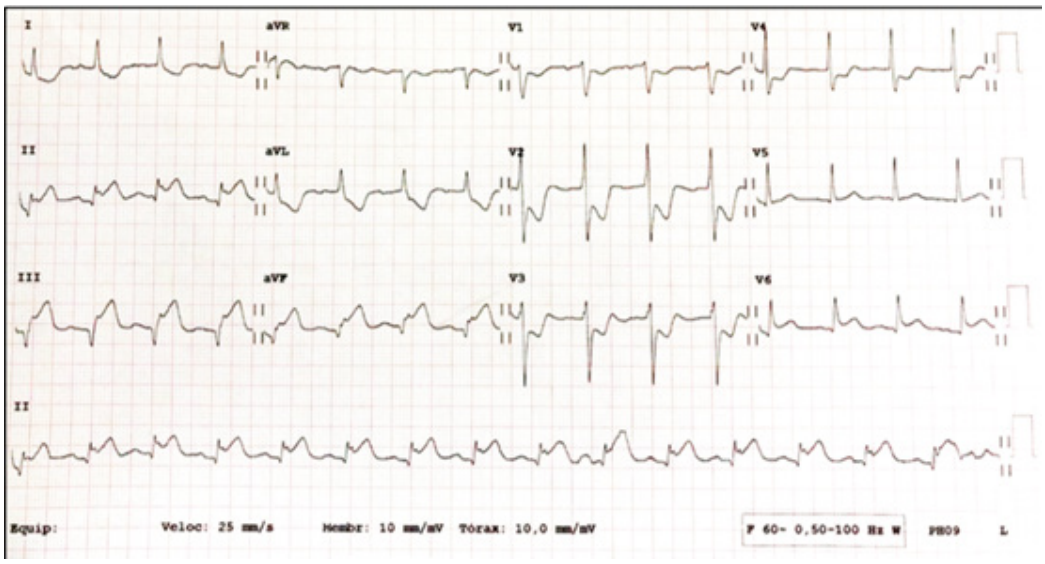

Figure 1 – EKG with ST elevation in II, III, aVF and ST depression in V2,V3, V4.

of thrombus was found and a primary percutaneous intervention (PCI) with 2 drug-eluting stents (DES) was performed. There was also a severe lesion at the proximal segment of the left anterior descending artery (LAD), which was not treated in the index procedure. The treatment of the LAD, as routinely carried out in multivessel disease patients with STEMI, was successfully performed within 48 hours with one DES. Later on that day, the patient had 2 episodes of fever without any respiratory symptoms, which were initially attributed to post-infarction stress. In the next morning, due to persistence of the fever and considering the pandemic scenario, a nasopharyngeal swab was collected, which was positive for SARS-CoV-2. Computed tomography (CT) of the chest revealed infectious focus and ground-glass opacities at the right lung. The patient was transferred from the Coronary Unit to an isolated intensive care unit dedicated to COVID-19 care. At that moment, antibiotics (Azithromycin included) were started in combination with Hydroxychloroquine (HCQ), but the fever persisted until the twelfth day of hospitalization, when there was a significant worsening of the respiratory condition, with hypoxemia and need of mechanical ventilation.

Laboratory tests revealed a leukocytosis of 19.390/mm^3, a D-dimer of 7.348 ng/dl new troponin-I elevation (1.85 ng/ml). Transthoracic echocardiography (TTE) did not reveal any worsening of left ventricular function.

A new chest CT showed increased consolidation area, at this point bilaterally, with approximately 50% of the parenchyma involved (Figure 2). The patient had an unfavorable evolution, which led to renal failure and refractory hypoxemia, despite the mechanical ventilation, evolving to death 14 days after hospital admission.

Case 2

A 69-year-old man with a previous history of hypertension and no coronary artery events in the past presented to the emergency room (ER) with fever, cough and fatigue in the previous week. His symptoms worsened within the next 24 hours, with onset of dyspnea and fatigue. He was lucid, with tachydyspnea and denied chest pain. Physical examination revealed blood pressure of 200 x 110 mmHg, a heart rate of 80 bpm and oxygen saturation of 78%, with no fever. Cardiac and pulmonary auscultation showed an S3 gallop and rales. Arterial gas analysis revealed a PH 7.47, oxygen partial pressure of 66%, a carbon dioxide partial pressure of 30mmHg and lactate level of 18.8 mg/dL. Since the patient had respiratory failure and a flu-like syndrome in times of COVID-19 pandemic, orotracheal intubation and invasive ventilation were needed. Low-dose vasopressor was given after a blood-pressure drop following sedation. Only after clinical stabilization had been achieved, a 12-lead ECG was performed, which showed anterior ST elevation,

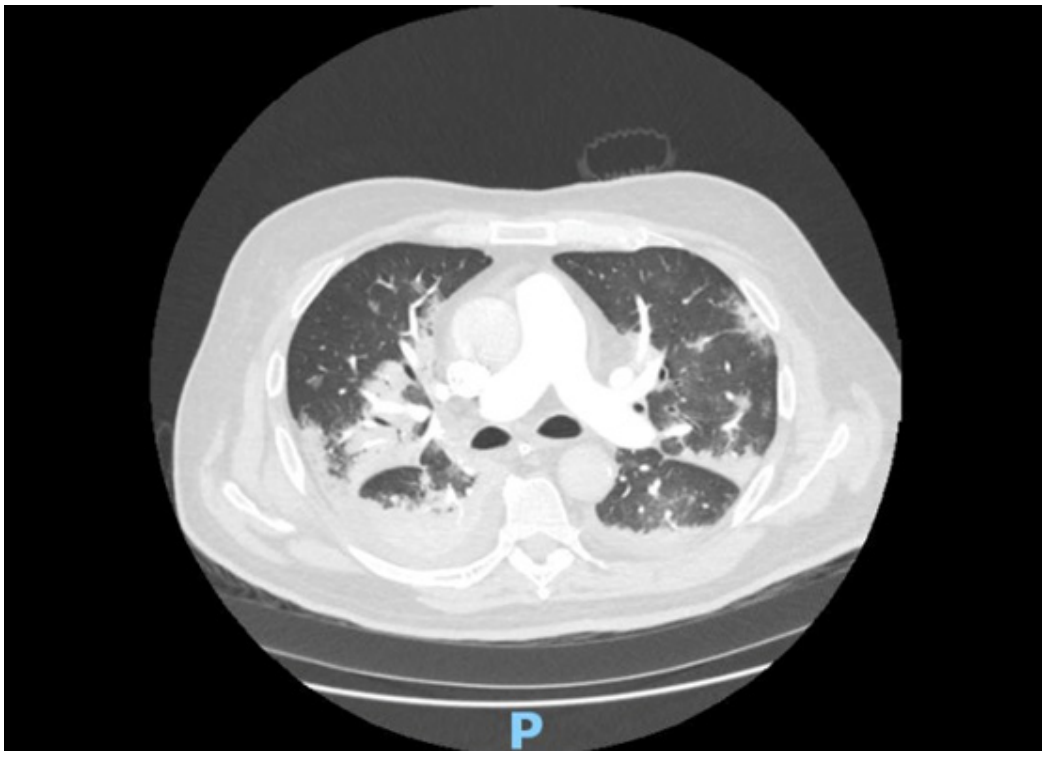

Figure 2 – Chest Computed Tomography with bilateral involvement.

Q-wave in anteroseptal leads, suggestive of a subacute transmural myocardial infarction. The chest x-ray revealed no cardiac enlargement with interstitial and alveolar edema. TTE showed normal left ventricular dimensions despite apical akinesis, with an estimated LV ejection fraction of 44%. There was no evidence of heart valve disease. In face of all these findings suggestive of an AMI combined with a flu-like syndrome, the patient was referred to CCL. The angiography revealed a thrombotic occlusion of the mid portion of the LAD artery. The patient underwent a 2 drug-eluting stent PCI in the LAD artery, with no-reflow phenomena, and was successfully treated with intracoronary adenosine. Door-to-reperfusion time was prolonged (162 min). After coronary treatment, the patient was sent to ICU hemodynamically stable, with an oxygen saturation of 99% and a FiO2 of 80%. His laboratory tests showed elevated troponin, lymphopenia and a normal renal function. A nasopharyngeal swab (PCR) test confirmed SARS-Cov-2 infection and a chest CT showed findings of pulmonary edema, pleural effusion and intersticial ground-glass infiltrate pattern (Figure 3). He had good clinical improvement, with discharge 16 days after admission.

Case 3

We present the case of a 42-year-old female without any comorbidities and onset of flu-like symptoms in the previous 7 days. She was admitted to the ER with weakness, cough and shortness of breath. She rapidly evolved with respiratory insufficiency and was submitted to orotracheal intubation and mechanical ventilation. Her initial D-dimer was 1706ng/ml and she had patterns of viral pneumonia on chest CT. Treatment with Hydroxychloroquine and Azithromycin was initiated; a nasopharyngeal swab was collected, which was positive for SARS-CoV-2. On the fourth day, the patient presented with hemodynamic instability, D-dimer elevated to 83.390 ng/ml and a troponin I level of 34.42 ng/dl. TTE revealed anterior wall hypokinesia and ECG showed anterior ST elevation. She was referred to CCL. Angiography did not reveal obstructive coronary artery disease and injection into the left ventricle showed a pattern of Takotsubo cardiomyopathy (Figure 4). Despite drug optimization and use of mechanical support, the patient had refractory shock and died within the next hours.

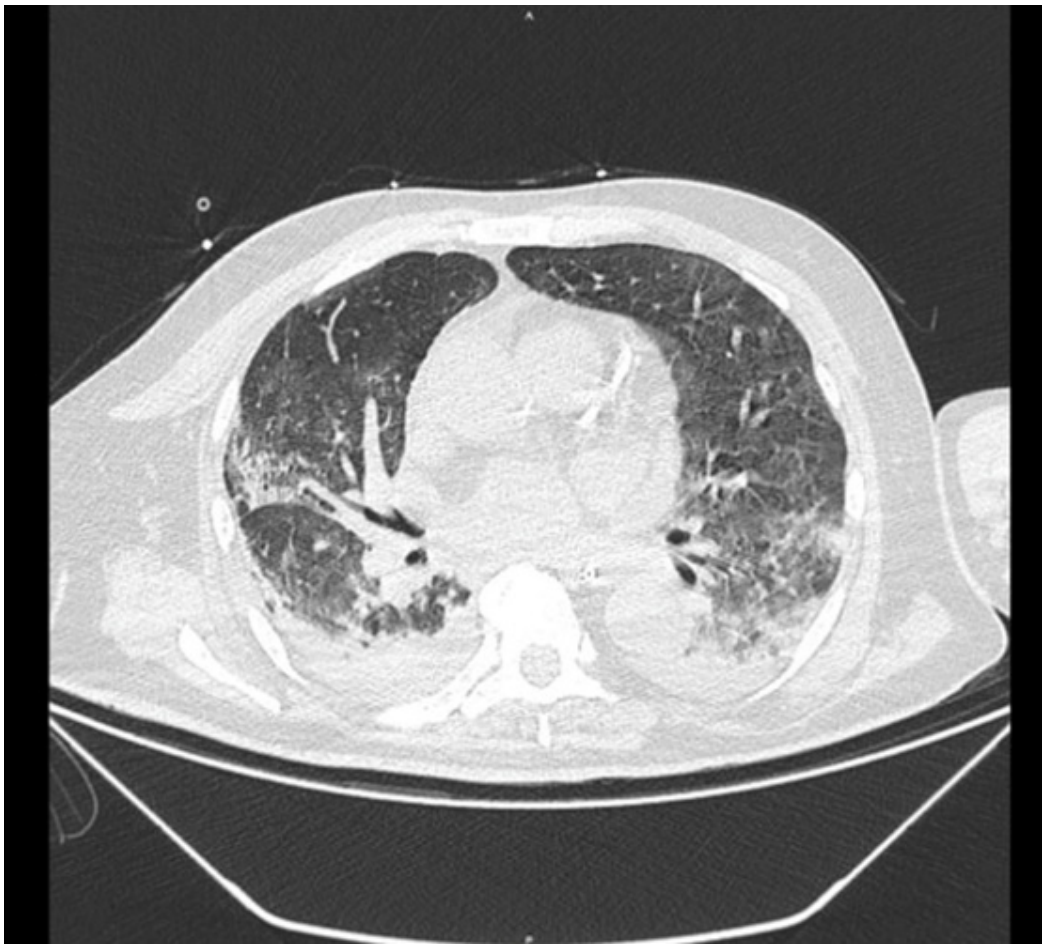

Figure 3 – Chest Computed Tomography with bilateral interstitial ground/glass infiltrate.

Discussion

Case 1 refers to an elderly patient with STEMI treated with the usual and recommended management of this clinical presentation. Despite no flu-like symptoms at admission and **denial** of contact with people who tested positive or are suspected to have Covid-19, the patient developed pneumonia caused by SARS-CoV-2 with a fatal endpoint. The wide incubation period (4-14 days) does not allow us to determine whether contamination occurred prior to admission or during hospital stay, but the presence of fever from the first days (<72 hours) suggests community infection.

Zhou et al.,[4] reported the clinical worsening that occurs in the second week after the onset of symptoms in advanced age and among severe comorbidity subgroups. Such clinical deterioration is caused not only by pulmonary parenchyma injury but also by thromboembolic phenomena. There is a positive correlation between elevated fibrinogen and D-dimer levels and in-hospital death in COVID-19 patients, which emphasizes the characteristic of a prothrombotic state[11] and may have contributed to the unfavorable evolution of the reported patient.

Another important issue to be discussed is the complete revascularization strategy in multivessel patients with STEMI, especially at the moment of a pandemic. The institution current practice is based on recent data published in the literature,[12] with complete revascularization performed during the same hospital stay, usually 48-72 hours after the index procedure. There were two other possibilities in this scenario: 1) complete revascularization in the index procedure, aimed at shortening hospital length of stay and exposure to SARS-CoV-2, but with a higher contrast load; 2) to treat the culprit lesion and postpone the second procedure

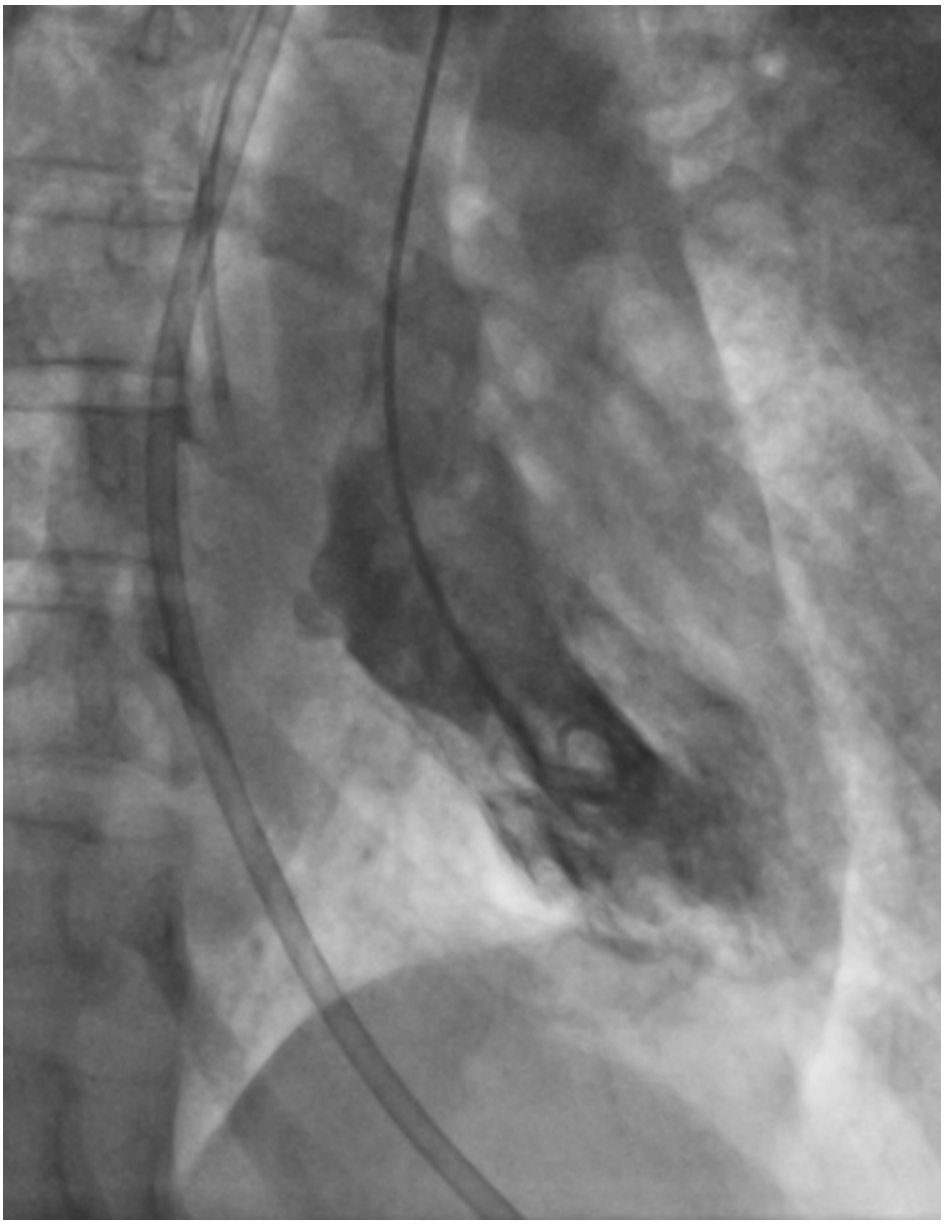

Figure 4 – Left venticulography with akynesia of the apical portions of the left ventricle – Takotsubo Syndrome pattern.

to a second elective procedure; on the other hand, this specific patient with a severe lesion in the proximal LAD would be exposed to a higher risk for ischemic events. Considering this completely new situation, with a highly spread infectious disease and with individual experience-based evidence, it is difficult to determine which would be the best approach in this case.

Finally, it is important to emphasize the adequate use of personal protective equipment (PPE) by healthcare professionals. During both procedures performed at the CCL, the patient was not suspected of COVID-19. Still, all the staff was fully equipped with PPE. Based on the experience of European centers,[8,9,13] the institution took several precautions and a new service flow chart was validated and has been applied since the reports of the first cases in Brazil. This new protocol suggests close communication between the multidisciplinary cardiology team. In addition, all cases referred to the CCL are considered suspected of infection by SARS-CoV-2, even in the absence of flu-like symptoms. Thus, all professionals in the unit are fully equipped. So far, no healthcare professional was quarantined.

The second case refers to a patient with AMI, probably triggered by a flu-like syndrome, in the context of COVID-19 pandemic. Not only can viral infections trigger cardiac events, they can also decompensate cardiac status. The known mechanisms involved are vasoconstriction, endothelial inflammation, platelet dysfunction and thrombogenicity. An increased systemic inflammatory status can raise the incidence of arrhythmias and myocarditis, destabilizing coronary plaques and leading to coronary events. In this context, there is a higher incidence of coronary events during infections.[14,15] This case showed an AMI with atypical clinical manifestations during a COVID-19 infection. The non-specific case of fever and myalgia, evolving after a few days into dyspnea, is typically described in severe presentations of COVID-19. Even though the patient's admission interview was brief, since he presented with respiratory failure, the absence of chest pain delayed essential specific cardiac procedures. Although the ECG was not performed immediately, as recommended, it was used to guide the treatment. The need for a differential diagnosis with an adrenergic cardiomyopathy (Takotsubo Syndrome)[16] made coronary angiography essential for defining the diagnosis, since Takotsubo cardiomyopathy can mimic AMI and is associated with COVID-19. As indicated by institutional protocols during pandemic, confirmed or suspected cases should be treated after all precautions and safe procedures have been taken, during transportation and inside the CCL, sometimes leading to prolonged reperfusion. Efforts have to be made to reduce reperfusion times in ST-elevation AMI during the COVID-19 pandemic.[9]

Case 3 reports the unfavorable outcome of a patient with a typical flu-like presentation and COVID-19 confirmation that may have triggered a cardiovascular manifestation. The association with a cardiovascular disease contributed to clinical worsening. Despite early invasive measures, such as orotracheal intubation and administration of antiretrovirals, antibiotics and anticoagulants, the clinical presentation of STEMI posed a major challenge to the medical team. The differential diagnoses were myopericarditis, acute myocardial infarction, stress myocarditis and vasospasm. Even though this was a young patient, with no cardiovascular risk, it was not possible to rule out an AMI and, in this context, the indication of a TTE before the angiography was fundamental for the diagnosis of a stress cardiomyopathy. This decision, considering the significant alterations in the ECG, would not be the same outside the COVID-19 pandemic. This case also reinforces the exacerbated inflammatory and thrombotic reactions caused by the association between SARS-CoV-2 and cardiovascular complications. D-dimer elevation over 80.000 and interleukin 100 times over the normal values are clear parameters of this alteration that can lead to thrombotic events with AMI and/or inflammatory presentations, such as myocarditis, which hinders the diagnostic elucidation of cases and promotes changes in diagnosis and treatment protocols.

Conclusion

COVID-19 is a global pandemic that in association with cardiovascular disease can lead to high morbidity and mortality rates. SARS-CoV-2 infection can trigger decompensation of coronary-artery plaques, leading to STEMI. Clinical presentation, ECG changes and elevated cardiac biomarkers can mimic AMI, but without obstructive coronary artery disease. Patients with COVID-19 and STEMI may require a long period of hospital stay, demanding multidisciplinary efforts to overcome critical clinical conditions.

Learning objectives:

1 - Association between SARS-CoV-2 and STEMI can lead to high morbidity and mortality rates.

2 - COVID-19 can mimic AMI in clinical presentation and complementary exams in the absence of CAD.

3 - The use of personal protective equipment (PPE) by healthcare professionals is crucial to avoid system collapse.

4 - Cardiovascular disease clinical presentation in patients with COVID-19 is variable.

Author Contributions

Conception and design of the research: Esteves V, deLuca F, Zukowski CN, Feldman A. Acquisition of data: Arruda G, Camiletti A, Bandeira B. Critical revision of the manuscript for intellectual content: Souza OF.

Potential Conflict of Interest

No potential conflict of interest relevant to this rticle 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 *Instituto D´Or de Pesquisa e Ensino* under the protocol number CAAE: 31478820.0.0000.5249. 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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