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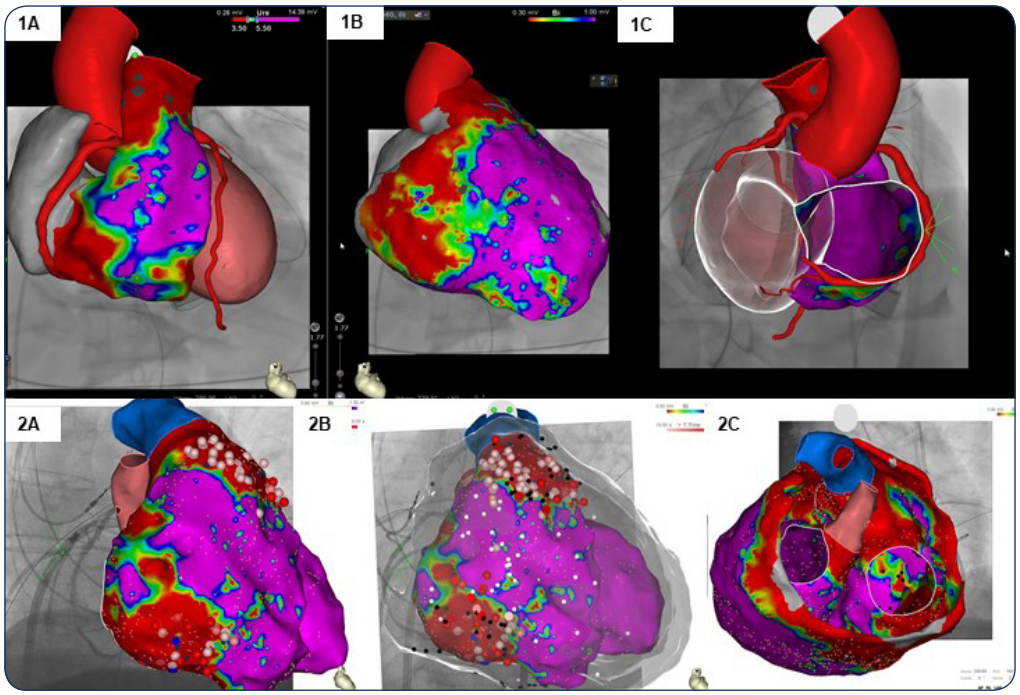

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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SUPPORT

Coronary Artery Calcium – From Screening to a Personalized Shared Decision-Making Tool: The New American Prevention Guidelines

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The United States (US) National Cholesterol Education Program (NCEP) formed the Adult Treatment Panel (ATP) in 1985 with the aim to educate clinician and provide guideline recommendations for the treatment of dyslipidemias. In its first 1998 recommendations, the approach to primary prevention of cardiovascular disease included LDL-cholesterol (LDL-C) reduction in individuals with more than two risk factors and LDL-C levels above 160mg/dL and optional treatment in those with "borderline" LDL-C levels between 130 – 159 mg/dL.[1] In its second version, in 1994, a category of secondary prevention with a target LDL-C below 100mg/dL was introduced.[2] In 2001 the third version of the document, ATP-III introduced the concept of "optimal" LDL-C < 100mg/dL and introduced the use of the 10-year Framingham risk score (FRS) for the estimation of risk to define the intensity of treatment and target LDL-C levels,[3] and an update of this document introduced a more aggressive LDL-C < 70 mg/dL target for those at extremely high risk. The ATP-III also mentions coronary artery calcium (CAC) as an "emerging risk factor", stating it could be of value for additional risk stratification, predominantly in intermediate risk groups. Interestingly, at this point the recommendations were that CAC could be of use in individuals with multiple risk factors or older individuals in whom "traditional risk factors lose some of their predictive power". In both cases CAC was proposed as a tool to screen for individuals at an even higher than expected risk, though the ATP-III clearly advised against the widespread use of CAC as a screening tool.

After the update of ATP-III there was a considerable gap before the publication of the 2013 ACC/AHA Blood Cholesterol guidelines,[4] and a completely new approach towards the selection of candidates for treatment of LDL-C was taken. First, this document updated the equations for calculating 10-year cardiovascular risk (the Framingham Risk Score only predicted risk of coronary heart disease). Second, it identified higher risk groups which should be treated irrespective of risk (LDL-C > 190 mg/dL, diabetics). Third, it proposed a much broader recommendation of statin use for primary prevention including all individuals with LDL-C > 70 mg/dL and a calculated atherosclerotic cardiovascular disease risk > 5% in 10 years. This broader approach has been criticized by many , as it resulted in a substantial increase in the number of individuals in whom statins would be recommended,[5] including treatment recommendations of lower risk individuals due to overestimation of risk derived from the risk assessment tool.[6] This document also gave CAC a class IIb indication for a selective use in individuals fitting the vague description "in whom the decision to start treatment was unclear". In this document additional markers of risk included CAC, high sensitivity C-reactive protein, ankle braquial index, family history of premature cardiovascular disease or individuals with LDL-C > 160 mg/dL – and all were given similar IIb recommendations with little to differentiate their predictive power. As recommended in ATP-III, the use of those markers was as an additional screening tool to identify individuals with a higher risk for more aggressive treatment, though no clear recommendation on its use was provided.

The history of treatment recommendation of dyslipidemias in primary prevention in Brazil follows a similar pattern, with an initial consensus published in 1994 where basic definitions of dyslipidemias were given but no clear recommendations or LDL-C targets were defined. In its fifth recommendation, the Brazilian Society of Cardiology included for the first time the use of CAC as an "aggravating" risk factor, and suggested a more aggressive treatment of individuals with CAC > 100 or above the 75th percentile,[7] yet this was still a recommendation of CAC as a screening tool to identify higher risk individuals.

The most recent update of the US recommendations provided several changes to prior recommendations. First, an intermediate risk group was reincorporated as part of the risk stratification. In the new guidelines individuals with a 10 year risk < 5% are considered low risk, those between 5–7.5% are considered borderline, those between 7.5–20% are considered intermediate risk and those above 20% are considered high risk individuals. The recognition of borderline and intermediate risk groups can be interpreted as a need to recognize the considerable uncertainty let from the risk estimations currently used in practice. While treatment strategies are probably well defined for the majority of individuals in the extremes of risk, a considerable proportion of the population still lies in the two "gray zone" groups were uncertainty in the recommendation may arise during the clinician-patient risk discussion.

This, in fact, highlights another aspect of the new guidelines. The document highlights the need for shared decision making before any new medication prescription including a discussion of risks and benefits of pharmacological and

Keywords

Cardiovascular Diseases/prevention and control; Dyslipidemias/prevention and control; Health Care/Public Health); Decision Making; Cholesterol,LDL; Risk Factors; Calcium Score.

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non-pharmacological treatment strategies. Particularly for those individuals at intermediate, and maybe borderline, risk one may expect considerable uncertainty in the need for therapy for many individuals. For this group of patients, the guidelines recommend considering additional risk factors as potential tools to favor pharmacological treatment.

For the use of CAC, a completely new approach has been proposed. Instead of a tool used only to selected higher risk individuals in whom treatment should be more aggressive, CAC is now proposed as a two-way tool (can move individuals both up and down the risk spectrum) for individuals in who treatment might be considered. On the one hand, if CAC = 0, pharmacologic treatment can be withheld or delayed for most individuals, whereas CAC > 0 favors treatment, particularly if > 100 units, > 75th percentile or if > 0 in individuals younger than 55 years old.

This unique ability of CAC to "derisk" individuals of intermediate risk is not trivial. In this group approximately, half of the population has a CAC = 0 and could be withheld for treatment for a considerable follow up.[8] Based on these new recommendations, a considerable reduction in the need for treatment can be anticipated in CAC is implemented as recommended. Interestingly, some data suggests that this approach can be cost effective from a societal perspective.[9]

Still, some gaps in knowledge still remain for the widespread use of this strategy. First, the guidelines highlight that this approach might not be recommended in diabetics, smokers and individuals with a history of premature cardiovascular disease, though this is largely based on the limited data available for those subgroups rather than on evidence of harm. Second, this approach is not supported by randomized clinical trial, though trials in this area have been proposed. While some have also cautioned on the use of radiation, the current exposure from a CAC scan (0.89 mSv), less than one third of the annual background radiation exposure. Finally, a major gap in the widespread use of CAC both in the US and in Brazil is the current lack of reimbursement by most health care providers or the public system in Brazil.

Despite those areas in need of further study and challenges in implementation, the new approach towards individualized risk assessment and shared decision making with the optional inclusion of CAC as part of the decision-making toolkit is a huge step toward a more precise treatment targeted at the individual's preferences.

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Rapamycin Combined with α-Cyanoacrylate Contributes to Inhibiting Intimal Hyperplasia in Rat Models

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Abstract

Background: Vein graft restenosis has an adverse impact on bridge vessel circulation and patient prognosis after coronary artery bypass grafting.

Objectives: We used the extravascular supporter α-cyanoacrylate (α-CA), the local application rapamycin/sirolimus (RPM), and a combination of the two (α-CA-RPM) in rat models of autogenous vein graft to stimulate vein graft change. The aim of our study was to observe the effect of α-CA, RPM, and α-CA-RPM on vein hyperplasia.

Methods: Fifty healthy Sprague Dawley (SD) rats were randomized into the following 5 groups: sham, control, α-CA, RPM, and α-CA-RPM. Operating procedure as subsequently described was used to build models of grafted rat jugular vein on carotid artery on one side. The level of endothelin-1 (ET-1) was determined by enzyme-linked immunosorbent assay (ELISA). Grafted veins were observed via naked eye 4 weeks later; fresh veins were observed via microscope and image-processing software in hematoxylin-eosin (HE) staining and immunohistochemistry after having been fixed and stored" (i.e. First they were fixed and stored, and second they were observed); α-Smooth Muscle Actin (αSMA) and von Willebrand factor (vWF) were measured with reverse transcription-polymerase chain reaction (RT-PCR). Comparisons were made with single-factor analysis of variance and Fisher's least significant difference test, with $p < 0.05$ considered significant.

Results: We found that intimal thickness of the α-CA, RPM, and α-CA-RPM groups was lower than that of the control group ($p < 0.01$), and the thickness of the α-CA-RPM group was notably lower than that of the α-CA and RPM groups ($p < 0.05$).

Conclusion: RPM combined with α-CA contributes to inhibiting intimal hyperplasia in rat models and is more effective for vascular patency than individual use of either α-CA or RPM. (Arq Bras Cardiol. 2019; 112(1):3-10)

Keywords: Myocardial Revascularization/surgery; Cyanocrylates; Sirolimus; Hyperplasia; Graft Occlusion, Vascular; Vascular Patency; Rats.

Introduction

Coronary artery bypass grafting (CABG) is one of the main therapies for coronary heart disease. However, 40% of bridge vessels are totally obstructed and 30% of bridge vessel blood flow is reduced after CABG, which seriously affects patient survival and prognosis.[1,2] Mechanisms of restenosis include thrombosis, intimal hyperplasia, and atherosclerosis. Immigration of endothelial cells and vascular smooth muscle cells is vital for intimal hyperplasia, which is the main cause of restenosis.[3]

Although drugs for inhibiting cytokinin and cell cycle regulation contribute to inhibiting intimal hyperplasia, the systemic side effects are harmful for patients. Therefore, local application is very important. Rapamycin (sirolimus) is widely used for anti-rejection after transplant operations, and drug-eluting stents are widely used in coronary arteries. Researchers have found that applying rapamycin to grafted veins is effective in inhibiting intimal hyperplasia by inhibiting proliferation and promoting apoptosis of smooth muscle cells.[4]

In 1963, Parsonnet et al. observed that perivenous supporters were effective for vascular patency.[5] Subsequently, basic and clinical researchers found that perivenous supporters could enhance patency rates by reducing intimal hyperplasia in grafted veins. α-CA, which is liquid at room temperature, is harmless to the human body. Degradation time is 1-3 months, depending on the dosage. α-CA is used in surgery for bleeding closure and wound binding.[6]

α-CA and RPM are usually used as perivenous supporters and local applications, respectively. We innovatively investigated the pathophysiological process of neointima hyperplasia in grafted veins after CABG via rat models of autogenous vein graft. We are interested in finding new methods to inhibit intimal hyperplasia.

Methods

Reagent and method

α-CA (99% n-octyl-α-cyanoacrylate + n-butyl-α-cyanoacrylate) was purchased from Beijing Fuaile Science and Technology Development Co. (Beijing, China). RPM was purchased from Selleck Company. We dissolved 8 mg of RPM in

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1 ml of α-CA (taken by pipette) in a sterile EP tube. A magnetic stirrer was then used to mix them to α-CA-RPM of 8 mg/ml, stored in a refrigerator between 2-8°C. RPM was hydrosolvent, prepared by the same method.[7]

Models and groups

Fifty SD rats (provided by Anhui Lab Animal Research Center and identified by the medical ethics committee of Anhui Medical University), male and female, aged 10-12 weeks, weighing 220-280 g, were randomized (completely randomized design) into 5 groups, each group containing 10 rats, and fed for 4 weeks after operation. Operating procedure and sample size were determined according to pilot experiments and previous studies, as subsequently described.

Operating procedure: an intraperitoneal injection of 10% chloralic hydras was used to anaesthetize rats. Heparin (700 IU/Kg) was injected through the caudal vein to induce heparinization. A vertical incision of approximately 1 cm was made in the middle of the neck (deflected to the operation side), and veins were dissociated on one side. Epitheca of 1-2 mm were taken from 20G red arterial puncture needle (BD Company), used as cannula. The carotid artery was isolated until the branches. Then two suture traction lines and hemoclips were placed at both ends of the artery to block blood flow. The middle of the artery was isolated and turned carefully to 1-1.2 mm above the cannula. A 6/0 silk suture was used to knot and fix in order to isolate the vein from arteries; we were then able to open vascular clamps. The incision was sutured after we verified that the pulse of the grafted vein was normal and there was no bleeding. We checked rats' vital status and incisions every day. We maintained the environment cool, changed their bedding regularly, and gave them sufficient fodder and water. Three days after the operation, 400,000 IU penicillin were delivered via intramuscular injection to every rat on a daily basis.

Sham group: we merely simulated the operation process. Jugular veins were dissociated and collateral vessels were ligatured, without dividing or transplanting; Control group: jugular arteriovenous graft on the same side; α-CA group: jugular arteriovenous graft and application of α-CA glue to grafted veins; RPM group: jugular arteriovenous graft and application of RPM to grafted veins; α-CA-RPM group: jugular arteriovenous graft on the same side and application of α-CA-RPM to grafted veins.

Collection of samples

Blood samples were taken preoperatively at 0 h and postoperatively at 12 h, 36 h, and 4 weeks after operation. Serum was collected by centrifugation and stored at -80°C until cytokine analysis. Four weeks later, we collected each group's vein sample. Fully anaesthetized rats were fixed on the operating table, heparinized as previously described and operated in the same way through the same path. We observed grafted veins' shapes and circulation and ligatured and isolated vessels at both ends of cannulas; we then removed intact and fresh veins and washed lumens fully with normal saline. Samples with HE staining and immunohistochemistry were placed in microtubes full of paraformaldehyde. Samples with RT-PCR were placed in microtubes full of RNA-EZ regents and then kept in the fridge at -80°C. Rats were euthanized by cervical dislocation method and handled properly.

Enzyme-linked immunosorbent assay for ET-1

ET-1 was determined by ELISA Kits (R&D, USA) using 50 μl of serum for the assay. Three measurements were performed for each blood sample. The ELISA plate was read at 450 nm in a plate reader.

Histological examination of graft tissue

Immersed in formalin, grafted veins were cut into 4 mm sections. Hematoxylin-eosin (HE) staining was subsequently performed using a hematoxylin and eosin staining kit (Beyotime Biotechnology, Shang Hai, China). Olympus microscope image acquisition system was used to collect section images (×100 objective lens) and measure intima thickness. Two independent researchers performed the measurements and data analysis. Sections were selected randomly from grafted and non-grafted veins; we then measured 16 points' thickness and calculated the mean. Three sections were selected and measured from every rat. We then calculated intima thickness.

Determination of proliferation index

Tissue sections were incubated with the immunohistochemistry analysis kit for proliferating cell nuclear antigen (PCNA) (Santa Cruz Biotechnology, Dallas, TX) at 4°C overnight. After washing with phosphate-buffered saline (PBS) (DAKO, Glostrup, Denmark) and incubating with the secondary antibody, color was developed using the DAB system. The tissue sections were dehydrated and installed on slides. All images (×200 objective lens) were captured by Olympus microscope image acquisition system and SPOT Digital Camera (Diagnostic Instruments, Sterling Heights, MI). PCNA-positive cells were counted in the intima. A total of 10 observation views were used to calculate the average percentage of PCNA-positive cells for each rat.

RT-PCR

Total RNA of the vessel tissues was isolated by the TRIzol Kit (Life Technology, USA). The RNA was reverse-transcripted to cDNA using the RNA reverse transcription kit (Promega, USA). 2 μg total RNA and 1 μl of random primer were denatured at 70°C for 10 min and annealed at 4°C for 10 min, and then 2 μl of 10× buffer, 2 μl of $MgCl_2$ (20.8 mol/l) and 1 μl of reverse transcriptase were added to the reaction system. Double distilled water (ddH_20) was added to bring the volume to 20 μl. The condition for cDNA synthesis was 37°C for 1 h and 4°C for 10 min. The PCR also contained 10 μl 2× SYBR Mixture (Takara, Japan), 7 μl ddH_20 and 1 μl forward and 1 μl reverse primers. The PCR conditions were 95°C for 5 min, 95°C for 15 s, 60°C for 60 s, and 40 cycles. The sequences of the primers used for RT-PCR were as follows: Forward, 5'-CATCTCCGTGGTCCTGAAGT-3' and reverse, 5'-GGCAAGGGAAACGTCTAGTG-3' for von Willebrand factor; forward, 5'-CAGAGTCCAGCACAATACCAG-3' and reverse, 5'-GACCCAGATTATGTTTGAGACC for α-Smooth Muscle Actin ; and forward, 5'-ACATGAATGACCTCGTCTCTGA-3' and reverse, 5'-CCTCTTCTTCTGCCTCCTCTCC-3' for GAPDH. The instrument for quantitative real-time PCR was purchased from ABI (USA).

Statistical analysis

All data were analyzed using statistical analysis software SPSS 17.0. Data are presented as mean ± standard deviation. Because data showed a normal distribution, comparison among multiple groups was analyzed by single-factor analysis of variance (ANOVA) and comparison between two groups was conducted by Fisher's least significant difference (LSD) test. A value of $p < 0.05$ was considered statistically significant.

Results

Rats survived well 4 weeks after operation

Operating procedure as previously described was used to build models of grafted rat jugular vein on carotid artery on one side. Post-operation, the transplanted veins were well filled and the blood vessels beat well; the glue was spread evenly over the surface of the veins in the α-CA and α-CA-RPM group. Rats' vital status and incisions were checked every day. Subsequently, we found that one rat in the RPM group and one rat in the α-CA group had died of low temperature 2 weeks after operation and the other rats survived and recovered well with strong pulse in grafted veins. The rats were euthanized 4 weeks after surgery; notably, there were only 2 rats who presented venous occlusion, one in the α-CA group and one the RPM group. Correspondingly, blood flow in other grafted veins was patent. Veins in the sham group slightly expanded. What is more, veins in the control group had new granulation tissue, thickened tubes, edema, and light stiffness; however, veins in the α-CA, RPM, and α-CA-RPM groups had few fresh tissues which were easily separated, with no obvious expansion and clear boundary from the surrounding, and the glue was not fully degraded (Figure 1).

α-CA-RPM reduced intimal thickening of the vein graft

In order to observe what impacts each group's intervention had on intimal hyperplasia, grafted veins were stained with HE 4 weeks after surgery. Afterwards, we used computer image analysis system to analyze intimal hyperplasia. This showed that the intima of the control group was strikingly thicker than that of α-CA group, RPM group, and α-CA-RPM group; the difference was statistically significant (91.3 ± 3.9, 133.6 ± 8.0, 50.6 ± 5.4 vs. 233.6 ± 29.1 μm, $p < 0.01$; Figure 2B, C, D, E and F); the intima of the RPM group was thicker than that of α-CA group; the difference was statistically significant (133.6 ± 8.0 vs. 91.3 ± 3.9 μm, $p < 0.05$; Figure 2C, D and F); the intima of α-CA group and RPM groups was thicker than that of α-CA-RPM group; the difference was statistically significant (50.6 ± 5.4 vs. 91.3 ± 3.9 μm, 133.6 ± 8.0 μm, $p < 0.05$; Figure 2 C, D, E and F). What is more, as shown in Figure 3, our results from immunohistochemical staining of PCNA demonstrate that the control, α-CA, RPM, and α-CA-RPM groups had a significantly higher proliferating index than the sham group ($p < 0.01$; Figure 3A, B, C, D, E and F), and the percentage of PCNA-positive cells in the α-CA, RPM, and α-CA-RPM groups was significantly less than in the control group ($p < 0.01$; Figure 3B, C, D, E and F). Moreover, it is worth noting that the proliferating index in the α-CA-RPM group was markedly less than in the α-CA or RPM group ($p < 0.01$; Figure 3C, D, E and F). Taken together, our results strongly demonstrate that α-CA, RPM, and α-CA-RPM inhibit intimal hyperplasia in vein grafts, and the effect of α-CA-RPM is stronger than that of α-CA or RPM.

α-CA-RPM diminished intimal hyperplasia and inflammatory responses

In order to further study the mechanism through which the three intervening methods prevent intimal hyperplasia, we examined the value of αSMA and vWF in grafted veins 4 weeks after surgery. The αSMA values in the α-CA, RPM, and α-CA-RPM groups were much lower than in the control group, as detected by RT-PCR ($p < 0.01$; Figure 4A). The αSMA values in the α-CA-RPM group were lower than in the α-CA and RPM groups ($p < 0.01$; Figure 4A). Similar results were found in the value of vWF in α-CA-RPM group ($p < 0.01$; Figure 4B). This result verified that α-CA, RPM, and α-CA-RPM inhibition might reduce intimal hyperplasia by blocking αSMA and vWF over-expression.

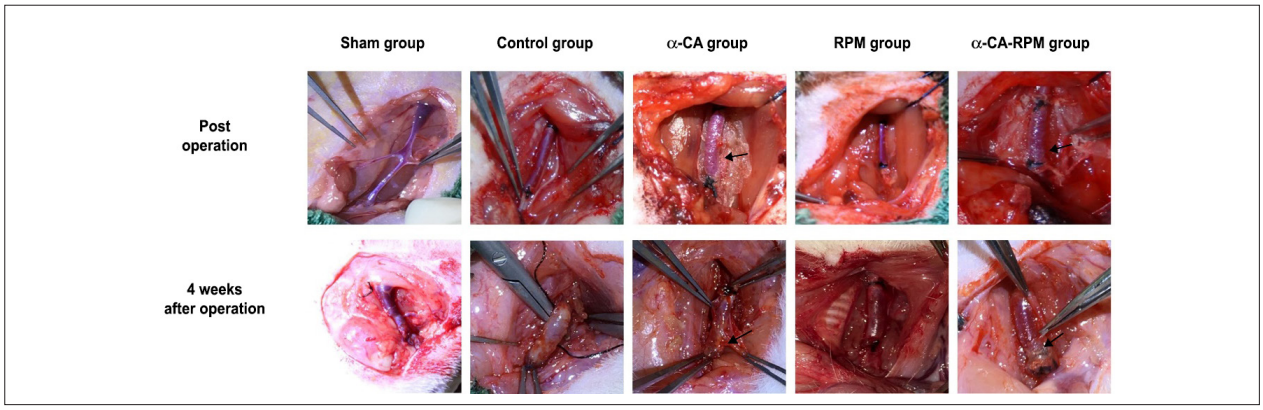

Figure 1 – *Rats survived well 4 weeks after operation. Operating procedure as previously described was used to build models of grafted rat jugular vein on carotid artery on one side. Post-operation, the transplanted veins are well filled and the blood vessels beat well, and the glue was spread evenly over the surface of the veins in the α-CA and α-CA-RPM groups (arrow). Four weeks after operation, veins in the sham group slightly expanded; the control group had new granulation tissue, thickening tubes, edema and light stiffness; the α-CA group had few fresh tissues which were easily separated, with no obvious expansion and clear boundary from the surrounding, and the glue was not fully degraded (arrow); the RPM group had clear boundaries from the surrounding tissue, and they were fresh and no obvious expansion. The general form of α-CA-RPM group was similar to α-CA group.*

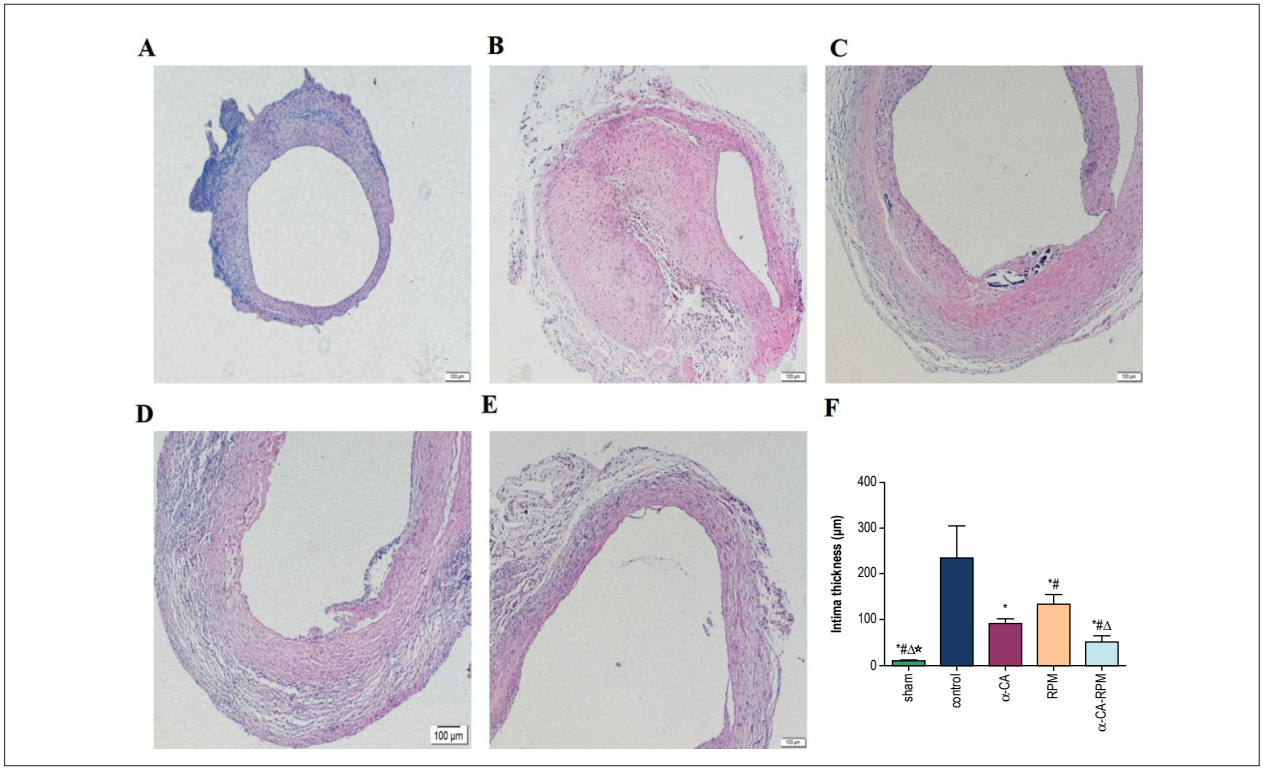

Figure 2 – *α-CA-RPM reduced intimal thickening of the vein graft. The vessel tissue was harvested 4 weeks after the operation, fixed in formalin, sliced to 4 μm tissue sections and stained with HE. Images (×100 objective lens) were collected and analyzed by Olympus micro-imaging system. The rats were divided into 5 group: Sham group (A), control group (B), α-cyanoacrylate group (C), Rapamycin group (D) and α-CA-RPM group (E). (F) Represented the statistical graph of each group's intima thickness. The intima of control group was dramatically thicker than that of α-CA, RPM and α-CA-RPM groups; the difference was statistically significant (91.3 ± 3.9, 133.6 ± 8.0, 50.6 ± 5.4 vs. 233.6 ± 29.1 μm, p < 0.01); the intima of the RPM group was thicker than that of α-CA group (133.6 ± 8.0 vs. 91.3 ± 3.9 μm, p < 0.05); the intima of α-CA group and RPM group was thicker than that of α-CA-RPM group (50.6 ± 5.4 vs. 91.3 ± 3.9 μm, 133.6 ± 8.0 μm, p < 0.05). * The control group had obvious difference with other groups, p < 0.05. # The α-cyanoacrylate group had obvious difference with other groups, p < 0.05. △ The rapamycin group had obvious difference with other groups, p < 0.05. ☆ The α-CA-RPM group had obvious difference with other groups, p < 0.05.*

In order to investigate the effect of α-CA-RPM on inflammatory responses, we performed ELISA assays to examine serum levels of ET-1. We found the ET-1 level of the control, α-CA, RPM, and α-CA-RPM groups gradually increased 36 hours after operation; those of the control, α-CA, and RPM groups was still high 4 weeks after operation and that of the α-CA-RPM group had basically returned to normal. The ET-1 level in the control group was significantly higher than that of the α-CA, RPM, and α-CA-RPM groups 36 hours and 4 weeks after operation (96.1 ± 7.9 ng/l vs. 84.0 ± 10.9 ng/l, 79.5 ± 5.7 ng/l, and 72.7 ± 9.9 ng/l; 99.7 ± 7.7 ng/l vs. 87.1 ± 13.3 ng/l, 65.4 ± 23.4 ng/l, and 43.7 ± 20.1 ng/l; $p < 0.05$, respectively). Additionally, at 4 weeks after surgery, the ET-1 level of the α-CA-RPM group was significantly lower than in the α-CA, RPM, and control groups (43.7 ± 20.1 ng/l vs. 87.1 ± 13.3 ng/l, 65.4 ± 23.4 ng/l, and 99.5 ± 7.7 ng/l; $p < 0.05$, respectively) (Figure 4C). These findings indicate that α-CA, RPM, and α-CA-RPM seem to reduce inflammatory responses and that α-CA-RPM is more effective.

Discussion

The main finding of our study is that the application of α-CA, RPM, or α-CA-RPM can improve the patency of the vein graft in rat models by inhibiting intimal hyperplasia.[8] More importantly, the use of RPM combined with α-CA is more effective than either α-CA or RPM alone.

The complicated remodeling process of vessels leads to restenosis of vein grafts, but the exact mechanism is not explicit. Studies have shown that restenosis is related to dysfunction of intima endothelial cells, proliferation, immigration of vascular smooth muscle cells, adventitial fibroblasts, inflammatory reaction, shear force, and hemodynamic changes.[9,10] The pathological process of restenosis of bridge vessel may include early thrombosis, intimal hyperplasia, and atherosclerosis; intimal hyperplasia is the most important reason. When separating, ligaturing, dividing, transplanting, and revascularizing bridge vessels, factors such as aggregation of platelets and neutrophils, release of cytokine and chemokine, activation of transduction pathway, and enzymatic reaction may prompt hyperplasia of vascular smooth muscle cells and accumulation of endothelial cells. All these factors are expected to result in intimal hyperplasia, and restenosis of grafted vessels follows.[11,12]

In 1963, Parsonnet and colleagues first pointed out that extravascular supporters could enhance the patency rate of grafted veins.[5] Several foundational and clinical tests have proved that extravascular supporters could inhibit intimal hyperplasia and enhance patency rate. Four extravascular

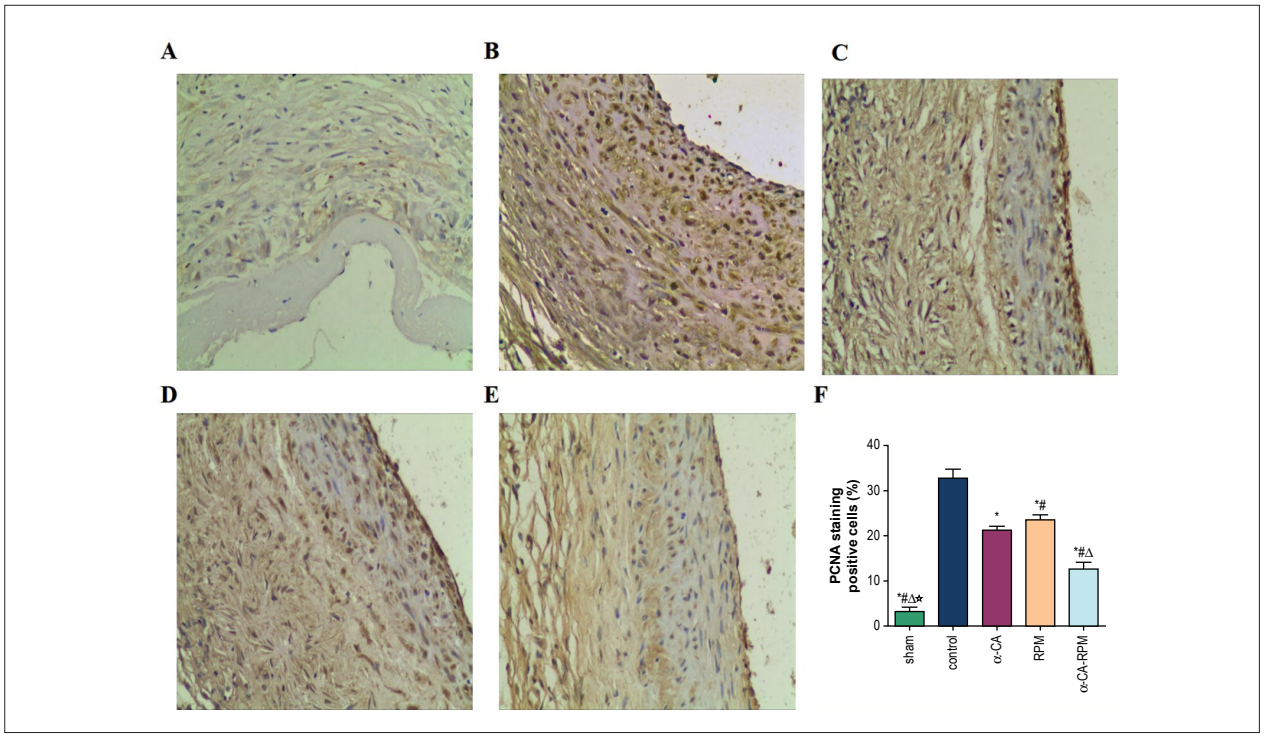

Figure 3 – *α-CA-RPM decreased the proliferating index of vein graft. The vessel tissue was harvested 4 weeks after the operation, fixed with formalin, sliced to 4 μm tissue sections and stained with the primary antibody anti-PCNA. Images (×200 objective lens) were collected and analyzed by Olympus micro-imaging system. Likewise, the rats were also divided into 5 group: Sham group (A), control group (B), α-cyanoacrylate group (C), Rapamycin group (D) and α-CA-RPM group (E). (F) Represented the statistical graph of each group's PCNA proliferation index. * The control group had obvious difference with other groups, p < 0.01. # The α-cyanoacrylate group had obvious difference with other groups, p < 0.01. △ The rapamycin group had obvious difference with other groups, p < 0.01. ☆ The α-CA-RPM group had obvious difference with other groups, p < 0.01.*

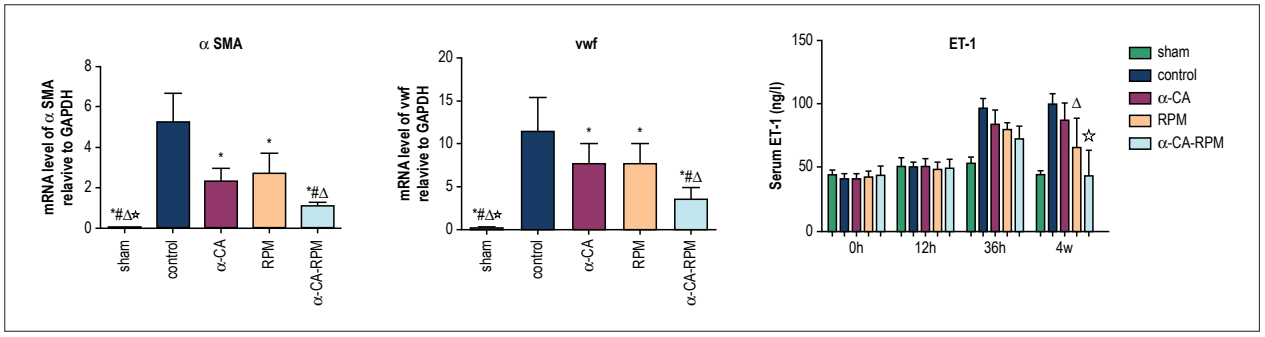

Figure 4 – *α-CA-RPM diminished the expression of αSMA and vWF and inflammatory responses. Four weeks after the surgery, RT-PCR was used to detect αSMA and vWF in grafted veins. (A) Value of αSMA in α-CA, RPM, and α-CA-RPM groups was much lower than in the control group, as detected by RT-PCR. Value of αSMA in α-CA-RPM group was lower than that of α-CA group and RPM group (p < 0.01). (B) Similar results were found in the value of vWF in α-CA-RPM group (p < 0.01). (C) The serum levels of ET-1 are shown for each group at different times. The level of ET-1 in the control group was significantly higher than that in the α-CA, RPM and α-CA-RPM groups 36 hours and 4 weeks after operation (96.1 ± 7.9 ng/l vs. 84.0 ± 10.9 ng/l, 79.5 ± 5.7 ng/l and 72.7 ± 9.9 ng/l; 99.7 ± 7.7 ng/l vs. 87.1 ± 13.3 ng/l, 65.4 ± 23.4 ng/l and 43.7 ± 20.1 ng/l; p < 0.05, respectively). Additionally, at 4 weeks after surgery, the level of ET-1 of the α-CA-RPM group was significantly lower than that of the α-CA, RPM, and control groups, (43.7 ± 20.1 ng/l vs. 87.1 ± 13.3 ng/l, 65.4 ± 23.4 ng/l and 99.5 ± 7.7 ng/l; p < 0.05, respectively). * The control group had obvious difference with other groups, p < 0.01. # The α-cyanoacrylate group had obvious difference with sham group, control group and α-CA-RPM group, p < 0.01. △ The rapamycin group had obvious difference with sham group, control group and α-CA-RPM groups, p < 0.01. ☆ The α-CA-RPM group had obvious difference with other groups, p < 0.01.*

supporters have been widely used in foundational and clinical tests, i.e., nitinol extravascular stent, polymeric extravascular stent, fibrin glue extravascular supporter, and α-CA. It is acknowledged that α-CA not only can prevent post-transplantation vessels from expansion, but also can prompt vascular smooth muscle cells' migration to vascular outer membrane.[13,14] Stimulated by α-CA, many neutrophils and monocytes aggregated to adventitia, especially mononuclear phagocytes which can release amounts of chemotactic factors to attract vascular smooth muscle cells and fibroblast immigration and colonization.[15] A series of changes mentioned above will activate a range of antiatherosclerotic

factors: NO, PGI2, cAMP and cGMP. They can also decrease intimal cholesterol and inhibit pro-atherosclerotic factors.[16] Outcomes in our experiment revealed that veins in the α-CA group had few fresh tissues and were easy to separate and had clear boundary from the surrounding tissues 4 weeks after the operation. The glue was not fully degraded and the intima of α-CA group was thinner than in the control group. Additionally, the percentage of PCNA-positive cells was significantly less than in the control group. Most importantly, α-CA as the extravascular supporter was able to inhibit intimal hyperplasia and enhance the patency rate.

The proliferation, immigration, and secretion of vascular smooth muscle cells are key to intimal hyperplasia, which contribute to restenosis of vein grafts. Although certain drugs are effective for inhibiting intimal hyperplasia by inhibiting cytokinin and regulating cell cycle, severe toxic reactions and side effects limit their extensive use, as a consequence of which local application becomes particularly significant. RPM, colchicine, and other drugs are used locally on grafted veins. After anastomosis, these drugs are smeared evenly on grafted veins. RPM can accelerate vascular smooth muscle cells' apoptosis by inhibiting the transformation of cells from G1 to S phase, thus suppressing vascular smooth muscle cells' proliferation and immigration. Additionally, RPM protects endothelial cell function and reduces the release of vasoactive peptide when endothelial cells get injured.[17-19] Furthermore, RPM can also inhibit the differentiation, proliferation, and immigration of endothelial progenitor cells (EPC) and reduce NOS-mRNA expression in EPC.[20,21] Our results verified that veins in the RPM group had clear boundaries from the surrounding tissue; they were also fresh and clearly not expanded. Moreover, the intima of the RPM group was thinner than the control group's and the percentage of PCNA-positive cells was remarkably lower than in the control group. In summary, RPM may inhibit intimal hyperplasia and enhance patency rate.

This study aimed to experiment the combination of an extravascular supporter and a local drug application. We chose α-CA as the extravascular supporter, RPM as the local application, and α-CA-RPM as the combination. α-CA-RPM was used in rat models of autogenous vein graft to stimulate grafted veins' pathophysiological process after CABG. Interestingly, we found the percentage of PCNA-positive cells in the α-CA-RPM group was markedly less than in the control, α-CA, and RPM groups, which indicated that α-CA-RPM was more effective in inhibiting intimal hyperplasia than either α-CA or RPM separately. We concluded that α-CA-RPM can combine the effectiveness of extravascular supporters and local drugs and thus better inhibit intimal hyperplasia. Meanwhile, α-CA is an ideal carrier for the formulation of long-term control drug release which surrounds the vein graft tightly so that RPM will be released slowly and no RPM will be wasted.

The endothelin-1 (ET-1) has been implicated in the pathogenesis of restenosis and vascular hypertrophy via enhancing aggregation of platelets and neutrophils, release of cytokine and chemokine, accumulation of endothelial cells, and promotiong of vascular smooth muscle cell migration towards the intimal layer.[22] Our results indicate that α-CA, RPM, and α-CA-RPM can stabilize endothelial cell function and diminish the release of ET-1 to inhibit intimal hyperplasia. An endothelin A/B receptor antagonist contributed to reduction of intimal hyperplasia in an organ culture of human saphenous veins and prevented neointimal development of coronary angioplasty in pigs, which is in accordance with our experiment.[23,24] αSMA is the specific protein of vascular smooth muscle cells and the expression of αSMA can reflect the hyperplasia of vascular smooth muscle cells. In our experiment, we examined the values of αSMA in grafted veins with RT-PCR and found that the values in the α-CA, RPM, and α-CA-RPM groups was lower than in the control group. Notably, the value of the α-CA-RPM group was lower than that of the α-CA and RPM groups. A study in which the αSMA component of vascular progenitor cells correlated with the coronary artery Gensini score also made the same point.[25] An experiment in a swine model of arteriovenous bypass grafting also provided tangible evidence to support this point of view.[26]

The vWF is a glycoprotein encoded by the short arm of chromosome 12 and can be combined with collagen fibers and platelets; it is closely related to a range of cardiovascular diseases such as atherosclerosis, acute coronary syndrome, and atrial fibrillation.[27] vWF directly stimulates vascular smooth muscle cell proliferation, resulting in a direct dose-response effect. It also accelerates intimal hyperplasia in intact endothelium without platelet activation or platelet-derived growth factor release.[28] Likewise, we found the vWF values of the α-CA, RPM, and α-CA-RPM groups was lower than that of the control group, and the α-CA-RPM group was lower than the α-CA or RPM groups. Our results in rats have been supported by experiments in other animals, such as an efficacy study in dogs and intimal hyperplasia of rabbit carotid arteries.[29,30] These results demonstrate that α-CA, RPM, and α-CA-RPM might reduce intimal hyperplasia by blocking ET-1, αSMA, and vWF overexpression.

Our results show that rapamycin combined with α-cyanoacrylate contributes to inhibiting intimal hyperplasia and is more effective for vascular patency than individual use of either α-CA or RPM in rat models 4 weeks after operation. The long-term effects of α-CA-RPM on vein graft remodeling are still unclear. Our team will conduct further research on intimal hyperplasia pathophysiological processes in pigs after CABG and the impacts of related interventions on grafted veins.

Conclusion

Our results confirmed that α-CA-RPM contributes to inhibiting intimal hyperplasia and is more effective for vascular patency than individual use either α-CA or RPM in rat models of artery bypass grafting. The positive effects appear to be associated with decreased intimal thickening, reduced cell proliferation in the vein graft, and decreased inflammatory responses. Although the shor-term effects of α-CA-RPM seem promising, the long-term effects and clinical significance of α-CA-RPM in CABG need to be studied in the future.

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Author contributions

Conception and design of the research: Tianshu-Chu, Congrong-Gao, Zhiwei-zhao; acquisition of data: Tianshu-Chu, Fei-Ling, Ayu-Sun; analysis and interpretation of the data: Tianshu-Chu, Jing-Cao, Yuanbiao-Zheng, Jianjun Ge; statistical analysis: Tianshu-Chu, Congrong-Gao, Zhiwei-zhao; writing of the manuscript: Tianshu-Chu, Congrong-Gao, Fei-Ling, Ayu-Sun; critical revision of the manuscript for intellectual content: Tianshu-Chu, Congrong-Gao, Zhiwei-zhao, Fei-Ling, Ayu-Sun, Jianjun Ge.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Tianshu-Chu, from Anhui Medical University.

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the Anhui Animal Ehtics Committee under the protocol number ah56743.

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Synergy of Rapamycin and Cyanoacrylate in Reducing Intimal Hyperplasia

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Short Editorial related to the article: Rapamycin Combined with α-Cyanoacrylate Contributes to Inhibiting Intimal Hyperplasia in Rat Models

Myocardial revascularization (CABG) surgery remains one of the main therapies for coronary disease. However, vascular disease that follows CABG remains a challenge to medicine. The mechanical, molecular and cellular changes undergone by the venous vascular graft when inserted into the coronary artery flow culminate in thrombosis, intimal hyperplasia, and atherosclerotic process, and end with restenosis.[1,2]

CABG experimental models were crucial to the understanding of mechanisms present in the course of vascular disease. The vascular graft model with anastomosis of the external jugular vein with the carotid artery represents an experimental model of vascular disease similar to that occurring after CABG. Pigs, rabbits, and rats may be used in this model because of protocol reproducibility, cost, and benefit.[3,4]

Strategies interfering with the mechanisms of vascular disease after CABG may reduce venous graft restenosis. Rapamycin, an immunosuppressive, showed antiproliferative effect of vascular smooth muscle cells in experimental models.[4,5] Tianshu-Chu et al.,[6] in an experimental study in rats that reproduces vascular disease after CABG, demonstrated that the combination of rapamycin and cyanoacrylate showed synergy to prevent intimal thickening. The combination of rapamycin and cyanoacrylate inhibited cell proliferation, primarily of dedifferentiated vascular smooth muscle cells (myofibroblasts) and vascular cells, preventing intimal hyperplasia, extracellular matrix deposition and neoangiogenesis. Thus, the combination of rapamycin with cyanoacrylate shows synergy when compared to the isolated use.

Keywords

Coronary Artery Diseases; Myocardial Revascularization; Vascular Diseases; Imunosupressive Agents; Cianoacrilates; Hyperplasia; Rats.

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Assessment of the Relationship between Monocyte to High-Density Lipoprotein Ratio and Myocardial Bridge

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Abstract

Background: Assessing the monocyte to high-density lipoprotein ratio (MHR) is a new tool for predicting inflamation, which plays a major role in atherosclerosis. Myocardial bridge (MB) is thought to be a benign condition with development of atherosclerosis, particularly at the proximal segment of the brigde.

Objective: To evaluate the relationhip between MHR and the presence of MB.

Methods: We consecutively scanned patients referred for coronary angiography between January 2013- December 2016, and a total of 160 patients who had a MB and normal coronary artery were enrolled in the study. The patients' angiographic, demographic and clinic characteristics of the patients were reviewed from medical records. Monocytes and HDL-cholesterols were measured via complete blood count. MHR was calculated as the ratio of the absolute monocyte count to the HDL-cholesterol value. MHR values were divided into three tertiles as follows: lower (8.25 ± 1.61), moderate (13.11 ± 1.46), and higher (21.21 ± 4.30) tertile. A p-value of < 0.05 was considered significant.

Results: MHR was significantly higher in the MB group compared to the control group with normal coronary arteries. We found the frequency of MB ($p = 0.002$) to increase as the MHR tertiles rose. The Monocyte-HDL ratio with a cut-point of 13.35 had 59% sensitivity and 65.0% specificity (ROC area under curve: 0.687, 95% CI: 0.606–0.769, $p < 0.001$) in accurately predicting a MB diagnosis. In the multivariate analysis, MHR ($p = 0.013$) was found to be a significant independent predictor of the presence of MB, after adjusting for other risk factors.

Conclusion: The present study revealed a significant correlation between MHR and MB. (Arq Bras Cardiol. 2019; 112(1):12-17)

Keywords: Biomarkers/blood; Cholesterol, HDL/blood; Monocytes/citology; Myocardial Bridging; Atherosclerosis; Inflammation.

Introduction

Myocardial bridge (MB), which was described early in the cardivascular literature, is an anatomical variation characterized by the narrowing of some of the epicardial coronary arterial segments during systole. MB, also known as muscular bridge, is a rare congenital disease with a relatively good prognosis.[1-3] It has an estimated frequency of 0.5-2.5% in angiographic series, and it frequently involves the left anterior descending artery.[1] Although it is considered a benign anomaly, it may lead to complications such as angina pectoris, acute myocardial infarction, coronary spasm, arrhythmias, syncope, and sudden cardiac death.[4,5] Systolic compression of the epicardial artery is visible on angiographic imaging. Diagnosis can be made using quantitative angiography, intracoronary ultrasound, or Doppler flow measurement.[6-8]

Monocyte activation has been known to play an important role in chronic inflammation and cardiovascular disease, in which monocytes and differentiated macrophages can modulate inflammatory cytokines.[9] HDL is highly effective at inhibiting the endothelial expression of adhesion molecules and preventing monocyte recruitment to the artery wall.[9] Therefore, while monocytes exert a proinflammatory effect, HDL functions as a reversal factor during this process. Monocyte to HDL-cholesterol ratio (MHR) is a simple assessment method for inflammatory status.[10] MHR has also been reported as a new prognostic marker in cardiovascular diseases.

It is known that atherosclerosis is an inflammatory process and that MHR is a simple tool for assessing proinflamatory status.[9,10] Atherosclerosis has been shown to develop especially at the proximal and distal segments of MB in most patients.[11-13] In the present study, we evaluate the association between MHR and MB.

Methods

Study Population

We consecutively scanned patients referred for coronary angiography between January 2013- December 2016, and a total of 160 patients who had a MB and normal coronary

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artery were enrolled in the study. The patients' angiographic, demographic and clinic characteristics of the patients were reviewed from medical records. Patients with acute coronary syndrome, previous cardiac surgery, known coronary artery disease, concomitant valvular disease, cardiomyopathy, heart failure, atrial fibrillation, congenital heart defects, renal or hepatic disease, malignancy, hematological disorders, and acute or chronic inflammatory disorders were excluded from this study. The study was approved by the local ethics committee.

Angiographic analysis

Coronary angiography was performed using the standard Judkins' technique with a biplane cineangiography system. Coronary arteries in the left and right oblique planes and in the cranial and caudal angles were demonstrated. Iopromide (Ultravist-370; Schering AG, Berlin, Germany) was used as the contrast agent, and it was manually injected (4–6 ml of contrast agent in each position) during the coronary arteriography. All of the angiograms were evaluated by two experienced physicians. The presence of MB was defined according to the following criteria: narrowing of coronary vessel lumen during systole and dilation during diastole; no evidence of coronary vasospasm. Based on the findings of coronary angiography, the patients were divided in two subgroups: group A (n = 84) with normal coronary arteries; and group B (n = 76) with MB.

Laboratory measurements

Blood sample was collected from the antecubital vein using a 21-gauge sterile syringe in laboratory. Monocytes and HDL-cholesterols were measured via complete blood count. MHR was calculated as the ratio of the absolute monocyte count to the HDL-cholesterol value.

Statistical analysis

All the statistical data were analyzed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation, and the categorical data were expressed as percentages. Continuous variables were tested for normal distribution using Kolmogorov-Smirnov test. Both groups were compared using chi-square test or Fisher's exact test for qualitative variables when appropriate, and independent t-test for normally distributed continuous variables. The non-normally distributed continuous variables are presented as median and interquantile range. Pearson test was used in the correlation analysis between parametric variables. Receiver-operating characteristic (ROC) analysis was performed for MHR in order to determine optimal cut-off values and to obtain the sensitivity and specificity for each variable to predict the presence of MB. A multivariate logistic regression model was performed by including the parameters that differed significantly between the groups in order to identify the independent predictor of patients with MB. A p-value of < 0.05 was considered significant.

Results

Seventy-six MB (mean age: 52.3 ± 11.7 years, 82.0% male) and 84 age- and gender-matched control participants with normal coronary arteries (mean age: 53.8 ± 12.2 years, 75.0% male) were enrolled in this study.

Both groups' baseline demographics, as well as their clinic and laboratory characteristics, are summarized in Table 1. Diabetes mellitus and smoking were found to be lower in the MB group compared to the control group. There was no difference between two groups in terms of other demographic or clinic findings. When laboratory parameters were compared, creatinine, white blood cell and neutrophil were significantly higher in the MB group compared to the control group. However, HDL and total cholesterol were found to be significantly lower in the MB patients. Moreover, the monocyte/HDL ratio was found to be significantly higher in the MB group compared to the control group. The remaining laboratory parameters did not differ between both groups.

MHR values were divided into three tertiles as follows: lower (8.25 ± 1.61); moderate (13.11 ± 1.46); and higher (21.21 ± 4.30) tertile (Table 2). We found the frequency of MB ($p = 0.002$), male gender ($p = 0.04$) and the WBC count ($p < 0.001$) to increase as the MHR tertiles rose.

A receiver operating curve (ROC) was generated for sensitivity and specificity, with the respective areas under the curve (AUC), to investigate the predictive value of monocyte/HDL ratio for the presence of MB (Figure 1). The Monocyte/HDL ratio with a cut-point of 13.35 had 59.0% sensitivity and 65.0% specificity (ROC area under curve: 0.687, 95% CI: 0.606–0.769, $p < 0.001$) in accurately predicting MB diagnosis.

In a univariate regression analysis, age, gender, total cholesterol, neutrophil to lymphocyte ratio (NLR), and hemoglobin were significantly related with MB. In the multivariate analysis, MHR ($p = 0.013$) was found to be significant as the independent predictor of MB, after adjusting for other risk factors (Table 3).

Discussion

The main findings of the present study were as follows: 1) A raised monocyte/HDL ratio was found to be significantly higher in patients with MB; 2) The monocyte/HDL ratio with a cut-point of 13.35 had moderate sensitivity and specifity to diagnose MB; and 3) MHR was found to be a significant independent predictor for presence of MB, after adjusting for other risk factors in multivariate analysis.

Myocardial bridging, which is the compression of a coronary artery segment during systole, is generally accepted to be clinically benign, but it can result in a wide clinical spectrum, from angina to myocardial infarction.[12,14-16] In general, the coronary vessel segment proximal to the bridge has been reported to develop atherosclerosis at an increased rate – up to 90%.[12,14] However, one study has also demonstrated diffuse intimal thickening in the tunneled segment.[16] Besides the tunneled and proximal artery segments, other parts of the same coronary artery, as well as different arteries, could show atherosclerosis.[16] Endothelial cell morphology variations occur before and after tunneled segment due to blood flow shear stress.[1] Endothelial dysfunction, inflammation and unknown increased expression of vasoactive agents, such as endothelial nitric oxide synthase, endothelin-1, and angiotensin, all of which

Table 1 – Demographic, clinic and laboratory characteristics of the groups studied

Variables	Control	Myocardial bridge	p value
Age in years	53.8 ± 12.2	52.3 ± 11.7	0.435
Male gender, n(%)	63(%75)	62(%82)	0.315
Hypertension, n(%)	32(%38)	19(%25)	0.076
Diabetes mellitus, n(%)	18(%21)	6(%8)	0.017
Smoker, n(%)	36(%43)	19(%25)	0.018
Glucose, mg/dl	104 ± 23	97 ± 13	0.088
Creatinine, mg/dl	0.83 ± 0.18	0.95 ± 0.72	0.035
Hemoglobin, gr/dl	13.8 ± 1.8	14.3 ± 1.7	0.077
White blood cell count, x 10^3/L	7.4 ± 1.8	8.2 ± 2.1	0.018
Neutrophil count, x 10^3/L	4.28 ± 1.42	4.81 ± 1.57	0.021
Lymphocyte count x 10^3/L	2.31 ± 0.89	2.44 ± 0.75	0.121
Monocyte count x 10^3/L	0.56 ± 0.15	0.62 ± 0.21	0.149
RDW	14.4 ± 1.7	14.9 ± 1.6	0.060
PDW	15.2 ± 3.2	17.1 ± 2.9	< 0.001
Platelet count x 10^3/L	238 ± 59	255 ± 76	0.222
LDL cholesterol, mg/dl	123 ± 32	117 ± 27	0.168
HDL cholesterol, mg/dl	49 ± 12	39 ± 8	< 0.001
TG, mg/dl	152 ± 103	136 ± 54	0.909
Total cholesterol, mg/dl	200 ± 48	186 ± 32	0.021
MHR	12.20 ± 4.87	16.31 ± 6.47	< 0.001

RDW: red cell distribution width; PDW: platelet distribution width; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglyceride; MHR: mononcyte count/ HDL cholesterol ratio.

convert enzyme in the proximal segment of the MB artery, are the main pathophysiological mechanisms for increased atherosclerotic plaque formation.[13,17] Coronary angiography, intracoronary doppler ultrasonography, intravascular ultrasound, fractional flow reserve and cardiac computed tomography angiography are main tools for diagnosing coronary MB.[18]

Monocytes are a source of various cytokines and molecules that interact with endothelial cells, which leads to an aggravation of inflammatory pathways.[19] Inflamation play a major role in atherosclerosis development and progression.[10] HDL cholesterol, which has antiinflammatory, antioxidant, and antithrombotic properties, strongly decreases the endothelial expression of adhesion molecules and prevents monocyte recruitment to the artery wall.[20] Furthermore, HDL decrease pro-inflammatory and pro-oxidant effects of monocytes by inhibiting the migration of macrophages and the oxidation of the low-density lipoprotein (LDL) molecules, as well as by promoting the efflux of cholesterol from these cells.[21] Therefore, it seems logical to combine these two parameters into a single ratio as an MHR, which can reflect the underlying inflammation process. A prognostic value of MHR has been reported in various cardiovascular diseases.[22-24] MHR was found to be related with major cardiovascular adverse events (MACE) including stent thrombosis and mortality after primary percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) patients.[25] Moreover, it has been demonstrated to be a new potential marker for predicting bare metal stent restenosis.[26] An important association between pre-procedural MHR levels and atrial fibrillation recurrence after ablation procedures was demonstrated by the study of Canbolat et al.[24] MHR is alwo well demontrated to be associated with coronary slow flow and coronary actesia, which are different forms of inflammation and atherosclerosis.[10,27] Our study has reported, for the first time, an important relationship between admission MHR and the presence of MB. Moreover, and concordant with previous studies on various cardiovascular diseases, MHR was found to be a significant independent marker associated with MB, with moderate sensitivity and specifity.

The main pathophysiological links between MHR and MB can be endothelial dysfunction and inflammation. Inflammation not only leads to monocyte secretion and aggregation, but it also reduces HDL blood levels and its anti-oxidative feature.[10] Increased MHR was associated with systemic inflammation and endothelial dysfunction, and it was defined as a novel inflammation-based prognostic marker in cardiovascular diseases.[22-24] In our study, concordant with previous studies on cardiovascular disease, increased MHR was found to be related with the presence of MB, in whose pathophysiology inflammation plays a significant role.

Even though previous studies demonstrated that MHR is associated with systemic inflamation, we found in the present study that MHR is associated with MB. As generally known, a local atherosclerotic process is present in patients with MB, particularly in the proximal and distal segments of

Table 2 – Demographic, clinic and laboratory characteristics of the MHR tertiles

Variables	1st tertile (n:54)	2nd tertile (n:53)	3rd tertile (n:53)	p-value
MHR	8.25 ± 1.61	13.11 ± 1.46	21.21 ± 4.30	< 0.001
NLR	2.10 ± 1.35	1.98 ± 0.96	2.31 ± 1.16	0.332
Myocardial bridge, n(%)	16(%30)	26(%49)	34(%64)	0.002
Male gender, n(%)	37(%69)	41(%77)	47(%88)	0.041
Hypertension, n(%)	20(%37)	16(%30)	15(%28)	0.593
Diabetes mellitus, n(%)	8(%15)	10(%19)	6(%11)	0.553
Smoker, n(%)	13(%24)	19(%36)	23(%43)	0.105
Age	56 ± 11	55 ± 10	49 ± 14	0.006
White blood cell count, x 10^3/L	6.80 ± 1.63	7.80 ± 1.99	8.72 ± 1.88	< 0.001
Hemoglobin, gr/dl	13.5 ± 1.8	14.1 ± 1.5	14.5 ± 1.8	0.011
RDW	14.6 ± 1.9	14.6 ± 1.4	14.7 ± 1.6	0.973
Platelet count x 10^3/L	250 ± 65	240 ± 76	248 ± 63	0.739
PDW	9.2 ± 1.6	9.1 ± 1.5	9.1 ± 1.6	0.940
Glucose, mg/dl	100 ± 15	101 ± 21	101 ± 21	0.964
Creatinine, mg/dl	0.84 ± 0.17	0.85 ± 0.18	0.86 ± 0.16	0.703
LDL cholesterol, mg/dl	127 ± 31	121 ± 29	111 ± 27	0.020
HDL cholesterol, mg/dl	53 ± 11	43 ± 8	37 ± 8	< 0.001
TG, mg/dl	123 ± 47	153 ± 88	159 ± 104	0.060
Total cholesterol, mg/dl	204 ± 40	197 ± 46	179 ± 34	0.004

RDW: red cell distribution width; PDW: platelet distribution width; MHR: Mononcyte count/HDL cholesterol ratio; NLR: neutrophil / lymphocyte ratio; TG: triglyceride.

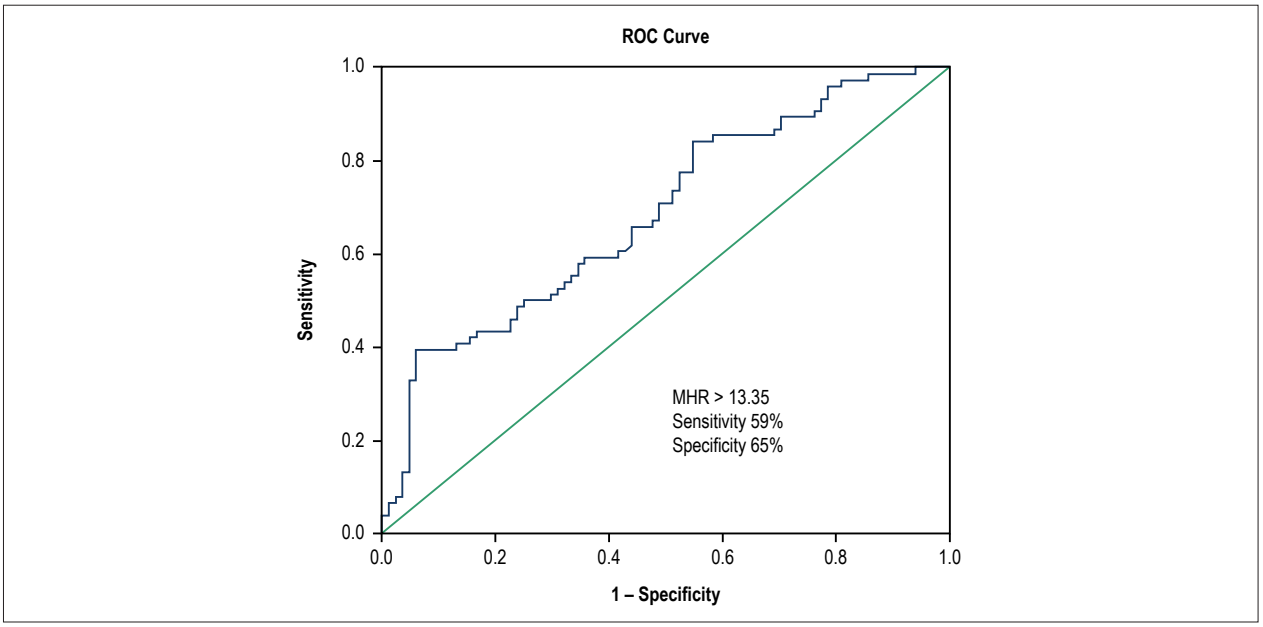

Figure 1 – *The receiver operative characteristic curve analysis of monocyte to high density lipoprotein cholesterol rate for predicting the presence of myocardial bridge.*

the MB. We suppposed that MHR could demonstrate not just systemic artheriosclerosis, but also local artheriosclerosis. With the addition of the local changes at the near of the MB atherosclerosis could be started earlier.

There are some limitations in our study. It was conducted with a small population, and it is a single-center study. Since we measured MHR only at baseline, serial MHR changes were not assessed. A prognostic value of MHR for MB was not

Table 3 – Multivariate analysis to detect independent variables for the diagnosis of myocardial bridge

Variables	Odds ratio	Confidence İnterval(%95)	p-value
Age	1.010	0.979 – 1.041	0.540
Gender	1.273	0.463 – 3.494	0.640
Total cholesterol	0.995	0.986 – 1.004	0.288
MHR	1.128	1.055 – 1.207	< 0.001
NLR	1.012	0.750 – 1.367	0.936
Hemoglobin	1.145	0.896 – 1.463	0.278

MHR: Mononcyte count/HDL cholesterol ratio; NLR: neutrophil / lymphocyte ratio.

determined due to a lack of follow-up of the study patients. Moreover, the effect of other inflamatory markers, like C-reactive protein, was not assesed due to a lack of records.

Conclusions

In conclusion, since increased MHR is a marker of inflammation and atheroclerosis, MB could be one of the factors associated with increased MHR.

Author contributions

Conception and design of the research: Enhos A, Bakshaliyev N; acquisition of data: Enhos A, Cosansu K, Huyut MA, Bakshaliyev N, Nadir A; analysis and interpretation of the data: Enhos A, Cosansu K, Huyut MA; statistical analysis: Turna F; obtaining funding: Enhos A, Cosansu K, Turna F, Karacop E, Nadir A; writing of the manuscript and critical revision of the manuscript for intellectual content: Enhos A, Karacop E, Ozdemir R, Uluganyan M.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Bezmialem Vakif Universty under the protocol number 342018. 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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A New Marker of Myocardial Bridge?

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Short Editorial related to the article: Assessment of the Relationship between Monocyte to High-Density Lipoprotein Ratio and Myocardial Bridge

Myocardial bridges (MBs) have been associated with an increased incidence of cardiovascular events. Even though the pathophysiology of this association is still elusive, it seems to be related to the development of atherosclerosis. This hypothesis is based on changes in blood flow resulting from systolic compression of coronary arteries and leading to changes in arterial wall shear stress, which could act as a proatherogenic event affecting the endothelium of the arterial segment proximal to the MB.[1]

Recently, Akishima-Fukasawa et al.[2] assessed 150 autopsies of individuals without cardiovascular heart disease to verify the influence of MBs on the development of atherosclerosis. The authors found the occurrence of MBs in 93 hearts, and using computer-assisted histomorphometry, observed a higher frequency of luminal stenosis in segments proximal to the MB. Using a multiple comparison test, the authors showed a relation between the presence of risk factors like hypertension, diabetes, and dyslipidemia to a higher rate of stenosis affecting segments located 2.5 cm proximally to the MB. Despite the absence of MB flow evaluation, the authors documented an anatomical association between significant atherosclerotic lesions and the presence of MBs.[2] We could speculate that this may be one of the explanations for the increased incidence of cardiovascular events in patients with MB.

The detection of MBs by imaging methods has increased with the use of cardiac computed tomography, which allows for multiplanar and three-dimensional evaluations. Studies using this method have reported prevalence rates of MBs ranging from 5% to 76%, depending on the population studied and the type of MB and equipment used for its detection.[3,4] However, the availability of this method for clinical use is limited.

In this issue of the *Arquivos Brasileiros de Cardiologia*, Enhos et al.[5] proposed that a newly described tool for the assessment of inflammation and atherosclerosis – the relationship between monocytes and high-density lipoprotein (HDL), abbreviated as MHR (monocyte-to-HDL-cholesterol ratio) – could be associated with atherosclerosis in segments proximal to an MB. The authors studied 160 patients with MBs and without significant coronary lesions and observed that at a cut-off value of 13.55, the MHR was able to detect the presence of MBs with a 59% sensitivity, 65% specificity, and an area under the ROC curve of 0.687 (95% confidence interval 0.606-0.769, $p < 0.001$). On multivariate analysis, the MHR emerged as an independent risk factor for the presence of MB. The authors attributed this association to the occurrence of endothelial dysfunction and inflammation in patients with MB.[5]

Monocytes have a fundamental role in the inflammatory cascade and participate actively in the development and progression of the atherosclerotic plaque, while HDL particles behave otherwise, reducing the expression of tissue factor in monocytes, hindering cell migration and LDL oxidation in the vascular wall.[6] Observations from biochemical assays have allowed a better understanding of the complex interactions between monocytes and HDL on atherogenesis, and both of them combined seem more appropriate to assess inflammation when compared with the measurement of each of them alone.[6]

The MHR has been associated with different clinical conditions with pathophysiological bases that include an inflammatory component. In regard to chronic coronary disease, Korkmaz et al.[7] studied 301 patients with intermediate lesions undergoing functional evaluation by fractional flow reserve (FFR) and found that those with an FFR ≤ 0.8 showed the highest MHR values (11.6 ± 3.3 vs. 12.6 ± 2.5, respectively)[7]. In another study, Akboga et al.[8] assessed the relationship between MHR and the SYNTAX score. In the study, which included 1229 patients, the highest MHR values were found in patients with a score equal to or greater than 23, demonstrating an association with the burden of atherosclerotic disease, according to the interpretation of the authors.[8] The study by Enhos et al.[5] excluded patients with known atherosclerotic disease, and since the authors found a positive association between MHR and MB, the inflammation present in both conditions seems to be the likely link.

In addition to being a marker associated with the presence of MB, the MHR has also demonstrated a possible association with prognosis in patients with this condition. In a study with 1598 patients with ST-elevation acute myocardial infarction, the group with the highest MHR tertile (30.1 ± 10.5) showed higher mortality and higher incidence of cardiovascular events during hospitalization and along a 5-year follow-up.[9] The authors concluded that the MHR was an independent predictor of prognosis in these patients.[9] Similar findings have been reported by Cetin et al.[10] in a study with 2661 patients. The authors found an association between higher MHR and increased mortality, as well as an increased rate of stent thrombosis. The study by Enhos et al.[5] does not allow conclusions about the prognosis of the patients.

In addition to coronary disease, studies have associated higher MHR values to diabetic nephropathy (in patients with diabetic nephropathy compared with healthy subjects and with patients with diabetes and without proteinuria),[11] presence and severity of metabolic syndrome,[12] presence

Keywords

Myocardial Bridging/physiopathology; Inflammation; Atherosclerosis; Risk Factors; Monocytes; Lipoproteins, HDL.

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of coronary ectasia,[13] cardiac syndrome X,[14] and smoking.[15] Even though these results derived from observational studies, they suggest a relationship between conditions that cause vascular inflammation and MHR changes.

The study by Enhos et al.[5] has several limitations, including a small cohort derived from a single center and an assessment of the MHR measured transversely, although no relevant differences were observed between individuals with MB and controls regarding factors that are known to influence the MHR. Additionally, other potential causes of alterations in this relationship were not evaluated, such as the practice of physical activity, diet, smoking, and the presence of other underlying inflammatory processes.

However, a great merit of the study is to present further evidence of a possible association between MBs and inflammation, which should be further evaluated in longitudinal studies verifying if the association relates to increased cardiovascular outcomes. Until such data become available, modification of diagnostic and therapeutic approaches based on the routine determination of this association in patients with MB does not seem relevant, considering that most MBs have a benign course and their treatment is still controversial.

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Regional QT Interval Dispersion as an Early Predictor of Reperfusion in Patients with Acute Myocardial Infarction after Fibrinolytic Therapy

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Abstract

Background: Patients with ST-elevation acute myocardial infarction attending primary care centers, treated with pharmaco-invasive strategy, are submitted to coronary angiography within 2-24 hours of fibrinolytic treatment. In this context, the knowledge about biomarkers of reperfusion, such as 50% ST-segment resolution is crucial.

Objective: To evaluate the performance of QT interval dispersion in addition to other classical criteria, as an early marker of reperfusion after thrombolytic therapy.

Methods: Observational study including 104 patients treated with tenecteplase (TNK), referred for a tertiary hospital. Electrocardiographic analysis consisted of measurements of the QT interval and QT dispersion in the 12 leads or in the ST-segment elevation area prior to and 60 minutes after TNK administration. All patients underwent angiography, with determination of TIMI flow and Blush grade in the culprit artery. P-values < 0.05 were considered statistically significant.

Results: We found an increase in regional dispersion of the QT interval, corrected for heart rate (regional QTcD) 60 minutes after thrombolysis (p = 0.06) in anterior wall infarction in patients with TIMI flow 3 and Blush grade 3 [T3B3(+)]. When regional QTcD was added to the electrocardiographic criteria for reperfusion (i.e., > 50% ST-segment resolution), the area under the curve increased to 0.87 [(0.78-0.96). 95% IC. p < 0.001] in patients with coronary flow of T3B3(+). In patients with ST-segment resolution >50% and regional QTcD > 13 ms, we found a 93% sensitivity and 71% specificity for reperfusion in T3B3(+), and 6% of patients with successful reperfusion were reclassified.

Conclusion: Our data suggest that regional QTcD is a promising non-invasive instrument for detection of reperfusion in the culprit artery 60 minutes after thrombolysis. (Arq Bras Cardiol. 2019; 112(1):20-29)

Keywords: ST Elevation Myocardial Infarction; Electrocardiography; Myocardial Reperfusion; Percutaneous Coronary Intervention; Biomarkers.

Introduction

Despite advances in its treatment, acute myocardial infarction (AMI) rates are still high. In this regard, reperfusion of the culprit artery has become the main objective of ST-elevation acute myocardial infarction (STEMI) treatment. Early reperfusion with preservation of arterial permeability is responsible for mortality reduction in the acute phase, and in medium and long term.[1,2] Nevertheless, once arterial flow is reestablished, myocardial stunning is not resolved due to the injury-reperfusion process.[3,4]

Primary percutaneous coronary intervention (PCI) is considered the gold standard for the treatment of STEMI.[5] Nevertheless, when PCI is not available or cannot be performed in a timely manner, pharmaco-invasive strategy (PIS) is an alternative for reperfusion, consisted of intravenous fibrinolysis, conducted in primary or prehospital care.[6-8] Classical criteria for reperfusion include improvement of ischemic symptoms and ST-segment resolution (> 50% in the highest lead within 60–90 min of fibrinolytic administration).[9,10]

There is some controversy about the behavior of the heart rate-corrected QT interval (QTc) after STEMI. While some studies have reported an increase in QTc in the acute phase followed by its decrease after reperfusion, others reported increased QTc, which was associated with non-reperfusion.[11,12] QTc dispersion (QTcD) was reduced in patients with successful fibrinolytic therapy and decreased in non-revascularized patients. A reduction in QTcD after fibrinolysis was predictive of coronary reperfusion.[13] There is evidence that recanalization after an acute event is associated with a decrease in QTcD, as observed in the TEAM-2 and TEAM-3 studies.[14,15] To our knowledge, there is no study on QTcD after PIS combined with angiographic perfusion imaging (TIMI flow and Blush grade) after tenecteplase (TNK) administration.

Therefore, our study aimed to evaluate the behavior of QTcD in electrocardiography (ECG) before and 60 minutes after thrombolysis according to PIS, as an early marker of reperfusion after thrombolytic therapy when added to classical criteria.

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Methods

This was an observational, prospective study. The study was approved by the local ethics committee and all patients or their legal representatives signed an informed consent form before participating in the study.

Patients

We selected patients with STEMI that sought medical care at public health centers in the city of Sao Paulo, Brazil, who had undergone thrombolytic therapy using TNK, referred for angiography in a tertiary hospital, regardless of electrocardiographic criterion for reperfusion (ST-segment resolution > 50%). Only patients with primary diagnostic of myocardial infarction, considered eligible to thrombolytic therapy in PIS were consecutively included. One hundred and ten patients were initially included, and six were excluded for electrocardiographic reasons. Exclusion criteria were: known contraindications to fibrinolysis, and electrocardiographic findings that could affect QT interval measurements, such as bundle branch block, atrial fibrillation or previous myocardial infarction.

Thus, in the present study, 104 patients of both sexes were included, all of them with primary AMI, treated with TNK within 6 hours of symptoms' onset at primary care centers and subsequently referred for coronary angiography at a tertiary hospital within 2-24 hours of fibrinolysis, or immediately, in situations when a rescue therapy was needed. The operation of the STEMI network in Sao Paulo has been previously published.[7,8]

Clinical and demographic data of the patients were obtained. An experienced echocardiographer, who did not know about their clinical history performed the measurements of the ventricular ejection fraction on the fifth day following AMI in all patients.

Electrocardiographic analysis

Electrocardiographic analysis consisted of an ECG before and 60 minutes after fibrinolysis, using certified and calibrated devices, with patients in prone position. Two independent observers, unaware of patients' clinical characteristics, analyzed the ECG results. The criteria to undergo electrocardiographic reperfusion was a reduction in ST-segment greater than 50% in the highest lead within 60 minutes of fibrinolytic administration.

QT interval was manually measured using a digital caliper, with a lineal, non-contact measurement system, with a resolution of 0.1 mm/0.01'', accuracy of ± 0,2 mm / 0.001" (< 100 mm) and ± 0.03 mm / 0.01"(>100 - 200 mm) and repeatability of 0.1 mm / 0.01". QT values were converted to milliseconds (ms) and corrected for heart rate by the Hodges' linear method using the formula [QTc = QT + 1.75 (RR - 60)]. In order to minimize intraobserver variability, QT interval was calculated by the mean of three measurements in consecutive QRS complexes and in all ECG leads. Kappa coefficient was calculated to minimize the interobserver variability. QT measurements were performed using the tangent method, in which the end of T-wave was defined as the intersection of this tangent with the baseline, at the maximal slope at the end of the QT interval.[16] In the presence of a U-wave, the end of T wave was taken as the nadir between T and U waves. Additionally, we excluded from the analysis all ECG leads where some variables, particularly the T-wave, could not be clearly determined.

QTcD was defined as the difference between the maximum (QT_{max}) and minimum QT (QT_{min}) interval in 12-lead ECG. Regional dispersion was calculated as the difference between QT_{max} and QT_{min} only in leads with ST-segment elevation. Acute anterior wall myocardial infarction was defined as ST-segment elevation in DI, aVL, V1-V3 or V1-V6 leads, whereas non-anterior wall myocardial infarction defined as ST-segment elevation in DII, DIII, aVF, and V_5-V_6 leads.

Angiographic analysis

Angiographic analysis was performed in a tertiary hospital according to a PIS protocol previously described. Two experienced hemodynamic technicians (more than 15 years of practice), unaware of any information that could affect angiographic analysis, analyzed the epicardial flow according to TIMI flow grade,[17] and myocardial perfusion according to myocardial Blush grade.[18] Myocardial blush, defined as contrast density in myocardial microcirculation (Chart 1), was assessed only in patients with TIMI3 grade.

Statistical analysis

Numerical data were expressed as mean and standard deviation (SD) in case of variables with normal distribution, or as median and interquartile range (IQR) in case of quantitative variables with non-normal distribution. The normality of data distribution was tested with the Shapiro-Wilk test and the Kolmogorov-Smirnov test; kurtosis and asymmetry of data distribution were also examined. Categorical variables were expressed as number (n) and percentage (%) and compared by the Pearson's chi-square test, or Fisher's exact test, as

Chart 1 – Definitions for myocardial perfusion (microperfusion) by Myocardial Blush Grade

Grade 0 (absence of myocardial perfusion): absence of myocardial blush or contrast density
Grade 1 (minimal myocardial perfusion): minimal myocardial blush or contrast density
Grade 2 (partial myocardial perfusion): moderate myocardial blush or contrast density, but less than that obtained during contrast injection into a contra-lateral or ipsilateral non-infarcted-related coronary artery
Grade 3 (complete myocardial perfusion): normal myocardial blush or contrast density, comparable with that obtained during contrast injection into a contra-lateral or ipsilateral non-infarcted-related coronary artery

Adapted from Van´t Hof et al.[18]

appropriate. Continuous variables were compared by Student's t-test for independent samples or the Mann-Whitney test, as appropriate. Within-group comparisons were made by t-test for related samples or the Wilcoxon test. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Area under the ROC (receiver operating characteristic) curves, based on C-statistics, were constructed to determine optimal cut-off values for some of the variables. All tests were performed using the Statistical Package for Social Sciences (SPSS)® software version 17.0, da SPSS Inc, Chicago, IL, USA.

Results

Baseline characteristics of the population

A total of 104 patients attending public primary care centers, with clinical and electrocardiographic diagnosis of STEMI, treated with a fibrinolytic agent (TNK) and submitted to coronary angiography within 2-24 hours thereafter were included in the study. Main demographic and clinical characteristics of these patients are described in Table 1. Age ranged from 35 to 74 years old, and most patients were men. Time (median and IQR) between symptom onset and initiation of thrombolytic therapy was 180 minutes (120-240 minutes).

Localization of infarction

AMI was classified according to the ventricular wall involved. For statistical analysis purpose, AMI was grouped into anterior (n = 42) and non-anterior wall infarction (n = 62).

Distribution of QTc and QTcD by electrocardiographic criterion for reperfusion

Sixty-seven (64%) patients met the electrocardiographic criterion for reperfusion. Electrocardiographic tracings were analyzed by two independent observers, with a Kappa coefficient of 0.84. Patients were categorized into two groups – patients with signs of reperfusion and patients without signs of reperfusion, considering only a ST-segment resolution of 50% or more. Values of QTc and QTcD before and after fibrinolysis are shown in Table 2. QTc and QTcD intervals in all 12 leads were not different between the groups. Regional QTcD increased in patients with criterion for reperfusion and, considering the involvement of ventricular wall, in patients with anterior wall myocardial infarction with criterion for reperfusion (p = 0.023) (Table 3).

Distribution of QTcD by angiographic data

Patients were categorized into two groups according to TIMI and Blush grades. Patients with optimal reperfusion, *i.e.*, TIMI 3 and Blush grade 3 – group T3B3 (+) – and those with TIMI < 3 and Blush < 3 – group T3B3 (-). Regional QTcD for anterior wall infarction significantly increased in the T3B3(+) group (p = 0.06), but not in non-anterior wall infarction (p = 0.77). To rule out the possibility of measurement bias in non-anterior wall infarction, regional QTcD in unipolar leads (V_1-V_6) was compared with that in bipolar leads, with no statistically significant difference.

Distribution of coronary flow by TIMI and Blush grades

Distribution of the flow in the culprit artery according to TIMI grade flow 0, 1, 2 and 3 was 20.2%, 7.7%, 13.5% and 58.7%, respectively. Figure 1 depicts (a) percentage distribution of patients according to TIMI grade flow and the electrocardiographic criterion for reperfusion (ST-segment resolution); (b) distribution of patients (in relative frequency) according to TIMI and Blush scores (T3B3) and ST-segment resolution. Few patients with TIMI3 did not show adequate myocardial perfusion according to myocardial Blush grade. Distribution of myocardial blush grades 0, 1, 2 and 3 was 4.9%, 3.3%, 4.9% and 86.9%, respectively in patients with TIMI 3.

With respect to the prediction of optimal coronary reperfusion [T3B3(+)], the criterion for reperfusion by ECG and analysis of QTcD showed a positive predictive value of 73%, negative predictive value of 89%, sensitivity of 93% and specificity of 73%. Baseline demographic characteristics according to TIMI/Blush were not different between T3B3(+) and T3B3(-), except for left ventricular ejection fraction, which was lower in T3B3(-) [(52.6 ± 9.8 *vs* 47.8 ± 8.5; p =0.009)] (Table 4). ECG parameters were not different before and 60 minutes after thrombolysis (Table 5). ROC curves were constructed to evaluate the classification performance of the regional QTcD and to establish the best cutoff point, as illustrated in Figure 2.

If we consider only patients in which the classical electrocardiographic criterion for reperfusion failed to identify coronary reperfusion, there were 18 patients with ST-segment resolution in which optimal angiographic reperfusion was not achieved (failed reperfusion by ECG), and four patients without ST-segment resolution showed TIMI grade 3 and Blush grade 3 (failed rescue). In the groups with failed reperfusion by ECG, no difference was found in regional QTcD between pre-thrombolysis and post-thrombolysis electrocardiographic analysis (p = 0.46) (Figure 3). Therefore, of the 104 patients who received TNK, we detected incorrect reperfusion in 22 cases (21%).

Discussion

QT interval between different ECG leads and this range of intervals is considered an index of spatial dispersion of ventricular recovery, serving as a signal of repolarization

Table 1 – Baseline clinical and epidemiological characteristics of the patients (n = 104)

Age (years)	Men n (%)	Type 2 DM n (%)	SAH n (%)	Dyslipidemia n (%)	Smokers n (%)	Symptom onset (min), m ± SD
55.6 ± 8.78	66 (62.9)	21 (20)	60 (57.1)	36 (34.3)	51 (48.6)	192.16 ± 94.35

Data expressed as mean and standard deviation (m±SD), or number and percentage, n (%), DM: diabetes mellitus; SAH: systemic arterial hypertension

Table 2 – QT interval corrected for heart rate (QTc) and QTc dispersion behavior in the 12 leads and in the leads with ST-segment elevation only (regional QTcD) in patients who met and in those who did not meet electrocardiographic criteria for reperfusion

Variable	With ST-segment resolution (n =67)	p-value	Without ST-segment resolution (n =37)	p-value
QTc (ms), m ± SD	**Pre-TNK**	0.25	**Pre-TNK**	0.06
	423.79 ± 27.89		416.10 ± 26.17	
	Post-TNK		**Post-TNK**	
	429.02 ± 44.60		424.86 ± 24.12	
QTcD (ms), md (IQR)	**Pre-TNK**	0.28	**Pre-TNK**	0.29
	59.0 (45-84)		61 (42-73.5)	
	Post-TNK		**Post-TNK**	
	63.0 (47-76)		64 (44.5-90)	
Regional QTc (ms), ± SD	**Pre-TNK**	0.12	**Pre-TNK**	0.24
	420.30 ± 26.27		420.00 ± 30.67	
	Post-TNK		**Post-TNK**	
	430.00 ± 45.70		423.89 ± 31.95	
Regional QTcD (ms), md (IQR)	**Pre-TNK**	0.01	**Pre-TNK**	0.13
	28 (16-44)		11.5 (23-44)	
	Post-TNK		**Post-TNK**	
	33 ± (20-59)		42 (20-64)	

Data expressed as mean and standard deviation (m ± SD); median and interquartile range, md (IQR); QTcD: QTc dispersion; regional QTc: mean QTc in infarcted area (leads with ST-segment elevation); regional QTcD: regional QTc dispersion (leads with ST-segment elevation); TNK: tenecteplase. Student's t-test for related samples or Wilcoxon test, as appropriate.

Table 3 – Regional QT interval, corrected for heart rate (QTc) in anterior wall infarction in patients with or without ST-segment resolution and patients with or without TIMI 3 and Blush 3 (n = 42)

Variable	With ST-segment resolution n = 23	p-value	Without ST-segment resolution (n = 19)	p-value
Regional QTc (ms), m ± SD	**Pre-TNK**	0.35	**Pre-TNK**	0.17
	428.54 ± 28.24		419.56 ± 28.44	
	Post-TNK		**Post-TNK**	
	429.75 ± 42.59		424.26 ± 30.55	
Regional QTcD (ms), md (IQR)	**Pre-TNK**	0.023	**Pre-TNK**	0.07
	28 (17.5-51.25)		21.5 (9.5-39.25)	
	Post-TNK		**Post-TNK**	
	40 (30-66.7)		38.5 (17.5-59)	
	T3B3 (+) n =18	**p-value**	**T3B3 (-) n =24**	**p–value**
Regional QTc (ms), m ± SD	**Pre-TNK**	0.26	**Pre-TNK**	0.70
	425.53 ± 28.24		421.66 ± 28.44	
	Post-TNK		**Post-TNK**	
	439.88 ± 42.59		417.62 ± 30.55	
Regional QTcD (ms), md (IQR)	**Pre-TNK**	0.006	**Pre-TNK**	0.07
	23 (15.75-39.25)		25 (18-46)	
	Post-TNK		**Post-TNK**	
	38 (24.25-73.0)		42 (21-61)	

Data expressed as mean and standard deviation (m±SD); median and interquartile range, md (IQR); regional QTc: regional QTc in anterior wall infarction; regional QTcD: regional dispersion of the QTc interval in anterior wall infarction; TNK: tenecteplase; T3B3 (+): TIMI 3 and Blush grade 3; T3B3 (-): TIMI < 3 and Blush < 3. Student's t-test for related samples, or Wilcoxon test, as appropriate.

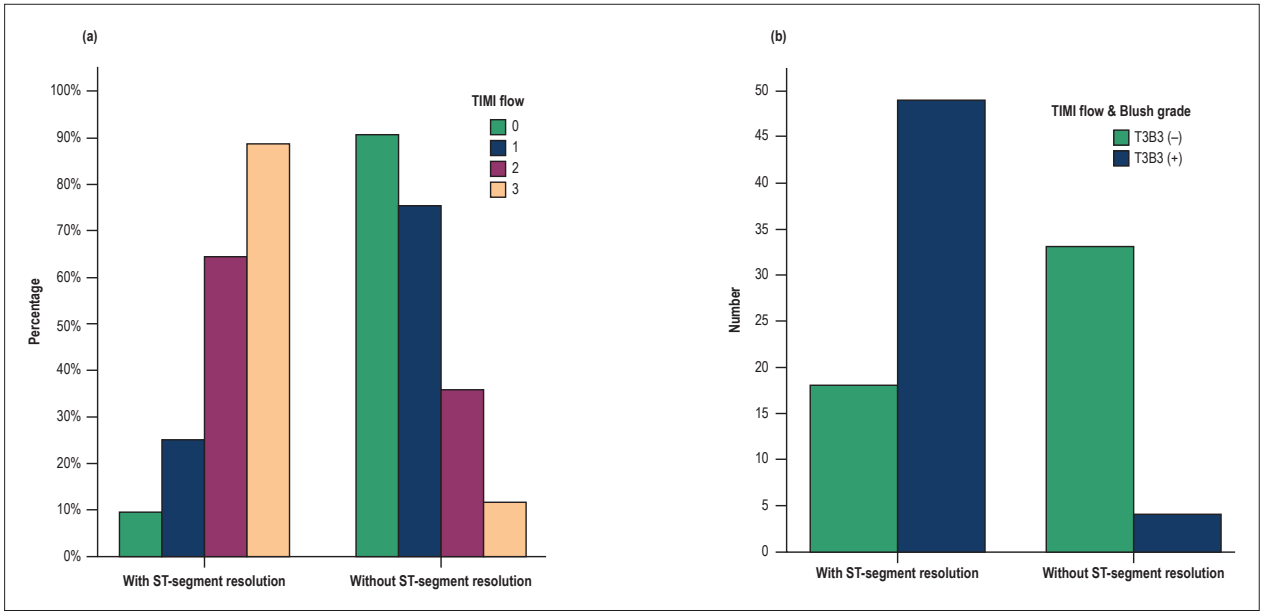


Figure 1 – *Distribution of patients by the presence of ST-segment resolution (classical electrocardiographic criteria for reperfusion) and angiographic profile of TIMI flow (1a) or perfusion pattern (TIMI flow and Bulsh grade); in the culprit artery; T3B3 (+): patients with TIMI 3 and Blush grade 3 in the culprit artery; T3B3 (-): patients with TIMI 3 and Blush grade < 3 in the culprit artery (1b).*

Table 4 – Clinical characteristics in the groups of patients with or without angiographic criteria for adequate reperfusion according to TIMI flow and Blush grades

Characteristics	T3B3 (+)	T3B3 (-)	p-value
	n =53	n =51	
Age (years), md (IQR)	54 (47-63)	56 (52-62)	0.51
Male, n (%)	28 (52.8)	38 (74.5)	0.02
Type 2 DM, n (%)	8 (15.1)	13 (25.5)	0.19
Hypertension, n (%)	27 (50.9)	33 (64.7)	0.16
Dyslipidemia, n (%)	15 (28.3)	21 (41.2)	0.17
Smokers, n (%)	24 (45.3)	27 (53)	0.43
Time for TNK administration, (min): md –IQR	185 (137-257)	138 (110-240)	0.18
Time < 180, (min): n (%)	32 (60)	22 (43)	0.12
Ejection fraction, (%): m ± DP	52.6 ± 9.8	47.8 ± 8.5	0.009
Anterior AMI, n (%)	18 (34)	24 (47)	0.17
Non-anterior, n (%)	35 (66)	27 (53)	0.17

Data expressed as mean and standard deviation (m ± SD), median and interquartile range (md, IQR), number and percentage, n (%); T3B3 (+): patients with TIMI 3 and Blush grade 3 in the culprit artery; T3B3 (-): patients with TIMI 3 and Blush grade < 3 in the culprit artery; DM: diabetes mellitus; AMI: acute myocardial infarction; TNK: tenecteplase. Categorical variables were compared by Pearson's chi-square test or Fisher's exact test, and continuous numerical variables were compared by the Student's t test for independent sample or Mann-Whitney test, as appropriate.

heterogeneity.[19] Many studies have shown that patients with increased QTcD (approximately > 60 ms) had 2-3.4 increased risk of cardiovascular mortality. Multivariate analysis of these studies showed a 34% increased cardiovascular risk for each increment of 17ms in QTbD or QTcD > 60 ms in patients with diabetes mellitus without previous AMI.[20-22]

There is a QTcD variation during the first days of AMI; it increases in the first hours and decreases some days thereafter, especially following fibrinolytic therapy[23-25] or revascularization procedure.[26,27] A reduction in QTcD in the days following fibrinolysis shows the efficacy of the therapy.[28] Based on the speculation that changes in QTcD could predict reperfusion assessed 90 minutes after fibrinolysis, in a small study with 47 patients, the authors analyzed QTcD only in precordial leads and found a higher QTcD in the group that met the electrocardiographic criterion for reperfusion. However, the parameter was not predictive of angiographic reperfusion.[29] One limitation of this study was the small number of patients

Table 5 – Electrocardiographic parameters evaluated before and after tenecteplase (TNK) administration in patient with TIMI 3 and Blush grade 3 [T3B3 (+)] and patients with TIMI < 3 and Blush grade < 3 [T3B3 (-)] in the culprit artery

Pre-TNK	T3B3 (+)	T3B3 (-)	p-value
N	53	51	
QTc (ms), m ± SD	421.56 ± 28.51	423.29 ± 25.77	0.72
QTcD (ms), md (IIQ)	59 (44-82)	59 (43-81)	0.97
Regional QTc (ms), m ± SD	418.86 ± 27.01	423.55 ± 30.41	0.38
Regional QTc (ms), md (IQR)	25 (11.5-40)	29 (18-50)	0.09
Pre –TNK	**T3B3 (+)**	**T3B3 (-)**	**p-value**
N	18	24	
Regional QTcD (ms), md (IIQ)	23 (11.75-39.25)	25 (18-46)	0.65
Post –TNK	**T3B3 (+)**	**T3B3 (-)**	**p-value**
N	53	51	
QTc (ms), m ± DP	426.90 ± 43.98	431.94 ± 27.47	0.42
QTcD (ms), md (IIQ)	62 (49-75)	66 (40-91)	0.62
Regional QTc (ms), m ± DP	430.53 ± 44.01	424.14 ± 36.12	0.19
Regional QTcD (ms), md (IIQ)	33 (20-59)	42 (19-63)	0.71
Post –TNK	**T3B3 (+)**	**T3B3 (-)**	**p-value**
N	18	24	
Regional QTcD (ms), md (IIQ)	38 (24.25-73)	42 (21-61)	0.05

Data expressed as mean and standard deviation (m ± SD), median and interquartile range (md and IQR). QTc: mean QT interval, corrected for heart rate in the 12 leads; QTcD: dispersion of the QTc interval in the 12 leads; regional QTc: mean regional QTc in anterior wall infarction; regional QTcD: regional QTc dispersion in anterior wall infarction. Continuous numerical variables were compared by the Student's t-test for independent samples or the Mann-Whitney test, as appropriate.

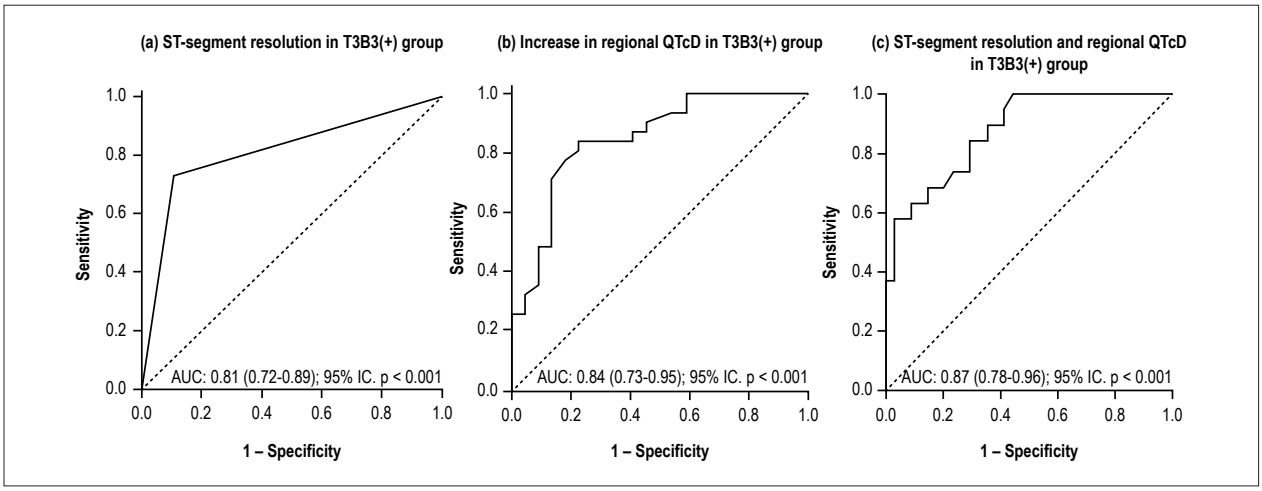
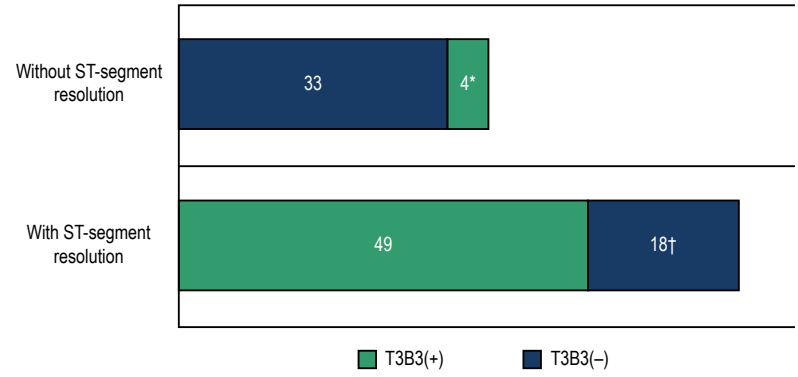


Figure 2 – *ROC curves for the classical electrocardiographic criterion for reperfusion (ST-segment resolution); regional dispersion of the QT interval, corrected for heart rate (QTc); and ST-segment resolution combined with regional dispersion of the QTc interval in patients with optimal reperfusion profile, i.e., TIMI flow and Blush grades 3 [T3B3 (+)]. (a) In patients with ST-resolution, the area under the ROC curve was 0.81 [(0.72-0.89); 95%CI, p < 0.001) to detect TIMI flow 3 and Blush 3 [T3B3(+)]; (b) increased regional QTc dispersion 60 minutes after thrombolysis resulted in an area under the ROC curve of 0.84 [(0.73-0.95); 95%CI, p < 0.001 to detect T3B3 (+), using a cutoff point of > 13 ms, a 94% sensitivity and a 74% specificity were obtained; (c) increased regional QTcD associated with ST-segment resolution 60 minutes after thrombolysis resulted in an area under the ROC curve of 0.87 [(0.78-0.96); 95%CI, p < 0.001 to detect T3B3 (+). Using a cutoff point of > 13 ms, a 93% sensitivity and a 71% specificity were obtained. Six patients (approximately 6%) could be reclassified based only on electrocardiographic measurements. Validated by angiographic criteria of coronary reperfusion in this cohort of patients treated with pharmaco-invasive strategy.*

and the analysis of QTcD in precordial leads only. Another study involving 36 patients did not show any difference in QTcD in the group with criterion for reperfusion on the first day of AMI. Interestingly, the authors observed a decrease in QTcD since the second day of thrombolysis, particularly in the group with anterior wall myocardial infarction.[30] Another study also reported decreased QTcD six months after AMI.[31]

Our findings indicate an increase in QTcD on ECG 60 minutes after fibrinolysis in patients with angiographic findings of complete vascular and tissue revascularization (TIMI flow



	Failed reperfusion n = 18	p-value	Failed rescue n = 4	p-value
dQTcR (ms)	**Pre-TNKase**	0.46	**Pre-TNKase**	0.06
	42.5 (23.0-69.5)		8.0 (3.7-10.0)	
	Post-TNKase		**Post-TNKase**	
	31.0 (17.7-56.2)		35.0 (22.7-64.0)	

Figure 3 – *Behavior of the regional QT interval, corrected for heart rate, in subgroups of patients with failed reperfusion or failed rescue; data expressed as median and interquartile range (m,IQR); QTcD: dispersion of the QTc interval; TNK: tenecteplase; T3B3 (+): patients with TIMI 3 and Blush grade 3 in the culprit artery; T3B3 (-): patients with TIMI 3 and Blush grade < 3 in the culprit artery; Wilcoxon test. *Failed rescue: patients without ST-segment resolution and with optimal coronary and tissue perfusion [T3B3 (+)]; †failed reperfusion: patients with ST-segment resolution, without optimal coronary and tissue perfusion [T3B3 (-)].*

and Blush grades 3), especially in anterior wall infarction. On the other hand, different from previous reports on streptokinase and alteplase,[31,32] we used TNK, a fibrin-specific, recombinant tissue plasminogen activator, which has been shown better results regarding coronary reperfusion. Besides, we included a larger number of patients compared with previous studies. Regional QTcD in anterior wall infarction significantly increased in ECG obtained 60 minutes after thrombolysis in patients with adequate reperfusion (TIMI 3 and Blush grade 3), reinforcing the idea that QTcD following AMI depends on permeability of the culprit artery, as well on dimension and localization of the ventricular wall involved.

One possible mechanism for our results is based on the effect of cardiac stunning caused by reperfusion injury. Besides, there is evidence that vascular, metabolic, mitochondrial, neuronal, thermal and electric processes contribute to post-reperfusion dysfunction.[33-35] Nevertheless, the exact mechanism, the adequate prevention of the ischemia-reperfusion lesion, and above all, the correlation of reperfusion injury with electrocardiographic findings have not been elucidated in the literature.[36]

Considering the correlation between ECG leads and the infarcted area, it is possible to analyze the repolarization of the injured area. Calculation of the regional QTcD estimates heterogeneity of ventricular repolarization in the area at risk. Thereby, the need for a decision-making tool for fibrinolytic therapy emphasizes the importance of post-thrombolysis electrocardiographic reperfusion markers. ECG plays a crucial and more important role in PIS than in primary PCI. The identification of patients that meet reperfusion criteria and of those who should be referred for rescue PCI should be promptly and fast performed. A crucial point is the cost-benefit of the system and the delay in the ideal time between fibrinolysis and PCI. Despite the large variation in this time window in the clinical trials, a time interval of 2-24 hours after successful fibrinolysis.[37]

The classical electrocardiographic criterion for reperfusion has a sensitivity and specificity of 60% and 80%, respectively.[38] We showed that both sensitivity and specificity increased when regional QTcD was added to ST-segment resolution, suggesting that this method may help to stratify patients in a more accurate way.

Analysis of subgroups did not show significant differences in regional QTcD between patients with at least 50% ST-segment resolution and inadequate flow by angiography [T3B3(-)], *i.e.*, patients with failed reperfusion, and patients without ST-segment resolution but who showed angiographic reperfusion [T3B3 (+)].

Our study showed an increase in QTcD and regional QTcD in anterior wall infarction particularly in patients T3B3(+). In agreement with a previous study,[39] QTcD depends on the localization of AMI, and higher QTcD was observed in the anterior wall as compared with inferior wall acute myocardial infarction. The large area of infarction in this subgroup should have greater influence on repolarization vectors than on non-anterior wall infarction.

This study indicates a possible step forward in the analysis of electrocardiographic variables, in light of current controversies of angiographic data, T3B3(-) showed worse ejection fraction and higher QTcD compared with the T3B3(+) subgroup, which may also have prognostic implications.

Although QTcD is still a matter of controversy in electrocardiology,[40] some questions remain unanswered in the specialized literature. Studies on electrocardiographic variables using better estimation methods may yield interesting information in many medical scenarios.

Importance and limitations

So far, there are no studies specifically examining the behavior of regional QTcD in AMI patients who underwent PIS. Therefore, our data need to be further validated and replicated in future studies. Our cohort was relatively small, although larger than in previous studies. Also, advances in the methods used for the measurement of QT interval and ventricular repolarization are still needed. The lack of standardization and systematization negatively affects the accuracy in the measurement of ST-segment and T-wave in the presence of ischemia. Finally, analysis of QTcD by ECG at late follow-up could give interesting information on QTcD behavior.

Conclusions

Our study suggests that an increase in regional QTcD may detect adequate reperfusion 60 minutes after fibrinolysis, which could be a potential non-invasive method for evaluation of regional perfusion especially in anterior wall infarction.

Author contributions

Conception and design of the research: Dotta G, Póvoa RMS, Bianco HT; acquisition of data: Dotta G, Souza MT, Pinheiro LFM, Barbosa AHP, Caixeta AM; Carvalho AC; analysis and interpretation of the data: Fonseca FAH, Izar MC, Moreira FT, Pinheiro LFM, Barbosa AHP, Póvoa RMS, Carvalho AC, Bianco HT; statistical analysis: Fonseca FAH, Izar MC, Bianco HT; writing of the manuscript: Dotta G, Souza MT, Moreira FT; critical revision of the manuscript for intellectual contente: Dotta G, Fonseca FAH, Izar MC, Moreira FT, Póvoa RMS, Carvalho AC, Bianco HT.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de São Paulo under the protocol number 2.000.970. 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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Reperfusion Criteria in Patients Submitted to Fibrinolysis: Is There Room for Improvement?

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Short Editorial related to the article: Regional QT Interval Dispersion as an Early Predictor of Reperfusion in Patients with Acute Myocardial Infarction after Fibrinolytic Therapy

Many ST-elevation acute myocardial infarction (STEMI) patients seek care in hospitals without percutaneous coronary intervention (PCI) capability and cannot be submitted to PCI within the guideline-recommended timelines, and, instead, they are often submitted to fibrinolysis as the initial reperfusion therapy. Rapid, simple and readily available bedside measures are of utmost importance for timely assessment of the efficacy of reperfusion therapy early after fibrinolysis in acute STEMI,[1] in order to immediately identify the ones who require rescue PCI.[2,3]

In an editorial for Circulation in 2001, Gibson[4] stated "In a time of dizzying advances in diagnostic modalities, it is refreshing to see what a useful, simple, noninvasive, broadly accessible, easily repeatable/applied, and affordable tool the electrocardiography (ECG) is".[4] This is still up to date. Multiple studies have demonstrated improved outcomes among patients who achieve complete ST resolution at 60-90 minutes after fibrinolytic therapy, and it is recommended that the absence of > 50% reduction in ST elevation in the worst lead at 60-90 minutes should prompt strong consideration of coronary angiography and rescue PCI. [2,3] However, this measure, combined with the absence of reperfusion arrhythmias at 2 hours after treatment, has a positive predictive value of 87% and a negative predictive value of 83% to predict failure of reperfusion, [2,5] indicating that there is still room for improvement in accuracy.

In the well-structured analysis by Dotta et al.[6] in the article "*Regional QT Interval Dispersion as an Early Predictor of Reperfusion in Patients with Acute Myocardial Infarction after Fibrinolytic Therapy*", published in this Arquivos Brasileiros de Cardiologia issue,[6] the results reinforced Gibson's statement. The authors assessed the performance of QT interval dispersion in addition to classical reperfusion criteria as an early marker of reperfusion in 104 STEMI patients from emergency care units in Sao Paulo who underwent fibrinolysis with tenecteplase (TNK).

The concept of QT interval dispersion was introduced in the 1990s, as a non-invasive method for the detection of ventricular repolarization heterogeneity, and previous studies have shown that reduction of QT interval dispersion post-thrombolysis was an independent predictor of coronary reperfusion.[7] Dotta et al.[6] study was the first one to assess QT interval dispersion in STEMI patients who underwent pharmaco-invasive strategy. Interestingly, the authors observed an increase in regional dispersion of corrected QT interval 60 minutes after TNK in anterior wall infarction in patients with angiographic findings of complete recanalization (TIMI flow 3 and Blush grade 3). When they added regional QTcD to electrocardiographic criteria for reperfusion, the area under the receiving operating characteristic curve (ROC) changed from 0.81 (0.72-0.89) to 0.87 (0.78-0.96), demonstrating an improved discriminatory ability.[6]

Some limitations should be pointed out and most of them are recognized by the authors. This measure was not tested in patients with bundle branch block, atrial fibrillation or previous myocardial infarction, as those could compromise the QT interval dispersion assessment. Although a good concordant agreement was noted between examiners (kappa coefficient = 0.84),[6] errors in manual measurement of QT intervals are common[8] and, in the real world, there are consistent differences in the measurements between cardiologists, what can compromise the acuity of the evaluation of the QT dispersion, especially in an emergency situation as the management of the myocardial infarction.

To overcome these limitations, the authors commented about the need to advance in the methodology to measure QT interval and ventricular repolarization. The use of computerized programs for automated ECG interpretation has shown good accuracy levels for ECG interval measurements,[9,10] and it might improve regional QT dispersion assessment. More than ever, development of computerized automatic calculation and studies in different populations, with a larger sample size, are needed to allow the external validation of including regional QT dispersion together with traditional reperfusion criteria in reperfusion assessment after fibrinolysis.

Keywords

ST Elevation Myocardial Infarction/mortality; Percutaneous Coronary Intervention/economics; Fibrinolysis; Thrombolytic THerapy/methods; Time Factors; Electrocardiography/methods.

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Whole-Body Vibration Training Increases Myocardial Salvage Against Acute Ischemia in Adult Male Rats

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Abstract

Background: Whole body vibration training (WBV) is a new training program, which is safe and effective. It can be followed by the public. However, data on the safety and efficacy of vibration on myocardial ischemia reperfusion (IR) injury are lacking.

Objective: To examine the effect of WBV on the tolerance of the myocardium to acute IR injury in an experimental rat model.

Methods: Twenty-four male Wistar rats were divided into control and vibration groups. Vibration training consisted of vertical sinusoidal whole body vibration for 30 min per day, 6 days per week, for 1 or 3 weeks (WBV1 and WBV3 groups, respectively). All the rats were submitted to myocardial IR injury. Myocardial infarct size and ischemia-induced arrhythmias were assessed. Differences between variables were considered significant when $p < 0.05$.

Results: No differences were observed between the groups regarding the baseline hemodynamic parameters. Infarct size was smaller in the experimental group (control, 47 ± 2%; WBV1, 39 ± 2%; WBV3, 37 ± 2%; $p < 0.05$, vs. control). Vibration produced a significant decrease in the number and duration of ventricular tachycardia (VT) episodes compared to the control value. All ventricular fibrillation (VF) episodes in the vibration groups were self-limited, while 33% of the rats in the control group died due to irreversible VF ($p = 0.02$).

Conclusion: The data showed that vibration training significantly increased cardiac tolerance to IR injury in rats, as evidenced by reduction in the infarct size and cardiac arrhythmias, and by facilitating spontaneous defibrillation. (Arq Bras Cardiol. 2019; 112(1):32-37)

Keywords: Rats Wistar; Body Composition; Vibration; Osteoporosis/prevention and control; Blood Viscosity; Ischemia; Cardiovascular Diseases; Ischemic Preconditioning.

Introduction

Whole body vibration training (WBV) has been recently proposed as an exercise training method with a potential for improving body composition and preventing osteoporosis and bone mass loss.[1] In recent years, some studies have shown that WBV may be a beneficial training mode in patients with multiple sclerosis,[2] type 2 diabetes,[3] chronic obstructive pulmonary disease,[4] and heart transplant recipients.[5] The effects of WVB on the cardiovascular system were investigated in a number of published studies. Decreased arterial stiffness after WBV can reduce the risk of cardiovascular disease.[6,7] An experiment conducted by Robbins et al.[8] showed a significant increase in blood flow velocity with no significant changes in heart rate, blood pressure or peripheral skin temperature. Increased muscle blood volume and blood flow velocity after vibration exercise were attributed mainly to the effect of vibrations in reducing blood viscosity and increasing its velocity through the arteries.[9] These findings indicate that WBV may represent a mild form of exercise for the cardiovascular system.[10]

Cardiovascular disease (CVD), which is induced by ischemia, is the leading cause of death worldwide. Restoration of blood flow, after a period of ischemia, can elicit pathological processes that exacerbate injury due to the ischemia itself.[11] Preconditioning describes a pretreatment or premaneuver that is able to adapt the myocardium to ischemic stress. We have demonstrated some preconditioning interventions in previous experiments, reducing infarct size and arrhythmias.[12,13] The cardioprotective effect of exercise preconditioning was reported as a reduction in infarct size in previous studies.[14,15] Accumulating evidence indicates that both short-term (i.e. 1-5 days) and long-term (i.e. weeks to months) exercise can protect the heart during an ischemia-reperfusion (IR) insult. While much is currently known about exercise preconditioning, to our knowledge, the effect of whole-body vibration on IR injury has not been investigated. Thus, the purpose of this study was to determine whether the vibration exercise would be able to reduce infarct size and arrhythmia during IR injury in an experimental rat model.

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Methods

Male Wistar rats weighing 250 to 300 g (10-12 weeks old) were obtained from the animal house of Shiraz University of Medical Sciences and housed under standard conditions, with free access to food and water. The investigation was approved by the University Ethics Committee in accordance with the Guide for the Care and Use of Laboratory Animals.

Experimental designs

A total of 24 rats were randomly assigned to 1 of 3 treatment groups (control vs. two experimental groups) by picking numbers out of a hat. The sample size (n) was established based on studies that evaluated the effects of exercise against myocardial IR injury.[16,17] Animals in the vibration groups were placed in a compartment attached to a vibration platform (Crazy Fit Massager/Model: YD 1002, Union Brilliant Group Co., LTD, Fujian, China). The vibration training consisted of a 5-min cycle on day 1, followed by an extra 5-min cycle each time for the next five sessions in the first week and then each rat was exposed to vertical sinusoidal vibration for 30 min per session (3 × 10 min cycles), 6 days a week for one week (WBV1 group) or 3 weeks (WBV3 group). The animals were given 1–2 min rest break between the cycles. The vibration was performed at mode 1 with amplitude of 1–10 mm and at a frequency of 10–50 Hz. The speed of mode 1 in each cycle increased gradually and then decreased with the same trend within each time period. The control animals remained in their cages and were placed over the vibration platform, without vibration treatment. Each training session was performed between 8.30–10.00 A.M.[18]

Surgical procedure

The protocol used has been thoroughly described in detail in our previous publication.[12] Briefly, 24 hours after the last training session, the animals were anesthetized and ventilated with room air enriched with oxygen at a rate of 70 breaths per min. A standard limb lead II electrocardiogram was monitored and recorded throughout the experiment. Catheters were inserted into the left carotid artery and tail vein for monitoring of blood pressure and infusion of Evans blue solution, respectively. After the thoracotomy, a 6-0 silk suture was passed around the left anterior descending coronary artery (LAD). Following a stabilization period of 20 min, the LAD was occluded for 30 min of ischemia and released for 120 min of reperfusion. Rectal temperature was continuously monitored and maintained at 37 ± 0.5°C.

Determination of infarct size and area at risk

At the end of reperfusion, the LAD was reoccluded and 1 mL of 2% solution of Evans Blue dye (Sigma, St. Louis, MO) was injected into the tail vein to identify the non-perfused area, also known as area at risk (AAR), from the perfused area. The rats were then killed with a pentobarbital overdose and their hearts were excised and frozen for one hour. The atria and right ventricle were removed, and the left ventricle was cut into transverse slices of 2 mm thickness from the apex to the base. Tissue samples were then incubated with a 1% solution of 2,3,5 triphenyltetrazolium chloride (Sigma)] for 20 min at 37°C, and subsequently fixed in 10% phosphate-buffered formalin for one hour. Viable myocardium was stained red by triphenyltetrazolium chloride, whereas necrotic myocardium appeared as pale yellow. In each slice, areas at risk and infarcted areas were determined by computerized planimetry using an image analysis software (Image Tool, University of Texas, San Antonio, TX). Infarct size (IS) was expressed as percentage of the AAR (IS/AAR).[12]

Assessment of ventricular arrhythmias

Ischemia-induced ventricular arrhythmias were determined in accordance with the Lambeth conventions[19] including ventricular ectopic beat as premature ventricular complexes (PVC), ventricular tachycardia (VT) as a run of four or more consecutive ventricular premature beats at a rate faster than the resting sinus rate, and ventricular fibrillation (VF) as a signal for which individual QRS deflection can no longer be distinguished from one another. Complex forms (bigeminy and salvos) were added to PVC count and not analyzed separately. In order to determine the incidence of VT and VF, they were recorded as either occurring or not occurring during the first 30 min of ischemia in each group.

Statistical analyses

Unless stated otherwise, the results were expressed as Mean ± SD. All data were processed with the SPSS 16.0 statistical package for Windows version. The normality of distributions was verified by the Kolmogorov-Smirnov test. Fisher exact test (Chi-square) was used to analyze the incidence of VT and VF. Analysis of baseline, ischemia, and reperfusion HR and BP was done by repeated measures analysis of variance (ANOVA). The other data were analyzed using one-way ANOVA and then significant differences were examined by Tukey's post-hoc test. Differences between the groups were considered significant at a level of $p < 0.05$.

Results

Hemodynamic parameters

Table 1 summarizes the hemodynamic data. There were no significant differences at baseline values for heart rate (HR) and mean arterial blood pressure (MBP) among the groups. Ischemia caused a marked reduction in blood pressure without any significant effect on the HR in the groups. MBP was nearly restored to the baseline level during the reperfusion period.

Infarct size

Figure 1 shows AAR and IS following 30 min of regional ischemia and 120 min of reperfusion. There was no marked difference in AAR/LV ratio among the groups ($p = 0.92$). Infarct size was 47 ± 5% in the control group. WBV1 or WBV3 resulted in a smaller infarct size, i.e. 39 ± 5% and 37 ± 5% ($p = 0.047$ and $p = 0.009$ vs. the controls), respectively.

Table1 – Hemodynamics parameters in the experimental groups

Group	Baseline		Ischemia		Reperfusion	
	HR	MBP	HR	MBP	HR	MBP
Cont	346 ± 48	113 ± 21	349 ± 51	100 ± 15* (0.04)	361 ± 44	107 ± 17
WBV1	373 ± 41	114 ± 7	385 ± 25	97 ± 8** (0.001)	383 ± 26	107 ± 13
WBV3	376 ± 26	107 ± 15	372 ± 18	91 ± 7* (0.01)	378 ± 27	108 ± 15
p-value	0.282	0.670	0.130	0.267	0.399	0.996

*Note: Data presented as mean ± SD (P-value). HR: heart rate; MBP: mean arterial blood pressure. Cont: control, WBV1: whole body vibration training for one week, WBV3 = whole body vibration training for 3 weeks. *p < 0.05, **p < 0.01 compared to baseline value.*

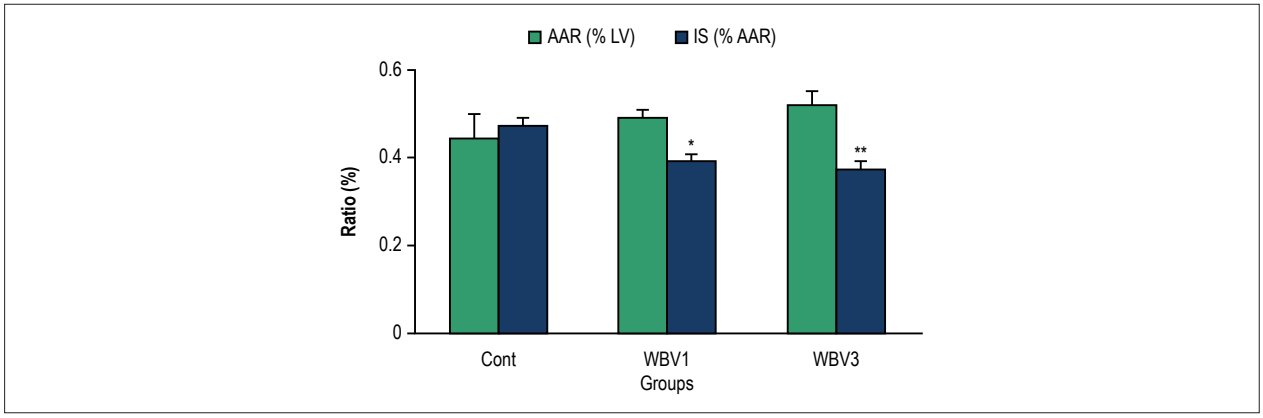

Figure 1 – *Infarct size (IS) and area at risk (AAR) following 30-min of ischemia and 120-min of reperfusion in rats. LV: left ventricle; * p < 0.05 and ** p < 0.01 compared with the control group. Cont: control; WBV1: whole body vibration training for one week; WBV3: whole body vibration training for 3 weeks.*

Ischemia-induced arrhythmias

Table 2 represents the number of PVC, VT and VF episodes and their duration during the 30-min ischemic period. The arrhythmias occurred after approximately 5–7 min of ischemia. The number of PVC decreased non-significantly in the experimental groups (p = 0.702). Vibration produced a significant decrease in the number and duration of VT episodes compared to the control value. The mean duration of reversible VF in the WBV3 group was reduced from 32.3 ± 19.4 s in the control group to 13.7 ± 10.3 s (as a non-significant trend). Although the longest VF episodes in the vibration groups lasted as much as 116 s, all VF episodes were self-limited. However, the longest observed non-fatal VF episode in the control group was 87 s. and 33% of the rats died due to irreversible VF (p = 0.02). The occurrence (% incidence per group) of VT during the 30-min ischemia was 100, 100 and 88% (p = 0.35) and the occurrence of VF was 75, 63 and 50% in the control, WBV1 and WBV3 groups, respectively (p = 0.58).

The numbers of premature ventricular complexes (PVC), the ventricular tachycardia (VT) and ventricular fibrillation (VF) episodes and duration are shown as means ± SEM. * p < 0.05 and ** p < 0.01 compared with the control group. Cont: control; WBV1: whole body vibration training for one week; WBV3: whole body vibration training for 3 weeks.

Discussion

There are three main findings of the present study. First, WBV caused a significant decrease in IS following 30 min of ischemia and 120 min of reperfusion. Second, WBV had a protective effect on ischemia-induced arrhythmia. Third, all VF episodes were self-limited in the vibration groups, so the vibration improved arrhythmia-related mortality.

There are conflicting results regarding the effect of WBV on BP and HR. Performing dynamic exercise on a vertical vibration platform (30-35 Hz, 2 mm) for 12 weeks resulted in decreased systolic blood pressure in patients suffering from type 2 diabetes.[20] Figueroa et al.'s study showed that 6 weeks of WBV decreased systemic arterial stiffness and systolic blood pressure in young overweight/obese normotensive women.[7] Unlike these results, it was demonstrated that one session of exercise with vibration increased systolic and diastolic blood pressure and stroke volume compared with exercise with no vibration in sedentary adults.[21] In contrast, some researchers have reported that WBV had no effect on the systolic and diastolic blood pressure, which is similar to our study results.[6,8,22] These conflicting results may be explained by the different experimental conditions, including duration of the treatment and possibly the heterogeneity of the health status of participants in the different studies.

Table2 – Incidence and duration of ventricular arrhythmias during 30 min of ischemia

Groups	PVC (n)	VT		VF	
		Episodes	Duration	Episodes	Duration
Cont	283 ± 50	31 ± 4	70 ± 14	2.0 ± 0.9	32.3 ± 19.4
WBV1	271 ± 32	17 ± 1*	54 ± 19	2.3 ± 0.8	33.2 ± 17.9
WBV3	229 ± 55	13 ± 3**	12 ± 4*	1.0 ± 0.6	13.7 ± 10.3
p-value	0.702	0.002	0.018	0.559	0.475

PVC: premature ventricular complexes; VT: ventricular tachycardia; VF: ventricular fibrillation; WBV1: whole body vibration training for one week; WBV3: whole body vibration training for 3 weeks

The ischemia reperfusion model in the experimental animals provides an option to evaluate the occurrence of ischemia-induced arrhythmias and infarct size after an intervention. Posa et al. demonstrated that 6 weeks of voluntary exercise was protective against IR injury by reducing the myocardial infarct size.[23] An important finding is that one-to-several days of exercise can also reduce myocardial damage due to IR injury.[24] Studies have demonstrated that regular exercise increases antioxidant capacity in the heart, which can minimize oxidative stress following IR.[25] During all sporting activities, externally-applied forces induce vibrations within the body tissues.[10] WBV has been proposed as an efficient alternative to moderate intensity exercise.[26]

Although recent studies have suggested that WBV leads to improvements in numerous health outcomes, including bone mineral density,[27] muscle strength, or cardiovascular fitness,[28] no research has been performed so far to evaluate the effects on IR injury.

The present study demonstrated that WBV is able to reduce myocardial infarct size and ischemia-induced arrhythmia during IR injury in rats. In the course of myocardial infarction, ventricular arrhythmias such as VT and VF are the most important cause of mortality.[29] There was no difference in the ratio of AAR/LV between the control and vibration animals, indicating that all animals suffered a comparable degree of ischemic area. Therefore, the reduction of infarct size and arrhythmia in vibration-treated animals was due to the effect of the training. There are two types of VF: a sustained VF (SVF) that never terminates spontaneously and requires electrical defibrillation and a transient VF (TVF) that terminates by itself and spontaneously reverts into a sinus rhythm. Although it was believed for many years that TVF appears only in small mammals (rats, guinea pigs and rabbits), no differences were found in cardiac muscle mass, heart rate and action potential duration between animals with TVF and those with SVF. Intercellular uncoupling during ischemia most likely due to an increase in the intracellular Ca^{2+} and H^{+} ions or a decrease in the intracellular cAMP may lead to SVF. Therefore, any defibrillating intervention should prevent intercellular uncoupling, most probably by increasing the intracellular concentration of cAMP, decreasing elevated $[Ca^{2+}]_i$ or preventing Ca^{2+} overload.[30] The results of the present study suggested that all VF episodes were self-limited in the vibration groups. Thus, vibration training could reduce the risk of sudden death during ischemia, through both attenuation of the ischemia-induced arrhythmia and facilitation of spontaneous defibrillation. The exact mechanism of action by which vibration reduces the incidence of fatal VF episodes cannot be directly assessed by our study. However, the increased ventricular fibrillation threshold in trained hearts during acute regional ischemia was shown in previous studies.[31] Additionally, exercise training has been reported to increase the levels of cAMP[32] and to improve cardiomyocyte function and diastolic Ca^{2+} control in rats with post-infarction heart failure.[33,34] Several studies have also shown a positive correlation between infarct size and the occurrence of severe ventricular arrhythmias.[35,36]

Currently, exercise training has been introduced as the only practical method of providing cardioprotection against IR injury. If vibration-induced protection is nearly as effective as the exercise, it could be an alternative to exercise training, especially for those who are unable to perform traditional exercises. Delineating the mechanisms mediating vibration-induced protection against IR injury is important and could lead to the development of pharmacological or molecular approaches against cardiovascular diseases.

Limitations of the study

One of the limitations of the present study is that it was carried out on rats. Even though the large number of animal studies have conducted and contributed much to our understanding of disease mechanisms, their findings for predicting the effectiveness of strategies in humans has remained controversial.[37,38] Therefore, the results need to be confirmed by clinical trials in the future.

The frequency, amplitude, and the time of exposure of the subjects to vibration are important variations in clinical and experimental trials. However, due to lack of knowledge regarding optimum training protocols, the method was based on the methodology available in our laboratory. The proposed method has shown that is effective in improving health status by influencing cardiovascular disease (CVD) risk factors.[18,39] We recommend evaluating the various vibration regimes on the IR injury in future studies.

Conclusions

The present experimental data provide new evidence that vibration training can enhance cardiac tolerance to IR injury in an *in vivo* rat infarct model. It reduces infarct size and ischemia-induced arrhythmias and improves arrhythmia-related mortality by reducing fatal VF episodes and by facilitating spontaneous defibrillation. The finding that vibration training increases myocardial resistance to VF in this model offers experimental support for the epidemiological data associating exercise training with decreased sudden cardiac death. However, more evidence is needed in this regard.

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Author contributions

Conception and design of the research, writing of the manuscript and critical revision of the manuscript for intellectual content: Shekarforoush S, Naghii MR; acquisition of data, analysis and interpretation of the data, statistical analysis and obtaining funding: Shekarforoush S.

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

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

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This study was approved by the Ethics Committee on Animal Experiments of Islamic Azad University, Arsanjan Branch (13940215).

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Is There a Role For Whole Body Vibration in Protecting Cardiovascular Disease?

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Short Editorial related to the article: Whole-Body Vibration Training Increases Myocardial Salvage Against Acute Ischemia in Adult Male Rats

Cardiovascular disease is the leading cause of death worldwide. In this context, it is well accepted that physical activity plays a critical role as a powerful therapeutic strategy for prevention and progression of cardiovascular disease, both in experimental models and in different clinical situations.[1,2]

Whole body vibration training (WBV) is a new intriguing training program. Importantly, if vibration-induced protection is an effective method of exercise, it could be an alternative to exercise training especially for those who are unable to perform the traditional exercise. Therefore, the effects of WVB on different systems, including the cardiovascular system, has been investigated in recent years.

Considering clinical studies, the results suggesting benefits with this strategy have been conflicting. For example, the effects of WBV on neuromuscular performance, mobility, spasticity, and cardiovascular responses have been studied after stroke. Although some positive results were reported, recent systematic review concluded that there is no solid evidence confirming the beneficial effects of WBV among people with stroke.[3] On the other hand, in pediatric cancer patients, WBV improved lower extremity muscle mass and strength, balance control, gait, and walking ability.[4] Likewise, in patients with moderate COPD, WBV increased physical performance and quality of life. However, there were no effects on inflammatory and oxidative biomarkers.[5]

Keywords

Cardiovascular Diseases; Mortality; Exercise/prevention and control; Vibration; Exercise Movement Techniques; Mobility; Stroke/rehabilitation.

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In experimental models, WBV therapy after ischemia reduced brain damage in senescent rats.[6] In another model, WBV attenuates oxidative stress to ameliorate liver steatosis and improves insulin resistance in db/db mice.[7] Likewise, whole-body vibration reversed ageing-induced increases in hepatic lipid storage in mice.[8]

In this issue of the Arquivos Brasileiros de Cardiologia, Autor et al studied the safety and efficacy of vibration on myocardial ischemia-reperfusion injury.[9] Twenty four male Wistar rats were divided into control and vibration groups and all the rats were subjected to myocardial IR injury. Vibration training consisted of vertical sinusoidal whole body vibration for 30 min per day, 6 days per week. The data showed that vibration training increased the cardiac tolerance to IR injury in rats, as evidenced by the reduction of infarct size and cardiac arrhythmias, and by facilitation of spontaneous defibrillation.

Although promising, these results should be interpreted with caution, because not infrequently, the success of the experimental treatments studied does not replicate when applied to clinical studies. Additionally, cardioprotection strategies in situations of ischemia reperfusion is the main model used to exemplify the difficulties of translational medicine, since positive results from experimental studies are obfuscated by the fact that to date, cardioprotection strategies in clinical studies have shown negative results.[10]

For the above, although the data are not consistent, there is evidence of the benefit of WBV in different models. However, the vast majority of the evidence comes from experimental research and clinical studies with small numbers of patients, single-centre, non-randomized, and not having cardiovascular events as the main outcomes. Therefore, more studies are needed to clarify the exact role of this new modality of physical activity in the management of cardiovascular disease.

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Clinical Outcomes and Cost-Effectiveness Analysis of FFR Compared with Angiography in Multivessel Disease Patient

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Abstract

Background: In multivessel disease patients with moderate stenosis, fractional flow reserve (FFR) allows the analysis of the lesions and guides treatment, and could contribute to the cost-effectiveness (CE) of non-pharmacological stents (NPS).

Objectives: To evaluate CE and clinical impact of FFR-guided versus angiography-guided angioplasty (ANGIO) in multivessel patients using NPS.

Methods: Multivessel disease patients were prospectively randomized to FFR or ANGIO groups during a 5 year-period and followed for < 12 months. Outcomes measures were major adverse cardiac events (MACE), restenosis and CE.

Results: We studied 69 patients, 47 (68.1%) men, aged 62.0 ± 9.0 years, 34 (49.2%) in FFR group and 53 (50.7%) in ANGIO group, with stable angina or acute coronary syndrome. In FFR, there were 26 patients with biarterial disease (76.5%) and 8 (23.5%) with triarterial disease, and in ANGIO, 24 (68.6%) with biarterial and 11 (31.4%) with triarterial disease. Twelve MACEs were observed – 3 deaths: 2 (5.8%) in FFR and 1 (2.8%) in ANGIO, 9 (13.0%) angina: 4(11.7%) in FFR and 5(14.2%) in ANGIO, 6 restenosis: 2(5.8%) in FFR and 4 (11.4%) in ANGIO. Angiography detected 87(53.0%) lesions in FFR, 39(23.7%) with PCI and 48(29.3%) with medical treatment; and 77 (47.0%) lesions in ANGIO, all treated with angioplasty. Thirty-nine (33.3%) stents were registered in FFR (0.45 ± 0.50 stents/lesion) and 78 (1.05 ± 0.22 stents/lesion) in ANGIO (p = 0.0001), 51.4% greater in ANGIO than FFR. CE analysis revealed a cost of BRL 5,045.97 BRL 5,430.60 in ANGIO and FFR, respectively. The difference of effectiveness was of 1.82%.

Conclusion: FFR reduced the number of lesions treated and stents, and the need for target-lesion revascularization, with a CE comparable with that of angiography. (Arq Bras Cardiol. 2019; 112(1):40-47)

Keywords: Fractional Flow Reserve, Myocardial; Cost-Benefit Analysis; Coronary Artery Disease/economics; Angioplasty, Balloon, Coronary; Stents.

Introduction

In stable coronary artery disease (CAD), angiographic lesions that would benefit most from myocardial revascularization (MR) are those associated with ischemia.[1]

Non-invasive tests (NITs) for ischemia may yield conflicting results, which make it difficult to identify culprit lesions based on symptoms, and consequently to make better therapeutic decisions.[2] In multivessel coronary disease patients, angiography may fail to evaluate the prognosis, especially in those with moderate stenosis (50-70%).[3]

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FAME-2[4] trial compared the use of fractional flow reserve (FFR) and angiography alone to identify coronary stenosis that required treatment. The study could be discontinued earlier due to the superiority of FFR-guided revascularization.

Although most percutaneous coronary interventions (PCIs) are still performed without NITs, 70% of patients referred for PCI have multivessel diseases, and 80% have moderate lesions.[5] However, it is estimated that 40-50% of these lesions are ischemic.

FFR is the best method to associate obstruction with ischemia. A FFR < 0.75 is considered to be associated with ischemia, with sensitivity, specificity, positive and negative predictive values greater than 90%.[6,7] PCI for ischemic lesions is cost-effective and decreases the occurrence of major adverse cardiac events (MACE).[8]

Fearon et al.[9] showed that FFR-guided PCI in patients with one-vessel CAD was superior to other therapeutic strategies based on angiography or scintigraphy.

Our study aims to add to the knowledge of the cost-effectiveness (CE) of FFR-guided PCI in patients with multivessel CAD.

Objectives

To assess the occurrence of MACE and CE of FFR, compared with angiographic criteria for patients with multivessel diseases undergoing PCI.

Methods

Prospective, randomized, clinical study on PCI in 70 patients with multivessel disease attending Pedro Ernesto University Hospital of the Federal University of Rio de Janeiro and Aloysio Castro Institute of Cardiology between April 2011 and May 2016.

Patients were randomized using computer-generated random numbers (R software, 2.11) to:

1. FFR measurements of significant lesions and PCI with stent implantation for lesions with FFR < 0.75 (FFR group);
2. PCI with stent implantation for stenosis > 60% by visual assessment with angiography (ANGIO group).

Each computer-generated number corresponded to one group. The numbers were put into opaque, sealed envelopes, which were sequentially opened for each patient recruited for the study by an independent person who was unaware of the allocation.

Sample size was calculated using Epi-Info software, version 3.4, considering a power (1-β) of 80% and 95% confidence interval. An estimated 17% difference in the costs between the two groups was used for calculation of the sample size required to reach statistically significant difference.

The sample size calculated was 200 (100 for each group); however, due to financial constraints, the number of patients included was 70.

Population

Patients aged 21 years or older with stable multivessel disease or at day 7 after acute coronary syndrome (ACS), with at least one moderate stenosis (>60%) without severe left ventricular dysfunction, and with NIT for ischemia, were divided into two groups (Table 1). In group 1 (FFR, n = 34), PCI was performed for FFR < 0.75, whereas in group 2 (ANGIO, n = 35), patients underwent PCI with stent implantation in all significant lesions. One patient was lost to follow-up, and a total of 69 patients were studied. Dual antiplatelet therapy (DAPT) was used for at least 6 months. Patients were assessed at 30 days, six months and one year of follow-up (Table 2). At six months, NIT and coronary angiography were performed in symptomatic or ischemic patients; FFR measurements were performed again in the first group, and restenosis was treated according to the course of disease.

Cost-effectiveness

We used the CE model proposed in the Brazilian study by Polanczyk et al.[10] CE outcome measure was "one-year restenosis-free survival".

Effectiveness analysis

Estimates were obtained from the literature,[10] and the cost of procedure index calculated under the perspective of the Brazilian Unified Health System (SUS). We analyzed the mean costs of each intervention, considering SUS's reimbursement to the hospitals. For each intervention, we calculated expected costs and the clinical outcomes described above.

Statistical analysis

Data were described as frequency, mean and standard deviations, and median and interquartile ranges. The Kruskal-Wallis test was used for outcome comparisons between the groups, and the Pearson's chi-square test or Fisher's exact test was used for comparisons of dichotomous variables. Logistic regression was used to analyze the association between independent variables and outcomes. Kaplan-Meier survival curves were constructed and compared by log-rank test. Survival was analyzed by bivariate and multivariate Cox regression analysis. SATAT 14 (SATA Inc) software was used for analysis. The level of significance was set at $p \leq 0.05\%$. All tests were two-tailed.

Results

Patients' characteristics are described in Table 1. Most patients had a stable disease, or those with ACS patients were asymptomatic for 7 days. MACEs were reported by 12 patients (17.3%) – 6 patients (17.1%) in FFR group and 6 patients (17.1%) in ANGIO group. Three deaths occurred, 2 (2.8%) in the FFR group and 1 (1.4%) in the ANGIO group (AMI, without DAPT discontinuation). Nine (13.0%) had angina, 4 (5.7%) in FFR group and 5 (7.2%) in the ANGIO group (Figure 1). In the 4 patients of the FFR group, based on FFR measurements, 2 patients did not require a second PCI and continued in medical treatment. In the other 2 patients, intra-stent restenosis was confirmed, and these patients were treated with pharmacological stents (PS), with satisfactory results.

In group 2, one symptomatic patient with mild apical ischemia (according to scintigraphy), continued on medical treatment despite restenosis of marginal branch, but without restenosis of right coronary artery (Table 3). Event-free survival curve in the study population and by groups during the 18-month period of follow-up is depicted in Figure 2.

Angiographic results

In the analysis by group, no difference was observed in the number of lesions evaluated (vessels that require treatment) between the groups. There was a balanced distribution of lesions between anterior descending artery, circumflex artery and right coronary artery.

Lesions by study group

No difference was found in the number of stents per patient, with a mean of 1.0 ± 0.2 stents per lesion in the ANGIO group, and 0.4 ± 0.5 in the FFR group (p = 0.0001) (Kruskal-Wallis), i.e. a 50% reduction. The number of lesions treated in ANGIO group was 65% greater than in FFR group. On the other hand, 45% of lesions analyzed in FFR were treated. In ANGIO group, stent implantation per patient was more than twice the number observed in FFR group (1.1 vs. 2.2 *stents*/patient). Characteristics of the lesions were assessed by angiographic quantification. In group 1, FFR were measured before and after procedure (Table 4).

Table 1 – Characteristics of the study population (overall and by group)

	Overall study population (%)	FFR n (%)	ANGIO n (%)	p
Number of patients	69 (100.0)	34 (49.3)	35 (50.7)	–
Male sex	47 (68.1)	25 (53.2)	22 (46.8)	0.342*
Female sex	22 (31.9)	9 (40.9)	13 (59.1)	0.342*
Diabetes	24 (35.8)	12 (50.0)	12 (50.0)	0.930*
Hypertension	51 (73.9)	25 (49.0)	26 (50.9)	0.943*
Dyslipidemia	50 (72.5)	24 (42.0)	26 (52.0)	0.731*
Family history	40 (57.9)	21 (52.5)	19 (47.5)	0.529*
Current smoker	19 (27.5)	10 (52.6)	9 (47.4)	0.731*
Previous AMI	15 (21.7)	8 (53.3)	7 (46.7)	0.722*
Stable angina	42 (60.8)	20 (47.6)	22 (52.3)	0.930‡
Acute coronary syndrome	27 (39.1)	14 (57.1)	13 (42.8)	0.930‡
Age (years) mean ± SD	62.0 ± 9.0	62.7 ± 8.4	59.5 ± 9.4	0.117*
LV ejection fraction (%) (mean ± SD)	67.0 ± 13.3	70.0 ± 14.0	64.0 ± 12.0	0.110†

*AMI: acute myocardial infarction; FFR: fractional flow reserve group; ANGIO: coronary angiography group; SD: standard deviation; LV: left ventricle. * Pearson's chi-square test; † Kruskal-Wallis test; ‡ Fisher's exact test.*

Table 2 – Major adverse cardiovascular events in the study population

	Study population (%)	FFR n (%)	ANGIO n (%)
MACE	12 (17.3)	6 (17.6)	6 (17.1)
Total deaths	3 (4.3)	2 (5.8)	1 (2.8)
Deaths from cardiovascular causes	2 (2.8)	1 (2.9)	1 (2.8)
Deaths from non-cardiovascular causes	1 (1.4)	1 (2.9)	0 (0.0)
Angina	9 (13.0)	4 (11.7)	5 (14.2)
Target lesion revascularization	6 (8.6)	2 (5.8)	4 (11.4)*

*FFR: fractional flow reserve group; ANGIO: coronary angiography group; MACE: major adverse cardiovascular events; * 1 patient missed second coronary angiography and was lost to follow-up.*

Cost-effectiveness

Estimates of the main clinical outcomes and probabilities to be included in the decision model were obtained from the literature, by review of randomized trials involving non-pharmacological stents (NPS) and PCI. Procedure-index cost and, the cost of post-PCI stable stage, and other costs were expressed in Brazilian Reals (BRL) (Table 5).[10] The difference in effectiveness, costs and incremental CE ratio (ICER) were 1.8%, BRL384.61, and BRL21,156.55, respectively (Table 6).

Discussion

The present study shows that FFR-guided PCI is a cost-effective strategy compared with angiographic criteria in patients with multivessel diseases, reducing the number of stenosis, stents and need for target lesion revascularization (TLR).

Asymptomatic patients, even elderly patients older than 75 years,[11] with percent myocardial ischemia ≥ 10% ischemic benefit from MR. In the COURAGE trial nuclear substudy,[12] patients that achieved a reduction in ischemic myocardium from ≥10% to <5%, showed better outcomes. Reduction of risk factors is essential in medical therapy. In this regard, to reduce the extension and severity of ischemic myocardium may contribute to the improvement of patients' quality of life, particularly among those whose medical treatment was shown to be ineffective. The correlation of coronary anatomy with ischemic parameters may provide a rational and safe basis for revascularization. The ISCHEMIA trial,[13] still under way, was designed to compensate for existing limitations in the literature. In the present study, we attempted to show a reduction in MACE with FFR-guided invasive strategy compared with optimized medical treatment, and only for patients that did not respond to medical treatment.

The key point in performing or not MR is the possibility of quantifying ischemic lesions per segment in case of multiple lesions, especially when associated with moderate lesions, which represent most of the cases. In this context, the only method capable of showing this relationship is FFR. However, the method is not only an invasive strategy, but also involves higher costs. In Brazil, the reality of PCI is very

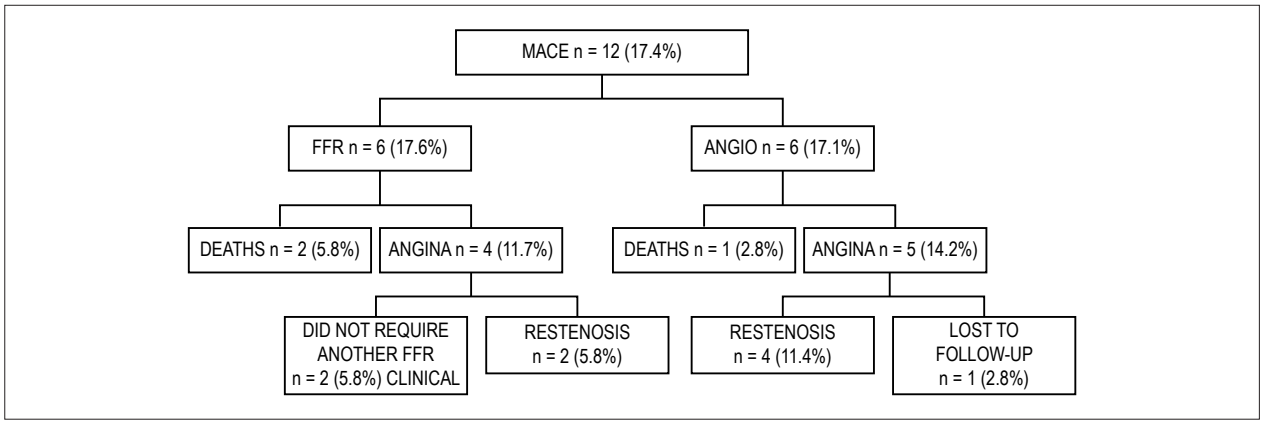

Figure 1 – *Flowchart of major cardiac events (MACE) by study group. FFR: fractional flow reserve group; ANGIO: coronary angiography group.*

Table 3 – Characteristics of patients with compound events (Angina/Restenosis)

	FFR				Total	ANGIO					Total
Number of patients	1	2	3	4		1	2	3	4	5	
Angina								No			
Asymptomatic / (+) ischemia	No	No	No	No	No	No	No	No	No	No	
Vessels to be treated	2	2	2	2	8	3	2	3	2	2	12
Vessels treated	1	0	1	0	2	3	2	3	2	2	12
Control catheterization									No		
Vessels with restenosis	1	0	1	0	2	2	3	1	(?)	1	7
Target-lesion revascularization	1	0	1	0	2	2	1	No	No	1	4

FFR: fractional flow reserve group; ANGIO: coronary angiography group.

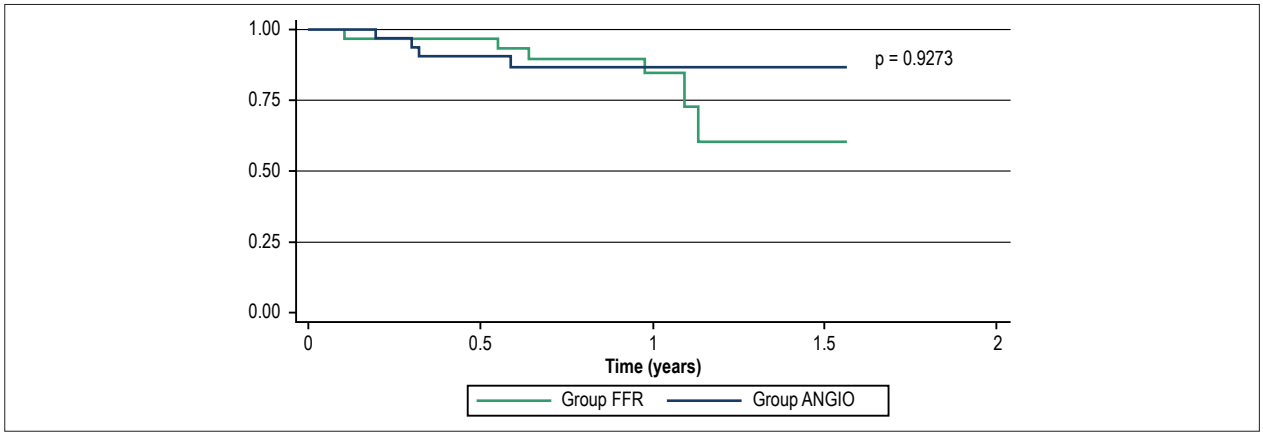

Figure 2 – *Event-free survival curve (Kaplan-Meier) by group in an 18 month-period FFR: fractional flow reserve group; ANGIO: coronary angiography group.*

particular. Although their coverage by SUS was approved in August 2014, due to their high costs, PSs are not widely provided by the system. Instead, their use is restricted to diabetic patients in whom vessels with diameter <2.5 mm and extension >18 mm is observed.[14]

The choice to treat with percutaneous revascularization mutivessel diseases was grounded in studies on FS – the SYNTAX,[13] FAME[15] and FAME-2[4] studies.

Data on revascularization with NPS and FFR are scarce. However, the use of FFR in multivessel diseases have been evaluated, with no difference in mortality or non-fatal infarction, despite differences in TLR.[16]

This randomized, prospective study on patients with multivessel diseases referred for FFR- or angiography-guided PCI was based on FAME study,[15] using NPS though. Also, in our study, lesions with FFR > 0.75 were not treated, different

Table 4 – Mean fractional flow reserve before and after percutaneous coronary intervention

	n	FFR (mean ± SD)	p
Before PCI	87	0.74 ± 0.15	0.290*
Post-PCI	39	0.90 ± 0.06	0.290*

*FFR: fractional flow reserve; PCI: percutaneous coronary intervention; SD: standard deviation; * Pearson's chi-square test.*

Table 5 – Estimates for the model: procedure and outpatient service costs

Procedures	Costs (BRL)	
	ANGIO	FFR
Procedure-index	1,503.00	1,503.00[28]
(*Stent* and FFR – mean cost)	2,034.50	2,517.25
Restenosis management (ICP + c/ SF*)	7,904.01[29]	
Revascularization surgery – elective	7,620.60[29]	
- emergency	8,950.50[28]	
AMI-index	2,716.95[29]	
One year without events following ICP or stable MRS	1,383.00[28]	
Cardiac catheterization	539.00[28]	
Mean PCI	5,386.76[29]	
PCI with balloon	1,599.02[29]	
Death for CAD	2,577.00[28]	

*PCI: percutaneous coronary intervention; AMI: acute myocardial infarction; CAD: coronary artery disease; MRS: myocardial revascularization surgery; ANGIO: coronary angiography group; FFR: fractional flow reserve group. * Management of restenosis with percutaneous coronary intervention + covered stent.*

Table 6 – Results of cost-effectiveness analysis: coronary angiography (ANGIO) group versus fractional flow reserve (FFR) group

Strategy	One-year effectiveness	Difference in effectiveness	Cost (BRL)	Cost difference (BRL)	ICER
ANGIO	78.52%	–	5,045.97	–	–
FFR	80.34%	1.82%	5,430.60	384.62	21.156.55

ICER: incremental cost-effectiveness ratio; ANGIO: coronary angiography group; FFR: fractional flow reserve.

from FAME, that used a cut-off of 0.80. The choice for a lower cut-off point was justified by a 100%[16] predictive value for a FFR value of 0.75. A cut-off of 0.75 would hence represent a lower chance of restenosis, since it would be expected a higher incidence of restenosis with the use of NPS.

Li et al.[17] evaluated more than 7,300 patients, 1,090 of them undergoing FFR-guided PCI, 30% with NPS. After the exclusion of patients with FFR > 0.75 and < 0.80, there was a decrease in the rates of AMI and in the composite of AMI and death. In patients with FFR > 0.80, a conservative approach was used.

Clinical data

Although the increment of 1.45% in mortality in the FFR group was not statistically significant, the result contrasts with the literature, although we attributed this finding to the small number of randomized patients.[17-19] Zhang et al.[20] showed in a meta-analysis including nearly 50,000 patients that FFR reduced the absolute risk of late mortality by 7.7%.[20]

The frequency of MACE in our study group was 17.3%, with similar distribution between the groups, in accordance with the FAME study.[15] The incidence of angina in the FFR group was identical between the groups.

In the present study, 9 (13.0) patients had angina and/or ischemia according to ergometric test, 4 (44.4%) in the FFR group and 5 (55.6%) in the ANGIO group. In the ANGIO group, one patient was lost to follow-up before reassessment. All the four patients reassessed were treated for intra-stent stenosis defined by angiographic criteria, whereas in the FFR group, functional analysis indicated that 2 of these 4 patients required treatment. When we evaluated the need for new revascularization considering the presence of clinical restenosis (angina/ischemia) and functional reassessment, only half of patients in the FFR group was subjected to another PCI for intra-stent restenosis. In the ANGIO group, according to angiographic criteria, 12 vessels with restenosis were identified, which were later treated. In the FFR group, 8 vessels were reassessed, and only 2 required treatment. Thus, in the former group, the number of treated vessels was six times greater, with twice the number of TLR compared with the latter group.

These results contrast with those reported in the FAME study,[15] probably because only PS (without inclusion of NPS) was used by the authors.

In addition, we could speculate that, considering the use of NPS in patients with multivessel diseases, the choice for FFR could provide additional benefit. Since the incidence of restenosis was higher in this population, although the percentages of lesions did not differ with the use of PS, there was a significant reduction in the total number of lesions, in absolute numbers, as described as follows:

For NPS:

Situation 1: considering a hypothetical restenosis rate of 20%, there will be 20 restenosis for every 100 lesions considered significant according to angiographic criteria.

Situation 2: for every 100 lesions functionally analyzed, 50 will be treated; considering the same hypothetical restenosis rate of 20%, there will be 10 restenosis.

For PS:

Situation 1: considering a hypothetical restenosis rate of 5%, there will be 5 restenosis for every 100 lesions considered significant according to angiographic criteria.

Situation 2: for every 100 lesions functionally analyzed, 50 will be treated; considering the same hypothetical restenosis rate of 5%, there will be 2.5 restenosis.

Thus, the use of functional analysis to determine the likelihood of recommending revascularization could prevent more restenosis (in absolute numbers) than NPS.

Considering TLR, only half of patients of the FFR group underwent another PCI, whereas in the ANGIO group, the number of vessels treated was six times greater and the need for TLR was twice higher. These findings differ from those reported in the FAME study,[15] again, probably because only PS was used in their study.

Logistic regression of demographic, clinical and angiographical factors did not show increased risk for MACE, similar to the FAME study.[15]

Angiographic data

In the FFR group, 45% of the lesions analyzed were treated, with a mean of 1.14 stent per patient; in the ANGIO group, all lesions were treated, with a mean of 2.2 stents per patient. The number of stents was 50% greater in the ANGIO group. In the FAME[15] study, however, only 30% of the lesions were treated (2.7 stents per patient in the ANGIO group and 1.9 in the FFR group). The mean extension of stent coverage was 51.4 ± 2.0 mm and 37.9 ± 27.0 mm, respectively,[15] and in our study we found a mean of 14.65 ± 6.91 mm. The mean FFR was 0.74 ± 0.15 mm in our study, very similar to that of the FAME study.[15] Based on functional analysis, 55% and 37% of the lesions analyzed were not treated in the present study and in the FAME study,[15] respectively; this difference may be due to the inclusion of more complex lesions treated by PS in our study. In addition, although mean stenosis percentage (60%) was similar in both studies, mean diameter of target vessel was greater in our study (2.9 ± 0.4 mm and 2,8 ± 0,5 mm in FFR and ANGIO groups, respectively) compared with the FAME study[15] (mean of 2.5 mm in both groups).

Cost-effectiveness

CE compares costs and effects of different health technologies to identify which technique provides the greatest benefit, and the incremental cost (IC) for it. In this economic analysis, costs are expressed in monetary units, whereas effects in clinical-epidemiological units or natural units (prevented cases, survival, cure, etc.). The main of CE analysis is to maximize the outcomes in health with the financial resources available. The most common outcome measure of CE analysis is ICER, which represents the ratio between costs of the techniques (cost of A – cost of B) and effectiveness of the techniques (effectiveness of A – effectiveness of B). This ratio is used to identify which of these strategies result in maximal effectiveness for a given cost, or the degree of investment required to obtain incremental benefit in health.

CE criterion is one of many criteria that should be used to determine whether an intervention should be offered. In addition, equity, needs and priorities should also be considered in the decision-making process. CE relates costs with clinical outcomes and compare relative value of interventions; it translates the difference of costs between two strategies of treatment. The monetary value is divided by the difference of their effectiveness, expressed in years of life gained (life expectancy) or other prevented or avoided events.[21]

Quality-adjusted life year (QALY) is a measure of disease burden, of both quality and quantity of life. QALY is used to evaluate the cost-benefit ratio of a therapeutic intervention.[21] In monetary values, therapies with costs lower than USD20,000/QALY are considered favorable strategies; those with costs from USD20,000 to USD40,000/QALY are consistent with habitual interventions, and therapies with costs higher than USD40,000/QALY are considered of little benefit.

CE of an intervention is known to vary with overall individual or population risk;[21] however, in Brazil, the incremental costs of an intervention that provide clinical benefits have not been established. In both American and Canadian health systems, the value of USD50,000 per QALY, and more recently USD10,000 per prevented major event is considered a reasonable utilization of health resources.

In the present study, the difference of effectiveness in one year was 1.82%; however, ICER, established as the difference of costs between PCI in the ANGIO group and PCI in the FFR group divided by the difference in effectiveness (one-year-restenosis-free survival) was BRL21,156.55. This value is consistent with optimal therapies as well as with overall individual or population risk, and therefore considered cost-effective.

We did not find in the literature studies on the CE of FFR-guided PCI and NPS in patients with multivessel diseases, which is hence a strength of our study. Our findings demonstrate clinical benefits of CE during one year of follow-up, which is not commonly seen in new therapeutic strategies, as shown by Fearon et al.,[22] suggesting an economic or social impact. The use of FFR in PCI in multivessel disease patients is a more cost-effective approach than treating all significant lesions identified by angiography. This can help change the paradigm and reduce costs[23] at the same time and thereby consolidate the practice of medicine based on physiological data, which would lead to better medical care.

Study limitations

The sample size was small, particularly due to limited funding resources, which made it difficult to obtain more consistent clinical data. Despite that, we did show significant differences in CE and reduction in TLR.

Due to the long period of patient recruitment, some multivessel disease patients treated by angioplasty could not be recruited because of logistic and financial issues.

Conclusions

FFR-guided PCI, as compared with angiographic criteria,is a cost-effective strategy that reduces the number of lesions treated, stents, and the need for TVR in patients with multivessel diseases.

Author contributions

Conception and design of the research: Quintella EFQ, Ferreira E, Sant`Anna FM, Albuquerque DC; acquisition of data: Quintella EFQ, Ferreira E, Sant`Anna FM, Amorim B; analysis and interpretation of the data: Quintella EFQ, Ferreira E, Azevedo VMP, Araujo DV, Sant`Anna FM, Albuquerque DC; statistical analysis: Quintella EFQ, Azevedo VMP, Araujo DV; writing of the manuscript: Quintella EFQ, Ferreira E, Albuquerque DC; critical revision of the manuscript for intellectual content: Quintella EFQ, Ferreira E, Azevedo VMP, Araujo DV, Albuquerque DC.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Edgard Freitas Quintella, from Universidade do Estado do Rio de Janeiro.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário Pedro Ernesto/UERJ under the protocol number 146.445. 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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Analysis of FFR Measurement Clinical Impact and Cost-Effectiveness Compared to Angiography In Multi-Arterial Patients Undergoing PCI

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Short Editorial related to the article: Clinical Outcomes and Cost-Effectiveness Analysis of FFR Compared with Angiography in Multivessel Disease Patient

The study by Quintella et al.[1] published in this issue of the journal, brings us valuable information about the use of an important physiological evaluation tool in the hemodynamic laboratory. FFR-guided treatment (myocardial fractional flow reserve), used in the percutaneous coronary intervention (PCI) with bare-metal stent (BMS) implantation in multi-arterial patients treated in the Unified Health System (SUS) has been shown to be useful in decreasing the incidence of new revascularization of the target vessel (clinical restenosis), as well as being cost-effective when compared to the angiography-guided treatment.

The value of FFR to predict major adverse cardiovascular events (MCAEs) prior to PCIs has been established for many years. Its ability to detect ischemia and, with this, to guide the most appropriate treatment, has undergone the test of time, and passed. The 15-year follow-up of the DEFER[2] study in single-vessel patients, and the 5-year studies, FAME 1,[3] and FAME 2,[4] in multiarterial patients, showed consistent and unquestionable results, with a better, or at least similar, clinical progression, in the FFR-guided groups, using less stents with fewer lesions and consequently lower costs, as well as evidenced the safety of leaving lesions whose FFR was not indicative of ischemia only on drug treatment.

The limited value of angiography to predict ischemia has long been known. Sant'Anna et al.[5] showed a weak correlation between angiography, expressed as a percentage of stenosis diameter (SD), and FFR (rho = - 0.33), especially in intermediate lesions (between 40% and 70%). This disagreement between SD and physiology has already been documented in several other studies, such as that by Toth et al.[6] and Park et al.,[7] which also showed disagreement rates between FFR and angiography of 36% and 39% respectively. In a study published in 2007,[8] in 250 patients (452 lesions) assessed by FFR before PCI, 32% of the lesions had their initially planned treatment strategy modified after FFR measurement, which is a major change because it would imply inadequate treatment in more than one third of the patients. More recently, Ciccarelli et al.[9] in a FAME 2 substudy, analyzed the value of angiography compared to FFR to predict the natural history of coronary lesions, correlating MCAE index with the angiographic and physiological importance of these lesions in patients (n = 607) who were initially left only on drug treatment. In the subgroups in which FFR was discordant of angiography (FFR > 0.80 and SD ≥ 50% or FFR ≤ 0.80 and SD < 50%), clinical progression was worse in those in whom FFR was ≤ 0, 80, even if the lesion was not significant, and benign in those in whom FFR was > 0.80, regardless of SD.

In the study by Quintella et al.,[1] MCAE that was reduced in the FFR group was due to the need for new revascularization of the target vessel, with no difference in mortality or infarction. Even with the limited number of patients involved in the study, this data is in agreement with what was presented in the FAME studies, in which, after 5 years of progression, only the need for new revascularization remains different in the groups. We call the attention to the low rate of clinical restenosis in the FFR group (5.8%) of the study by Quintella et al.,[1] because he used only BMS, which may be due to the fact that much less lesions were treated compared to the angio group (1.14 vs. 2.22 stents per patient), and with better selection criteria.

Another interesting finding of the study is the cost-effectiveness (CE) relationship, measured by the incremental cost-effectiveness ratio (ICER), which represents the ratio between the costs of technologies under analysis, and their effectiveness. This ratio is usually adjusted for quality of life, and expressed as QALY (quality-adjusted life year). Costs below USD 20,000/QALY are accepted to be highly supportive of the technology tested. The ICER calculated for the study by Quintella et al.[1] was of R$ 21,156, 55, totally within the CE criteria, mainly if we consider that only BMS were used, that is, if DES were used, ICER would be even lower. Fearon et al.[10] have published an interesting study on FFR CE in the population of FAME 1,[10] in which the author points out that the FFR-guided strategy has a lower cost compared to that guided by angiography in 90.74%, and is cost-effective in 99.96% of cases, being one of those rare situations where a new technology not only improves outcomes, but also saves resources. Siebert et al.[11] found similar findings in the Australian population, where 1.776 USD would also be saved per patient over 1 year with the use of FFR during PCI.

Although we cannot extrapolate these results from other countries to ours, because the prices practiced and the reimbursement system are different, we can still assume that now, when SUS begins to allow the use of drug-eluting stents at a more competitive price, the strategy of use of FFR becomes even more attractive.

Keywords

fractional Flow Reserve,Myocardial; Cost-Benefit Analysis; Coronary Artery Disease/economics; Angioplasty, Balloon Coronary; Stents.

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Left Ventricular Regional Wall Motion Abnormality is a Strong Predictor of Cardiotoxicity in Breast Cancer Patients Undergoing Chemotherapy

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Abstract

Background: **Chemotherapeutic agents of anthracyclines class and humanized monoclonal antibodies are effective treatments for breast cancer, however, they present a potential risk of cardiotoxicity. Several predictors have been recognized as predictors in the development of cardiac toxicity, and the evaluation of left ventricular segmental wall motion abnormalities (LVSWMA) has not been studied.**

Objective: **To analyze prospectively the role of LVSWMA among echocardiographic parameters in the prediction of development of cardiotoxicity in breast cancer patients undergoing treatment with chemotherapy.**

Methods: **Prospective cohort of patients diagnosed with breast cancer and in chemotherapy treatment with potential cardiotoxicity medications including doxorubicin and trastuzumab. Transthoracic echocardiograms including speckle tracking strain echocardiography were performed at standard times before, during and after the treatment to assess the presence (or lack thereof) of cardiotoxicity. Cardiotoxicity was defined by a 10% decrease in the left ventricular ejection fraction, on at least one echocardiogram. Multivariate logistic regression models were used to verify the predictors related to the occurrence of cardiotoxicity over time.**

Results: **Of the 112 patients selected (mean age 51,3 ± 12,9 years), 18 participants (16.1%) had cardiotoxicity. In the multivariate analysis using the logistic regression model, those with LVWMA (OR = 6.25 [CI 95%: 1.03; 37.95], p < 0,05), LV systolic dimension (1.34 [CI 95%: 1.01; 1.79], p < 0,05) and global longitudinal strain by speckle tracking (1.48 [CI 95%: 1.02; 2.12], p < 0,05) were strongly associated with cardiotoxicity.**

Conclusion: **In the present study, we showed that LVWMA, in addition to global longitudinal strains, were strong predictors of cardiotoxicity and could be useful in the risk stratification of these patients. (Arq Bras Cardiol. 2019; 112(1):50-56)**

Keywords: **Ventricular Dysfunction, Left; Drug Therapy; Cardiotoxicity; Breast Neoplasms; Anthracyclines; Trastuzumab.**

Introduction

The introduction of new chemotherapeutic agents, and the use of advanced and precise radiotherapy techniques in the last decades have dramatically improved breast cancer survival.[1] Chemotherapeutic drugs of the anthracycline class, and the humanized monoclonal antibodies, such as trastuzumab, are widely used and highly effective agents for breast cancer treatment.[2] Unfortunately, anthracyclines can induce cardiotoxic effects, and the severity of these adverse effects is compounded by concomitant use of trastuzumab.[3]

Chemotherapy may induce numerous cardiovascular complications, including hypertension, congestive heart failure, thromboembolic diseases, ischemic heart disease, QT prolongation, and bradycardia.[3] When used in combination, anthracyclines and trastuzumab may result in heart failure in up to 27% of patients.[4] Among cancer survivors, a third will die of cardiovascular disease. Thus, the need for optimal cardiac care in the cancer population has become evident. Early detection of cardiac dysfunction may allow implementation of cardioprotective strategies before potentially irreversible myocardial damage has occured.[5]

The definition of cancer therapy-related cardiac dysfunction (CTRCD) is based on a serial decline in left ventricular (LV) ejection fraction (EF). Two-dimensional echocardiography (2DE) is increasingly used for monitoring cardiac function during cancer treatment due to its widespread availability and safety. Echocardiography allows assessment of systolic and diastolic function, pulmonary pressures, valvular function, right ventricular function, and the pericardium.[6]

Reduction in LV EF likely occurs late in the natural history of CTRCD patients as reduction in LV EF may not be overt until a substantial amount of myocardial reserve has been

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exhausted, therefore more sensitive screening modalities for LV dysfunction are needed. Despite the recognition of several echocardiographic parameters associated with CTRCD, including novel echocardiography-derived parameters of myocardial mechanics, such as strain and strain rate, currently there is no consensus in the medical practice to fully predict which patients are prone to develop cardiotoxicity.[6-8] Previous studies have demonstrated the presence of regional myocardial dysfunction in patients with CTRCD,[9-11] however its role as a risk predictor has not been established. The purpose of this study is to verify the association between the occurrence of LV segmental wall motion abnormality and the development of cardiotoxicity in patients with breast cancer undergoing chemotherapy.

Methods

Study population

This study is part of a prospective cohort study of patients with breast cancer recruited from the Mater Dei Hospital in the city of Belo Horizonte - MG from January 2010 through December 2016. Inclusion criteria were, age above 18 years, histologically confirmed breast cancer diagnosis, treatment with doxorubicin and/or trastuzumab, and who underwent echocardiography, according to the rules of the hospital protocol. Exclusion criteria were patients with previous diagnosis of ventricular dysfunction including regional wall motion abnormality, significant valve disease, congenital heart disease, arrhythmias, chronic coronary artery disease and left bundle branch block by electrocardiography. Treatment regimens were at the discretion of the oncologist and consisted of the use of the following drugs alone or in combination: 1) doxorubicin and cyclophosphamide; 2) paclitaxel; 3) trastuzumab. The dosages of the medications were prescribed according to guidelines.[12]

Clinical (e.g., hypertension, dyslipidemia, diabetes) laboratorial (e.g., sodium, potassium, calcium, magnesium, hemoglobin, creatinine and BNP) and transthoracic echocardiograms were collected at baseline and standardized time intervals for each treatment regimen, 6 months after treatment completion and annually thereafter.

Echocardiography

All patients were referred to a transthoracic echocardiogram, including longitudinal strain assessment with two-dimensional speckle-tracking echocardiography (2D STE). The echocardiographic studies and analyses were performed by an experienced cardiologist (M.V.L.B.). The following echocardiographic parameters were assessed: LV end-systolic and end-diastolic diameters and left atrial diameter. LV ejection fraction was assessed using Simpson's biplane method. Visual assessment of regional myocardial function was assessed on the basis of the observed wall thickening and endocardial motion of the myocardial segment, as described previously.[13] Abnormal septal motion was characterized as a atypical movement of the interventricular septum during cardiac cycle with a two-dimensional echocardiography–guided M-mode approach. Diastolic function was assessed and classified using published criteria.[14] LV diastolic dysfunction was stratified into four grades as normal, impaired relaxation, pseudo normal filling or restrictive.

Longitudinal strain by 2D STE was obtained from apical four-chamber, two- chamber, and long-axis views. Three cardiac cycles from each view were recorded for offline analyses with a frame rate > 50 frames/sec. Peak negative longitudinal strain was assessed in 16 LV segments, defined as the peak negative value during the entire cardiac cycle, hence including post systolic shortening, and was averaged to global longitudinal strain (GLS). CTRCD was defined as a decrease in LVEF of > 10 percentage points, to a value < 53% at repeated cardiac imaging studies during follow-up after chemotherapy.[15]

The echocardiographic studies were performed at standardized intervals according to the treatment regimen. 1) Patients treated with anthracyclines without trastuzumab underwent an echocardiographic study at baseline, at completion of chemotherapy, and every six months after completed treatment. 2) Patients treated with anthracyclines and trastuzumab underwent an echocardiographic study at baseline, after completion of the anthracycline treatment regimen, every 3 months during trastuzumab therapy, and every six months after completed treatment. 3) Patients treated with trastuzumab without anthracyclines underwent an echocardiographic study at baseline, every 3 months during trastuzumab therapy, and every six months after completed treatment.

Echocardiographic assessment was completed in patients with at least three echocardiographic studies performed during the research period.

Statistical Analysis

To describe the qualitative variables, the absolute and relative frequencies were used, while to describe the quantitative variables, measures of central tendency, dispersion and position were used.

In order to identify the factors that influenced the occurrence of cardiotoxicity over time, the Generalized Estimation Equations (GEE) approach was used. An exchangeable correlation structure was assumed for the repeated observations of the same individual. Univariable and multivariable models with a logit link function were considered. There was no occurrence of cardiotoxicity at the first measurement occasion and therefore we also included the baseline values of the time-dependent predictors. Missing values were excluded from the analyses. Variables that were statistically significant at the 0.20 level were included in the multivariable model. For this final model, a level of significance of 0.05 was adopted. Reproducibility of visual assessment of abnormal regional myocardial function was evaluated by the kappa statistics.

ROC curves were built and the discrimination ability of the model was assessed by the area under the ROC curve. All statistical analysis was performed using R Statistical Software 3.4.1 and the R packages gee, pROC and PredictABEL.

Ethical considerations

The study complies with the Declaration of Helsinki and was approved by the Research and Ethical Council of the Mater Dei Hospital.

Results

Studied population

A total of 112 patients were included. Mean follow-up time was 491 days. The characteristics of the population studied are summarized in Table 1. Most of the patients in the cohort were female (98.2%). Mean age was 51.3 ± 12.9 years.

Of the 112 patients followed up, 18 (16.1%) presented CTRCD.

The characteristics of the patients with abnormal LV segmental wall motion are summarized in table 2. LV segmental wall motion abnormality was found in 16 (14%) patients, most commonly at the time of the second echocardiographic study (43%). LV segmental wall motion analyses by visual assessment showed abnormalities most frequently in the interventricular septum (78.5% - Figure 1), the inferior (14.3%), and the inferolateral (7.1%) walls. During the follow-up, no patient presented left bundle branch block by electrocardiography study.

Among the variables studied, it was observed at multivariable analysis that GLS measurements as well as LV systolic dimensions and the presence of LV regional wall motion abnormalities at the baseline study could predict development of cardiotoxicity (Tables 3 and 4). The analysis of ROC curve of the final model (Figure 2) showed an area under the curve (AUC) of 0.93 (0.88 – 0.98). When we exclude the presence of wall motion abnormality in the model, the AUC was 0.84 (0.72-0.96) showing additive predictive power of this variable (p = 0.047). Intraobserver variability and interobserver variability for wall motion assessment were 0.89 and 0.81, respectively.

Table 1 – Clinical and laboratorial characteristics of 112 patients undergoing chemotherapy

Variable	n
Age (mean ± SD)	51,4 ± 11,1
Female (n/%)	111 (99,1%)
BMI (kg/m^2)	26,1 ± 5,8
Mastectomy (n/%)	111 (99,1%)
Median follow-up time (months)	16
Radiotherapy (n/%)	74 (66)
Chemotherapy (n/%)	
AC-T	90 (80)
Anti HER2	29 (26)
Others	20 (18)
Hormone Therapy (n/%)	72 (64)
Cardiovascular risk factors (n/%)	
Hypertension	39 (35)
Diabetes	8 (7)
Hyperlipidemia	21 (19)
Smoking	25 (22)

BMI: body mass index; AC-T: Doxorubicin/cyclophosphamide - Taxol (Paclitaxel).

Discussion

In this prospective, longitudinal cohort study, we showed that the presence of regional wall motion disturbance and decreased GLS are strong predictors of CTRCD.

Earlier histopathological studies performed from endomyocardial biopsies have demonstrated an initially focal and dispersed involvement of myocytes, surrounded by normal cells in patients treated with anthracyclines.[16] As the toxicity evolves, the frequency of these alterations increases, leading to significant myocardial damage and later on to diffuse myocardial fibrosis. Thus, segmental contractile dysfunction may precede the intense and diffuse involvement of the heart seen in CTRCD. In this context, interventricular septum dyssynchrony, as well as segmental hypokinesia may be present due to tissue edema and/or focal cellular damage.[17]

Indeed, Piotrowsk et al.[9] demonstrated that in 60.9% of patients with LV systolic dysfunction regional wall motion abnormalities were observed in the first echocardiography that revealed a significant drop of LVEF. In the majority of these cases (64%), regional hypokinesis involved the interventricular septum.[9] Previous studies using tissue Doppler and 2D strain have also shown regional contractile alterations in patients treated with chemotherapy.[10,11] Boyd et al.[18] demonstrated that in the group with subclinical LV dysfunction (> 11% reduction in GLS compared to before therapy) 58% of regional segments had a reduction in strain by > 11%, compared to 29% of regional segments in the group without subclinical LV dysfunction (p < 0.001).[18]

It is well known that reduction of longitudinal strain is an early predictive factor of cardiotoxicity induced by treatment with anthracyclines and trastuzumab, as confirmed by our results. Negishi et al. showed that GLS was an independent predictor of subsequent reductions in EF, with a discrimination improvement by adding GLS of -18.6% to traditional parameters by echocardiography in patients at risk for trastuzumab-induced cardiotoxicity.[19] In another study, Sawaya el al.[20] showed that in patients with breast cancer treated with chemotherapy, GLS measured at the completion of anthracycline therapy was useful in the prediction of subsequent cardiotoxicity.[20]

It was shown in a systematic review that an early reduction of 10% to 15% in GLS was a useful parameter for the prediction of cardiotoxicity.[21] A small cohort study was associated with subclinical LV dysfunction as early as 1 week after treatment, showing a significant decrease in GLS and annular systolic velocity of the lateral LV wall 7 days after by trastuzumab treatment.[22] Fei et al.[23] found, in a cohort of 95 patients treated with anthracycline and trastuzumab, and followed for a mean time of 17 months, 20% with cardiotoxicity, demonstrating a significant association between GLS reduction and LVEF decline.[23]

The presence of diastolic dysfunction was not an independent predictor of CTRCD in our study. The use of diastolic dysfunction as a surrogate marker for predicting trastuzumab-induced cardiotoxicity is controversial. Earlier studies have shown that diastolic impairment of the LV occurs before deterioration in LV EF in anthracycline[24,25] and transtuzumab[26,27] induced cardiotoxicity. Development

Table 2 – Characteristics in patients with segmental wall motion abnormality during chemotherapy

Patient	Age	Treatment*	Abnormal contraction	Echocardiographic follow-up	Risk factors	CTRCD	Follow-up
2	49	1,2,	Infero-septal Hypokinesis	5	no	yes	Death
5	40	1,2	Abnormal Septal motion	2	no	yes	NYHA I
12	68	1,2	Ínfero-lateral Hypokinesis	5	no	yes	NYHA I
21	30	1,2	Abnormal Septal motion	3	dyslipidemia	no	
27	43	1,2	Abnormal Septal motion	2	no	no	
52	73	1,	inferior Hypokinesis	4	Diabetes, Hypertension	yes	NYHA I
63	53	1	Septal Hypokinesis	2	no	no	
67	77	1,2	Abnormal Septal motion	4	hypertension	yes	NYHA II
72	44	1,2	Abnormal Septal motion	2	no	no	
84	59	1,2	Inferior Hypokinesis	4	no	no	
88	34	1	Abnormal Septal motion	3	no	no	
92	39	1	Abnormal Septal motion	3	no	yes	death
100	41	1	Infero-septal Hypokinesis	2	no	no	
110	62	1	Septal hypokinesis	2	no	yes	NYHA !

**1: anthracycline; 2: transtuzumab; CTRCD: cancer therapy-related cardiac dysfunction.*

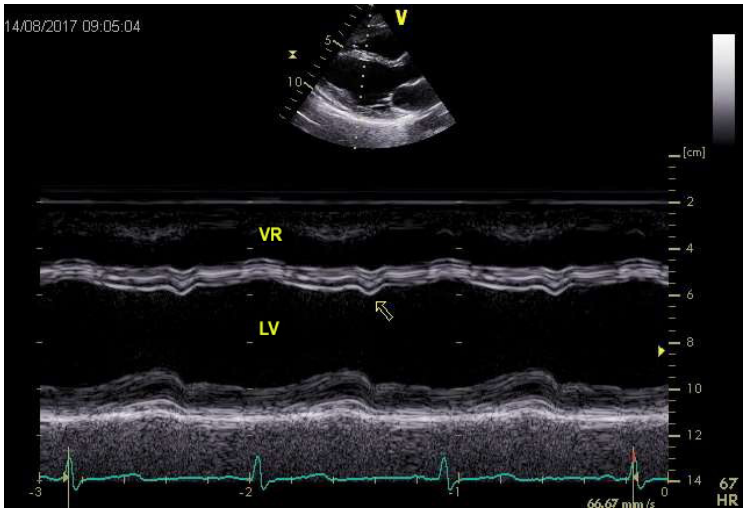

Figure 1 – *Two-dimensional echocardiography–guided M-mode showing abnormal motion of interventricular septum (arrow) during chemotherapy treatment. LV: left ventricle; RV: right ventricle.*

of diastolic dysfunction has been reported in up to 57% of patients after treatment with anthracyclines or anthracyclines plus trastuzumab.[28] Cochet et al.[28] Serrano et al.[29] evaluated MUGA-derived diastolic parameters and found that impaired LV diastolic function before treatment was an independent predictor of trastuzumab-mediated cardiotoxicity. Boyd at al.[18] showed in a cohort involving 140 patients followed for seven days that LV diastolic dysfunction grade significantly increased from 46% to 57% ($p < 0.001$) after treatment with anthracyclines. Importantly, diastolic dysfunction was more prevalent in the subgroup with a significant reduction in GLS, demonstrating the close association between systolic and diastolic dysfunction.[18] A study using MUGA-derived diastolic function parameters investigated whether impairment of systolic function was preceded by diastolic dysfunction in a group of 77 female breast cancer patients undergoing trastuzumab therapy. The results of this study showed a nearly even number of patients with diastolic dysfunction preceding systolic dysfunction (54%), as compared to the number of patients with the opposite order (42%).[30] Discrepancy among those studies is probably related to the different designs and interpretation of the results.

Table 3 – Univariate analyses of predictors related of cardiotoxicity

Variable	O.R.	95% CI	p
Age	1.03	[0.99; 1,07]	0.151
LVDD	1.22	[0.99; 1.50]	0.061
LVSD	1.69	[1.35; 2.12]	0.000
Diastolic dysfunction	3.55	[1.34; 9.44]	0.011
Regional wall motion abnormality	8,91	[2.75; 28.82]	0.000
LA	0.95	[0.78; 1.16]	0.624
GLS	1.96	[1.25; 3.09]	0.022
PASP	1.86	[0.32; 10.99]	0.491
BNP	1.24	[00.91; 1.70]	0.306
Troponin	3.36	[0.49; 23.14]	0.219
Creatinine	0.04	[0.00; 2.20]	0.113
Hemoglobin	0.90	[0.60; 1.35]	0.608
Sodium	1.01	[0.98; 1.03]	0.623
Potassium	1.33	[0.51; 3.51]	0.559
Calcium	1.06	[0.81; 1.39]	0.657
Magnesium	6.20	[0.67; 57.73]	0.204
Hypertension	0.79	[0.26; 2.39]	0.673
Dyslipidemia	0.41	[0.07; 2.21]	0.298
Diabetes	1.15	[0.15; 8.83]	0.894

LVDD: left ventricular diastolic dimension; LVSD: left ventricular systolic dimension; GLS: global longitudinal strain; LA: left atrium dimension; PASP: pulmonary artery systolic pressure; BNP: brain natriuretic peptidium.

Table 4 – Multivariate analysis of predictors related of cardiotoxicity

Variable	O.R.	95% CI	p
LVSD	1.34	[1.01; 1.79]	0.044
Regional wall motion abnormality	6.25	[1.03; 37.95]	0.046
GLS	1,48	[1,02; 2.12]	0.036

LVSD: left ventricular systolic dimension; GLS: global longitudinal strain.

Limitations

All patients were recruited from one center and the study consisted of a limited number of patients. The study was limited by a short duration of patient follow-up, and therefore any possible long term impact of the early echocardiography abnormalities are uncertain. Long term follow up is therefore necessary to determine the significance of these early observations. The proposed treatment was individually defined, including the use of cardio-protective drugs, which may have influenced our results.

Conclusion

In this prospective cohort of 112 patients undergoing treatment with chemotherapy for breast cancer, we found segmental wall motion abnormality to be a strong predictor of cardiotoxicity. Therefore, assessment of segmental wall motion might be a useful tool in the evaluation of patients at risk of developing CTRCT, resulting in early detection of myocardial dysfunction and potential reduction in morbidity and mortality in these patients.

Author contributions

Conception and design of the research and critical revision of the manuscript for intellectual contente: Barros MVL, Macedo AVS, Sarvari SI, Faleiros MH, Felipe PT, Silva JLP, Edvardsen T; acquisition of data: Barros MVL, Faleiros MH, Felipe PT; analysis and interpretation of the data: Barros MVL, Macedo AVS, Sarvari SI, Silva JLP; statistical analysis: Silva JLP; writing of the manuscript: Barros MVL, Macedo AVS, Sarvari SI, Felipe PT, Edvardsen T.

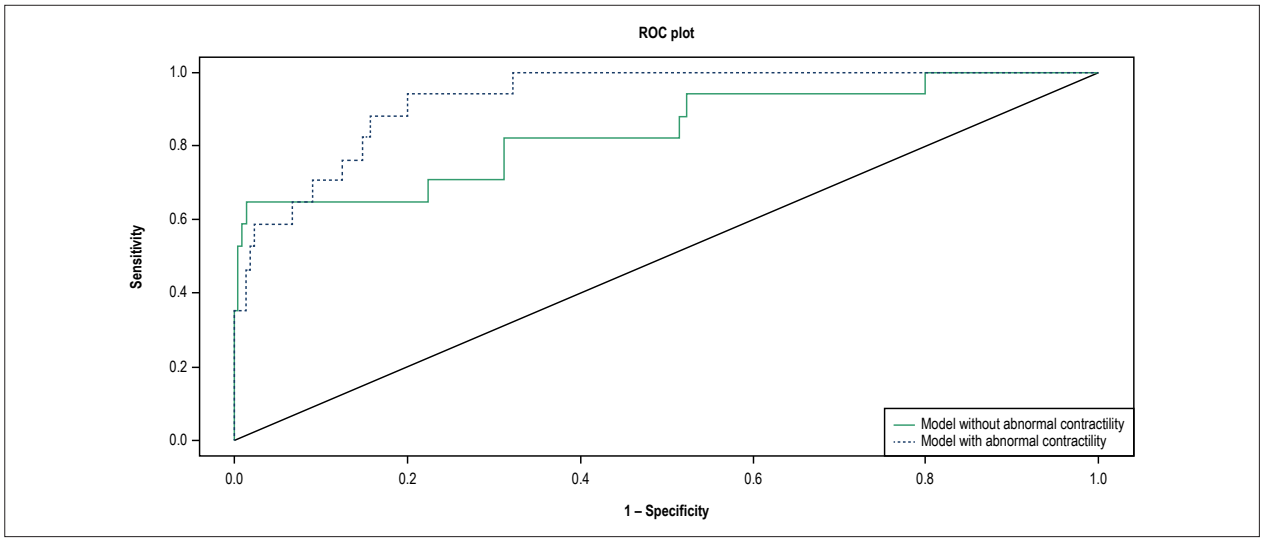

Figure 2 – *Roc curve of the multivariate model with and without evaluation of segmental abnormal contractility.*

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 of the Faculdade de Saúde e Ecologia Humana (FASEH) under the protocol number CAAE 55029916.6.0000.5101. 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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Usefulness of Myocardial Deformation Indices in Preventing Cardiotoxicity in Breast Cancer Patients

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Short Editorial relate to the article: Left Ventricular Regional Wall Motion Abnormality is a Strong Predictor of Cardiotoxicity in Breast Cancer Patients Undergoing Chemotherapy

The first description of chemotherapy-induced heart failure (Stage C) was published in 1967.[1] There has been a therapeutic evolution in oncological treatment since then, as shown by the fact that, as of 2005, the survival rate exceeded that of mortality.[2] This has resulted in a new epidemiological problem for these survivors, since at least 30% of them will show some degree of cardiotoxicity, which can occur up to decades after the end of the chemotherapy. Moreover, cardiovascular mortality is already considered the second most common cause of death, second only to cancer.[3-5]

The classically accepted definition for cardiotoxicity during treatment was proposed in 2014, which described it as an absolute decrease in left ventricular (LV) ejection fraction of 10 percentage points to values below 53%, with its re-evaluation being recommended after 2 to 3 weeks. Additionally, the subclinical lesion is based on the relative decrease in global LV longitudinal strain by 15% in relation to the baseline.[6] The major concern is that systolic dysfunction can lead to a therapeutic dose adjustment, less effective alternative therapy regimens, or, in the worst-case scenario, to chemotherapy discontinuation.

In 2016, the European Society of Cardiology reviewed the definition of chemotherapy-induced cardiotoxicity and extended it to include any structural or functional alteration in the heart and circulation, whether during cancer treatment, post-treatment or late post-treatment.[7] That requires a conceptual amplification of the rationale in the cardiac monitoring of the oncological patient, which was previously restricted to an arbitrary ejection fraction value, without respecting the individualization of the patient's hemodynamic parameters, gender and age, which all influence ejection fraction calculation.

It is important to note that the ejection fraction calculated by Simpson's two-dimensional method does not evaluate alterations in LV segmental contractility corresponding to 25% of its segments, considering the segmentation of 16 segments:[8] the mid-basal portion of the inferolateral wall (two segments) and the mid-basal portion of the anteroseptal wall (two segments) are not analyzed, and this technical limitation is overcome by the three-dimensional echocardiogram.[9]

Keywords

Ventricular Dysfunction; Drug Therapy; Cardiotoxicity; Breast Cancer; Antineoplastic Agents.

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Considering this problem and a pragmatic observation of those who follow this patient population, the relevance of the isolated LV segmental alterations as chemotherapy-induced toxicity and its prognostic impact has been considered.

A case-control study published in 2017 showed that the segmental motility alteration in the interventricular septum was associated with a reduction in left ventricular performance, despite the presence of a preserved ejection fraction.[10]

The study published in this issue evaluated a prospective cohort of breast cancer patients and showed the incremental value of altered LV segmental motility in predicting cardiotoxicity induced by anthracyclines and/or trastuzumab.[11] It is noteworthy that a high cardiotoxicity rate (16.1%) was observed in a population of which 35% were hypertensive; 22% were smokers; 19% were dyslipidemic and 7% were diabetics. There is no description in the present study of the doxorubicin and trastuzumab doses used in the treatment, the interval between examinations was variable between the groups, and whether the appearance of segmental motility alterations could be related to obstructive coronary disease, since several patients had risk factors.

Weberpals et al. in 2018[12] described a cohort of 347,476 breast cancer patients exposed to chemotherapy or radiotherapy during a follow-up of more than 10 years and who showed no increase in cardiac mortality when compared to the general population.[12]

Another relevant piece of information not described in the text was whether there was a decrease of more than 15% of the LV global longitudinal strain (GLS) in patients who showed segmental contractility alterations. It is already well established that LV GLS is capable of predicting the reduction in LV ejection fraction[13] and, in some institutions, it is indicated to initiate cardioprotection drugs even in the presence of a preserved ejection fraction. It is interesting to note that the segmental motility alterations described in 14% of the patients in the aforementioned article (interventricular septum, inferior and inferolateral) are the same regions that physiologically show coronary flow reduction.[14]

The proposed concept as one of the pathophysiological possibilities for the preferential segmental involvement described in Chagas' disease is that the terminal circulation - between the anterior descending coronary artery and the posterior descending artery (LV apex) and the terminal circulation between the right coronary artery and the left circumflex artery (the basal inferolateral segment) - contributes to the Chagasic lesion in these regions. Thus, it is likely that the aggressive agent (chemotherapy agent, or the *Trypanosoma cruzi*, for instance) would show a slower clearing in these regions, increasing the time of cardiomyocyte deleterious exposure.

Undeniably, chemotherapy-induced cardiotoxicity is multifactorial, but perhaps such a pathophysiological hypothesis might have a clinical consequence when endothelial and coronary vasomotor functions are improved prior to exposure to chemotherapy (statins, vasodilators, beta-blockers). Of the 14 patients with altered segmental contractility, 50% of cases consisted of atypical septal movement. Nevertheless, changes in septal movement constitute a nonspecific finding, as there is an extensive range of etiologies that alter septal motility, such as conditions that cause LV volume or pressure increase; primary involvement of the cardiomyocyte (cardiomyopathies); electric conduction changes; post-surgical status; pericardial disease; congenital cardiomyopathies; post-systolic shortening and interventricular mass[15] and, therefore, one should be cautious in attributing such finding to cardiotoxicity, despite its plausibility.

An alternative that would help to understand the findings would be to expose the evolution of the LV GLS fall between the different groups and to analyze if there was any similarity between the findings of segmental alterations and the parametric arrangement of LV GLS. Although the importance of myocardial deformation segmental alterations is still debatable, there are studies that have shown the incremental role of this type of analysis.[16,17]

The present cohort described in the article mentioned in this editorial does not clarify how the groups were divided, making it difficult to understand how the statistical calculation was carried out. It would be interesting to have a univariate and a multivariate analysis of the factors that contributed to the ejection fraction decrease (systolic blood pressure, radiotherapy dose and site, chemotherapy dose, relative decrease in LV strain, initial absolute strain values, etc.). Moreover, a more detailed analysis of ventricular volumes and diastolic function would allow a better understanding of ventricular remodeling. Similarly, another limitation would be the inclusion of post-systolic shortening at the maximum strain peak, without considering the cardiac cycle phase.

Regardless of the exposed limitations, the article shows the relevance of a limited discussed finding, the alterations in LV segmental motility during chemotherapy treatment, which may be secondary to the disease, the treatment, or the decompensation of an underlying disease.

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Association Between Non-Dipping and Fragmented QRS Complexes in Prehypertensive Patients

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Abstract

Background: Fragmented QRS (fQRS) is a sign of adverse cardiovascular events in various cardiovascular diseases. It is also associated with increased blood pressure and non-dipping in hypertensive patients. However, no study has investigated the importance of fQRS in prehypertensive patients.

Objectives: The aim of our study is to investigate the relationship between fQRS and non-dipper status in prehypertensive patients.

Methods: Two hundred and sixteen eligible, newly diagnosed prehypertensive patients who underwent 24-hour ambulatory blood pressure monitoring (ABPM) for further evaluation of blood pressure between June 2015 and July 2016 were included into the study. Patients were divided into three groups according to ABPM results: normotensives, dipper prehypertensives, and non-dipper prehypertensives. Groups were compared regarding presence of fQRS on electrocardiography. Additionally, multinomial logistic regression analysis was used to determine the relationship between fQRS and blood pressure pattern in prehypertensive patients.

Results: According to ABPM recordings, 61 patients had normotensive blood pressure pattern (systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg). Of the remaining 155 prehypertensive patients, 83 were dippers and 72 were non-dippers. Non-dipper prehypertensives had a significantly higher frequency of fQRS compared to normotensives (p = 0.048). Furthermore, multinomial logistic regression analysis revealed that fQRS is an independent predictor of non-dipping blood pressure pattern in prehypertensive patients (p = 0.017, OR: 4.071, 95% CI: 1.281-12.936).

Conclusions: We found that fQRS is a predictor of non-dipping in prehypertensives. As a marker of fibrosis and higher fibrotic burden within myocardium, fQRS may be useful in identifying high-risk prehypertensive patients before the development of hypertension. (Arq Bras Cardiol. 2019; 112(1):59-64)

Keywords: Prehypertension; Hypertension; Electrocardiography; Fragmented QRS; Ambulatory Blood Pressure Monitoring; Non-dipping.

Introduction

Increased blood pressure is one of the leading causes of cardiovascular morbidity and mortality around the globe. Because of the difficulties involved in diagnosing prehypertension, the definition of prehypertension remains controversial. Prehypertension is not a benign condition; it indicates future hypertension and adverse cardiovascular events and is generally defined as systolic blood pressure (SBP) of 120–139 mmHg and/or diastolic blood pressure (DBP) of 80–89 mmHg.[1,2] Normal blood pressure has a circadian variability with a morning surge and reduction during the rest of the day with a 10% to 20% decline at nighttime, and this phenomenon is known as dipping. Non-dipping pattern, which is defined as less than 10% decrease in blood pressure levels at nighttime, is associated with worse adverse cardiovascular events compared to dipping blood pressure pattern.[3,4]

A narrow fragmented QRS complex (fQRS) on electrocardiography (ECG) is a sign of inhomogeneous and delayed ventricular conduction and is associated with myocardial scarring, fibrosis, and adverse cardiovascular events in various cardiovascular diseases.[5-7] It is defined by the presence of notches in the R or S wave in two contiguous leads in one of the major coronary artery territories without a typical bundle branch block and with a QRS duration of < 120 milliseconds.[8] Importantly, increased blood pressure is associated with presence of fQRS on ECG.[9] Furthermore, non-dipper hypertensive patients have higher frequency of fQRS on ECG compared to dippers, thus indicating myocardial fibrosis and higher fibrotic burden in non-dippers.[10,11] However, the importance and usefulness of fQRS in prehypertensive patients is not clear. The present study aimed to investigate the relationship between prehypertensive blood pressure patterns and the presence of fQRS on ECG to identify the myocardial fibrotic burden and risk assessment of prehypertensive subjects before the development of hypertension.

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Methods

Patient selection

A total of 283 consecutive patients who were defined as newly diagnosed prehypertensive patients after routine cardiac examination at our outpatient clinic between June 2015 and July 2016 were screened for the study. Prehypertension was defined as SBP of 120–139 mmHg and/or a DBP of 80–89 mmHg in accordance with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).[1] Figure 1 demonstrates the flow chart of our study design. Subsequently, all patients underwent 24-hour ambulatory blood pressure monitoring (ABPM) for final blood pressure pattern diagnosis. Of the patients screened, 67 were excluded from the study: 37 who were diagnosed with hypertension after 24-hour ABPM recordings, fourteen with a history of coronary artery disease (CAD), seven with complete or incomplete bundle branch block and QRS duration ≥ 120 ms, three with left ventricular hypertrophy (LVH), three with left ventricular ejection fraction (LVEF) < 50%, two with moderate to severe valvular heart disease, and one with a permanent pacemaker. Consequently, 216 patients were included into the study. Data regarding patients' medical history were recorded on admission. All biochemical analyses were conducted after an overnight fast. Hypertension was defined as 24-hour mean SBP of ≥ 130 mmhg and/or DBP ≥ 80 mmhg and/or daytime mean SBP ≥ 135 mmhg and/or DBP ≥ 85 mmhg on ABPM recordings.[4,12] Diabetes mellitus was defined as at least two fasting plasma glucose levels of ≥ 126 mg/dL, two-hour plasma glucose levels of ≥200 mg/dL, or treatment with antidiabetic drugs, and smoking was defined as the regular use of cigarettes. All patients underwent a detailed echocardiographic examination, and LVH was defined based on electrocardiographic modified Sokolow-Lyon index and/or an increased left ventricular mass index of > 95 g/m^2 for women and >115 g/m^2 for men, detected by echocardiography.[12]

The study protocol complied with the Declaration of Helsinki and was approved by the local ethics committee.

24-h ABPM recordings

Final diagnoses of blood pressure level and pattern were made based on ABPM recordings. All measurements were taken with an oscillometric device. The cuff was placed on the non-dominant arm and automated recordings were obtained every 30 minutes during 24-hours. Recordings were made on working days and patients were encouraged to undertake their normal daily activities. If >20% of the ABPM recordings were invalid, the test was repeated. Sleep durations were evaluated based on the information obtained from the patients, and no patient reported a change in the daily sleeping and waking periods linked to the ABPM device. The 24-h mean and the daytime and nighttime blood pressure values were calculated for each patient from ABPM recordings. Dipper blood pressure pattern was described as more than 10% decline in SBP and DBP at nighttime and non-dipper pattern was defined as less than 10% decline in SBP and DBP at nighttime.[4,12]

Electrocardiography

A standard 12-lead surface ECG was performed on all patients and blindly analyzed by two independent cardiologists. When there was a disagreement, the final decision on the presence of fQRS was reached by consensus. A narrow fQRS complex was defined as the presence of various RSR' patterns, or notching in R or S waves in the absence of typical bundle branch block in at least two contiguous leads in one of the major coronary artery territories in the original QRS complex[8] (Figure 2).

Statistical analysis

Statistical analyses were performed with SPSS (Inc, Chicago, Illinois) version 22.0. Continuous variables were expressed as mean ± standard deviation/median (25-75 percentiles) according to normality and distribution characteristics and were compared using one-way ANOVA, independent samples t-test, or Mann-Whitney U-test, according to group number and distribution characteristics. Categorical variables were expressed as number and percentage (%) and were compared using the $\chi 2$ test or the Fisher exact test. Multinomial logistic regression analysis (using normotensive patients as the reference category) was used to determine the relationship between fQRS and blood pressure pattern in prehypertensive patients. Impact significance was reported as odds ratio (OR) and corresponding 95% confidence interval (CI). $P < 0.05$ was considered significant in all statistical analyses.

Results

The patients were divided into three groups based on 24-hour ABPM recordings. According to ABPM recordings, 61 patients had a normotensive blood pressure pattern (SBP < 120 mmHg and DBP < 80 mmHg), and we designated these patients as the control group. Of the remaining 155 prehypertensive patients, 83 had dipper blood pressure pattern and 72 had non-dipper pattern. The mean age of the study population was 50.5 years, with 45.8% being female. The frequency of fQRS was 13.9%. The groups were similar regarding cardiovascular risk factors, laboratory parameters, and clinical characteristics. The baseline characteristics, laboratory parameters, and blood pressure levels of the groups are presented in Table 1. Statistical analysis revealed a statistically significant difference between the groups regarding presence of fQRS ($p = 0.028$). This difference was mainly due to higher frequency of fQRS in non-dipper prehypertensives than in normotensives. Despite the higher frequency of fQRS in non-dippers than in dippers, there was no statistically significant difference regarding the presence of fQRS between non-dipper prehypertensives and dipper prehypertensives ($p = 0.400$). A similar condition was observed between dipper prehypertensives and the control group ($p = 0.784$). However, non-dipper prehypertensives had a significantly higher frequency of fQRS than normotensives ($p = 0.048$). Furthermore, multinomial logistic regression analysis revealed that the presence of fQRS on ECG is an independent predictor of non-dipping blood pressure pattern in prehypertensive patients ($p = 0.017$, OR: 4.071, 95% CI: 1.281-12.936), (Table 2).

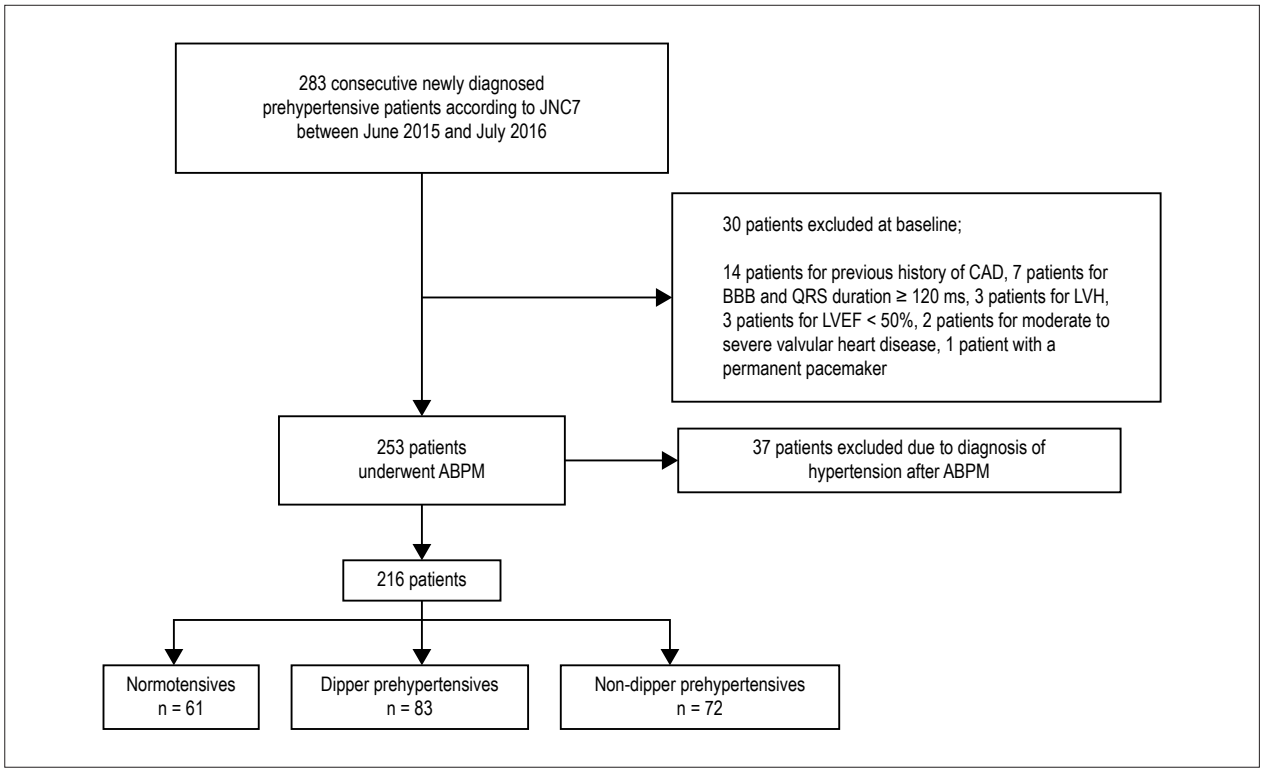

Figure 1 – *Flow chart of the study design. JNC7: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, CAD: coronary artery disease; BBB: bundle branch block; LVH: left ventricular hypertrophy; LVEF: left ventricular ejection fraction; ABPM: 24-hour ambulatory blood pressure monitoring.*

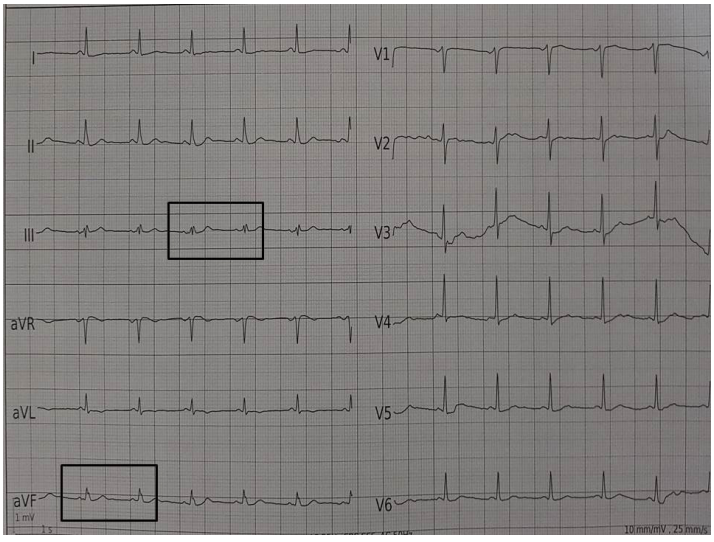

Figure 2 – *An example of fragmented QRS in our study population.*

Discussion

The main finding of our study was that the frequency of fQRS was significantly higher in patients with non-dipper prehypertension compared to normotensives. Furthermore, the presence of fQRS on ECG was found to be a predictor of non-dipping in prehypertensive patients. To our knowledge, this is the first study to report the importance of fQRS in prehypertensive patients.

Prehypertension confers a high risk of progression to hypertension, and it may be associated with increased adverse cardiovascular events, inflammation, and target organ damage.[2,13,14] Similarly to hypertension, prehypertension consists

Table 1 – Baseline demographic and clinical characteristics of the study population according to blood pressure pattern

		All Patients (n:216)		Control (n:61)		Dippers (n:83)		Non-dippers (n:72)		p*
Age (years)		50.5	± 4.3	50.7	± 4.5	50.1	± 4.6	50.7	± 3.7	0.651
Female gender, n (%)		99	(45.8)	30	(49.2)	39	(47.0)	30	(41.7)	0.664
Diabetes, n (%)		18	(8.3)	5	(8.2)	7	(8.4)	6	(8.3)	0.999
Smoking, n (%)		38	(17.6)	10	(16.4)	11	(13.3)	17	(23.6)	0.232
Fragmented QRS, n (%)		30	(13.9)	4	(6.6)	10	(12.0)	16	(22.2)	0.028
Number of leads with fragmented QRS, n (%)	2	27	(90.0)	4	(100.0)	9	(90.0)	14	(87.5)	0.765
	3	3	(10.0)	0	(0.0)	1	(10.0)	2	(12.5)	
24h mean SBP, mmHg		122.5	± 5.2	114.8	± 1.7	124.8	± 2.1	126.4	± 1.7	< 0.001
24h mean DBP, mmHg		74.3	± 5.3	66.2	± 1.8	77.1	± 1.2	78.0	± 1.0	< 0.001
Day SBP, mmHg		128.7	± 1.0	116.2	± 1.6	128.9	± 1.1	128.4	± 0.8	< 0.001
Day DBP, mmHg		78.9	± 1.0	66.0	± 1.8	78.8	± 1.2	79.1	± 0.6	0.175
Night SBP, mmHg		117.6	± 3.4	113.4	± 1.7	114.8	± 2.1	120.8	± 0.8	< 0.001
Night DBP, mmHg		72.0	± 3.4	66.4	± 1.7	69.0	± 0.9	75.5	± 1.5	< 0.001
LVEF (%)		63.1	± 2.4	63.2	± 2.4	62.8	± 2.5	63.3	± 2.4	0.396
Hemoglobin (g/dl)		14.3	± 1.5	14.0	± 1.5	14.5	± 1.5	14.4	± 1.5	0.175
WBC (10^3/ml)		7.7	± 1.0	7.9	± 0.9	7.5	± 1.1	7.8	± 1.0	0.071
Creatinine (mg/dl)		0.8	± 0.1	0.8	± 0.1	0.8	± 0.1	0.8	± 0.1	0.688
LDL (mg/dl)		108.8	± 19.7	109.5	± 18.3	106.8	± 20.7	110.6	± 19.7	0.359
HDL (mg/dl)		43.0	± 6.2	43.4	± 6.2	43.8	± 6.1	41.7	± 6.1	0.074
Triglycerides (mg/dl)		135.7	± 23.1	133.8	± 21.7	135.7	± 23.7	137.3	± 23.8	0.582
LVEDD, mm		45.2	± 3.1	45.1	± 3.2	45.3	± 3.3	45.1	± 3.1	0.429
IVST, mm		9.8	± 1.1	9.7	± 1.0	9.8	± 1.1	9.8	± 1.1	0.613
LA diameter, mm		35.8	± 3.8	35.7	± 3.6	35.8	± 3.8	35.8	± 3.8	0.374

*SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; WBC: White blood cell count; LDL: low-density lipoprotein; HDL: high-density lipoprotein; LVEDD: left ventricle end-diastolic diameter; IVST: interventricular septum thickness; LA: left atrium. *One-way ANOVA was performed to study differences among the three groups.*

Table 2 – Multinomial logistic regression analysis shows fragmented QRS is a predictor of non-dipping in prehypertensive patients

Blood Pressure[a]	Variable	p	Odds Ratio	95% Confidence Interval
Dipper Prehypertension	Fragmented QRS	0.279	1.952	0.582-6.547
Non-dipper Prehypertension	Fragmented QRS	0.017	4.071	1.281-12.936

[a]: The reference category is: Control.

of non-homogeneous patients. Therefore, early identification of high-risk prehypertensives could lead to adequate prevention. Previous studies reported that deteriorated circadian blood pressure variability in prehypertensive patients may be associated with repolarization abnormalities detected by ECG.[15] However, as a marker of depolarization abnormality, the importance of fQRS in prehypertensive patients is not clear. fQRS is a sign of inhomogenous ventricular conduction caused by myocardial scar, ischemia, or fibrosis.[8] It has been shown that fQRS is a predictor of mortality and adverse cardiovascular outcomes in various cardiovascular diseases.[6-8] Additionally, fQRS is a well described fibrotic factor in hypertension.[11,16] It has been demonstrated that the frequency of fQRS is significantly higher in hypertensive patients than in normotensives,[9] and non-dipper hypertensive patients have higher frequency of fQRS on ECG compared to hypertensive dippers.[10,11] These studies revealed that increased blood pressure levels and elevated nighttime blood pressure levels are associated with the presence of fQRS on ECG in hypertensive patients, which indicates the higher fibrotic burden within myocardium in these patients.

Our study demonstrated that non-dipping blood pressure patterns are significantly associated with the presence of fQRS on ECG in prehypertensive patients, similarly to in

hypertensive patients. Since the presence of fQRS on ECG is an important predictor of fibrosis and fibrotic burden within myocardium, the results of our study indicate a higher fibrotic burden in prehypertensive non-dippers compared to normotensives. The possible underlying mechanism for the association between fQRS and non-dipper blood pressure pattern in prehypertensives might be similar in hypertensive patients. Autonomic dysfunction-related increased sympathetic activity during nighttime, and chronic-continuous pressure overload related collagen fibers and connective tissue matrix accumulation within the myocardium might play the key roles for higher fibrotic burden and fibrosis in these patients.[17-19]

Non-dipping hypertension is a prognostic factor, and increased nighttime blood pressure levels indicate worse adverse cardiovascular outcomes compared to dipper patterns.[4,20] Hence, definition of non-dippers is clinically important. In addition to being the precursor of hypertension, prehypertension includes a variety of patients who are at high risk for adverse cardiovascular events. Therefore, our results suggest that fQRS may be useful in defining the deteriorated circadian blood pressure variability which indicates high-risk prehypertensives.

Another aspect of our study is the importance of using 24-hour ABPM for detailed evaluation of blood pressure and final blood pressure pattern diagnosis. It is known that blood pressure patterns vary between ABPM and office records.[4,21] Similarly, our study revealed that an important proportion of prehypertensive patients were not prehypertensive after 24-hour ABPM results. Since 24-hour ABPM is the gold standard for evaluation and diagnosis of hypertension, our study includes real prehypertensives.

Our study has some limitations. First, the study sample size is relatively small; however, the detection of prehypertensive patients is not an easy procedure in clinical practice. Second, our study included only newly diagnosed prehypertensive patients. Third, definition of prehypertension based on ABPM records is not clear. Hence, we designated patients with non-hypertensive elevated blood pressure as prehypertensives. Finally, lack of data regarding confirmation of fibrosis within myocardium by magnetic resonance imaging is another limitation.

Conclusions

Fibrosis within myocardium is an important predictor of adverse cardiovascular events in patients with elevated blood pressure. fQRS is a simple and easily detectable ECG finding that indicates fibrosis within myocardium. This study revealed an important relationship between fQRS and non-dipper status in prehypertensive patients. We found that non-dipper prehypertensives have significantly higher frequency of fQRS compared to normotensives, and fQRS is an independent predictor of non-dipping in prehypertension. Our results suggest that fQRS may be useful in identifying high-risk prehypertensive patients before the development of hypertension. This identification may be helpful in terms of adequate prevention for future cardiovascular events. Future studies are necessary to demonstrate the prognostic value of fQRS in prehypertensive patients and to understand whether a more aggressive prehypertension treatment could normalize the ECG findings.

Author contributions

Conception and design of the research: Eyuboglu M; acquisition of data, analysis and interpretation of the data and critical revision of the manuscript for intellectual content: Eyuboglu M, Akdeniz B; statistical analysis: Eyuboglu M; writing of the manuscript: Eyuboglu M.

Potential Conflict of Interest

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

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Cardiac Fibrosis Occurs before Arterial Hypertension Becomes Well Defined?

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Short Editorial related to the article: Association Between Non-Dipping and Fragmented QRS Complexes in Prehypertensive Patients

Target organ damage (TOD) of systemic arterial hypertension (AH) in the heart modifies the cardiomyocyte, Interstice and its arteries. Alterations that occur in AH include cardiomyocyte hypertrophy, connective tissue hyperplasia and neovascularization stimulation, among others.[1-3] These alterations depend essentially on the stimulus of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS)[1-3] which may not homogeneously impact Kidneys, heart, brain and blood vessels. The response of the connective tissue to AH induces collagen production by fibroblasts and consequently interstitial fibrosis.[1-3]

Since 2006 with the data published by Das MK et al.,[4] we have started to correlate the presence of notches that form the fragmented QRS (fQRS) with non-homogeneous electrical conduction resulting from myocardial fibrosis which can be restorative or reactive.

With this information, Eyuboglu e Akdeniz[5] proposed to correlate the presence of the fQRS and absense of the nocturnal decline in individuals with prehypertension, considering the existence of evidence of higher chances of TOD of AH in these cases.[3,5,6]

Keywords

Myocites, Cardiac; Myoblasts, Cardiac; Prehypertension; Hypertension; Blood Pressue Monitoring Ambulatory/methods; Renin-Angiotensin System.

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In the study population, Eyuboglu e Akdeniz[5], found 13.9% of fQRS, in spite of the small "n". Moreover, these were statistically correlated to the absence of nocturnal decline of selected pre-hypertense through the ambulatory blood pressure monitoring (ABPM) without previous therapeutic approach, that is, without previous SRAA or SNS blockage. It was unclear in their methodology if the absence of the dipping referred to systolic blood pressure or diastolic blood pressure alone or both simultaneously. It was also unclear how those patients that didn't sleep adequately due to pressure measures of ABPM were approached in the study. However, diurnal measurements showed levels compatible with prehypertension that may ease possible criticism.

Another item to be considered in Eyuboglu e Akdeniz[5] is that although that study excluded left ventricular hypertrophy carriers identified by the echocardiogram and electrocardiogram, there would be interest in exploring the further correlation of mass index of VE /corporal surface area and fQRS since this would not be improbable.

Finally, the clinical relevance of the study is to alert us to the necessity of early treatment of the fQRS carriers, because they already show some reactive interstitial response, which is an evidence of early TOD in AH. We could also have in mind that the undertaking of the cardiomyocyte, interstice and vessels may not be simultaneous. Not even in terms of the response of AARS and SNS. Therefore in a group of pre-hypertense, the interstice could respond precociously with collagen production leading to fibrosis impacting not only diastolic function of left ventricle but also with repercussions on left atrium, overloading the contractile function before AH becomes evident. Therefore, cardiac fibrosis can occur before AH becomes evident!

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Sex–Related Effects of Prenatal Stress on Region-Specific Expression of Monoamine Oxidase A and β Adrenergic Receptors in Rat Hearts

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Abstract

Background: Prenatal stress may increase risk of developing cardiovascular disorders in adulthood. The cardiotoxic effects of catecholamines are mediated via prolonged adrenergic receptor stimulation and increased oxidative stress upon their degradation by monoamine oxidase A (MAO-A).

Objectives: We investigated long-term effects of prenatal stress on β (1, 2, 3) adrenergic receptors and MAO-A gene expression in the hearts of adult rat offspring.

Methods: Pregnant rats were exposed to unpredictable mild stress during the third week of gestation. RNA was isolated from left ventricular apex and base of adult offspring. Quantitative PCR was used to measure gene expression in collected ventricular tissue samples. The level of significance was set to $p < 0.05$.

Results: β3 adrenergic receptor mRNA was undetectable in rat left ventricle. β1 adrenergic receptor was the predominantly expressed subtype at the apical and basal left ventricular myocardium in the control females. Male offspring from unstressed mothers displayed higher apical cardiac β1 than β2 adrenergic receptor mRNA levels. However, β1 and β2 adrenergic receptor mRNAs were similarly expressed at the ventricular basal myocardium in males. Unlike males, prenatally stressed females exhibited decreased β1 adrenergic receptor mRNA expression at the apical myocardium. Prenatal stress did not affect cardiac MAO-A gene expression.

Conclusions: Collectively, our results show that prenatal stress may have exerted region- and sex-specific β1 and β2 adrenergic receptor expression patterns within the left ventricle. (Arq Bras Cardiol. 2019; 112(1):67-75)

Keywords: Pregnancy; Stress, Physiological; Oxidative Stress; Heart; Catecholamines; Rats; Sex; Female; Cardiotoxicity; Adrenergic beta1 beta2 Receptor Antagonists.

Introduction

Emerging data from epidemiological and experimental studies have pointed out that disturbed intrauterine environment is related to the increased risk of developing pathologies later in life. Increased susceptibility to adult hypertension has been observed in offspring prenatally exposed to unbalanced maternal nutrition,[1-3] synthetic glucocorticoids,[4] or maternal stress.[5] It has long been recognized that exposure to prenatal stress results in enhanced hypothalamo-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) activity in adulthood.[6,7]

The hallmark of cardiovascular disorders is dysregulated SNS activity. Hence, it is not surprising that the key pharmaceutical targets in the management of these disorders are mostly modulators of adrenergic receptor activity. Cardiotoxic effects of catecholamines are mainly mediated via persistent or acute over-stimulation of β adrenergic receptors (ADRB).[8] A healthy human heart expresses three ADRB subtypes, with ADRB1 being the most and ADRB3 the least abundant.[9,10] Downregulation in the ADRB1 subpopulation is one of the molecular features of cardiac pathologies, such as human heart failure.[9,11] Furthermore, animal transgenic studies demonstrated that early effects of ADRB2 overexpression led to increased cardiac contractility.[12] However, later in life these transgenic animals developed ventricular dysfunction.[13] Furthermore, another myocardial pathological condition triggered by high circulating catecholamines is defined by a region-specific, mostly apical, contractile dysfunction within the left ventricle.[14]

Additionally, cardiotoxicity may result from the production of reactive oxidative species (ROS) upon catecholamine degradation by monoamine oxidase A (MAO-A) in the heart.[15] Cardiac MAO-A expression and activity is increased in different animal models of heart failure[16-18] and aging.[19]

Epidemiological studies showed that female and male patients suffering from cardiovascular disease exhibit differential responsiveness to diverse recommended treatments,[20,21] emphasizing the necessity to include both sexes in cardiovascular research.

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In order to better understand molecular mechanisms by which prenatal stress may potentially contribute to the development of cardiovascular diseases in adulthood, the present study was designed to investigate region-specific gene expression of adrenergic receptor subtypes (ADRB1, ADRB2 and ADRB3) and MAO-A in the left ventricular myocardium of female and male offspring.

Methods

Animals

Three-month-old virgin female Wistar rats (266 ± 11.9 g) were housed with free access to food and water under constant light-dark cycle (12 h) in temperature-controlled conditions (22 ± 1°C) in the animal facility of the Faculty of Biology, University of Belgrade. Sample size was determined by convenience, and each of six pairs of female rats was caged with a sexually experienced male during a whole oestrus cycle. Day 0 of pregnancy was marked by appearance of sperm in vaginal smear. One female remained non-pregnant. To avoid selection bias, pregnant females who were mated with the same male were randomly assigned to control (n = 5) or stressed (n = 6) group and housed individually. All procedures were conducted according to the rules for animal care proposed by the Federation of European Laboratory Animal Science Associations (FELASA), and approved by the Ethics Committee of the Faculty of Biology, University of Belgrade.

Prenatal stress protocol

During the third week of gestation (gestational day 13-20, GD13-GD20) pregnant rats were exposed to a chronic unpredictable mild stress (CUMS) protocol that included random and intermittent exposure to a variety of stressors. Detailed CUMS protocol is shown in Table 1. Briefly, animals were exposed to the following stressors in random order twice a day for 1 h or overnight: damp bedding, restraint in a Plexiglas® tube, cold room (4°C), cage displacement and noise, overnight illumination, and cage tilt. Control mothers were left undisturbed for the duration of their pregnancies with the exception of general handling. During the entire pregnancy, water and food intake were recorded.

Biochemical assays

Before first and after last exposure to the stressor, blood was collected from dam's tail vein in EDTA-containing tubes. Adrenocorticotropic hormone (ACTH) plasma levels were measured with a CLIA kit and glucose levels were measured with an Exac-tech glucose analyzer using Dextrostix reagent strips, both according to the manufacturers' instructions.

Litters

At birth pups were counted and weighed, and litters were adjusted to eight pups with an equal number of males and females to avoid effects of litter size and litter sex-distribution on development. All pups were raised by their biological mothers. The offspring were weaned at 28 days, separated by gender and housed in groups of two per cage, according to the experimental group (C- offspring from unstressed mothers, PS- offspring from stressed mothers). Offspring's body weight and water and food consumption were recorded during both pre- and post-weaning periods. The offspring were sacrificed by decapitation at two months of age. To avoid oestrus cycle dependent fluctuations, female offspring were sacrificed in dioestrus, as confirmed by vaginal smears.

RNA isolation

Total RNA from the basal and apical portions of the left ventricles was isolated using TRI Reagent (Sigma, Germany) according to manufacturer instructions. Total RNA concentrations were quantified by absorbance measurements at 260 and 280 nm using a spectrophotometer (Ultrospec 2000, Pharmacia Biotech, USA) according to manufacturer instructions. RNA quality was analyzed on 1.5% agarose gel containing ethidium bromide and visualized by UV transillumination (ChemiDoc-It imager, UVP, Germany).

cDNA synthesis and quantitative real-time PCR

RNA samples (2 μg) were subjected to DNase I treatment, using rDNase I, according to manufacturer protocol (DNA-free kit, Ambion, USA). Ready-to-go You-Prime First-Strand beads transcription kit (GE Healthcare, USA) was used to generate cDNA for subsequent quantitative real-time PCR. Samples without reverse transcriptase were used to control for possible contamination of gDNA. All reactions were carried out in

Table 1 – Stress regime

	10:00-11:00	14:00-15:00	18:00-08:00
GD14	Restraint	Damp bedding	Cage tilt
GD15	Cold room (4˚C)	Displacement and noise	Continuous illumination
GD16	Damp bedding	Restraint	Cage tilt
GD17	Displacement and noise	Cold room (4˚C)	Continuous illumination
GD18	Restraint	Damp bedding	Cage tilt
GD19	Cold room (4˚C)	Displacement and noise	Continuous illumination
GD20	Damp bedding	Restraint	Cage tilt

** GD: gestational day.*

duplicate, using 1x TaqMan Master Mix (Applied Biosystems) and 1x TaqMan expression assays for each gene (Table 2: Adrb1, Adrb2, Adrb3, MaoA, ActB), with 2 μg of cDNA template in a total volume of 20 μl.

Real-time PCR reactions were performed on an Applied Biosystem 7900 Real-Time PCR System with standard PCR conditions (50°C for 2 min; 95°C for 10 min; 95°C for 15 s, and 60°C for 1 min for 40 cycles). The relative gene expression levels were determined by comparative $2^{\wedge}(-\Delta\Delta C_T)$ quantification method[22] using beta-actin as the reference gene.

Statistical analysis

Statistical analysis was performed using GraphPad Prism Software-version 6.01 (San Diego, USA). Parameters measured in mothers and offspring were expressed as means ± standard deviation (SD). Data were analyzed by unpaired Student's t-test, unless otherwise indicated. Offspring data obtained by real-time PCR analysis were expressed as median with interquartile range. Two-way ANOVA analysis with Bonferroni's multiple comparison test was used to examine the effect of prenatal stress and pregnancy on maternal serum ACTH levels as well as the effects of prenatal stress on ADRB genes expression patterns in examined regions of offspring's left ventricle. The statistical significance of differences among the real-time PCR data obtained from experimental groups was evaluated by nonparametric Mann-Whitney U-test. The level of significance was set to $p < 0.05$.

Table 2 – TaqMan expression assays

Gene	TaqMan assay ID
Beta 1 adrenergic receptor (*Adrb1*)	Rn00824536_s1
Beta 2 adrenergic receptor (*Adrb2*)	Rn00560650_s1
Beta 3 adrenergic receptor (*Adrb3*)	Rn01478698_g1
Monoamine oxidase A (*Maoa*)	Rn01430955_A1
Beta-actin (*Actb*)	Rn01412977_g1

Results

Effects of CUMS on maternal and offspring parameters

In order to determine whether the stress protocol applied activated HPA axis in pregnant females, maternal plasma ACTH levels were evaluated. Prior to the start of the stress protocol (GD13), maternal plasma ACTH levels were not significantly different between experimental groups (Figure 1). Following random and intermittent exposure of the pregnant female rats to a variety of stressors during the third week of gestation (GD13-21), maternal plasma ACTH levels increased compared to control pregnant females (Figure 1, $p < 0.001$, 2-way ANOVA with Bonferroni's multiple comparison test). Additionally, in the group of stressed mothers, following exposure to diverse stressors, plasma ACTH levels increased compared to GD13 suggesting that HPA axis was activated in this experimental group (Figure 1, $p < 0.001$, 2-way ANOVA with Bonferroni's multiple comparison test).

CUMS did not affect maternal weight gain during the last week of pregnancy (Table 3) or water and food intake throughout pregnancy (data not shown). Maternal blood glucose levels were similar in both experimental groups before and after application of the CUMS protocol (Table 3). There was no effect of prenatal stress on litter size or offspring sex ratio (Table 3). Maternal stress during the last week of pregnancy did not affect offspring birth weight or weight gain during either pre- or post-weaning periods (Table 4).

Effects of prenatal stress on regional ADRB subtype gene expression in left ventricle of female and male

Using quantitative PCR analysis, relative mRNA levels of ADRB1, ADRB2, and ADRB3 were examined at the apical and the basal region of left ventricle harvested from control (C) and prenatally stressed (PS) adult female and male offspring.

ADRB3 mRNA was undetectable at the examined regions of the left ventricle in male and female offspring.

We detected higher ADRB1 mRNA expression at the apex and the base of left ventricle from control female offspring, in comparison to ADRB2 mRNA levels (Figure 2A

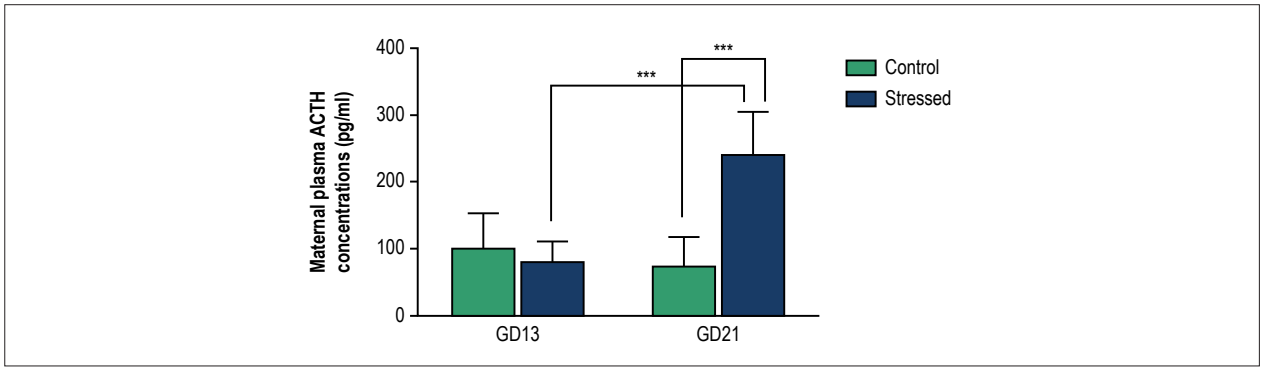

Figure 1 – *Maternal plasma ACTH concentrations before (GD13) and following (GD21) exposure to CUMS during pregnancy. Data are expressed as mean ± SD, control group (open bars, n =5), stressed group (black bars, n = 6). In the stressed group on GD21 two samples were excluded due to hemolysis. ***p < 0.001, 2-way ANOVA and Bonferroni's multiple comparison test*

Table 3 – Maternal weight before treatment, maternal weight gain during last week of pregnancy (GD13-GD21), gestation length, maternal blood glucose level before and after stress exposure, litter size, and sex ratio

Variable	Control (n = 5)	Stressed (n = 5)	p
Maternal weight before treatment (g)	347 ± 37.3	337 ± 40.2	0.6646
Maternal weight gain (g)	62.5 ± 4.43	50.5 ± 11.6	0.0872
Gestation length (days)	22.0 ± 0.71	22.2 ± 0.41	0.6355
Blood glucose levels (mM) before stress (GD13)	5.44 ± 0.21	5.55 ± 1.00	0.8162
Blood glucose levels (mM) after stress (GD21)	5.30 ± 0.42	5.63 ± 0.69	0.3737
Litter size	11.2 ± 2.77	11.8 ± 2.32	0.6891
Sex ratio	1.38 ± 0.4	1.18 ± 0.3	0.3805

GD13: gestational day 13; GD21: gestational day 21; Data are expressed as means ± standard deviation (SD).

Table 4 – Offspring weight at birth, postnatal day 28 (PND28) and 60 (PND60)

Variable		C	PS	p
Birth weight (g)	Group	6.67 ± 0.904	6.39 ± 0.685	0.1562
Weight at PND28 (g)	Group	94.5 ± 11.4	96.9 ± 13.2	0.6360
	Male	96.8 ± 12.3	94.5 ± 10.3	0.7286
	Female	92.2 ± 11.1	99.3 ± 16.2	0.3924
Weight at PND60 (g)	Group	316 ± 50.9	317 ± 70.5	0.9790
	Male	355 ± 29.7	377 ± 42.7	0.3354
	Female	277 ± 33.6	257 ± 21.7	0.2454

C: offspring from unstressed mothers; PS: offspring from stressed mothers; PND28: postnatal day 28; PND60: postnatal day 60; Number of animals (n): n = 5-8 per group. Data are expressed as means ± standard deviation (SD).

and 2C, approx. ADRB1:ADRB2 = 73%:23%, $p < 0.01$). Decreased apical ADRB1 mRNA levels were detected in PS females compared to control animals (Figure 2A, $p = 0.048$). Additionally, in PS females, we observed a trend of increase in apical ADRB2 mRNA levels compared with control. Since these changes resulted in the loss of differential ADRB subtype expression levels at the apical myocardium of PS females, two-way ANOVA analysis was performed. ANOVA test revealed significant interaction between prenatal treatment and receptor subtype expression levels ($F(1,20) = 6.817$, $p = 0.0167$). Altogether, these results indicate that prenatal stress differently affected ADRB1 and ADRB2 at the apical myocardium of female animals. Furthermore, we observed a trend of decrease in basal ADRB1 mRNA levels of PS females compared with control (Figure 2C $p = 0.3434$), such that basal myocardium of PS females did not display differential ADRB1 and ADRB2 mRNA expression pattern compared with control animals. One cannot exclude the effect of limited sample size to detect significant differences in ADRB gene expression between control and PS groups. Further research will be necessary to obtain a more detailed understanding of the underlying mechanisms resulting in altered gene expression pattern of basal cardiac adrenergic receptors of PS females.

Male offspring from unstressed mothers, similar to female offspring, displayed higher ADRB1 than ADRB2 mRNA levels at the apex of left ventricle (Figure 2B, $p = 0.0087$). However, differently from female offspring, prenatal stress did not affect the predominant apical ADRB1 mRNA expression pattern of left ventricle in male offspring (Figure 2B). On the other hand, we detected similar ADRB1 and ADRB2 mRNA expression levels at the base of the left ventricle in control and PS male offspring (Figure 2D).

Effects of prenatal stress on regional MAO-A gene expression in left ventricle of female and male offspring

Prenatal stress did not significantly affect MAO-A mRNA expression at either apical or basal region of left ventricle in female and male offspring (Figure 3). Based on our results we observed a trend toward higher relative expression of MAO-A at the basal myocardium compared to the apical region of the left ventricle in male offspring (approximately 35-fold in control and 17.5-fold in PS animals, Figure 3B, D). Additionally, basal cardiac MAO-A demonstrated a trend toward higher expression in males than in females (Figure 3C, D, approximately, 4.7-fold between control groups and 5.1-fold between PS groups).

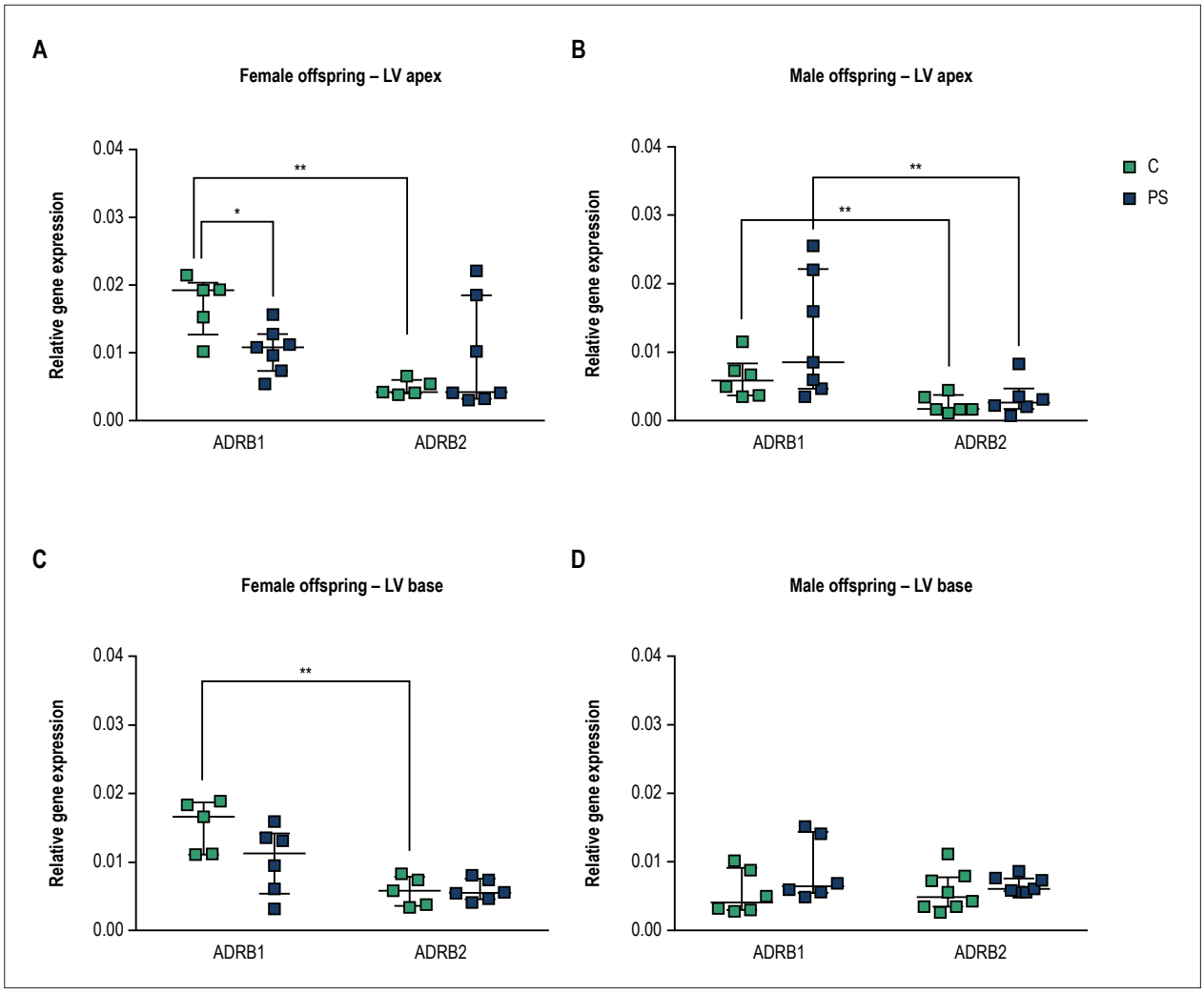

Figure 2 – *Effects of prenatal stress on expression of beta 1 (ADRB1) and beta 2 (ADRB2) adrenergic receptors mRNA at the apex and base of the left ventricle in the offspring (LV). Results are presented for female (A and C) and male (B and D) offspring from unstressed (control-C) and stressed mothers (prenatal stress-PS). Data are expressed as median with interquartile range (number of animals per group, n = 5-8 per group). *p < 0.05; **p < 0.01, Mann-Whitney U-test*

Discussion

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide.[23] It has been shown that various disturbances of fetal development may contribute to development of cardiovascular disorders in adulthood. Offspring from stressed mothers or mothers undergoing glucocorticoid therapy during pregnancy display various neuroendocrine and behavioral alterations during adulthood.[24-26]

This study examined expression of ADRB subtypes and MAO-A in different regions of the left ventricle in the offspring of both sexes prenatally exposed to maternal stress.

We applied stress protocol to pregnant rat females that could potentially mimic everyday life stress that pregnant females are exposed to. Our stress protocol involved chronic exposure to various mild stressors which prevents habituation, which can be observed after repeated exposure to the same stressor.[27] Plasma ACTH level was increased in stressed mothers compared to pregnant unstressed rats, which indicated that HPA axis activity of pregnant females was increased by the CUMS protocol, which is consistent with previous studies.[28,29] We did not observe any significant difference in metabolic parameters such as maternal weight gain during pregnancy, water and food consumption, or blood glucose level between stressed and unstressed mothers. Nor did maternal stress during the last week of pregnancy affect litter size or birth weight. Taken together, these results imply that our model of CUMS was potent enough to induce a stress response in pregnant rats but did not affect offspring weight, which is known to be one of the risk factors for development of adult cardiovascular disorders.[2]

To the best of our knowledge, this is the first study to report relative gene expression levels of beta-adrenergic receptor subtypes in two different regions within rat left ventricle. Our results show that ADRB1 is the predominantly expressed subtype of the cardiac ADRB population at

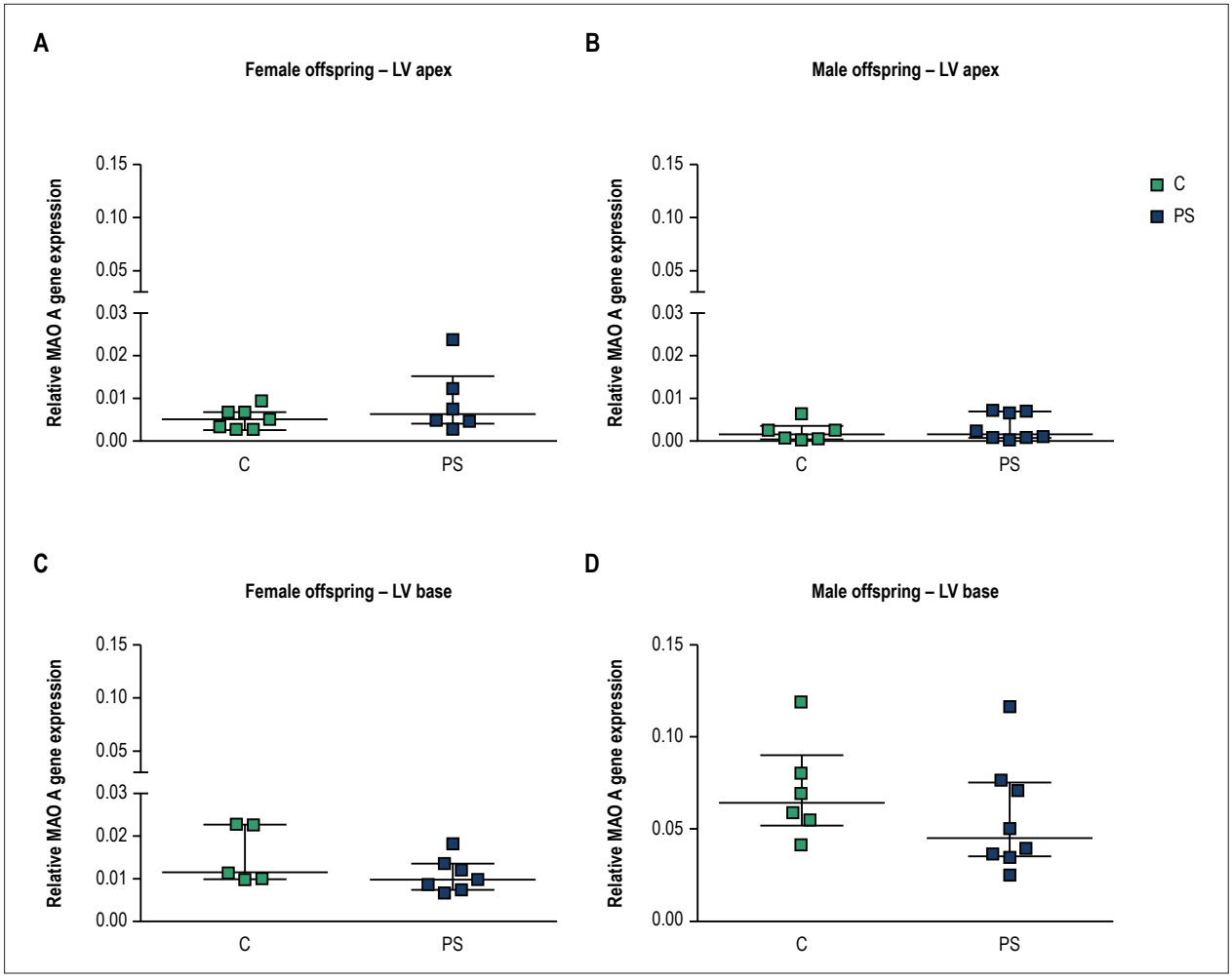

Figure 3 – *Effects of prenatal stress on monoamine oxidase A (MAO-A) mRNA at the apex and base of the left ventricle (LV) in the offspring. Results are presented for female (A and C) and male (B and D) offspring from unstressed (control-C) and stressed mothers (prenatal stress-PS). Data are expressed as median with interquartile range (number of animals per group, n = 5-8).*

apical and basal myocardium of left ventricle in female rat offspring from unstressed mothers. We also detected higher expression of ADRB1 compared to ADRB2 mRNA levels at the apical ventricular region in the control male offspring. Indeed, several human and other animal studies have demonstrated higher ADRB1 than ADRB2 density in left ventricle.[30-34] However, our results are not in accordance with the findings reported by Paur et al.,[35] who used radioligand binding-displacement assays. They demonstrated increased ADRB2:ADRB1 ratio in the apical cardiomyocytes isolated from adult male Sprague Dawley rats. This discrepancy may be accounted for by different methods and model systems. Differently from in female offspring, ADRB1 and ADRB2 mRNA levels were similarly expressed in the left ventricular basal myocardium in male rat offspring. We did not detect ADRB3 mRNA in rat left ventricle.

Our results suggest that there are sex- and region-specific gene expression representations of ADRB subpopulations within left ventricular rat myocardium. Additionally, data from our study indicate that prenatal stress may have affected ARB1 and ARB2 gene expression pattern at the apical region of the left ventricle in female offspring, but not in male offspring. Disturbed representation of cardiac adrenergic receptors subtypes has been described in cardiovascular pathologies. Heart failure is characterized by altered ADRB1:ADRB2 ratio, in part due to the decreased ADRB1 protein and mRNA within left ventricle.[11,36] The nonselective reduction of beta-adrenergic receptor subpopulations was also observed in the heart of both aged animals[37] and elderly patients.[31,34] Our results indicate that prenatal stress resulted in decreased apical ADRB1 mRNA expression suggesting that apical myocardial region of the female rat offspring might be sensitive to stress exposure during fetal life. Interestingly, higher sensitivity of the apical region within left ventricle to stress during adulthood has been described in Takotsubo (stress-induced) cardiomyopathy.[35,38] Moreover, this syndrome is predominantly diagnosed in women.[38]

Another protein that is involved in the sympathetic modulation of cardiac function is MAO-A. This enzyme catalyses the oxidation of monoamines during which ROS is produced and may contribute to the pathogenesis of cardiovascular diseases.[15] To the best of our knowledge this is the first study to investigate the effects of prenatal stress on cardiac MAO-A gene expression in the offspring. In the present study we did not detect significant changes in the MAO-A mRNA levels in the prenatally stressed heart of either sex.

There are several limitations to this study. As mentioned above we cannot exclude the effect of limited sample size on detecting additional significant differences in region specific gene expression of myocardial beta-adrenergic receptor subpopulations. The mechanism for decreased apical myocardial ADRB1 mRNA expression in prenatally stressed female, but not male, offspring is unknown. We can only hypothesize based on available literature that sex hormones might have an effect. Thus, it would be of interest to investigate earlier developmental stages of prenatally stressed offspring. Furthermore, we did not compare cardiac expression levels of MAO-A between male and female offspring. However, based on the relative expression levels of MAO-A, we can hypothesize that our results suggest that cardiac MAO-A exhibits a sex dimorphic gene expression pattern, which is likely expressed more abundantly in the heart of male rats than in female rats. As MAO-A is a main source of hydrogen peroxide in the heart, our observation would be in agreement with the reported lower production of hydrogen peroxide in cardiac mitochondria of female, compared to male Wistar rats.[39]

Conclusions

In summary, our data suggest that prenatal stress may exert, already at young adult age, sex-specific changes in apical and basal cardiac adrenergic receptor subpopulations in offspring. Whether these changes correlate with diminished cardiac performance and predispose organisms to develop cardiovascular diseases during their lifetime remains to be determined in future experiments.

Author contributions

Conception and design of the research, statistical analysis and writing of the manuscript: Jevjdovic T; acquisition of data: Dakic T, Kopanja S; analysis and interpretation of the data: Jevjdovic T, Dakic T, Kopanja S, Lakic I, Vujovic P; o btaining financing: Djordjevic J; critical revision of the manuscript for intellectual content: Lakic I, Vujovic P, Jasnic N, Djordjevic J.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Tanja Jevjdovic, from Faculty of Biology, University of Belgrade.

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the FELASA), and approved by the Ethics Committee of the Faculty under the Protocol number is EK-BF-2015/25.

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Prenatal Stress: Molecular Mechanisms and Cardiovascular Disease

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Shor Editorial related to the article: Sex–Related Effects of Prenatal Stress on Region-Specific Expression of Monoamine Oxidase A and B Adrenergic Receptors in Rat Hearts

Concern of the researchers in finding the causes of cardiovascular disorders is evident. Recently, scientists are focusing in intrauterine environment investigations in order to seek early causes of these diseases.[1] Studies indicates that prenatal stress increases risk of cardiovascular diseases in adulthood.[2,3] Among the risks, susceptibility to adult hypertension is a concern, and the sympathetic nervous system is one of the targets of interest, specifically the activity of beta-adrenergic receptors, which has subtype β1 cardiac predominance.[4,5] These receptors modulates cardiac changes and may lead to ventricular dysfunction as well as severe conditions of heart failure,[6] which increases mortality risk as showed in hypertensive rats studies.[7,8]

Another factor associated with the occurrence of heart failure is monoamine oxidase A (MAO-A). This enzyme has its activity increased in hypertension and is responsible for the degradation of catecholamine, which increases the reactive oxygen species generation leading to cardiotoxicity.[9] Therefore, it is extremely important target the causes to prevent or attenuate the of alterations resulting from cardiovascular diseases.

Keywords

Stress, Psychological; Cardiovascular Diseases; Hypertension; Heart Failure; Rats.

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Jevjdovic et al.[10] developed a study in order to investigate region-specific gene expression of adrenergic receptors subtypes (ADRB1, ADRB2 e ADRB3) and of the MAO-A in the female and male offspring myocardium. The mentioned study is one of the few studies that evaluated the difference between gender and regions of left ventricle (apex and base).

The authors highlighted that the occurrence of a stressful situation increased the plasmatic level of the adrenocorticotrophic hormone (ACTH), which characterizes maternal stress. However, prenatal stress did not cause changes in the gestational period on the evaluated parameters, such as maternal weight gain, water and food consumption, blood glucose, litter size, neonatal weight and offspring weight gain, with the latter as one of the main risk factors for the development of cardiovascular diseases in adults.[10]

Adrenergic receptors evaluation has elucidated a decrease of ADRB1 expression in the left ventricle apical region in female offspring. The reduction of ADRB1 apical expression is characteristic of cardiac diseases. ADRB3 expression was undetectable in rats left ventricle. In addition, the authors did not found significant modifications in mRNA level of MAO-A in female or male prenatal heart. This was the very first study that reported gene expression level of the β adrenergic receptor in different regions of rats left ventricle.[10]

Jevjdovic et al.[10] showed very relevant data regarding sex-related effects of prenatal stress on region-specific expression in heart rats. The results of gene expression suggests that prenatal stress may lead to cardiovascular diseases. However, protein expression evaluation would be important to corroborate and consolidate the statements of the mentioned article.

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Validation of the Brazilian Version of CADE-Q II to Assess Knowledge of Coronary Artery Disease Patients

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Abstract

Background: The Coronary Artery Disease Education Questionnaire (CADE-Q), an instrument aimed at assessing patients' knowledge about coronary artery disease (CAD), was originally developed and psychometrically validated in Brazil. It was later translated, cross-culturally adapted, and validated to English. Although both versions demonstrated good reliability and validity, new studies in the area have pointed out the need of implementing the CADE-Q with other components of cardiac rehabilitation (CR) programs, such as psychologic factors, which had not been considered in previous version and were added in the subsequent, adapted version. Thus, a second version of CADE-Q was developed in English, the CADE-Q II.

Objective: to translate, culturally adapt and psychometrically validate the CADE-Q II in Brazilian Portuguese.

Methods: After translation and review by a Committee of specialists in CR, a version in Brazilian Portuguese was generated and tested in 307 patients in CR. Test-retest reliability was assessed by intraclass correlation coefficient (ICC) in 49 patients; internal consistency was assessed using Cronbach's alpha (α); and, criterion validity was assessed regarding patients' educational level and family income. The level of significance adopted for all tests was 5%.

Results: After the ICC analysis, 4 items were excluded. The questionnaire was considered internally consistent ($\alpha > 0.7$). Associations were found between the mean total scores and the variables schooling ($p < 0.001$) and income ($p < 0.001$). Median total score was 53 (14) points corresponding to 65.4% of the total possible score.

Conclusion: The Portuguese version of the CADE-Q II showed sufficient reliability, consistency and validity, supporting its use in future studies. (Arq Bras Cardiol. 2019; 112(1):78-84)

Keywords: Cardiovascular Diseases/physiopathology; Coronary Artery Disease; Patient Education as Topic; Surveys and Questionnaires; Validation Studies; Cardiac Rehabilitation

Introduction

Cardiovascular diseases are the main cause of mortality in Brazil, as a result of both population aging and epidemiologic changes in disease,[1-3] that contribute to high costs in health.[4,5] Cardiac rehabilitation (CR) stands out among the recommended therapies to coronary artery disease (CAD). CR is a multidisciplinary approach for secondary prevention, that can effectively reduce rehospitalization rates by up to 18% and cardiovascular mortality by up to 26%.[6]

Most CR benefits are related to behavioral changes, and in this context, patient education is considered and important component of these programs. Education in health allows patient to understand the nature of the disease and its treatment. Consequently, inadequate understanding of the condition may lead to unwarranted emotional distress, inappropriate behavior in coping with the disease, non-adherence to treatment, and disease progression.[7,8]

Therefore, the management of chronic diseases such as CAD is crucial for secondary prevention.[9,10] Recent studies have corroborated the benefits of educational intervention in CAD patients. That includes knowledge increase that promotes changes in self-management and health behavior resulting in improvement of quality of life,[10-12] and potentially reduce health-related costs.[8]

Precise information on the level of cardiovascular disease knowledge in patients with this disease are essential in planning and proposing effective CR interventional programs.[7,8] Education in health should be provided and analyzed by a simple manner, aiming at targeting many populations, including low-income patients.[13] In this context, the coronary artery disease education questionnaire (CADE-Q) is one of the few psycometrically validated instruments available in CR, developed and validated in Brazil and also validated in other countries.[14,15] However, the focus of CR has

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changed over the years,[11,16] and a second version of the CADE (CADE-QII) was developed aiming at updating the instrument and including additional educational components, such as psychosocial health.[17] The aim of the present study was to translate, cross-culturally adapt and psychometrically validate a Brazilian Portuguese version of the CADE-QII.

Methods

Study design and procedures

This study was approved by the human research ethics committee of the University Universidade Federal de Minas Gerais (approval number 1.350.973), according to the 466/12 resolution of the Brazilian National Health Council. This was an observational, cross-sectional, multicenter study, involving research centers in the cities of Belo Horizonte and Florianopolis in Brazil. Data were collected from January to May 2016.

First, the processes of translation and cross-cultural adaptation of the instrument were performed according to precise criteria previously approved by the authors, based on the protocol proposed by Guillemin et al.[18] – (1) initial translation, (2) back translation, (3) review of the questionnaire versions built by specialist committee members, (4) pre-testing for equivalence with bilingual individuals, and (5) revision of the weighting of scores. The translated, cross-culturally adapted version of the instrument was then tested for clarity in coronary patients. The results were used to refine the CADE-QII version in Portuguese.

Second, psychometric validation was conducted. The refined instrument was administered to a larger sample of patients, participants of three CR programs in the metropolitan area of Florianopolis, Brazil (one private and two public programs) and of one public program in Belo Horizonte, Brazil. The instrument was administered by interview. The interviewers maintained a neutral position, answering questions about the study and encouraging respondents to answer all the questions. The questionnaire was readministered two weeks following the first administration in patients selected by convenience for test-retest analysis.

Participants

For psychometric validation, we recruited participants of CR programs developed in four participating institutions, where a total of 500 patients attended every month. A convenience sample was recruited from these patients, based on availability of recruiters and patients that accepted to participate in the study. The sample was composed of 307 patients, corresponding to 61.4% of the patients attending the participating institutions. The programs lasted for at least three month and none of them had a structured educational component.

Inclusion criteria were a confirmed diagnosis of CAD or the presence of cardiovascular risk factors and signing of the consent form. Exclusion criteria were age younger than 18 years and any significant visual, cognitive or mental impairments that could limit patients' ability to answer the questionnaire.

CADE-QII

CADE-QII was constructed to verify the level of knowledge of coronary patients, participants of CR programs about CAD. CADE-QII evaluates the knowledge of patients for five domains consisting of medical condition, risk factors, exercise, nutrition and psychosocial risk, based on official documents and guidelines in the area.[17] The instrument has 31 items, each item with four possible answers about one of these domains of knowledge. One of the answers is the most "correct" one, *i.e.*, the answer states complete and true information about the domain, and gets a score of 3; one of the answers is "partially correct" and gets a score of 1, and the two other options are "incorrect", one describing incorrect information and "I don't know", which should be chosen when the patient is not sure about any of the previous options. Both incorrect and "I don't' know" options get a "0" score. The total sum is calculated, and it represents the level of patients' knowledge about the domains.[17] Thus, CADE-QII not only quantifies the level of knowledge about cardiovascular disease but also identify the domains where patients get the lowest scores, *i.e.*, in which knowledge is deficient.

Variables

The following characteristics of the patients participating in the psychometric validation were collected for analysis – sex, age, educational level, monthly family income, comorbidities, cardiac risk factors and previous diseases. All these characteristics were self-reported.

The Brazilian version of the CADE-QII were tested for the following psychometric properties – clarity, content validity, test-retest reliability, internal consistency and criterion validity. A descriptive analysis of total score was also performed, both per question and per domain.

Statistical analysis

The Statistical Package for Social Sciences (SPSS), version 20.0 was used for data storage, classification and analysis. The level of significance was set at 5%. Data were excluded from analysis when more than 20% of the CADE-QII items were incomplete.

To test clarity and validity of the content, a pretest was conducted with the patients, in order to get a feedback on the items and to verify the time required to complete the questionnaire. In addition, five specialists evaluated the clarity of the CADE-QII version in Brazilian Portuguese.

The intraclass correlation coefficient (ICC) was used in the test retest reliability analysis. Values with ICC lower than 0.7 were excluded from analysis.[19] The internal consistency of the instrument was assessed by Cronbach alpha coefficient; values above 0.70 were considered acceptable.[20] Criterion validity was assessed by comparing CADE-QII scores with family income and educational level.[17]

Data normality was tested using the Kolmogorov-Smirnov test. Descriptive analysis of the Brazilian version of the CADE-QII was also performed; continuous variables with normal distribution were described as mean and standard deviation,

and continuous variables not normally distributed were expressed as median and interquartile range. Absolute and relative frequencies were used for categorical variables. The chi-square test was used to assess associations between categorical variables.

Overall knowledge of patients was expressed as the median of the total CADE-QII score. Median scores obtained in each domain were also described.

Translation, cultural adaptation and pretest

Initial translation of CADE-QII was made by three independent translators, aware of the objectives and underlying concepts of the study. They were asked to detect ambiguities and unexpected meanings in the Brazilian version compared with the original one. Back translation was conducted by four translators unaware of the initial objectives of the study as well as of the original version of the instrument. A commission composed of five bilingual specialists reviewed all the versions and made necessary changes according to Brazilian culture. A final version was generated, and the clarity of the questions tested in 23 coronary patients.

During translation and cultural adaptation processes, question 4 of the physical activity domain ("Three things that one can do to exercise safely outdoors in the winter are") was adapted to the Brazilian cultural context; the change was related to the weather, the expression "hot and dry weather", referring to summer season, were substituted for "winter" ("What one can do to exercise safely outdoors in hot and dry weather are"), which better reflects the reality of Brazil, a tropical country. No further changes were required.

Mean time required to complete the CADE-QII among participants was 22.5 ± 3.5 minutes. Mean rates for clarity of the instrument was 7.0 ± 1.77. Regarding content validity, following the administration of the instrument and discussion between patients and researchers, it was concluded that the CADE-QII clearly describes the aim of the measurements, the target population, the concepts measured and the selection of the items.

Psychometric validation

Three hundred and seven patients that participated in CR programs completed the CADE-QII. Sociodemographic and clinical characteristics of the patients are described in Table 1. Of these patients, 228 were participants of CR in Florianopolis, and 77 in Belo Horizonte. Most patients were men (n = 200, 65.1%) and had low educational attainment (incomplete elementary school, n = 188, 61.2%). Mean age was 63.3 ± 10.4 years (minimum = 31 years old; maximum = 88 years old).

For test retest reliability analysis, 49 patients were selected by convenience and asked to complete the questionnaire again, with an interval of 15 days between the evaluations. Among these patients, 24 participated in a private CR program, and 25 in a public one. The test retest reliability was assessed by the ICC of each item, and the results are described in Table 2. The following items did not meet the minimum standards – question 4 ("A heart attack occurs") of the medical condition domain, question 4 of factor risk domain ("The first step towards controlling a risk factor, such as blood pressure or cholesterol, is", question 7 of nutrition domain ("How many servings of fruits and vegetables should adults consume?") and question 5 of psychosocial risk domain ("*Chronic stress* is defined as"). These items were excluded from the Brazilian version of the CADE-QII. Thus, from the 31 items of the original version, 27 items composed the Brazilian CADE-QII in Portuguese, with a maximum score of 81 points.

The internal consistency of the 27-item instrument was tested, with a Cronbach alpha coefficient of 0.78. Regarding criterion validity, as described in Table 1, patients with higher educational level ($p < 0.001$) and higher family income ($p < 0.001$) showed higher level of knowledge about the disease as compared with the other patients.

Medians and interquartile ranges of the items and domains are described in Table 2. The median total score was 53 (14) points, corresponding to 65.4% of the possible total score. The highest scores were obtained for the items: "What is the best source of omega 3 fats in food?" ("What one can do to exercise safely outdoors in hot and dry the winter are" and "Which of the following describes your best option for reducing your risk from depression". The lowest scores were observed for the items "The first step towards controlling a risk factor (such as blood pressure or cholesterol) is", "How many servings of fruits and vegetables should adults consume?" and "The *statin* medications have a beneficial effect in the body by". Domains with the highest and the lowest scores were "Exercise" and "Psychosocial Risk" domains, respectively.

Discussion

This study aimed to validate and adapt the CADE-QII in Brazilian Portuguese. During these processes, we followed strict standards, since adaptation of an instrument to be used in a country other than that in which it was developed may require more than simply semantic and idiomatic analyses.[18] The psychometric properties – content validity, test retest reliability, internal consistency and construct validity – were established, confirming the validity of the CADE-QII for the Brazilian population.

Our results were consistent with those reported in the original validation,[17] particularly with respect to internal consistency (Cronbach alpha of 0.91 vs. 0.78), indicating an adequate correlation between the questionnaires' items, both in the original and in the adapted version.[17] Nevertheless, the fact that the CADE-QII was validated in a multicentric study may have affected alpha's value (not as high as in the original version). Another difference between the original and the adapted version was in the way the questionnaire was administered; while the adapted CADE-QII was administered by a questionnaire, in the version in English was self-administered.

With respect to criterion validity, there was a positive association of the level of knowledge about the disease with educational attainment and family income, suggesting that socioeconomic factors may be determinants to knowledge in health, which is consistent with previous studies.[14,17,20] This is corroborated by the fact that, in the present study, there was a positive association between enrollment in a

Table 1 – Sociodemographic and clinical data, and characteristics of cardiac rehabilitation programs of patients included in the psychometric validation of the CADE-QII version in Brazilian Portuguese and association of these variables with their level of knowledge about coronary artery disease (n = 307)

Characteristics		n (%)	CADE Q II total score Median (IQR)	p†
Sociodemographic				
Sex				
	Men	200 (65.1)	54 (15.75)	0.24
	Women	107 (34.9)	51 (13)	
Educational level				
	Never been to school	3 (1)	59 (15)	< 0.001*
	Incomplete elementary school	88 (28.7)	45 (16)	
	Complete elementary school	39 (12.7)	48 (13)	
	Incomplete high school	19 (6.2)	51 (19)	
	Complete high school	66 (21.5)	55 (11)	
	Incomplete higher education	8 (2.6)	53.5 (11.75)	
	Complete higher education	64 (20.8)	58 (13.5)	
	Undergraduate education	20 (6.5)	60 (8.75)	
Family income (per month)				
	< one minimum wage	50 (16.3)	48.5 (14.25)	< 0.001*
	1 - 5 minimum wages	159 (51.8)	50 (14)	
	5-10 minimum wages	40 (13)	60 (14.75)	
	10-20 minimum wages s	32 (10.4)	56.5 (9)	
	> 20 minimum wages	26 (8.5)	57 (15.75)	
Clinical features				
Comorbidities /risk factors				
	Systemic arterial hypertension	178 (58)	52.5 (17)	0.84
	Dyslipidemias	160 (52.1)	54 (14.75)	0.11
	Obesity	77 (25.1)	51(17)	0.34
	Type I and II diabetes	76 (24.8)	54 (14.5)	0.68
	Stroke	26 (8.5)	52 (14)	0.95
	Heart failure	33 (11.0)	49 (14)	0.11
	Smoking	12 (3.9)	52 (22.5)	0.41
	Chronic obstructive pulmonary disease	11 (3.6)	55 (11)	0.12
	Peripheral arterial occlusive disease	4 (1.3)	52 (22.5)	0.96
Acute event				
	Myocardial infarction	222 (72.3)	52 (16.25)	0.11
Procedures				
	Percutaneous transluminal angioplasty	172 (56)	53.5 (16.5)	0.62
	Myocardial revascularization surgery	62 (20.2)	54 (14.75)	0.70
Type of CR program				
	Public	219 (71.3)	50 (17)	< 0.001*
	Private	88 (28.7)	56 (13)	

*IQR interquartile range; CR: cardiac rehabilitation; † chi-square test; * p < 0.001*

Table 2 – Median and interquartile range of CADE-QII scores by question and domain, percentage of items completed and intraclass correlation coefficient (ICC) (n = 49)

Domain	Item	Median (IQR) scores by item	Items completed (%)	ICC	Median (IQR) scores by domain
Medical condition	1. Coronary artery disease is:	3 (2)	100%	0.77	12 (6)
	2. Angina (chest pain of discomfort) occurs:	3 (2)	100%	0.82	
	3. In a person with coronary artery disease, which of the following is a usual description of angina?	3 (2)	100%	0.77	
	4. A heart attack occurs:	1 (2)	100%	0.47‡	
	5. The best resources available to help someone understand his/her medications are:	1 (0)	100%	0.71	
	6. Medications such as aspirin (ASA) and clopidogrel (PlavixTM) are important because:	1 (2)	100%	0.72	
	7. The "statin" medications, such as atorvastatin (LipitorTM), rosuvastatin (CrestorTM), or simvastatin (ZocorTM), have a beneficial effect in the body by:	1 (1)	100%	0.87	
Risk factors	1. The risk factors for heart disease that can be changed are:	3 (2)	100%	0.72	10 (4)
	2. The actions that can be taken to control cholesterol levels include:	3 (0)	100%	0.82	
	3. The actions that can be taken to control blood pressure include:	3 (2)	100%	0.79	
	4. The first step towards controlling a risk factor (such as blood pressure or cholesterol) is:	0 (1)	100%	0.36‡	
	5. The actions to prevent developing diabetes include	1 (2)	100%	0.90	
Exercise	1. What are the important parts of an exercise prescription??	3 (2)	100%	0.71	14 (7)
	2. For a person living with heart disease, it is important to do a cardiovascular warm-up before exercising because:	1 (2)	100%	0.80	
	3. The pulse can be found:	3 (2)	100%	0.86	
	4. What one can do to exercise safely outdoors in hot and dry weather are:	3 (0)	100%	0.78	
	5. The benefits of doing resistance training (lift weights or elastic bands) include:	3 (2)	100%	0.87	
	6. If a person gets chest discomfort during a walking exercise session, he or she should:	1 (2)	100%	0.83	
	7. How does a person know if he/she is exercising at the right level?	1 (3)	100%	0.85	
Nutrition	1. What is the best source of omega 3 fats in food?	3 (0)	100%	0.85	13 (5)
	2. Trans fat are:	1 (2)	100%	0.70	
	3. What is one good way to add more fiber to your diet:	3 (2)	100%	0.80	
	4. Which of the following foods has the most salt:	3 (2)	100%	0.73	
	5. What combination of foods can help lower blood pressure?	3 (2)	100%	0.81	
	6. When reading food labels, what should one look at first?	1 (0)	100%	0.92	
	7. How many servings of fruits and vegetables should adults consume?	0 (1)	100%	0.55‡	
Psychosocial Risk	1. Which of the below are effective stress management techniques?	3 (0)	100%	0.92	9 (4)
	2. What stresses have been related to increased risk for heart attacks?	1 (3)	100%	0.73	
	3. Which of the following describes your best option for reducing your risk from depression:	3 (0)	100%	0.86	
	It is important to recognize "sleep apnea" because:	1 (3)	100%	0.70	
	5. "Chronic stress" is defined as:	1 (3)	100%	0.59‡	
Total		53 (14)	100%	0.77	-

IQR interquartile range; ‡ Items excluded from the final version in Brazilian Portuguese due to ICC values below 0.70

private CR program and knowledge level about the disease, reinforcing the influence of socioeconomic disparities on education in health.[21] These data make clear the need for developing strategies aiming at overcoming the obstacles between health knowledge and patients of different social classes. In this regard, these proposals should be grounded in simple models, with high population coverage, since less educated patients are the ones who would benefit most from educational interventions.[22]

In addition, we found that patients with more comorbidities, risk factors, previous procedures and acute events did not show higher knowledge level about the disease compared with patients without these conditions. These results contrast with those found in validation of the original version, since those patients with more risk factors showed higher knowledge about the disease.[17] These findings may be related to differences in the health education approach to the patients by the healthcare members and in patients' ability to understand the information received in different contexts.[23]

These findings should be interpreted with caution. First, our results cannot be generalized, since our sample was selected by convenience and recruited from four CR programs only, which may limit the extrapolation of the results. Second, CADE-QII is based on education curriculum of Canadian CR programs, which are based on more rigorous educational processes than the Brazilian programs. Third, although all patients were recruited from CR programs, these were conducted at distinct centers (public and private), located in different regions of the country. Therefore, the type of educational approach and variability between the investigators may have influenced the results. Fourth, reliability analysis was performed with 49 patients enrolled in only two of the four programs. The occurrence of a response trend, hence, may not be ruled out, since data in the literature consider that a sample size of at least 50 patients is adequate for this analysis.[19] In addition, it is possible that participants gained additional education during the 15 minute-interval between questionnaire applications, which could have also influenced the results. Fifth, CADE-QII was not developed using plain (or simple) language techniques, which may have had a negative impact on interpretation of the questions and consequently on the responses.[23] Sixth, as previously mentioned, during validation of its original version, CADE-QII was self-administered, in contrast to the adapted version, that was administered by means of a questionnaire. Even though the interviewers have been trained, bias intrinsic to questionnaire-based methods may have influenced the answers to the instrument.

To address this, further studies are needed to validate and use the short version of the CADE-Q,[24] as an alternative. Also, some questions were excluded during the construction of this adapted version, since they did not meet minimum standards of ICC; new validation studies proposing reformulation and inclusion of these questions are also encouraged. Also, future studies are needed to evaluate whether the Brazilian version is sensitive to longitudinal changes in assessment of patients' knowledge before and after their participation in CR programs.

Conclusions

This study showed that CADE-Q II version in Brazilian Portuguese version has enough reliability, consistency and validity, supporting its use in future studies to evaluate the level of knowledge of CAD patients enrolled in CR programs. This instrument could support the evaluation of the educational component in CR programs and identify knowledge domains compatible with patients' need for information.

Author contributions

Conception and design of the research: Santos RZ, Ghisi GLM, Britto R; acquisition of data: Bonin CDB, Chaves G, Haase CM; analysis and interpretation of the data: Santos RZ, Bonin CDB; statistical analysis: Santos RZ, Chaves G, Benetti M; writing of the manuscript: Santos RZ, Ghisi GLM, Bonin CDB, Chaves G, Haase CM, Britto R, Benetti M; critical revision of the manuscript for intellectual contente: Santos RZ, Ghisi GLM, Britto R, Benetti M.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Minas Gerais under the protocol number 1.350.973. 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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Cardiovascular Rehabilitation in Coronary Artery Disease and Better Knowledge of Its Own Disease

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Short Editorial related to the article: Validation of the Brazilian Version of CADE-Q II to Assess Knowledge of Coronary Artery Disease Patients

In the last ten to fifteen years, we are seen more and more concern with patients´ awareness about their diseases.[1-3] Campaigns have been brought to the public to teach them about symptoms and signs that might bring concern and make them ask for help and go to an emergency room or, in the United States to call 911. This is true especially for patients with coronary artery disease (CAD), given the possibility of better quality of life and in some cases even a better prognosis of the disease in respect to morbidity and mortality.

Beside this kind of campaigns, recently others started to aware people already with a diagnosis of CAD to the symptoms that may alert them of a problem and the consciousness about all medicines that modify the course of the disease and ways of life that are proved to contribute to this amelioration, as is physical activity.[4-8]

In this issue, dos Santos et al.[9] did validate a questionnaire to evaluate patients with CAD and on cardiovascular rehabilitation (rehab) programs in order to assess their knowledge about their own disease. Interestingly they first validate a previous (CADE-Q) questionnaire in Portuguese, then validated an English translated version. After that, they do construct a CAD-Q II questionnaire, but in English. The motivation to do this second version was that some questions should be better structured to the understanding of the patients and a psychosocial approach might be a part of it. After publishing it in the English language then they decide to translate to the Portuguese language. It is really a different approach going from one language to another and coming back to the first one, what is not usually done.

Keywords

Coronary Artery Disease/rehabilitation; Health Promotion; Preventive Medicine; Cardiac Rehabilitation; Exercise; Patient Health Questionnaire.

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The need for implementing the CADE-Q with other components was based on cardiac rehabilitation programs focused on patients with CAD. The objective of this paper is to validate the English version of CAD-Q II. The job was done according to the available tests used to validate questionnaires from one language to other, using Cronbach's alpha test. What they found called attention, although already known from other studies with questionnaires.

As higher the intellectual level of participants or their family income, better are they know of their disease, as shown in this validation. As the authors comment at discussion, they applied the questionnaire asking the questions, rather than applying a self-questionnaire as was done in the validation of the English version. Someone can think of this being a consequence of the intellectual level of our people. If this is true, it may be really an inadequacy for this questionnaire to be applied and it will be of importance to test more times to make sure it is truthful to be generally applied elsewhere. This does not invalidate this questionnaire, on the contrary, it can be otherwise be retested and then confirm confidence and feasibility.

We know the importance of awareness of people already with CAD, in this case specifically to patients on cardiac rehab, for symptoms that can be a warning for acute coronary events. But a questionnaire first done in the Portuguese language would be better validated if the second version had been also done in Portuguese and not a change to English, plus validation in that language and then a way back to the Portuguese language with cultural adjustments needed in the first and the second paths for validation. Besides it is important to understand, many times we treat patients with CAD and do not be aware of the costs/benefits of its treatment and many times, after years of observation, we do not find any difference between treatments and strategies[8] to the most frequent and first killer in the world. Cardiac rehab is known to reduce mortality in those with CAD, at least in a medium period of follow-up what probably justify a positive cost/effectiveness of these programs. Otherwise, we need longer follow-up, seven to ten years, studies to assure that really cardiac rehab programs are cost/effective.

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Diuretics are Similar to Losartan on Echocardiographic Target-Organ Damage in Stage I Hypertension. PREVER-Treatment Study

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Abstract

Blood pressure (BP)-lowering therapy improves left ventricular (LV) parameters of hypertensive target-organ damage in stage II hypertension, but whether there is a drug-class difference in echocardiographic parameters in stage I hypertension patients is less often studied. In the PREVER treatment study, where individuals with stage I hypertension were randomized for treatment with diuretics (chlorthalidone/amiloride) or losartan, 110 participants accepted to participate in a sub-study, where two-dimensional echocardiograms were performed at baseline and after 18 months of antihypertensive treatment. As in the general study, systolic BP reduction was similar with diuretics or with losartan. Echocardiographic parameters showed small but significant changes in both treatment groups, with a favorable LV remodeling with antihypertensive treatment for 18 months when target blood pressure was achieved either with chlorthalidone/amiloride or with losartan as the initial treatment strategy. In conclusion, even in stage I hypertension, blood pressure reduction is associated with improvement in echocardiographic parameters, either with diuretics or losartan as first-drug regimens.

Introduction

Heart failure with preserved ejection fraction (HFPEF) is an increasingly prevalent condition where hypertension has an important role.[1] Echocardiography identifies increased left ventricular mass (LVM),[2] LV concentric remodeling,[3] left atrial (LA) enlargement and diastolic dysfunction,[4] which are used to diagnose HFPEF,[1] and are independently associated with cardiovascular events.

Blood pressure (BP)-lowering treatment improves diastolic function and reduces LVM, LA size, especially in stage II hypertension, but the degree of benefit may be different among medications.[5] Whether there are differences in echocardiographic parameters with different antihypertensive drug classes in stage I hypertension is less often studied.

Keywords

Angiotensin-Converting Enzyme Inhibitors; Anihypertensive Agents; Antihypertensive Agents/therapy; Blood Pressure; Hypertension/complications; Hypertension/therapy; Calcium Channel; Echocardiography

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The present study was undertaken to compare the effects of chlorthalidone/amiloride versus losartan on echocardiographic evidence of hypertensive consequences in patients with stage I hypertension.

Methods

This is an echocardiographic sub-study at a single center of the PREVER-treatment study,[6] a multicenter double-blind randomized controlled trial (RCT) comparing chlorthalidone together with amiloride versus losartan for the management of stage I hypertension as the first option in the management of stage I hypertension.

Population, methods and results of the PREVER-treatment study are described in detail elsewhere.[6] In summary, all eligible participants of the PREVER-treatment study were aged 30 to 70 years old, with stage I hypertension according to the Eighth Joint National Committee (JNC 8) guidelines on hypertension (systolic BP between 140 and 159 or diastolic BP 90 and 99 mmHg)[7] and were not taking antihypertensive medication. They were submitted to a pre-enrollment lifestyle intervention phase; if BP remained inadequately controlled after 3 months of lifestyle intervention, they were enrolled in the RCT. Participants were randomly assigned in a 1:1 ratio to a chlorthalidone/amiloride 12.5/2.5 mg combination pill or to losartan 50 mg. A reassessment was performed every 3 months and, if necessary, treatment was scaled up with open label add-on BP drugs according to the protocol. The final visit occurred after 18 months of follow-up.

Transthoracic echocardiography was obtained at baseline and after 18 months of treatment. All echocardiographic examinations were performed using the same equipment (Envisor C HD or HD 11, Philips) with a standard multifrequency sectorial transducer by 2 trained cardiologists blinded to trial information and treatment allocation, following a previously described standardized protocol.[8] Echocardiographic studies were blindly read by a single physician using a dedicated workstation (Image Arena version 4 – TomTec, Germany). Measurements were performed in accordance with international society guidelines.[9] The study was approved by the institution's human research committee and informed consent was obtained from each patient.

Comparisons between the initial and final echocardiographic measurements in each treatment group were assessed by paired t-tests. Comparisons between the differences in treatment groups were assessed by independent-sample t-tests. An overall linear model was used to adjust echocardiographic outcomes for mean blood pressure variation, baseline echocardiographic parameter and time between randomization and echocardiographic examination. Intraobserver reproducibility was evaluated in 20 randomly

chosen studies using intraclass correlation coefficient, and varied between 0.99 and 0.67, with the lowest reproducibility found for the posterior wall thickness measurement.

Results

Of the 655 participants of the PREVER-treatment study, 230 participants from Hospital de Clínicas de Porto Alegre center were invited to participate in the echocardiographic evaluation, of which 133 participants were willing to participate, and 110 underwent the echocardiograms at baseline and after 18 months of follow-up.

Baseline demographic and clinical characteristics are shown in Table 1. Systolic blood pressure (SPB) was lower in the losartan group than in the main study, but it was similar between patients receiving diuretics and losartan who underwent echocardiograms. All other baseline characteristics were similar between the treatment groups and the main study group, including previous use of antihypertensive drug (diuretics: 71.4%, losartan: 65%, p = 0.47).

As shown in Table 2, there was no significant difference between the treatment groups regarding the final SBP. There was a similar proportion of patients receiving full dose of amlodipine (10 mg per day) after 18 months of follow-up in both treatment groups (5,3% in diuretics group, 9,2% in losartan group, p = 0.43).

Baseline echocardiographic parameters were similar among the groups (Table 2), except for LA volume index (LAVI) which was higher in the losartan group (28.2 ± 7.8 mL/m² vs 25.4 ± 6.5 mL/m², p < 0.05). After 18 months of treatment, there was a significant reduction in interventricular septal thickness (IVST), posterior wall thickness (PWT) and relative wall thickness (RWT), with a significant rise in E-wave deceleration time (EDT) in the diuretics group; in the losartan group, there was a significant reduction in LA volume index (LAVI), LVM index (LVMI), IVST, PWT and RWT (Table 2).

After adjustment for mean blood pressure variation, baseline echocardiographic parameter and time between randomization and echocardiographic examination, individuals in the losartan group had a greater interventricular septal thickness reduction (-0.7 ± 1.1 mm *vs*. -0.3 ± 1.2 mm; adjusted difference: 0.6 mm; p=0.009). However, this reduction was not sufficient to translate into differences in geometric patterns or diastolic function parameters between the treatment groups.

Discussion

This study shows that, in stage I hypertension, LV mass and LA size reductions, and changes in diastolic function parameters were similar with chlorthalidone/amiloride or with losartan treatment for 18 months.

Detection of target-organ damage is important for an adequate estimate of prognosis of the hypertensive patient. Increased LV mass and hypertrophy independently predict cardiovascular events. Despite concerns about echocardiographic variability,[10] it is the first-line imaging study for LV mass evaluation. In our study, to increase reproducibility of measurements, all studies were blindly read to visit and treatment allocation, and the paired analysis of data allowed the measurement of the intrinsic variation for each participant.

Two large studies directly compared different antihypertensive drug classes. The TOMHS study, in the pre-angiotensin receptor antagonist (ARB) era, evaluated 844 patients with stage I hypertension randomized for non-pharmacological treatment and chlorthalidone, acebutolol, amlodipine, enalapril, doxazosin or placebo.[11] Only chlorthalidone promoted regression of LVH compared to placebo in 12 months (-4.8g vs -18.2g; p = 0.04), with no difference observed in 48 months. It is important to note that, during follow-up, 33% of patients on the placebo group were prescribed active medication.

The LIFE substudy evaluated 960 patients with a higher SBP (160-200 mmHg) randomized for losartan or atenolol.[12] After 5 years, LVM showed greater reduction with losartan than with atenolol (-21.7 g vs -17.7 g; p = 0.01), although BP reduction was similar. In this study, LVM reduction was also more pronounced during the first 12 months of treatment. It should be noted that more patients on the losartan group were also using hydrochlorothiazide.

As far as we know, only one study directly compared diuretic (hydrochlorothiazide) and ARB (telmisartan) use in 69 patients with DBP of 90-114 mmHg, showing a higher reduction of LVM estimated by three-dimensional echocardiography with telmisartan (16 g *versus* 4 g in 12 months).[13] It is noteworthy that ARB was used at a maximum dose and the diuretic at a low dose.

The results of our study are in line with the findings of a meta-analysis[5] summarizing randomized comparative studies of antihypertensive treatment on LV mass regression in patients with stage II hypertension. There was less LV mass regression with beta-blockers, while diuretics, calcium

Table 1 – Baseline clinical and demographic characteristics of participants by treatment group

	PREVER-treatment study		Echo substudy	
	Diuretics (n = 333)	Losartan (n = 322)	Diuretics (n = 56)	Losartan (n = 54)
Sex (male)	167 (50.2)	167 (51.9)	34 (60.7)	28 (51.9)
Age (years)	53.9 ± 8.4	54.7 ± 7.9	55.5 ± 7.6	54.1 ± 8.3
BMI (kg/m²)	29.1 ± 5.0	28.8 ± 4.7	28.5 ± 4.4	28.5 ± 4.3
SBP (mmHg)	142.6 ± 7.1	142.1 ± 6.5	142.2 ± 8.2	139.4 ± 6.0
DBP (mmHg)	89.7 ± 6.3	89.4 ± 6.1	90.6 ± 5.9	90.2 ± 5.6

Diuretics: chlorthalidone/amiloride; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. Data are expressed as mean ± SD or number (%).

Table 2 – Adjusted differences in blood pressure and echocardiographic parameters between diuretics (chlorthalidone/amiloride) and losartan treatment groups*

Variable	Drug	Baseline	18-Month Follow-Up	Change from baseline	p	Between group change	p	Adjusted between group change**	p
SBP (mmHg)	Diuretics	142.2 ± 8.2	129.8 ± 10.0	-12.4 ± 11.1	< 0.001	2.7	0.18	1.18	0.51
	Losartan	139.4 ± 6.0	129.7 ± 8.7	-9.7 ± 9.4	< 0.001				
DPB (mmHg)	Diuretics	90.6 ± 5.9	83.7 ± 7.0	-6.8 ± 5.9	< 0.001	1.2	0.33	0.77	0.49
	Losartan	90.2 ± 5.6	82.1 ± 6.8	-8.0 ± 6.6	< 0.001				
LVMI (g/m^2)	Diuretics	84 ± 17	81 ± 19	-3 ± 16	0.11	1.78	0.48	3.84	0.14
	Losartan	82 ± 17	77 ± 16	-4 ± 14	0.02				
IVST (mm)	Diuretics	10.0 ± 1.2	9.7 ± 1.3	-0.3 ± 1.2	0.03	0.34	0.13	0.60	0.009
	Losartan	10.0 ± 1.1	9.4 ± 1.2	-0.7 ± 1.1	< 0.001				
PWT (mm)	Diuretics	10.1 ± 1.1	9.5 ± 1.1	-0.6 ± 3.3	< 0.001	-0.13	0.47	0.16	0.38
	Losartan	9.8 ± 1.1	9.4 ± 1.0	-0.46 ± 1.1	0.002				
RWT	Diuretics	0.45 ± 0.06	0.42 ± 0.05	-0.04 ± 0.06	< 0.001	-0.009	0.47	0.007	0.53
	Losartan	0.44 ± 0.06	0.41 ± 0.05	-0.03 ± 0.07	0.006				
LAVI (ml/m^2)	Diuretics	25.4 ± 6.5	24.1 ± 6.9	-1.4 ± 6.2	0.12	1.24	0.28	0.26	0.83
	Losartan	28.2 ± 7.8	25.7 ± 5.9	-2.6 ± 5.2	0.001				
Medial E/e' ratio	Diuretics	8.1 ± 2.1	8.5 ± 2.6	0.42 ± 2.52	0.23	0.61	0.21	0.22	0.65
	Losartan	8.8 ± 2.3	8.6 ± 2.3	-0.19 ± 2.39	0.57				
EDT (ms)	Diuretics	229.2 ± 47.4	252.2 ± 67.2	23.0 ± 63.0	0.01	11.0	0.37	13.33	0.34
	Losartan	230.0 ± 45.4	243.8 ± 66.9	12.0 ± 64.2	0.19				

** Diuretics: n = 56; Losartan: n = 54. ** Analysis of covariance adjusted for mean blood pressure variation, corresponding baseline echocardiographic parameter and time between randomization and echocardiographic exam. Diuretics: chlorthalidone/amiloride; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVMI: left ventricular mass index; IVST: interventricular septum thickness; PWT: posterior wall thickness; RWT: relative wall thickness; LAVI: left atrial volume index; EDT: E-wave deceleration time. Data are expressed as mean ± SD.*

channel blockers, angiotensin-converting enzyme inhibitors and ARB had similar effectiveness. We showed that there was no difference on LV mass regression after 18 months between a diuretic-based *versus* an ARB-based treatment of patients with stage I hypertension.

The study limitations should be acknowledged. The anticipated breach in randomization is not likely to have impacted the results, as demographic characteristics of the studied sample and the magnitude of SBP reduction were similar to those achieved in the whole sample study. Also, study power could be underestimated to find statistically significant differences in echocardiographic parameters between randomized treatments, as the PREVER-treatment study sample size was estimated for its primary endpoint. These potential limitations, however, reinforce the reported findings, which are even more noticeable if we consider the relatively low burden of hypertension organ damage, and the follow-up of only 18 months.

Conclusion

In stage I hypertension, blood pressure reduction is associated with improvement in echocardiographic parameters of target-organ damage, with a favorable LV remodeling achieved with either diuretics or losartan as the initial treatment strategy.

Author contributions

Conception and design of the research, analysis and interpretation of the data and statistical analysis: Bertoluci C, Foppa M, Fuchs SC, Fuchs FD; acquisition of data: Bertoluci C, Foppa M; obtaining funding: Fuchs SC, Fuchs FD; writing of the manuscript and critical revision of the manuscript for intellectual content: Bertoluci C, Foppa M, Santos ABS, Fuchs SC, Fuchs FD.

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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Review Article

Arrythmogenic Right Ventricular Cardiomiopathy/Dysplasia (ARVC/D) - What We Have Learned after 40 Years of the Diagnosis of This Clinical Entity

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Abstract

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) was initially recognized as a clinical entity by Fontaine and Marcus, who evaluated a group of patients with ventricular tachyarrhythmia from a structurally impaired right ventricle (RV). Since then, there have been significant advances in the understanding of the pathophysiology, manifestation and clinical progression, and prognosis of the pathology. The identification of genetic mutations impairing cardiac desmosomes led to the inclusion of this entity in the classification of cardiomyopathies. Classically, ARVC/D is an inherited disease characterized by ventricular arrhythmias, right and / or left ventricular dysfunction; and fibro-fatty substitution of cardiomyocytes; its identification can often be challenging, due to heterogeneous clinical presentation, highly variable intra- and inter-family expressiveness, and incomplete penetrance.

In the absence of a gold standard that allows the diagnosis of ARVC/D, several diagnostic categories were combined and recently reviewed for a higher diagnostic sensitivity, without compromising the specificity. The finding that electrical abnormalities, particularly ventricular arrhythmias, usually precede structural abnormalities is extremely important for risk stratification in positive genetic members. Among the complementary exams, cardiac magnetic resonance imaging (CMR) allows the early diagnosis of left ventricular impairment, even before morpho-functional abnormalities. Risk stratification remains a major clinical challenge, and antiarrhythmic drugs, catheter ablation and implantable cardioverter defibrillator are the currently available therapeutic tools. The disqualification of the sport prevents cases of sudden death because the effort can trigger not only the electrical instability, but also the onset and progression of the disease.

Keywords

Arrhythmogenic Right Ventricular Dysplasia/physiopathology; Arrhythmias, Cardiac/diagnostic imaging; Catheter Ablation; Defibrillators, Implantable; Magnetic Resonance Imaging.

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Introduction

ARVC/D is an inherited disease of the heart muscle that predominantly affects the right ventricle (RV). It is characterized by the progressive loss of the right ventricular myocardial tissue and its replacement for fibrous and fatty tissue.[1,2]

Originally described by Fontaine and Marcus in 1982, ARVC/D is one of the leading causes of sudden arrhythmic death (SAD) in young people and athletes.[3] Recently, there have been substantial advances in the understanding of its pathogenesis, clinical manifestations and long-term progression.[4]

The disease was initially referred to as dysplasia because it was thought to be a congenital defect of the RV myocardial development. The subsequent finding that the disease is caused by a genetic defect in cardiac desmosomes allowed its description as cardiomyopathy, and its inclusion in the classification of cardiomyopathies by the American Heart Association (AHA).[4-7]

Etiopathogenesis

Histopathological characteristics

The characteristic histopathological finding of ARVC/D is the progressive loss of RV myocardial tissue that is replaced by fibrous and fatty tissue.

The presence of irregular mononuclear inflammatory infiltrate (predominantly lymphocytic) is common, suggesting that the process may have an immunological mediation.[8] It has been proposed that the inflammatory infiltrate can extend the lesion to previously healthy regions, a process associated with worsening of the electrocardiographic abnormalities with consequent increase in symptomatic arrhythmias. This type of progression may be confused with acute myocarditis.[8]

Contrary to what was observed in several forms of heart disease, in which there was a predominance of subendocardial muscle involvement, in the ARVC/D the greatest impairment is evident in the subepicardial region of the RV free wall. In addition, segments of the RV free wall that experience the greatest mechanical stress during the cardiac cycle are more impaired. In general, the trabecular muscles of the RV endocardial region and the interventricular septum (relevant aspect when differentiating from sarcoidosis) are spared. When the left ventricle (LV) is involved, myocardial degeneration and fibrosis are more visible in the subepicardium and in the middle myocardium of the lateral wall.[1,8]

In the typical ARVC/D form, the LV is affected to a lesser degree than the RV; however, there are variants of the disease characterized by equivalent or even predominant involvement of the LV.[1,4,5]

Genetic and molecular characteristics

In most cases, ARVC/D is an inherited disease with an autosomal dominant pattern, with variable penetrance and expressivity. Among the probands diagnosed with the disease, a screening of first-degree relatives allows the identification of the presence of genetic mutations in approximately 50% of cases, regardless of gender. In a small number of cases, ARVC/D has an autosomal recessive pattern as part of a cardiocutaneous syndrome (Naxos disease or Carvajal syndrome), characterized by woolly hair and palmoplantar keratoderma.[4,6]

As observed in other familial diseases, there is a high degree of heterogeneity in ARVC/D. To date, mutations in more than 12 genes have been identified as causing ARVC/D, although many of these genes are also responsible for other diseases.[9]

Other patients with ARVC/D may have genetic abnormalities whose mutations have not been identified yet. These mutations may be inherited from family members or be the result of a new mutation.[9]

An individual who has a ARVC/D mutation may or may not develop signs and symptoms of the disease. Recent studies suggest the presence of one or more additional genetic abnormalities in a single gene class, such as plakophilin-2 (PKP2), for example, which may determine when a mutation-carrier individual may be clinically affected by the disease.[10-12]

Mutations may be in desmosomal and non-desmosomal genes. These mutations can be found and registered at the electronic address: https://doi.org/10.1002/humu.22765 o.[13]

Importance and Limitations of Genetic Testing

Genetic testing can be useful to determine the diagnosis in an individual suspected of having ARVC/D, and to identify relatives who do not have signs and symptoms of ARVC/D but who are carriers of the genetic defect. If an abnormal gene is identified in a proband and not in family members, it is unlikely that these members will have the disease based on this genetic abnormality.[4,5,10,11] However, there are several observations that limit the analysis and the use of the genetic test in ARVC/D:

- The proband may have a second unidentifiable genetic defect.
- The gene most commonly related to the manifestation of signs and symptoms of ARVC/D is that of *PKP2*. However, this genetic abnormality may require a second mutation in that same gene or in another desmosomal gene for the disease to manifest itself. That is, the simple identification of the gene cannot define whether it is the cause of the disease.
- Not being able to identify all the genes associated with the pathology, as well as the existence of combined mutations, make ARVC/D a genetically complex disease, which makes family counseling difficult.[11]

Periodic examinations should be performed on all individuals with genetic abnormalities for ARVC/D. It is recommended that cardiac evaluation be started between 10 and 12 years of age, because the manifestation of the disease before this age is rare. It is suggested that the tests include electrocardiogram, high resolution electrocardiogram (ECG-HR), echocardiogram and, if possible, CMR and 24-hour Holter. It is recommended that this evaluation is repeated every 2 years, between 10 and 20 years of age, and every 5 years after 20 years of age. The evaluation may be interrupted between 50 and 60 years of age because the presentation of the disease in this age group is uncommon.

An additional advantage of the genetic test lies in the aid of the differential diagnosis, as in the case of cardiac sarcoidosis, which can mimic the signs and symptoms of ARVC/D.

In addition, recent molecular biology studies have again put into perspective the debate about a possible pathogenic link between ARVC/D and Brugada syndrome (BS).[4,12,13]

Clinical presentation and natural history

Epidemiology

ARVC/D has an age-dependent penetrance and is typically manifested between the 3rd and 5th decade of life in the form of episodes of ventricular arrhythmias that may progress to SAD. The estimated prevalence ranges from 1:2,000 to 1:5,000, with a predominance in the Caucasian population and in participants in strenuous exercise or competitive sports.[1,6,7]

Despite its low prevalence, ARVC/D accounts for approximately 5% to 20% of SAD cases in young people. The occurrence of ARVC/D in individuals younger than 12 years of age, or older than 60 years is extremely rare.[7,14,15]

The disease is more malignant in men than in women, a finding that can be explained by a direct influence of sex hormones on the mechanisms involved in the phenotypic expression of the disease, or by differences in the amount and intensity of physical effort.[5]

Clinical and natural history

The natural history of ARVC/D, in its classic form (dominant RV), can be classified into 4 distinct phases, according to the progression of structural alterations and clinical symptomatology:

- **Occult phase:** this is the subclinical phase, in which the patient remains asymptomatic and with discrete structural abnormalities in the RV or without them. At this stage, SAD may be the first manifestation of the disease.
- **Arrhythmic phase:** the patient has palpitations, syncope and, generally, symptomatic ventricular arrhythmias originating in the RV, triggered by physical effort. Arrhythmias may range from isolated ventricular ectopies (non-sustained ventricular tachycardia) (NSVT) with left bundle-branch block morphology (LBBB) until reaching SAD episodes due to ventricular fibrillation.
- **Right ventricular failure**: The progressive replacement of myocardial tissue with fibro-fatty tissue leads to progressive impairment of RV function, which can lead to heart failure.

- **Biventricular failure:** In an advanced stage of the disease, the interventricular septum is involved causing congestive heart failure. At this stage, mural thrombosis may occur, especially in aneurysms that form in the RV or in the presence of atrial fibrillation. The phenotype may mimic advanced dilated cardiomyopathy, hindering the differential diagnosis in the more advanced stages of the disease.[16]

Recently, Calkins et al.[6] reported the clinical follow-up of a cohort of 102 patients diagnosed with ARVC/D after 50 years of age. The authors observed that, although SVT is also frequent in this age group, the incidence of syncope, typical electrocardiographic changes, ventricular ectopy to the Holter, and pathogenic mutation were less prevalent than in the younger age groups.[6] A later manifestation of ARVC/D does not translate into a better prognosis of survival free of high-risk arrhythmic events.[14]

Clinical diagnosis

In general, the diagnosis of ARVC/D should be considered in any young or middle-aged individual presenting: (1) frequent ventricular ectopies; (2) ventricular tachycardia with LBBB morphology with superior or multiple QRS morphologies; and (3) SAD. This hypothesis is reinforced in cases of arrhythmic events that occur during exercise in individuals with inverted T-waves in right precordial leads.[7]

Although these clinical indicators lead to the diagnostic hypothesis, the definitive diagnosis of ARVC/D remains a challenge because it is a disease with a low prevalence that lacks a single conclusive diagnostic test.[17]

To standardize the clinical diagnosis of ARVC/D, in 1994 an international task force (TFC 94) proposed guidelines in the form of a qualitative scoring system with major and minor criteria.[1,4] In 2010, the task force reviewed the guidelines for improving diagnostic sensitivity, especially for family members (TFC 2010),[18] providing quantitative criteria for the diagnosis of RV abnormalities and aggregating molecular genetic criteria (Table 1).[4,16]

Although it is the current gold standard, TFC 2010 does not apply to the predominant forms of involvement of the left chambers[19] that may be included in future reviews.[4,20]

Patients are diagnosed as having ARVC/D if they present a total of 4 points considering that the major criterion value is 2 points; and the minor criterion, 1 point. Patients who reach the "3-point" score are classified as probable ARVC/D carriers, while those with 1 or 2 points are classified as not meeting the criteria for ARVC/D.[6,18]

The initial evaluation consists of non-invasive examinations (ECG, ECG-HR, echocardiogram (ECHO) and/or CMR, 24-hour Holter and genetic analysis), while invasive examinations (right ventriculography and endomyocardial biopsy) are recommended only for individuals with high risk of the disease.[1,5]

The tissue criteria used in TFC 2010, obtained by endomyocardial biopsy, focused on the severity of myocyte loss and the quantification of fibrosis.[21] However, endomyocardial biopsy is invasive and its diagnostic sensitivity may be limited due to the heterogeneous and variable distribution of the disease. Although RV free wall is often affected, biopsy is usually performed on the septum due to the fear of perforation, which further compromises its sensitivity.[22] Rarely, outside the US, its value in the diagnosis of ARVC/D lies mainly on the differential diagnosis with other cardiomyopathies, myocarditis and sarcoidosis.[4]

Electrocardiogram

Sinus rhythm

The 12-lead ECG usually presents abnormalities in most patients with ARVC/D, indicating that electrocardiographic changes may precede the development of malignant ventricular arrhythmias (Figure 1). Thus, knowing the common manifestations of ARVC/D in the 12-lead ECG, the exercise test, and the 24-hour Holter test may be useful in increasing the diagnostic accuracy when generating the clinical suspicion.[7] In addition, it can help with the identification of relatives affected.[6,9] However, although ECG analysis is crucial to initial stratification, about 12% of patients with ARVC/D may present with a normal ECG, which reinforces the need for clinical evaluation that is based on the criteria proposed by TFC 2010.[9]

In addition to electrocardiographic changes classically described in ARVC/D, other alterations can be identified in the baseline ECG: sinus bradycardia, P wave abnormalities (secondary to atrial involvement), and AV conduction disorder (more often first-degree AVB). The occurrence of severe atrioventricular conduction disturbance in ARVC/D is rare.[9]

Several multicenter studies have shown that T-wave inversion in V1-3 is the most common ECG finding in ARVC/D. As a result, in TFC 2010, this T wave alteration was considered a major criterion for its diagnosis. The presence of inversion of the T wave only in V1 and V2 is a minor criterion. The inversion of T is secondary to the structural alterations of the RV. The observation of inversion beyond V3 translates a very advanced stage of the disease with severe RV dilation and possible LV involvement and can therefore be considered as indicative of worse prognosis (Figure 1A).[5,6,9]

One of the common findings of ARVC/D is complete or incomplete right bundle branch block (RBBB), especially in patients with severe structural impairment, and its presence may compromise the interpretation of ventricular depolarization abnormalities.[6] RBBB in ARVC/D may have the following characteristics: (1) low amplitude of R wave and QRS in V1-2; (2) low R'/S ratio in V1-2; (3) inversion of the T wave in V1-3 or in the other leads of the frontal plane. Epicardial and histopathological mapping studies have demonstrated that RBBB in ARVC/D is not due to a proximal right bundle branch block, but represents the result of the distal changes inherent in delayed stimulus propagation in the regions of fibrous-fatty transformation.[9]

Epsilon wave, a low-frequency deflection that occurs at the end of the QRS and before the T wave (Figure 1), although uncommon, is a sign of the presence of an advanced stage of

Table 1 – Task Force Criteria reviewed

1. Structural changes and global or regional dysfunction
Major criteria
• Two-dimensional echocardiogram
□ Akinesia, dyskinesia or regional RV aneurysm associated with one of the following diastole measures:
– PLAX RVOT ≥ 32 mm (PLAX / BSA ≥ 19 mm/m^2) or
– PSAX RVOT ≥ 36 mm (PSAX/BSA ≥ 21 mm/m^2) or
– Fractional area change ≤ 33%
• CMR
□ Akinesia or regional RV dyskinesia or dyssynchronism of RV contraction associated with one of the following measures:
– RV EDV/BSA ≥ 110 mL/m^2 (male) or ≥ 100 mL/m^2 (fem.)
– RV ejection fraction ≤ 40%
• Right ventriculography
□ Akinesia, dyskinesia or RV aneurysm
Minor criteria
• Two-dimensional echocardiogram
□ Akinesia, RV dyskinesia or dissyncronism of RV contraction and one of the measures of diastolic function below:
– PLAX RVOT ≥ 29 to < 32 mm (PLAX/BSA ≥ 16 to < 19 mm/m^2) or
– PSAX RVOT ≥ 32 to < 36 mm (PSAX/BSA ≥ 18 to < 21 mm/m^2) or
– Fractional area change> 33% ≤40%
• CMR
□ Akinesia or regional RV dyskinesia or dyssynchronism of RV contraction and one of the following measures:
– RV EDV/BSA ≥ 100 to 110 mL/m^2 (male) or ≥ 90 to 100 mL/m^2 (fem.)
– RV ejection fraction > 40 to ≤ 45%
2. Tissue aspects
Major criteria
• Residual myocyte count <60% by morphometric analysis (or <50%, if estimated), with fibrous RV free wall replacement in ≥1 sample, with or without fat replacement of endomyocardial biopsy tissue
Minor criteria
• Residual myocyte count of 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous RV free wall replacement in ≥1 sample, with or without fat replacement of endomyocardial biopsy tissue
3. Repolarization abnormalities
Major criteria
• Inverted T waves in the right precordial vessels (V1, V2, and V3) or extending beyond V3 in individuals > 14 years of age (in the absence of RBBB-QRS ≥ 120 ms)
Minor criteria
• Inverted T waves in V1 and V2 in ind. > 14 years of age (in the absence of RBBB)
• Inverted T waves in V1, V2, V3, AND V4 in ind. > 14 years, in the presence of RBBB
4. Depolarization / conduction abnormalities
Major criteria
• Epsilon wave (reproducible low amplitude signals between the end of the QRS and the beginning of the T wave) in the right precordial leads (V1 - V3)
Minor criteria
• Late potentials on the ECG-HR in ≥ 1 of the 3 parameters in the absence of QRSd ≥ 110 msec in the 12-lead ECG:
□ Filtered QRS duration (fQRS) ≥ 114 msec
□ Duration of terminal QRS < 40 micro V ≥ 38 ms
□ Root-mean-square voltage of terminal 40 ms ≤ 20 micro V
• Duration of the final QRS portion ≥ 55 ms (measurement of nadir from S wave to end of ventricular depolarization - including R') in V 1, V 2 or V 3

Continuation

5. Arrhythmias
Major criteria
• Non-sustained or sustained VT with LBBB type morphology and upper axis
Minor criteria
• Non-sustained or sustained VT with RVOT morphology (LBBB type morphology and lower or indeterminate axis) > 500E vs/24h - 24h Holter
6. Family History
Major criteria
• ARVC/D in first-degree relative who meets TFC2010 criteria
• ARVC/D pathologically confirmed in first degree relative (autopsy or biopsy)
• Identification of pathogenic mutation classified as associated or probably associated with ARVC/D in the patient under evaluation
Minor criteria
• History of ARVC/D in first degree relatives
• History of ARVC/D in a first-degree relative for whom it is not possible to determine whether it meets TFC criteria
• Sudden premature death (< 35 years of age) with suspected ARVC/D in first degree relative
• ARVC/D confirmed pathologically or through TFC in second degree relative

Adapted from Pinamonti et al., 2014.[16] ARVC/D: right ventricular arrhythmogenic cardiopathy/dysplasia; BSA: body surface area; CMR: cardiac magnetic resonance; ECG: electrocardiogram; EDV: end-diastolic volume; RBBB: right bundle Branch block; LBBB: left bundle Branch block; PLAX: parasternal long axis; PSAX: parasternal short axis; RV right ventricle; RVOT: right ventricular outflow tract; ECG-HR: high resolution electrocardiogram; Ventricular tachycardia; TFC task force criteria.

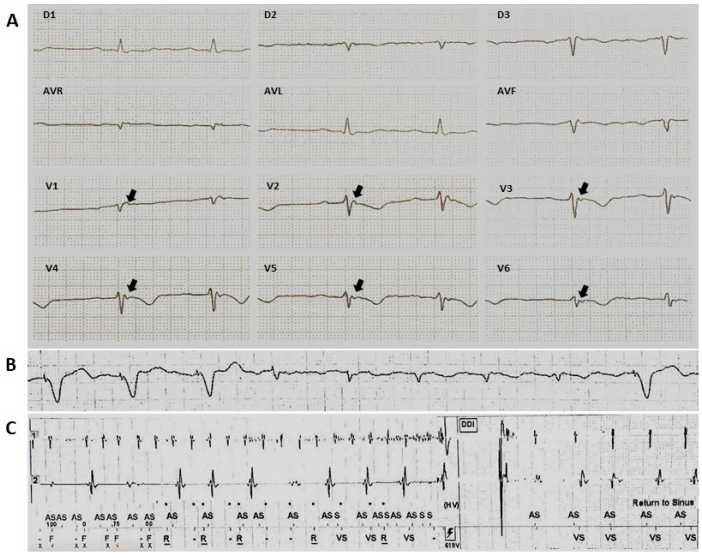

Figure 1 – *Evolution example of ARVC/D. Patient diagnosed with ARVC/D at age 32, after recovery from SAD during sports practice. He underwent implantation of ventricular ICD with multiple episodes of VF in clinical progression. At age 50, he developed sinus dysfunction and episodes of atrial fibrillation with a need for exchange for bicameral ICD. A) 12-lead ECG at diagnosis. Presence of T-wave inversion of V1-V6. Epsilon wave present in all precordial leads and final duration of QRS ≥ 55 ms. B) ECG with atrial fibrillation. C) inappropriate therapy due to atrial fibrillation.*

ARVC/D.[1,2,23] It reflects the presence of large late potentials on the surface ECG. Although considered a major criterion for the diagnosis of ARVC/D, LPs may also be present in other pathologies, particularly cardiac sarcoidosis.[9] These activation delays are best diagnosed with ECG-HR. Currently, a positive ECG-HR is considered a minor criterion.

Also included as a diagnostic criterion was the detection of a final activation delay, which is defined as prolongation of QRS duration (> 110 ms) and S wave (≥ 55 ms) in V1-3.

Arrhythmias

Increased susceptibility to ventricular tachyarrhythmia and SAD is the main characteristic of ARVC/D.[1] In general, ventricular arrhythmias, in an isolated and frequent form, or non-sustained and sustained ventricular tachycardia are associated with symptoms of palpitation, dizziness, presyncope and syncope. Due to the most common RV origin, this ventricular arrhythmia presents LBBB morphology with a variable axis depending on the affected site.[5,6,9]

Frequent ventricular ectopy recording in the 24-hour Holter (> 500 VEx/24h) is considered a minor criterion.[7]

Few studies have evaluated the frequency of supraventricular arrhythmia in ARVC/D. Although not related to mortality, the presence of atrial arrhythmia is associated with an increase in disease morbidity, and to the increase of inappropriate therapies by ICD. The incidence of atrial arrhythmia in ARVC/D varies between 14% and 24%, and atrial fibrillation is the most prevalent supraventricular arrhythmia (Figure 1B).[24,25] The occurrence of atrial arrhythmia is particularly associated with the presence of tricuspid insufficiency, atrial involvement and significant RV dilation.[9]

Complementary examinations

Echocardiogram

A structural and functional evaluation is fundamental for the diagnosis of ARVC/D. Echocardiography, as a result of its accessibility, has been the image exam of choice for the beginning of the investigation of ARVC/D. However, the unique geometry and complex pattern of RV contraction, together with the increased recognition that structural abnormalities may not be apparent in the earlier stages of the disease, limit its diagnostic utility.[7] Echocardiographic findings suggestive of ARVC/D include: (1) global or segmental abnormality of the ventricular wall in association with dilatation of the cavity (mainly right); (2) RV hypertrophy and systolic dysfunction; (3) dilatation of the RV outflow tract (diameter > 30mm).[6]

Cardiac magnetic resonance

In the last decade, CMR has emerged as the image modality of choice in the ARVC/D investigation, because it allows for a non-invasive morphological and functional evaluation, as well as for analysis of the tissue changes (fibro-fatty transformation) that characterize this pathology.[6,7] However, misinterpretation of CMR findings is the most common reason for misdiagnosis of ARVC/D. The most common errors include inadequate diagnosis of physiological or artefactual fat infiltration, misinterpretation of normal variants of RV wall movement, and inappropriate diagnosis in cases of sarcoidosis and myocarditis.

This "pathological" connotation given to the existence of fat in the RV led to a high incidence of false positivity, especially when using the TFC criteria of 1994. 2010 TFC brought a better definition of the criteria to be sought in the CMR, leaving the use of specific protocols for fat screening in the right chamber aside.

Abnormalities of CMR in ARVC/D can be grouped into morphological and functional abnormalities (Table 2). These abnormalities were initially observed in the classically described "triangle of dysplasia"[3] which refers to the RV entry tract, the outflow tract and the apex. However, a recent study suggests that these changes preferentially involve the subtricuspid epicardial region, the RV free basal wall and the LV lateral wall, with the RV apex and the endocardium generally spared.[6,9]

In addition to the parameters included in the TFC 2010, there are other characteristic abnormalities of the ARVC/D that can also be visualized by the CMR. These parameters include the RV microaneurysms and the presence of an "accordion signal", which is the focal wrinkling of the RVOT or RV free subtricuspid wall, which is more prominent during the systole. In addition, the presence of intramyocardial fat in the RV suggests ARVC/D; however, its presence is not specific and has been observed in the elderly, in chronic users of steroids, and in other cardiomyopathies.[4,5]

Table 2 – Cardiac magnetic resonance imaging findings in cardiomyopathy / arrhythmogenic right ventricular dysplasia

Functional abnormalities
Regional abnormalities of RV wall movement
Focal aneurysms
RV Dilation
Diastolic/systolic dysfunction of the RV
Morphological abnormalities
Intramyocardial fat infiltration
Focal fibrosis
Focal decrease of RV wall thickness
Wall hypertrophy
Trabecular disarrangement
Hypertrophy of the moderating band
RVOT diameter change

RV: right ventricle; RVOT: right ventricular outflow tract.

Although the increase in late enhancement by gadolinium (LE) has been frequently detected in patients with ARVC/D, this criterion was not incorporated in 2010 TFC due to several limitations (RV thin walls, difficulty in differentiating fat from fibrosis, and irregular impairment of the RV). Despite this, we believe that it is of diagnostic value, especially those with biventricular or left dominant forms.[4]

The increasing use of CMR is leading to the recognition that LV is more frequently changed than previously thought, leading to the expression arrhythmogenic cardiomyopathy. LV involvement is mainly located in the inferior and basal inferolateral walls, typically in the form of fat infiltration extending from the epicardium to the myocardium. These sites may also present LE, often without an association of ventricular wall motility abnormality.

Electrophysiological study

The electrophysiological study (EFS) with programmed ventricular pacing is nowadays less used in the diagnostic and therapeutic evaluation of ARVC/D.[7] The largest multicenter study on patients with ARVC/D who received ICD implantation showed that the EFS has limited value in predicting the risk of a severe arrhythmia. In this study, the incidence of effective therapies for fatal events (VF/VFL) did not differ significantly among patients with inducible arrhythmia or not, during baseline EFS.[26]

In spite of these recent results, 2010 TFC considers that the EFS should be taken into account for the diagnosis and

evaluation of patients with suspected ARVC/D (class IIa) and may also be used in the risk stratification of asymptomatic patients (class IIb).[18]

Recent studies using electroanatomic voltage mapping (bipolar and unipolar) to assess the existence and extent of the scar area in the RV have added interest in the use of EFS in the evaluation of ARVC/D (Figure 2).

This mapping technique proved to be useful in directing the region to be biopsied, as it is more sensitive than the CMR to identify myocardial scar areas, and in the differential diagnosis between an idiopathic VT of the RVOT, and a VT in a patient with ARVC/D. Nevertheless, due to the fact that it is an invasive, high cost and dependent operator, this diagnostic method should be reserved for cases with a high index of suspicion and an indefinite diagnosis.[5]

Differential diagnosis

The main differential diagnoses that should be considered in suspected cases of ARVC/D include: idiopathic RVOT VT, VT originating from the aortic cusps, and cardiac sarcoidosis.[6]

The idiopathic RVOT VT is a generally benign form of ventricular arrhythmia without association with cardiac structural alteration.[27] The differential diagnosis is based on the fact that idiopathic VT is a non-familial arrhythmia and that the patient does not present the classic ARVC/D electrocardiographic alterations.[28] An evaluation with the CMR should be carried out in all cases.

Another differential diagnosis is sarcoidosis. This granulomatous disease, when it involves the heart, may be very similar to ARVC/D. Cardiac sarcoidosis should be suspected when cardiac manifestations are associated with mediastinal lymphadenopathy, extracardiac sarcoidosis, especially the pulmonary one, to severe atrioventricular conduction disturbances, and the presence of a scar in the interventricular septum in the imaging evaluation.[6] In addition, more advanced age at onset of symptoms, presence of cardiovascular comorbidities, and non-familial disease pattern should also raise suspicion of cardiac sarcoidosis.[4] Cardiac position emission tomography may be useful for differential diagnosis.[29]

Other less frequent pathologies are: myocarditis; Brugada syndrome;[30] dilated cardiomyopathy, in cases with biventricular dysfunction; myocardial infarction with involvement of both cardiac chambers; pulmonary hypertension (RV pressure overload), and/or significant tricuspid regurgitation (RV volume overload); congenital heart defects such as Uhl's anomaly and corrected Fallot's tetralogy; and left-right intracardiac *shunts* (usually interatrial septal defect and anomalous drainage of the pulmonary veins) that may cause right ventricular overload.

Recently, there has been much discussion of the phenotypic overlap between ARVC/D and Brugada syndrome.[30] The ultrastructural changes that result from mutations in the desmosomes may explain this observation. From the clinical point of view, both conditions may manifest as abnormalities in the ventricular repolarization in right precordial leads, right bundle branch conduction disorder, and ventricular arrhythmias stemming from the RV.[31] Pathologically, fatty myocardial infiltration has been reported in both conditions.[4,32,33] As a consequence, ARVC/D and Brugada syndrome may be part of a subgroup of structural myopathies due to changes in the sodium current, due to the involvement of the inter-cellular connection.[30]

Risk stratification

The natural history of ARVC/D is predominantly related to electrical instability that can lead to arrhythmic SAD, especially in young athletes. At a later stage of the disease, progressive RV impairment and left ventricular involvement may result in right and/or left failure.[1,6]

Data regarding the clinical progress come from small cohorts performed in tertiary centers and with a relatively short clinical follow-up. The total mortality estimated in these studies

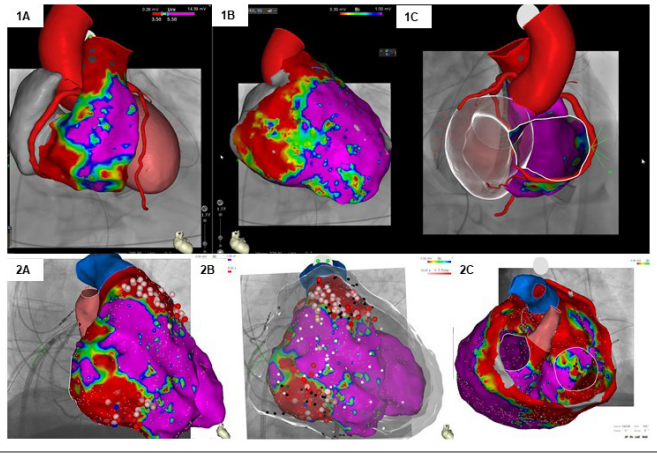

Figure 2 – *Two examples of voltage mapping for ventricular tachycardia ablation in patients with ARVC/D. 1A) Mapping of epicardial voltage showing (in red) areas of scar in the outflow tract and basal region of the RV. 1B) Mapping of endocardial voltage showing the presence of more extensive scar areas in the same region. 1C) Perspective showing the correlation of the scar areas with the coronary tree. 2A and 2B) Voltage mapping used for substrate ablation in a patient with ICD with multiple therapies. Radiofrequency applications (white and red circles) distributed in the endocardial and epicardial regions. 3C) Mapping image showing scar presence affecting the LV.*

ranges from 0.08% to 3.6% per year. In community studies, which provide real-world data, annual mortality is < 1%.[4,5]

Several factors were proposed for stratification of mortality risk and / or ventricular tachyarrhythmias in the ARVC/D. Corrado et al.[34] developed a risk stratification categorized as high, intermediate and low risk. Thus, the authors sought to facilitate the early recognition of individuals who would benefit from ICD implantation (Figure 3).[4,34]

The main clinical variables considered as independent predictors of worse evolutionary prognosis are: arrhythmic malignant events (SAD, cardiac arrest due to VF, appropriate intervention of ICD, or therapy of ICD for fast VT/VF); heart transplantation; and in some studies, unexplained syncope.[5]

Other criteria, such as the result of genetic mapping and the invasive electrophysiological study, are still controversial in the literature.[5]

Treatment

The most important goals of treating patients with ARVC/D include:

- Reduction in mortality from arrhythmic SAD or death from heart failure.
- Prevention of disease progression with consequent RV, LV or biventricular dysfunction and heart failure.
- Improvement of symptoms and quality of life by means of reduction/abolition of palpitations, VT relapses, or discharges from ICD (appropriate or inappropriate).
- Limitation of symptoms of heart failure and increased functional capacity.

Therapeutic options consist of lifestyle changes, pharmacological treatment, catheter ablation, ICD, and cardiac transplantation.[1,6,7] Available evidence indicates that family members with a negative phenotype (carriers of healthy genes or with an unknown genotype) do not require any specific treatment other than sports restriction.[5]

Lifestyle change

Competitive sports activity increases the risk of SAD by two to five times in adolescents and young adults with ARVC/D.[25]

In a recent study, Ruwald et al. have established a link between SAD and intense effort in young individuals with ARVC/D. The authors followed 108 probands and demonstrated that competitive sports practice is associated with a significant increase in the VT/death combined outcome, and early phenotypic manifestation when compared to the inactivity of sedentary patients, or to the practice of recreational sports.[15] Another finding was that the earliest start of competitive sports is associated with the early onset of clinical symptomatology.[15]

Early identification, prior to the symptomatic phase, of athletes affected by preparatory screening for the onset of physical activity and their disqualification from competitive sports activity may "save lives" (Italian experience).[34]

It is postulated that myocyte intercellular adhesion impairment can lead to tissue and organ vulnerability with

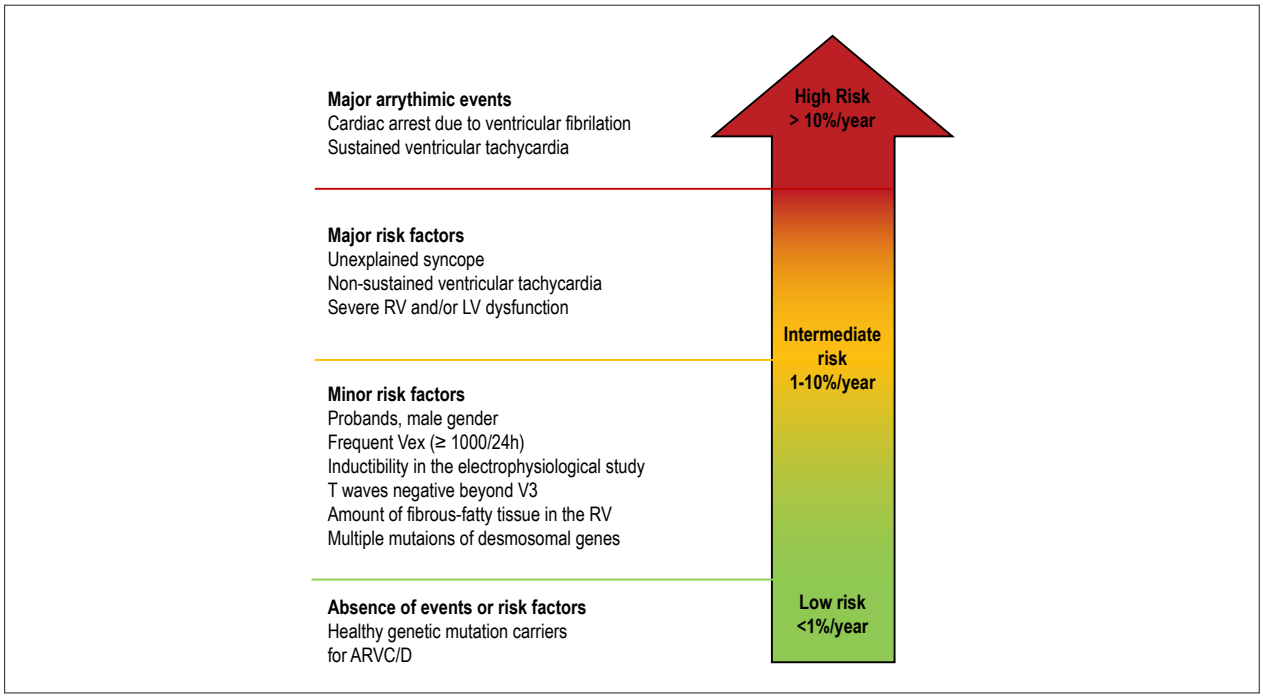

Figure 3 – *Proposed scheme for the prognostic stratification of patients with ARVC/D, according to the clinical presentation. The risk subgroups shown in the figure were defined based on the estimated probability of a major arrhythmic event (sudden cardiac death, cardiac arrest due to ventricular fibrillation, ventricular tachycardia or an event requiring ICD intervention) during follow-up, in relation to arrhythmic events or previous risk factors. An estimated annual risk of more than 10% defines the high-risk group; a risk between 1% and 10% defines the intermediate risk group; and a risk below 1% defines the low-risk group. VEx: ventricular extrasystoles; ARVC/D: cardiomyopathy/right ventricular arrhythmogenic dysplasia. Adapted from Corrado et al., 2017.*[5]

consequent death of myocytes, especially during mechanical stress that occurs during competitive sports activity.[34] Since the RV is a cardiac chamber with greater compliance than the LV, particularly during physical exercise, it becomes more susceptible to injuries, resulting in inflammation, fibrosis and, as a consequence, arrhythmias.[7]

Based on this, ITF recommends that patients with a definitive diagnosis of ARVC/D do not participate in competitive or resistance sports (class I), and may only participate in low intensity recreational sports (class IIa). The same restrictions can be applied to relatives with negative phenotype, even those that do not carry genetic mutations or with unseen genotype (class IIb).[35]

Pharmacological treatment

The pharmacological treatment of ARVC/D consists of the use of antiarrhythmic drugs, beta-blockers and drugs used in the treatment of heart failure.[1]

Antiarrhythmic therapy

The goal of antiarrhythmic treatment in ARVC/D is to prevent arrhythmic events. Literature data suggest that antiarrhythmic drugs are ineffective in preventing the occurrence of severe tachyarrhythmias in high-risk patients with ICD.[6] Thus, antiarrhythmic therapy should be indicated as adjunctive therapy to ICD in patients with multiple appropriate therapies (class I), and may also be considered in those patients with frequent ectopic activity and/or NSVT (class IIa). In patients not having ICD and with hemodynamically tolerated VT, combined ablation/antiarrhythmic therapy may be applied (class IIb). On the other hand, the use of antiarrhythmic drugs should not be considered in asymptomatic carriers of genetic mutation and without documented ventricular arrhythmia (class III).

Amiodarone alone or in combination with beta-blockers (because it combines the synergistic effects of class III antiarrhythmic and beta-adrenergic blockade properties) is the most commonly used therapeutic regimen for the treatment of ARVC/D.[36] Sotalol is a good therapeutic alternative, given the side effects resulting from the chronic use of amiodarone, particularly in the younger population.[7]

Although not available in our country, flecainide, when associated with a beta-blocker, may be an effective antiarrhythmic strategy of control in patients that are refractory to treatment with amiodarone or sotalol and/or catheter ablation.[37]

Betablockers

The ventricular arrhythmia in the ARVC/D often manifests itself in a situation of increased sympathetic tone. The current consensus is that beta-blocker therapy should be empirically instituted in all patients with a clinical diagnosis of ARVC/D.[5,7] In contrast, there is no indication of prophylactic use of beta-blockers in healthy carriers of ARVC/D.[34]

Other drugs

Preload reduction drug therapy (usually diuretics and nitrates) is not yet part of the regular therapeutic arsenal of ARVC/D patients.[33]

Angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers have been advocated in patients with ARVC/D, especially in patients with evidence of structural impairment, although there are no studies demonstrating this indication in this specific condition.[6]

Continuous oral anticoagulant use is indicated for secondary prevention in patients with documented intracavitary thrombus, atrial flutter or fibrillation type arrhythmias, or with a history of thromboembolic event.[5,34]

Catheter ablation

VT catheter ablation is a therapeutic option for patients with continuing VT, or appropriate ICD shocks, despite optimal pharmacological therapy, including the use of amiodarone (Figure 2).[1,4,5,38,41]

Long-term VT relapses have been attributed to the progressive nature of ARVC, which leads to the development of multiple arrhythmogenic foci over time. The epicardial location of many TV reentry circuits, which reflects the propensity of the ARVC lesions to originate and progress from the epicardium, may also explain the failure of conventional endocardial mapping and catheter-only endocardial ablation.[1,2]

The increasing understanding of the arrhythmogenic substrate and the possibility of an epicardial approach allowed the observation of a significant increase in the success rate of catheter ablation in the treatment of VT in ARVC/D in recent years.[27,28]

The advent of three-dimensional (3D) navigation systems has enabled a significant advance in VT ablation in ARVC/D patients. This technique allows the mapping of the endocardial and epicardial substrate using a colored tissue voltage map, particularly in the areas that are adjacent to the tricuspid valve region and the RVOT (Figure 2).[27,28] Based on this latest experience, ITF proposed that, in cases of unsuccessful endocardial approach, the epicardial approach should be attempted. It also recommends an endo/epi approach, as an initial strategy, in services with experience with this type of technique.[28]

The technique used for ablation depends on the patient's hemodynamic response during tachycardia. In cases of well-tolerated VT, the electrophysiological mapping and activation mapping techniques with the 3D system are the most commonly used. In the case of a VT with hemodynamic instability, the treatment consists of modifying the arrhythmogenic substrate, with ablation being done on the possible channels between areas with different voltages in combination with the elimination of fractional endocardial and epicardial signals (Figure 2).[27,28]

Implantable cardioverter-defibrillator

CDI implantation is the most accepted therapeutic strategy for ARVC/D patients, because the natural history of this pathology is characterized mainly by the risk of SAD, and only secondarily by contractile dysfunction that leads to progressive heart failure.[1] Although there are no prospective randomized studies, observational studies of large registries have shown that the implantation of an ICD increases patients' survival. These studies have shown that 48-78% of patients receive appropriate ICD therapy during long-term follow-up.[4,6,29]

An observational study evaluated the clinical impact of ICD in the natural history of ARVC/D patients. At an average follow-up of 3.3 years, 24% of the patients had as an arrhythmic manifestation an episode of VF/VFL that would have been fatal in the absence of an ICD.[26]

Despite these results, it is important to note that the survival benefit with ICD is obtained at the expense of a high prosthesis cost, and a significant rate of complications during follow-up, mainly related to the occurrence of inappropriate therapies around 4%/year and changes in the electrodes.[33] Inappropriate interventions occur between 10% and 25% of the patients, mainly in young patients and usually due to sinus tachycardia or atrial tachyarrhythmia (Figure 1C). The high rate of adverse events related to the electrodes can be explained by the peculiar pathophysiology of ARVC/D that leads to progressive loss of myocardium and to fibrous and fatty replacement that can both generate difficulties in locating a suitable place to implant the leads, and affect the thresholds of command and sensitivity during clinical follow-up.[4,5] Another aspect is that it became evident that ICDs may be inappropriately implanted in patients with a false diagnosis of ARVC/D based on misinterpretation of CMR studies.[4,5]

Unicameral ICDs are recommended to minimize the risk of complications related to prolonged use of this device, especially in young patients. Although the number of inadequate interventions can be reduced by a dual chamber detection system, the additional lead predisposes to a greater risk of short-and long-term complications.[22] Anti-tachycardia pacing is highly successful in terminating ventricular arrhythmia, and should be programmed into all devices.[42] The role of the subcutaneous ICD is under investigation.

Based on the results of studies that defined independent predictors of major arrhythmic events (i.e. SAD, cardiac arrest due to VF, sustained VT and appropriate ICD interventions), ITF proposed an ICD indication flowchart based on three categories (Figure 4).[4,5,34] The recommendations for the implantation of the ICD for each risk category are based not only on the statistical risk, but also on the general health, socioeconomic, psychological and adverse factors of the device.

Heart transplant

It is rare for a ARVC/D patient to require a heart transplant. Transplantation would be indicated as final therapy in cases of severe heart failure, and when not responsive to pharmacological treatment and resynchronization therapy (in those patients with significant LV involvement), or in patients with intractable arrhythmias (eg, incessant VT, or VF storms refractory to catheter ablation and ICD therapy).[4,5]

Prevention of progression

The last aspect to be considered in patients with ARVC/D is the prevention of disease progression. It is important to note that no study examined aspects that signal the evolutionary characteristics and the rate of progression of ARVC/D. Progression is slow but steady. It is suggested that the restriction of physical exercise may interfere with the rate of disease progression.[15] A definitive curative treatment will require a deeper understanding of the biological mechanisms and environmental factors involved in the pathogenesis of ARVC/D.[5]

Future perspectives

Significant advances were achieved if we consider the 30 years or more of the diagnosis of this pathology. However, given its rarity, many gaps persist.

It is possible to define some areas of interest that will allow better clinical management of patients and definition of the population at risk of sudden death:

- Although not yet routinely available, the future possibility of genetic screening of patients and family members with clinical suspicion of ARVC/D may become of extreme relevance with potential implications for understanding the pathogenesis and management of affected individuals.
- Further refinement in the detection of morphological abnormalities will allow a greater refinement in the algorithm for the identification of ARVC/D carriers and a better understanding of their natural history. An improvement in imaging techniques (magnetic resonance imaging and echocardiography), and the possibility of MR follow-up in patients who received MR-compatible ICD implantation.
- Studies that try to analyze the phenotype-genotype correlation may clarify the natural history of the disease, and the greater propensity for the development of malignant arrhythmias and, therefore, define the best time to initiate a medical intervention.

The denomination of this cardiomyopathy has been discussed for years. The debate between naming it RVAD or RVAC is the representation of two different views of its pathophysiology, degenerative process or developmental abnormality. Probably both visions are involved; although the terminology initially proposed by Fontaine – "dysplasia" - is probably questionable, this term has been used and accepted for 40 years, and it will persist, incorporated to the history and description of this cardiomyopathy.

Tribute

Guy Fontaine died on March 7, 2018 at the age of 82.

He pioneered modern electrophysiology and cardiac arrhythmia therapy; a visionary investigator and mentor for many electrophysiologists. Fontaine began his contributions by studying the first cardiac pacemakers in the 1960s, and pioneered the study of catheter arrhythmias by introducing surgical cardiac mapping in 1972 for ablation of severe arrhythmias, WPW syndrome, and ventricular tachycardias, which allowed the recognition and study of RVAD, its main subject of research. He introduced catheter ablation with fulguration procedures, and studied 3D mapping methods thoroughly.

Guy Fontaine is the author of more than 700 manuscripts and book chapters. He received numerous international awards for his contributions and continued active until his last day of life, despite of a severe disabling illness.

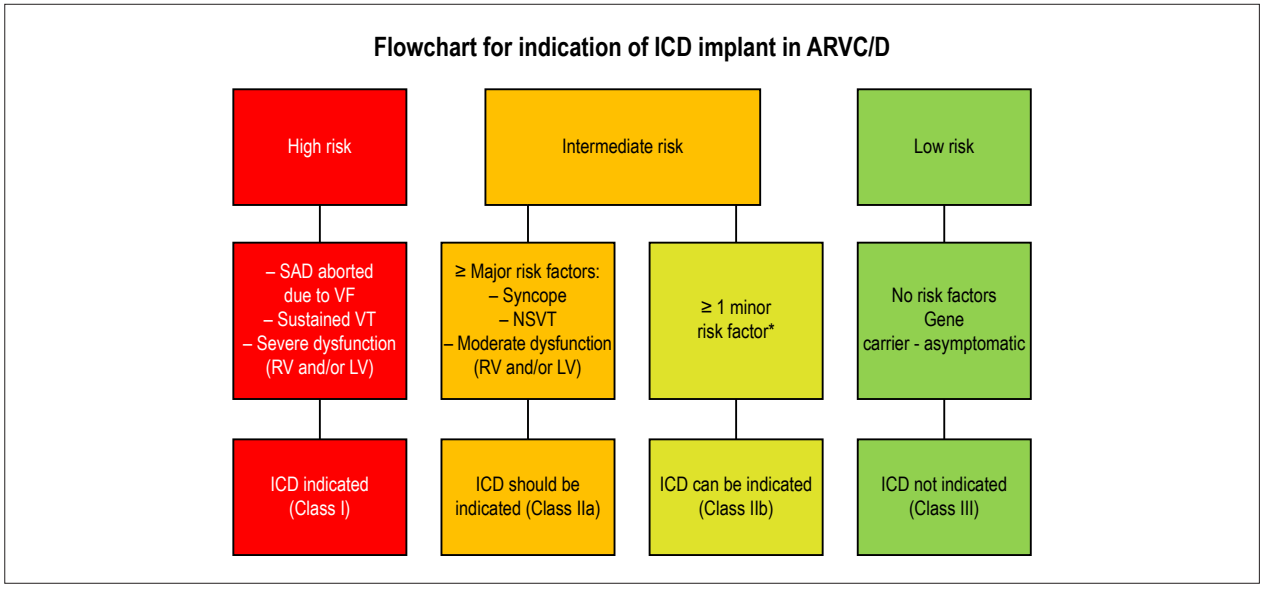

Figure 4 – *Flowchart of indications for implantation of ICD in ARVC/D. The flowchart is based on available data on annual mortality rates associated with specific risk factors. High risk of major arrhythmic events: > 10%/year; intermediate risk: 1% to 10%/year and low risk: < 1%/year. The indications for ICD implantation were determined by consensus, taking not only the statistical risk into account, but also the general health status, socioeconomic factors, psychological impact and adverse effects of the device. SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia; RV: right ventricle; LV: left ventricle. *See the text for the distinction between major and minor risk factors. Adapted from Corrado et al., 2017.*[22]

Author contributions

Conception and design of the research and acquisition of data: Elias Neto J, Tonet J, Fontaine G; analysis and interpretation of the data and critical revision of the manuscript for intellectual content: Elias Neto J, Tonet J, Frank R; statistical analysis, obtaining funding and writing of the manuscript: Elias Neto J.

Potential Conflict of Interest

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

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Study Association

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

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Coronary Computed Tomography Angiography Takes the Center Stage and Here is Why

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Max Planck once said that "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it." In its beginnings, coronary computed tomography angiography (CCTA) was accused of having too low accuracy for the diagnosis of obstructive coronary artery disease (CAD) to be used in clinical practice. Over the last decade, major technical developments such as larger axial coverage (from 2 cm to 16 cm) and improved temporal resolution, have enabled CCTA to become by far the most accurate non-invasive imaging method for diagnosis of obstructive CAD, with sensitivity and specificity of approximately 95% and 90%, respectively.[1]

Then CCTA was burdened with the accusation of exposing patients to radiation doses so high, that warranted some society guidelines to specifically point this out and limit its use. At that time, CCTA exposed patients to doses ranging from 20 to 25 mSV, while triphasic abdomen CT exposed patients to 30 to 40 mSv and scintigraphic myocardial perfusion studies with Thallium used up to 40 mSv. In 2018, radiation exposure from CCTA dropped to well below 5 mSv (most advanced clinical centers use much less), a fraction of the dose used in myocardial perfusion studies with MIBI tetrophosmin.[2] Then the cost-effectiveness wave came with societies rightfully demanding proof that CCTA offered more value at an acceptable cost compared to other imaging modalities, and CCTA once again proved to be more cost-effective than other modalities.[3] Although one hardly finds cost-effectiveness studies comparing nuclear scans with ECG treadmill tests, providing better diagnosis performance is not enough anymore. More recently, this strategy has even been put into challenge in large randomized clinical trials comparing CCTA with the standard of care in the investigation of suspected CAD both in the acute and in the outpatient settings.[4-9]

Keywords

Coronary Artery Disease/diagnostic imaging; Coronary Artery Disease/prevention and control; Coronary Artery Disease/physiopathology; Computed Tomography Angiography; Tomography, X-Ray Computed.

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But then CCTA adoption had to face another hurdle. People started demanding that CCTA, a diagnostic study, should demonstrate that it would alter clinical outcomes. Let's stop here for a moment: a diagnostic study makes the diagnosis. It does not provide the cure, but it could lead to changes in therapy which could eventually lead to improved outcomes. As such, although a CCTA study is not therapeutic, it could guide and inform therapeutic decisions. Measuring blood pressure was never proven to alter clinical outcomes, treatment did. The same with cholesterol measurements, ischemia testing and resting ECG recordings. And yet, everybody has always rightly assumed that diagnosis is a fundamental part of sound medical practice and an angular stone of clinical management. Cardiovascular disease, predominantly in the form of atherosclerosis and hypertension, starts as early as 30 or 40 years, silently progressing across the years to finally kill around one-third of the adult population in the developed world. The conventional strategy "to sit and wait" until patients present with symptoms certainly misses the golden period of the early disease, when treatment is much more efficient and less expensive. Early detection and diagnosis of atherosclerosis using CCTA, might lead to significant downstream changes which could consequently improve outcomes.

Despite those initial criticisms and the sceptical view of the use of CCTA in the investigation of suspected CAD, the evidence supporting its clinical use has been steadily increasing over the years. From the initial studies defining the technical feasibility and accuracy of CCTA, followed by the development of techniques aimed at reducing radiation dose and improving imaging quality, CCTA has evolved to be part of the routine armamentarium for the investigation of suspected CAD. More recent evidence has led a wide variety of interpretations, as CCTA lead to an increase in the diagnosis of CAD, accompanied by a 31% reduction in the rate of myocardial infarction, while also being associated with a modest increase in the use of invasive coronary angiography (ICA) and revascularization, according to a recent meta-analysis.[6] The potential impact of those findings have recently been enhanced by the publication of the 5 years follow up data of the SCOT-HEART trial.[5]

The SCOT-HEART study randomized more than 4,000 individuals with symptoms suggestive of CAD to usual care (UC), which includes the use of stress treadmill testing or nuclear perfusion studies, versus UC combined with CCTA. In their initial report in 2015,[9] the authors demonstrated that the use of CCTA led to change in the initial clinical diagnosis in more than one in every four

patients. It is particularly interesting to note that this was driven by an increase in the prevalence and certainty for the diagnosis of CAD overall, but also by an increase in certainty with a decrease in the prevalence of angina due to CAD. Those changes in diagnosis also led to meaningful changes in the management of this population.

When compared to the UC arm, the addition of CCTA resulted in a changed in the use of additional testing in 15% of the population (vs. 1% in the UC), and the use of medications in 23% (vs. 5% in the UC, $p < 0.001$) for both. It is particularly important to dissect those changes to appropriately understand the impact of CCTA on the initial management of this population. The additional information provided by the CCTA improved diagnostic certainty both due to the increase and decrease in the likelihood of disease after a positive and negative CCTA result, respectively. Thus, for the downstream use of diagnostic testing in the UC group, upon the 6-week return visit, there were overall 6 additional stress imaging tests, 8 ICAs performed and only one ICA cancelled. On the other hand, in the UC + CCTA group there were 121 stress imaging tests, 29 ICA cancelled, 5 additional stress imaging tests and 94 ICA tests performed. Collectively, this suggests that these differences in downstream additional testing were the result of additional information provided by the CCTA.

A similar pattern of change was also noted on the use of medications in both groups. In the UC there was minimal cancellation of preventive and antianginal medication (0.4% and 0.3% of patients, respectively), but a significant increase in its use (4.1% and 0.5% patients, respectively). On the other hand, a much larger shift in the use of medications was noted in the UC + CCTA arm, in both directions and both for preventive and antianginal medications. Those medications were started in 14.1% and 4.0% individuals, respectively, and stopped in 3.7% and 5.4% individuals, respectively. It is also worth noting that those results might underestimate the true changes in management, as the authors did not capture changes in medication dose/intensity, nor were any documentation of changes in non-pharmacological therapy available. Importantly, the changes in revascularization did not reach statistical significance, though they were numerically more frequent in the UC + coronary CTA arm (11.2 vs. 9.7%, $p = 0.06$).

It is important to highlight that even this extent of detail in medication change during the course of the SCOT-HEART study still overly simplifies its potential impact in event reduction. The actual change in therapy cannot be fully appreciated simple by counting the number of individuals who underwent changes in prescription without qualitative information on this population. Individuals in whom therapy was reduced were, in general, individuals with no or mild coronary atherosclerosis, whereas individuals in whom therapy was increased were individuals with more extensive and severe CAD. Thus, therapy was targeted and individuals more likely to derive benefit.

Despite those changes in management, the initial publication of SCOT-HEART left some gaps in the understanding of the impact of those findings, as both groups had similar improvement in the angina frequency and stability after 6 weeks, and the changes in hard outcomes did not reach formal statistical significance despite the almost 40% reduction in events noted in the study. Those results were questioned even further as the concurrent U.S. based study PROMISE, published simultaneously, showed no difference in outcomes in individuals with suspected CAD investigated with coronary CTA vs. UC, which in the U.S. was mostly based on imaging stress testing. However, several differences between the two studies justify differences in the findings, from differences in patient population, age, sex, symptoms, as well as pre-test probability of disease. Additionally, differences in medication changes during the follow up were noted. While care after testing was left at the discretion of the attending physician in both trials, SCOT-HEART had a structured protocol to recommend preventive medical therapy to individuals with non-obstructive CAD on the coronary CTA, whereas PROMISE did not make any recommendations.[10]

The trend in outcomes reduction documented in SCOT-HEART was further replicated in a meta-analysis and in a large Danish registry.[5,11] In both studies an increase in revascularization was also noted, and the Danish study also demonstrated that a concurrent increase in the use of preventive therapy (aspirin and statin) was noted.

Yet, none of those results led to nearly as much repercussion on the topic as the recent publication of the 5-year follow up of the SCOT-HEART.[12] In the longer term follow up of the same cohort of patients, several important differences need to be highlighted. First, with the larger number of events, there is a higher precision on the estimates of benefit, and a 40% reduction in the rate of coronary heart disease death or myocardial infarction ($p < 0.004$) was now documented. A second important finding of the study is the fact that the initial increase in the rate of ICA and revascularizations was no longer seen at 5 years. While the rate of ICA was 23.6% in the UC + coronary CTA arm, it was 24.2% in the UC arm (hazard ratio: 1.00, 95% confidence interval 0.88 – 1.13). This fact occurred as the UC arm had higher rates of ICA and revascularizations after the initial evaluation. Using a landmark analysis with a starting point at 12 months, the UC + CCTA arm had a 30% reduction in the rate of ICA through 5 years and a 40% reduction in late revascularizations when compared to UC.

Another relevant aspect of SCOT-HEART is that approximately half of the myocardial infarctions occurred in individuals without the obstructive coronary disease. Although it is well known that nonobstructive plaques may be responsible for a significant proportion of those events, no study had provided data on its prevalence in lower risk stable individuals until these recent CCTA studies. This finding highlights the need to incorporate the investigation of nonobstructive CAD, regardless of the presence of ischemia (and perhaps symptoms), as those findings can have significant clinical impact and should prompt pharmacological and non-pharmacological interventions.

The recent NICE guidelines from the United Kingdom delineates CCTA as a first line test for the investigation of suspected CAD, regardless of the pretest probability of disease.[13] The findings from SCOT-HEART, along with the results of Danish registry,[11] as well as cost-effectiveness analyses[14] all support the NICE guidelines in its recommendation. Together they provide a consistent and sound body of evidence to challenge the current clinical practice recommendations. As a medical community, we

need to embrace these changes and to challenge ourselves whether there is any rationale not to consider CCTA as a first line strategy for the investigation of individuals with suspected obstructive CAD.

Author contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, obtaining funding, writing of the manuscript and critical revision of the manuscript for intellectual contente: Gottlieb I, Bittencourt MS, Rochitte CE, Cavalcante JL.

Potential Conflict of Interest

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

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Study Association

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

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Case 1 / 2019 – Natural Evolution of Double Outlet Right Ventricle with Noncommitted Ventricular Septal Defect and Pulmonary Stenosis in a 28-Year-Old Asymptomatic Woman

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Clinical data

The patient evolved without symptoms from birth, when the diagnosis of heart disease was made, as evidenced by heart murmur. Two years ago, supraventricular extrasystoles caused the use of atenolol, propafenone, and magnesium, without improvement. Infective endocarditis was effectively treated 10 years ago. The patient uses levothyroxine 50 mcg for hypothyroidism.

Physical examination: good overall status, eupneic, acyanotic, normal pulses in the four limbs. Weight: 60 Kg, Height 160 cm, right upper extremity blood pressure: 120 x 70 mmHg, HR: 60 bpm.

Precordium: non-palpable apex beat, without systolic impulses. Hyperphonetic heart sounds, intense systolic murmur, with a thrill in the upper left sternal border, 4/6 +. Non-palpable liver and clean lungs.

Complementary examinations

Electrocardiogram: Sinus rhythm, right bundle-branch conduction disorder, with a wide QRS of 129 ms (AQRS = + 60º), right ventricular overload with Rs complex in V1, presence of left potentials with qRs complex in V6, positive T-wave in V1 (AT = + 60º), normal P wave (AP = + 60º) (Figure 1).

Chest X-ray: Slightly enlarged cardiac area, with elongated and rounded left ventricular arch (WC = 0.50). Normal pulmonary vascular network (Figure 1).

Echocardiogram: Normal atrioventricular connection and double outlet right ventricle (DORV) with anterior aorta on the right. The inferior vena cava was dilated with 21 mm and with spontaneous contrast. The ventricular septal defect (VSD) of the inflow tract with an extension to the outflow tract was large and unrelated, measuring 23 mm, with bidirectional flow, with preferential left-to-right shunting and without restriction, with an interventricular pressure gradient of 12 mmHg. There was another discrete apical VSD. The atria were moderately enlarged (LA = 51 mm). The right ventricle was hypertrophic and dilated with preserved systolic function, infundibular and pulmonary valve stenosis in the outflow tract with a systolic gradient of 90 mmHg. The left ventricle (LV) was hypertrophic and dilated (67 mm), with normal function. The aorta measured 35 mm and the pulmonary arteries measured 31 mm to the right and 29 mm to the left (Figure 2).

Magnetic nuclear resonance: The diagnosis was confirmed with similar measurements: the left atrium and the two ventricular cavities were enlarged. Thus, RVEDV = 134 ml/m^2 and RV function = 48%. LVEDV = 180 ml/m^2 with LV function = 68%. There was late enhancement in the lower junctional region. The pulmonary artery was posterior and located to the right, whereas the aorta was anterior and located to the left.

Holter: Supraventricular extrasystoles (3% of the total) and no supraventricular or ventricular tachycardias.

Ergospirometry: Maximal oxygen consumption of 24.4 mL/kg/min.

Clinical diagnosis: Double Outlet Right Ventricle with anterior aorta to the right, with large unrelated inflow tract VSD and pulmonary stenosis, undergoing natural evolution in adulthood.

Clinical reasoning: There were clinical elements suggesting a diagnosis of congenital heart disease, with arterial malposition considering the hyperphonetic heart sounds and pulmonary stenosis in the presence of intense systolic murmur in the pulmonary area that irradiated to the entire left sternal border. The RV overload on the electrocardiogram with clear LV potentials denotes the presence of two well-formed ventricles and, hence, the presence of associated VSD is invoked. One defect offsets the other in such a way that the patient remained acyanotic, with preferential left-to-right shunting and no symptoms. This overall picture could be found in the presence of transposition of the great arteries and also in the double right ventricular outflow tract and in the tetralogy of Fallot, given the observed long-term evolution. These supposed clinical diagnoses were then well established by echocardiography and nuclear magnetic resonance.

Differential diagnosis: Other cardiopathies that accompany VSD and PS show other elements that differentiate them in the usual complementary examinations, such as the double LV or RV inflow tract, atrioventricular valve atresia, corrected transposition of the great arteries, and in other rarer ones.

Conduct: In view of the balance of the pulmonary and systemic flows over time, with the absence of signs of hypoxemia and/or heart failure and in the presence of good physical tolerance, the expectant clinical management was considered.

Keywords

Double outlet Right Ventricle; Heart Septal Defects, Ventricular; Pulmonary Valve Stenosis; Clinical Evolution; Adult.

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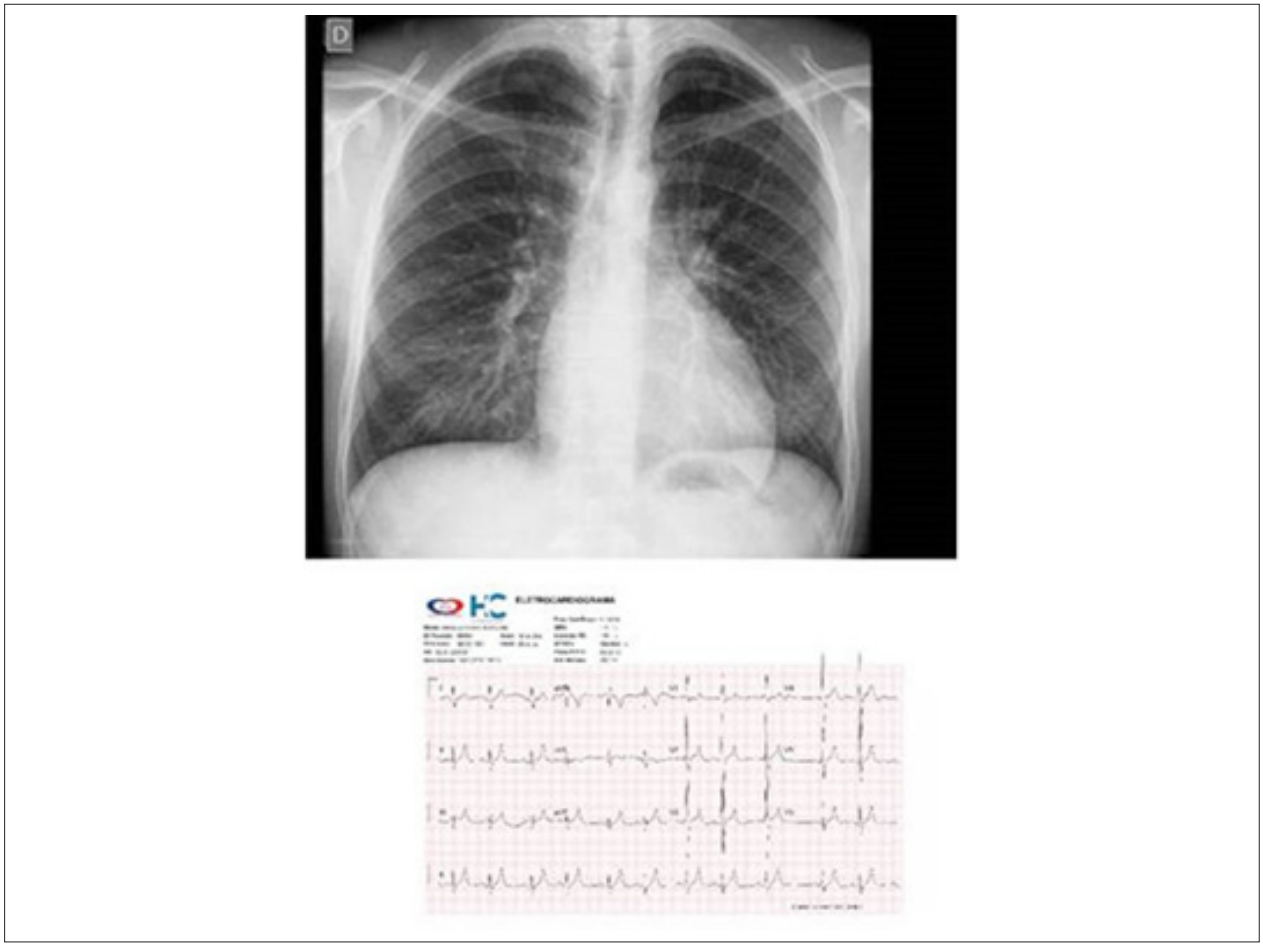

Figure 1 – *Chest X-ray showing the cardiac area within normal limits, with an elongated and rounded ventricular arch, normal pulmonary vascular network, and electrocardiogram showing signs of right ventricular overload.*

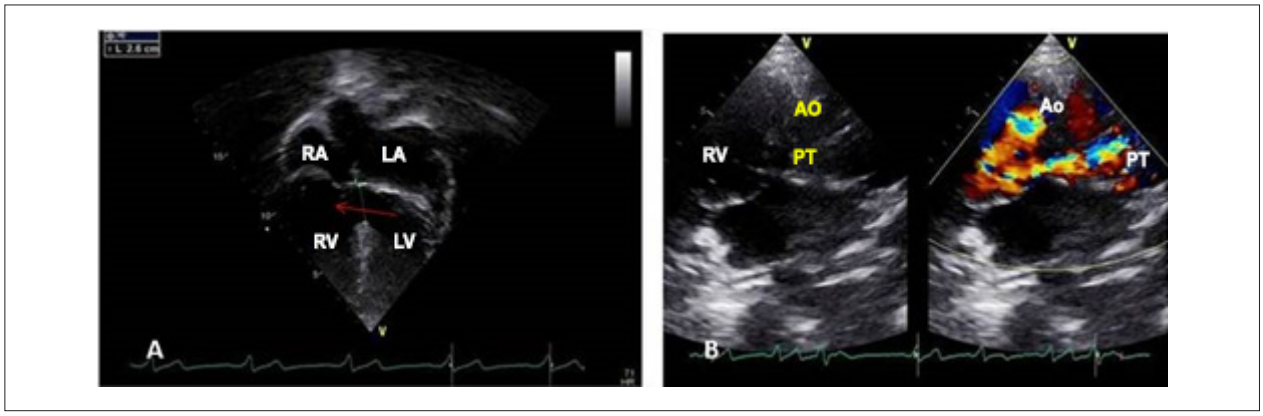

Figure 2 – *Echocardiogram shows in the 4-chamber view the large ventricular septal defect (arrow) in the inflow tract and in the subcostal view, the two large vessels emerging from the right ventricle, with the aorta to the right of the pulmonary artery. RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle; Ao: aorta; PT: pulmonary trunk.*

Comments: The natural evolution of this patient into adulthood emphasizes unfavorable elements, although she has been shown to be in good clinical and hemodynamic conditions. They are the acquired characteristics that interfere in the evolution over the elapsed time. In this case, they are represented by enlarged heart cavities, caused by pulmonary hyperflow at some time, and by the progression of pulmonary stenosis, with hypertrophy and even confirmed myocardial

fibrosis. Despite the maintenance of good ventricular function, this patient will probably experience more arrhythmias, diastolic heart failure, progressive hypoxemia, infective endocarditis, which are the reasons for the lack of clinical control caused by the disease evolution.

On the other hand, little can be offered at this moment, from the surgical point of view, since the technique considered as adequate would be the Fontan procedure, contraindicated by the absence of hypoxia. The corrective technique would be very difficult due to the presence of the unrelated VSD and anterior aorta. Therefore, a question is raised, whether in similar cases in childhood, it would not be more convenient to attempt the correction in this age group, even with greater surgical risk. This technique, created by Barbero-Marcial et al.,[1] directs the LV to the aorta, with ensuing pulmonary stenosis relief, and it has been applied with relative success, considering the 5-year survival rate of 87.5%.[2]

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Myocardial Infarction Due to an Anomalous Origin of the Left Coronary Artery with Unique Aggravating Features

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Introduction

Anomalous left coronary artery arising at the right sinus of Valsalva is a relatively rare congenital cardiac anomaly that can cause myocardial ischemia.[1] It can follow one out of five aberrant courses: interarterial, subpulmonic, pre-pulmonic, retroaortic, or retrocardiac.[2]

We present the case of a young patient with an anomalous left coronary artery arising at the right sinus of Valsalva with severe stenosis and hypoplasia throughout the interarterial segment, which hampered corrective surgery. The timely detection and adequate treatment of this specific anomaly gains relevance because of its association with increased risk of sudden cardiac death. Although the true prevalence of interarterial anomalous left coronary artery is unknown, owing to the lack of population-wide screening studies and at times asymptomatic course, its frequency has been reported at 0.03%.[3] Imaging techniques allow the characterization of the coronary anomalous origin, course, morphology and surrounding structures. Transthoracic echocardiography, magnetic resonance angiography, and computed tomography (CT) angiography are first line noninvasive tests available while invasive tests such as coronary angiography and intravascular ultrasound are second line diagnostic alternatives. Treatment approaches are still controversial and election of the optimal surgical procedure, whenever applicable, must be an individualized and patient-centered decision.

Case report

A fourteen-year-old otherwise healthy boy with no family history of disease presented with severe chest pain while he had been jogging for 5 minutes. The pain lasted for 2 hours and was followed by generalized weakness, dyspnea and confusional state. He was initially treated on a secondary care local clinic in which a baseline electrocardiogram reported ST segment depression in all precordial leads and serum Troponin I taken within 24 hours of symptom onset reached > 30 ng/mL (reference level of fluorescence immunoassay 0-0.4 ng/mL). The patient developed pulmonary edema and spent 7 days in the intensive care unit. After stabilization, he was referred to our tertiary care hospital. On hospital admission, he was hemodynamically stable, cardiac and pulmonary examination were normal. Plain chest x-ray was normal and the electrocardiogram showed sinus rhythm with ST segment depression and repolarization abnormalities in precordial leads V1 to V3. Complete blood count reported leukocytosis with neutrophilia; lipid profile and the toxicologic screening, including cocaine, came back normal. A transthoracic echocardiogram was performed which revealed a hypokinetic anteroseptal wall with normal systolic and diastolic function; no report of coronary anomalies was documented in the first place. Polymerase chain reaction tests for various viruses (Coxsackie type A and B, Parvovirus, Ebstein Barr, Cytomegalovirus, Poliovirus, Echovirus and Herpes Simplex 1,2,6,7 and 8) on peripheral blood samples were negative. He was pharmacologically managed with aspirin, atenolol and ivabradine. A rest perfusion magnetic resonance imaging detected an anterior, anteroseptal and lateral nontransmural myocardial infarction with systolic left ventricular dysfunction (ejection fraction of 45%) alongside an anomalous origin of the left coronary artery arising at the right sinus of Valsalva with an interarterial stenotic tract. A CT angiography demonstrated a left coronary artery arising at the right sinus of Valsalva from a separate ostium with an acute take-off angle and proximal oval-like narrowing with an extension of 11 mm running throughout the interarterial segment (Figures 1 and 2). Coronary translocation was discarded because the proximal interarterial segment was very stenotic and hypoplastic. Translocation was technically difficult and would not have restored normal coronary flow. Instead, through median sternotomy, cardiovascular surgeons performed revascularization of the anterior descending coronary artery with an internal mammary artery graft. Seven days after surgery he was discharged. The patient underwent treadmill stress testing according to the Bruce protocol and accomplished 9 sessions achieving a work level of 10.2 METS with adequate tolerance. He has been followed up in the cardiology outpatient clinic. Up to 18 months after surgery he is reported asymptomatic with normal electrocardiograms and echocardiographic evidence of normal systo-diastolic function. The cardiology team decided to restrict any strenuous physical activity.

Discussion

We deem important the presentation and discussion of this case considering its unique high-risk features, particular evolution and nonstandard surgical approach with good clinical outcome.

Structural heart diseases are among the causes of sudden cardiac death in young patients.[4,5] Clinicians must bear in mind that anomalous origin of the left coronary artery is

Keywords

Heart Defects Congenital; Myocardial Infarction; Echocardiography/methods; Magnetic Resonance Spectroscopy/methods; Myocardial Revascularization.

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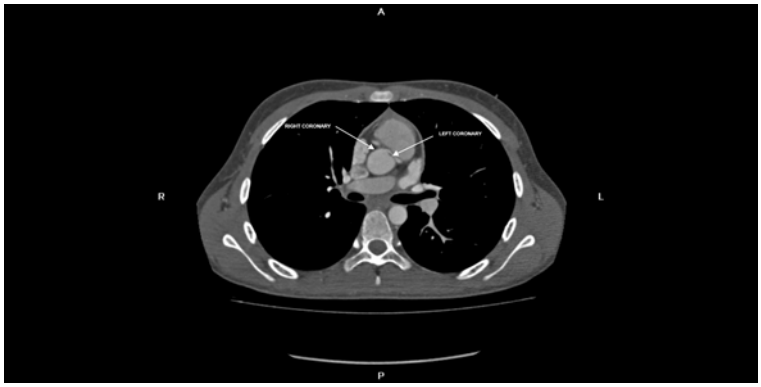

Figure 1 – *CT angiography shows anomalous origin of the left coronary artery arising at the right sinus of Valsalva from a separate ostium.*

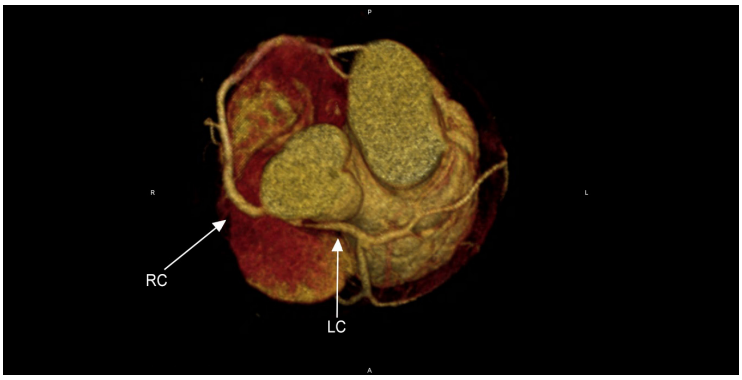

Figure 2 – *Three-dimensional reconstruction shows high-risk coronary anatomy: acute take-off angle, no intramural interarterial segment, long stenotic-hypoplastic segment (11 mm). RC: right coronary artery; LC: left coronary artery.*

a differential diagnosis in every previously healthy young patient with acute onset chest pain and evidence of acute myocardial ischemia. Transthoracic echocardiography can be the ideal diagnostic test in low-income settings; however, it must be noted that its accuracy is limited[6] and a specific evaluation may obtain better results in the diagnosis. The detailed description of the anomaly should always be sought considering that there are three anatomical features that have been linked to a worse prognosis: intramural course, slit-like coronary ostium, and acute take-off angle of the anomalous coronary.[7] In this case, apart from an acute take-off angle, a stenotic and hypoplastic course added to the disease burden. Given the aggravating coronary features encountered in this patient, aborted cardiac arrest or even sudden cardiac death could have been an expected outcome. Furthermore, the surgical approach could not tackle the coronary anomaly. Regardless of these apparently adverse factors, the patient fully recovered and reports asymptomatic with no evidence of cardiac lesion at more than one year follow up, which gives light to the fact that there must be other factors, such as vasoreactive ability and early collateral circulation, that can influence the course of this disease.

Corrective surgery, such as coronary translocation, must be offered to symptomatic patients with this coronary anomaly and high-risk features.[7] Although the safety of corrective surgery has been demonstrated,[8,9] its efficacy in the prevention of sudden cardiac death in the long term remains to be proven with further prospective studies. Besides, whenever we encounter aggravating features that make corrective surgery a difficult approach, coronary artery bypass grafting poses an alternative without undermining patient's short- and long-term prognosis. Comparing these surgical approaches in cohort studies should be advocated.

The poorly understood physiopathology and natural history of this coronary anomaly hinder the development of risk stratification strategies and causes controversies in management algorithms. The presence of knowledge gaps regarding true worldwide prevalence, specific mechanisms of myocardial ischemia and optimal surgical options call for ongoing research to improve evidence-based decision making.

Author contributions

Acquisition of data: Silva-Estrada JA, Domínguez-Camacho A; writing of the manuscript: Silva-Estrada JA, Reyes-de-la-Cruz L, Reyna-Figueroa J; critical revision of the manuscript for

intellectual contente: Silva-Estrada JA, Domínguez-Camacho A, Reyes-de-la-Cruz L, Reyna-Figueroa J.

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.

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A Large Cardiac Metastasis of a Parathyroid Tumour Presenting with Ventricular Tachycardia

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Hospital CUF Infante Santo – Imagem,[2] Lisboa – Portugal

A-81-years old woman was admitted after an episode of ventricular tachycardia with hemodynamic instability converted after electrical cardioversion (Figure 1). Past medical history was significant for poorly differentiated squamous cell carcinoma of left parathyroid, diabetes and hypertension.

Echocardiogram revealed a large mass in the right ventricle prolapsing into the right atrium and a moderate pericardial effusion (Figure 2, Video 1).

Cardiac magnetic resonance demonstrated a large infiltrative mass occupying almost the entire right ventricle cavity, slightly hypointense in T1 weighted images (image not available), hyperintense in T2 weighted images, with heterogeneous early and late gadolinium enhancement (Figure 3). These findings suggested cardiac sarcoma or metastasis.

On histopathological investigation performed with catheter biopsy, there were malignant cells positive for CK5/6 and p63 and negative for oestrogens consistent with a cardiac metastasis from a squamous cell carcinoma.

Keywords

Carcinoma, Squamous Cell; Neoplasms Metastasis; Parathyroid Neoplasms; Arrhythmias, Cardiac; Diagnosis, Imaging; Echocardiography/methods; Neoplasms Metastasis/therapy.

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The primary malignancies most commonly metastasizing to the heart are breast cancer, lung cancer, leukaemia, and melanoma.[1] Distant metastasis of head and neck tumours are highly unusual, especially of parathyroid.[2] Generally, patients with distant metastases are considered to be inoperable, and only palliative treatments, such as chemotherapy or irradiation of a tumour, are indicated.[3] Although infrequently, ventricular arrhythmia can be the initial presentation of a cardiac metastasis.[4,5] We report a rare case of cardiac metastasis from a poorly differentiated squamous cell carcinoma of parathyroid presenting with ventricular arrhythmia.

Author contributions

Acquisition of data and analysis and interpretation of the data: Moreira RI, Rosa SA, Galrinho A, Tavares NJ; writing of the manuscript: Moreira RI, Rosa AS; critical revision of the manuscript for intellectual content: Ferreira RC.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

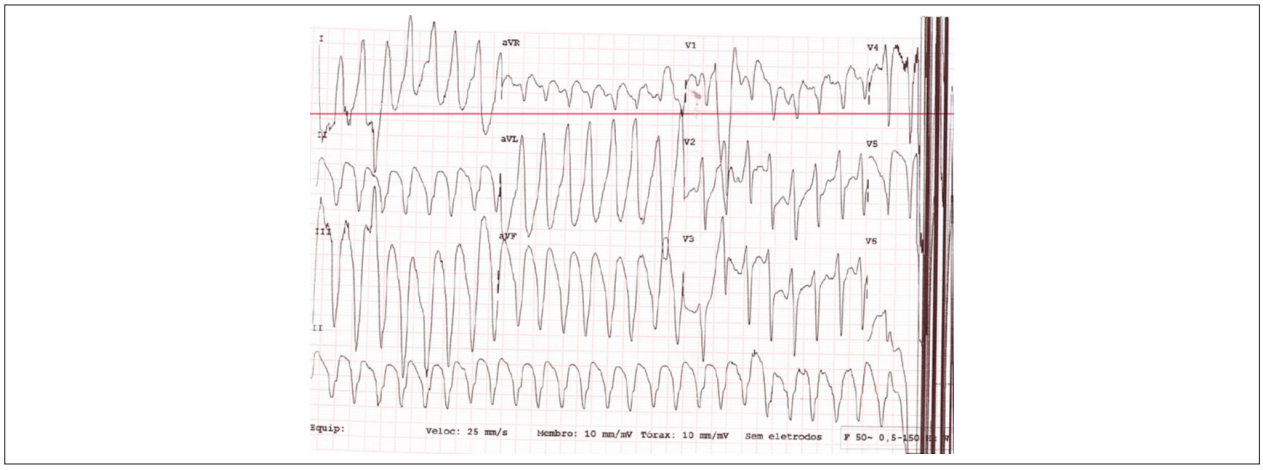


Figure 1 – *Twelve-lead electrocardiogram: Ventricular tachycardia with left bundle branch block morphology and superior and leftward axis consistent with a right ventricular origination of a tumour.*

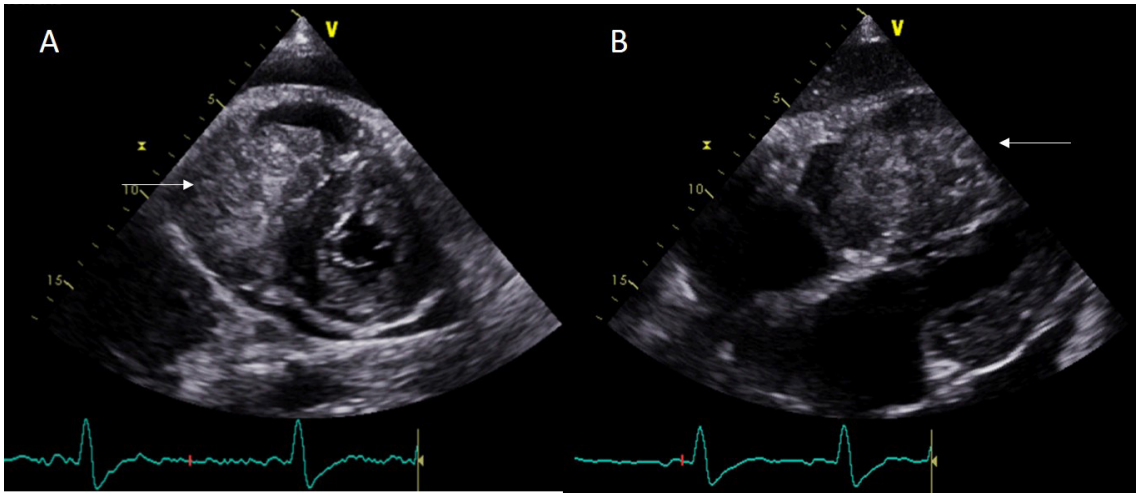
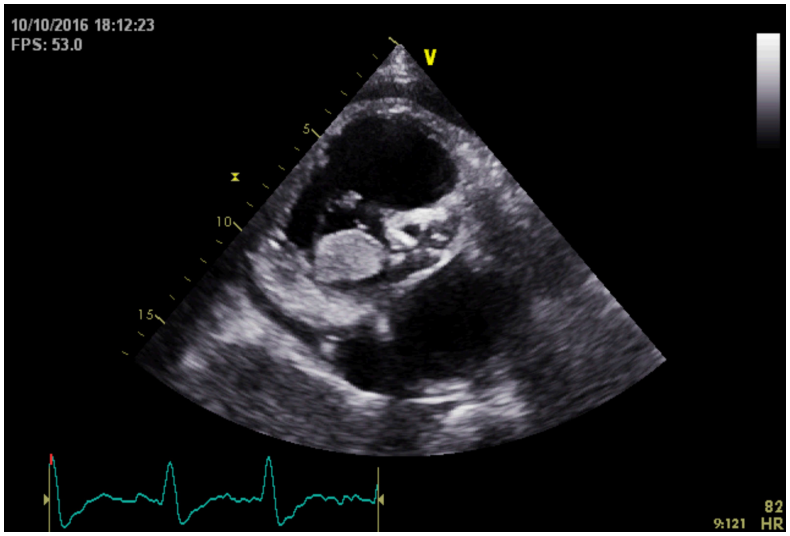


Figure 2 – *Transthoracic echocardiogram: Large mass in the right ventricle prolapsing into the right atrium in parasternal short axis view (panel A) and subcostal view (panel B). 230x99mm (150 x 150 DPI).*



Vídeo 1 –

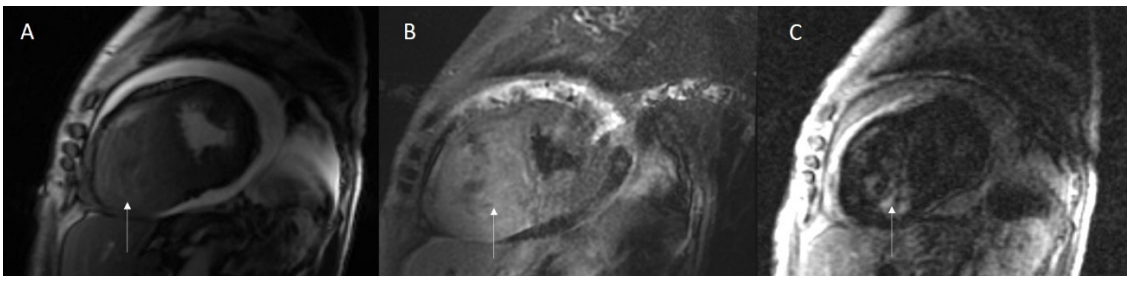


Figure 3 – *Cardiovascular Magnetic Resonance: Steady-state free precession imaging, in short axis view, documenting right ventricular mass (panel A); T2 weighted images showing mass with higher signal intensity compared to myocardium, in short axis view (panel B); Late gadolinium enhancement, acquired 10 minutes after gadolinium intravenous administration, showing a heterogeneous uptake of the mass, in short axis view (panel C). 328x78mm (150 x 150 DPI).*

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August issue of 2018, vol. 111(2), pages 230-289

Consider correct the following page numbering of contents for the items: for page 4, consider 231; respectively: 5, 234; 6, 235; 7, 236; 10, 239; 11, 240; 13, 242; 15, 244; 16, 245; 18, 247; 19, 248; 20, 249; 21, 250; 22, 251; 23, 252; 29, 258; 30, 259; 33, 262; 34, 263; 35, 264; 37, 266; 39, 268; 41, 272; 44, 273; 46, 275; 47, 276; 48, 277; 49, 278; 50, 50; 51, 280. For the items indicated with the pages 24-28 and 31-32, consider: 4.1.2, 4.1.2.1, 4.1.2.2, A) Ciclosporina – page 253; B) Tacrolimus, 4.1.2.3, A) Azatioprina, B) Micofenolato, 4.1.2.4, A) Sirolimus – page 255; B) Evrrolimus, 4.1.3, 4.2, 4.2.1, 4.2.2, 4.2.2.1 – page 256; 4.2.2.2 – page 257; 4.2.3 – page 258; 4.2.3.1 – page 258; 4.2.3.2 – page 258; 4.3.2, 4.3.3, 4.3.3.1 – page 260; 4.3.3.2 – page 261. On page 251, the correct numbering of the items "Gravidade" e "Biomarcadores", respectively, is 3.4.4 and 3.4.5. On page 252, the correct numbering of the "Estratégias de Prevenção e Tratamento" item is 3.4.6.

August issue of 2018, vol. 111(2), pages 290-341

Consider correct the following page numbering of contents for the items: for page 3, consider 292; respectively: 4, 293; 5, 294; 6, 295; 7, 296; 8, 297; 10, 299; 12, 301; 13, 302; 14, 303; 15, 304; 16, 305; 17, 306; 18, 307; 19, 308; 20, 309; 21, 310; 22, 311; 23, 312; 24, 313; 25, 314; 28, 317; 29, 318; 30, 319; 31, 320; 32, 321; 33, 322; 24, 323.

September issue of 2018, vol. 111(3), pages 436-539

In the content, items "5.3.4.4. Reposição volêmica" and "5.3.4.5. Diurético" should be disregarded, because they are repeated. The item "5.3.4.6. Betabloqueadores" is "5.3.4.4.". The item "5.3.4.5. Vasoconstritores e inotrópicos" was not mentioned.

Consider correct the following page numbering of contents for the items: for page 4, consider 441; respectively: 5, 442; 6, 443; 7, 444; 8, 445; 9, 446; 10, 447; 11, 448; 12, 449; 13, 450; 14, 451; 15, 452; 16, 453; 17, 454; 18, 455; 19, 456; 20, 457; 21, 458; 22, 459; 23, 460; 24, 461; 25, 462; 26, 463; 27, 464; 28, 465; 29, 466; 30, 467; 31, 468; 32, 469; 33, 470; 34, 471; 35, 472; 36, 473; 37, 474; 38, 475; 40, 477; 41, 478; 44, 481; 45, 482; 47, 484; 51, 488; 52, 489; 53, 490; 54, 491; 56, 493; 57, 494; 58, 495; 59, 496; 60, 497; 61, 498; 62, 499; 63, 500; 64, 501; 67, 504; 70, 507; 71, 508; 73, 510; 74, 511, 75, 512; 76, 513; 77, 514.

On page 514, the correct numbering of the items "Reposição volêmica", "Diuréticos", "Betabloqueadores" and "Vasoconstritores inotrópicos", respectively, is 5.3.4.2, 5.3.4.3, 5.3.4.4 and 5.3.4.5.

June issue of 2018, vol. 110(6), pages. 558-567

In the Original Article "Endothelial Dysfunction and Inflammation Precedes Elevations in Blood Pressure Induced by a High-Fat Diet", pages 558-567, by authors Jorge Camargo Oishi, Cynthia Aparecida Castro, Karina Ana Silva, Victor Fabricio, Evelin Capelari Cárnio, Shane A. Phillips, Ana Claudia Garcia de Oliveira Duarte, Gerson Jhonatan Rodrigues, the correct affiliation of Dr. Shane A. Phillips is University of Illinois at Chicago, Illinois - USA.

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