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Cardiovascular SCIENCES

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Consumption of Brazil Nuts Provides Cardiovascular Health Benefits

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Clinical Course of Patients Undergoing Myocardial Revascularization Surgery in a Public Cardiology Referral Hospital in Pará, Brazil

Implementation of an Acute Coronary Syndrome Simulation Training Strategy for Emergency Healthcare Professionals

Antioxidant and Vasodilatory Action of Grape Juices Produced in Different Regions of Brazil

Effect of Short-Term Inhalation of The Herbicide 2,4D on Cardiac Remodeling: Morphological Aspects

Adductor Pollicis Muscle Thickness as a Marker of Nutritional Status in Heart Failure

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EDITORIAL

Open Science, Cardiology and 20 years of SciELO (Scientific Electronic Library Online)

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Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world.

Louis Pasteur

The SciELO 20 Years Conference, held from September 24 to 28, 2018, in São Paulo, was remarkable in many ways, as it represented the recognition of one of the most important scientific initiatives in Latin America and a focal point for the latest innovations in scientific thinking these days. The focus of the meeting was "Open Science," which is the practice of science that allows collaboration and contribution among researchers, where research data, laboratory observations and other research processes are available free of charge, under terms that allow the reuse, redistribution and reproduction of research and its underlying data and methods. In the past, Open Science consisted in efforts to offer open access to articles in view of the increasing journal subscription costs charged by the publishers, but the movement quickly condensed several democratizing initiatives of knowledge.[1] This innovative and disruptive way of understanding the very meaning of science has been recently analyzed by Vicente-Saez and Martinez-Fuentes, who concluded that the best definition for Open Science is transparent and accessible knowledge that is shared and developed through collaborative networks (Figure 1).[2] Current trends in Open Science were addressed at the SciELO 20 Years Conference and are in line with the path mapped out for the journals of the Brazilian Society of Cardiology, such as: open codes, open data, open access to articles, alternative systems for assessing the impact of publications (social impact factor), open data sheets, open laboratory notes, science blogs, collaborative references, citizen science, online data repositories, open peer reviews and access to the manuscripts before they are peer-reviewed (preprints).[1]

The multiple advantages of Open Science include access of information to a bigger number of people, the possibility of building collaborative knowledge to make scientific growth faster, and greater scientific visibility of data, as well as faster access to scientific information. With access to research data, these can be checked by anyone who accesses the data repository. Opening of data reduces the possibilities of scientific misconduct, such as plagiarism, fabrication and falsification of data.[3] Another advantage of open data is the possibility of combining data from different research studies, allowing the generation of new information and answers to questions that would be difficult to be answered individually.

Open science is not only about free-access scientific articles. It involves a much greater movement of encouraging publication in free-access journals and standardizing information to facilitate access by data analysis tools. Another very important initiative is the one that makes science more popular and widespread, by changing the behavior of scientific community, so that the scientists can be more open towards each other

Keywords

Access to Information; Biomedical Research; Open Access Publishing/standards; Open Access Publishing/history; Open Access Publishing/trends; Information Dissemination/methods; Costs and Costs Analysis; Publishing/economics.

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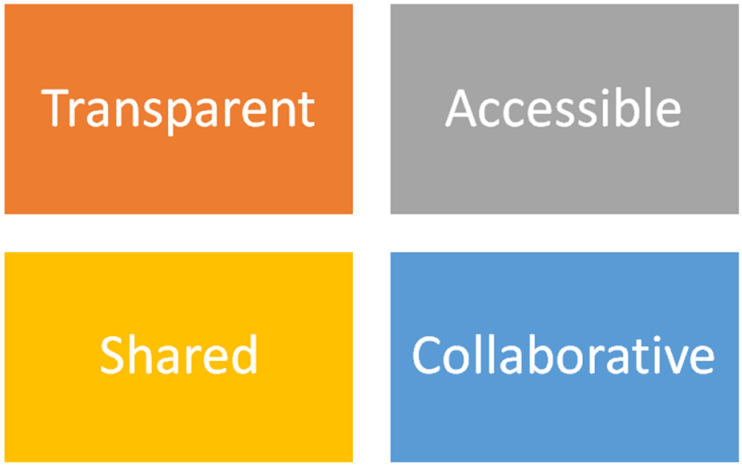

Figure 1 - Unique and fundamental characteristics of knowledge within Open Science. (Adapted from ref.[2]).

and with the public and the media.[4] Making society more aware of science is fundamental in order to avoid the dissemination of fake news, which has caused significantly adverse impacts, such as the decline in vaccination figures.[5]

In short, the movement for open science is irreversible, with data showing that in 2016, about one in every five published articles was immediately available after publication, either by access in open journals (15%) or because the authors had paid for publication in journals that require an amount to be paid to make the manuscript open to the readers on a free-of-charge basis (the so-called gold open access model).[6] The European Union's initiative to require that articles resulting from research funded by public research funding agencies be published only in open-access journals from January 2020 is one of the most hard-hitting ways to encourage the dissemination of open science (S Plan).[6] Many people question whether the model of scientific publications will be sustainable in the future, and whether closed-access journals requiring paid subscriptions will be thrive in this fast-changing scenario. The International Journal of Cardiovascular Sciences and *Arquivos Brasileiros de Cardiologia* have been closely watching this global initiative, whose main characteristics include the promotion of cardiovascular knowledge among its readers in a free and open way, with no publication costs and with the incorporation of new scientific progress approaches, such as acceptance of preprints and encouragement to include databases in online repositories.

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International Journal of Cardiovascular Sciences. 2019;32(3)205-206

EDITORIAL

Consumption of Brazil Nuts Provides Cardiovascular Health Benefits

Mariana Sarto Figueiredo

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Indroduction

The prevalence of chronic diseases, such as metabolic syndrome, obesity, dyslipidemia, type 2 diabetes mellitus (DM2), cancer, and neurodegenerative and cardiovascular disorders have been increasing in the world population. However, cardiovascular diseases remain the leading cause of mortality and morbidity worldwide. According to the Barker's Theory (1993), hormonal, nutritional or environmental changes during critical periods of development such as gestation, lactation or adolescence may result in changes to the basic functions of the human body in childhood and "program" the progeny for the emergence of chronic diseases in the adult life, like DM2, obesity, cardiovascular diseases, intestinal dysbiosis, and hormonal and metabolic dysregulation. This phenomenon is known as "metabolic programming" or "developmental plasticity".[1,2]

In the same direction, many authors have demonstrated the impact of an unhealthy diet on the development of chronic diseases such as metabolic syndrome, obesity, dyslipidemia, type 2 diabetes mellitus, cancer, neurodegenerative diseases and increased cardiovascular disorders.[3,4] On the other hand, we know that the regular consumption of plant-based foods (cereals, fruits, vegetables, legumes, tree nuts and seeds), moderate consumption of seafood, fish and dairy and reduced consumption of alcohol, red meat and meat products may prevent and/or protect against diseases and provide health benefits, which is now widely recognized by health professionals.[5,6]

Keywords

Nuts; Brazil Nuts; Cardiovascular Diseases; Risk Reduction Behavior; Healthy Diet; anti-Inflammatory Agents.

Nutrition is essential for life and essential chemical compounds from foods and drinks such as proteins, fatty acids, carbohydrates, vitamins and minerals are required by the organism to support its physiological functions, like energy production, growth, development and reproduction.[7] Thereby, nutrients are one of the most important elements that can regulate enzymes and molecular and functional events in the cells or in the whole body, which, depending on the quality and quantity, can predispose humans to chronic diseases.[8] It is important to highlight that, particularly after the Industrial Revolution worldwide, the diet of modern human society is actually based on processed foods, , which are rich in sugar, salt and saturated fat and poor in minerals and vitamins.

Thus, the inclusion of food with functional properties or bioactive compounds such as monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), phenolic compounds and minerals are gaining increasing recognition as integral components of lifestyle changes against the development of cardiovascular diseases. Recently, the review that presents the association of nuts with cardiovascular diseases highlights some of these compounds present in food that can add important benefits to the cardiovascular health.[9] In this direction, the nuts (Brazil nuts, American almonds, pistachios, walnuts and hazelnuts) are an important source of MUFA and PUFA, which present anti-inflammatory and antioxidant effects, improve dyslipidemia and contain selenium and phenolic acids. These compounds could also benefit the cardiovascular health.

Silva et al. (2018) showed that regular consumption of 5 to 50 grams of Brazil nuts from 1 day to 16 weeks can increase plasma selenium, improve oxidative balance (increase GPx activity and nitric oxide with decreased MDA), improve lipid profile (increase HDL-c, decrease LDL-c and triglycerides) and reduce inflammation

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markers (decrease IL-6, TNF-alfa and Nf-kB) in different human populations such as adults, normolipidemic subjects, healthy volunteers, obese adolescents and women, as well as dialysis, hypertensive and dyslipidemic patients.[9] Silva et al.[9] did not only revise the effects of nuts on cardiovascular diseases but also highlighted Brazil nuts in terms of their source of unsaturated fatty acids, proteins, fibers, minerals, vitamins, phenolic compounds and properties, biological effects, and proposed mechanisms of action.[9] They also discussed promising research directions for the future to identify additional health-related benefits of dietary Brazil nuts against cardiovascular diseases.

Recently, Garcia-Aloy et al.,[10] demonstrated that some nuts and vegetables oils are sources of fatty acids, micronutrients and phytochemicals that can be found in blood circulation and in urine according to their intake, and useful to determine habitual intake of nuts as wells as their derived metabolites.[10] Thus, it is important to evaluate the specificity, sensitivity, dose-response relationships, and determine the relationship with cardiovascular diseases.

In conclusion, it is known that dietary intervention based on the use of foods with functional properties, especially Brazil nuts, can be considered a good strategy to prevent, treat or reduce the progression of cardiovascular diseases worldwide. In my opinion, more studies are necessary to elucidate which cellular mechanisms are involved in the nutritional route of the body metabolism and gene expression of this bioactive compounds and its impact on the cardiovascular health.

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ORIGINAL ARTICLE

Curcuma Longa Abolishes Phenylephrine-Induced Contractions in Isolated Aortic Artery of Rats

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Abstract

Background: *Curcuma longa* has biological effects. Its cardiovascular activities are yet to be scientifically studied.

Objectives: To investigate the vasorelaxant effects of the aqueous extract of *Curcuma longa* (AECL).

Methods: Aortic annuli of normotensive rats, with or without endothelium, were set up in a data storage system with nutrient solution in recipients, with scientifically recommended temperature, aeration and tension. Over contraction by Phenylephrine, the AECL (1, 3, 10, 30, 100, 300 and 1000 μg/mL) was incubated before and after incubation with atropine or L-name or indomethacin. An AECL concentration-response curve was also built over contractions caused by elevation of extracellular K^+. Data were significant when $p < 0.05$, with GraphPad Prism 6.0 software resolutions.

Results: The AECL induced 100% vasorelaxation also in the endothelium-free annuli. The part of the endothelium-dependent effect had EC_{50} = 4.32 ± 0.05 μg/mL. With inhibition of NO production, the EC_{50} increased to 126.50 ± 2.35 μg/mL; after inhibition of prostacyclin production, to 124.6 ± 0.05 μg/mL; and after muscarinic blockade, to 437.10 ± 0.2 μg/mL. Opening of K^+ channels (relaxation of 56.98%) and VOCC blockade (relaxation of 31.56%) were evident.

Conclusion: AECL induced significant vasorelaxation, being more significant in the presence of endothelium. The muscarinic pathway seems to be the main one involved in this effect, followed by the NO production and prostacyclin pathways. The activity in K^+ channels by AECL was more significant than its VOCC blockade. The use of other models and tools to study action mechanisms will be important and elucidating. (Int J Cardiovasc Sci. 2019;32(3)207-216)

Keywords: Curcuma/adverse effects; Crocus; Receptors, Muscarinic; Vasodilator Agents; Cardiotonic Agents; Antioxidants; Hypertension.

Introduction

According to the World Health Organization (WHO) and the Pan American Health Organization (PAHO), heart diseases are one of the major causes of death worldwide1 and in low- and middle-income countries, more than three-quarters of the deaths are due to cardiovascular diseases.[1,2]

Hypertension is the main risk factor for the development of cardiovascular diseases, affecting more than one billion people worldwide.[3-5] The use of allopathic drugs has been the main type of therapy used to fight hypertension and, consequently, all the other diseases that result from it, even though it is known that one of the major problems of this treatment option are its side effects.[5]

Recently, more attention has been paid to the use of medicinal plants to attenuate the damage of several diseases, including arterial hypertension.[6,7] The rhizome of *Curcuma longa Linnaeus*, which belongs to the *Zingiberaceae* family of Malay-Indigenous origin,[8] popularly known as Yellow Ginger or Saffron, was used only as a food dye in many countries, and its

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leaves were used to wrap fish and to give aroma and flavor to the food preparation.[9] More recent studies report cardioprotective,[10] anti-inflammatory,[8,11] antimicrobial,[12] antiproliferative,[12] antioxidant,[13] antifungal[14] and vasorelaxant[15] properties. There is still little available information on its mechanism of action and effects on the cardiovascular system. The present study aims to investigate AECL action on vascular contractions induced in the isolated aortic artery of normotensive rats. Preclinical scientific studies of this nature may not only serve as the basis to obtain alternative phytomedicinal sources of attenuation of cardiovascular system-related diseases among the traditional needy populations, but they can, primarily, indicate to the scientific community and to the pharmaceutical industry new sources of raw materials to obtain medicinal principles available in nature, which already have discreet and crucial scientific information.

Methods

Preparation of the *Curcuma longa L* extract

The plant was collected in a private property located in Vila Campinas, Ramal das chácaras, in the municipality of Plácido de Castro, in the state of Acre, northern Brazil. A voucher specimen was deposited at the herbarium of *Universidade Federal do Acre* (UFAC), under number 20002. The healthy-looking leaves were selected, washed under running water and placed in a greenhouse at 40°C for 48 hours, where dehydration occurred, and then they were ground in a knife-type mill at the Food Technology Unit (UTAL) of Universidade Federal do Acre. To obtain the aqueous extract of *Curcuma Longa* (AECL), 4 liters of distilled water with 370 grams of the crushed plant material were placed in a heated balloon flask for 10 minutes at 100°C, followed by filtration. The filtrate was lyophilized, stored in an amber glass vial and kept under refrigeration at 4°C.

Drugs

Phenylephrine hydrochloride (PHE), atropine sulfate, acetylcholine chloride (ACh), NG-nitro-L-arginine-methyl ester (L-NAME) and Indomethacin were used, all from SIGMA-ALDRICH. Stock solutions of indomethacin were dissolved together with 5 N sodium bicarbonate ($NaHCO_3$) in distilled water. The other drugs, including AECL and solutions, were diluted in distilled water. The perfusion medium used was Krebs-Henseleit nutrient solution, containing (in mM): NaCl (118.4); KCl (4.75); KH_2PO_4 (1.18); $NaHCO_3$ (25); $MgSO_4$ (1.18); $CaCl_2$ (1.9) and glucose (5). The nutrient solution had the pH adjusted with 1M HCl or 1M NaOH to 7.3 and 7.4. The AECL concentrations that were cumulatively used in all experiments were, invariably, 1, 3, 10, 30, 100, 300 and 1000 μg/mL. PHE and ACh concentrations were 0.1 μM in all experimental protocols.

Toxicity Assay

To assess possible toxic effects of the AECL, a Fixed Dose Procedure (FDP) parameter was used according to the Acute Toxic Class Method of 2001 (OECD).[16] In this test, mice fasted for 12 hours prior to the experiment and were divided into 3 groups (n sample = 6, used for convenience): group 1 (control), 2 (dose of 2000 mg/kg) and 3 (dose of 5000 mg/kg), comprising a total number of 18 animals. Only saline solution was administered in group 1, and in group 2, the dose of 2000 mg/kg. In the absence of lethality or toxicity, then the dose of 5000 mg/kg was administered in group 3. The toxicity assessed by observing the following behavioral parameters, described in the hippocratic test of Malone and Robichaud[17] are: attention, alertness, analgesia, spontaneous motor activity, locomotion, lack of appetite, apathy, response to tact, piloerection, ptosis, respiratory rate, cyanosis, stereotypy, contortion, aggressiveness, ataxia, posture, sweating, urination, diarrhea and seizure.

The parameters were observed every 60 minutes for 3 hours after the administration of the extract. Subsequently, they were also observed after 24, 48, and 72 hours and on the 15th day. At the end of the observations all the animals were euthanized according to the euthanasia practice guidelines of the National Council for the Control of Animal Experimentation (*Conselho Nacional de Controle de Experimentação Animal* – CONCEA). Traditional barbiturates and anesthetics were used for the euthanasia procedure, with a rapid, gentle effect and with minimal discomfort to the animals. These drugs are potent Central Nervous System depressants, of which effects are widely known and predictable.

Assessment of AECL activity in the annuli of isolated thoracic aorta of rats

A total of 14 rats were used in this study, resulting in 42 aortic annuli. Initially the annuli were divided into

two groups (n = 6), being sufficient to perform *in vitro* experiments for each concentration of the same group with the same nature, defined as group 1 (annulus with present endothelium) and 2 (annulus without endothelium). Subsequently, the subgroups were divided into five groups (n = 6) for the assessment of the verified action mechanism, namely: group 1.1 (L-NAME), group 1.2 (Indomethacin), group 1.3 (Atropine), group 2.1 (KCl 20) and group 2.2 (KCl 80).

Preparation and setting-up of the vascular annulus

Male rats of the Rattus norvegicus species, of the Wistar lineage, weighing 200-300 g, were euthanized by cervical dislocation and then a ventral incision was performed with opening of the rib cage by performing an excision in the sternum and part of the ribs, for visualization and removal of the intrathoracic organs. The thoracic aorta was removed and transferred to a Petri dish containing Krebs nutrient solution aerated by carbogenic mixture (95% CO_2 + 5% O_2) and cleansed by removing the adipose tissue and connective tissue adhered to the artery segment. The artery segment was fractionated into 4 mm-rings and set up, fixed between 2 small wire triangles. One side of one of the triangles was introduced into the annulus lumen, with the vertex opposite to the annulus, being fixed to the base of a thin metallic rod attached to the system, and the opposite vertex of the other triangle, by a cotton thread, attached to a isometric force transducer (AdInstruments).

The aorta preparations for all experiments were preliminarily stabilized for 1 hour in Krebs nutrient solution, with replacement of the solution every 15 minutes to eliminate and minimize metabolite effect; constant adjustment of the passive voltage applied to the annulus was also performed to 1 g (baseline initial tension), maintained at 37°C and continuously aerated by carbogen (95% O_2 + 5% CO_2). The data on voltage variations, as a function of tissue reactivity to drug administration, were obtained after the conversion of the electrical signals captured by the transducer into digital signals and transmitted by an amplifier-recorder (AdInstruments). The variation records of the degree of contraction of the annulus smooth musculature were sent to a microcomputer, where they were processed and stored in the Protowin organ baths software (Pan Lab) for later analytical and statistical treatment.

All protocols were carried out according to the norms issued by the National Council for the Control of Animal Experimentation (CONCEA) and approved by the Ethics Committee on Animal Use (*Comitê de Ética no Uso de Animais* – CEUA) of UFAC (*Universidade Federal do Acre*) under number 23107.018498 / 2016- 40.

Evaluation of the AECL activity in aortic annuli with and without endothelium contracted with phenylephrine

Immediately after the preparations' stabilization period, the presence (E^+) or absence (E-) of functional endothelium in the annuli was verified by adding ACh on the plateau of the sustained tonic phase of the PHE-induced contraction, establishing as (E^+) annuli those of which relaxation percentages induced by ACh were ≥ 70% and as (E-), those with < 5% of relaxation. The tissues prepared in the recipients were again contracted by PHE and, after five to seven minutes of sustained tonic phase contraction, increasing concentrations of AECL (1, 3, 10, 30, 100, 300 and 1000 μg/mL) were cumulatively added to the preparations containing (E^+) or (E-) annuli. The relaxation percentage was determined by comparing the PHE contraction values before and after the cumulative addition of the extract and also by calculating the EC50 values.

Evaluation of the AECL effect after inhibition of the enzymes of the nitric oxide (NO) production pathway, the prostacyclin (PGE2 and PGI2) production pathway and the endothelial muscarinic blockade

In annulus-containing preparations (E^+), the cumulative administration of AECL at the PHE-induced contraction plateau was performed before and after the L-NAME (100 μM), and incubated for 30 minutes, for the evaluation of nitric oxide (NO) involvement in the AECL effect. To assess the involvement of prostacyclines, indomethacin (10 μM), instead of L-NAME, was also incubated for 30 minutes. To verify the probable participation of muscarinic receptors, following the same experimental protocol, atropine incubation (1 μM) was previously performed for 15 minutes, instead of the two enzyme inhibitors.

Evaluation of AECL activity in contracted aortic rings with depolarizing KCl solution

To evaluate the involvement of ion channels, experiments were performed using (E-) annuli. In these approaches, after stabilization of the preparations and other mandatory preliminary procedures, instead of

contractions caused by PHE, contractions induced by increased K^+ concentrations in the bath – extracellular medium ($[K^+]e$), were produced; these operations were performed with 20 mM KCl or 80 mM KCl solutions, in separate individual samples; at their plateaus, a cumulative administration of increasing concentrations of AECL was performed.

Statistical analysis

All points plotted in the graphs are expressed as mean ± standard deviation (SD) and represent the individual experiments (control and treatments) (n sample = 6, by convenience) for each one of them, performed individually. The nature of biological responsiveness and the biochemical processes triggered by the injection of exogenous substances and the reactivity due to the induction of endogenous releases, as well as considering the very nature of the crude extracts (consisting of many active principles), naturally justify the fact that the EC_{50} values resulting from the analyses on individual concentration-response curves were carried out through non-linear regression. The D'Agostino normality test was performed. As the data were normal, the two-way analysis of variance (ANOVA) was applied. Statistical differences between the means of the results were determined by the paired Student's t test and when appropriate (for multiple comparisons). The authors did not observe limiting factors in this study. The analyses and representations were carried out with the software GraphPad Prism 6.0 (GraphPad Software Inc., San Diego, CA, USA), with significance being set at $p < 0.05$.

Results

Toxicity

None of the animals died or showed deleterious behavioral changes capable of compromising the limits of normality during the toxicity studies (data not shown). The group receiving the 2000 mg/kg dose, even up to the fifteenth day of observation, showed no alterations as a result of the treatment. At the dose of 5000 mg/kg there was mild sedation in the first hour after the extract administration in only one animal in the group. At the subsequent hours and days, none of the animals showed any behavioral change or died. Therefore, AECL did not show any alterations of clinical importance in the animals submitted to the treatments.

Influence of the vascular endothelium on AECL activity in isolated aortic artery annuli of normotensive rats pre-contracted with PHE

In E^+ annuli, the AECL abolished contractions induced by PHE, with an $EC_{50} = 4.32 \pm 0.05$ μg/mL. Significant vasorelaxation ($p < 0.01$) occurred in a concentration-dependent manner. In the E- annuli, it also reached 100%, but the AECL response was significantly ($p < 0.01$) modified by the removal of the vascular endothelium and EC_{50} increased to 134.20 ± 1.80 μg/mL, indicating that the effect of AECL strongly depends on factors derived from the vascular endothelium (Figure 1).

Involvement of NO in the AECL relaxant effect on isolated aortic artery annuli of normotensive rats pre-contracted with PHE

After inhibition of the NO synthesis enzyme by L-NAME, the AECL vasorelaxant effect on intact aorta annuli was significantly ($p < 0.01$) inhibited, an event evidenced by an increase in the EC_{50}, from 4.32 ± 0.05 μg/mL to 126.50 ± 2.35 μg/mL (Figure 2), indicating clear involvement of the NO production pathway in the AECL effect.

Involvement of the prostacyclin production pathway in the AECL relaxant effect on isolated aortic artery annuli of normotensive rats pre-contracted with PHE

After blocking prostaglandin synthesis with indomethacin, the vasorelaxant response induced by AECL was significantly ($p < 0.01$) inhibited after indomethacin incubation, a fact disclosed by the EC_{50} elevation, from 4.32 ± 0.05 μg/mL to 124.6 ± 0.05 μg/mL), suggesting that the AECL effect is also related to the prostacyclin production pathway (Figure 3).

Involvement of the muscarinic pathway in the AECL relaxant effect on isolated aortic artery annuli of normotensive rats pre-contracted with PHE

In this approach, the vasorelaxant response induced by AECL was the most significantly attenuated, as shown by the prominent ($p < 0.01$) increase in EC_{50}, from 4.32 ± 0.05 μg/mL to 437.10 ± 0.2 μg/mL (Figure 4). These data suggest that, of the investigated pathways, muscarinic receptors seem to be the most significantly implicated in the vasorelaxant effect induced by the AECL on the isolated thoracic aorta of rats.

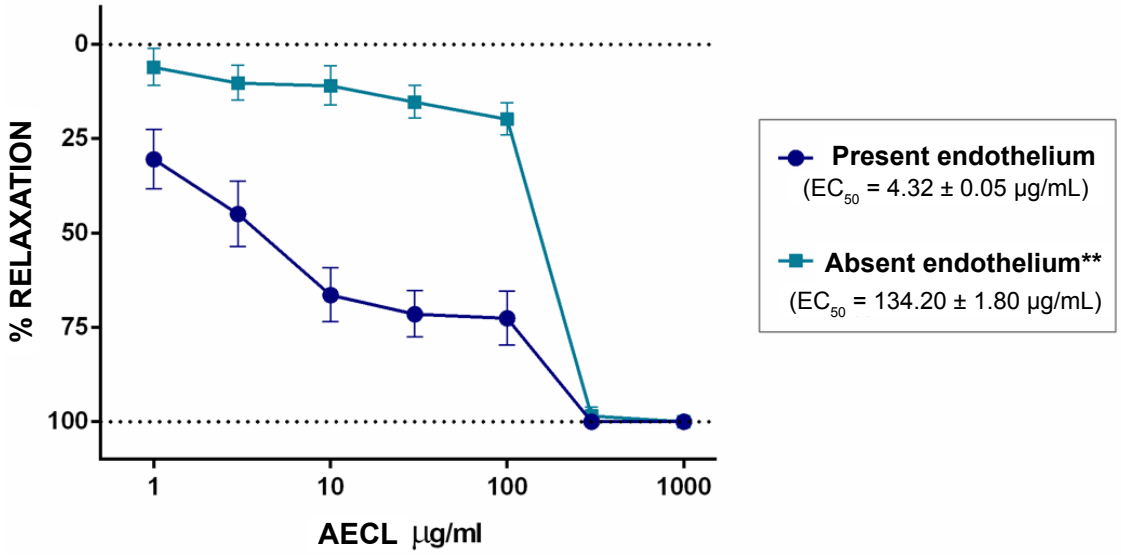

Figure 1 - Concentration-response curve for CLAE (1, 3, 10, 30, 100, 300 and 1000 µg/mL) on PHE-induced contractions (0.1 µM) in isolated aortic annuli of normotensive rats in the presence and absence of functional endothelium. The dots represent the mean ± SD of the concentrations used with n = 6 and **(p < 0.01) versus E+.

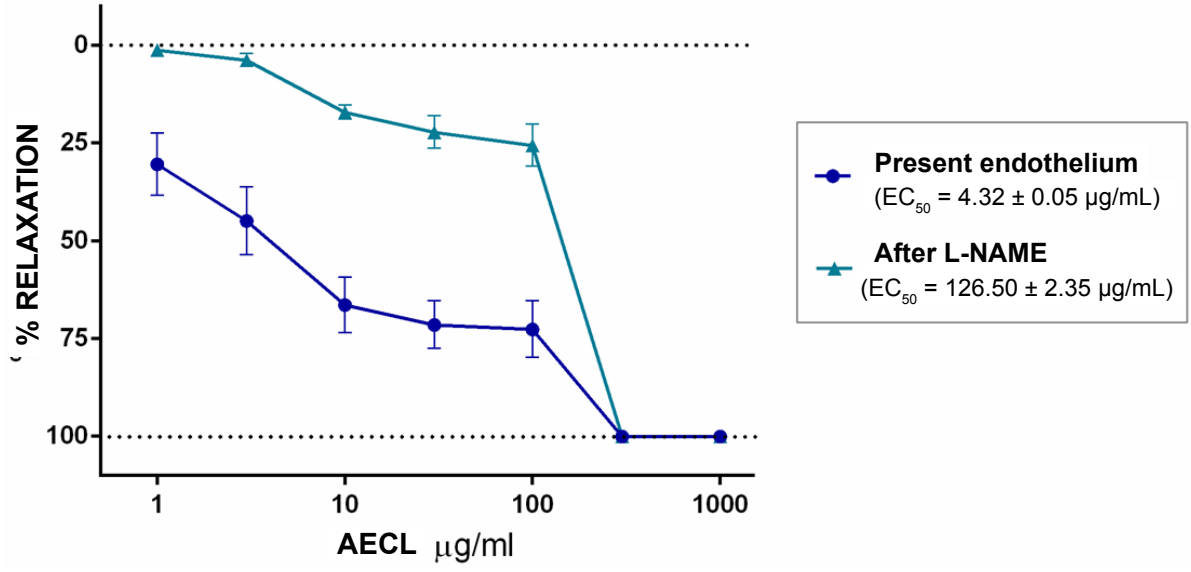

Figure 2 - Concentration-response curve for CLAE (1, 3, 10, 30, 100, 300 and 1000 µg/mL) in rat isolated thoracic aorta annulus with intact endothelium and pre-contracted with PHE (0.1 µM) before E+ and after NO synthase inhibition. The dots represent the mean ± SD of the concentrations used with n = 6 and **(p < 0.01) versus E+.

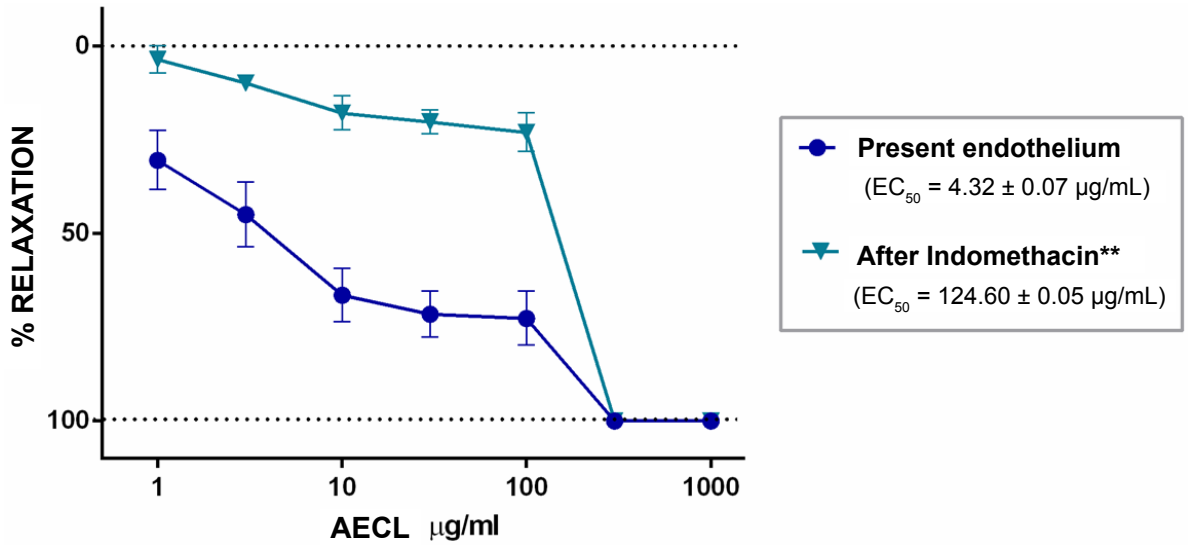

Figure 3 - Concentration-response curve for CLAE (1, 3, 10, 30, 100, 300 and 1000 µg/mL) in rat isolated thoracic aorta annulus with intact endothelium and pre-contracted endothelium with PHE (0.1 µM) before E^+ and after cyclooxygenase-1 (COX-1) inhibition. The dots represent the mean ± SD of the concentrations used with n = 6 and **($p < 0.01$) versus E^+.

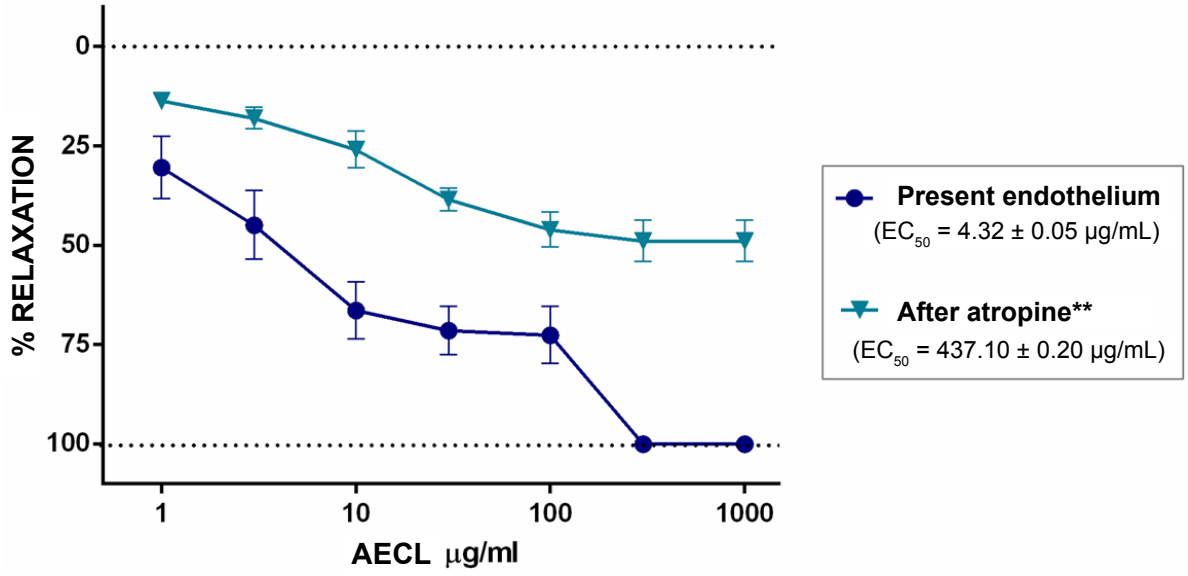

Figure 4 - Concentration-response curve for CLAE (1, 3, 10, 30, 100, 300 and 1000 µg/mL) in rat isolated thoracic aorta annulus with intact endothelium and pre-contracted endothelium with PHE (0.1 µM) before (E^+ control) and after incubation with atropine (1µM). The dots represent the mean ± SD of the concentrations used with n = 6 and **($p < 0.01$) versus E^+.

AECL effect on the contraction caused by blocking the intracellular K^+ efflux

In annuli without endothelium, although with much less significance, the AECL continued to show a significant vasorelaxant activity ($p < 0.01$). The AECL-induced response in the isolated thoracic aortic annuli of rats precontracted with 20 mM KCl was significantly ($p < 0.01$) lower than the AECL-induced vasorelaxation on PHE-induced contraction in (E-) annuli (Figure 5). The percentage of vasorelaxation over the 20 mM KCl contraction was 56.98% and 31.56%, over the 80 mM KCl contraction. Therefore, it seems that the effect of AECL has a greater significance for the opening of K^+ channels than for the blockade of voltage-operated calcium channels (VOCCs) (Figure 5).

Discussion

In the first approach (Figure 1) with (E^+) and (E-) annuli, it was observed that the AECL effect strongly depends on factors derived from the vascular endothelium, due to its greater relaxation in E^+ annuli.

The vascular endothelium, through the layer of cells that covers it internally, produces different mediating substances that regulates the vascular smooth muscle tone.[18-23] There is a natural control of these mediators' release, and at the limit of the physiological functions, the release of the relaxant factors precedes the contracting agents,[19] of which NO is the first to be released, followed by prostacyclin and other endothelium-derived relaxant agents.[20]

In many studies, the NO produced by endothelial cells with physiological vasodilation function[21,22] has been indicated as the main relaxant factor derived from the vascular endothelium. It crosses space from the endothelium to the vascular smooth muscle, promoting the relaxation of this musculature cells,[23] acting by stimulating the guanylyl cyclase of the cytoplasm soluble fraction, converting Guanosine triphosphate (GTP) into cyclic Guanosine Monophosphate (cGMP), which is the second messenger responsible for the vascular relaxant effect.[24]

In the NO synthesis, first the hydroxylation of one of the guanidine nitrogens of L-arginine occurs to generate NG-hydroxy-L-arginine (NHA), followed by the conversion of NHA into NO and citrulline.[25] All NOS (Nitric Oxide synthase) isoforms can be inhibited by L-arginine analogs, such as NG-monomethyl-L-arginine (L-NMMA), N-imino-ethyl-L-ornithine (L-NIO), NG-amino-L-arginine (L-NAA), NG-nitro-L-arginine

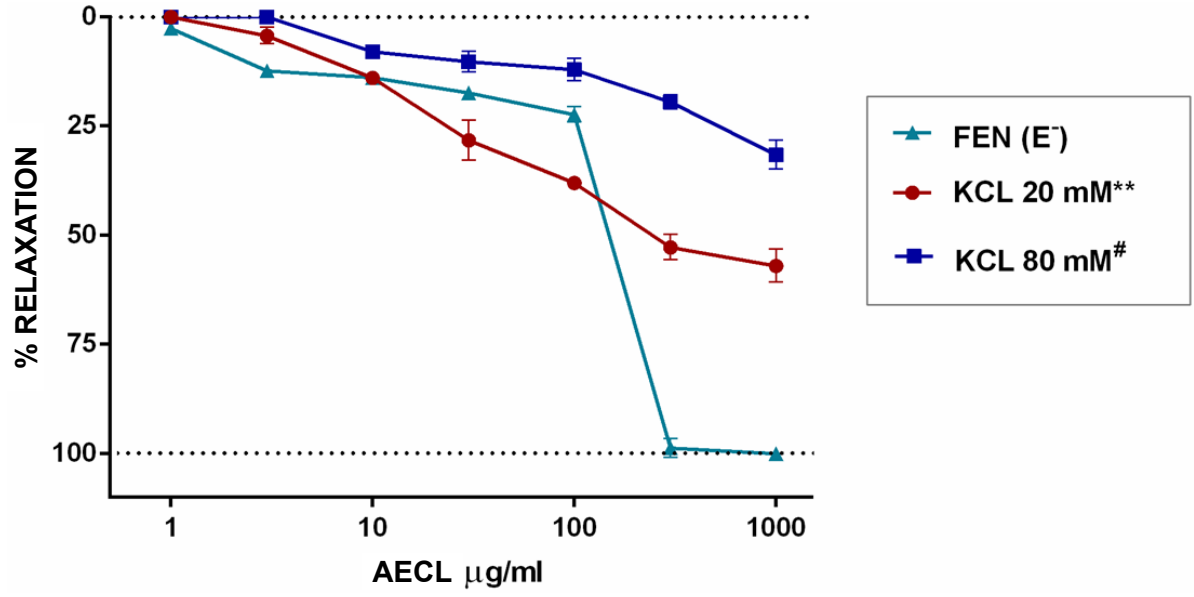

Figure 5 - Concentration-response curve for CLAE (1, 3, 10, 30, 100, 300 and 1000 µg/mL) in rat isolated thoracic aorta annulus without endothelium pre-contracted with PHE, KCl 20 and KCl 80. The dots represent the mean ± SD of the concentrations used with n = 6 and # ($p < 0.01$) versus KCl 20.

(L-NA) and the corresponding methyl ester, NG-nitro-L-arginine-methyl ester (L-NAME).[26] These analogues compete with L-arginine and act as stereospecific inhibitors of NOS.[21]

After the blockade of NO production (Figure 2), it was verified that during the AECL effect there is an important involvement of NO in the vasorelaxant effect production. In addition to the involvement of NO in the AECL effect, it is scientifically obligatory to investigate the participation of other pathways in relation to the observed effects, especially since it is a crude extract and, thus, a compound consisting of many substances. Therefore, it is possible to suggest that other endothelium-derived vasorelaxant pathways and other independent ones may also be involved in the AECL vasorelaxant activity.

The prostaglandins are synthesized from the arachidonic acid, which is released from the phospholipids of the endothelial cell membrane by the activated phospholipases (A2 and C), and through the action of cyclooxygenase enzymes (COX-1 and COX-2).[27] Once released, primarily PGI2 and PGE2, they diffuse into smooth muscle cells, promoting the vasorelaxant effect through IP and EP4 receptors, increased cAMP and by reducing intracellular Ca^{2+}.[28]

The blockade of vasorelaxant prostaglandins synthesis occurs through the inactivation of arachidonic acid-degrading enzymes (COX-1 and COX2).[27] Indomethacin is a non-selective inhibitor of these prostaglandins.[29] In the presence of this blockade and the reduction of the vasorelaxant effect produced by the extract (shown in Figure 3), it is also possible to suggest the involvement of prostaglandins.

The muscarinic receptors are also present in the vascular endothelium; they can be found in many cell types and participate in cell signaling as soon as they are activated by the ligand acetylcholine.[30] There are five subtypes of muscarinic receptors that are currently accepted, namely M1, M2, M3, M4 and M5, with the M3 receptors being the ones that contribute to smooth muscle contraction, glandular secretion and endothelial NO secretion. It is through the production of endothelial NO that ACh has vasodilatory effects *in vivo*.[31] Aiming to verify the involvement of the muscarinic pathway in the AECL relaxant effect, the antagonism of the muscarinic receptors was performed through incubation with atropine, a muscarinic receptor antagonist that acts through competitiveness in these receptors, preventing ACh from binding and exercising its activity. In this approach (Figure 4), where the vasorelaxant response of AECL was more attenuated, muscarinic receptors seem to be the most significantly implicated ($p < 0.01$) in the vasorelaxant effect induced by the AECL in the isolated thoracic aorta of rats.

The relaxant response in annuli (E-) was also important in these approaches to evaluate the possible involvement of ion channels. The activity of K^+ channels is an essential mechanism for the regulation of the vascular muscle cell membrane potential, being an important determinant of vascular tone.[32] The opening of a potassium channel present in the membrane of vascular muscle cells causes an increase in ion output, from the intracellular medium into the extracellular medium, causing cell membrane hyperpolarization and then a blockade of voltage-dependent Ca^{2+} channels and a consequent decrease in the input of Ca^{2+} ions into the intracellular medium, causing vascular relaxation.[32,33] Conversely, the closing of potassium channels causes a state of depolarization, opening of voltage-dependent Ca^{2+} channels, increase in intracellular Ca^{2+} and vasoconstriction.[32]

This mechanism of smooth-muscle relaxation and contraction differs regarding the PHE mechanism of action, which directly stimulates the α-adrenergic receptors of the G protein, acting via phospholipase C, increasing the levels of IP3, and resulting in the release of intracellular Ca^{2+}, causing muscular contraction.[34]

These results, shown in Figure 5, demonstrate that part of the AECL relaxant effect is related to the influence that the extract seems to have on the opening of ion channels, especially K^+ channels, since the hyperpolarization of the smooth muscle cell membrane can be produced by agents that open the K^+ channels, leading to the cell's K^+ efflux.[35]

K^+-induced contraction in the aorta seems to be dependent on the influx of Ca^{2+} through VOCCs, whereas the contraction is inhibited by the removal of Ca^{2+} from the external environment and by the blockers of these channels.[36] At the same time that the opening of Ca^{2+} channels may be required by a membrane depolarization process, the agents that produce membrane hyperpolarization can cause the Ca^{2+} channels to close, reducing the Ca^{2+} influx and promoting smooth muscle relaxation.[37]

Ionic channels also seem to be involved in the AECL significant vasorelaxant activity, with a greater expression in the opening of K^+ channels than in the blockade to VOCCs.

Conclusion

The AECL induced an important vasorelaxant effect, being more significant in the presence of the endothelium. The muscarinic pathway seems to be the main one involved with this effect, followed by the NO production pathway, the Prostacyclin's. The opening of K^+ channels by the AECL, although with a prominently lower degree of participation when compared to the retro-reported pathways, seems to have greater expression than its blockade to VOCCs. AECL showed no evidence of toxicity at the administered concentrations. Further studies are needed on the phytochemistry of AECL, as well as better pharmacological investigation through many other approaches and experimental models, including the use of tools to elucidate the action mechanisms of the extract.

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Author´s contribution

Study Project and Design and writing of the manuscript: Brozzo NPM; data acquisition and Critical review of the manuscript regarding important intellectual content: Brozzo NPM, Cunha RM, Meneguetti DUO. Data analysis and interpretation: Brozzo NPM, Cunha RM, Silva EF, Silva DA. Statistical analysis: Brozzo NPM, Gonçalves EA. Financial support provision: Cunha RM.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the *Universidade Federal do Acre* under the protocol number 23107.018498.

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ORIGINAL ARTICLE

Clinical Course of Patients Undergoing Myocardial Revascularization Surgery in a Public Cardiology Referral Hospital in Pará, Brazil

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Abstract

Background: Myocardial revascularization surgery (MRS) is the most frequently performed cardiac surgery in Brazil. However, data on mortality rates among patients undergoing MRS in hospitals other than the main referral centers in the northern Brazil are scarce.

Objective: To describe the clinical course of patients that submitted to MRS in the major public cardiology referral hospital in the Brazilian Amazon.

Methods: Retrospective cohort analysis, by review of medical records of patients who had undergone MRS at *Hospital das Clínicas Gaspar Vianna* (FHCGV) from January 2013 to June 2014.

Results: A total of 179 patients were evaluated. Mortality rate was 11.7% until 30 days after surgery. Waiting time for surgery ≥ 30 days (OR 2.59, 95%CI 1.02 – 6.56, p = 0.039), infection during hospitalization (OR 3.28, 95%CI 1.15 – 9.39, p = 0.021) and need for hemodialysis after surgery (OR 9.06 95%CI 2.07 – 39.54, p = 0.001) were predictors of mortality after CABG.

Conclusion: A high mortality rate in the study population was found, higher than that reported in the literature and in other regions of Brazil. (Int J Cardiovasc Sci. 2019;32(3)217-226)

Keywords: Myocardial Revascularization / mortality; Hospitals, Public; Epidemiology; Postoperative Complications.

Introduction

Ischemic heart disease is the main cause of death and work disability, causing high costs in public health and socio-economic impact in Western countries.[1] In Brazil, coronary artery disease (CAD) accounted for approximately 250 thousand hospitalizations and 16 thousand deaths in 2015. In the city of Belem, CAD caused nearly 800 hospitalizations and 151 deaths.[2]

Management of ischemic heart disease is complex and encompasses the control of risk factors and symptoms, aiming at reducing morbidity and mortality and optimizing patients' quality of life by means of optimized clinical therapy associated or not with revascularization procedures – percutaneous coronary intervention (PCI) or myocardial revascularization surgery (MRS).[3-6]

Despite historical advances in clinical therapy and percutaneous intervention in terms of technique and materials, results of multicenter studies have shown that MRS is superior to both PCI and clinical treatment alone in reduction of major cardiovascular events in specific groups of patients, such as diabetics, patients with multiple vessel disease or complex CAD involving left coronary trunk.[5,7-10]

MRS is the most performed cardiac surgery in Brazil, approximately 80% of them in public health centers. Mean mortality rate i is 6.2% in the country,[11] with wide variation by region (1.9% - 11.2%),[12] and higher in small surgical volume hospitals, public hospitals, and among female and older patients.[11]

In a recent national registry, a total of 1,722 patients who had undergone cardiac surgery were prospectively

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evaluated. The study involved 17 centers from four Brazilian regions (the North region was not included). Of all procedures, 83% were performed in public or private hospitals of the Brazilian Unified Health System (SUS). MRS accounted for 48.8% of the procedures, with a 7-day mortality of 2.6%.[13]

In the state of Pará, Brazil, 341 MRSs were performed in 2014, with a mortality rate of 7.0%. Of these surgeries, 46.0% were conducted at *Fundação Hospital de Clínicas Gaspar Vianna* (FHCGV) (city of Belem, Para), the main public center for treatment of cardiovascular diseases of Amazonia, with documented institutional death of 10.8%.[2] Today, nearly 50% of all MRSs carried out in the public system of Para state are conducted at FHCGV.[2]

Considering that current recommendations of guidelines of cardiology societies are based on clinical trials performed in American and European institutions, it is urgently necessary, for scientific knowledge and healthcare administration, to verify whether the global evidence can be reproduced to the Amazonian population, considering preoperative conditions, previous comorbidities, severity of underlying disease and postoperative course.

The aim of this study was to describe the clinical course of patients undergoing MRS at the largest, referral public cardiology center in the Brazilian Amazon.

Methods

Study design and selection of patients

This is an observational study, with analysis of a retrospective cohort from a historical series of patients who had undergone MRS at *Fundação Hospital de Clínicas Gaspar Vianna* from January 2013 to June 2014. The study was approved by the ethics committee of this institution.

The study population was composed of adult patients (> 18 years old) who had undergone MRS.

Patients who had undergone MRS combined with valvuloplasty or valve replacement, repair of congenital heart defects or aortic surgery were excluded from the study. We also excluded patients whose medical records were not located, had illegible handwriting, or whose data were unavailable for any reason.

Data collection

Data were collected from medical records using a standard half-open questionnaire of clinical and demographic characteristics of the study population. We collected all data registered from hospital admission to outpatient follow-up, until one year of the procedure.

Clinical outcomes

Main outcome was postoperative mortality from the admission day until one year after the procedure. Secondary outcomes were the following surgical complications – need for hemodialysis, major bleeding (as defined in the medical records), need for blood transfusion, cardiogenic shock and hospital infection.

Statistical analysis

The Kolmogorov-Smirnov test was used to verify the normality of distribution of continuous variables, expressed as mean ± standard deviation.

Categorical variables were described as frequency and percentage, and respective 95% confidence interval. Differences in the occurrence of the variables were evaluated by the chi-square test.

For mortality-related variables, odds ratio analysis was performed, with confidence interval of 95%.

For all statistical tests, a $p < 0.05$ was set as statistically significant. Statistical processing of the data was performed using the IBM SPSS Statistics Client for Trial 21.0 Mac OS Multilingual®.

Results

A total of 179 medical records of patients of both sexes who had undergone elective and urgent MRS were analyzed. All patients were submitted to extracorporeal circulation. Due to characteristics of our institution, as compared with the assistance provided by other public hospitals in which MRS is also performed, located in southern Para state, all patients underwent MRS after an episode of acute coronary syndrome (ST segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction or unstable angina). Despite this, only 7.8% of patients underwent urgent surgery and 92.2% to elective procedure.

Mean age of patients was 62.1 ± 9.2 years; most patients were aged between 60 and 70 years (45.8%), followed by 50-60 years (24.6%) and older than 70 years (19.0%). Most patients were male (74.9%) and originated from the capital and metropolitan area (65.4%) (Table 1).

Table 1 - Clinical and demographic characteristics of patients who underwent myocardial revascularization surgery between 2013 and 2014

Variable	N	% or mean ± SD	95% CI	
			Lower limit	Upper limit
Sex				
Male	134	74.9	67.8	81.0
Female	45	25.1	19.0	32.2
Age (years)	179	62.1 ± 9.2	-	-
Origin				
Belem (capital)	90	50.3	42.7	57.8
Metropolitan area* of Belem	29	16.2	11.1	22.4
Countryside cities	58	32.4	25.6	39.8
Other state	2	1.1	0.1	4.0
Risk factors[1]				
SAH	149	83.2	76.9	88.4
Dyslipidemia	38	21.2	15.5	27.9
Diabetes mellitus	87	48.6	41.1	56.2
Family history of CAD	4	2.2	0.6	5.6
Smoking	103	57.5	49.9	64.9
Previous comorbidities				
Previous stroke/TIS	3	1.7	0.4	4.8
Left ventricular contractile dysfunction (LVEF < 45.0%)	59	33.0	26.3	40.0
Chronic obstructive pulmonary disease	7	3.9	1.6	7.9
Peripheral artery disease	2	1.1	0.1	4.0
Baseline chronic kidney disease	7	3.9	1.6	7.9
Previous cardiac surgery	6	3.3	1.2	7.2
Previous percutaneous coronary intervention	28	15.6	10.6	21.2
Previous medication				
ACEi or ARB	74	41.3	34.6	48.6
Betablocker	29	16.2	26.7	21.2
Statin	18	10.0	5.6	14.5
AAS	34	19.0	13.4	24.6
Clopidogrel	9	5.0	2.2	8.4
Potassium-sparing diuretics	6	3.3	1.1	6.1
Thiazide and loop diuretics	11	6.1	2.8	10.0
Calcium channel blockers	8	4.5	1.7	7.8
Oral nitrate	16	8.9	5.0	13.4
Glucose lowering drug	36	20.1	14.0	26.3
Insulin	7	3.9	1.7	7.3

*ASA: acetylsalicylic acid. TIA: transient ischemic attack; ARB: angiotensin receptor blockers. CAD: coronary artery disease. SD: standard deviation. LVEF: left ventricular ejection fraction. SAH: systemic arterial hypertension. 95%CI: 95% confidence interval. ACEi: angiotensin converting enzyme inhibitors; *cities of Ananindeua, Benevides, Castanhal, Marituba, Santa Bárbara and Santa Izabel.*

Systemic arterial hypertension was the most common cardiovascular risk factor (83.2%), followed by active smoking at admission (57.5%) and diabetes mellitus (48;6%). The most common comorbidities were left ventricular contractile dysfunction (33.0%), chronic obstructive pulmonary disease (3.9%) and baseline chronic kidney disease (3.4%). A small proportion of patients had undergone any myocardial revascularization procedure. Less than half of patients were on medical therapy for coronary artery disease (Table 1).

Most patients underwent elective surgeries. Mean extracorporeal circulation and anoxia time was 77.6 and 46.2 minutes, respectively. Mean time from admission to surgery was 23.4 days, and the length of stay at the intensive care unit and hospital stay was 10.5 days and 15.6 days, respectively (mean) (Table 2).

A high incidence of hospital infection was found (52.5%), 16.2% during the admission-to-surgery period and 47.5% after surgery (Table 3); hospital-acquired respiratory tract infection was the most frequent (p = 0.003) (Figure 1).

Other common postoperative complications during hospitalization were bleeding (37.4%), blood transfusion (37.4%), complex arrhythmias (21.8%) and acute renal injury requiring hemodialysis (4.5%) (Table 3). There was no case of perioperative myocardial infarction documented.

Mortality rate was 11.7%; 85.7% of deaths (n = 18) occurred during hospital stay and 1.3% (n = 3) during the first year of follow-up. The most frequent cause of death was septic shock (57.1%) and cardiogenic shock (33.3%) (Table 4).

Of patients discharged after MRS, 18.9% were lost to outpatient follow-up. Among the others, 24.5% had 1-2 outpatient visits, more than half of patients (56.6%) had 3 or more visits during the first year after surgery; 10.1% reported recurrence of stable angina, 1.5% stroke and 0.8% needed another revascularization procedure.

Mortality-related factors were previous MRS, age ≥ 80 years (Figure 2), infection before or after surgery, baseline chronic kidney disease, renal failure requiring hemodialysis, previous MRS, prolonged hospital stay and patients waiting for surgery (Table 5).

Discussion

MRS is a therapeutic option for some CAD patients, aiming not only to increase patients' survival but also to alleviate symptoms, especially angina.[14]

Table 2 - Characteristics of myocardial revascularization surgeries of the patients who underwent the procedure at Fundação Hospital de Clínicas Gaspar Vianna between 2013 and 2014

Variable	N	% or mean ± SD	95%CI	
			Lower limit	Upper limit
Year of surgery				
2013	113	63.1	55.6	70.2
2014	66	36.9	29.8	44.4
Emergency of MRS				
Elective	165	92.2	87.2	95.7
Urgent	14	7.8	4.3	12.8
Time of ECC (minutes)	179	77.6 ± 28. 2	-	-
Time of anoxia (minutes)	179	46.2 ± 18.8	-	-
Time to surgery (days)	179	23.4 ± 15.9	-	-
Postoperative time (days)	179	15.6 ± 14.2	-	-
ICU stay (days)	179	10.5 ± 9.8	-	-

ECC: extracorporeal circulation; MRS: myocardial revascularization surgery; SD: standard deviation. ICU: intensive care unit.

Table 3 - Complications of myocardial revascularization surgery during hospitalization at Fundação Hospital de Clínicas Gaspar Vianna between 2013 and 2014

Complications	N	%	95%CI	
			Lower limit	Upper limit
Infection	94	52.5	45.2	59.8
Hospitalized, waiting for surgery	29	16.2	10.6	21.8
Postoperative	85	47.5	40.2	54.7
Bleeding	67	37.4	30.3	44.9
Blood transfusion	67	37.4	30.3	45.0
Complex arrhythmias	39	21.8	16.0	28.6
ARI requiring hemodialysis	8	4.5	1.9	8.6
ARI without dialysis	1	0.6	0.1	3.1
Stroke/acute ischemic attack	5	2.8	0.9	6.4
Need for new surgery	1	0.6	0.1	3.1
Others	1	0.7	0.1	3.7

ARI: acute renal injury.

Expected benefits may be significantly reduced by factors related to the surgical procedure itself, to the center where the surgery was performed, and to the patient.

In our study, surgical mortality was high (11.1%), higher than national mortality (6.2%) and much higher than that reported in European and American countries (2.13% and 4.4%, respectively).[15,16] In the northern region of Brazil, global mortality between 2005 and 2007 was 7.24%.[11] Studies conducted in other regions showed a wide variation in mortality rates, ranging from low rates as 1.7%, observed in a private hospital in Pernambuco to 14.2% in a hospital renowned for the cardiology service provided, located in the south of Brazil.[17,18] In another study carried out at this institution from January 2008 and December 2011, involving 233 patients, a mortality rate of 5.4%[19] was reported. Nevertheless, intraoperative and immediate (first 24 hours after surgery) postoperative deaths were excluded from the study, different from our study that considered all deaths for analyses.

Such wide variation in mortality may be explained by differences in healthcare services provided in each institution. FHCG is a referral center for emergencies in cardiology in the northern region of Brazil to which highly complex patients are referred, as exemplified in our study group. All patients undergoing surgery had been admitted for acute coronary syndrome (ST segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction or unstable angina), which may have contributed to high preoperative mortality. The lack of scores for predicting preoperative mortality at FHCGV, such as EuroScore or STS, which are widely used in many countries and were validated in some centers in Brazil,[18,20] does not allow the comparison between our study group and patients from other centers. Another explanation for the different results may be the type of health care provided; lower mortality rates were observed in private than public centers. In general, people have lower access to primary health care and centers specialized in highly complex cases. Also, higher availability and more effective use of financial resources are seen in private centers than in public ones.

Although postoperative mortality rate seemed to be positively associated with age, particularly considering patients older than 80 years, the number of patients at this age range was considerably small, so that a definite conclusion cannot be made. Rocha et al.,[21] reported higher mortality and postoperative complications such as need for new surgery, respiratory complications, mediastinitis, stroke, acute kidney failure, sepsis, atrial fibrillation and

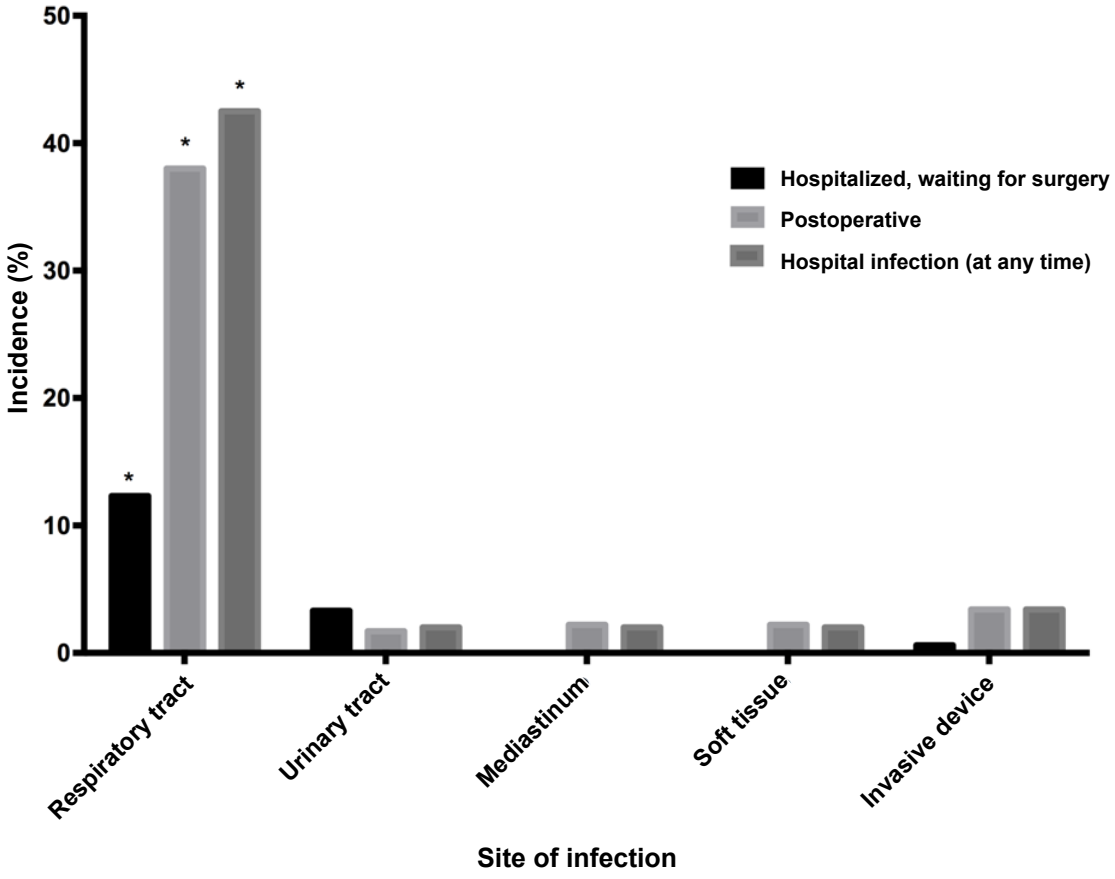

Figure 1 - Frequency of hospital infection by infection site during hospital stay.

complete atrioventricular block in patients older than 70 years undergoing MRS.

We did not observe a relationship of mortality with age. Some studies have reported higher mortality rates among women, as in a study conducted from 2002 to 2010 including 655 patients.[22]

Mean admission-to-surgery time was 23 ± 15.9 days, mean intensive care unit stay was 10.5 ± 9.8 days and the mean number of days from surgery to hospital discharge/death was 15.6 ± 14.2 days. The longer waiting time for surgery was associated with higher risk of infectious events during hospitalization, which was probably the main cause of mortality in our study.

In a study carried out in Rio de Janeiro, the authors found that the waiting time for MRS had no effect on operative mortality; however, approximately 11.0% of patients died in this period. Factors associated with mortality in these patients were left ventricular ejection fraction < 45% and a waiting time longer than 16 weeks.[23] In our population, left ventricular dysfunction was not a predictor of death. Another study conducted at *Santa Casa de Limeira*, including patients older than 70 years, showed that an intensive care unit stay longer than 48 years was associated with higher mortality, whereas hospital stay was not a predictor of mortality in these patients.[24]

With respect to comorbidities, only previous MRS and chronic kidney disease were associated with mortality. Anatomic localization of the arteries affected or postoperative complications (major bleeding, need for transfusion of blood derivatives, complex arrhythmias, stroke and angina) showed no association with mortality. On the other hand, both postoperative infection and kidney injury were associated with higher mortality. Results of a study conducted in a referral center for cardiology care differ from ours, as no difference in mortality was reported among patients who had infection. A study carried out at HCGV from

Table 4 - Clinical outcomes and postoperative complications in the first year of follow-up of patients who underwent myocardial revascularization surgery at Fundação Hospital de Clínicas Gaspar Vianna between 2013 and 2014

Variable	N	%	95%CI	
			Lower limit	Upper limit
Clinical outcome				
Discharge	158	88.3	82.6	92.6
Postoperative mortality	18	10.0	6.1	15.4
Mortality after discharge	3	1.7	0.4	4.8
Cause of death				
Septic shock	12	57.1	34.0	78.2
Cardiogenic shock	7	33.3	14.6	57.0
Acute myocardial infarction	1	4.8	0.1	23.8
Ventricular tachycardia	1	4.8	0.1	23.8
Outpatient follow-up				
Lost to follow-up	30	18.9	12.8	24.9
1-2 visits	39	24.5	17.8	31.2
3 or more visits	90	56.6	48.9	64.3
Complications after discharge				
Recurrent angina	13	10.1	5.5	16.6
Stroke/TIA	2	1.5	0.2	5.5
Need for new MRS	1	0.8	0.1	4.2

TIA: transient ischemic attack; MRS: myocardial revascularization surgery.

2008 to 2011 showed that acute kidney failure, blood transfusion and sepsis in the postoperative period, as well as urgency/emergency procedures were associated with higher mortality. These findings were different from ours, since emergency surgery had no significant effect on mortality.[19,25]

An important finding was the lack of acute myocardial infarction in the perioperative period in our study group, which differs from studies in the literature that report an incidence ranging from 2 to 30%, depending on the criteria used by the authors.[26] In a study on 116 patients, 24.1% had perioperative acute myocardial infarction, which was related with worse ventricular function and death.[26] This can be explained by the fact that acute myocardial infarction may be difficult to be detected in the perioperative period due to its particular characteristics during this phase, different from usual manifestation. For example, patients are usually under sedation and anesthesia and thereby not able to identify pain, requiring a high degree of suspicion by the clinician and complementary tests such as markers of myocardial necrosis, ECG and echocardiography for the diagnosis. Besides, endarterectomy, an important risk factor for perioperative acute myocardial infarction, is rarely performed in our center.

The most frequent causes of mortality were septic shock, followed by cardiogenic shock, acute myocardial infarction (at clinical follow-up, after discharge) and arrhythmia. A study conducted at *Instituto Nacional de Cardiologia* (National Institute of Cardiology) between 2004 and 2009 showed that main causes of mortality after MRS were cardiac-related (38.7%), infection (14.1%), multiple organ failure (3.8%), neurological (1.9%) and others (41.5%).[27]

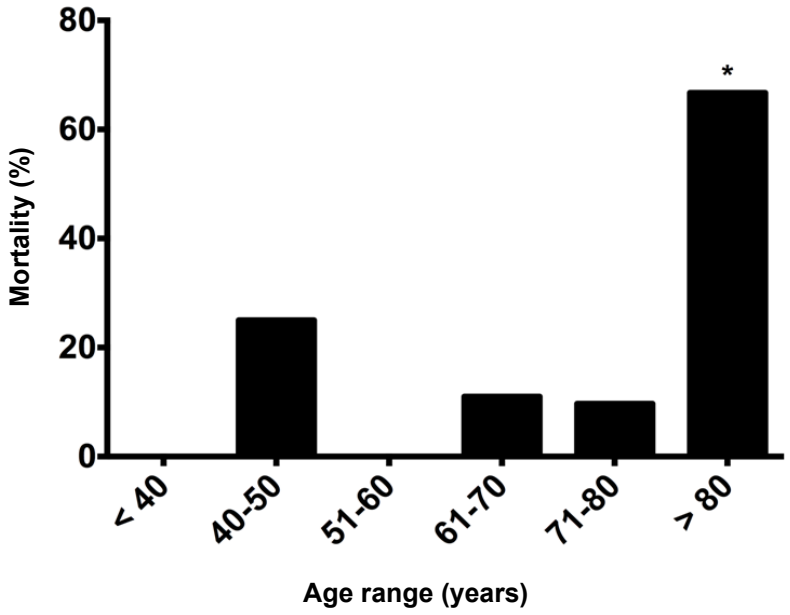

Figure 2 - Mortality rate by age range. In patients older than 80 years, mortality rate was 66.7%, significantly higher than other ages (p = 0.03).

Table 5 - Variables associated with hospital mortality and mortality in the first year of follow-up in patients who underwent myocardial revascularization surgery at Fundação Hospital de Clínicas Gaspar Vianna between 2013 and 2014

Variable	*Odds Ratio*	95%CI		p value
		Lower limit	Upper limit	
Previous MRS	18.3	3.1	107.7	< 0.001
Age > 80 years	16.5	1.4	191.0	0.003
Need for hemodialysis after MRS	9.1	2.1	39.5	0.001
Baseline chronic kidney disease (GFR < 60 mL/min)	6.4	1.3	31.0	0.009
Infection in patients waiting for surgery	3.1	1.1	8.5	0.023
Postoperative infection	3.1	1.2	8.5	0.019
Hospital infection at any time	3.3	1.2	9.4	0.021
Prolonged preoperative hospitalization (> 30 days)	2.6	1.0	6.6	0.039

MRS: myocardial revascularization surgery; GFR: glomerular filtration rate. p < 0.05.

Most patients were discharged, approximately 20% were lost to outpatient follow-up; three deaths occurred in the first year after discharge. A study conducted in four public hospitals in Rio de Janeiro showed a mortality rate of 14.9% one year after discharge.[12] Such divergency may be explained by the high loss to follow-up rate in our study, which may have underestimated mortality rate after discharge (since no information of these patients were obtained).

Based on the high mortality rate, the increased waiting time for surgery and the high incidence of infection related to waiting time, it would wise to

increase the number of patients referred to percutaneous coronary intervention instead of MRS. This would alleviate, at least in part, excessive waiting times for surgery. Further studies are needed to compare the use of both strategies in our institution to identify the group of patients that would benefit most from percutaneous coronary intervention.

In addition, limitations of the retrospective cohort design of the study include missing data in the registry database, which may have affected the analysis.

Conclusion

We found a high mortality rate in patients undergoing MRS, higher than that reported in the literature and in other regions of Brazil. Further studies are needed to determine the causes of these findings and find effective solutions.

Author contributions

Conception and design of the research: Lobato PHM, Vieira Junior FM, Nunes MBG, Galucio VAQL. Acquisition of data: Lobato PHM, Vieira Junior FM, Nunes MBG, Galucio VAQL, Barreto EL. Analysis and interpretation of the data: Lobato PHM, Vieira Junior FM, Nunes MBG, Galucio VAQL. Statistical analysis: Lobato PHM, Vieira Junior FM, Nunes MBG, Galucio VAQL. Obtaining financing: Lobato PHM, Vieira Junior FM, Nunes MBG, Galucio VAQL. Writing of the manuscript: Lobato PHM, Vieira Junior FM, Nunes MBG, Galucio VAQL. Critical revision of the manuscript for intellectual content: Lobato PHM, Vieira Junior FM, Nunes MBG, Galucio VAQL.

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 Fundação Pública Hospital de Clínicas Gaspar Vianna under the protocol number CAAE: 66557717.0.0000.0016. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Implementation of an Acute Coronary Syndrome Simulation Training Strategy for Emergency Healthcare Professionals

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Abstract

Background: The knowledge on the management of patients with acute coronary syndrome (ACS) is essential to reduce the gap between evidence and practice.

Objective: To describe a simulation training strategy for emergency healthcare professionals and provide preliminary data on knowledge acquisition, learners' confidence and prescription of medications after training.

Methods: The training was part of the implementation of two myocardial infarction systems of care. It comprehended lectures and simulation-based learning using high and low-fidelity mannequins and actors. It was tested in two phases: the first one in Belo Horizonte and the second one in Montes Claros, both in the state of Minas Gerais. A test was applied before and after training to assess knowledge acquisition. Confidence to perform thrombolysis in ST-elevation myocardial infarction (STEMI) patients was assessed using a questionnaire, and the impact on medication prescription analyzed STEMI patients admitted to hospitals in Montes Claros.

Results: In the first phase, 156 professionals answered both tests: 70% of them improved their results and the median number of right answers increased (6, interquartile range [IQR] 5-7; vs 7 ([IQR] 6-9; $p < 0.05$). In the second phase, 242 professionals answered both tests: 58% of the physicians and 83% of the nurses obtained better test scores. Participants referred a positive impact on their clinical practice, 95% reported feeling very secure when perform fibrinolysis after the training, and there was also an impact on medication prescription.

Conclusions: There was an impact on the learners' knowledge acquisition and confidence using our two-phase training model , with evidence of impact on performance. (Int J Cardiovasc Sci. 2019;32(3)227-237)

Keywords: Acute Coronary Syndrome; Myocardial Infarction; Myocardial Reperfusion; Emergency Service Hospital; Quality Indicators, Health Care.

Introduction

The knowledge on the management of patients with acute coronary syndromes (ACS) is essential to any emergency healthcare provider. This condition is highly prevalent globally and potentially hazardous, responsible for 31% of all deaths in 2015.[1,2] It is also known that mortality is income-related and at least three quarters of deaths occur in low-and middle-income countries (LMICs), such as Brazil.[1] In this country, ACS is an important cause of hospitalization and the leading cause of mortality, accountable for almost 28% of deaths in 2014.[3,4] The gap between research knowledge and guideline recommendations to their utilization in clinical practice impacts on the quality of care delivered and clinical outcomes.[5,6] Therefore, it is necessary to provide means to keep staff updated on ACS guidelines aiming to enhance performance and, ultimately, to improve patient care.

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Simulation-based techniques are well-established means to improve both individual and teamwork performance by increasing awareness of current protocols, development of practical skills and enhancing clinical reasoning.[7-9] Issenberg et al.,[10] reviewed studies to evaluate the features of simulation techniques on medical education and observed that it is an effective learning technique that complements bedside medical education.[10]

However, studies evaluating the use of simulation education in LMICs are limited. There is a lack of permanent education programs and restrained funds to invest in simulations.[11] We hypothesize that using simulations in LMICs can improve the healthcare team's performance and knowledge on ACS, leading to a more effective care to be delivered to the patients.[12,13]

Thus, the purpose of this study is to evaluate the implementation of a two-phased, large-scale ACS training program across multiple learners in resource-limited areas. Furthermore, we provide preliminary data on knowledge acquisition, learner confidence, and impact on medication prescription after the strategy to foster further use of the program.

Methods

Participants

Physicians and nurses from public hospitals, emergency care units (*Unidades de Pronto Atendimento*, UPA) and the ambulance service (*Serviço de Atendimento Médico de Urgência*, SAMU) of Belo Horizonte and 89 municipalities in the north of Minas Gerais state, Brazil, were invited to join the training, focusing mainly on professionals responsible for the care of patients with ACS. Also, professionals from institutions belonging to the Telehealth Network of Minas Gerais (TNMG) were also invited to participate.

The TNMG is a large public telehealth service launched in 2005 by seven public universities in Minas Gerais state. At first, TNMG focused on telecardiology and assisted primary care settings of remote municipalities in Minas Gerais state, Brazil. The initiative has expanded to other municipalities (covering 813 of the 853 municipalities of the state) and also to emergency services.[14,15] Furthermore, the service participated in the development of the acute myocardial infarction (AMI) system of care in Belo Horizonte and in the north of Minas Gerais, and this training was part of the implementation of those care systems.[16,17]

Intervention design

The training consisted of four sections: (1) pre-assessment, (2) lectures, (3) simulation-based stations and (4) post-assessment.

Firstly, the participants' previous knowledge on the subject was assessed through a pre-test, which consisted of 10 multiple-choice questions related to diagnosis, management and treatment of ACS patients based on standard protocols. Afterwards, they had lectures about those topics, based on current ACS protocols.[18-24] At the end of the section, the lecturer dedicated a moment to listen to and answer queries from the audience. Then, they participated in a simulated environment to perform what they had learned in a practical setting. Lastly, they completed the same test taken at the beginning of the training. The goal was to determine knowledge acquisition.

Simulation setting

The simulation-based session comprehended five stations to practice the following situations: (1) ST-elevation myocardial infarction (STEMI) with thrombolysis indication, (2) STEMI with indication of referral for primary angioplasty, (3) AMI with cardiogenic shock and respiratory failure, (4) Non-ST-elevation myocardial infarction (NSTEMI) and (5) Recording and transmitting the digital electrocardiogram. Each situation was reproduced in a simulated scenario guided in real-time by a facilitator. The simulation stations used one high-fidelity mannequin, one low-fidelity mannequin and three actors simulating patients (Figures 1 and 2).

The facilitator followed a simulation plan that included: 1) primary and secondary objectives of each station; 2) case description; 3) response plan to the simulator depending on the participants' possible actions; 4) scripts for the actors responsible for voice simulator and other participants; and 5) a debriefing plan. All scenarios were previously tested.

In each station, two individuals created the learning environment and 6-7 others watched the two first ones. The simulation followed the consecutive sequence: (i) participants were welcomed by the facilitator; (ii) explanation of basic simulation techniques; (iii) introduction of the simulator and simulation environment; (iv) separation in two groups: "hot seats" and observers (v) introduction of the scenario; (vi) performance of the scenario; (vii) facilitated debriefing, stage in which the facilitator mediated constructive feedback

Figure 1 - Scenario in which participants can practice recording and transmitting the digital electrocardiogram, using an actor, simulating a non-ST elevation myocardial infarction.

Figure 2 - Instructor performing introduction of the simulator and simulation environment in the station about ST-elevation myocardial infarction with indication of thrombolysis, using a high-fidelity mannequin.

in order to stimulate critical reflection about the simulation; (viii) summarizing of the most important topics.[25]

First phase

This phase was developed in Belo Horizonte, Brazil. Physicians and nurses from emergency care units and SAMU were invited to join the training, focusing mainly on professionals responsible for the care of ACS patients.

Second phase

This phase was developed in Montes Claros, Brazil. It was part of a quasi-experimental study, Minas Telecardio 2 project, a three-phase study (baseline, implementation and post-implementation phases) which assessed the impact of the implementation of the myocardial infarction care system in the north of Minas Gerais state. The training reported here was part of the implementation phase.[17,26]

In this region, the health system is divided into nine micro-regions, covering 89 municipalities in an area consisting of 128,000 km² and comprising a population of 1.6 million inhabitants. There are 18 public hospitals in the area, but 9 of those are concentrated in Montes Claros, the main municipality of the region. SAMU has 47 ambulances (7 with doctors and 40 with nurse technicians).[26]

There were two training sessions. The first one, on April 2014, was carried out in Montes Claros, and physicians and nurses from emergency services of the 18 public hospitals and ambulance services (SAMU) of the north region of Minas Gerais were invited to participate.

The model and duration of the training were similar to the first phase, except for the test applied to nurses, which included specific questions about their role in the management of ACS patients. All professionals were invited to answer a feedback survey. It included questions about the participant's clinical practice, how often they had managed chest pain in the last month and how secure they felt when performing thrombolysis (when indicated) after the course.

The second training session was carried out in August/September 2014. This one took place in five different municipalities distributed throughout the region, to make it easier for professionals who lived far away from Montes Claros to participate. Physicians and nurses from the emergency services of the 18 public hospitals and ambulance services (SAMU) of the north region of Minas Gerais were invited to participate. For this one, no pre and post-tests were applied.

Data about medication prescription was collected in three different moments: baseline (June 19th, 2013 to March 31st, 2014); post-implementation phase, just after the training sessions happened (September 1st, 2014 to May 31st, 2015); and eight months after the end of the Minas Telecardio 2 project (June 1st, 2015 to January 31st, 2016). Data on the prescription of aspirin, P2Y12 inhibitor, heparin and statin medication within the first 24 hours after admission and at discharge were collected from STEMI patients admitted to hospitals in Montes Claros.

Statistical analysis

The data were analyzed using the program Statistical Package for the Social Sciences, version 20.0 (SPSS Inc, Chicago, IL, EUA). The evaluation of the distribution of continuous variables was performed using the Kolmogorov-Smirnov test. The continuous variables were expressed as mean and standard deviation or median and interquartile range, as appropriate, while categorical variables were expressed as absolute number and percentage. The test questions were classified into different categories depending on the subject: diagnosis, treatment or both. This classification was used to analyze the results of both tests stratified by the subject. The results of the pre- and post-tests were compared using McNemar test. In order to evaluate the influence of workplace and years since graduation on the participants' performance in the test, the non-parametric Spearman's correlation coefficient was calculated. The p value considered significant was set at 0.05.

Results

First phase

A total of 189 professionals participated in the training, of which 86 were doctors and 103 nurses. Most were females (68.0%), and there was a predominance of professionals from the emergency care units (50.8%), hospitals (29.5%) and ambulance services (17.2%). Additionally, 18.9% of them had graduated up to 1 year before, 24.6% had graduated 2 to 5 years before, 16.4% had graduated 6 to 10 years before and 38.5% had been working for more than ten years in the profession.

One hundred and fifty-six professionals answered both tests, which corresponds to 82.5% of the total (Figure 3). In the comparative data analysis, it was observed an improvement in the participants' performance in the post-test, since 66.0% of the professionals achieved better scores.

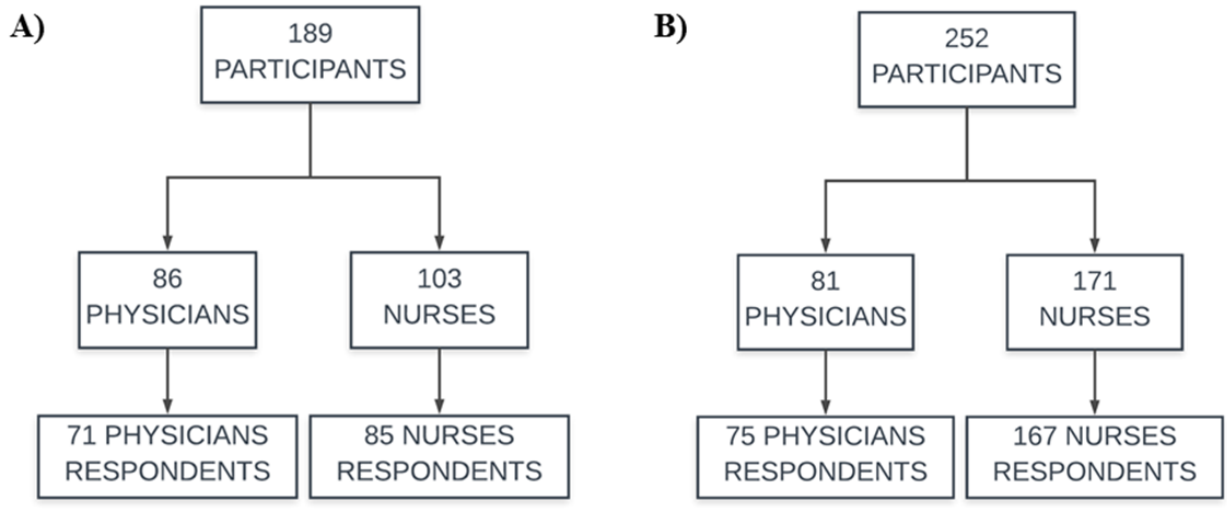

Figure 3 - Flowchart of the participants in the first (A) and second (B) phases of the training.

To highlight the improvement in the professionals' knowledge acquisition, a comparative analysis of the total number of correct answers in both tests was performed and is shown in Table 1. An increase in the number of correct answers was observed in the post-test when compared to pre-test, with a median of 6 right answers in the pre-test (interquartile range [IQR] 5-7) and 7 in the post-test (IQR 6-9) ($p < 0.0001$). In addition, the lowest score comprised two correct answers to questions in the pre-test and increased to four in the post-test. Based on the type of question, an individual analysis showed an increase in the number of correct answers in 8 out of 10 questions ($p < 0.05$). As for the remaining questions, in one of them the number of right answers in the pre-test was high (97.4%) and remained high in the post-test results (99.4%). In the last question, the number of correct answers remained low in both tests, as shown in Table 2. No correlation was observed between years of work experience (Spearman -0.058, $p = 0.53$) or workplace (Spearman -0.034, $p = 0.71$) and knowledge acquisition. These results were similar when assessing only medical doctors (occupation time Spearman's = -0.041, $p = 0.75$; workplace Spearman's = -0.10 $p = 0.42$).

Second phase

A total of 252 professionals participated in the first training session, of which 81 were doctors and 171 nurses. Two-hundred and forty-two professionals (75 doctors and 167 nurses) answered both tests, which corresponded to 96% of the total (Figure 3). The profile analysis of physicians (n = 75) revealed that most were males (76.0%). There was a predominance of the ambulance service professionals (51.0%), followed by hospital employees (45.0%) and 21.0% had graduated up to one year before, 41.0% had graduated 2 to 5 years before, 20.0% had graduated 6 to 10 years before and 17.0% had been working for more than ten years in the profession. As for nurses, the analysis of their profile (n = 167) indicated that most were women (58.0%), with a predominance of professionals working in hospitals (73.1%) followed by those working in ambulance services (25.7%). Ten percent had graduated up to one year before, 42.0% had graduated 2 to 5 years before, 42.0% had graduated 6 to 10 years before and 5.0% had been working in the profession for more than ten years.

In the comparative data analysis shown in Table 1, an improvement in the results was observed in the post-test, since 78.0% of the sample (58.0% of physicians and 83.0% of nurses) obtained better results. Medical doctors reached a median of 7 correct answers in the pre-test (interquartile range [IQR] 2-8) and 8 in the post-test (IQR 7-9) ($p < 0.0001$). Nurses had a median of 6 right answers in the pre-test (interquartile range [IQR] 4-7) and 9 in the post-test (IQR 7-9) ($p < 0.0001$). Furthermore, as shown in Table 2, the lowest score for physicians was two questions in pre-test and increased to four in post-

Table 1 - Number of right answers by the participants (n = 156) in the first phase, and physicians (n = 75) and nurses (n = 167) in the second phase

Right answers	First phase		Second phase			
			Physicians		Nurses	
	Pre-test	Post-test	Pre-test	Post-test	Pre-test	Post-test
0	-	-	-	-	1 (0.6)	-
1	-	-	-	-	3(1.8)	-
2	2 (1.3)	-	1 (1.4)	-	4(2.4)	-
3	11 (7.1)	-	1 (1.4)	-	25 (15.0)	-
4	14 (9.0)	6 (3.8)	4 (5.3)	1 (1.4)	20 (12.0)	-
5	37 (23.7)	20 (12.8)	10 (13.3)	5 (6.7)	24 (14.4)	8 (4.8)
6	32 (20.5)	32 (20.5)	18 (24.0)	11 (14.7)	33 (19.8)	15 (9.0)
7	30 (19.2)	23 (14.7)	18 (24.0)	19 (25.3)	23 (13.8)	23 (13.8)
8	15 (9.6)	32 (20.5)	17 (22.6)	10 (13.3)	18 (10.4)	32 (19.2)
9	12 (7.7)	23 (14.7)	6 (8.0)	19 (25.3)	14 (8.4)	53 (31.7)
10	3 (1.9)	20 (12.8)	-	10 (13.3)	2 (1.2)	36 (21.6)

Table 2 - Comparative analysis of the number of right answers per question (n = 156) in the first phase

	Type of question	Pre-test	Pos-test	p-value
		n (%)	n (%)	
1	Diagnosis	152 (97.4)	155 (99.4)	0.250
2	Therapy	68 (43.6)	84 (53.8)	< 0.0001
3	Therapy	90 (57.7)	126 (80.8)	< 0.0001
4	Diagnosis and Therapy	104 (66.7)	132 (84.6)	< 0.0001
5	Diagnosis and Therapy	118 (75.6)	108 (69.2)	0.002
6	Diagnosis and Therapy	103 (66.0)	134 (85.9)	< 0.0001
7	Therapy	72 (46.2)	104 (66.7)	< 0.0001
8	Diagnosis and Therapy	61 (39.1)	100 (64.1)	< 0.0001
9	Therapy	61 (39.1)	58 (37.2)	0.250
10	Diagnosis	109 (69.9)	139 (89.1)	< 0.0001

test and for nurses it went from zero to five questions. Table 3 shows the individual analysis of each question, for physicians and nurses.

One-hundred and thirty-seven healthcare professionals filled out the survey, of which 58 were nurses (29.9% of the total) and 76 were physicians (93.8% of the total). Most of the sample (52.6%) had had less than 5 years of work experience since graduation. A total of 58 physicians (76.3% of the respondents) informed having treated at least five patients with chest pain during the last month, while 26 (34.2%) reported having treated 5 to 10 patients and 32 (42.1%) professionals treated over 10 patients. After the training, 128 professionals (95.5%) reported feeling "very secure" when performing fibrinolysis.

A total of 24 physicians and 119 nurses participated in the second training session.

Regarding the impact on medication prescription,, the results are shown in Table 4.

Discussion

In this study, a training strategy for ACS management using simulation techniques for emergency healthcare professionals improved knowledge acquisition,

Table 3 - Comparative analysis of the number of right answers per question for physicians (n = 75) and nurses (n = 167) in the second phase

	Pre-test n (%)	Post-test n (%)	p-value	Pre-test n (%)	Post-test n (%)	p-value
		Physicians			Nurses	
1	71 (94.7)	75 (100.0)	n/a	146 (87.4)	158 (94.6)	< 0.001
2	30 (40.0)	48 (64.0)	< 0.001	72 (43.1)	149 (89.2)	< 0.001
3	72 (96.0)	75 (100.0)	n/a	91 (54.5)	111 (66.5)	< 0.001
4	39 (52.0)	44 (58.7)	0.608	73 (43.7)	123 (73.7)	< 0.001
5	59 (78.7)	63 (84.0)	0.424	100 (59.9)	164 (98.2)	< 0.001
6	45 (60.0)	71 (94.7)	< 0.001	142 (85.0)	163 (97.6)	< 0.001
7	57 (76.0)	53 (70.7)	0.424	91 (54.5)	119 (71.3)	< 0.001
8	38 (50.7)	40 (53.3)	0.167	60 (35.9)	88 (52.7)	< 0.001
9	38 (50.7)	50 (66.7)	0.029	86 (51.5)	153 (91.6)	< 0.001
10	52 (69.3)	60 (80.0)	0.077	74 (44.3)	156 (93.4)	< 0.001

**n/a: not available.*

Table 4 - Prescription of medications within 24 hours after admission and at discharge in the second phase

Within 24 hours after admission			
	Baseline	Post-implementation (period where trainings occurred)	After the end of the project
	Jun/13 to Mar/14 (n = 208)	Sep/14 to May/15 (n = 143)	Jun/15 to Jan/16 (n = 164)
Aspirin	94.2%	100%	91.5%
P2Y12 inhibitor	87.5%	100%	92.0%
Heparin	74.5%	95.1%	78.7%
At discharge			
	Baseline	Post-implementation (period where trainings occurred)	After the end of the project
	Jun/13 to Mar/14 (n = 169)*	Sep/14 to May/15 phase (n = 122)*	Jun/15 to Jan/16 (n = 132)*
Aspirin	96.4%	100%	93.9%
P2Y12 inhibitor	75.7%	94.3%	81.1%
Statin	90.5%	100%	84.8%

** After excluding patients who died. †p-value was < 0.05 for all medications from the first to the second period, and from the second to the third period.*

measured by pre- and post-test assessments in two different scenarios of AMI care system implementation. It provided evidence of an increase in physicians' confidence to perform thrombolysis in STEMI patients, and an improvement in medication prescription within the first 24 hours after admission and at discharge.

In both phases, the performance of healthcare practitioners in the post-test was better than in the pre-test. More than 66.0% of the professionals achieved better results in the post-test in the first phase and 78.0% in the second phase. There was a significant improvement in 8 out of the 10 questions with statistical significance ($p < 0.05$) in the first phase. It shows that, after training, professionals had an increase in the theoretical domain regarding managing ACS patients, which contributes to better use of these lessons in clinical practice.

In the second phase, the number of right answers increased for physicians and nurses, but nurses achieved greater improvement. Nurses improved their performance in all questions with statistical significance and the median number of correct answers increased significantly. Meanwhile, physicians improved their performance in 9 out of 10 questions, yet there was no statistically significant difference in 5 of them, due to sample size limitations (it was not possible to apply the McNemar Test in 2 questions, as the entire sample answered correctly in the post-test). As it was evident when looking at the pre-test results, medical doctors tended to have better previous knowledge about ACS than nurses. Considering that, we hypothesize that the training was especially valuable for professionals with less previous knowledge on the subject. As for medical doctors, a huge disparity in medical education was also evident, as the result of pre-test varied significantly among participants: the pre-test IQR of correct answers was 2-9 in the pre-test and decreased to 7-9 in the post-test.

The training also impacted on the participants' self-confidence, as 95% reported feeling very secure when performing fibrinolysis after the training. Even though participants did not have previous experience with simulation during graduation, they accepted and adapted well to the training model. They participated in the simulated scenarios, debriefing and in the feedback sessions.

This simulation experience had strengths and barriers. A specific characteristic that contributed to the success of our training was the fact that physicians and nurses were trained together. It was based on the idea that effective collaboration between these professionals can lead to a reduction in morbidity and mortality, fewer medical errors and enhance job satisfaction.[27] Recently, training models have been recognized as important tools to improve teamwork and communication skills across the healthcare staff.[28,29] Thus, we developed a framework that emphasized teamwork and communication. In each station, two participants (one physician and one nurse) worked together to respond to the clinical scenario and all participants were engaged in the debriefing. Furthermore, our training was also helpful to increase awareness of current guidelines. As Sussman et al.,[30] points out, lack of familiarity of practitioners with the presenting literature is one of the causes leading to the bridge between research and clinical routine.[30] For instance, the use of pre-hospital electrocardiogram (ECG) to diagnose and manage patients is accepted in the literature as an effective method to reduce morbidity and mortality of ACS.[24,31] Nevertheless, this recommendation is not always followed in clinical practice.[32,33] This divergence between scientific knowledge and its implementation reinforces the importance of strategies to increase awareness of the guidelines and their application.

On the other hand, despite the common use of simulation in high-income countries (HIC)[34], its use in LMICs are still scarce.[11,35] In these countries, restrained funding remains an obstacle to the implementation of simulation training programs.[11] Building a simulation center involves the acquisition of equipment, trained personnel and adequate facilities, thus the costs are high.[36] In our experience, funding was a great barrier to turn this program into a continued education program. The professionals underwent a similar training session for only one additional time and the program is current on hold due to lack of resources. Looking at successful simulation trainings in LMICs, they usually involve a collaborative network between various departments and institutions and we believed that it could be an alternative to our scarcity of funding.[11] As for other barriers, it is important to mention the lack of employers' support, in the sense that the hours healthcare professionals spent on training were not paid. In the second phase, we can highlight the distance from the workplace to the simulation center, which increased transportation costs and precluded the participation of physicians and nurses who lived far from the city where the training was being held (Montes Claros).

This experience was part of the implementation of the AMI care system in Belo Horizonte and in the northern region of Minas Gerais state. This initiative encompassed a multifactorial intervention across multiple institutions to improve the quality of treatment, which also included tele-electrocardiogram implementation and AMI care reorganization. Previous studies concluded that to achieve success in the implementation of care systems, the action plan has to be defined not only considering established guidelines, but also taking into consideration

the regional differences.[37,38] Several studies performed in developing countries highlighted the existence of obstacles related to poor infrastructure to the establishment of a care system.[38,39] In those situations, the training strategy might be even more important, since any improvement in health represents significant benefits in patient care. Although using the same test to evaluate the participants makes it difficult to appraise the influence of the pre-test on the post-test performance, the increase in medication prescription within the first 24 hours after admission and at discharge is an evidence of the impact of the training strategy. The fact that the benefit decreased aftertime following the training (the prescription increased in the nine months after the two training sessions but decreased after this period) showed the importance of continued education for healthcare professionals. Due to the high turnover of emergency professionals, training sessions need to be repeated periodically to increase effectiveness.

The use of simulation-based education has increased gradually in recent years and it has been considered an important method to improve professional development, patient safety[25,40] and to enable team work practice.[8] It is a student-centered learning process that enables students to build their own knowledge from mistakes. A basic assumption is that learning from mistakes in a simulated environment can reduce the occurrence of errors in clinical practice and increase the practice of the correct attitudes.[40] In a systematic review by Issenberg et al., debriefing was considered the most important step to determine effectiveness in simulation-based learning.[10] We considered that the use of these principles had an important role for our training success. The feedback from the health professionals showed a positive impact on their daily tasks, as most participants submitted to the training stated that the strategy added confidence and safety to their clinical practice.

Corroborating our findings, the BRIDGE-ACS study (Brazilian Intervention to Increase Evidence Usage in Acute Coronary Syndromes) performed in Brazilian public hospitals, demonstrated the effectiveness of a multifactorial intervention to improve quality of treatment. This intervention included the use of reminders, checklists, distance and presential training using simulation techniques. There was a significant increase in the proportion of patients who received the recommended therapies (aspirin, P2Y12 inhibitors, anticoagulants and statins) within 24 hours after admission and at discharge.[41]

Thus, there is evidence of an impact on the increase in adherence to the ACS guidelines. Another gain that is not possible to be measured is the impact on physicians' and nurses' motivation, which was very important for the success of the MI care system.

The study has limitations. Knowledge acquisition was assessed immediately after training. We tried to assess the long-term impact of the training by collecting data on medication prescription (and there was no other intervention to improve it), but further studies should perform a thorough assessment of the impact on clinical outcomes.

Conclusion

This study showed how a theoretical educational intervention, associated with simulation-based training strategy, in the context of the implementation of MI care systems in resource-limited areas, showed an impact on learners' knowledge acquisition in two different scenarios, with evidence of impact on the health providers' confidence in performing thrombolysis in STEMI patients and medication prescription within 24 hours after admission and at discharge. These experiences can be used to guide future programs that can be expanded to the rest of the country.

Author contributions

Conception and design of the research: Marcolino MS, Ribeiro AL; acquisition of data: Dias TD, Machado GSB, Carvalho EAS, Rocha GAS, Marino BCA; analysis and interpretation of the data: Marcolino MS, Souza-Silva MVR, Passos PFOP, Lemos TR, Carvalho EAS, Rocha GAS; writing of the manuscript: Marcolino MS, Souza-Silva MVR, Passos PFOP, Lemos TR; and all authors participated in critical revision of the manuscript for intellectual content.

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 PHD thesis submitted by Bárbara Campos Abreu Marino, from Program in Infectious Diseases and Tropical Medicine (PG-IMT) at the Medical School of the *Universidade Federal de Minas Gerais*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Federal de Minas Gerais* under the protocol number 260/09. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent (and permission to use images) was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Antioxidant and Vasodilatory Action of Grape Juices Produced in Different Regions of Brazil

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Abstract

Background: Grapes and its derivatives (wines and juices) are rich in polyphenols that have high antioxidant and vasodilator capacity. These biological activities may vary in the juices marketed and produced in different regions of Brazil.

Objectives: To determine the antioxidant and vasorelaxant effects of grape juice samples produced in different regions of Brazil.

Methods: The content of phenolic compounds and antioxidant capacity were evaluated by the methods of Folin-Ciocalteau, DPPH, ABTS and a new electroanalytical approach (differential pulse voltammetry - DPV). Vasodilator effects were analyzed in isolated aorta from rats in an organ bath.

Results: The samples from RJ and SP presented respectively the higher and lower phenolic content and also antioxidant capacity by the methods used (ABTS and DPPH). The results of the electrochemical index corroborate to the other tests, with the best results to RJ (21.69 ± 3.15 μA/V) and worse to the SP sample (11.30 ± 0.52 μA/V). In the vascular reactivity studies, the relaxation induced by each sample presented more distinct differences, following the order: RJ (87.9 ± 4.8%) > RS1 (71.6 ± 8.6%) > GO (56.2 ± 7.2%) > SP (39.9 ± 7.8%) > PR (39.4 ± 9.5%) > RS2 (19.5 ± 6.2%). Inhibition of endothelial NO practically abolished ($p < 0.001$) the relaxation for all samples, except one.

Conclusion: The phenolic content and antioxidant capacity vary greatly among samples. The results obtained for the order of antioxidant activity were: RJ > RS1 > GO > RS2 > PR > SP. The juices were able to induce vascular relaxation at quite varied levels, and the RJ sample the most effective. The L-NAME practically blocked all samples except one (RS2). (Int J Cardiovasc Sci. 2019;32(3)238-246)

Keywords: Antioxidants/pharmacology; Vasodilatation; Vasodilatador Agents/analysis; Vitis; Fruit and Vegetable Juices/analysis; Epidemiology; Cardiovascular Diseases/prevention and control; Neoplasms/prevention and control.

Introduction

Epidemiological evidence shows that the ingestion of foods rich in polyphenols (such as grapes and grape products) is associated with decreased mortality worldwide due to reduced cases of cancer and cardiovascular diseases.[1]

Polyphenols have beneficial antioxidant effects against oxidative stress, the main pathophysiological mechanism in the development of cardiovascular diseases, such as hypertension, diabetes and atherosclerosis.[2] They cause vasodilation by increasing the production of vasodilatory agents produced by the vascular endothelium (as NO) and decreasing vasoconstricting agents, such as endothelin-1.[2,3] In addition, there is a direct correlation between the number of polyphenols in red wine and its capacity to induce endothelium-dependent vasodilation.[4]

Despite the great benefit of chronic red wine consumption, the alcohol present in the drink generates some limitations of use, mainly in psychiatric patients,

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the elderly, children and pregnant women. However, studies have found that the consumption of grape juice also has positive results, often comparable to wine consumption, such as an antioxidant and vascular relaxation action.[5,6]

Despite the existence of several studies with red wine from different parts of the world, including Brazil, a smaller number of information exists regarding the biological properties of red grape juice. Research on the functional properties of grapes was boosted by the benefits derived from wine consumption, encouraged by the "French paradox", an expression that is known worldwide. Moreover, there is an increasing number of studies that demonstrate that grape juice has beneficial functional properties similar to wine, especially on the cardiovascular system.[7,8]

In Brazil, the consumption and production of whole-grape juice has increased by around 15% per year.[9] However, the quantity and quality of the functional ingredients of grapes may be largely influenced by the climate, soil and geographic region of the crops.[10,11] As Brazil is an enormous country, the juices produced in different regions may contain different antioxidant potentials and chemical compositions, which would certainly modify their functional properties. In this study, we evaluated the antioxidant properties and the vasodilatory capacity of grape juice of various brands produced in different regions across Brazil.

Methods

Sourcing of the juices analyzed

Samples of 6 whole-grape juices produced in a few regions in Brazil, marked with the acronym of the state where they were produced, have been purchased. The acronyms are the following: RS (2 samples: $RS_{(1)}$ and $RS_{(2)}$), RJ, GO, PR and SP. The eligibility criteria were: i) whole red grape juice; (ii) no added preservatives, stabilizers or antioxidants; (iii) no added water; (iv) no added sugar; and v) samples whose ingredients were only "100% grape juice". The juice samples were selected at random from the main producer states. We did not have access to any samples produced in the North and Northeast regions.

For the spectrophotometric and electroanalytical experiments, each sample was diluted in the concentration of 10% in an ethanolic solution. All tests were performed in triplicate.

Reagents

The radicals ABTS.+ (2,2 azino-bis-(3-ethylbenzothiazoline-6-sulfonate), DPPH (2,2-diphenyl-1-picrylhydrazyl) and the reagents used in the analyzes were all analytically pure and sourced from Sigma Chemical Co. (St. Louis, MO, USA). All electrolytic solutions were prepared with purified water using the Millipore Milli-Q system, conductivity ≤ 0.1μS.cm^{-1} (Millipore S.A., Molsheim, France). Other reagents were purchased off-the-shelf.

Evaluation of antioxidant action by the DPPH radical sequestration method

The purple radical DPPH (2,2-diphenyl-1-picrylhydrazyl), when reduced by the antioxidant, is discolored and turns yellow. Reduction of radical DPPH is followed by a decrease in absorbance by 517 nm. The amount of analyte in μL required to reduce the DPPH absorbance by 50% (Efficient Concentration, EC50) is calculated to evaluate the antioxidant capacity of each sample and the free radical sequestering activity or percentage of discoloration. The analytes were solutions of 10% whole juices and the standard solution of gallic acid evaluated at different concentrations. Absorbance was monitored with a UV-Vis spectrophotometer (Jasco® V-530) and all tests were performed in triplicate.

Evaluation of the antioxidant activity by the ABTS radical method

The radical ABTS.+ (2,2' azino-bis-(3-ethylbenzthiazoline-6-sulfonate) is formed from the ABTS reaction (7 mM) with 88 μl of potassium persulfate (140 mM) in the absence of light. To perform the analyses, a volume of 300 μL of the ethanolic analyte solution was placed in a test tube with 2.7 mL of the ABTS radical, then the tubes were covered with Parafilm® and kept in the dark for 20 minutes and the absorbance was monitored at 734 nm using a UV-Vis spectrophotometer (Jasco® V-530) and all tests were performed in triplicate.

Determination of total phenols

The method Folin-Ciocalteau (FC) allows the quantification of phenolic compounds by evaluating the reduction of the FC reagent by these antioxidants with the formation of a blue complex whose intensity increases linearly at 765 nm. The total amount of phenols was obtained by constructing a standard curve prepared

with gallic acid. The total phenolic content was expressed as μg equivalents of gallic acid (GAE) per ml of sample. All analyses were done in triplicate.

Electrochemical analyses

To perform the electrochemical measurements, an μAutolab III potentiostat/galvanostat integrated with the software GPES 4.9 (Eco-Chemie, Utrecht, The Netherlands) was used. The analyses were carried out in an electrochemical cell with capacity for 3 mL of a solution operated with a three-electrode system, an Ag/AgCl reference electrode (KCl 3 mol.L^{-1}), an auxiliary platinum electrode and, as a carbon paste electrode prepared with 0.075 g of carbon and 0.035 g of mineral oil was used as a working electrode.

The tests using differential pulse voltammetry (DPV) were performed with pulse amplitude of 50 mV and scanning velocity of υ = 10mVs^{-1}. The analyses were carried out in an electrochemical cell containing 1.75 ml of phosphate buffer pH 7.0 (0.1 M), adding 25 μL of the ethanolic solution of the analyte. The electrochemical index (EI) of the samples was calculated by summing up the result of each division of the current by the potential (I/E) for each anodic peak observed on the differential pulse voltammograms.

Animals used and preparation of isolated arteries

Male Wistar rats (200-230 g) from the UFG central vivarium were used. All experimental protocols respected the protocols approved by the UFG Research Ethics Committee (protocol: 044/17). This study is in line with the European Union Guide for the Care and Use of Experimental Animals (2010/63/EU).

The rats were euthanized by exsanguination under inhalational anesthesia (n = 5-6). The thoracic aorta was isolated, separated from the connective and adipose tissues and cut into rings (± 4 mm), which were mounted between two metal hooks, one of which was connected to a power transducer to record the isometric voltage (DATAQ Instruments, Akron, OH, USA) and the other was attached to the vial for the isolated organ containing modified Krebs solution [composition in mM: NaCl, 130.0; KCl, 4.7; KH 2 PO 4, 1.2; $CaCl_2$, 1.6; $MgSO_4$, 1.2; $NaHCO_3$, 14.9; glucose, 5.5], pH 7.4, under gasification with carbon dioxide (95% O_2 + 5% of CO_2) at 37°C and maintained at baseline at 1.5 g (optimal rest tension, as previously standardized in our laboratory).

Experimental protocols

After 60 minutes of basal tension stabilization, the arteries were pre-contracted with phenylephrine (0.1 μM) and the presence of endothelium was determined using ACh (1 μM). The rings were disposed of when the relaxation for ACh was smaller than 80%. The whole grape juices analyzed were filtered on a filter paper under light and immediately divided and frozen at -20°C for future experiments.

The arteries with intact precontracted endothelium (phenylephrine, 0.1 μM) were stimulated to relax by increasing the concentration of juice directly in the bath solution (0 to 30 μL/mL). As wine is popularly known throughout the world as a vasodilator, we also perform relaxation curves stimulated with Cabernet Sauvignon red wine, produced in France in 2015, in order to compare the vascular effect.

In another experiment series, the vasodilatory effect of the juice samples was repeated after treatment with the NOS, L-NAME (100 μM, 30 min) inhibitor in order to determine the participation of NO in the mediated juice-stimulated vasodilation.

Statistical analysis

The charts were made and analyzed by the software GraphPad Prism (GraphPad Software Corporation, version 5.0) by ANOVA plus Bonferroni post-test. In the analyses, the continuous variables showed normal distribution and the results were expressed as the mean ± standard deviation of the mean of at least five experiments (n = 5-6) obtained from different animals. All analyses considered a statistical significance level of 5% ($p < 0.05$).

Results

Evaluation of antioxidant activity and determination of total phenols

Antioxidant activity was evaluated using two different methods: DPPH and ABTS. Although the sample from RJ had the best result (lower CE_{50}), we can see in Figure 1A that the four samples obtained from $RS_{(1)}$, $RS_{(2)}$, RJ and GO had similar DPPH discoloration indexes (CE_{50}: 18.2 ± 0.8; 22.4 ± 2.1; 17.1 ± 0.6; 20.5 ± 0.7 μL, respectively), indicating equivalent antioxidant activity. The samples from PR and SP presented similar results comparing each other, and lower antioxidant capacity ($p < 0.05$) compared to the other samples (CE_{50}: 29.1± 1.1; 28.6 ± 1.6, respectively).

The ABTS technique (Figure 1B) confirmed the best antioxidant activity of the RJ sample (CE_{50}: 0.59 ± 0.11 μL). The SP sample had a lower antioxidant potential (CE_{50}: 1.25 ± 0.19 μL), being statistically different ($p < 0.05$) from the best sample (RJ). In turn, the other samples presented similar results ($p > 0.05$). The order of activity for the ABTS TEST was RJ > $RS_{(1)}$ (0.83 ± 0.1 μL) > $RS_{(2)}$ (0.91 ± 0.18 μL) > GO (0.65 ± 0.01 μL) > PR (0.90 ± 0.13 μL) > SP.

In Figure 1C, we can see the number of phenolic compounds (expressed in μg equivalents of gallic acid / mL of the sample) present in the samples. The results are according to the antioxidant activity (Figures 1A, B), and the sample with the highest antioxidant potential presented a higher concentration of phenolic compounds (RJ: 2.25 ± 0.06 μg/mL). The lowest concentration of phenolic compounds was observed in the SP sample (1.26 ± 0.08 μg/mL), being different ($p < 0.05$) from all others.

Electrochemical analyses

Figure 2A shows the results of the electroanalytical analyses of the samples. Although the electrochemical indices showed a higher activity for the RJ sample (21.7 ± 2.1 μA/V), the samples from $RS_{(1)}$, $RS_{(2)}$, GO and PR presented equivalent electrochemical indices ($p > 0.05$) (18.8 ± 1.9; 16.3 ± 1.5; 19.8 ± 2.5; 17.2 ± 3.3 μA/V, respectively). Only the SP sample (11.3 ± 0.5 μA/V) showed a statistical difference ($p < 0.05$) compared to most effective sample (RJ).

The IE values are calculated from the main electrochemical parameters, that is, an anode peak potential — E_{pa}. The lower the anode peak potential the higher the thermodynamic capacity of the species to reduce others, and anodic peak current intensity — I_{pa} — which in addition to being related to concentration, also concerns the speed with which the reduction process occurs. The presence of electroactive compounds in both the most effective sample (RJ) and in the least effective sample (SP), which presented two oxidation peaks (1_a and 2_a). The oxidation peak of the RJ sample occurs at a lower voltage than the SP sample, showing its greater reducing potential. (Figure 2B).

Vasodilator effect

Vasodilator activity was demonstrated in vitro for the 6 juice samples tested and the red wine sample (for comparison purposes). All 6 juice samples induced concentration-dependent relaxation, whose efficacy was variable among them (Figure 3A). The RJ sample (as well as in the antioxidant activity tests) was the most effective one, inducing maximum relaxation of 88.2 ± 4.8%. This sample was the only one that had a similar maximum relaxation ($p > 0.05$) compared to red wine induced relaxation (112.9 ± 5.1%). The other samples (except RJ) showed lower relaxation ($p < 0.05$) than that produced by red wine. The $RS_{(2)}$ sample was the least effective one in inducing vascular dilatation (19.5 ± 6.1%), being significantly ($p < 0.05$) different from the $RS_{(1)}$ (71.6 ± 9.6%), RJ (88.2 ± 4.8%) and GO (53.6 ± 7.2%) samples. The PR and SP samples induced relaxation in similar magnitudes (39.8 ± 7.4 and 39.9 ± 10.4%, respectively) and only showed a significant difference ($p < 0.05$) over the RJ sample. These results are presented in figure 3B.

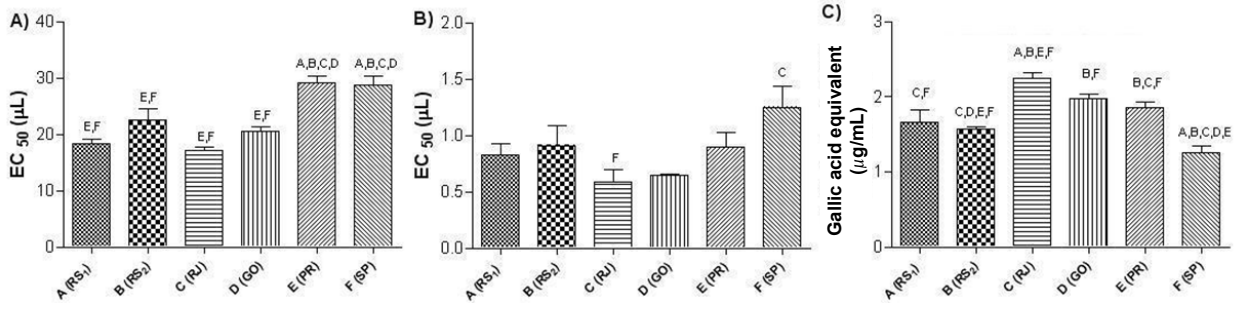

Figure 1 - Graphical representation of the results of antioxidant tests DPPH (A), ABTS (B) and total content of phenolic compounds by Folin-Ciocalteu reaction (C), expressed in μg gallic acid equivalent (GAE/mL). The letters on the bars represent the statistical difference ($p < 0.05$) between the indicated groups.

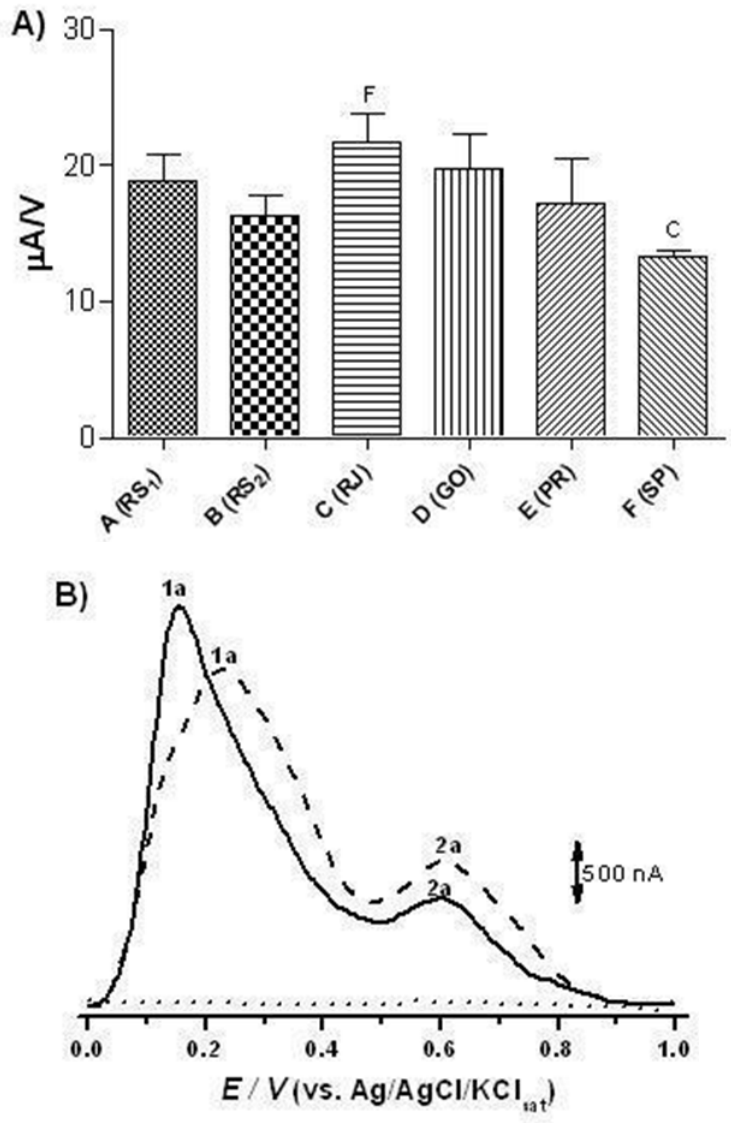

Figure 2 - Electrochemical Index (EI) chart representing the sum of the I_{pa}/E_{pa} (A) rates and differential pulse voltammograms (B) obtained using carbon paste electrode for analysis of C (RJ) (—) and F (--) (SP), which presented the highest and the lowest potential of antioxidant activity, respectively. The white (...) was achieved in 0.01 M pH 7 sodium phosphate buffer.

Regarding the mechanism of action, all juice samples tested revealed a major participation in the endothelial NO in the induction of relaxation, as L-NAME nearly completely inhibited relaxation (Figure 4). Only the $RS_{(2)}$ sample showed no difference ($p > 0.05$) after inhibition of NO with L-NAME, revealing an action mechanism unrelated to NO release by the vascular endothelium.

Discussion

The greatest finding of this study is that the grape juices marketed in Brazil do not have the same functional properties. Its antioxidant capacities, phenolic compound concentration and vasodilator activity are different among samples tested from different regions. Moreover, the vasodilatory capacity of grape juice is not equivalent to the red wine-induced dilation, except for one sample (obtained from RJ).

To investigate some factors that may influence the antioxidant power and health-related benefits of different grape juices produced in Brazil, the sampling included juices from different geographical locations. The first finding is that the samples have different antioxidant properties, which can also be seen in other beverages such

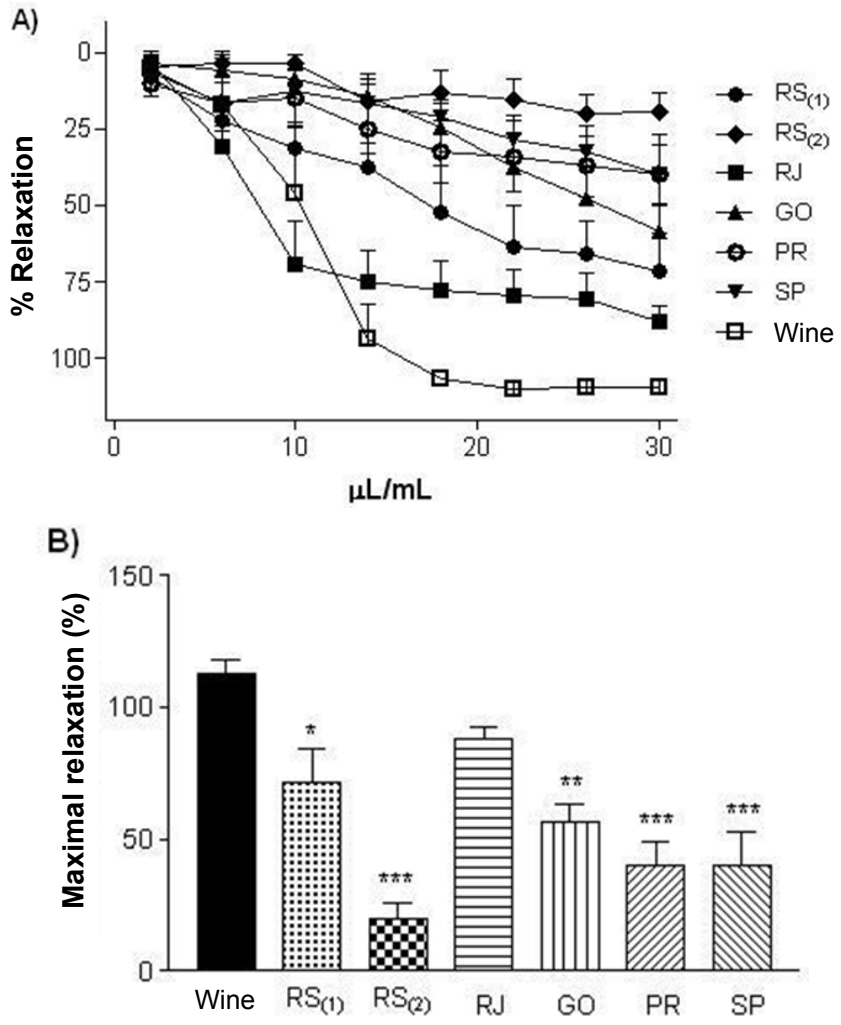

Figure 3 - Vascular relaxation curve induced by different juice samples in aortas of rats precontracted with phenylephrine (A) and maximal vascular relaxation (B). Red wine was used for comparison. The dots represent means ± SEM of the relaxing effect expressed in % relaxation. * Significant difference ($p < 0.05$) vs. red wine.

as red wines, which have different properties depending on the brand and place of manufacture.[12] In fact, the juice sample obtained from RJ was the most powerful in the tests of antioxidant activity and the one from SP was the worst one. With regard to the DPPH radical elimination activity, it was found that the juice from RJ had the highest antioxidant potential, with similar results for the $RS_{(1)}$, $RS_{(2)}$ and GO samples. The samples produced in SP and PR were the worst ones, presenting the same potential compared to each other, and lower than the others.

Similar results were obtained with the ABTS technique, where the best and the worst antioxidant activity was found in the RJ and SP samples, respectively. Grape juices are sources of different antioxidant substances, mainly polyphenols, which includes them in the range of foods with high antioxidant potential.[1,5,13] As expected, the sample of highest antioxidant capacity (RJ) also presented the highest concentration of polyphenols. Likewise, the sample of lowest antioxidant activity also had the lowest concentration of polyphenols (SP). This different concentration of polyphenols may be responsible for the antioxidant capacity of the samples, as it was also found in other foods and beverages.[13,14]

Antioxidant substances are electroactive compounds. Therefore, the electrochemical analysis can be considered

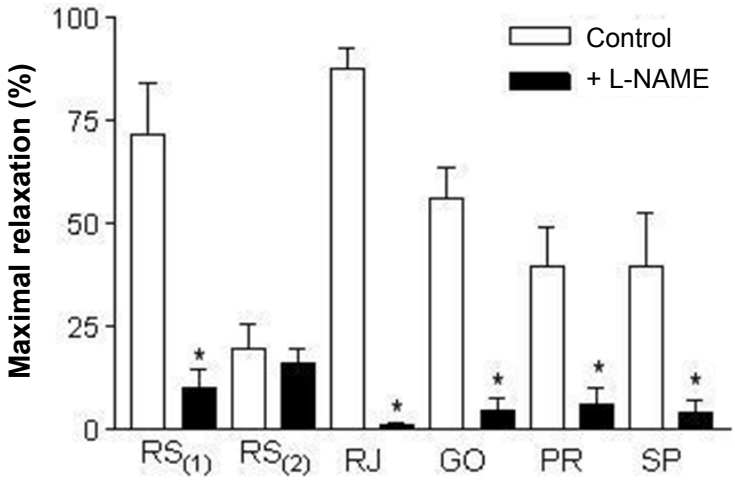

Figure 4 - Maximum vascular relaxation induced by grape juice samples in aortas of rats pre-contracted with phenylephrine. The bars represent the maximal relaxation percentage (Emax) with or without treatment with L-NAME (100 µM, 30 min). * Significant difference ($p < 0.05$) vs. Control (with no L-NAME).

one of the main tools to determine antioxidant activity. In fact, good electron-donating agents (antioxidants) can reversibly oxidize at lower peak potentials (Epa < 0.5 mV, pH = 7). Following this idea, the concept of electrochemical index (EI) was previously proposed to qualify compounds with antioxidant capacity.[15]

The evaluation of antioxidant activity using spectrophotometric and electrochemical methods shows that the analyses conducted with the classical methods (DPPH, ABTS and FC) agree with the electrochemical index, which allows the comparison of the antioxidant activity measured by electroanalytical methods. The small differences presented in the analyses are due to the color of the analyte, which generates interference in the spectrophotometric tests. In these analyses, the RJ sample also presented the best antioxidant activity, while the SP sample was the worst of them. The decreasing order of antioxidant activity obtained by EI calculations was: $RJ \geq GO \geq RS_{(1)} \geq PR \geq RS_{(2)} > SP$.

Differential pulse voltammetry (Figure 2B) of the best (RJ) and worst (SP) sample had two anode peaks, one with Epa approximately at 0.1V and the other at 0.6V. Therefore, it can be stated that the electroactive species found in the juice are oxidizing at a low potential and this behavior is observed in samples that are rich in antioxidants.[16] Resveratrol, a phenolic compound that is very present in the grapes, oxidizes at a potential close to 0.6V; this finding justifies the presence of the second peak (2_a) presented in the voltammogram.[17]

Several studies report that the ingestion foods rich in polyphenols (mainly vegetables, fruits, wines and teas) are associated with a protective effect on the cardiovascular system in humans and animals.[18] In most published studies, red wine was highlighted as a functional food that is used to test the benefits of intake of antioxidants. Its effects include vascular dilatation in laboratory animals or patients with or without hypertension.[19,20] However, not only red wines can induce protection against cardiovascular risk factors. Many researchers have shown that the consumption of other beverages such as grape juice and teas can bring important benefits, often comparable to those of wine.[5,21]

Our results showed that the different juice samples produced different cardiovascular results, having different levels of efficacy in the induction of vascular relaxation. The RJ sample was the one that presented the best result, being the only one that induced vascular relaxation at a similar level to the red wine tested. This result may be associated with a greater quantity of phenolic compounds, whose vasodilatory and cardioprotective action has been well documented.[22-24]

Multiple mechanisms contribute to the beneficial action of polyphenol-rich beverages on the cardiovascular system, including direct effects on smooth muscle or

endothelial cells.[25] In the blood vessels, endothelial cells play a critical role in maintaining local homeostasis by producing various autacoids that act on neighboring vascular cells. Among these endothelial-derived factors, NO, which is synthesized by the endothelial NO synthase, is the main one and produces a potent vasodilator action. Some studies have shown that NO can be stimulated by red wine in isolated arteries.[18,26] In contrast, other studies have shown that inhibition of NO synthase has no effect on red wine-induced relaxation.[25]

In this study, the inhibition of NO synthase with L-NAME significantly inhibited the relaxation of almost all samples, revealing the important role of endothelial NO in the vasodilator effect of grape juices. Only the $RS_{(2)}$ sample showed no difference in the vascular relaxation effect when NO production was inhibited. This shows that the mechanism of induction of vasodilation in this sample is little effective and is not related to the endothelial NO release stimulus, like most of the samples tested.

Conclusion

This study shows that the grape juices analyzed have different levels of antioxidant activity. Besides, the vasodilatory effect also presented a varying intensity from one sample to another. The mechanism of vasodilatory action seems to be related to the release of endothelial NO, except for one of the samples ($RS_{(2)}$). Only one sample (RJ) has a vasodilator activity comparable to that of red wine. Finally, these findings help understanding that the functional qualities of grape juice can vary greatly across different regions of Brazil. Even though all the samples meet the eligibility criteria, not all of them have functional effects as an appreciable antioxidant and vasodilator activity, some of which are probably incapable of providing protection against cardiovascular diseases.

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Author contributions

Conception and design of the research:Britto Junior J, Rocha ML. Acquisition of data: Britto Junior J, Leite KCS. Analysis and interpretation of the data: Britto Junior J, Leite KCS, Gil ES, Rocha ML. Statistical analysis: Rocha ML. Writing of the manuscript: Gil ES, Rocha ML. Critical revision of the manuscript for intellectual content: Gil ES, Rocha ML.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

This article is part of the thesis of master submitted by José Britto Junior, from *Universidade Federal de Goiás*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the *Universidade Federal de Goiás* under the protocol number 044/17.

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ORIGINAL ARTICLE

Effect of Short-Term Inhalation of The Herbicide 2,4D on Cardiac Remodeling: Morphological Aspects

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Abstract

Background: Brazil is the worldwide leader in the long-term use of pesticides and herbicides. This compromises the health of handlers by causing harmful neurological, respiratory, and cardiovascular changes. The herbicide 2.4D has been shown to cause cardiac overload with subsequent pathological remodeling.

Objective: To analyze the cardiac morphological repercussions on the left ventricle (LV) of mice submitted to nebulization by the herbicide 2.4D.

Methods: Fifteen mice were divided into three groups: control group (CG; n = 5) exposed to nebulization with sodium chloride solution; low concentration group (LCG; n = 5) exposed to nebulization of the herbicide 2.4D with 3.71 x 10-3 grams; and high concentration group (HCG; n = 5) exposed to nebulization of the herbicide 2.4D with 9.28 x 10-3 grams for 15 minutes. The fractal dimension analysis was performed through the box-counting method. Later, the ImageJ program was used to calculate the fractal dimension of each group. To evaluate cardiac remodeling, histological slides were prepared and stained with Hematoxylin-Eosin (HE). Fifty areas of cardiomyocytes were analyzed per animal. The comparisons between groups were performed by ANOVA One-Way with Tukey's posttest ($p < 0.05$).

Results: There was no change in fractal dimension values between the CG = 1.37 ± 0.02, LCG = 1.33 ± 0.04 and the HCG = 1.33 ± 0.07 groups. However, cardiac hypertrophy occurred in the HCG = 303.9 ± 38.80 μm^2 when compared to the CG group = 236.9 ± 61.71 μm^2 ($p = 0.034$).

Conclusion: The herbicide 2.4D used for 72 hours did not promote cardiotoxicity when evaluated by fractal dimension. However, cardiomyocyte hypertrophy was observed in the LV. (Int J Cardiovasc Sci. 2019;32(3)247-252)

Keywords: Mice; Pesticides / adverse effects; Herbicides / adverse effects; Agrochemicals; Neurologic Manifestations; Respiratory Tract Diseases; Hypertrophy,Left Ventricular.

Introduction

Herbicides are pesticides used in agriculture, plants and crops (green vegetables, fruits and vegetables) used to protect, repel and fight the proliferation of living organisms (pests, fungi, insects, weeds, birds, mollusks, microbes and arachnids) that are harmful to the agricultural production.[1-5] They are classified according to their toxicity, which may range from low to extreme, constituting a great risk to the health and the environment.[1,3-5]

According to the Brazilian Department of the Environment, Brazil is the worldwide leader in the consumption of agrochemicals, due to the vast culture and source of labor in agriculture.[6] Since 2003, the agrochemical market has increased its use

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by 93%, with Brazil being the leader in consumption worldwide, a position previously occupied by the United States.[7] The Ministry of Health considers that there are more than 100,000 chemical substances capable of causing chemical, physical, morphological and pathophysiological damage to the health of populations.[8-12] Among those who suffer the most from the exaggerated use of agrochemicals are rural workers, when these substances are utilized incorrectly.[6,9]

In 1990, the World Health Organization (WHO) estimated that approximately 3,000,000 cases of pesticide poisoning occurred per year in the world, with 220,000 deaths per year.[13] Only in 2009, more than 1 billion liters of agrochemicals were utilized in Brazil; it is the same as if each one of the Brazilian individuals consumed an average of five liters of poison per year.[14] In Brazil, pesticide poisoning is a public health problem and a matter of compulsory notification.[15]

The toxicity can be fast or slow and it can take from months to years for symptoms to appear in the worker exposed to the pesticide. Among the harmful effects are allergic reactions, skin and eye irritation, neurological, respiratory, hematopoietic, hepatic, nephrological, gastrointestinal, pancreatic, and cardiovascular alterations, as well as several toxic reactions.[9-12] The effects of several types of pesticides have already been well established, resulting in cardiotoxicity with mitochondrial alterations, oxidative stress, hypotrophy, and molecular alterations of gene expression related to cardiac calcium.[16-19]

One of the herbicides frequently used to fight weeds in sugarcane plantations is 2,4D (2,4-dichlorophenoxyacetic acid),[6] which has harmful effects when ingested, absorbed by the skin and/or inhaled. This herbicide can cause peripheral neuritis and transient diabetes during exposure to it, as well as loss of appetite, skin irritation, nausea, gastrointestinal tract irritation, vomiting, chest and abdominal pain, exhaustion, weakness, muscle twitching, mental confusion, seizures and even coma. If 2,4 D is used at high concentrations, it may cause degenerative liver and kidney lesions.[20] However, to the best of our knowledge, there have been no studies evaluating the cardiotoxic effects of 2,4 D using a nebulizing spray containing a sodium chloride (NaCl) solution during a 72h-period. The aim of this study was to analyze the cardiac morphological effects on the left ventricle (LV) of mice submitted to daily nebulizing sprays containing the 2,4D herbicide for 15 minutes. It is hypothesized that exposure to high concentrations of 2,4D herbicide will lead to cardiac remodeling.

Methods

Ethical aspects

This was an experimental cross-sectional study submitted to the Animal Ethics Committee of *Universidade do Oeste Paulista* and evaluated by the Animal Use Ethics Commission (CEUA, from the Portuguese *Comissão De Ética do Uso De Animais*), and approved under protocol n. 3331 to be performed according to the Guide for the Care and Use of Laboratory Animals of the Institutes of Health (USA).

Sample characterization

For the experiment, 15 male Swiss mice (30-40 g) were provided by the Animal Center of *Universidade do Oeste Paulista*, where they were housed in collective plastic cages (5 animals per cage) measuring 30x16x19 centimeters, under a mean temperature of 22 ± 2ºC, with 12-hour cycles of light and dark, i.e., light from 7AM to 7PM and dark from 7PM to 7AM. To perform the experiment, the 15 animals were randomly divided into three groups, using the simple randomization method (random sequence performed through Excel):

- CG: control group (n = 5) exposed to nebulization with sodium chloride solution (NaCl) for 15 minutes/day, for 3 consecutive days.

- LCG: low concentration group (n = 5) exposed to nebulization of 2,4D herbicide with 3.71 x 10-3 grams of active ingredient per hectare (g.i.a./ha) for 15 minutes/day, for 3 consecutive days.

- HCG: high concentration group (n = 5) exposed to nebulization of 2,4D herbicide with 9.28 x 10-3 grams of active ingredient per hectare (g.i.a/ha) for 15 minutes/day, for 3 consecutive days.

2.4D Herbicide Exposure Protocol

The experimental protocol used two boxes of 2.4D (32x24x32 cm), each attached to a Pulmosonic Star®9 ultrasonic nebulizer, and the following concentrations were administered after being diluted in 10 mL of 0.9% sodium chloride:

- CG: 10 mL of 0.9% sodium chloride;

- LCG: Solution consisting of 3.71 x 10-3 grams of active

ingredient per hectare (g.i.a/ha) of 2,4D, diluted in 10 mL of 0.9% sodium chloride. The time of exposure consisted of 15 minutes/day on 3 consecutive days.

- HCG: Solution consisting of 9.28 x 10-3 grams of active ingredient per hectare (g.i.a/ha) of 2,4-D diluted in 10 mL of 0.9% sodium chloride. The time of exposure was 15 minutes/day for 3 consecutive days.

On the first day of exposure, all 15 animals were submitted to the nebulization with the recommended concentration for each group. After the 3 consecutive days of nebulization, they were anesthetized with Thiopental Sodium, at a dose of 100 mg/kg of weight, administered in the peritoneal cavity. Soon after being euthanized, the animals had their hearts fixed in 10% buffered formalin for 72 hours.

Histological and histomorphometric analyses

After being fixed in formalin, the tissue was embedded in paraffin blocks to obtain 4-micrometer thick coronal histological sections. The histological sections were stained on a slide with the Hematoxylin-Eosin (HE) solution to measure cardiomyocyte cross-sectional areas using a LEICA microscope (model DM750, Germany), which sends digital images to the computer using the LeicaApplication Suite LAS 4.2.0 image analysis system (Media Cybernetics, Silver Spring, Maryland, USA).[21,22]

The images were obtained using a binocular optical microscope. All images were captured by video camera at 400x magnification (40x objective). Four LV sections were obtained from each animal and different field captures were analyzed, which were chosen according to the place where more cells could be visualized in a cross-sectional view.[22,23] Fifty cells were measured per analyzed ventricle. The selected cardiomyocytes were transversely sectioned and exhibited a round shape, with a nucleus visible in the center of the cell and were located in the subendocardial layer of the LV muscle wall.[22,23] The mean sectional areas obtained for each group were used as indicators of cell size.[23] We also performed the fractal dimension analysis through the box-counting method, in which 3 images were captured per each analyzed slide; after that, the ImageJ program was used to calculate the fractal dimension of each group (Figure 1). This careful technique aims to standardize the set of cardiomyocytes from the different groups to the maximum. The mean sectional areas obtained for each group were used as indicators of cell size.[23]

Statistical analysis

The software GraphPadPrism was used for the statistical analysis. The Shapiro-Wilk test was performed to analyze data normality. The data showed normal distribution and were presented as mean ± standard deviation. One-Way ANOVA followed by Tukey test ($p < 0.05$) were performed for comparison between the groups.

Results

There was no alteration in the fractal dimension parameter between the CG = 1.37 ± 0.02, LCG = 1.33 ± 0.04 and HCG = 1.33 ± 0.07 groups ($p > 0.05$). The animals submitted to a high dose of the herbicide had cardiomyocyte hypertrophy (HCG = 303.9 ± 38.80 μm^2) when compared to the control group (CG = 236.9 ± 61.71 μm^2; $p = 0.034$). (Figure 2).

Discussion

To the best of our knowledge, this is the first study showing that the inhalation of 2,4D herbicide at high concentrations for a short time in mice causes cardiac remodeling.

The 2,4D herbicide, when inhaled, is absorbed and distributed by the lungs, kidney and circulatory system. Enzymes promote the metabolism of the herbicide in these organs and tissues, which results in the formation of free radicals, which can be often more toxic than the herbicide itself.[24] Oxidative stress is caused by the release of free radicals, and it is an important mechanism that causes cell mutations.[24-26] There is strong evidence that oxidative stress plays a prominent pathophysiological role in cardiac remodeling.[27-28] The remodeling process is associated with changes in different mechanisms related to cardiac dysfunction, such as alterations in LV geometry, wall thickness, cavity diameter and normal configuration.[24-26]

The animals of this study that inhaled 2,4D herbicide at a high concentration showed left ventricular hypertrophy, which suggests the development of cardiotoxicity and confirms the action of the 2,4D in the development of cardiac remodeling. Other studies using the same experimental model in rats indicate that the ingestion of a dose equivalent to 10% of the lethal dose (LD50) of oral pyrethroid insecticides causes changes in ventricular depolarization and repolarization, suggesting cardiotoxicity.[27,28]

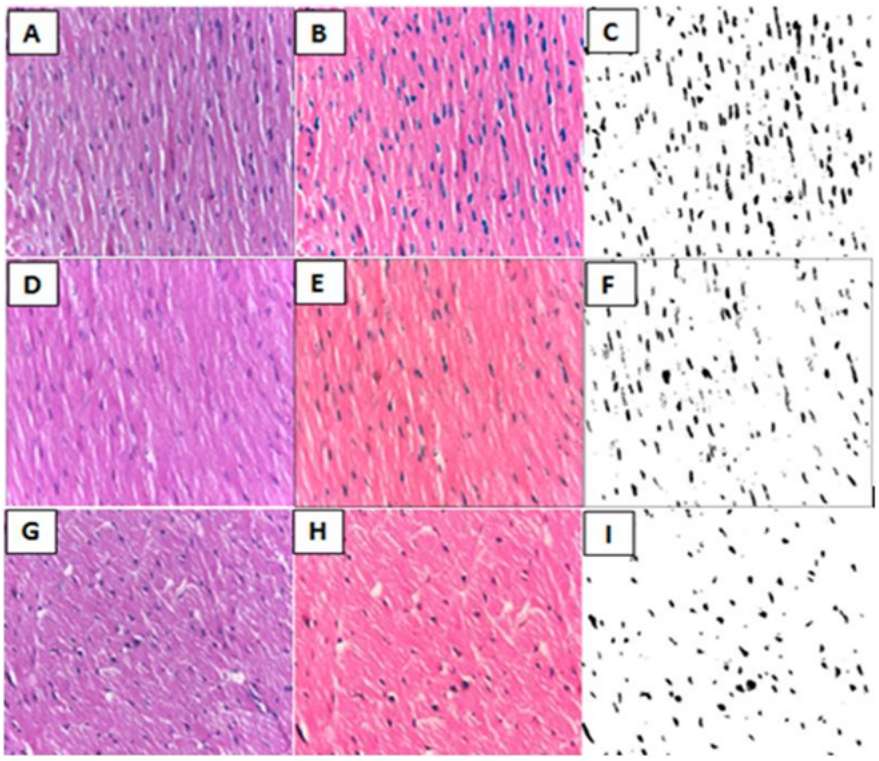

Figure 1 - Letter: A, D, G) Histological section of the left ventricle stained with Hematoxylin and Eosin (HE), 40x increase in the Control Group (CG, n = 5), Low Concentration Group (LCG, n = 5) and High Concentration Group (HCG n = 5). B, E, H) Binarization process in the Control Group (CG, n = 5), Low Concentration Group (LCG, n = 5) and High Concentration Group (HCG n = 5). C, F, I) HE image after the binarization process in the Control Group (CG, n = 5), Low Concentration Group (LCG, n = 5) and High Concentration Group (HCG n = 5). The cell nuclei can be observed in black and the rest of the cell (cytoplasm, plasma membrane and other elements), in white.

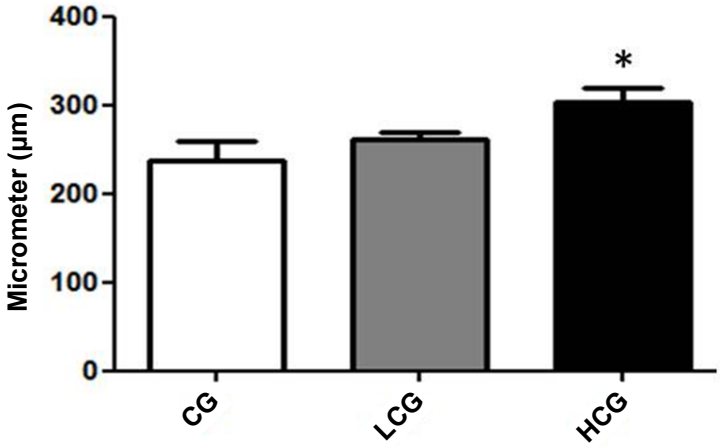

Figure 2 - Analysis of cardiomyocyte hypertrophy.
*CG: control group, LCG: low concentration group, HCG: high concentration group. (*p < 0.05 when comparing HCG versus CG).*

In another study, Razavi[26] shows that exposure to Diazinon (DZN) through a catheter once a day, during a 4-week period, also resulted in cardiac lesions in rats and cardiac hypertrophy in the DZN group, showing that this exposure chronically induces infiltration of inflammatory cells and necrosis in cardiac tissue, where they play an important role in cardiotoxicity.

The analysis of the fractal dimension did not demonstrate a significant increase in the animals exposed to the 2,4D herbicide in the HCG (n = 5) when compared to the CG animals (n = 5), suggesting that there was no cardiotoxicity when it evaluated by the fractal dimension method. This method reveals the irregularities in the histological slides, and the increase in the inflammatory process and the collagen can cause these alterations, as it occurs in cardiac remodeling.[29,30] Possibly, these changes did not occur in the short term. Further studies involving the inhalation route and chronic exposure might disclose these alterations.

This study becomes extremely relevant from the clinical point-of-view, as it demonstrates the acute potential for short-term cardiac damage when herbicides are inhaled. Considering that the workload of rural workers exceeds this period, it is important to use personal protective equipment (PPE), and this information must be disclosed to farmers, alerting them to the risks of heart disease.[30,32]

As a study limitation, we can cite sample size, with only 5 animals per group.

The results of this study, which is a translational research, show the possible heart damage that can be caused by pesticide exposure in the body of rural workers during their work routine. The pesticides can result in damage to the cardiac function and thus cause signs and symptoms of intolerance to exertion, such as fatigue and dyspnea. Control strategies to prevent the inhalation of these substances by rural workers are necessary to prevent progression to pathological cardiac remodeling.[8] Moreover, further analyses may also be used to characterize other pathological cardiac alterations, such as molecular analyses of the heart and evaluations of systolic and diastolic functions by echocardiography. The mechanisms involved in cardiac hypertrophy should also be elucidated.[33]

Conclusion

The 2,4D herbicide at acutely inhaled concentrations promoted cardiomyocyte hypertrophy in mice, showing its potential in causing pathological cardiac remodeling.

Author contributions

Conception and design of the research: Pacagnelli FL, Mariano TB, Sabela AKDA, Silva RCR, Nai GA. Acquisition of data: Negrão ALR, Oliveira B, Gonçalves MG, Oliveira TFS. Analysis and interpretation of the data: Negrão ALR, Oliveira B, Gonçalves MG. Statistical analysis: Mantovani RO. Obtaining financing: Pacagnelli FL. Writing of the manuscript: Pacagnelli FL, Negrão ALR, Oliveira B, Gonçalves MG. Critical revision of the manuscript for intellectual content: Silva RCR, Nai GA. Supervision / as the major investigador: Pacagnelli FL.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the University of Western São Paulo (UNOESTE) under the protocol number 3331.

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ORIGINAL ARTICLE

Adductor Pollicis Muscle Thickness as a Marker of Nutritional Status in Heart Failure

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Abstract

Background: Malnutrition is associated with morbidity and mortality in patients with heart failure (HF). Thus, it is essential to apply reliable indicators to assess the nutritional status of these individuals.

Objective: To evaluate the thickness of the adductor pollicis muscle (APM) in patients with HF as an indicator of somatic protein status and correlate the obtained values with conventionally used parameters and electrical bioimpedance (EBI) markers.

Methods: Cross-sectional study with patients with HF undergoing regular outpatient treatment. APM thickness was measured in the dominant arm, and the values obtained were classified according to gender and age. The anthropometric parameters assessed included the body mass index (BMI) and specific parameters to assess the muscle (arm muscle circumference [AMC] and arm muscle area [AMA]). Values of phase angle (PA), standard PA (SPA), and lean mass were obtained by EBI. Statistical analyses were performed with the software Statistical Package for the Social Sciences, version 19, using unpaired Student's t, Mann-Whitney, or one-way analysis of variance (ANOVA) tests for comparisons between groups, as appropriate. The correlation between variables of interest was performed using Pearson's or Spearman's correlation coefficient, as adequate. The level of significance was set at 5%.

Results: About 70% of the 74 patients evaluated were classified as malnourished according to the APM thickness. Values of AMC, AMA, and lean mass correlated positively with APM thickness ($p < 0.005$). The APM thickness also correlated positively with PA and SPA ($r = 0.49$, $p < 0.001$ and $r = 0.31$, $p = 0.008$, respectively).

Conclusion: Patients with HF presented a high frequency of protein malnutrition when APM thickness was used as an indicator of nutritional status. APM thickness values correlated with conventional measures of somatic protein evaluation and may be related to the prognosis of these patients, since they correlated positively with PA and SPA. (Int J Cardiovasc Sci. 2019;32(3)253-260)

Keywords: Heart Failure; Thumb; Malnutrition / mortality; Nutrition Assessment; Anthropometry.

Introduction

A series of neurohormonal modifications, such as chronic inflammation, anorexia, and resistance to anabolic hormones, are common in heart failure (HF) and are closely related to the emergence of malnutrition in this population.[1,2] Malnutrition, in turn, is associated with a higher prevalence of comorbidities and constitutes an important predictive factor for decreased survival regardless of variables like age, functional class, and ejection fraction (EF).[2]

Although the classification of nutritional status according to body mass index (BMI) indicates a higher prevalence of eutrophy, overweight, and obesity, when evaluating anthropometric measures specifically used to estimate the muscle compartment, patients with HF commonly present different stages of protein malnutrition, independent of total body mass,[1,3,4] which can be explained by the fact that BMI does not clearly reflect the body composition.[5,6]

Dual-energy X-ray absorptiometry is one of the techniques considered the gold standard for assessment

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of body composition; however, difficult logistics associated with its implementation hinders the routine use of this technique in clinical practice. In contrast, electrical bioimpedance (EBI) is considered an alternative and appropriate instrument capable of estimating the body components, distribution of fluids, and cellular quality and integrity.[7]

Anthropometric variables obtained in the upper part of the body, such as the arm muscle circumference (AMC), can also be considered good indicators of somatic protein mass since they are less affected by the presence of edema.[5] In this sense, the measurement of the thickness of the adductor pollicis muscle (APM) emerges as a promising alternative to evaluate the muscle compartment, since it is a simple, noninvasive, and low-cost method.[8,9]

The APM is the only muscle in the human body whose thickness can be directly measured without requiring estimating equations, reflecting the loss of working capacity due to limitations from the underlying disease.[8,9] Due to the lack of scientific evidence on the applicability of APM thickness and its reliability in classifying the nutritional status in individuals with HF, the objective of this study was to evaluate the APM thickness in patients with HF and correlate the results with conventional anthropometric parameters for assessment of the somatic nutritional protein status and with EBI parameters.

Methods

This cross-sectional study evaluated patients regularly attending the Heart Failure Outpatient Clinic at *Hospital Universitário Pedro Ernesto* (HUPE) and was approved by the institution's Research Ethics Committee (HUPE/UERJ, n. 47828915300005259). All patients were previously informed about the methods and objectives of the study and signed an informed consent form. Considering the absence of data on the average values of APM thickness in patients with HF, standard deviation values for APM thickness found in patients undergoing cardiac surgery[9] were considered to determine the sample size required for this study. Thus, a minimum of 66 patients would be sufficient to ensure a maximum estimation error of 0.7 mm for APM thickness, with a significance level of 5%.

A total of 90 patients with a diagnosis of HF, of both genders, and aged between 18 and 74 years were considered eligible. The exclusion criteria were patients with clinical evidence of edema and ascites, amputees, with a pacemaker, or with a BMI < 16 kg/m² or > 34 kg/m², since most equations used to estimate body composition using EBI are unable to predict reliably the body composition in extreme BMI values.[10] Patients were also excluded when failing to follow the standardization protocol for EBI or not using diuretics, resulting in a sample of 74 patients.

The etiology and the HF functional class were defined according to the proposal by the New York Heart Association (NYHA).[11] Values of EF were obtained by echocardiography at the moment of the clinical and nutritional evaluation of the patient. The presence of comorbidities was obtained from the patients' clinical records. A patient was considered as having type 2 diabetes mellitus when presenting fasting glucose ≥ 126 mg/dL on at least two occasions or using hypoglycemic agents,[12] and as having chronic renal disease when presenting a glomerular filtration rate < 60 mL/min for 3 months.[13]

The assessment of the nutritional status was performed by two previously trained nutritionists and consisted in the assessment of anthropometric measures and EBI.

Anthropometry

Body mass was measured with a mechanical scale (Balmack®, São Paulo, Brazil) with a maximum capacity of 200 kg and subdivisions of 100 grams. Height measurement was obtained with a stadiometer coupled to the scale mentioned above, with an accuracy of 0.1 cm, following the technique proposed by Lohman et al.[14] The nutritional status was assessed according to the BMI, which was classified according to the proposal by the World Health Organization.[15]

The technique described by Harrison et al.[16] was used to measure the arm circumference (AC) and triceps skinfold (TSF). The AC was measured on the dominant arm using an inelastic measuring tape. The TSF thickness was measured in triplicate with the adipometer Lange Skinfold Caliper (Cambridge Scientific Industries, Inc., Watertown, MA, USA), with an accuracy of 1 mm, and the mean value of the three measurements was used in the analysis. The AC and TSF values were used to calculate the AMC and arm muscle area (AMA), according to the formulae described by Frisancho.[17] The AMC was classified according to the calculation of the percentage of adequacy in relation to the value corresponding to the 50th percentile according to gender and age, and later compared with the percentages of reference established

by Frisancho.[17] The AMA was directly classified based on the percentiles of reference defined by Frisancho.[18]

The APM thickness was measured thrice with the scientific adipometer Lange Skinfold Caliper on the dominant side of the body, in the center of an imaginary triangle formed by the index finger and thumb. During this assessment, the individual remained seated with the hand relaxed and resting on his or her thigh, and the arm positioned so as to form a 90° angle with the forearm.[19] The mean values obtained for the dominant arm were classified according to gender and age, and patients with values below the 5th percentile were considered malnourished. The 5th percentile values are 20, 23, and 18 mm for men in the age range of 18 - 29 years, 30 - 59 years, and above 60 years, respectively. Considering the same age ranges, the 5th percentile values for women are 16, 17, and 14 mm, respectively.[20]

Electrical bioimpedance

EBI was assessed with the tetrapolar equipment BIA 450 (Biodynamics Corporation, Shoreline, WA, USA) with a 50 kHz sine wave and 800 mA current. The evaluation was performed at the same moment as that of the anthropometric measurements and followed the measurement protocol known as horizontal EBI,[21] in addition to the criteria proposed by the Brazilian Medical Association.[10]

The following EBI parameters were evaluated: phase angle (PA), percentage of body fat (BF), and lean mass. Standard PA values (SPA) were estimated according to the following equation: PA value observed minus the PA reference value according to gender and age, divided by the respective standard deviation.[22] Values of PA exceeding 4.2° were considered adequate.[23]

Statistical analysis

The distribution of the variables was assessed with the Kolmogorov-Smirnov test, and the data are presented as mean ± standard deviation or median (interquartile range) values, as appropriate. Categorical data are presented as percentage. Comparisons between groups were performed with unpaired Student's t test for parametric variables or Mann-Whitney test for nonparametric variables. One-way analysis of variance (ANOVA) was used to compare parametric variables among three or more groups. The correlation between the variables of interest was performed using Pearson's or Spearman's correlation coefficients, as appropriate. The significance level was set at 5% ($p < 0.05$), and the statistical analysis was performed using the software Statistical Package for the Social Sciences (SPSS), version 19.0.

Results

A total of 90 patients with HF were considered eligible, of whom 16 (17.7%) were excluded for meeting the exclusion criteria. Of the 74 patients evaluated, most (66.2%) were male and the most frequent etiology of HF was ischemia (28.4%), followed by idiopathic (24.3%), hypertensive (18.9%), alcoholic and infectious (both with 8.1%), and hereditary (5.4%) causes. Chagas' disease and drug use had frequencies of 4.1% and 2.7%, respectively.

Among the patients evaluated, 31 (41.9%) had type 2 diabetes mellitus, 7 (9.5%) had chronic renal disease receiving conservative treatment, and 3 (4.1%) had chronic obstructive pulmonary disease. Approximately 8% of the patients had undergone angioplasty with stent placement. The HF functional class of higher prevalence was NYHA II (40.5%), followed by I (33.8%), III (23.0%), and IV (2.7%). With respect to EF, 88% (n = 65) of the patients presented a value below 50%. Only 7% (n = 5) of the patients presented PA values below 4.2°. The characteristics of the study population are described in Table 1.

The classification of the nutritional status according to the different nutritional parameters evaluated is presented in Table 2. Most patients presented malnutrition according to the APM thickness, corresponding to approximately 80% (n = 39) of the men and 56% (n = 14) of the women.

The mean APM values in individuals classified as malnourished and well-nourished were 13.1 ± 3.9 and 18.9 ± 2.9 mm, respectively ($p < 0.0001$, unpaired Student's t test). Patients considered malnourished had lower SPA values when compared with those classified as eutrophic (-0.5 ± 1.42 versus -0.05 ± 1.56, $p = 0.012$, Mann-Whitney test).

The mean APM thickness values were not different when patients were stratified according to the HF etiology, classification of BMI, AMC or AMA (performed by one-way ANOVA). Also no difference was observed in APM thickness when the patients were stratified by age (< or ≥ 60 years, unpaired Student's t test). However, the APM values were higher in patients with NYHA I when

Table 1 - Anthropometric and clinical characteristics of the study population

	Total sample (n = 74)	Men (n = 49)	Women (n = 25)	p value
Age (years)	60 (14.5)	59 (19)	65 (11)	0.012†
APM (mm)	14.8 ± 4.4	15.7 ± 4.0	13.0 ± 4.8	0.015*
EF (%)	35.8 ± 12.3	36.2 ± 13.0	34.9 ± 11.1	0.67*
BMI (kg/m²)	26.9 ± 3.6	26.8 ± 3.5	27.1 ± 3.9	0.70*
TSF (mm)	21.2 ± 6.1	19.8 ± 4.8	23.8 ± 7.4	0.02*
AMA (cm²)	45.9 (16.4)	49.8 (13.9)	42.0 (12.1)	0.005†
AMC (cm)	24.0 (4.2)	25 (3.4)	23.0 (3.25)	0.005†
LM (kg)	51.9 ± 10.9	57.3 ± 8.2	41.5 ± 7.6	< 0.001*
BF (%)	30.2 ± 6.9	26.9 ± 5.1	36.8 ± 5.1	< 0.001*
PA (°)	6.4 ± 1.2	6.7 ± 1.1	5.7 ± 1.1	< 0.001*
SPA (°)	-0.30 (1.22)	-0.42 (1.28)	-0.20 (1.27)	0.458†

*P values refer to comparisons between men and women. †Mann-Whitney test; *Unpaired Student's t test. APM, adductor pollicis muscle; EF: ejection fraction; BMI: body mass index; TSF: triceps skinfold; AMA: arm muscle area; AMC: arm muscle circumference; LM: lean mass; BF: body fat; PA: phase angle; SPA: standard phase angle.*

Table 2 - Nutritional status of patients with heart failure according to assessed nutritional indicators

Parameter	Classification	N (%)
APM	Malnutrition	53 (71.6)
	Eutrophy	21 (28.4)
BMI	Malnutrition	-
	Eutrophy	21 (28.4)
	Pre-obesity	37 (50.0)
	Obesity	16 (21.6)
AMC	Malnutrition	29 (39.2)
	Eutrophy	37 (50.0)
	Overweight/obesity	8 (10.8)
AMA	Severe malnutrition	3 (4.1)
	Mild/moderate malnutrition	7 (9.5)
	Eutrophy	64 (86.5)

AP: adductor pollicis muscle; BMI: body mass index; AMC: arm muscle circumference; AMA: arm muscle area.

compared with those with NYHA II (16.6 ± 4.1 versus 13.7 ± 4.3 mm, p = 0.045, unpaired Student's t test). No significant difference was observed in APM thickness values between groups with EF above and below 50% (unpaired Student's t test).

The APM thickness correlated with the PA, SPA, and anthropometric variables, as shown in Table 3.

Discussion

Protein malnutrition is a frequent condition in patients with HF.[3,24] Despite the assessment of the APM thickness being considered a useful tool to assess somatic protein status in general,[20] its use in the assessment of the nutritional status in patients with HF is still emerging. In this sense, our study was a pioneer in assessing APM thickness in patients with HF and found that about 70% of the patients were considered malnourished when the values of the APM thickness were compared to reference values according to gender and age.

The reduction in muscle mass in patients with HF can be explained by physical inactivity, hypermetabolic status, and drug-nutrient interaction, which leads to symptoms such as anorexia, diarrhea, and intestinal edema which, once present, are responsible for the reduction in food ingestion and absorption of nutrients.[1] In addition, chronic inflammation is closely related to the development of protein depletion in these patients.[1,2]

Table 3 - Correlations between the thickness of the adductor pollicis muscle and variables of interest

	Total sample (n = 74)		Men (n = 49)		Women (n = 25)	
Variables	R	p value	R	p value	r	p value
BMI	0.28*	0.015	0.29*	0.046	0.34*	0.92
AMC	0.35†	0.003	0.20*	0.16	0.45*	0.02
AMA	0.34†	0.003	0.15†	0.29	0.44†	0.03
LM	0.31*	0.009	0.14*	0.92	0.41*	0.04
PA	0.49*	< 0.001	0.41*	0.003	0.46*	0.02
SPA	0.31†	0.008	0.34†	0.016	0.33†	0.09

**Pearson's correlation coefficient; †Spearman's correlation coefficient. BMI: body mass index; AMC: arm muscle circumference; AMA: arm muscle area; LM: lean mass; PA: phase angle; SPA: standard phase angle.*

The APM thickness has been related to mortality and risk of complications in different clinical conditions. Bragagnolo et al.[25] observed that the APM thickness was associated with a higher risk of death and postoperative complications in patients undergoing gastrointestinal surgery. In patients undergoing dialysis, APM thickness was demonstrated to be associated with a higher risk of hospitalization during 6 months of follow-up.[26] When assessed before cardiac surgery, APM was able to predict clinical outcomes, such as septic complications, length of hospital stay, and mortality.[9] Although the association between APM and mortality/morbidity has not yet been established for the HF population, the present study demonstrated a direct relationship between APM thickness and PA.

PA is generated from the storage of part of the electric current by the cell membrane,[27] and decreased PA values are suggestive of death or reduced cellular integrity, while increased values are suggestive of a greater amount of intact cell membranes. This result is useful even in patients with fluid alteration or in those in whom body weight cannot be measured. In addition, PA values have the advantage of not requiring regression equations, unlike other EBI parameters, such as lean body mass.[28]

For a healthy population, the mean PA values vary between 4° and 10°, depending on gender and age. Low PA values are related to decreased cellular integrity, reduced lean mass, and increased morbidity and mortality.[29] As for an unhealthy population, the cutoff values differ among pathologies. In patients with liver cirrhosis, PA values ≤ 5.4° are associated with greater mortality when compared with patients with PA values greater than these.[30] In the same context, studies have identified PA as being a strong prognostic indicator and an important tool to assess clinical signs and monitor disease progression in patients on peritoneal dialysis (PA = 6.0°),[31] HIV-positive (PA = 5.4°),[32] or with lung cancer (PA = 4.5°).[33]

Collin-Ramírez et al.[23] also observed in patients with HF that a PA below 4.2° was an independent predictor of mortality. In parallel, patients with PA below this cutoff value (1st distribution quartile) presented lower values of hemoglobin, BMI, and manual dynamometry.

Malnutrition can be detected early by changes in cell membrane and fluid imbalance, which precede anthropometric or biochemical alterations. According to Barbosa-Silva et al.,[34] the first level to be affected during the process of malnutrition would be related to metabolic changes, such as alterations in cell membranes detected by PA. Functional muscle changes would be the next affected level, and only after that would anthropometric parameters be modified.

In general, studies show a good correlation between APM thickness and classic anthropometric parameters.[19,35] Bragagnolo et al.[25] observed a positive correlation of APM thickness with BMI, AMC, and TSF in surgical patients. Oliveira et al.,[36] when assessing patients on hemodialysis, also found a positive correlation of APM thickness with BMI, AMC, AMA, and PA. An important correlation between APM and lean mass estimated by EBI has also been observed in patients with stroke.[35] The present study corroborates these findings, since it showed a correlation

of APM thickness with BMI, AMC, AMA, and lean mass obtained by EBI, especially in women.

Although the present study has observed a correlation between APM thickness and BMI, over half of the patients were classified as having excess weight according to the BMI, and approximately 70% were considered malnourished according to APM thickness. This can be explained by the fact that the BMI is unable to differentiate body compartments, in addition to the fact that increased BMI is associated with a chronic proinflammatory status able to lead to protein depletion.[6]

The APM thickness was also associated with the SPA. The SPA corresponds to the PA adjusted for gender and age from reference values for the Brazilian population.[22] Thus, the SPA can be used to compare studies from different populations with different age and gender distributions. The cutoff value of -1.65 represents the 5th percentile and can be considered as the lowest acceptable limit for a healthy population.[25] Still, no studies have defined cutoff values for SPA specific to the HF population.

The use of EBI in patients with HF is considered valid by several authors.[37-39] However, there is still debate about its use in these patients. According to the Brazilian Medical Association,[10] the use of EBI is not appropriate in situations of ionic or fluid imbalance, such as edema and ascites, conditions frequently observed in patients with HF and which promote water retention and increase in extracellular compartment and, therefore, overestimate the fat-free mass,[36] a situation highlighted as one of the main sources of error in the application of the method. Martinez et al.[40] claim that due to the variation in tissue hydration in patients with HF, it would be more appropriate to use "raw measures" generated by EBI, such as reactance, resistance, and PA, since these do not depend on regression equations or the patient's weight.

In the present study, the standardization of assessment using widely known protocols,[10,21] in addition to the exclusion of patients not using diuretics, maintaining a homogeneous group, and those with clinical evidence of edema and ascites, were essential for better reliability of the EBI results.

When the HF functional classification was assessed, the APM thickness values were observed to be significantly higher in NYHA I patients when compared with NYHA II ones. The NYHA functional classification[11] is an instrument with established validity and reliability, used to evaluate the symptomatic effect of cardiac disease, allowing to stratify the degree of limitation imposed by the disease on daily activities.[41] HF is related to a low tolerance to exercises with pronounced metabolic and respiratory responses capable of leading to inactivity, causing muscle atrophy, which is ultimately associated with fatigue and decreased muscle strength.[42,43] This way, it is reasonable to propose that the greater the physical limitation, the higher the NYHA functional class[11] and, consequently, the lower the somatic protein mass. Therefore, it is possible that the reduction in APM thickness is related to a reduction in daily activities and is independent from the catabolism and the disease itself.[43]

Although the present study has been a pioneer in evaluating APM thickness as an indicator of nutritional status in patients with HF, it has some limitations. Due to financial and infrastructure limitations, methods that are more accurate in assessing body composition, such as dual-energy X-ray absorptiometry, could not be carried out. Therefore, the sensitivity and specificity of APM thickness compared with the methods considered the gold standard for the evaluation of the somatic nutritional protein status could not be measured. Additionally, the intraobserver and interobserver variability of APM measurements were not evaluated. However, in order to standardize the protocols of assessment and minimize the variability in APM measurements, the nutritionists responsible for the nutritional assessment were previously trained to perform anthropometric assessment and EBI.

Conclusions

The present study showed an increased frequency of malnutrition when APM thickness was used as a diagnostic indicator of nutritional status. Traditional indicators used to categorize the nutritional status were also directly associated with APM thickness. In addition, APM thickness values were directly associated with PA and SPA, recognized prognostic markers in different clinical situations. Additional prospective studies should be conducted in order to evaluate alterations in APM thickness in relation to disease duration and severity, as well as the presence of clinical complications and survival of patients with HF.

Author contributions

Conception and design of the research: Rosário FS, Giannini DT, Leal VO, Mourilhe-Rocha R. Acquisition

of data: Rosário FS, Giannini DT, Leal VO, Mourilhe-Rocha R. Analysis and interpretation of the data: Rosário FS, Giannini DT, Leal VO, Mourilhe-Rocha R. Statistical analysis: Rosário FS, Giannini DT, Leal VO, Mourilhe-Rocha R. Writing of the manuscript: Rosário FS, Giannini DT, Leal VO, Mourilhe-Rocha R. Critical revision of the manuscript for intellectual content: Rosário FS, Giannini DT, Leal VO, Mourilhe-Rocha R.

Potential Conflict of Interest

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

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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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ORIGINAL ARTICLE

Association between Smoking and Alcohol Consumption and the Severity of Coronary Artery Injuries in Patients with AMI

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Abstract

Background: Smoking is the most important risk factor for coronary heart disease (CHD) and ischemic events; alcohol consumption, on the other hand, appears to have a protective role.

Objective: Assess the association between smoking and alcohol consumption with the severity of coronary artery injuries in patients with acute myocardial infarction (AMI).

Methods: Cross-sectional study, performed in Santa Catarina. Variables were evaluated using the Chi-squared T/ Fisher's exact test, Kendall's correlation coefficient, Student's t test or Mann-Whitney U test. Values of $p < 0.05$ were considered significant.

Results: Between August 2016 to June 2017, 226 patients were evaluated with first episode of AMI. There was a difference in sex distribution, showing that 59.7% of men and 85.4% of women were not alcoholic ($p < 0.001$). There was a higher prevalence of non-hypertensive patients who consumed alcohol than hypertensive ones (40.7% vs. 24.4% and $p = 0.010$) and patients without diabetes who had drinking habits than those diabetic (36.4% vs. 12.0% and $p = 0.001$). There was also a higher prevalence of non-diabetic patients who smoked than diabetic ones (38.1% vs. 22.0% and $p = 0.035$). A weak and negative correlation was found between the number of cigarettes per day and the pack-year with the TIMI frame count ($r = -0.174$ and $p = 0.041$ and $r = -0.192$ and $p = 0.027$, respectively). The other associations did not show statistical significance.

Conclusion: The study showed that the number of cigarettes consumed per day and the pack-year is related to a smaller TIMI frame count, i.e., to a better coronary flow, which may be related to the Smoker's Paradox. There was no correlation between the beverage type and quantity with the SYNTAX score, Ejection fraction and TIMI frame count. (Int J Cardiovasc Sci. 2019;32(3)261-268)

Keywords: Coronary Artery Disease Myocardial Infarction, Alcohol Drinking; Tobacco Use Disorder; Risk Factors.

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide.[1] Every year in Brazil, cardiovascular diseases account for more than one-third of deaths.[2] CAD is a chronic disease that progresses over a period of years or decades[3] and results in major social impact. Acute Myocardial Infarction (AMI) is one of the main and often the first manifestation of CAD.

Protective and risk factors for CAD and AMI are widely known in the literature. Several studies indicate that mild-to-moderate alcohol consumption is associated with a 40 to 70% decreased risk of CAD, compared to no alcohol consumption or heavy alcohol use.[4] This decreased risk is found in both men and women,[5] and this protective effect has been observed in various groups.[6] Smoking, on the other hand, is the most important isolated risk factor – following advanced age – for coronary artery disease. Coronary ischemic events are the cause of death in more than one-third of these patients.[7] It is undoubtedly the most relevant preventable risk factor of cardiovascular disease.[8]

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Smoking cessation virtually benefits all smokers, regardless of age, duration or tobacco smoking load. A reduction in mortality rate is observed with smoking cessation at any age.[9] However, the sooner smoking cessation occurs, the greater the benefits: those who stop smoking by 40 years of age avoid 90% of the increased risk of death of continuing smoking.[10]

Until this day, tobacco use is clearly present in society, despite numerous efforts of public policies and warnings from the medical community about the harms that smoking causes to a person's health. It is also known that alcohol is toxic for several organs and systems. However, light/moderate and regular alcohol consumption is a protective factor for coronary heart diseases, contributing with reduced AMI risk. In spite of their clear association with cardiovascular morbidity and mortality, there are still gaps concerning the association of these two factors with the severity and complexity of coronary injuries in patients with AMI. Thus, this study aims at assessing the relationship of smoking and alcohol consumption with the severity of coronary injuries in patients with AMI.

Methods

This was a cross-sectional, observational study carried out in the emergency units of public hospitals in the metropolitan region of Florianopolis, centers of reference in the treatment of patients with AMI, with a population composed by 226 patients seen in the emergency department for AMI, in the period of August 2016 to June 2017. The objectives of this study were to describe the demographic and clinical characteristics of the population; to associate these data with the severity (expressed by the left ventricular ejection fraction - LVEF) and complexity (measured by the SYNTAX score) of coronary injuries and with coronary perfusion after PCI in AMI patients, presenting with ST-segment elevation (assessed by TIMI frame count), and to correlate smoking, alcohol and wine consumption, using the SYNTAX score, LVEF and TFC.

The patients were selected consecutively when admitted to the emergency, diagnosed with first AMI. We included patients over 18 years of age; of both sexes; with precordial pain suggestive of acute myocardial infarction associated with electrocardiogram with new ST segment elevation at the J point in two contiguous leads: ≥ 0.1 mV in all leads, except for leads V2 and V3, to which the limits of ≥ 0.2 mV in men ≥ 40 years, ≥ 0.25 mV in men < 40 years and ≥ 0.15 mV in women are applied, or presence of precordial pain suggestive of acute myocardial infarction associated with elevation in troponin I or CK-MB levels above the 99th percentile of the upper reference limit. Patients with previous acute myocardial infarction were excluded.

This study is an integral part of another ongoing study called Catarina Heart Study, a project entitled "Follow-up of patients after first acute MI in the state of Santa Catarina: A study of prospective cohort (Catarina Heart Study)", with the general aim of assessing the mortality and severity of ischemic disease in patients with post-myocardial infarction and their potential protective and risk factors. The instrument of data collection used corresponds to that of Catarina Study.

The Catarina Study was submitted and approved by the Committee of Ethics in Human Researches of ICSC (CEP-ICSC), via the Brazil Platform (Plataforma Brasil), and approved with opinion number 1519838.

Statistical analysis

We calculated a sample of 192 patients to find a mean difference of 2 points in the SYNTAX score, with a standard deviation of 7.0, power (80%), alpha (0.05), among alcohol consumer patients and non-alcohol consumers based on previous data from our group.

The data were tabulated using the Windows Excel software and analyzed using the Statistical Package for the Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA, 2005) for Windows. Qualitative data were presented as simple and relative frequencies and assessed using the Chi-square test. Data normality was assessed through the Kolmogorov-Smirnov test. Quantitative data with normal distribution were expressed as mean and standard deviation and assessed using the t test for independent samples. Non-normal quantitative data were described as median and interquartile amplitude and assessed using the Mann-Whitney U test. Correlations were assessed using Kendall›s correlation coefficients, since in all evaluations at least one of the variables presented non-normal distribution. P-values less than 0.05 were considered statistically significant.

Results

From 2016 to 2017, we analyzed the data of 226 patients who participated of the Catarina Heart Study, admitted to public hospitals of the metropolitan region of Florianopolis, due to AMI.

The mean age of the patients included in the sample was 59.2 ± 11.5 years, 63.7% male. Of the patients, 59.7% had SAH, 22.1% had DM, 35.4% were dyslipidemic, 42.0% had a family history of cardiovascular disease and 45.3% presented with STEMI (Table 1).

With respect to the association between clinical characteristics and alcohol consumption, there was a difference in the distribution by gender: data showed that 59.7% of men and 85.4% of women had no alcohol drinking habit ($p < 0.001$). There was a significantly higher prevalence of patients without hypertension who consumed alcohol (40.7%) than alcoholic hypertensive patients (24.4%) ($p = 0.010$). Similarly, there was a higher prevalence of patients without diabetes (36.4%) than diabetic ones (12.0%) ($p = 0.001$). The other associations did not show any statistical significance (Table 2).

There was a significantly lower prevalence of patients with diabetes who smoked (22.0%) than those without diabetes who smoked (38.1%) ($p = 0.035$). The other associations did not show any statistical significance (Table 3).

None of the associations of alcohol consumption and smoking with coronary perfusion after PCI – assessed by the TIMI frame count method – and the severity of the AMI and the complexity of coronary injuries, measured respectively through the LVEF and the SYNTAX score, showed statistical significance (Tables 4 and 5).

A negative and weak correlation was found between the number of pack-year and cigarettes per day with coronary perfusion after PCI – assessed using the TIMI frame count method ($r = -0.174$ and $p = 0.041$ and $r = -0.192$ and $p = 0.027$, respectively). The other correlations did not show any statistical significance (Tables 6 and 7).

Table 1 - Demographic and clinical characteristics of patients

Variables (n = 226)	n	%
Sex		
Male	144	63.7
Female	82	36.3
Age*	59.2 ± 11.5	
Alcohol	70	30.9
Smoking	78	34.5
SAH†		
Yes	135	59.7
No	91	40.3
DM‡		
Yes	50	22.1
No	176	77.9
Dyslipidemia		
Yes	80	35.4
No	146	64.6
Family History		
Yes	95	42.0
No	131	58.0
STEMI§	102	45.3
NSTEMI ||	123	54.7

**Mean ± standard deviation; †Systemic arterial hypertension; ‡Diabetes mellitus; §ST-segment elevation myocardial infarction; || Non-ST segment elevation myocardial infarction. Source: Author's elaboration, 2017.*

Discussion

This is an unprecedented study, which used data from the Catarina Heart Study – a cohort study that has assessed patients admitted to the emergency department of public hospitals in Santa Catarina after a first episode of AMI – and found a negative correlation between variables related to smoking and the TIMI frame count (TFC), that is, to coronary perfusion after PCI.

In relation to the demographic and clinical characteristics, there was a prevalence of male patients with mean age of 59.97 years, similar to the profile of patients seen in other Brazilian hospitals.[11,12] More than half of the patients claimed to suffer from SAH, whereas only 22.1% of patients had DM and 35.4% had dyslipidemia. Similar data were found by Soares et al.,[13] who showed that the majority of patients had hypertension (60.3%), but only 24% and 35% had diabetes and dyslipidemia, respectively.[13] In the current study, less than half of the sample had a family history of cardiovascular disease (42%), superior to Brazilian literature data, in which prevalence ranges from 26.8 to 35%.[14,15]

The results of this study demonstrated no significant difference between the mean SYNTAX score, LVEF and TFC, comparing alcoholic patients with non-alcoholic

Table 2 - Association between the demographic and clinical characteristics of patients and alcohol consumption. Assessment using the Chi-square test

Variables	Alcohol - n (%)		p-value
	Yes	No	
Sex			
Male	58 (40.3)	86 (59.7)	< 0.001
Female	12 (14.6)	70 (85.4)	
SAH*			
Yes	33 (24.4)	102 (75.6)	0.010
No	37 (40.7)	54 (59.3)	
DM†			
Yes	6 (12.0)	44 (88.0)	0.001
No	64 (36.4)	112 (63.6)	
Dislipidemia			
Yes	20 (25.0)	60 (75.0)	0.151
No	50 (34.2)	96 (65.8)	
Family history			
Yes	32 (33.7)	63 (66.3)	0.453
No	38 (29.0)	93 (71.0)	

**Systemic arterial hypertension; †Diabetes mellitus. Source: Author's elaboration, 2017.*

Table 3 - Association between the demographic and clinical characteristics of patients and smoking. Assessment using the Chi-square test

Variables	Smoking - n (%)		p-value
	Yes	No	
Sex			
Male	52 (36.1)	92 (63.9)	0.503
Female	26 (31.7)	56 (68.3)	
SAH*			
Yes	40 (29.6)	95 (70.4)	0.060
No	38 (41.8)	53 (58.2)	
DM†			
Yes	11 (22.0)	39 (78.0)	0.035
No	67 (38.1)	109 (61.9)	
Dislipidemia			
Yes	29 (36.3)	51 (63.8)	0.684
No	49 (33.6)	97 (66.4)	
Family history			
Yes	34 (35.8)	61 (64.2)	0.731
No	44 (33.6)	87 (66.4)	

**Systemic arterial hypertension †Diabetes mellitus. Source: Author's elaboration, 2017.*

ones. Furthermore, both alcohol and wine intake did not show any correlation with the complexity of injuries and the severity of the infarction – assessed by the SYNTAX score and the LVEF, as well as with the post-infarction coronary perfusion – assessed by the TIMI frame count method. This may indicate that, although alcohol has a protective effect on CAD risk and prevents development of atherosclerosis,[16] once CAD is established with coronary injuries, alcohol consumption or the amount of alcohol consumed has no effect on the complexity and the severity of injuries in AMI patients. However, the literature lacks studies that determine the correlation of alcohol consumption with the severity and complexity of coronary injuries.

A negative correlation was found between the number of pack-year and the number of cigarettes per day with the TIMI frame count in STEMI patients – that is, with coronary perfusion after PCI. Thus, we can infer that the greater the number of cigarettes smoked or the tobacco smoking load, the lower the TFC value and, therefore, the faster the coronary reperfusion after PCI will take place.

Table 4 - Association of alcohol consumption (g) with the severity of coronary injuries and with ventricular function. Assessment using the independent sample t-test

Variables	Alcohol - mean ± standard deviation		
	Yes	No	p-value
SYNTAX score	12.46 ± 7.85	13.26 ± 10.72	0.544
LVEF*	50.41 ± 11.95	50.24 ± 15.14	0.947
TIMI frame count †	25 (14 - 34)	24 (15 - 36)	0.885

**Left ventricle ejection fraction; †Median (interquartile amplitude). Source: Author's elaboration, 2017.*

Table 5 - Association of smoking (year-pack) with severity of injuries and with ventricular function. Assessment using the independent sample t-test and the Mann-Whitney test

Variables	Smoking - mean ± standard deviation		
	Yes	No	p-value
SYNTAX score	13.10 ± 10.02	12.97 ± 9.89	0.924
LVRF*	50.54 ± 13.61	50.16 ± 14.67	0.882
TIMI frame count †	20 (12.5 - 34)	28 (16 - 36)	0.123

**Left ventricle ejection fraction; †Median (interquartile amplitude). Source: Author's elaboration, 2017.*

Table 7 - Correlation between smoking and severity of coronary injuries and ventricular function. Assessment using Kendall's correlation coefficients

Variables	SYNTAX score r (p)	LVEF* r (p)	TIMI frame count r (p)
Years of smoking	0.010 (0.855)	-0.015 (0.806)	0.019 (0.823)
Pack-year	-0.025 (0.635)	0.019 (0.763)	-0.174 (0.041)
Cigarettes per day	-0.029 (0.593)	0.017 (0.788)	-0.192 (0.027)

**Left ventricle ejection fraction. Source: Author's elaboration, 2017.*

Table 6 - Correlation between alcohol consumption and severity of coronary injuries and ventricular function. Assessment using Kendall's correlation coefficients

Variables	SYNTAX score r (p)	LVEF* r (p)	TIMI frame count r (p)
Amount of alcohol consumed (g)	0.019 (0.728)	-0.026 (0.683)	0.072 (0.404)
Amount of wine consumed (g)	0.056 (0.325)	-0.095 (0.159)	0.030 (0.745)
Amount of alcohol consumed per week (g)	0.007 (0.896)	-0.007 (0.912)	0.049 (0.562)
Amount of wine consumed per week (g)	0.027 (0.632)	-0.097 (0.154)	0.033 (0.725)

**Left ventricle ejection fraction; †Median (interquartile amplitude). Source: Author's elaboration, 2017.*

Several data in the literature have found results compatible with the so-called Smoker's Paradox, according to which there is fewer mortality among smoker patients who suffered AMI, in addition to an apparent better coronary perfusion after the use of the thrombolytic therapy or PCI.[17,18] Such reduction in mortality is attributable to the difference in the profile of patients who suffer an AMI and are smokers: in their vast majority they are younger, since AMI tends to occur up to eleven years earlier among smokers, with fewer associated morbidities – such as DM and SAH – and usually in the inferior wall – associated with lower mortality than anterior wall MI.[19,20] However, even after adjusting these clinical differences, such paradox persisted, which could be explained by differences in the coronary anatomy and flow patterns in smokers and non-smokers.[20-22] Angeja et al.,[19] confirmed that smokers demonstrated better epicardial flow than non-smokers, but when they studied microvascular flow measurements, they could not note any differences between these two groups.[19] A possible explanation for these better results seem to lie in the physiopathological differences between smokers and non-smokers with AMI – due to increased thrombus in smokers – which would induce a greater effectiveness of thrombolytic therapy and a better response to anti-plaquetary therapy.[23-26] However, the literature still lacks studies that quantitatively compare the TFC with the number of cigarettes smoked per day and the number of pack-years of smoking. This finding could thus be explained by the paradoxical effect of smoking on CAD and its association with a better response to post-AMI reperfusion procedures, assuming that smokers may have better myocardial vascularization, in addition to changes at the biochemical physiopathological levels and, therefore, present better TIMI frame count values. We cannot still rule out that this result may also be attributed to chance, given the small proportion of the sample, together with a weak correlation effect. Despite

the correlation between the number of pack-year and the TFC, there was no association of smoking with the mean SYNTAX score, LVEF and TFC.

The results showed a greater number of alcoholic patients among non-hypertensive than among hypertensive ones (40.7% versus 24.4%). Different studies in the literature show that, among hypertensive patients, the majority consumes alcoholic beverages,[27,28] which diverges from these results. It is known that excessive alcohol consumption is associated with hypertension[29] and that light-to-moderate alcohol consumption, on the other hand, does not have a substantial impact on blood pressure.[30] Therefore, we could explain this finding by admitting the possibility that the patients in this study consume less alcohol, which, perhaps, would not be associated with hypertension in the same way as excessive consumption.

The results also show a higher prevalence of non-diabetic patients (36.4%) among alcoholic patients than non-diabetic ones (12.0%), which may indicate that alcohol has a protective effect on diabetes. Skliros et al also showed that, among patients with light consumption of alcohol, 85.2% had no DM.[27] The literature shows that light-to-moderate alcohol consumption is associated with a reduced risk of DM and it seems to play a protective role for its development,[31,32] which might justify this result.

We also found that most patients who smoked had no diabetes (38.1%). On the other hand, studies show that there is an association of smoking with increased DM risk.[33,34] A possible explanation for this result would be the fact that diabetic patients, already aware of the severity and comorbities associated with their disease, choose to stop smoking. This result may also be attributed to chance.

There was also an association between gender and alcohol consumption, in which 59.7% of men and 85.4% of women had no drinking habits ($p < 0.001$). Such difference between sexes was also noted in the Greek study by Skilros et al.,[27] in which 40.2% of men and 59.8% of women did not consume alcoholic beverages.[27]

In spite of the careful design and performance of this study, it is worth pointing out that there are some limitations to the analysis and interpretation of the results: it has a cross-sectional design within a cohort that follows patients admitted to emergency departments with a first episode of AMI, and, thus, cannot prove cause/effect. In addition, it has a small sample size, which can be influenced by other variables that were not assessed. Furthermore, the SYNTAX scores found were low, and, therefore, they cannot be extrapolated to a population with higher SYNTAX scores. Certain differences and correlations found can be viewed as the result of mere chance. However, these biases do not invalidate the results found, because it is a study with valuable national data and which raises hypothesis for the development of potential clinical trials and cohorts for the assessment of specific variables, such as smoking and alcohol in AMI. It is worth to highlight that efforts to avoid that patients start smoking or to promote tobacco cessation should be massively employed, and the smoker's paradox should not be mistakenly interpreted and used to encourage cigarette consumption. Moreover, it is necessary to search for a better understanding of the effects of alcohol consumption on the pathogenesis of hypertension and diabetes on a greater number of studies, before encouraging its consumption.

Conclusion

There was a negative correlation between the number of cigarettes consumed per day and the number of pack-year with the TIMI frame count. There was no correlation between alcohol consumption – be it wine or other types – with the SYNTAX score, the LVEF and the TIMI frame count. The study found an association between alcohol consumption and the prevalence of hypertension, diabetes and patients' sexes. In addition, we found an association of diabetes with smoking. There was no association of the severity and complexity of coronary injuries and ventricular function with smoking and alcohol consumption.

Author contributions

Conception and design of the research: Albuquerque LG, Moreira DM. Acquisition of data: Albuquerque LG, Silva RL, Fattah T. Analysis and interpretation of the data: Albuquerque LG, Moreira DM. Statistical analysis: Albuquerque LG, Moreira DM. Obtaining financing: Albuquerque LG, Moreira DM. Writing of the manuscript: Albuquerque LG. Critical revision of the manuscript for intellectual content: Albuquerque LG, Moreira DM.

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 course completion submitted by Luis Gustavo Albuquerque, from *Universidade do Sul de Santa Catarina*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Instituto de Cardiologia de Santa Catarina* under the protocol number 1.519.838. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Impact of Coronary Artery Bypass Grafting on Muscle Mass Reduction on the 7th Postoperative Day

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Abstract

Background: Ischemic heart failure is a chronic and degenerative disease with high morbidity and mortality in the world. Coronary artery bypass grafting is indicated as elective treatment and may cause a catabolic state that depletes energy reserves. Data on body composition evaluation in the postoperative period of major cardiac surgery are limited.

Objective: To evaluate the influence of elective coronary artery bypass grafting on body composition on the seventh postoperative day of patients with ischemic heart failure.

Methods: A cross-sectional study was carried out in which eighteen volunteers with New York Heart Association Class II and III heart failure underwent coronary artery bypass grafting. The energy and protein reserves of the participants were evaluated by anthropometry in the preoperative and on the seventh postoperative day. Paired t-Test or Mann-Whitney test was used if applicable. A significance level was considered at p value < 0.05.

Results: A significant loss of muscle mass was observed through the reduction of arm muscle circumference after surgery (4.2%, p 0.007). Major surgery causes hypermetabolic state and systemic inflammatory stimulus, due to the release of hormones and cytokines that may justify the observed loss of muscle mass.

Conclusion: Coronary artery bypass grafting had an impact on muscle mass reduction seven days after surgery in patients with ischemic heart failure. (Int J Cardiovasc Sci. 2019;32(3)269-273)

Keywords: Heart Failure/physiopathology; Heart Failure/mortality; Coronary,Artery Bypass Grafting; Body Composition; Postoperative Period.

Introduction

Heart failure (HF) is a chronic and degenerative disease with high morbidity and mortality in the world. Coronary artery bypass grafting (CABG) is indicated as an elective treatment and, may cause a catabolic state that depletes energy reserves.[1]

Data from the preoperative body composition assessment, using the anthropometric method and clinical outcomes after myocardial revascularization are limited. Therefore, we aimed to demonstrate the influence of elective CABG on body composition in the postoperative period of patients with ischemic heart failure.[2]

Methods

This study is part of a clinical trial that assessed the association between CABG and cardiac reverse remodeling. This cross-sectional study was approved by the Research Ethics Committee of the University Hospital of *Universidade Federal Fluminense*. It was registered in the Brazilian Registry of Clinical Trials (RBR-7376mq).

Patients with ischemic HF New York Heart Association (NYHA) Class II and III,[2] of both genders, undergoing elective CABG were recruited from National Institute of Cardiology / RJ. The inclusion criteria were: clinical and hemodynamic stability and absence of protein or caloric

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restriction in the preoperative period. Participants who showed NYHA class worsening,[2] or had hemodynamic decompensation, renal failure, sepsis or myocardial infarction were excluded. All participants started preoperative fasting 12 hours before the surgery. Oral feeding with a liquid diet in small amounts was offered 24 hours after the surgery and was maintained until 48 hours postoperatively. It consisted of meatless vegetable soup, fruit juice and teas. Participants were recruited using convenience sampling.

The participants' energy and protein reserves were evaluated by anthropometry performed by the same trained evaluator in the preoperative period and on the seventh postoperative day. Height (m) and weight (kg) were measured in a portable stadiometer and electronic balance, respectively with participants dressed in lightweight clothes. Body mass index (BMI) was calculated as the ratio between weight and squared height (kg / m²). Normal weight was considered when BMI was between 22 - 27 kg / m²) and overweight as BMI > 27- < 30 kg/m².

Waist circumference (WC; cm) was measured with an inextensible metric tape, at midpoint between the lowest rib and the iliac crest after exhalation. The mean of the two measurements was considered in the analysis: high risk of metabolic complications was associated with obesity when WC > 102 cm.

In order to evaluate arm muscle circumference (AMC; cm), the arm circumference (AC; cm) was measured at arm midpoint between the acromion and the olecranon with the arm flexed, using a tape measure. Then, the triceps skinfold thickness (TST; mm) was measured in the same place using an adipose compass (Cescorf, Brazil). AMC was calculated based on the AC and TST using the formula: AMC = AC - (3.14 × TST). The AMC reference range for age 70–79 years was P_{50} = 27.2 cm. Adequacy percentage was calculated considering P_{50} value: normal weight > 90%.

The fat reserves were evaluated through TST and body fat percentage (BF%). TST reference range for age 70-79 years at P_{50} = 12.4 mm. Adequacy percentage was calculated considering P_{50} value: normal weight: 90 – 110%; obesity > 110%.

BF% was calculated based on the sum of the four folds: TST, bicipital (mm), suprailiac (mm) and subscapular (mm) folds. The bicipital fold was measured towards the longitudinal axis of the arm, on its anterior face, at the point of greatest apparent circumference of the biceps. The suprailiac fold was obtained in the medial axillary line at midpoint between the iliac crest and the last costal arch. The subscapular fold was measured one centimeter below the inferior angle of the scapula. Adequacy percentage of normal range for men is 15-18%; risk of diseases associated with obesity: ≥ 25%). The mean of two measurements was considered in the analysis. Serum albumin (g/dL) was also evaluated: normal range > 3.5 g/dL; medium risk: 2.8 – 3.4 g/dL.

Statistical analysis

Data were analyzed using the software SPSS, version 10 (SPSS Inc.), PASW version 18 (IBM) and Microsoft Excel. Data normality was verified by the Shapiro–Wilks test. Paired t Test was used to compare the pre- and postoperative periods when the variables had normal distribution. When the normality criterion was not met, the Mann-Whitney test was used. A significance level was considered at p value < 0.05.

Results

From July 2016 to August 2017, thirty-seven patients (94.6% males) were recruited and followed.

Nineteen (51%) patients were excluded: seven (18.9%) patients had NYHA class worsening, seven had hemodynamic decompensation, two (5.4%) had kidney disease, one (2.7%) had acute myocardial infarction, one (2.7%) had sepsis and one (2.7%) died.

Eighteen patients completed the study. Table 1[3-5] summarizes clinical and demographic characteristics of the study population.

The risk factors and comorbidities for ischemic heart disease were observed. The values found for body composition and plasma albumin in the preoperative period and on the 7th postoperative day are shown in table 2. BMI, AMC and albumin had values reduced by 4.2%, 25% and 1.8%, respectively.

Discussion

Preoperative nutritional risk assessment is well established and aims to minimize postoperative morbidity and mortality,[6] as well as targeting caloric and nitrogen support for healing and preventing excessive loss of lean body mass.[7]

Studies that evaluated the postoperative body composition of patients after major cardiac surgeries

Table 1 - Baseline characteristics

	n (%)
Age[a] (years)	69.3 ± 5
Male gender	18 (100)
Sedentary lifestyle	18 (100)
Alcohol consumption	2 (11.1)
Smoking	11 (61.1)
NYHA class	
II	14 (77.8)
III	4 (22.2)
Comorbidities	
Hypertension[b]	16 (88.8)
Type 2 diabetes[c]	8 (44.4)
Dyslipidemia[d]	9 (50.0)
Previous myocardial infarction	9 (50.0)
Drugs used	
Antidiabetic drugs	8 (44.4)
Lipid-lowering drugs	16 (88.8)
Antihypertensive drugs	16 (88.8)
Diuretics	14 (77.8)
Beta-blockers	9 (50.0)
Vasodilators	15 (83.3)

[a] Mean ± standard deviation. [b] On therapy. or resting blood pressure > 139/90 mmHg.[3] [c] On therapy. or fasting blood sugar > 126 mg/dL.[4] [d] Total cholesterol ≥ 239 mg/dL and triglycerides ≥ 150 mg/dL.[5]

Table 2 - Anthropometric and biochemical evaluation in the preoperative and postoperative periods of coronary artery bypass grafting

Parameters	Preoperative	Postoperative	p-value
BMI (kg/m²)[a]	28.4 ± 3.0 (overweight)	27.9 ± 2.9 (normal weight)	0.106*
AMC (cm)[a]	28.0 ± 2.2 102.9% (normal weight)	26.8 ± 2.1 98.5% (normal weight)	0.007*
TS (mm)[a]	15.6 ± 4.2 125.8% (obesity)	15.7 ± 5.3 126.6% (obesity)	0.973*
WC (cm)[b]	102.0 [99.33-104.3]	102.4 [99.4-105.8]	0.412**
BF (%)[b]	34.23 [30.8-36.8] (↑ risk)	34.0 [31.7-36.5] (↑ risk)	0.6514**
Albumin (g/dL)[a]	4.0 ± 1.0 (↓ risk)	3.0 ± 0.8 (medium risk)	< 0.00*

*[a] Mean ± standard deviation; b Median and interquartile range. *Paired t test. **Mann-Whitney test. BMI: body mass index; AMC: arm muscle circumference; TS: triceps skinfold; WC: waist circumference; BF: (%) body fat percentage; Serum albumin.*

are scarce. We have evidenced the impact of elective CABG on skeletal muscle mass reduction through anthropometry on the seventh postoperative day in patients with ischemic HF. This is a simple, low-cost method of assessing body composition.

Major surgeries, such as CABG, cause a hypermetabolic state and systemic inflammatory stimulus, due to the release of hormones and cytokines[3] that may justify the loss of muscle mass observed in this study. Iida et al.,[1] suggested surgical stress, extracorporeal circulation, and perioperative hypothermia as causes of muscle mass loss.

The muscle proteolysis after CABG in HF patients has been reported in studies that used biochemical parameters as an evaluation method. Iida et al.,[1] have identified protein hypercatabolism through serum IL-6, cortisol, insulin-like growth factor (IGF)-1, growth hormone, branched-chain amino acid, and aromatic amino acid levels and evaluated muscle proteolysis through the urinary ratio between 3-methylhistidine and creatinine.[3] They verified that muscle proteolysis was accelerated 24 hours postoperatively and suggested that interventions to preserve skeletal muscle mass should be carried out up to 48 hours after surgery. These findings suggested that muscle protein degradation was due to the metabolic response to surgical stress.

The inflammatory stimulus provoked by surgery also justifies the significant reduction in albumin levels observed in this study. It is known that albumin is a visceral protein that has its concentrations reduced at the expense of increased expression of inflammatory proteins, such as C-reactive protein. Despite being a biochemical marker widely used to assess nutritional risk, there are limitations for its use in inflammatory processes.[3] Thus, the use of serum albumin as an indicator

of visceral protein reserve should be carefully evaluated in the presence of an inflammatory process.

We also observed BMI reduction due to weight loss, but without statistical significance. Similar results were found by Dimaria-Ghalili.[8] He reported that BMI reduction was due to the continuous inflammatory response related to surgical stress.

Although the study has limitations because it did not quantify the energetic and protein content of the liquid diet offered 24 hours postoperatively, this diet certainly did not reach the energy and protein requirements, despite the early reintroduction of the oral feeding, as recommended by Evans et al.[7]

Based on these preliminary results, an additional study can be proposed with the aim of improving the composition of the liquid diet offered 24 hours postoperatively in order to minimize muscle mass loss. The metabolic response to trauma is more intense on the first and second postoperative days, is proportional to the type of surgery[9] and justifies a higher protein requirement at this moment.

Conclusion

Elective coronary artery bypass grafting had an effect on muscle mass reduction on the seventh postoperative day. The impact of muscle mass reduction after cardiac surgery justifies additional studies.

Study limitations

The study had a small number of participants.

Author contributions

Conception and design of the research: Costa BO, Maciel G, Huguenin AB, Silva G, Guimarães SMS, Cruz WMS, Colanfranceschi AS, Boaventura GT. Acquisition of data: Costa BO, Maciel G, Huguenin AB, Silva G, Guimarães SMS, Cruz WMS, Colanfranceschi AS, Boaventura GT. Analysis and interpretation of the data: Costa BO, Silva G, Guimarães SMS, Cruz WMS. Statistical analysis: Costa BO, Guimarães SMS, Cruz WMS. Obtaining financing: Costa BO, Guimarães SMS, Cruz WMS, Colanfranceschi AS, Boaventura GT. Writing of the manuscript: Costa BO, Guimarães SMS, Cruz WMS. Critical revision of the manuscript for intellectual content: Costa BO, Maciel G, Huguenin AB, Silva G, Guimarães SMS, Cruz WMS, Colanfranceschi AS, Boaventura GT.

Potential Conflict of Interest

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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 for Medical Research of *Faculdade de Medicina/ Hospital Universitário Antônio Pedro*. under the protocol number CAAE: 37659314.4.0000.5243. It was registered in the Brazilian Registry of Clinical Trials (RBR-7376mq). 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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REVIEW ARTICLE

Nuts and Cardiovascular Diseases: Focus on Brazil Nuts

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Abstract

Cardiovascular diseases (CVD) are the main cause of death globally and most CVD can be prevented by addressing their risk factors, such as an unhealthy diet. Many authors have studied the benefits of nut consumption on CVD. Nuts contain high amounts of vegetable protein, unsaturated fatty acids, dietary fibers, vitamins, minerals and many other bioactive compounds, like phytosterols and phenolic compounds, which are able to reduce cholesterol levels and promote antioxidant and anti-inflammatory effects, thereby reducing cardiovascular risks. This review aims to describe studies involving the consumption of nuts, including Brazil nuts and CVD risk factors with positive results in the improvement of lipid profile, glucose metabolism, vascular function, and inflammatory and oxidative stress biomarkers.

Introduction

Cardiovascular diseases (CVD) are the main cause of death globally: more people die annually from CVD than from any other cause.[1] Multiple cardiovascular risk factors, including hyperlipidemia, hypertension, diabetes and smoking are associated with excessive production of reactive oxygen species and increased oxidative stress and inflammation, and promote vascular cell damage. Consequently, increased inflammation and oxidative stress is considered the major mechanism of the pathogenesis of endothelial dysfunction.[2]

The use of bioactive compounds such as monounsaturated and polyunsaturated fatty acids, phenolic compounds and some minerals to reduce CVD-related oxidative stress and inflammatory processes have been investigated.[3] Nuts are known to contain high lipid content, mostly mono- (MUFA) and polyunsaturated fatty acids (PUFA). Together with others nutrients, MUFA and PUFA may promote plasma cholesterol reduction and exert an anti-oxidant and anti-inflammatory effect, thereby reducing cardiovascular risk factors.[3-5]

Edible nuts include tree nuts (almonds, hazelnuts, walnuts, pistachios, pine nuts, cashews, pecans, macadamias, Brazil nuts) and peanuts. They have a similar nutrient composition, containing high amounts of vegetable protein, unsaturated fatty acids, dietary fibers, vitamins, minerals and bioactive compounds, like phytosterols and phenolic compounds.[6]

Therefore, the present review aims to describe the effects of nut consumption, as a coadjutant therapy for prevention of cardiovascular diseases, with a special focus on Brazil nuts, considering the lack of studies on the direct effect of Brazil nuts on established cardiovascular risk factors.

Methods

A literature search was conducted using the PubMed / MEDLINE database for studies on the effects of nut consumption, including Brazil nuts, on CVD risk factors such as lipid profile, glucose metabolism, vascular function, inflammatory and oxidative stress biomarkers. The following MeSH terms were applied in the search: cardiovascular diseases / brazil nuts /

Keywords

Cardiovascular Diseases; Nuts; Seeds; Diet, High-Protein; Cholesterol; Anti-Oxidants; Anti-Inflammatory Agents.

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coronary artery disease / atherosclerosis / nuts / oxidative stress / inflammation.

Inclusion criteria for article selection were: full articles published in English; articles investigating the effects of the consumption of nuts on cardiovascular disease and risk factors; articles indexed in Pubmed / MEDLINE database in the last ten years.

Nuts and cardiovascular disease

Several studies have been conducted considering the beneficial association between nut consumption (Table 1) and CVD risk factors (Table 2).[3,7-16]

Dose-response analysis of nut consumption and the risk of coronary artery disease (CAD) have been described, and a higher consumption of nuts was significantly associated with reduced risk of CAD when compared with a lower consumption. In fact, an increase in nut consumption by one serving per week significantly decreased the risk of CAD by 5%, and the protective effect was associated with a consumption of two servings / week.[7]

A study that evaluated nut consumption and cardiovascular risk factors in the United States population, showed a mean usual intake of tree nuts of 44,3 ± 1,6 g / day. Nut consumption was significantly associated with beneficial effects in body mass index, waist circumference, blood pressure, insulin resistance, lower chance of obesity and overweight and increase in high-density lipoprotein cholesterol (HDL-c) levels.[8]

Table 1 - Nuts

Picture	Usual name	Scientific name
	Brazil Nuts	*Bertholletia excelsa H.B.K.*
	American almonds Pakistani almonds	*Prunus dulcis*
	Pistachios	*Pistacia vera*
	Walnuts	*Juglans regia*
	Hazelnuts	*Corylus avellana*

The lipid profile in CAD patients and the consumption of almonds was assessed by Jamshed et al.[9] In their study, participants were divided in three groups: non-intervention, Pakistani almonds and American almonds. After the consumption of 10g / day of Pakistani or American almonds for 6 weeks, the authors observed an increase in HDL-c levels, and a decrease in triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), very low density lipoprotein (VLDL), total cholesterol (TC) to HDL-c and LDL to HDL-c ratios, and in the atherogenic index (calculated by the non-HDL / HDL-c ratio) in comparison with non-consumers. There were no significant differences in the cardiovascular risk factors evaluated between the Pakistani almond consumers and the American almond consumers. The authors concluded that consumption of almonds can improve lipid profile and could be used as an adjuvant in the treatment of dyslipidemias.[9]

Kasliwal et al.,[10] evaluated the effects of daily supplementation of 80 g of pistachios in shell, roasted and salted for three months and observed a significant increase in HDL-c and decrease in LDL-c, TC / HDL-c ratio and fasting blood glucose. Vascular function was also evaluated by measurement of the brachial artery flow-mediated vasodilatation (BAFMD), and carotid femoral and brachial-ankle pulse wave velocity (cfPWV and baPWV, respectively). After supplementation, there was a significant reduction in left baPWV. These results demonstrated the positive effect of pistachios on the lipid profile and the vascular function in dyslipidemic adult patients.[10]

Sauder et al.,[11] evaluated the effects of 59 g – 128 g of pistachios on lipid profile, glycemic control, inflammation and endothelial function in type-2 diabetes patients. After four weeks the authors observed that TC, TC / HDL-c ratio and TG, as well as fructosamine levels were significantly reduced.[11]

Damasceno et al.,[12] evaluated three types of diets in hypercholesterolemic subjects - a diet enriched with virgin olive oil (35 to 50 g daily), almonds (50 to 75 g daily) or walnuts (40 to 65 g daily) for four weeks. The amounts of each nutrient were calculated according to total energy intake. Among the three diets, almond-enriched diet

Table 2 - Effects of nut consumption on cardiovascular risk factors

Study population	Intervention	Duration	Main outcomes
American adults (14,386)[8]	≥ ¼ ounce/day of tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts)	2 multiple pass 24-h dietary recalls	Decreased body mass index, waist circumference, blood pressure, insulin resistance Increased HDL-c Lowered chances of obesity and overweight
CAD patients with optimal LDL-c and low HDL-c (37)[9]	10 g/day of Pakistan or American almonds	6 weeks	Increased HDL-c Decreased TG, LDL-c, VLDL-c, TC/HDL-c and LDL/HDL-c ratio and atherogenic index
Indian dyslipidemic adults (60)[10]	80 g/day of pistachios in shell, roasted and salted	12 weeks	Increased HDL-c Decreased LDL-c, TC/HDL-c ratio and fasting blood glucose Improved vascular function
Adults with well-controlled type 2 diabetes (30)[11]	Roasted pistachios that provided 20% of daily energy (59 to 128 g)	4 weeks	Decreased TC, TC/HDL-c ratio, TG and fructosamine
Hypercholesterolemic patients (18)[12]	Virgin olive oil (35 to 50 g/day), almonds (50 to 75 g/day) and walnuts (40 to 6 g/day)	4 weeks	Decreased TC, LDL-c, LDL/HDL-c ratio (results were more expressive with the almonds supplementation, possibly due to the greater content of phytosterol)
Adults with metabolic syndrome (50)[17]	Mixed raw nuts with skin (15 g/day of walnuts, 7.5 g/day of almonds, 7.5 g/day of hazelnuts)	12 weeks	Decreased DNA damage (measured by 8-oxo-dG urinary excretion), inflammatory biomarker (IL-6)
Subjects at increased cardiovascular risk (22)[19]	300 g of walnut paste-enriched meat/week (containing 20% walnut paste)	5 weeks	Decreased sVCAM, sICAM and Leukotriene B4
Hypercholesterolemic volunteers (21)[20]	49 to 86 g/day hazelnut enriched diet	4 weeks	Decreased CRP and sVCAM Improved endothelial dysfunction

HDL-c: high-density lipoprotein cholesterol; TG: trygliceridies; LDL-c: low-density lipoprotein cholesterol; VLDL-c: very low-density lipoprotein cholesterol; TC: total cholesterol; IL-6: interleukin 6; sVCAM: soluble vascular cell adhesion molecule, sICAM: soluble intercellular cell adhesion molecule; CRP: C-reactive protein.

showed to have the greatest hypocholesterolemic effect, which could be explained by the presence the higher content of phytosterol in almonds compared with olive oil and walnuts.[12]

One of the hypothesis for the hypocholesterolemic effect of nuts is their high amounts of phytosterols. Phytosterols are non-nutritive components of plants that play an important structural role in membranes, where they serve to stabilize phospholipid bilayers just as cholesterol does in animal cell membranes.[6] These compounds are able to displace cholesterol from intestinal micelles thereby reducing its absorption and leading to a reduction in LDL-c and TC (Figure 1).[4,13]

Nuts are also an important factor to modulate hypertension, since MUFA and PUFA are able to reduce serum levels of thromboxane A2, which is a vasoconstrictor.[4] In addition, the mineral content of nuts develops a key role in hypertension, as magnesium found in nuts stimulates the production of nitrous oxide, a vasodilator, and blocks the calcium channels, promoting vasodilatation. Furthermore, potassium can modulate the extracellular fluid volume reducing peripheral vascular resistance (Figure 1).[4,14] A review study investigating the association between nut consumption, hypertension and endothelial dysfunction showed that there are insufficient epidemiological data associating nuts with the prevention of hypertension,[14] which was reported in only two prospective studies. The first study was a prospective cohort conducted by Djousse et al.,[15] with participants from the Physicians Health Study I, who were free of hypertension at

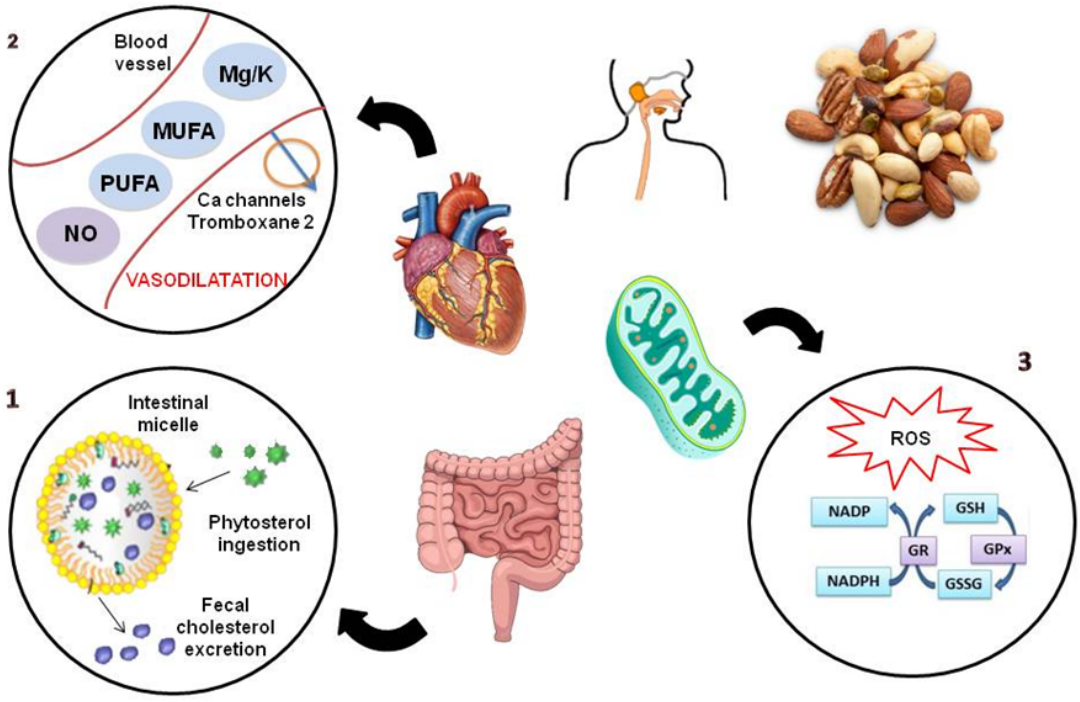

Figure 1 - Effects of nut consumption. The hypocholesterolemic effect is related to the rich content of phytosterols, non-nutritive components of all plants, able to displace cholesterol from intestinal micelles, reducing its absorption. Nuts are involved in the modulation of hypertension due to their high content of MUFA and PUFA, and which can reduce serum levels of thromboxane-A2, an important vasoconstrictor. Nuts are also rich in magnesium, stimulating the production of nitrous oxide and blockage of calcium channels, thus promoting vasodilatation. Concerning the antioxidant properties of Brazil nuts, its high content of selenium is particularly due to its presence in the glutathione peroxidase, an important enzyme that prevents the accumulation of reactive species of oxygen.

baseline. The authors showed a lower incidence of hypertension in usual consumers of nuts compared to non-consumers, although they did not consider the consumption of salt and body weight changes, two major factors associated with the risk of hypertension. The other study, conducted with Spanish university graduates followed-up for a median of 4.3 years in the SUN cohort, did not observe any association between nut consumption and the incidence of hypertension, after adjustment for several confounders.[15,16]

The effects of nuts on novel coronary heart disease risk factors including oxidative stress, inflammation and vascular reactivity have been evaluated,[6] and showed to promote beneficial effects on vascular reactivity by decreasing endothelial activation and improving flow-mediated vasodilatation[2] and nitric oxide-induced endothelial relaxation. As nuts are an excellent source of antioxidants, it's no coincidence that they are related to an improvement of the oxidative status.[6]

A study that evaluated oxidative stress and endothelial function in metabolic syndrome patients showed that the consumption of 30 g of mixed nuts for 12 weeks reduced significantly DNA damage (measured by the 8-oxo-dG urinary excretion).[17] Inflammatory biomarkers were also assessed and showed a significant decrease in interleukin-6 (IL-6) after nut consumption compared with the control group. After adjustment for changes in body weight, this statistical significance was reduced; however, there was still a borderline improvement in inflammatory markers in these patients.[18]

The effect of walnuts on inflammatory biomarkers in subjects with cardiovascular risk was also assessed in a cross-over study. Men and postmenopausal women (age ≥ 45 years and ≥ 50 years, respectively) were included in the study. Participants were obese or overweight and had one or more of the following risk factors: smoking habits, hypertension, familial hypercholesterolemia and type 1 diabetes. Intervention consisted of two 5-week

experimental period: during one period, participants consumed a walnut paste-enriched diet and a low-fat meat (LM) diet during the other. In the first group, there was a significant decrease of soluble vascular and intercellular cell adhesion molecules (sVCAM and sICAM, respectively) and leukotriene B4 (LTB4) compare to the baseline and also compared to the LM diet, improving the proinflammatory status and endothelium damage.[19]

A study evaluated the effects of hazelnut-enriched diet on cardiovascular biomarkers in hypercholesterolemic subjects. The diets were applied to the same group and divided in three periods of four weeks each: control diet I, preconized by the National Cholesterol Education Program adult treatment panel (ATP) III step 2 diet (7% energy from SFA and 200 mg/dietary cholesterol), a hazelnut-enriched diet that corresponded to 18 to 20% of the dietary daily energy intake (49 to 86 g/day) and control diet II, that was equivalent to control diet I. The association of the hazelnut diet with measures of endothelial dysfunction assessed by the flow-mediated dilatation (FMD) technique, showed a significant improvement, besides a significant negative correlation with sVCAM-1 and the enriched hazelnut diet. Among the inflammatory biomarkers, C-reactive protein (CRP) and sVCAM-1 showed a significant reduction during the hazelnut diet. The authors demonstrated that the improvement on biochemical parameters and endothelial dysfunction after the consumption of a hazelnut-enriched diet nearly returned to basal levels after the control diet II, showing the importance of a regular consumption.[20]

The recent publication in the Journal of the American College of Cardiology about nutrition trends for prevention and treatment of atherosclerotic cardiovascular diseases recommends the consumption of 30g/day of nuts, regarding portion control to avoid weight gain.[21]

Among the nuts, it is worth mentioning the Brazil nuts, as being the largest of the commonly consumed nuts from the Brazil nut tree (*Bertholletia excelsa*), which is a native of South America. The Brazil nut tree was originally discovered growing in hard, well-drained soil along the Amazon River in countries such as Brazil, Peru, Colombia, Venezuela, and Ecuador. Recent studies have been conducted associating Brazil nuts with many health benefits, mainly including cholesterol-lowering effects, antioxidant activity, and antiproliferative effects.[22]

Brazil nuts

Brazil nuts are the main source of selenium, constituents of selenoproteins, such as glutathione peroxidase (GPx) that promote cardiovascular benefits because of their antioxidant properties (Figure 1). Brazil nuts are also a good source of unsaturated fatty acids, with a high content of MUFAs (~50%), proteins, fiber, magnesium, phosphorus, thiamin, niacin, vitamin E, vitamin B, calcium, iron, potassium, zinc and copper.[22,23] (Tables 3[24,25] and 4).

Earlier studies involving the consumption of Brazil nuts and its effects on cardiovascular risk factors showed an improvement in antioxidant status and lipid biomarkers.[26,27] A randomized study conducted with 59 New Zealand adults, demonstrated a significant increase in plasma selenium and GPx activity in whole blood after the consumption of two Brazil nuts/day (corresponding to 53 μg of selenium) for 12 weeks, being as effective as the supplementation with 100 μg of selenium seleniomethionine.[26] A significant increase in plasma selenium was also seen in the study by Strunz et al.,[27] with 15 normolipidemic subjects after the consumption of 45 g/day (about 11 units) of Brazil nuts for 15 days. Concerning lipid abnormalities, although the lipid plasma profile did not alter, it was observed an

Table 3 - Nutritional composition of Brazil nuts in macronutrients, micronutrients and polyphenols (per 5 g)

Nuts	Energy (kcal)	Protein (g)	Fibre (g)	Fat (g)	SFA (g)	MUFA (g)	PUFA (g)	Vitamin E (mg)	Zinc (mg)	Selenium (µg)	Total polyphenols (mg)
Brazil nuts	36,7	0,75	0,4	3,53	0,81	1,19	1,22	0,28	0,2	290,5	12,2

SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids Sources: Ros E.,[3] Stockler-Pinto et al, 2010,[24] US Department of Agriculture Nutrient Data Base.[25]

Table 4 - Effects of Brazil nuts consumption

Study population	Intervention (Brazil nuts)	Duration	Main outcomes
New Zealand adults (59)[26]	2 units (about 10 g)	12 weeks	Increased Plasma Se Increased GPx activity
Normolipidemic subjects (15)[27]	45 g	15 days	Increased Plasma Se Increased Reception of cholesteryl esters by HDL
Healthy volunteers (10)[23,28]	5, 20 or 50 g	1 day	Decreased LDL-c Increased HDL-c Decreased AR index Increased Plasma Se Decreased IL-1, IL-6, TNFα, INFγ Increased IL-10
Obese Adolescents (17)[29]	15 to 25 g	16 weeks	Decreased LDL-c Decreased LDL-ox Decreased TC Decreased Tryglicerides Increased Plasma Se Increased RBCV
Obese Women(37)[30]	5 g	8 weeks	Increased HDL-c Decreased AR Index Increased Erythrocyte Se Increased Plasma Se Increased GPx activity
Dialysis patients(40)[31], (21)[32,33], (13)[34]	5 g	12 weeks	Decreased LDL-c Increased HDL-c- Decreased AR Index Decreased 8-isoprostane,8-OHdG Increased Plasma Se Increased GPx activity IL-6, TNFα, MDA, CRP, Nf-kB-Decrease Increased Nfr2
Hypertenses and dyslipidemics patients (91)[35,36]	13g	12 weeks	Decreased LDL-ox Decreased Apo A1 Decreased TC Increased Plasma Se Increased GPx activity Increased Nitric oxide

LDL-c: low-density lipoprotein cholesterol; LDL-ox: oxidized low-density lipoprotein; HDL-c: high-density lipoprotein cholesterol; AR index: atherogenic index ratio; IL: interleukin; TNFα: tumor necrosis factor alpha; INFγ: interferon gamma; TC: total cholesterol; RBCV: red blood cell velocity; GPx: glutathione peroxidase; 8-OHdG: 8-hydroxy-2-deoxyguanosine; MDA: malonilaldehyde; CRP: C-reactive protein; Nf-κB: factor nuclear kappa B; Nfr2: nuclear factor erythroid 2-related factor 2; Apo A1: apoliprotein A1.

increased reception of cholesteryl ester by HDL, which positively contributes to the nonatherogenic reverse cholesterol pathway.[27]

Studies involving healthy volunteers analyzed the lipid profile and inflammatory biomarkers after a single consumption of 20 g of Brazil nuts (about four units) and showed that Brazil nuts were able to significantly increase the levels of HDL-c and lower LDL-c and significantly decrease the atherogenic ratio index (AR index). On the other hand, serum triglycerides and total cholesterol did

not reduce significantly. Plasma selenium significantly increased after the ingestion of 5, 20 and 50 g of nuts, but its concentrations were not significantly different between the different levels of ingestion. The levels of inflammatory biomarkers IL-1, IL-6, tumor necrosis factor- alpha (TNF-α) and interferon gamma (IFN-γ) significantly decrease and the levels of IL-10 significantly increased after the ingestion of 20 or 50 g of nuts. Other inflammatory and oxidative stress biomarkers, such as C-reactive protein, erythrocyte glutathione peroxidase activity, DNA damage and δ-aminolevulinate dehydratase activity, did not show significantly results.[23,28]

Obese female adolescents were also evaluated after consumption of 15 to 25 g Brazil nuts daily during 16 weeks and compared with a placebo group (PG). The authors showed a significant reduction of TC, LDL-c and TG in the Brazil nuts group (BNG). Concerning the antioxidant capacity biomarkers, the oxidized LDL (LDL-ox) levels significantly decrease in BNG compared to PG after the supplementation. Plasma selenium and red blood cell velocity (RBCV), a marker of microvascular function, showed a significant increase after the supplementation, demonstrating the positive effect of Brazil nuts on lipid profile and microvascular function in this population.[29]

Similar results were described in a study with obese women; the consumption of one Brazil nut per day for 8 weeks, significantly increased HDL-c and decreased AR index, calculated through Castelli I and II indexes. Besides, a significant increase by 138% in plasma selenium status, and 46% in GPx activity were found after the consumption of Brazil nuts.[30]

In studies with hemodialysis patients, after 3 months of supplementation with one Brazil nut/day, there was a significant decrease in LDL-c and AR index, Castelli I and Castelli II, as well as an expressive increase in HDL-c. However, no significant changes were found in total cholesterol and TG levels. There was also a significant increase in plasma selenium and GPx activity. Regarding the oxidative DNA damage and lipid peroxidation, 8-hydroxy-2-deoxyguanosine (8-OHdG), malonilaldehyde (MDA) and 8-isoprostane showed a significant decrease, as well the inflammatory markers, IL-6, TNFα, CRP, and factor nuclear kappa B (Nf-κB) an important regulator of the transcription factor. Subsequently the authors evaluated the nuclear factor erythroid 2-related factor 2 (Nfr2), which plays an important role in the activation of several pathways against cellular oxidative stress and NAD(P)H:quinone oxide reductase 1 (NQO1), and phase II detoxifying enzymes, which also decreased significantly after the supplementation.[31-34] It's important to highlight, in this case, that most patients had selenium deficiency before the supplementation, which was reversed after the consumption of one Brazil nut per day.

Hypertensive and dyslipidemic patients were also studied after the supplementation of 13 g/day of granulated Brazil nut for three months. The results showed a significant increase in selenium plasma, GPx activity and decrease in LDL-ox.[35] The microvascular endothelial function was also assessed, showing a significant increase in nitric oxide, with no change in systemic microvascular reactivity or density.[36] Concerning the lipid profile, total cholesterol and apolipoprotein A1 (Apo A1) significantly decrease compared with pre-supplementation.[37]

Other studies evaluating Brazil nut supplementation were described in the review from Cardoso et al.[38] A study conducted with children that received 15 to 30 g (3 to 6 units) of Brazil nuts three days per week showed a significant excess of selenium intake, combined with high levels of selenium in plasma, erythrocytes, urine, hair and nails, with no signs of selenosis, though.[39] Another study involved older patients with mild cognitive impairment, and after the supplementation of one Brazil nut during six months, it was observed an improvement in selenium status, with a significant increase in plasma, erythrocyte and GPx activity, as well as an improvement in performance in cognitive tests.[40] The potential effect of Brazil nut regarding the development of colorectal cancer was also investigated, and after the supplementation of six nuts for six weeks, the selenium levels increased in plasma with upregulated expression of genes associated with selenoproteins (SePP) and decreased rectal gene expression of β-catenin, biomarkers related to colorectal oncogenesis.[41]

As previously discussed, Brazil nut consumption is effective in improving lipid profile, and inflammatory and oxidative stress biomarkers in different populations, including healthy subjects, obese women, and hemodialysis patients. This review showed the vast benefits of the consumption of nuts on cardiovascular risk factors and drew attention to the lack of studies showing the effects of Brazil nuts in this regard.

Conclusion

The nutritional composition of nuts, abundant in unsaturated fatty acids, antioxidant minerals and

phenolic compounds, play a significant role in the reduction of inflammation, oxidative stress and lipid profile, making them important alternatives to reduce the risks of chronic diseases.

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Author contributions

Conception and design of the research: Silva ACT, Cardozo LFMF, Cruz BO, Mafra D, Stockler-Pinto MB. Acquisition of data: Silva ACT, Cardozo LFMF, Stockler-Pinto MB. Analysis and interpretation of the data: Silva ACT, Cardozo LFMF, Cruz BO, Mafra D, Stockler-Pinto MB. Statistical analysis: Stockler-Pinto MB. Obtaining financing: Stockler-Pinto MB. Writing of the manuscript: Silva ACT, Cardozo LFMF, Stockler-Pinto MB. Critical revision of the manuscript for intellectual content: Silva ACT, Cardozo LFMF, Cruz BO, Mafra D, Stockler-Pinto MB.

Potential Conflict of Interest

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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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REVIEW ARTICLE

Cardiac Disorder in Chronic Hepatitis C

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Abstract

Chronic hepatitis C (CHC) has a high prevalence in the world. In addition to hepatic complications with cirrhosis in about 20% of patients and high risk for hepatocarcinoma, extrahepatic manifestations may also occur. Cardiac involvement in patients with CHC is associated with several factors, such as increased risk for coronary artery disease, primary cardiomyopathies, or hemodynamic and electrophysiological changes observed in liver cirrhosis. Furthermore, antiviral treatment may, in rare cases, causes cardiovascular adverse effects. Cardiac arrhythmias are the main form of clinical presentation, and, often, markers of poor prognosis in individuals with advanced liver disease. Although some mechanisms that justify these changes have already been reported, many questions remain unanswered, especially about the true involvement of the hepatitis C virus in the genesis of primary cardiac abnormalities, and the risk factors for cardiac-related complications of antiviral treatment.

Introduction

Chronic hepatitis C virus (HCV) infection affects more than 70 million people worldwide, accounting for about 1% of the global population.[1] In Brazil, the Ministry of Health estimates that 657,000 people are infected with HCV.[2] More than 70% of these infected individuals develop the chronic form of the disease, evolving with different degrees of liver conditions, and up to 20% develop advanced cirrhosis and 5% develop hepatocellular carcinoma.[3] The hepatic complications of hepatitis C account for about 400,000 deaths per year in the world.[1]

HCV infection can be considered a systemic disease and not simply restricted to the liver. Many forms of extrahepatic manifestations have been described, especially mixed cryoglobulinemia and other lymphoproliferative diseases. In addition, several authors have described a strong association of HCV with neurological, osteoarticular, pulmonary and thyroid disorders, as well as nephropathies (glomerulopathies), porphyria cutanea and even a higher incidence of diabetes mellitus.[4]

The association between heart diseases and chronic HCV infection has also been described. Since cardiac diseases, as well as HCV infection, have a considerable prevalence in the general population, the two conditions would be concomitantly expected in most of these individuals. However, HCV has been implicated as a risk factor for cardiovascular changes that will be described below, such as coronary atherosclerosis, cardiomyopathies, heart disease in advanced cirrhosis, cardiac arrhythmias and cardiotoxic effects of antiviral treatment.

This review aims to describe HCV-related cardiac disorders, discussing the possible pathophysiological mechanisms involved in these disorders.

Coronary artery disease

The association between HCV infection and increased risk of atherosclerotic disease, acute coronary syndromes (myocardial infarction and unstable angina), and fatal strokes has been reported, although the mechanisms that justify this predisposition are unclear. Ambrosino et al. published a recent meta-analysis involving 27 cohort studies and more than 200,000 HCV patients, in which they found an odds ratio of 1.38 for the development

Keywords

Hepatitis C, Chronic; Liver Cirrhosis; Cardiomiopathies; Arrhytmias, Cardiac; Drug Interactions; Drug - Related Side Effects and Adverse Reactions.

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of coronary artery disease (CAD) in these individuals. The presence of CAD, in the aforementioned systematic review, was defined as the onset of one of the following disorders: acute myocardial infarction, unstable angina, stable chronic angina, previous coronary artery bypass grafting, stenosis above 50% in one or more coronary vessels, as observed in coronary angiography, and electrocardiographic pattern compatible with myocardial ischemia. The findings also demonstrated an increased risk of cerebrovascular disease in individuals with hepatitis C.[5]

The possible mechanisms involved in an increased risk of coronary atherosclerosis would be related to the increase of oxidative stress, metabolic disorders such as the induction of diabetes mellitus due to the greater resistance to insulin in hepatitis C described by other authors,[6] inflammatory processes and local viral replication, a mechanism that is suggested by the demonstration of the presence of HCV in carotid atherosclerotic plaques.[7] Consistent data from these studies suggesting the association between CAD and HCV reinforce the need for monitoring patients with the virus regarding the risk of developing coronary events, and other cardiovascular risk factors should be closely monitored in this population.

Cardiomyopathies

Myocarditis

Myocarditis is related to several etiologies, such as the action of toxic and biological agents and autoimmune mechanisms (infections). Among the infections, viruses are most commonly involved. Classically, up to 1990, enteroviruses, including Coxsackie, have been described as the main causative agents. More recent studies with viral genome research on endomyocardial biopsy specimens have demonstrated the predominance of parvovirus B19 and Herpes virus 6 as etiological agents of myocarditis, although other viruses have been described, observing regional and temporal epidemiological characteristics.[8]

The description of HCV as a cause of myocarditis comes from reports in Asia where hepatitis C is very prevalent and the association between myocardiopathies of unknown etiology and HCV infection suggests that this virus could be implicated in the genesis of cardiac disorders.[9] The resolution of acute infection, myocardial fibrosis and subsequent cardiac remodeling could explain the onset of dilated cardiomyopathy, as described below.

Dilated cardiomyopathy

Idiopathic dilated cardiomyopathy (DCM) is a myocardial disease characterized by increased internal dimensions of the cardiac chambers and impairment of left ventricular (LV) systolic function without an identified etiology. Genetic mutations responsible for defects in the expression of cytoskeletal proteins from myocytes are often considered to cause this cardiac disorder. Despite the genetic mechanism demonstrated, previous myocarditis was observed in almost half of the cases, mainly of viral etiology, suggesting that the acquired component, influenced by other agents, does play an important role in the pathogenesis of this cardiac condition.[10] Although little reported in Brazil, DCM is responsible for about 25% of the causes of heart failure in developed countries.[10]

As previously described in this review, the occurrence of chronic myocarditis, mainly of viral etiology, has been postulated as one of the main hypotheses in the pathogenesis of DCM. Again, enteroviruses are the main agents pointed out in the different publications.[8] Matsumori et al.,[9] found 6.3% of HCV infection among 663 individuals with DCM in Japan.[9] These figures were not reproduced in a multicenter study conducted in Italy, which found the presence of HCV-positive serology in 12 of 309 (3.9%) patients with DCM.,[11] and in another study conducted in Brazil, which found only one case of HCV infection among 34 patients with DCM evaluated by a university hospital in Bahia.[12]

The pathophysiology of DCM as a consequence of myocarditis due to hepatitis C virus could be explained by three mechanisms described below. The first was by direct action of the virus, reinforced by viral replication in the myocytes and by the fact that the HCV core protein could damage the structure of these cells. The second mechanism would be the immune system through the activity of B, T cells and macrophages, where the latter are responsible for greater production of cytokines, of which the tumor necrosis factor alpha (TNF alpha) would play a predominant role, as demonstrated in previous studies that observed increased TNF alpha expression in the plasma and in the myocardial cells of individuals with myocarditis and DCM. TNF would affect ventricular systole by inhibition of calcium currents, reducing the entry of this ion in the myocyte, impairing the excitation-contraction coupling of the cardiac cell. In addition, it also contributes to increased nitric oxide production, inhibiting the beta-adrenergic effect on muscle contraction, causing a negative inotropic

effect. The third pathophysiological mechanism would be by induction of myocardial cellular apoptosis caused by mitochondrial disorders and fragmentation of the genomic DNA of the cell.[13] The emergence of hypofunctioning fibrotic areas during the myocardial healing process would lead to cardiac remodeling with progressive loss of ventricular systolic function, leading to heart failure, as well as a greater risk for severe ventricular arrhythmias and sudden death.[10]

Despite this association and the evidence of potential mechanisms that justify the occurrence of DCM induced by HCV, there are still no studies proving this fact.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an inherited disease characterized by an increased LV mass. This inappropriate myocardial hypertrophy is related to an architectural disorder of the cardiac fibers and different degrees of fibrosis, being a substrate for malignant ventricular arrhythmias, a frequent cause of sudden death in this population. Several types of mutations have been identified in genes that decode the structural proteins of myocyte, such as myosin heavy chains, tropomyosin and troponin T.[14]

In a multicenter study conducted by Matsumori in Japan in the early 1990s, serology for HCV was positive in 74 out of 697 patients diagnosed with HCM (10.6%), a result that contrasted with only 25 seropositives in 1,039 volunteering blood donors (2.5%). Another interesting fact in this survey was that the prevalence of HCV was higher in patients with HCM compared to the DCM population.[9] Among the clinical manifestations described in this study, arrhythmias and cardiac conduction disorders were present in nearly half of the patients. The factors that justify the association of HCM and HCV infection have not been reported.

Advanced liver disease

As we saw in the introduction to this article, about 20% of the individuals with chronic hepatitis C will develop cirrhosis. In cirrhotic patients, hepatic dysfunction and portal hypertension may lead to hemodynamic, neurohumoral and inflammatory disorders that affect cardiac function.[15]

Cirrhotic cardiomyopathy is characterized by increased cardiac output, autonomic disorders that influence the response to physiological or pharmacological stimuli, systolic and diastolic dysfunction and electrical abnormalities, without any other cause of heart disease being identified to justify the findings described. Myocardial hypertrophy is often observed and an association with fibrosis increases the risk of ventricular arrhythmias.[16] Paradoxically, some authors report that abnormalities related to liver cirrhosis could have a "protective" effect to the risk of coronary artery disease and acute coronary events. Such factors would be attributed to hepatic dysfunction and hemodynamic effects of portal hypertension, such as worsening of coagulation, presence of thrombocytopenia and platelet dysfunction, blood pressure decreased due to lower peripheral vascular resistance, abnormal lipid metabolism causing a decrease in cholesterol levels and increased levels of estrogen.[15] However, a lower incidence of coronary events in this population is controversial and, in the case of patients infected with HCV, the risk of atherosclerotic disease could be increased by other factors not well known, as previously reported.

Autonomic dysfunction is also an important marker of cirrhotic cardiomyopathy. Increased sympathetic activity and the renin-angiotensin-aldosterone system contribute to increased cardiac output, sodium and water retention and consequent increase in blood volume, associated with a reduction in peripheral vascular resistance due to the greater release of nitric oxide in the peripheral circulation, besides influencing ventricular remodeling with greater hypertrophy and worsening of the systolic and diastolic functions. The hyperadrenergic state facilitates the release of cytokines and the stimulation of cellular apoptosis, increasing myocardial impairment.[15]

One of the main disorders caused by cirrhotic cardiomyopathy is the relative hypoxemia caused by vasodilation of the pulmonary arterial bed (Hepatopulmonary Syndrome). A significant increase in the diameter of the pulmonary capillaries produced by a higher concentration of nitric oxide in the arteriolar and pulmonary capillary beds would allow the passage of several erythrocytes simultaneously in the alveolar exchange area, leading to a lower oxygenation of these, resembling the right-left shunt effect. On the other hand, increased production of vasoconstricting agents in the splanchnic circulation could cause the so-called portopulmonary hypertension — initially reversible — but with the development of endothelial hyperplasia, local thrombosis and vessel obstruction, this pulmonary arterial hypertension becomes irreversible.[17]

Special attention should be given to the electrophysiological disorders in cirrhotic cardiomyopathy. Previous studies have reported cardiac arrhythmias as the main clinical manifestation in patients with cardiac abnormalities related to HCV infection and in patients with liver cirrhosis due to any etiology. The increase in the QT interval is the most frequently observed abnormality, with an incidence of up to 50% in this population, apparently more pronounced the greater the activity of the disease and the worse the liver function.[18] Specifically in the case of hepatitis C, QT increase may be higher in patients coinfected with HIV.[19] Long QT has been described as a predictor of mortality in liver cirrhosis.[16]

The use of some common drugs in cirrhotic patients is also related to increased QT interval. An example are the fluoroquinolones used in the treatment of spontaneous bacterial peritonitis. Similarly, in HIV coinfected patients, the associated antiretroviral therapy has also been described as a cause of significant QT interval increase.[20] The onset of severe ventricular arrhythmias, such as polymorphic ventricular tachycardia (Torsade de pointes) associated with long QT, may be a rare cause of sudden death in this population.

In addition to ventricular arrhythmias, supraventricular tachyarrhythmias such as atrial fibrillation and flutter are more often diagnosed in cirrhotic patients. Lee et al.,[21] found that the presence of hepatic cirrhosis is an independent predictor for the occurrence of atrial fibrillation (AF), especially in the population younger than 65. However, although the presence of AF is related to higher mortality in the general population, this arrhythmia had no correlation with higher mortality in the cirrhotic group, which could be explained by the high proportion of deaths in this group, about five times higher compared to the control group.[21]

Atrioventricular and intraventricular conduction disorders are also described in these patients with a higher prevalence in the general population.[16] However, the findings related to autonomic dysfunction with chronotropic deficit are the main abnormalities related to heart rhythm. The explanation for this fact is mainly the progressive loss of sensitivity of cardiac beta-adrenergic receptors, despite the high sympathetic tone in cirrhosis. In addition, decreased response to beta-adrenergic stimulus would also be related to the involvement of other elements of sympathetic signal transduction, including the receptor itself, G protein and adenylyclase activity, decreasing AMPc levels.[22] Other studies reported that the chronotropic incompetence observed in physical or pharmacological stress response tests could be a predictor of cardiovascular events (myocardial infarction and heart failure) in cirrhotic patients that had a liver transplant.[23,24]

The treatment of cardiac disorders in cirrhotic patients presents some peculiarities in comparison to other forms of myocardiopathies. The use of non-cardioselective beta-blockers (e.g. propranolol) can prevent the bleeding of esophageal varices, decrease the risk of severe arrhythmias associated with increased QT interval and improve diastolic dysfunction, playing an important role in decreasing the deleterious effects of hyperadrenergic state. The use of angiotensin-converting enzyme inhibitors may prevent cardiac remodeling and arrhythmias such as atrial fibrillation and should be used with caution because of the risk of hypotension, since these patients already have a lower peripheral vascular resistance. Aldosterone inhibitors, such as spironolactone, have a better effect on blood volume reduction than loop diuretics in this population, and also contribute to the reduction of myocardial fibrosis. Liver transplant may reverse most of the cardiac abnormalities mentioned.[15]

Treatment of hepatitis C

Interferon and Ribavirin

Interferon (IFN) has several biological properties which mainly include antiviral, immunomodulatory and antiproliferative actions. Alpha-IFN (produced by leukocytes), widely used in the treatment of patients with hepatitis C, has several side effects, including cardiac abnormalities that are rare but may represent a greater risk of serious complications.[25]

In the early 1990s, Sonnenblik et al. published a record of 44 patients with cardiac complications related to IFN therapy, including 58% incidence of arrhythmias, 21% of acute coronary syndromes, 12% of cardiomyopathies and 9% of other manifestations, including pericarditis. Of the 25 patients that presented arrhythmias, two had severe ventricular tachyarrhythmias and one had sudden death. Of the eight patients with acute myocardial infarction, six died.[26]

The introduction of alpha interferon pegylate (peginterferon) allowed to increase the interval of subcutaneous administration of IFN to once a week, instead of three times a week in the previous treatment. The association of peginterferon with ribavirin added

greater efficacy to the treatment of hepatitis C compared to conventional IFN, with sustained virologic response rates (absence of viral RNA detection after treatment) in about 50% of the cases. However, many patients discontinued treatment because of adverse drug-related effects. The cardiovascular effects of this treatment are rare and arise as reports of cases in the literature involving supraventricular and ventricular arrhythmias, atrioventricular and intraventricular conduction disorders, cardiomyopathies and pericarditis.[27] On the other hand, Almawardy et al.,[28] studied 120 patients with heart disease that underwent antiviral therapy of hepatitis C with peginterferon and ribavirin and did not find any significant disorders in the incidence of complications or worsening of heart disease in this group of patients.[28]

Direct action antivirals

At the beginning of the current decade, direct-acting antivirals (DAAs) were incorporated into the treatment of hepatitis C in combination with peginterferon for patients with HCV genotype 1.[29] More recently, the introduction of new agents, including sofosbuvir, has led to sustained virologic response rates in more than 90% of the cases. Sofosbuvir is a nucleotide analogue (SN5b) that inhibits HCV polymerase and prevents viral replication. It presents a high genetic barrier to the development of resistance, but should be always associated with another second-generation antiviral such as daclatasvir, simeprevir or ledispavir and possibly ribavirin. The treatment of hepatitis C could be then done with drugs of oral administration only.[30]

In March 2015, an alert was issued by the FDA (Food and Drug Administration), reporting nine cases of bradycardia with severe clinical repercussion in patients using sofosbuvir associated with the concomitant use of amiodarone in the United States. Six of these cases were observed in the first 24 hours of treatment and the others before the end of the second week. Three patients required pacemaker implantation and another case resulted in death.[31] The mechanism by which this association would provoke such disorder has not been elucidated. Such information generated a warning that the use of sofosbuvir in patients using amiodarone should not be recommended or, if the latter were essential for the treatment of potentially serious arrhythmias, the patient should be monitored within the first 48 hours of treatment with sofosbuvir in a hospital environment.

Subsequently, in November 2015, a communication published in the New England Journal of Medicine reported three cases of severe bradyarrhythmia among more than 400 patients treated with AADs, including sofosbuvir, in a French reference center. Of these, two presented severe bradycardia due to sinus dysfunction and there was one case of atrioventricular block with syncope, requiring definitive pacemaker implantation in the three patients. Only one patient was on amiodarone, one was on low-dose propranolol, and the third one did not use drugs known to be heart rate depressants.[32]

Although the safety and efficacy profile of these regimens has been tested in controlled studies, the actual influence of the new antiviral agents on heart rhythm still remains unanswered. The occurrence of drug interactions between AADs and antiarrhythmic drugs or other hepatic metabolizing drugs and bradyarrhythmia prior to treatment are possible mechanisms that justify the complications described.

Most reported cases of severe bradyarrhythmia associated with the new antivirals were associated with previous use of the antiarrhythmic drug amiodarone. Amiodarone has extensive hepatic metabolism inhibiting CYP3A4, CYP2D6 and CYP2C9, CYP450 isoenzymes (Cytochrome P 450). In addition, it has a P-glycoprotein inhibitory effect (Gp-P), which is also present in cardiomyocytes. As sofosbuvir is a substrate of Gp-P, lower transport of this substance would lead to its increased intracellular concentration and consequent cardiotoxicity, leading to bradyarrhythmia. One criticism to this model is the fact that bradycardia has not been described as an adverse reaction in previous studies using high doses of sofosbuvir. On the other hand, other substrates of Gp-P, such as ritonavir (antiretroviral drug), have been related to bradyarrhythmia, raising the hypothesis that drugs with this potential could interact with sofosbuvir.[33] Simeprevir, one of the antivirals that may be associated with sofosbuvir in the treatment of hepatitis C, is a moderate inhibitor of CYP3A4, which has the potential to increase the effect of amiodarone. Another mechanism that could explain the events of bradycardia with the association between the antivirals and amiodarone would be the high plasma binding of this antiarrhythmic drug and the antivirals simeprevir and daclatasvir, promoting a higher plasma concentration of free amiodarone, increasing its effects on the cardiac tissue.[34]

Recently, Millard et al. published an experimental study demonstrating in vitro that the electrophysiological

disorders caused by the association between sofosbuvir and amiodarone are related to the intracellular calcium management in the myocytes, influencing the mechanism of excitation-contraction coupling. This disorder, whose molecular mechanisms involved were not elucidated, would affect the duration of the potential of action and the automatism of the cardiac cells.[35]

One of the cases of bradycardia reported in the treatment of hepatitis C with new antiviral agents was associated with the use of the beta-blocker propranolol, a drug widely used in patients with chronic liver disease, especially with cases of portal hypertension. The drug interaction of this agent with the direct-acting antivirals would not be expected according to the pharmacokinetic properties of these substances.[34]

In fact, the rare occurrence of severe bradyarrhythmia during the treatment of hepatitis C using the new direct-acting antivirals is not well understood. Caldeira et al., in a meta-analysis involving six large studies, did not find cardiovascular events in 1,625 patients using antiviral regimens, including sofosbuvir.[36] Durante-Mangoni et al.,[37] studied 26 patients with HCV using sofosbuvir treatment regimens by performing serial ECGs during treatment, not observing changes in HR behavior, including in patients using beta-blocker, suggesting that this medication does not present an additional risk to the development of bradyarrhythmia in association with new antiviral agents.[37] Hagiwara et al.,[38] described the cardiovascular disorders related to antiviral treatment in 3 cases (3.3%), among 91 patients using sofosbuvir and ledispavir. According to the authors, one of the patients presented bradycardia and increased QT interval, another patient developed atrial fibrillation and a third patient had increased QT interval associated with previous heart failure. The three patients presented clinical improvement with discontinuation of treatment.[38]

Conclusion

The questioning of the association between hepatitis C and the onset of heart diseases has been a target of study and controversy in recent years. A body of evidence suggests that HCV can directly or indirectly cause structural and electrical heart disorders, especially in cases of advanced liver disease. However, there is no consensus among the authors that HCV infection would be a risk factor for coronary artery disease and the onset of primary cardiomyopathies.

Similarly, it is still unclear whether treatment of hepatitis C with direct-acting antivirals could cause severe bradyarrhythmia or whether this risk is particularly observed with the combination of amiodarone or other drug interactions. While new studies do not clarify these issues, these hypotheses should not be overlooked in the clinical approach of this infection.

Author contributions

Conception and design of the research: Rezende AGS. Acquisition of data: Rezende AGS. Analysis and interpretation of the data: Rezende AGS. Writing of the manuscript: Rezende AGS. Critical revision of the manuscript for intellectual content: Rezende AGS, Lopes EP, Markman-Filho B.

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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

Abdominal Circumference or Waist Circumference?

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Circumference measures, also called perimetry, are part of the anthropometric evaluation.[1] Important Brazilian guidelines, as well as the Brazilian Society of Cardiology (SBC),[2] have considered the abdominal circumference values as a point of reference to classify the risk for cardiovascular disease development.

However, what is the adequate terminology that should be used to quantify the increased cardiovascular disease risk: abdominal circumference or waist circumference?

In national books,[3,4] measures of waist and abdominal circumferences are addressed as being distinct measures. The optimal point for waist circumference measurement is located between the last rib and the iliac crest, at its smallest perimeter. For the abdominal circumference, the most accurate measurement has been proposed as that taken on the umbilical scar.

According to the World Health Organization (WHO)[5] and the European Society of Cardiology (ESC),[6] the cardiovascular risk classification is carried out based on the waist circumference measure and this parameter should be measured at midpoint between the last rib and the iliac crest.

The same thing occurs in studies published in the English language, such as the one by Acar et al.[1] For them, the methodological criterion used to measure waist circumference was determined according to the same recommendations adopted by the WHO[5] and by the ESC.[6] This study[1], as well as the international guidelines,[5,6] calls this body segment as "waist circumference", which translates as "circunferência da cintura" in Portuguese, not "circunferência abdominal". Considering these facts, and even though there is a literature review on the subject,[7] why do the main Brazilian guidelines still use the nomenclature "abdominal circumference" instead of "waist circumference"?

The International Society for the Advancement of Kinanthropometry (ISAK),[8] which has a manual of anthropometric measurements, also describes the measurement process used to measure the waist circumference as the intersection between the last rib and the border of the iliac crest, corroborating other international guidelines.[5,6] Another classic article, which also used the "waist circumference" nomenclature as a component of some equations for predicting body fat, was that by Jackson and Pollock.[9] This study was crucial for the advancement and consolidation of anthropometry. Moreover, based on the measurement of some anthropometric parameters used in this study, it was possible to validate the predictive formula for fat percentage in the male gender.[9] However, the authors did not detail how the methodological process of this anthropometric measurement was performed, making it impossible to conclude whether the same criteria proposed by the WHO,[5] by ESC[6] and by ISAK[8] were used.

Other relevant points are the evaluation criteria proposed by different authors, which were assessed in another study.[10] What were the methodological standards used by the researchers who used the "waist circumference" nomenclature in their respective studies? Were there differences in these anthropometric assessments?

In the face of this impasse, Wang et al.[10] carried out a study in 2003 and reported the identification of 14 sites and, consequently, different methodological processes for the measurement of waist circumference. These 14 sites were separated into groups, aiming to identify possible differences after applying the statistical treatment.

The groups were divided as follows: (1) immediately below the last rib; (2) at the smallest circumference

Keywords

Waist Circumference; Waist - Hip Ratio; Abdominal Circumference; Cardiovascular Diseases; Risk Factors; Anthropometry.

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point; (3) at midpoint between the last rib and the iliac crest; and, (4) immediately above the iliac crest. After comparing the several anthropometric measurements, a significant difference was found only in women, according to the following order: measurement 2 < 1 < 3 < 4.[10] This result was perhaps expected by the authors and confirms the importance of standardization of the measurement site, in the case of female patients.

Considering this context, it is essential to reflect on and consider whether the current nomenclature to assess cardiovascular risk does not cause methodological confusion for the different health professionals, impairing the accuracy of future studies, to the detriment of imprecision during the measurement. It should be noted that in most classes taught in undergraduate courses, training courses in physical assessment and postgraduate courses, measurements of abdominal circumference and waist circumference are approached in the theoretical / practical scenario from completely different points.

The measurement standardization that technically evaluates the risk of cardiovascular disease is necessary, both in relation to the methodological process of measurement, and the nomenclature use. Otherwise, given the current scenario, individuals who would theoretically have moderate risk or low risk for cardiovascular disease could have overestimated results.

Figure 1 represents both genders and their respective measurements for waist circumference. The measurement was carried out at midpoint between the border of the iliac crest and the last rib, the same protocol proposed by the WHO,[5] ESC[6] and ISAK[8]. The image use was granted and authorized for publication by the Research Group on Cardiopulmonary Evaluation and Rehabilitation (GECARE).

Author contributions

Conception and design of the research: Chaves TO, Reis MS. Writing of the manuscript: Chaves TO, Reis MS. Critical revision of the manuscript for intellectual content: Chaves TO, Reis MS.

Potential Conflict of Interest

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

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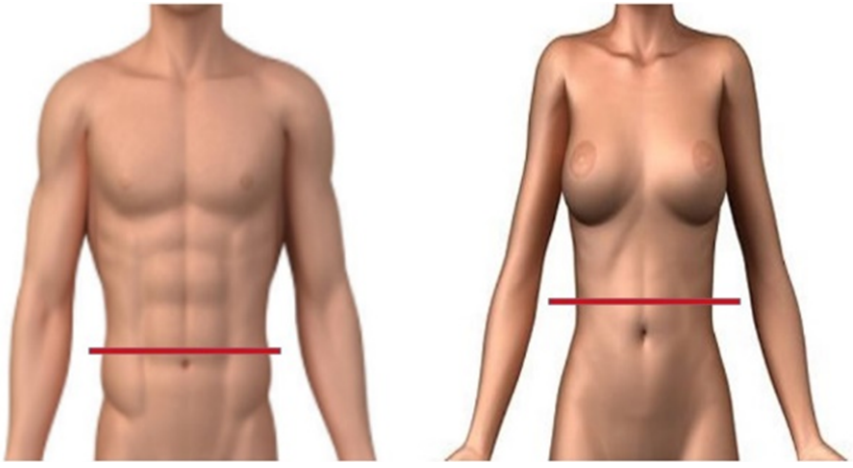

Figure 1 - Midpoint between the last rib and the iliac crest border in both genders.

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CASE REPORT

Isolated Non-Compacted Myocardium: Should We Consider the Presence of Extrasystoles as the Initial Manifestation?

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Abstract

Ventricular non-compaction occurs due to failure in myocardial morphogenesis during the fetal period. Patients can have heart failure, as well as systemic complications due to thromboembolism and cardiac arrhythmias. Early diagnosis is essential. We present the case of an asymptomatic 49-year-old woman who initially manifested ventricular extrasystoles and heart failure with reduced ejection fraction and a myocardial noncompaction diagnosis.

Introduction

The non-compacted myocardium, also known as spongy myocardium, is a distinct form of cardiomyopathy that occurs due to compaction failure during fetal development. It is characterized by prominent ventricular trabeculae and deep intertrabecular recesses, or sinusoids, in communication with the left ventricular cavity.[1-5]

It is currently classified as a primary genetic cardiomyopathy by the American Heart Association (AHA) and characterized as an unclassified cardiomyopathy by the World Health Organization (WHO) and the European Society of Cardiology (ESC).[1,4]

The prevalence of isolated non-compacted myocardium in adults remains unclear,[1,3,4,6] although observational studies have found a prevalence of 0.01 to 0.26% in specialized services.[1,2]

However, the estimated prevalence may be higher, as asymptomatic individuals rarely undergo imaging studies.[1] In this context, we will address the case of an asymptomatic and previously healthy patient, who had high-incidence ventricular extrasystoles during the preoperative period and anesthesia induction for a cholecystectomy procedure.

Case report

RASS, a 49-year-old female Caucasian patient, divorced, from Barra do Piraí, state of Rio de Janeiro, Brazil, a caregiver, with a diagnosis of cholelithiasis, had isolated, bigeminy ventricular extrasystoles during the preoperative examinations for a cholecystectomy procedure in August 2013. The procedure was cancelled, and the patient was referred to the cardiology outpatient clinic for assessment. She was asymptomatic and denied previous pathologies and medication use. She also denied smoking and alcohol consumption. She was unaware of heart disease in the family history. On physical examination, the patient had a third sound and frequent extrasystoles. She underwent a 12-lead resting electrocardiogram, which showed ventricular extrasystole and left atrial overload (Figure 1). Chest radiography showed no abnormalities.

Subsequently, she was submitted to an echocardiogram, which showed Left Atrium (LA) measuring 3.4 cm, Left Ventricular Diastolic Diameter (LVDD) of 6.1 cm and Left Ventricle Systolic Diameter (LVSD) of 4.7 cm; slightly thickened mitral valve; dilated cardiomyopathy with moderate LV systolic dysfunction; and ejection fraction

Keywords

Heart Failure; Isolated Noncompaction of the Ventricular Myocardium; Arrhythmias, Cardiac; Tachycardia,Ventricular; Diagnostic Imaging.

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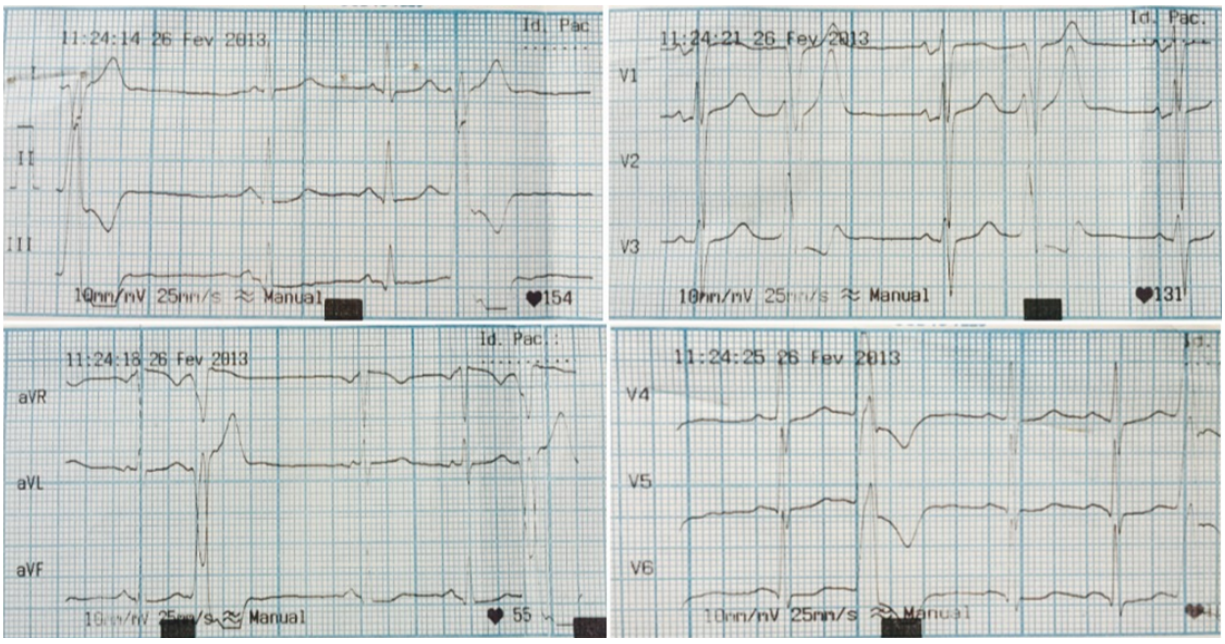

Figure 1 - 12-lead electrocardiogram showing ventricular extrasystoles.

of 46%. The 24-hour Holter showed the patient had 33,258 ventricular extrasystoles and one episode of non-sustained ventricular tachycardia.

The exercise test results showed sinus rhythm and presence of ventricular bigeminy in the pre-exertion phase, frequent ventricular extrasystoles, with a reduction of arrhythmias with isolated extrasystoles during the exertion. She was submitted to a coronary angiography, which did not show obstructive lesions. The patient started treatment for HF with optimized doses of carvedilol, enalapril and spironolactone.

In 2014, she was submitted to an echocardiogram, which showed inferomedial akinesia and mild LV systolic dysfunction. The 24-hour Holter showed a reduction in ventricular ectopies when compared to the initial exam, but still at high incidence (10,583 ectopies).

In 2015, the patient's systolic function normalized, but she still maintained the segmental alteration at the echocardiogram and the high incidence of ventricular ectopies. At that moment, she was submitted to a magnetic resonance imaging (MRI) assessment, which showed an increase in trabeculations in the LV mid-apical portion and a ratio between the non-compacted/compacted layers of 2.8 (1.4/0, 5 = 2.8) at the end of the diastole (Figures 2). These findings were compatible with the diagnosis of left ventricular non-compaction cardiomyopathy.

The last evaluation occurred in 2017, and the patient was in New York Heart Association (NYHA) functional class I, with low-incidence ventricular ectopies and receiving warfarin anticoagulation.

Discussion

During the embryonic development, the heart consists of a spongy network of muscle fibers and trabeculae, which are separated by recesses that connect the myocardium to the LV cavity. Blood is supplied to the myocardium through the intertrabecular spaces. Between the fifth and eighth weeks of fetal development, the ventricular myocardium undergoes compaction, with the transformation of the intertrabecular spaces into capillaries, and the residual spaces within the trabecular meshwork disappear. The process begins from the epicardium to the endocardium and from the base to the apex of the heart.[2] This trabeculation process is of utmost importance, since it allows a greater surface-to-volume ratio and an increase in muscle mass before coronary arteries are established.[5,6]

In the LV non-compacted myocardium, there is a persistence of the trabeculation and deep recesses,

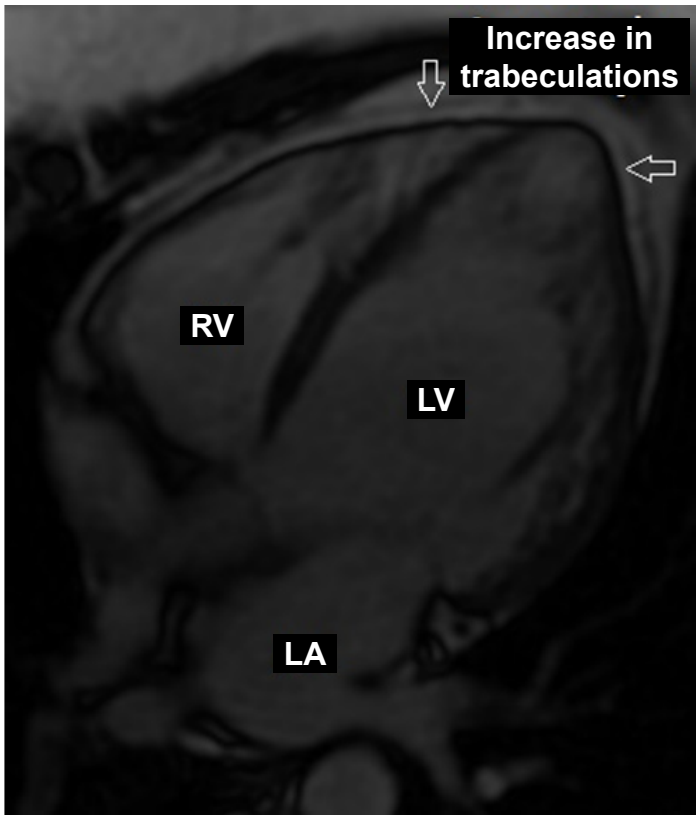

Figure 2 - Magnetic resonance imaging showing increased trabeculations. RV: right ventricle; LV: left ventricle; LA: left atrium.

which communicate with the ventricular cavity due to non-compaction.[2] Without the compaction completion, myocardial dysfunction occurs secondary to the failure of the efficient rotational ventricular system to develop contractile performance.[5]

The exact cause of the persistence of these trabeculations is unknown.[1-3] Studies point to familial recurrence of LV non-compacted myocardium.[1,4] The clinical status is variable, and it may be asymptomatic or present as heart failure, arrhythmias, thromboembolic events and sudden death.[2-4,6]

In the present report, the patient had ventricular arrhythmia and systolic heart failure as initial manifestations – found in more than 50% of the cases.[2-4,6] Ventricular arrhythmias were reported in 47% of adults.[2] Diastolic dysfunction occurs due to abnormal ventricular relaxation and restrictive filling caused by hypertrabeculation, whereas systolic dysfunction may result from subendocardial hypoperfusion and microcirculatory dysfunction.[2,6] Mechanical dyssynchrony between the compacted and non-compacted myocardium may cause global LV dysfunction.[2]

Other rhythm abnormalities were also reported on the electrocardiogram, such as ST-segment depression and T-wave inversion, along with right-bundle branch block.[2,4,6]

In view of the diagnosis of LV systolic dysfunction associated with non-compacted myocardium, full anticoagulation therapy with warfarin was initiated. Associated thromboembolic events may be secondary to extensive ventricular trabeculation, atrial fibrillation, and decreased ventricular function,[2,3] which may lead to cerebrovascular accidents, transient ischemic attacks, pulmonary embolism, and mesenteric infarction.[2,6] Sudden death represents approximately 40% of cases of death in these patients.[2]

In the present clinical case report, the patient was asymptomatic. The findings of ventricular extrasystoles were incidentally found during a preoperative examination. The alterations found on the echocardiogram showed heart failure with reduced ejection fraction and

dilated cardiomyopathy, which was underestimated by the patient's clinical history, who was sedentary. With the start of the treatment for heart failure, there was ventricular function, normalization, but the ventricular arrhythmia persisted.

At this time, the possibility of prior myocarditis due to segmental alteration identified on the echocardiogram was suggested, and the arrhythmogenic substrate was seen as a ventricular reentry mechanism. The MRI, previously described as the gold standard imaging method, defined the diagnosis.[4]

We also emphasize that, despite the lack of an electrocardiographic presentation typical of Chagas disease, this is part of the differential diagnosis, mainly due to the ventricular arrhythmia manifestation. Zuccarino et al.[4] reinforce the importance of other imaging methods in the diagnosis of non-compacted myocardium, with echocardiography being the first-line examination, but with limitations in the visualization of non-compaction.[4] However, the three-dimensional echocardiography can facilitate the identification of non-compaction.[7,8]

Conclusion

Left ventricular non-compaction cardiomyopathy can lead to fatal complications such as thromboembolic events, arrhythmias, and sudden death. These complications can be prevented with an early diagnosis and adequate treatment. Ventricular arrhythmias may be the initial manifestation of the disease, and imaging tests play a key role in its diagnosis.

Author contributions

Conception and design of the research: Nascimento EA, Santos RNC, Dutra FFT, Vitório MGI. Acquisition of data: Nascimento EA, Santos RNC, Dutra FFT, Vitório MGI. Analysis and interpretation of the data: Nascimento EA, Santos RNC, Dutra FFT, Vitório MGI. Writing of the manuscript: Nascimento EA, Santos RNC, Dutra FFT, Vitório MGI. Critical revision of the manuscript for intellectual content: Nascimento EA, Santos RNC, Dutra FFT, Vitório MGI.

Potential Conflict of Interest

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Ethics approval and consent to participate

All persons gave their informed consent prior to their inclusion in the study.

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CASE REPORT

Coronary Angioplasty with Stent in Woman with Active Vaginal Bleeding

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Abstract

Uterine leiomyoma and coronary artery disease are two common diseases in women. However, the association of uterine bleeding caused by leiomyoma with unstable coronary syndrome is not frequent. Here we describe a case of a patient with active vaginal bleeding and unstable angina who underwent a unique approach by performing percutaneous procedures. The report demonstrates that new interventional options can be used to control active bleeding in patients in need of coronary angioplasty.

Introduction

Percutaneous transluminal coronary angioplasty (PTCA) with stent requires dual antiplatelet therapy with acetylsalicylic acid and a $P2Y_{12}$ receptor inhibitor (clopidogrel, ticagrelor or prasugrel). However, this approach increases the risk of bleeding that should always be evaluated since hemorrhagic complications have an adverse impact on prognosis.[1]

Patients with an increased risk of bleeding or with active bleeding usually undergo surgical revascularization since they do not require dual antiplatelet therapy.[2]

We report a case of a patient with uterine leiomyoma with active vaginal bleeding who underwent, during the same surgical session, coronary angioplasty with stenting and uterine embolization.

Keywords

Embolization Therapeutic; Leiomyoma; Uterine Hemorrhage; Woman; Angioplasty; Stent; Hemorrhage/complications.

Case report

Female patient, 42 years old, with uterine leiomyoma, reporting chest pain with sweating on moderate exertion and progressive worsening. The patient had a history of hypermenorrhagia and progressive dysmenorrhea, three previous pregnancies with no complications and tubal ligation. The patient reported hypertension and non-insulin dependent diabetes mellitus (treatment initiated about five years ago) and no lesions in any other target organs.

During the bleeding episode, the patient had chest pain at rest, requiring blood transfusion to stabilize her condition (hemoglobin 7g/dL). No changes in myocardial necrosis markers or electrocardiogram were observed (unstable angina). Echocardiography showed normal sized heart chambers, left ventricular ejection fraction of 70% and no changes in segmental contractility.

Cardiac catheterization revealed 90% stenosis of the medial third of the left anterior descending (LAD). Due to frequent vaginal bleeding wich made the use of dual antiplatelet therapy impossible, myocardial revascularization surgery was performed and a hysterectomy was planned to be done after recovery. The surgery consisted of anastomosis of the left internal thoracic artery (LITA) to the LAD, without extracorporeal circulation, with no complications.

On the seventh postoperative day, the patient had severe vaginal bleeding followed by typical chest pain, hypotension and electrocardiogram showing dynamic T-wave changes in the anterior wall.

A second cardiac catheterization showed occlusion of the medial third of the LITA, and severe stenosis of the medial third of the LAD. Arteriography of the uterine arteries showed artery hypertrophy, coiling of intraparenchymal branches and tumor blush. At this

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same procedure, bilateral embolization of uterine arteries was performed with 500-700 μm polyvinyl alcohol bilateral to control vaginal bleeding, followed by PTCA of the LAD with 3.0 x 20 mm non-drug eluting stent (Omega, Boston Scientific Inc., Natick, USA) at 18 atm (Figures 1 and 2), without complications.

The patient showed good clinical response, with significant improvement of bleeding and cardiovascular symptoms until hospital discharge. The patient continued dual antiplatelet therapy for one month. During 150 days of cardiological follow-up, no recurrence of angina was reported. The patient continued gynecological follow-up, an no surgery was required for myomas.

Discusssion

Women's diseases generally have a temporal relationship with hormone profile. During menstrual period, women tend to develop estrogen-dependent diseases, such as endometriosis and uterine myomas, whereas in the postmenopausal period, hyperlipidemia, coronary artery disease (CAD), among others, are more frequent. Nagai et al.,[3] in a prospective cohort with 49,000 women, identified the age at peak incidence for 20 women's diseases. Peak incidence of uterine myoma was 44.8 years of old, and angina pectoris, 65. Therefore, the association between these two conditions is not common, with a 20-year difference between their peak of incidence.[3]

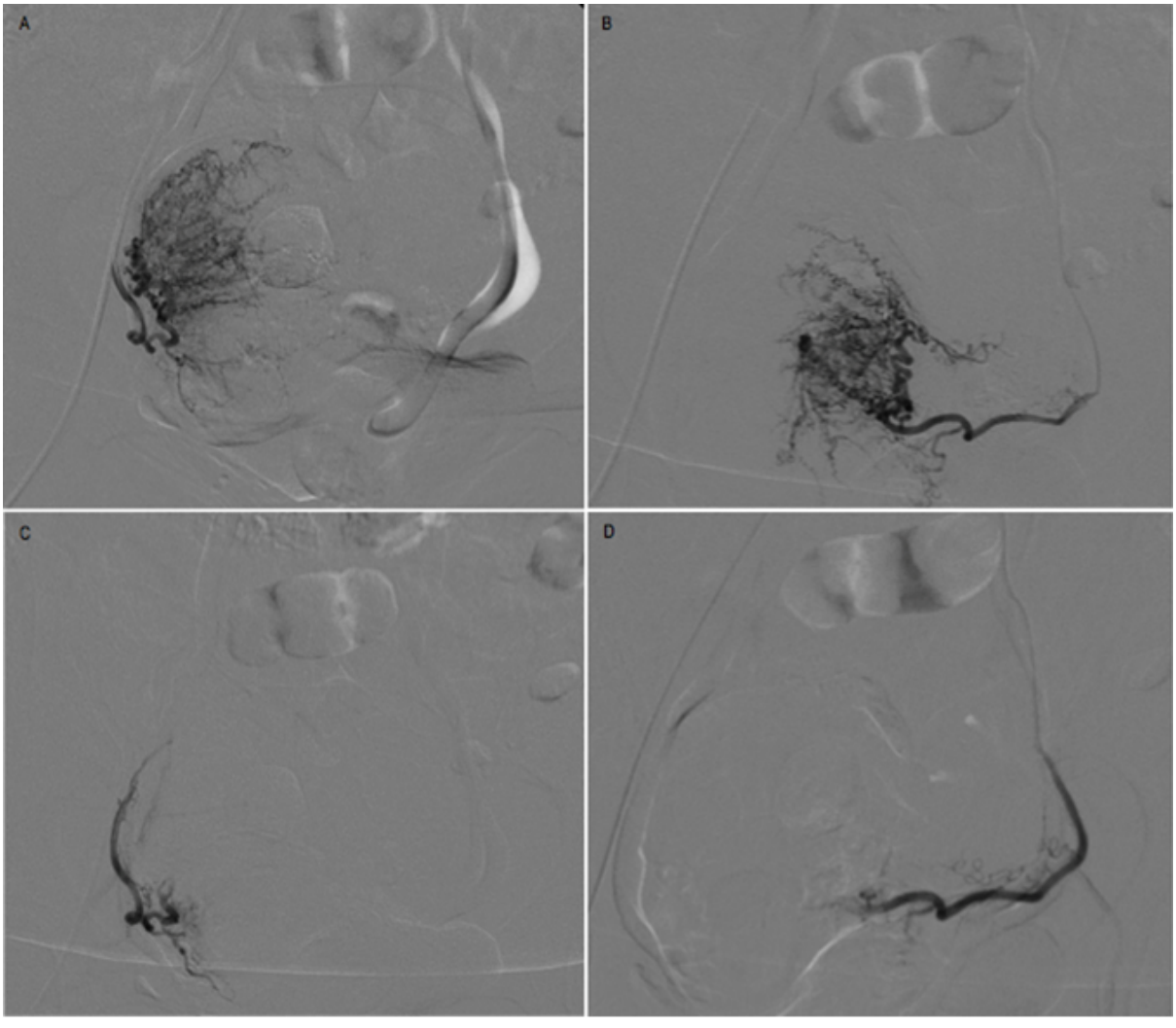

Figure 1 - Leiomyoma embolization. A: initial features of the right uterine artery; B: initial features of the left uterine artery. C: final features of the right uterine artery; D: final features of the left uterine artery.

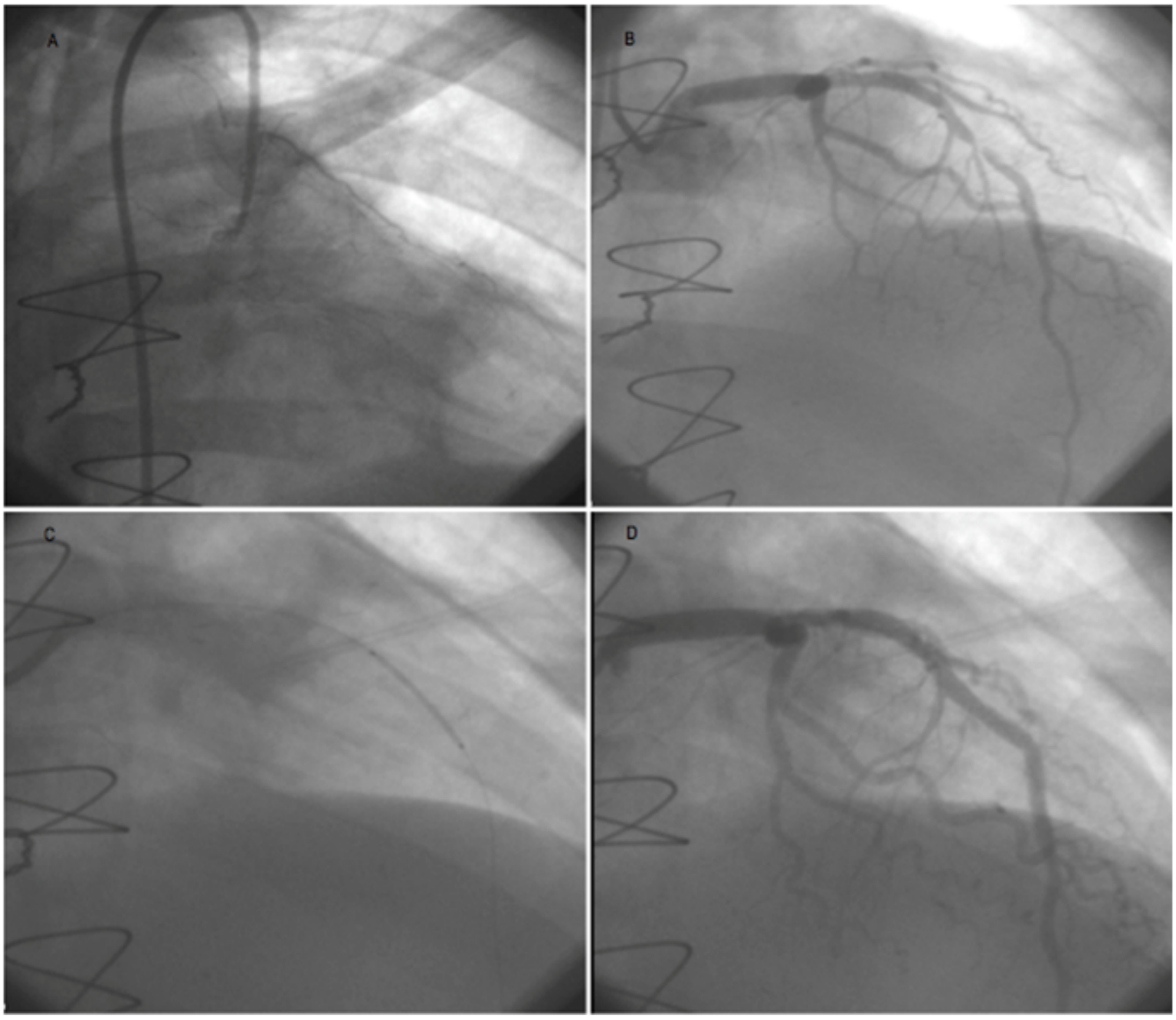

Figure 2 - Coronary angioplasty of left anterior descending artery. A: occlusion in the medial third of the left internal thoracic artery; B: stenosis of the medial third of anterior descending artery; C: stent positioning in the stenosis; D: final result in the left anterior descending artery.

Here we report a case of a 42 year old woman with risk factors for cad other than the age, such as diabetes mellitus and hypertension. In light of the epidemics of obesity, it is expected an earlier onset of cardiovascular diseases in women. Therefore, the association of CAD with estrogen-dependent diseases will be more common.

CAD is one of the main causes of mortality worldwide. Revascularization (PTCA or surgical revascularization) is indicated for patients with stable disease, refractory to clinical treatment, or with acute coronary syndromes. The choice of treatment depends on the analysis of several factors, such as severity of CAD, surgical risk and risk of bleeding.[2]

PTCA has a lower risk of bleeding, but requires antiplatelet therapy. High bleeding risk patients that require PTCA is a challenge. The risk of ischemia should always be evaluated together with the risk of bleeding, and the selection of both the stent type and the antiplatelet therapy regimen depends on such evaluation.[4] In the case reported, although the coronary stenosis was not complex, the patient was submitted to a surgical procedure. The choice was made because dual antiplatelet after this procedure was not necessary and hysterectomy was already schedule.

Dual antiplatelet therapy is mandatory after stent implantation and recommended to be maintained until

endothelization of the stent struts occurs. Discontinuation of the therapy before this process increases the risk of stent thrombosis. Although the mechanism of thrombosis has not been fully elucidated, the design of the stent platform, toxicity of antiproliferative drugs and the type of the stent polymer (biodegradable vs. durable polymers) are important factors. In general, antiplatelet therapy should be continued for at least 30 days in a case of conventional stents, and for one year if drug-eluting stents are used.[5]

Hemorrhagic complications in patients undergoing PTCA have been associated with increased risk of adverse events, such as acute infarction, stroke, stent thrombosis and death in patients with acute coronary syndromes and in patients with chronic diseases. Although the exact mechanism of this association is unknown, it may be related to discontinuation of therapies known to increase survival (antiplatelet drugs, beta-blockers), direct effects of blood transfusion, high prevalence of comorbidities of these patients, and deleterious effects of anemia. Thus, the anti-ischemic benefit of any therapy should always be weighed against the risk of bleeding.[6-10] Advanced age, female sex, chronic renal dysfunction and anemia are clinical predictors of bleeding after percutaneous procedures. The use of bleeding risk scores such as the CRUSADE and the HAS-BLED can make this assessment more effective.[11]

Early failure of arterial graft is not common. Early and long-term patency of the LITA, when anastomosed to the LAD, is of 95% and 85-90%, respectively. Only 1% of the patients at the immediate postoperative of myocardial revascularization involving the LITA have symptoms of angina. The most common causes of early graft failure are related to technical issues, such as the anastomosis, since progression of the atherosclerosis in a short time period is unlikely.[12,13]

In our patient, there was occlusion of the medial third of the LITA. Hypotension caused by vaginal bleeding created favorable conditions to occlusion of the LITA. As LITA failure is confirmed, the target of percutaneous revascularization may be the LITA or native coronary bed, depending on atherosclerosis severity. A second surgical approach should be indicated with caution in patients whose anatomy is unfavorable for interventionist procedure.[2]

Uterine leiomyomas, the most common pelvic tumor in women, are benign tumors originating from smooth muscle cells in the myometrium that cause pelvic pain, infertility and vaginal bleeding. Therapeutic options are hormone therapy, surgery (hysterectomy or myomectomy), or interventional procedures (uterine arterial embolization). Less aggressive therapies (myomectomy and embolization) are the therapies of choice for patients who want to get pregnant. Uterine arterial embolization allows reduced hospitalization time and early return to daily activities as compared with surgical procedures.[14]

The case reported exemplifies the combination of two common diseases in female patients that may be successfully treated by percutaneous procedures, with low risk of complications. Control of active bleeding by embolization procedures can be used for patients in need of coronary angioplasty and antiplatelet therapy.

Author contributions

Acquisition of data: Baião AH, Rivera M, Monteiro V, Oliveira FRA. Analysis and interpretation of the data: Cantarelli FL. Writing of the manuscript: Falcão FJA. Critical revision of the manuscript for intellectual content: Falcão FJA, Oliveira FRA.

Potential conflict of interest

The authors declare that they have no potential conflict of interest.

Sources of funding

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Study association

This study has no relationship with any thesis or dissertation.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Instituto de Medicina Integral Prof. Fernando Figueira* under the protocol number 4643. 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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GUIDELINE

Guideline for Ventilation / Perfusion Scintigraphy

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Abstract

This paper is about the Guideline for Ventilation / Perfusion Scintigraphy. It has been developed by the Brazilian Society of Nuclear Medicine to be a best practices guide used in Nuclear Medicine. Its function is to be an educational tool to help the Nuclear Medicine Services in Brazil to guarantee a quality care to the patients.

Introduction

This guideline presents the best practices for carrying out and interpreting Ventilation / Perfusion Scintigraphy.

The main indication for Ventilation / Perfusion Scintigraphy is the detection of acute pulmonary thromboembolism (PE). It is characterized by acute obstruction of a pulmonary artery, or one of its sub-branches, caused by venous thrombus. The typical picture includes symptoms such as dyspnea without other cause, chest pain on inspiration and hemoptysis, accompanied by signs of low blood oxygen saturation and tachycardia. Loss of consciousness, hemodynamic instability and death may occur in more severe cases.[1]

The American College of Radiology (2011) guideline classifies Ventilation / Perfusion Scintigraphy as highly recommended, combined with CT pulmonary angiography (CTPA). Both studies are highly accurate in the diagnosis of acute PE and the choice for one or the other will depend on the availability of each service and may follow some specific recommendations, as in the case of patients with allergy to iodinated contrast or renal failure, in which scintigraphy should be preferred.[2]

If adequately used and interpreted, ventilation / perfusion scintigraphy is an important tool for the detection of regional abnormality of pulmonary perfusion and ventilation, allowing for the accurate diagnosis of pulmonary embolism with low radiation exposure and minimum risks of complications.

Keywords

Pulmonary Embolism/complications; Pulmonary Embolism/diagnostic imaging; Ventilation-Perfusion Ratio; Pulmonary Artery/pathology; Radionuclide Imaging/methods.

Objectives

The purpose of this guideline is to provide practical guidance on the indication, performance and interpretation of the results of Ventilation / Perfusion Scintigraphy.

General information about the exam

It is an imaging diagnostic procedure that uses ventilation and perfusion scintigraphy to assess pulmonary diseases.

Indications

The main indications for ventilation / perfusion scintigraphy are listed on Table 1.

Relative contraindication

Pregnancy and breastfeeding. One should weight the cost/benefit and, if the procedure has to be performed, it should be done in such a way that exposure to radiation be minimized and, whenever possible, it would be preferable to carry out only the perfusion phase. It is worth noting that, in pregnant women with suspected pulmonary embolism and normal chest X-ray, the American Thoracic Society and the Society of Thoracic Radiology Clinical Practice recommend the use of

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Table 1 - Indications for ventilation / perfusion scintigraphy

1. Diagnosis of acute pulmonary thromboembolism;
2. Diagnosis of chronic pulmonary thromboembolism;
3. Assesment of the rate of resolution of PE (compared to previous study);
4. Assessment and quantification of right to left shunt;
5. Differential quantification of pulmonary function before pulmonary resection;
6. Lung transplant evaluation;
7. Assessment of the etiology of pulmonary hypertension;
8. Assessment of chronic parenchymal diseases.

Table 2 - Modified Wells Score

Modified wells criteria	Points
Clinical symptoms of DVT	3
PE is more likely than other diagnoses	3
HR > 100 bpm	1.5
Prior DVT / PE	1.5
Hemoptysis	1
Malignancy	1

Clinical probability: High > 6; Intermediate: 2 - 6; Low < 2.

perfusion lung scintigraphy as the method of choice for the diagnosis of PE, because it has the advantage of less exposure of the mother to radiation.[2]

Exam duration

About 1 hour in total (acquisition of ventilation and perfusion images).

Preparation

The patient must be capable of tolerating the dorsal decubitus position necessary to perform the images and be cooperative enough to carry out the preparation for inhalation, as described hereafter. The patient's standard chest radiograph, preferably in both posterior–anterior and lateral projections, and recently acquired (within a few-day-period), should be reviewed. The authors indicate a maximum interval of 48 hours. A CT scan can substitute for the chest radiography. In the assessment of PE, the standard chest radiography must be the first exam used to exclude other pathologies.[5]

Relevant information to perform the procedure

The likelihood of the patient having pulmonary thromboembolism[6] should be assessed (through D-dimer testing or using the modified Wells score [Table 2], for instance), as well as by assessing the patient's medical history (history of deep venous thrombosis (DVP), previous PE, chest X-rays, use of anticoagulant or thrombolytic).[4,5]

The patient should be instructed about the exam and how to adequately perform the aerosol ventilation procedure, if possible practicing before the exam starts.

Radiotracers

Ventilation: Tc-diethylenetriaminepentaacetic acid (DTPA) labeled with ^{99m}Tc, ^{99m}Tc labeled microcolloid or solid ^{99m}Tc-labeled carbon particles in argon carrier gas. The latter should be preferred, as far as available, because it has a more uniform distribution in the lungs with lower retention in the airways and bronchi.[7]

Perfusion: ^{99m}Tc macro aggregated albumin (^{99m}Tc-MAA).

Marking and quality control

Marking and quality must always be done according to manufacturer guidelines. However, pharmacopoeial criteria must be respected (pH between 5.0 - 6.0 and radiochemical purity ≥ 90%).[4,5]

Adult activity

Ventilation: The usual dispensed activity of ^{99m}Tc DTPA or sulfur colloid is 900–1300 MBq (25–35 mCi) in the nebulizer, from which only approximately 20–40 MBq (0.5–1.0 mCi) will reach the lungs.[8]

Solid ^{99m}Tc-labeled carbon particles in argon carrier gas – the activity administered should be calculated according to the distributor manual.

Since it is more difficult to achieve higher activity in the lungs with inhalation, it should always be performed first. It is essential that the perfusion activity should be

at least three times the counting rate of the ventilation activity to ensure that the image shows pulmonary perfusion, because both agents are labeled with ^{99m}Tc.[4,5]

Perfusion: 40–150 MBq (3–4 mCi); depending on the number of particles administered, this value could be higher), and should be in the range of 200,000–700,000 particles. The particles administered should be within a size range of 15 to 100 micrometers. In Brazil, currently available preparations have at least 90% of MAA particles between 10-100 micrometers in size.[9] In certain clinical conditions, the number of particles must be reduced, such as pulmonary hypertension and presence of right to left shunting. In the case of right-to-left shunt investigation, the number of particles should be decreased to 100,000 - 150,000.

Pregnant women: as mentioned before, it is preferable to perform only the perfusion analysis with ^{99m}Tc macroaggregated dose reduction (0.5 to 1 mCi).[4,5]

Pediatric dosage

Ventilation: Minimum activity should be no less than 10 MBq (0.27 mCi) to allow for sufficient count statistics to achieve good quality images. Since approximately 10% is retained within the lungs, it is suggested to administer as much as 15 times the activity of the DTPA needed (4 mCi).[3]

Solid ^{99m}Tc-labeled carbon particles in argon carrier gas - the activity administered should be calculated according to the distributor manual.

Perfusion: 1.11 MBq/kg (0.03 mCi/kg), with a minimum of 14.8 MBq/kg (0.4 mCi) if no ^{99m}Tc ventilation study is performed or 2.59 MBq/kg (0.07 mCi/kg) if a ^{99m}Tc ventilation study is performed. The number of particles depends on the age and weight, according with the table below:

Parameter	Newborn	1 year	5 years	10 years	15 years
Weight (kg)	3.5	12.1	20.3	33.5	55.0
Dosage (mCi)	0.2	0.5	1.0	1.5	2.5
Particles	10-50	50-150	200-300	200-300	200-700

In case of pulmonary hypertension and cardiac shunt investigation, these values should be reduced, depending on the age and the weight of the patient.

Precautions to be taken during tracer injection

Since the particles tend to decant, the syringe should be gently rotated prior to use. Blood should not be drawn back into the syringe to prevent MAA aggregation, because it can cause damage to the images. It is important that a single dose be administered over 30 seconds. The patient is oriented to inhale and breathe deeply during the tracer administration, facilitating its uniform distribution.

Imaging acquisition

Nowadays, there are 3 possibilities to acquire the images: planar imaging, SPECT imaging and SPECT/CT imaging.

Several studies have demonstrated that SPECT imaging yields a higher sensitivity compared to planar imaging. Major segmental defects and more periferal defects are detected by planar imaging. However, especially mesial defects and subsegmental defects are more easily detected by SPECT imaging. SPECT imaging can detect around 50% more defects compared to inhalation imaging. Despite this, the recent Apropriate Use Criteria published by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) recommends that both types of imaging (planar or SPECT) are valid in the clinical practice.[10,11] We recommend that SPECT imaging be performed whenever possible.

SPECT/CT combines increased sensitivity of SPECT imaging with high specificity of CT imaging. Several studies have shown that SPECT/CT provides increased sensitivity, specificity and accuracy compared to planar imaging. The improved specificity of SPECT/CT may reduce the number of false-positive results by 50%. Some studies have even demonstrated that SPECT/CT can increase specificity of scintigraphy to almost 100%, and make the study more accurate than CTA.[12-16] However, to our knowledge, there are no studies which assess the clinical impact on patient evolution when SPECT/CT is also used. Thus, the authors suggest that SPECT/CT imaging be performed whenever possible due to its higher accuracy, even though other studies are needed to confirm the impact on the clinical management of patients.

Ventilation:

Low energy high resolution collimator (LEHR), with an energy window of 20% centered at 140 keV.

Planar imaging must be obtained in anterior, posterior, left and right anterior and posterior oblique views, in addition to lateral views.

Counting recommendation:[8]

Posterior: 250,000 counts;

Other projections: use same time as the posterior view.

The following is a suggested protocol for image acquisition using SPECT/CT:

LEHR (Low Energy High Resolution) collimator;

64x64 matrix;

64 views (with a dual-head camera, 32 views per head);

20 sec acquisition;

Zoom 1.0

180 degrees (dual-head) or 360 degrees (single-head camera).

For CT image acquisition:

If the equipment allows it, the algorithm for dose reduction in CT (for example, CareDose, Auto mA);

130 kV;

5 mm slice thickness;

Pitch 1.8;

0.8 s rotation time;

Number of images = 61

Perfusion:

Low energy high resolution collimator (LEHR), with an energy window of 20% centered at 140 keV.

Planar imaging must be obtained in anterior, posterior, left and right anterior and posterior oblique views, in addition to lateral views.

Counting recommendation:[8]

500,000 to 750,000 counts per image.

In the case of perfusion SPECT with low-dose CT, perform tomographic imaging (see the acquisition protocol recommended above).

Acquisitions for other indications

Shunt investigation: the inhalation phase isn't performed. Following the administration of technetium Tc 99m injection, a whole-body scan should be performed in the anterior and posterior views; a static head imaging may be performed to better assess the brain.

Perform differential analysis of lung function prior to surgical procedure: the ventilation phase should not be performed; only lung perfusion imaging should be performed, as described above.

Assess lung transplantation: perfusion images and pulmonary ventilation.

Interpretation[4,5]

Acute PE Diagnosis:

The interpretation of ventilation/perfusion lung scans, both planar and SPECT/CT, is based on comparison. Thus, when there are ventilation-perfusion defects, a V/Q matched defect is characterized. When there is a defect in perfusion, but not in ventilation, it can be said that there was a mismatch defect. Thus, when there is a defect in ventilation, and there is not the same area in perfusion, we say that there was a reverse mismatch.

In the past, the PIOPED criteria were widely used. These are old criteria based on planar images. In addition, their classification as high, intermediate, and low probability does not meet clinical needs. It is also important to take into consideration the pretest clinical probability calculated using the modified Wells score (see below) and assess the laboratory tests. The observer's experience will also be an important factor. Thus, we believe that the report must be as accurate as possible, providing a "yes or no" response for the presence of acute PE. Below are the criteria used by the EANM, which are similar to the ones we use in our clinical practice.

The SNMMI has recently published an important document on appropriate use criteria for lung scintigraphy. The diagram below corresponds to the proposed investigation of pulmonary embolism in patients with low to moderate risk of PE (Wells Criteria: < 6). The presence of normal chest x-ray combined with increased D-Dimer values is associated with an accurate indication for ventilation/perfusion lung scintigraphy. In these patients the D-Dimer values are crucial to continue the investigation using imaging methods.

Thus, according to the SNMMI document, in patients with higher likelihood for PE (Wells Criteria: > 6), there is no clinical impact associated with the use of the D-Dimer assay for the diagnosis of PE (Figure 2). In these patients, imaging methods must be requested regardless of the D-Dimer values. In the same way, patients with normal chest x-ray are candidates for lung scintigraphy as diagnosis method of choice to CT pulmonary angiography. Lung scintigraphy will

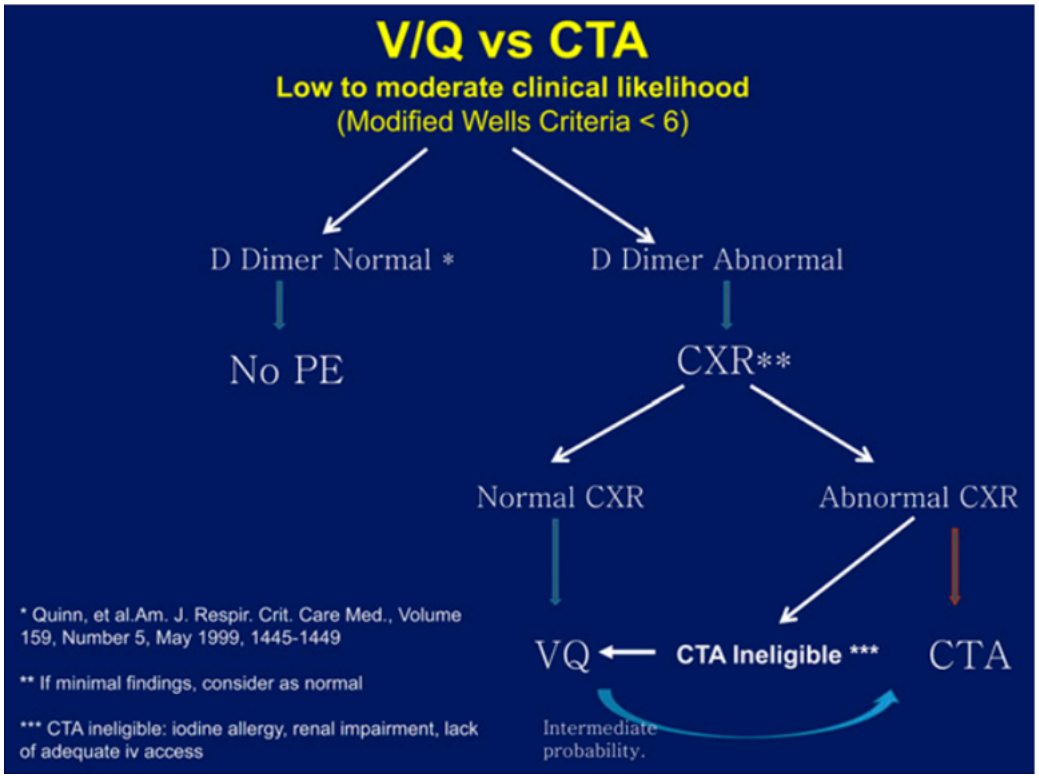

Figure 1 - Adapted from Waxman, et al. Appropriate Use Criteria for Ventilation–Perfusion Imaging in Pulmonary Embolism.

be the imaging modality of choice for investigation of suspected PE in patients with allergy to iodine, renal failure and inadequate venous access, even with abnormal chest x-ray.

Negative Acute PE:

Normal perfusion pattern conforming to the anatomic boundaries of the lungs;

Matched or reversed mismatch V/P defects of any size, shape, or number in the absence of mismatch;

Mismatch that does not have a lobar, segmental or subsegmental pattern, such as a stripe sign (perfusion defect with a normal perfusion stripe sign interposed between the defect and the adjacent pleural surfaces).

Positive Acute PE:

V/P mismatch of at least one segment or two subsegments that conforms to the pulmonary vascular anatomy (peripheral wedge-shaped defects – pleural based defects, and that conforms to the pulmonary vascular anatomy).

Inconclusive study:

Presence of multiple abnormalities identified in the images that do not correspond to any specific disease.

There are some causes for false-positive results. The main cause is an old or chronic PE. At the end of a hospital stay in which the patient was diagnosed with PE, it is recommended to perform a Ventilation/Perfusion Scintigraphy for this study to serve as reference for future suspicion of a PE. That is because, in some patients, the defect observed in the perfusion image may not normalize and remain as a mismatch defect. Nevertheless, in the vast majority of cases in which acute PE does occur, or the scintigraphy normalizes after treatment, or an infarction occurs in the region of the PE, the defect is regarded as a matched ventilation-perfusion defect. Other reasons for false positive results are: certain rare cases of pulmonary and mediastinal tumors, vasculitis and arteriovenous malformations; however, these possibilities, in general, do not represent a diagnostic problem when the overall patient's data is considered.

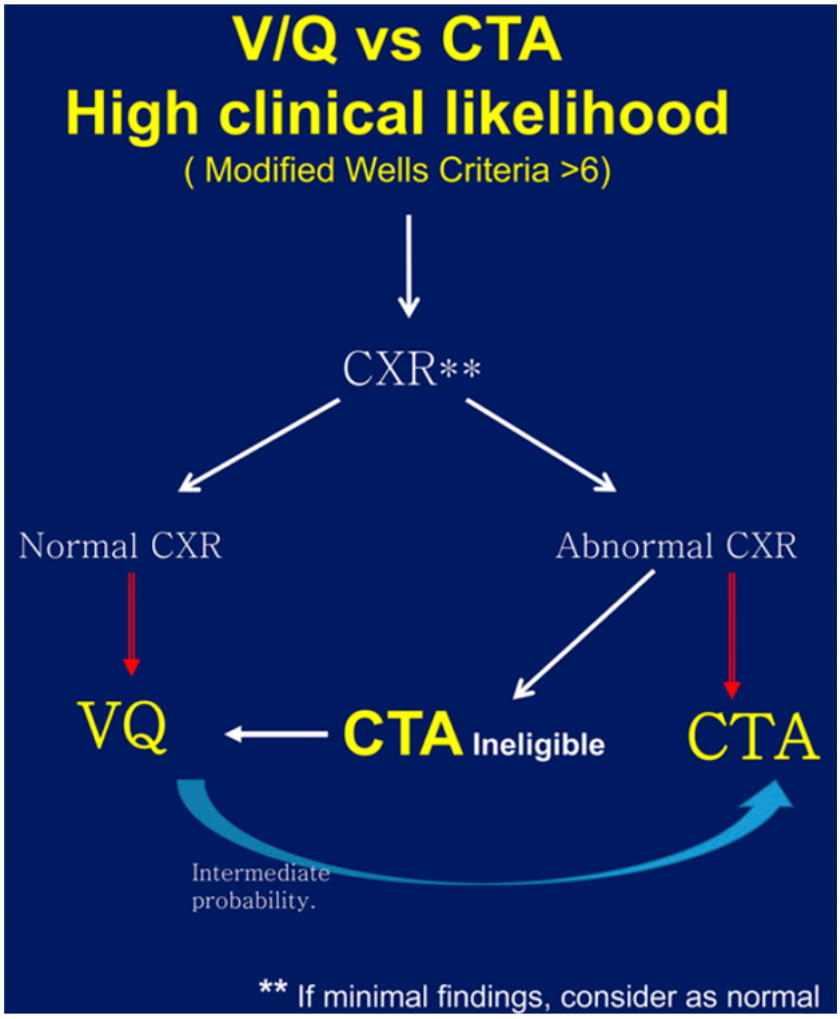

Figure 2 - Adapted from Waxman, et al. Appropriate Use Criteria for Ventilation-Perfusion Imaging in Pulmonary Embolism.

In cases in which the ventilation cannot be performed, only the perfusion phase may be performed, keeping good accuracy, with a sensitivity of 86% and a specificity of 93% compared to CTA;[17] and 80% and 96%, respectively, when combined with the interpretation of the chest x-ray.[18]

Evaluation of right to left shunts:

The presence of right to left shunts is detected through the presence of a tracer in extrapulmonary tissue, primarily in the brain. An image of the head complements the evaluation and helps detect small shunts. The presence of the radiopharmaceutical in the brain helps distinguish between a right-to-left shunt and free Tc-99m pertechnetate due to kit unlabelling, for instance, since the free Tc-99m pertechnetate would not be present in the brain.

The calculation of percentage shunts can be assessed using regions of interest (ROIs) drawn over the whole body and the lungs, in both anterior and posterior images, and through comparison of the radioactive activity in the lungs in relation to the whole body, resulting in a percentage number. Usually, it is considered as positive if the difference between the activity present in the lungs compared to the whole body is greater than 10%, following the formula:[19] (total number of whole body counts, including the background – total counts in the lungs) / total number of whole body counts, including the background x 100 = percentage of R-L shunt. Attention should always be drawn to radiopharmaceutical quality

control to ensure that the labeling efficiency is greater than 90%. Due to the presence of free Tc-99m pertechnetate. It should be remembered that visual analysis is always paramount and the presence of tracer in the brain and in renal cortex should be verified.

Perform differential analysis of lung function prior to surgical procedure:

The aim of this indication is to help predict the lung function reduction in the postoperative period following lung resection (e.g. lung cancer). This is particularly important in those patients who already have a reduced function in the preoperative period. The differential function is calculated by drawing ROIs on each lung in the anterior and posterior views. The lung can also be divided into three equal rectangular ROI: top, middle, and bottom. Alternatively, posterior oblique views can be used to assess lobar segmentation, assisting in cases of segmentectomy or lobectomy.[20]

Postoperative evaluation of lung transplantation

Evaluate the feasibility of vascular anastomosis. It is also possible to assess rejection, when there are matched defects suggestive of obstructive lung disease or changes in the perfusion between both lungs (in the case of unilateral transplantation).

Important observations

There may be hot spots on perfusion images, in case blood coagulation occurs in the syringe during injection of the tracer, which may occur when blood is aspirated into the syringe during injection.

The acquisition of images with the patient in different positions (dorsal decubitus or supine position) may hinder the comparability of the studies.

The unilateral absence of one of the lungs in the perfusion imaging, with normal ventilation, is not an indicative of PE. In these cases, the chest CT scan must be assessed in order to look for tumors, aortic aneurysm, vascular defects or other pathologies.

Author contributions

Conception and design of the research: Rigolon MY, Amorim BJ. Acquisition of data: Rigolon MY. Analysis and interpretation of the data: Rigolon MY, Mesquita CT, Amorim BJ. Writing of the manuscript: Rigolon MY. Critical revision of the manuscript for intellectual content: Mesquita CT, Amorim BJ. Supervision / as the major investigador: Amorim BJ.

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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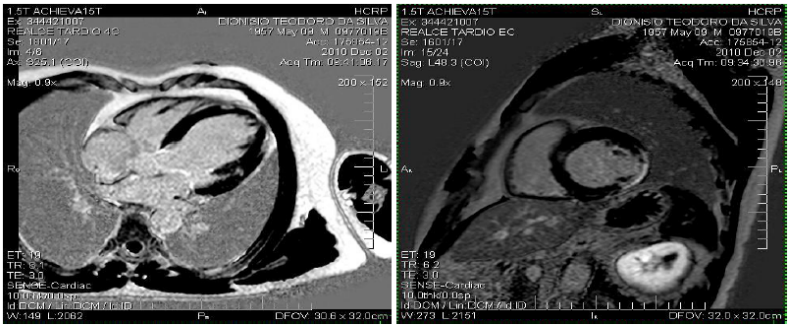
ERRATUM

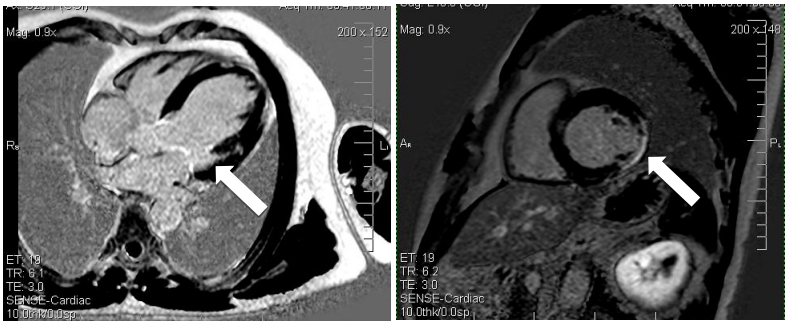
In the March / April (2018) issue vol. 31(2), p. 183

In the manuscript "Chagas Disease Cardiomyopathy", DOI number: : 10.5935/2359-4802.20180011, published in the International Journal of Cardiovascular Sciences, 2018;31(2)173-189, on page: 183, Figure 5 – Delayed enhanced images where fibrosis can be seen as the white area inserted in the (dark) muscle, indicated by arrows. Left panel shows a small mesomyocardial area in the LV lateral wall in a four-chambered image. Right panel shows extensive transmural impairment of the posterolateral wall.

Where it read:



Now it reads:



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