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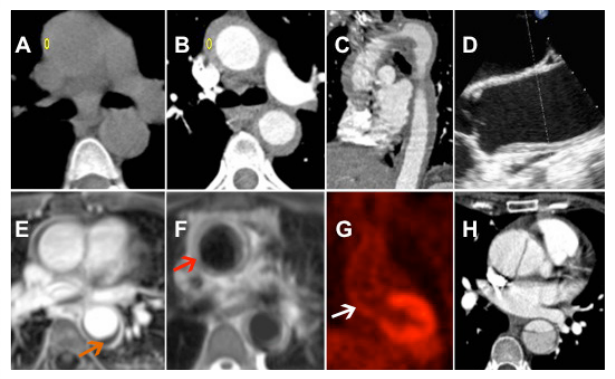

Figure 1 – *A) Non-contrast computed tomography showing low-attenuation concentric mural thickening of the thoracic and abdominal aorta (43 HU). B and C) Computed tomography angiography revealing enhancement of the mural thickening of the thoracic and abdominal aorta (73 HU). D) Transesophageal echocardiogram presenting thickening of the thoracic aorta after the Valsalva sinus. E and F) Cardiovascular magnetic resonance imaging demonstrating that mural thickening was hypointense on T1-weighted images (E, orange arrow) and hyperintense on T2-weighted images (F, red arrow), consistent with aortitis. G) Positron emission. Tomography after fifteen days of steroid therapy showing a discrete tracer uptake in the thoracic aorta (white arrow). H) Computed tomography angiography revealing type A aortic dissection six weeks after the initial diagnosis of Takayasu arteritis. Page 638*

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REVISTA DA SOCIEDADE BRASILEIRA DE CARDIOLOGIA - Publicada desde 1948

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Address: Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brasil
Phone.: (21) 3478-2700
E-mail: arquivos@cardiol.br
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SUPPORT

Endothelial Function and Physical Exercise

Luana Urbano Pagan, Mariana Janini Gomes, Marina Politi Okoshi

Faculdade de Medicina de Botucatu - Universidade Estadual Paulista (UNESP), Botucatu, SP – Brazil

The endothelium is considered an active and dynamic tissue with important properties such as maintenance of blood circulation, regulation of vascular tone, microvascular permeability, signaling, and vascular angiogenesis and inflammatory response.[1] The endothelium allows the connection among components of the circulation and body systems. Endothelial cells produce and, depending on the stimulus received, release factors that lead to vascular smooth muscle cells contraction or relaxation.[2] Vascular tone control by the endothelium is modulated by the production and release of mediators such as nitric oxide, prostacyclins, prostaglandins, thromboxane, angiotensin II, endothelin-1 and reactive oxygen species. Under physiological conditions, these factors are balanced. Imbalance in the production of substances by the endothelium leads to triggering and progression of several conditions and diseases such as ischemia, thrombosis, atherosclerosis, arterial hypertension, inflammation and tumor growth.[1,2] Therefore, vascular endothelial dysfunction is an important pathophysiological factor in human diseases.[3]

Endothelial dysfunction is mainly characterized by changes in endothelial actions involving the reduction of vasodilation and the induction of a pro-inflammatory or prothrombotic state.[3] Due to its clinical importance, endothelial dysfunction is considered an independent predictor of cardiovascular risk. In addition, it can also be observed in non-cardiovascular diseases, such as rheumatic and autoimmune diseases.[2]

Among the substances produced by the endothelium, nitric oxide stands out, being a potent modulator of vascular and cardiac function. Insufficient production of nitric oxide, such as in aging and in several diseases, may result in an increase in reactive oxygen species and blood pressure, and adversely affects the physical capacity and health in general.[2]

Physical exercises have been advocated for the promotion of health and the non-pharmacological treatment of cardiovascular diseases. Regular practice of exercises results in numerous health benefits, such as improvement in body composition, physical capacity, insulin resistance, endothelial function, arterial hypertension, antioxidant status, quality of life,[4-12] and an important effect on the endothelial system. During its practice, increased blood flow and shear stress improve vascular homeostasis by reducing the production of reactive oxygen species, and increasing the availability of nitric oxide in the endothelium.[13]

Because endothelial function and physical exercise have an important interface with cardiovascular diseases, we consider the review of this area in articles recently published by the *Arquivos Brasileiros de Cardiologia* in the Basic and Experimental Research Area relevant. In this Editorial, we have commented on three articles that have been published in the last two years, and which are related to endothelial changes from physical exercise, both in healthy rats and in spontaneously hypertensive rats.

Mota et al.[14] observed that a single resisted exercise session improves the endothelial function, and increases nitric oxide synthesis in both the endothelium and the smooth muscle layer of healthy rats. As a parameter of vascular reactivity, endothelium-dependent vasodilation in the mesenteric artery was evaluated. Exercise practice increased insulin-induced vasodilation. As vascular relaxation was abolished by the nitric oxide synthesis inhibitor, the methyl ester of L'NG-nitro-arginine (L-NAME), the importance of nitric oxide in the vasodilator response was enhanced. According to the authors, exercise stimulates factors that increase the production of nitric oxide, such as vascular distension, catecholamine release and intermittent hypoxia. The increase in nitric oxide production was dependent on the volume of exercise, which suggests that a greater demand of oxygen and nutrients is involved in the beneficial effects of exercise on the endothelium.

Similar results were observed in hypertensive rats.[15] A single session of resisted exercise provided the activation of endothelial nitric oxide synthase (eNOS), increased acetylcholine-induced aortic relaxation, and decreased reactivity to phenylephrine. The response to phenylephrine was abolished by L-NAME. Therefore, data reinforce that, even in arterial hypertension, the improvement of the endothelial function induced by a single session of resisted exercise is associated with the increase of nitric oxide synthesis.

Beneficial results were also observed after a long period of exercise (one hour/day on treadmill, 5 days a week, 8 weeks) in healthy rats.[7] Martinez et al.[7] observed that exercise reduced the contractile response of the aorta to noradrenaline and increased the relaxation induced by acetylcholine. On the other hand, the accumulated exercise protocol (four periods of 15 minutes per day on treadmill, 5 times per week, 8 weeks) did not result in improvement of endothelial function. Consequently, it is believed that the beneficial effects on the induction of regulatory factors that improve endothelial function are linked to the time of exercise exposure.

Keywords

Endothelium, Vascular/physiopathology; Nitric Oxide; Vascular Tonus; Cardiovascular Diseases; Exercise Therapy; Rats.

Mailing Address: Marina Politi Okoshi •
Departamento de Clinica Medica - Faculdade de Medicina de Botucatu - Universidade Estadual Paulista – UNESP - Rubião Junior, S/N. Postal Code 18618-687, Botucatu, SP – Brazil
E-mail: mpoliti@fmb.unesp.br
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These experimental studies suggest that the practice of physical exercises plays a relevant role in the treatment of endothelial dysfunction. However, additional studies are needed to establish the best type, intensity and duration of exercise, and to allow more efficient prescribing.

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Fractional Flow Reserve-Guided Strategy in Acute Coronary Syndrome. A Systematic Review and Meta-Analysis

José Luís Martins,[1] Vera Afreixo,[2] José Santos,[1] Lino Gonçalves[3]

Department of Cardiology, Baixo Vouga Hospital Center,[1] Aveiro - Portugal

CIDMA/IBIMED/Department of Mathematics, University of Aveiro,[2] Aveiro - Portugal

Department of Cardiology, Coimbra Universitary Hospital Center,[3] Coimbra - Portugal

Abstract

Background: There are limited data on the prognosis of deferral of lesion treatment in patients with acute coronary syndrome (ACS) based on fractional flow reserve (FFR).

Objectives: To provide a systematic review of the current evidence on the prognosis of deferred lesions in ACS patients compared with deferred lesions in non-ACS patients, on the basis of FFR.

Methods: We searched Medline, EMBASE, and the Cochrane Library for studies published between January 2000 and September 2017 that compared prognosis of deferred revascularization of lesions on the basis of FFR in ACS patients compared with non-ACS patients. We conducted a pooled relative risk meta-analysis of four primary outcomes: mortality, cardiovascular (CV) mortality, myocardial infarction (MI) and target-vessel revascularization (TVR).

Results: We identified 7 studies that included a total of 5,107 patients. A pooled meta-analysis showed no significant difference in mortality (relative risk [RR] = 1.44; 95% CI, 0.9–2.4), CV mortality (RR = 1.29; 95% CI = 0.4–4.3) and TVR (RR = 1.46; 95% CI = 0.9–2.3) after deferral of revascularization based on FFR between ACS and non-ACS patients. Such deferral was associated with significant additional risk of MI (RR = 1.83; 95% CI = 1.4–2.4) in ACS patients.

Conclusion: The prognostic value of FFR in ACS setting is not as good as in stable patients. The results demonstrate an increased risk of MI but not of mortality, CV mortality, and TVR in ACS patients. (Arq Bras Cardiol. 2018; 111(4):542-550)

Keywords: Acute Coronary Syndrome/physiopathology; Percutaneous Coronary Intervention/methods; Coronary Angiography/methods; Fractional Flow Reserve Myocardial/physiology; Microvessels; Vascular Resistance; Reproducibility of Results.

Introduction

Fractional flow reserve is a well-validated, effective technique to determine the functional significance of intermediate coronary lesions; FFR-guided percutaneous coronary intervention (PCI) improves clinical outcomes in patients with stable coronary disease.[1-3] Although robust data supports FFR use in stable coronary disease, its use in acute coronary syndrome (ACS) is less well investigated because maximal hyperemia is required to accurately measure FFR. In patients with ACS, microvascular changes may prevent vasodilatation thus affecting the validity of FFR.[1,4-6] These changes appear to be vessel-dependent (culprit vs. non-culprit) and related to the type of infarction – ST-elevation myocardial infarction (STEMI) vs. non-ST-elevation myocardial infarction (NSTEMI).[7] FFR values in the culprit vessel are recognized to be higher when measured during acute episodes than when measured after the microcirculation has had some time to recover. Higher FFR values are assumed to be caused by reduced levels of hyperemia in the culprit vessel due to embolization of thrombus and plaque, ischemic microvascular dysfunction and myocardial stunning. Hence, efficacy of the use of FFR in culprit artery disease remains uncertain.[8,9]

Multivessel coronary disease (MVD), observed in approximately 30-50% of patients presenting with STEMI and in 30-59% with NSTEMI, is associated with a poor prognosis.[10-12] Complete revascularization of hemodynamically significant vessels identified in the hemodynamic laboratory early after acute event appears attractive: this approach provides the patient with a well-defined, definitive therapeutic plan. However, several studies suggest that a FFR-guided revascularization strategy in ACS reduces the rate of coronary revascularization without compromising short-term safety.[13-15] However, the results of this approach are inconsistent in several studies involving patients with non-ACS.[13,14]

Therefore, the aims of this study are to provide a systematic review of the current evidence of the deferral of PCI based on FFR in ACS patients and compare it with that supporting this decision in non-ACS patients.

Methods

Data sources and searches

We systematically searched MEDLINE, EMBASE, and the Cochrane Library for relevant articles published between

Mailing Address: José Luis Martins •
Av. Artur Ravara. Aveiro
E-mail: zeluismartins@gmail.com
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January 2000 and September 2017. Previous qualitative and systematic reviews, if available, were searched for additional studies. The query terms "Flow Fractional Reserve" OR "Acute Coronary Syndrome" were used in the search. References of the studies identified by the search strategy were reviewed for potentially relevant articles not identified by the above search. No language restrictions were enforced.

Study selection

The title/abstract of citations were first screened by 2 independent reviewers (JM and VA), and complete manuscripts were retrieved if considered potentially relevant. Additional studies were identified by reviewing the bibliographies of included studies and relevant reviews. Disagreements were resolved by consensus. The same reviewers independently appraised identified articles according to the following inclusion criteria: studies that compared clinical outcomes of lesions after PCI deferred based on FFR between ACS patients and non-ACS patients (Figure 1).

Endpoints

The endpoints studied were: mortality, cardiovascular mortality, myocardial infarction (MI), and target vessel revascularization (TVR) during the follow-up period. TVR of the target vessel was defined as subsequent revascularization of the index vessel by either PCI or bypass grafting. In all trials, in the ACS group, distinction between culprit and non-culprit lesions was based on the operator's discretion, and hence subjective, similar to clinical practice.

Statistical analysis

Continuous variables were expressed as means ± standard deviations or median (with interquartile range) values, and categorical variables were described as numbers and percentages. To calculate pooled effect estimates, we used the inverse variance assuming a fixed-effects model and the DerSimonian-Laird method assuming a random-effects model.[16] Homogeneity among the studies was evaluated using Cochran's Q test and the I2 statistic (the values of 0.25, 0.50, and 0.75 indicated low, moderate, and high degrees of heterogeneity, respectively). Publication bias was evaluated using funnel plots. We performed a sensitivity analysis to evaluate the impact of each study on the results. MetaXL 2.0 (EpiGear International Pty Ltd, Wilston, Queensland, Australia) was used to calculate the pooled risk difference effect sizes (difference in occurrence risk between revascularization and conservative management groups).

Results

Study identification

The search strategy initially retrieved 129 citations. Of these, 96 articles were excluded after review of the title or abstract. After assessment or the studies for the selection criteria, we excluded an additional 26 studies. A total of 7 studies met criteria for the meta-analysis, involving 5,107 (3,540 non-ACS and 1,567 ACS) patients.

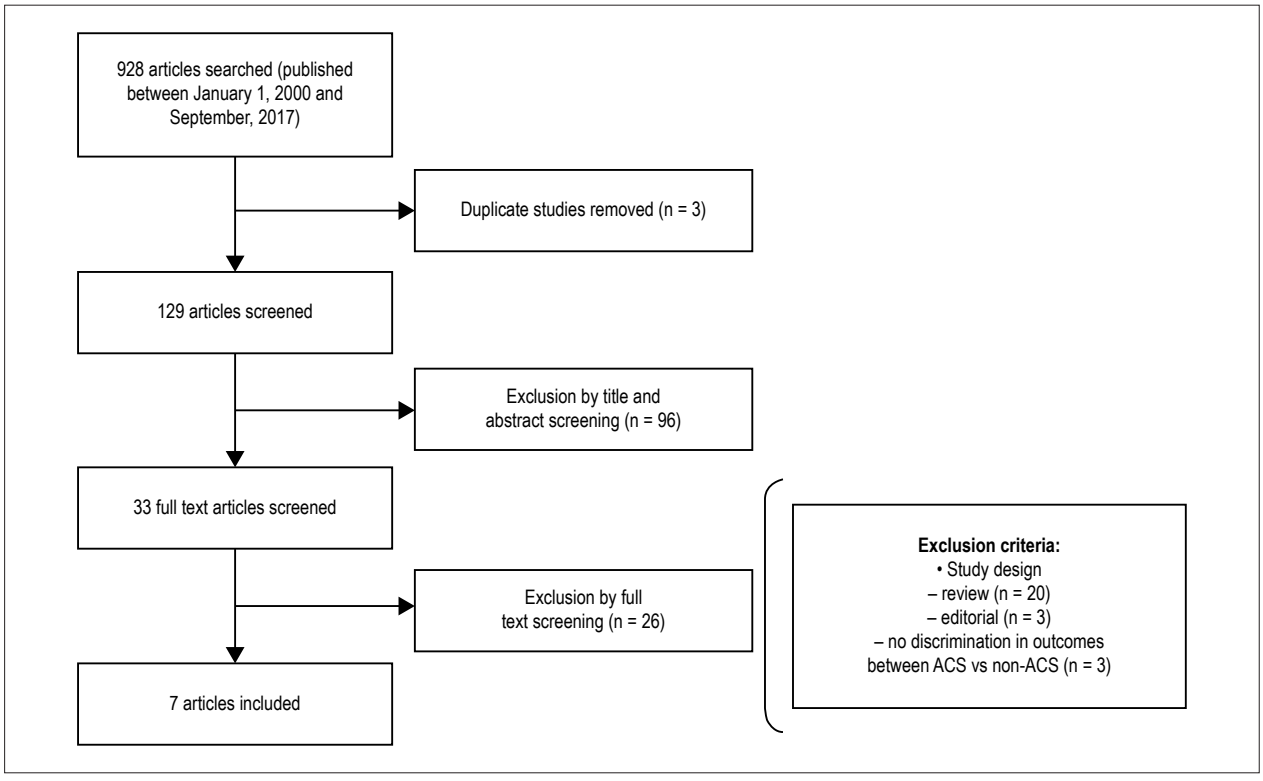

Figure 1 – *Flowchart of studies included in the meta-analysis.*

Characteristics of included studies

Of the 7 studies included, 1 was a prospective study and 6 had an observational, retrospective in design (Table 1 and Table 2).

Quantitative synthesis of outcomes

Mortality: We included 3 studies, a total of 2,074 patients, in the pooled analysis. The forest plot (Figure 2) describes the weighted meta-analysis for relative risk (RR) of mortality in ACS patients in comparison with non-ACS patients when revascularization decisions were based on FFR. Pooled analysis showed negligible heterogeneity among the studies (I2 = 0%; p = 0.78) and the ACS and non-ACS patients did not differ significantly; their pooled RR was 1.44 (95% CI = 0.89–2.35). Exclusion of any single study did not significantly alter the overall combined result.

Cardiovascular mortality: We included 5 studies, a total of 3,144 patients, in the pooled analysis. The forest plot (Figure 2) describes the weighted meta-analysis for mortality risk of basing revascularization decisions on FFR. Pooled analysis showed significant heterogeneity among the studies (I2 = 70%; p = 0.01) and the ACS and non-ACS patients did not differ significantly; their pooled RR was 1.29 (95% CI = 0.39–4.25). Exclusion of any single study did not significantly alter the overall combined result.

Myocardial Infarction: 7 studies were included, a total of 5,107 patients, in the pooled analysis. Deferring lesions based on FFR was associated with a significant additional risk of MI (RR = 1.83; 95% CI = 1.39–2.40) in ACS patients versus non-ACS patients. Figure 2 describes the weighted meta-analysis of MI. The pooled analysis showed negligible heterogeneity among the studies (I2 = 0%; p = 0.96).

Target-vessel revascularization: We included 5 studies, a total of 3,475 patients, in the pooled analysis. The forest plot (Figure 2) describes the weighted meta-analysis of TVR in patients when revascularization decisions were based on FFR. Pooled analysis showed negligible heterogeneity among the studies (I2 = 39%; p = 0.16). ACS and non-ACS patients did not differ significantly in RR of TVR; their pooled RR was 1.46 (95% CI = 0.93–2.29).

Study Bias

Visual inspection of the funnel plots for the outcomes did not reveal any asymmetry among the studies. Further, the Begg rank correlation test was not statistically significant.

Discussion

This report provides a systematic review and a meta-analysis comparing the strategy in patients in whom lesion treatment was deferred based on FFR, and no revascularization was undertaken in ACS patients to that in non-ACS patients. FFR-guided revascularization in ACS patients appears to be as safe as in non-ACS patients.[2,17-18] Briasoulis et al.,[15] in a meta-analysis, evaluated FFR-guided management in NSTEMI patients, where a modest reduction in incidence of MI was noted, with no significant differences in incidence of major adverse cardiac events (MACE), death or all-cause mortality, and target-vessel revascularization between the FFR guided approach in comparison with coronary angiography-guided approach.[15]

Four important pathophysiological considerations need to be considered when comparing the FFR results in ACS patients to those of non-ACS patients:

1. **Microvascular dysfunction:** The timing of FFR measurement in the ACS patient is an important issue. As described above, immediately after MI, the initial, temporary microvascular injury caused by the inflammatory environment may artificially elevate the initial FFR measurements. Antithrombotic therapy, administered for 3 to 4 days to stabilize the plaque, may reduce microvascular dysfunction, and FFR may then reflect the true hemodynamic situation. This approach of waiting > 5 days to measure FFR in ACS patients was suggested by the European Society of Cardiology guidelines.[19-21] However, most referral centers that study FFR in ACS perform early invasive evaluation of ACS patients, within 48 h of presentation, a practice that could lead to artificially higher FFR values.[19,22-27,34,37,38]
2. **Plaque instability:** At least two-thirds of lesions arising from vessels with < 50% stenosis are responsible for unstable syndromes involving plaque instability, assuming that these vessels previously had normal flow. A non-flow-limiting culprit lesion may be "anatomically significant" but "physiologically nonsignificant", and because FFR is not intended to evaluate plaque characteristics, care must be taken in the use of FFR in vessels with unstable characteristics but normal flow.[28,29]
3. **Myocardial mass involved:** The mass of viable myocardium being perfused by the artery in question is relevant pathophysiologically to the interpretation of FFR results in ACS patients. The FFR value is inversely proportional to the ejection fraction: hence, a lower ejection fraction, which implies a large area of infarction with less viable myocardium, could produce a higher FFR reading for the same degree of stenosis.[14,30]
4. **Presentation type of ACS:** Because ACS describe a range of myocardial ischemic states with distinct clinical and pathophysiological characteristics, the use of FFR should be differentiated by type of ACS. DANAMI3-PRIMULTI and COMPARE ACUTE were the only studies that evaluated the risk of events following FFR-guided PCI in patients with STEMI and MVD.[31,32] Of these, only COMPARE ACUTE reported the rate of events at follow-up in patients whose PCI was deferred based on FFR; patients who did not undergo additional revascularization had a similar event rate to those who were revascularized based on positive (elevated) FFR. On the other hand, FAME, which included 328 patients with ACS out of a total of 1,005 patients with MVD, reported similar rates of mortality, MI, or revascularization in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients who had PCI deferred based on an FFR cutoff value > 0.80 compared to non-ACS patients.[24] However, the FAME study did not define the exact time of FFR measurement nor the lesions assessed (culprit *vs.* non-culprit). Furthermore, the event rate in patients with deferred PCI based on FFR was not reported. In addition, the FAMOUS-NSTEMI trial compared a FFR-guided versus an angiography-only approach in NSTEMI and

Table 1 – Characteristics of included studies

Author	Year	Follow up	Study design	Total FU	Age (yrs)	Men	Non-ACS (n)	ACS (n)	STEMI (n)	NSTEMI/ UA (n)	FFR value used to defer	Median time between Clinical presentation and FFR measurement	Multivessel disease	Adenosine administration	Exclusion criteria
Potvin JM et al [9]	2006	11 ± 6 months	Retrospective cohort	201	62 ± 10	131	61	124	11	113	≥ 0.75	24 hours (range 2 to 144)	NR	intracoronary administration of adenosine (median dose 60 µg, range 30 to 300, for the left coronary artery and 30 µg, range 18 to 120, for the right coronary artery) and/ or nitroprusside (median dose 250 µg, range 100 to 1,000, for the left and right coronary arteries). Intracoronary adenosine was used in 135 cases, intracoronary nitroprusside in 14 cases, and adenosine and nitroprusside in 52 cases	Patients within 24 hours of acute STEMI were excluded
Fischer J et al [8]	2006	12 months	Retrospective cohort	111	ACS → 58 ± 14 Non-ACS → 63 ± 10	72	76	35	11	24	≥ 0.75	Recent (within 7 days) ST segment elevation MI treated with lytic Therapy	ACS → 9 Non-ACS → 9	intracoronary adenosine (30 µg bolus in the right coronary artery or 40–60 µg bolus in the left coronary artery	NR
Sels et al [24]	2011	2 years	Prospective cohort	1005	ACS → 64.8 ± 10.7 Non-ACS → 64.3 ± 10	744	677	328	0	328	≥ 0.80	NR	NR	Intravenous adenosine, administered at a rate of 140 µg/kg/min through a central vein.	Exclusion criteria were left main disease, previous CABG, and STEMI < 5 days before, because the use of FFR is not validated in recent STEMI. Patients admitted for UA and NSTEMI with positive troponin but total creatine kinase < 1,000 U/l could be included
Mehta et al [25]	2015	3.4 ± 1.6 years	Retrospective cohort	674	ACS → 63.8 ± 11.9 Non-ACS → 65.3 ± 10.2	380	340	334	7	327	> 0.80	NR	ACS → 221 Non-ACS → 209	Predominant use of intracoronary adenosine with similar maximum doses for both groups (120 µg)	NR
Hakeem A et al [34]	2016	3,4 ± 1,6 anos	Retrospective cohort	576	ACS → 66.6 ± 8 Non-ACS → 64.7 ± 8.7	554	370	206	0	206	> 0.75	NR	ACS → 135 Non-ACS → 216	Intravenous (140 mg/kg/min) or intracoronary (at least 60 mg) adenosine. The median dose of intracoronary adenosine in our cohort was 130 mg	NR
Van Belle et al [38]	2017	1 year	Retrospective cohort	958	ACS → 66 ± 11.2 Non-ACS → 66.4 ± 10	693	721	237	-	-	> 0.75 e > 0.80	NR	NR	NR	NR
Lee JM et al [37]	2017	722 days	Retrospective cohort	1596	ACS → 62.0 ± 11.1 Non-ACS → 62.4 ± 9.4	1112	1295	301	0	301	> 0.80	NR	NR	Hyperemia was induced with an intracoronary bolus administration (80 µg in left coronary artery, 40 µg in right coronary artery), intracoronary (240 µg/ min) or, iv continuous infusion (140 µg/Kg/min) of adenosine.	NR

FU: Follow-up; yrs: years; ACS: acute coronary syndrome; STEMI: ST segment elevation myocardial infarction; NSTEMI: non- ST segment elevation myocardial infarction; UA: unstable angina; FFR: fractional flow reserve; PCI: Percutaneous coronary intervention; MI: Myocardial Infarction; TVR: target vessel revascularization; CABG: Coronary artery bypass grafting; NR: not reported.

Table 2 – Clinical outcomes of ACS and non-ACS patients with deferred lesion treatment based on fractional flow reserve

Author	Year	Patients [FFR > cutoff] *	Mortality	CV Mortality	Myocardial infarction	Target lesion revascularization	Target vessel revascularization
Potvin JM et al [9]	2006	ACS → 124 Non-ACS → 61	NR	ACS → 0 Non-ACS → 1	ACS → 2 Non-ACS → 1	NR	ACS → 11 Non-ACS → 7
Fischer J. et al [8]	2006	ACS → 35 Non-ACS → 76	ACS → 3 Non-ACS → 5	ACS → 2 Non-ACS → 1	ACS → 1 Non-ACS → 1	NR	ACS → 6 Non-ACS → 7
Sels et al [24]	2011	NR**	ACS → 12 Non-ACS → 20	NR	Non-ACS → 36 Non-ACS → 44	NR	ACS → 45 Non-ACS → 72
Mehta et al [25]	2015	ACS → 334 Non-ACS → 340	NR	ACS → 23 Non-ACS → 8	ACS → 47 Non-ACS → 26	ACS → 78 Non-ACS → 66	NR
Hakeem A et al [34]	2016	ACS → 206 Non-ACS → 370	NR	ACS → 9 Non-ACS → 30	ACS → 16 Non-ACS → 11	ACS → 36 Non-ACS → 29	ACS → 15 Non-ACS → 14
Van Belle et al [38]	2017	ACS → 237 Non-ACS → 721	ACS → 10 Non-ACS → 17	NR	ACS → 3 Non-ACS → 7	NR	NR ***ACS → 9; ***Non-ACS → 42]
Lee JM et al [37]	2017	ACS → 301 Non-ACS 1295	NR	ACS → 3 Non-ACS → 5	ACS → 2 Non-ACS → 4		ACS → 8 Non-ACS → 10

*ACS: acute coronary syndrome; CV: cardiovascular; NR: not reported; *Cut-off values varied from 0.75 to 0.80 among the studies; ** Sels et al.[24] evaluated whether there is a difference in benefit of fractional flow reserve (FFR) guidance for percutaneous coronary intervention (PCI) in multivessel coronary disease in patients with acute coronary syndrome (ACS) vs. non-ACS without discriminating those patients with FFR > 0.80; *** Target-vessel revascularization was not specified.*

MVD patients; the rate of major adverse cardiac events (defined as cardiac mortality or hospitalization for MI or heart failure) was 7.5% in patients with deferred PCI based on FFR and 0% in those deferred PCI based on angiography.[13]

The aim of this analysis was not to evaluate FFR-guided decisions per-lesion level, but rather to focus on the relevance of FFR-guided decision per-patient level, considering that patients with ACS frequently have more than 1 lesion suitable for revascularization and the identification of the culprit lesion is not always straightforward. Undoubtedly, patients with MVD have worse outcomes than patients who present with single vessel disease. The natural history of patients who are revascularized in an acute setting is known to differ from those who are revascularized in a stable setting.[33] For example, the probability of malignant dysrhythmias is significantly more common in acute patients and is an important cause of mortality.[33]

This systematic review and meta-analysis summarizes all published studies that assessed and compared clinical outcomes in which revascularization decisions were based on FFR in ACS versus non-ACS setting. Among the clinical endpoints evaluated, only the RR of MI was significantly higher in patients with ACS.

The higher risk of subsequent MI found in this study and by several authors is explained by the different pathophysiology of ACS versus stable coronary disease.[34-36] Hakeem et al. compared the outcomes in NSTEMI patients who did not undergo PCI of any lesion on the basis of FFR to those in a similar group of non-ACS patients. After an average 3.4-years follow-up, using propensity score matching, the MI and TVR rates were higher in NSTEMI patients than in non-ACS patients (25% vs. 12%, respectively; $p < 0.0001$).[34] Similar results were reported recently by Lee et al. in non-ACS patients.[37]

When MI injury (defined as any MI attributable to a deferred revascularization based on the index FFR) was specifically evaluated, deferring treatment of lesions based on FFR did not differ significantly in the RR of MI injury between ACS and non-ACS patients [RR 1.84 (95% CI = 0.82–4.11); ($I2 = 0\%$; $p = 0.98$)] (Figure 3).

If on the one hand, Briasoulis et al.[15] showed that a FFR-guided strategy in ACS seems to be associated with a better prognosis compared to an angiography strategy, the primary finding of our study was that deferring the treatment of lesions was associated with an increased risk of MI in ACS patients compared to non-ACS patients, represented by the RRs of the target-vessel revascularization or MI lesion.[15] In addition, mortality and CV mortality did not differ between ACS and non-ACS patients.

Our results are consistent with the recently published study by Van Belle et al.,[38,39] who compared the impact differing the management of intermediate lesions, based on FFR, on the prognosis of ACS *vs*. non-ACS patients from two important registries, R3F and POST-iT. They concluded that revascularization decisions based on FFR for differing treatment of lesions were safe in ACS patients.[38-40]

Some authors have questioned whether we should be less permissive and adopt a different cut-off value for FFR in unstable vessels. Hakeem et al.,[34] recently determined that the best FFR cut-off value for predicting MI or TVR was > 0.80 in patients with stable coronary artery disease, supporting current practice. However, in NSTE-ACS patients, the best cutoff value was >0.84. However, some limitations suggested by some authors deserve consideration in interpreting their results. For example, it is unclear why mortality, the most important outcome, was not included in the composite endpoint in this study. In addition, medical therapy was not optimal for the patients, 14% of patients did not receive statin,

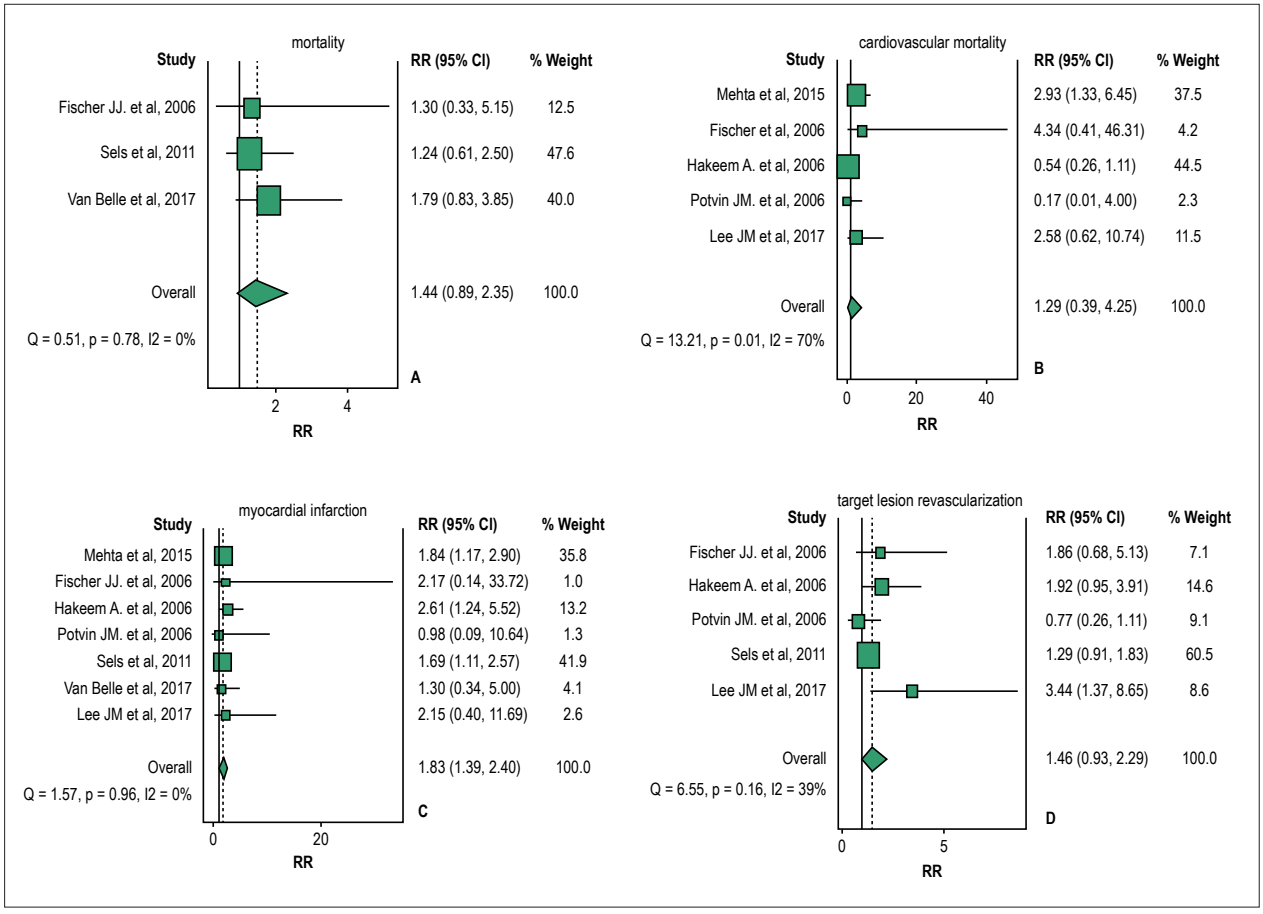

Figure 2 – *Forest plots of the pooled risk ratio of the outcomes. (A) mortality, (B) cardiovascular mortality; (C) myocardial infarction; (D) target-vessel revascularization. Size of data markers reflects the relative weight of the study. CI indicates confidence interval.*

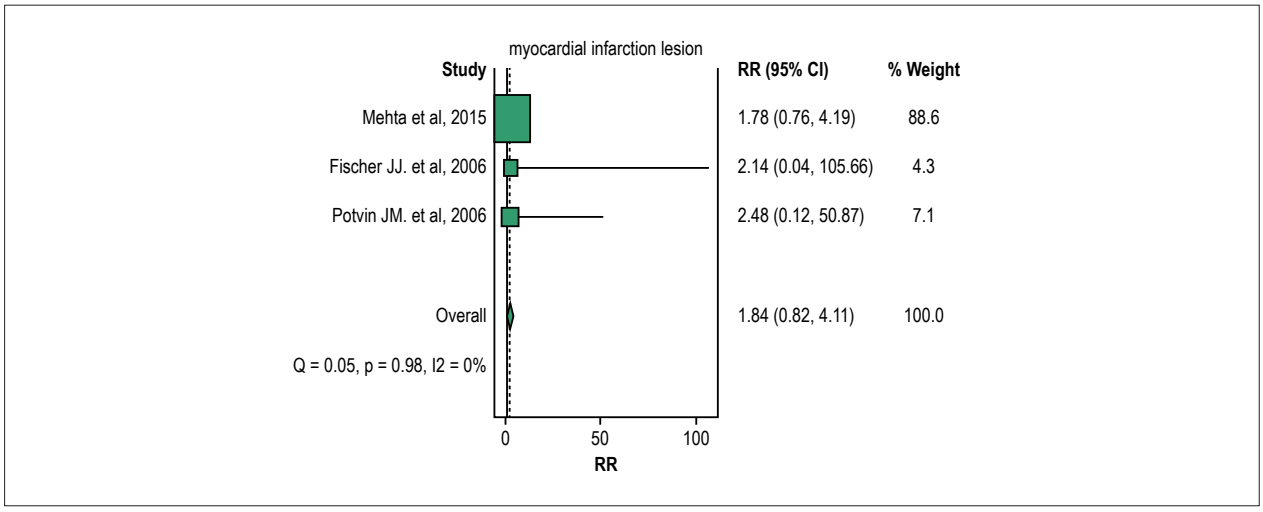

Figure 3 – *Forest plot of the pooled risk ratio for myocardial infarction injury. Size of data markers reflects the relative weight of the study. CI indicates confidence interval.*

and approximately two-thirds did not receive dual antiplatelet therapy. Moreover, several technical issues might explain the higher FFR cut-off values reported in these studies.[34,41-43]

Despite most of the studies included did not report clinical outcomes by type of lesions (culprit or non-culprit) lesions, available evidence suggests, as previously mentioned, that in patients with ACS, microvascular dysfunction may be less marked, and the ability to achieve maximal hyperemia is sufficient to maintain the diagnostic use of FFR, both in culprit and non-culprit vessels.[44]

Besides that, due to the great heterogeneity of inclusion criteria, follow-up period and the vessel assessed by FFR, results and conclusion of the current study should be the interpreted with caution.

Limitations

The conclusions drawn from this meta-analysis are subject to the limitations and differences of the original studies included in the analysis. First, our meta-analysis included both randomized clinical trials and (mostly) observational studies. The conclusions of this study may be somewhat limited due to biases inherent in the observational studies, including design, selection, and treatment bias. Another possible limitation is the potential publication bias because the results only included short-term mortality.

Conclusion

The prognostic value of FFR in ACS setting is not as good as in stable patients. More homogeneous studies with larger populations of patients are necessary to reach definitive and robust conclusions. Careful definition and interpretation of the clinical results is important when analysis of FFR is not performed in patient-level but in vessel-level only.

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Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Martins JL; Statistical analysis: Martins JL, Afreixo V; Critical revision of the manuscript for intellectual content: Martins JL, Afreixo V, Santos J, Gonçalves L.

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To Defer or Not Defer? The Challenges of Physiology in Acute Coronary Syndromes

Carlos M. Campos[1,2] and Pedro A. Lemos[1,2]

Hospital Israelita Albert Einstein,[1] São Paulo, SP - Brazil

Instituto do Coração (InCor), Faculdade de Medicina da Universidade de São Paulo,[2] São Paulo, SP - Brazil

Conventional angiography may unreliably estimate the functional severity of coronary lesions, particularly of intermediate stenosis.[1] It is in this context that intracoronary physiology, namely the measurement of fractional flow reserve (FFR), has been developed: to precisely differentiate stenoses that cause myocardial ischemia from those that are not significantly obstructive. Overall, FFR has been applied as a decision-making tool, helping to indicate (or defer) revascularization in intermediate or ambiguous coronary stenoses.[2] Compared with angiography alone, the addition of FFR-derived information has been shown to improve patient outcomes and procedural cost-efficiencies, with physiology-guided coronary revascularization being currently recommended in clinical practice guidelines, on the grounds of ample scientific evidence.[3]

Almost twenty years ago, the pivotal DEFER trial consolidated the concept that FFR-based postponement of revascularization is safe.[4] However, numerous reasons make the translation of the DEFER trial to contemporary clinical practice outdated: i) the excessively restrictive 0.75 cutoff (as used in the study) has been supplanted by the more permissive 0.80 threshold, ii) balloon angioplasty as a stand-alone therapy has been largely replaced by drug-eluting stents, iii) more potent antiplatelet agents and other medical therapies have become available, and iv) the relation between FFR and the obstructive profile of coronary lesion is yet being questioned by some authors.[5] Thus, the contemporary safety of deferring lesions in stable angina pectoris (SAP) and acute coronary syndrome (ACS) on the basis of FFR still deserves investigation.

In this issue of Arquivos Brasileiros de Cardiologia, Martins et al.[6] investigated the relative risks of deferring lesions in patients with SAP and ACS. The authors used a metanalysis of 1 prospective and 6 observational studies to compare the rates of events between these 2 groups of clinical presentations (n = 5107). There was no difference for all-cause mortality (relative risk (RR) = 1.44; (95% CI, 0.9-2.4), cardiovascular mortality (RR = 1.29, 95% CI = 0.4-4.3) and target vessel revascularization (RR = 1.46, 95% CI = 0.9-2, 3) for FFR-based revascularization within patients with ACS and SAP. However, there was a higher risk of myocardial infarction (RR = 1.83, 95% CI = 1.4-2.4) in deferring lesions without functional significance in patients with ACS.

By definition, any metanalysis serves from the amalgam of data comprised by works previously performed. Metanalyses, therefore, may become outdated, and need to be re-processed as fresh data is released in the literature. Recently, Escaned et al.[7] assessed the safety of the deferral of coronary revascularization based on invasive functional evaluation (instantaneous wave-free ratio [iFR] and FFR.[7] The safety of deferral of coronary revascularization in the pooled per-protocol population (n = 4,486) of the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome) randomized clinical trials was investigated. Unfortunately, this study was not included in the metanalysis by Martins et al.[6]. Escaned et al.[7] demonstrated that, overall, deferral of revascularization is equally safe with both iFR and FFR, with a low MACE rate of about 4%. The clinical presentation with ACS was associated with a higher MACE (MACE = major adverse cardiac events, defined as the composite of all-cause death, nonfatal myocardial infarction, or unplanned revascularization at 1 year) rate compared with SAP in deferred patients (5.91% vs. 3.64% in ACS and SAP, respectively; fully adjusted hazard ratio: 0.61 in favor of SAP; 95% confidence interval: 0.38 to 0.99; p = 0.04).

The higher risk for physiology-based stenosis deferral in patients with ACS may reflect the different physiological conditions from those with SAP. The microcirculatory vasodilation during hyperemia may be transiently affected in the acute phase of ACS, also in territories far from the culprit lesions.[8] Another factor related to this higher prevalence of events in ACS may be the widespread coronary inflammation in these patients.[8] Buffon et al.[9] have shown a depletion of the neutrophil myeloperoxidase content in blood from the great cardiac and femoral vein in patients with ACS, regardless of the site of the stenosis.[9] This was not present in patients with stable angina and multiple stenosis, patients with variant angina and recurrent ischemia, or controls. The myeloperoxidase content is an index of advanced inflammatory activation and its depletion in ACS can be translated as a widespread activation of neutrophils across the coronary vascular bed.

Today, interventional cardiologists have a vast diagnostic armamentarium to be used in the cath lab as adjunctive tools (e.g. FFR, intravascular ultrasound, optical coherence tomography). The question to be answered in the coming years is how to align the currently available scientific information to provide the best decision algorithms in selecting the most appropriate candidates for myocardial revascularization.

Keywords

Acute Coronary Syndrome/physiopathology; Percutaneous Coronary Intervention; Fractional Flow Reserve, Myocardial; Angina, Stable; Myocardial Revascularization

Mailing Address: Pedro A. Lemos •
Hospital Israelita Albert Einstein - Av. Albert Einstein, 627.
Postal Code 05652-900, São Paulo, SP- Brazil
E-mail: pedro.lemos@einstein.br

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Up to 15-Year Survival of Men and Women after Percutaneous Coronary Intervention Paid by the Brazilian Public Healthcare System in the State of Rio de Janeiro, 1999-2010

Christina Grüne de Souza e Silva,[1] Carlos Henrique Klein,[2] Paulo Henrique Godoy,[3] Lucia Helena Alvares Salis,[1] Nelson Albuquerque de Souza e Silva[1]

Instituto do Coração Edson Saad, Faculdade de Medicina, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro,[1] Rio de Janeiro, RJ – Brazil

Escola Nacional de Saúde Pública Sergio Arouca – Fundação Oswaldo Cruz,[2] Rio de Janeiro, RJ – Brazil

Universidade Federal do Estado do Rio de Janeiro,[3] Rio de Janeiro, RJ – Brazil

Abstract

Background: Percutaneous coronary intervention (PCI) is the most frequently used invasive therapy for ischemic heart disease (IHD). Studies able to provide information about PCI's effectiveness should be conducted in a population of real-world patients.

Objectives: To assess the survival rate of IHD patients treated with PCI in the state of Rio de Janeiro (RJ).

Methods: Administrative (1999-2010) and death (1999-2014) databases of dwellers aged ≥ 20 years old in the state of RJ submitted to one single PCI paid by the Brazilian public healthcare system (*SUS*) between 1999 and 2010 were linked. Patients were grouped as follows: 20-49 years old, 50-69 years old and ≥ 70 years old, and PCI in primary PCI, with stent and without stent placement (bare metal stent). Survival probabilities in 30 days, one year and 15 years were estimated by using the Kaplan-Meier method. Cox hazards regression models were used to compare risks among sex, age groups and types of PCI. Test results with a p-value < 0.05 were deemed statistically significant.

Results: Data of 19,263 patients (61 ± 11 years old, 63.6% men) were analyzed. Survival rates of men vs. women in 30 days, one year and 15 years were: 97.3% (97.0-97.6%) vs. 97.1% (96.6-97.4%), 93.6% (93.2-94.1%) vs. 93.4% (92.8-94.0%), and 55.7% (54.0-57.4%) vs. 58.1% (55.8-60.3%), respectively. The oldest age group was associated with lower survival rates in all periods. PCI with stent placement had higher survival rates than those without stent placement during a two-year follow-up. After that, both procedures had similar survival rates (HR 0.91, 95% CI 0.82-1.00).

Conclusions: In a population of real-world patients, women had a higher survival rate than men within 15 years after PCI. Moreover, using a bare-metal stent failed to improve survival rates after a two-year follow-up compared to simple balloon angioplasty. (Arq Bras Cardiol. 2018; 111(4):553-561)

Keywords: Myocardial Revascularization; Coronary Artery Disease; Percutaneous Coronary Intervention; Mortality.

Introduction

Ischemic heart disease (IHD) is the most frequent cause of death in adults[1] and, although its age-standardized mortality rate has decreased over the last decades,[2] IHD is still the cause of about 20% of all deaths worldwide.[2,3]

The most frequent invasive therapy for IHD is percutaneous coronary intervention (PCI).[4] Since it was first performed,[5-7] this procedure has been increasingly utilized, more expensive and possibly overused,[8,9] although the majority of the studies conducted have evidenced just a few scenarios where PCI can be beneficial in IHD.[10,11] Moreover, the information that guides physicians' decisions regarding its indication is mostly based on randomized controlled clinical trials (RCT), which usually enroll younger patients with fewer comorbid conditions than patients in the real-world, and exclude many treatment-related issues faced in clinical practice.[12,13] Therefore, extrapolating PCI's effectiveness observed in RCTs to the real world-population may not be entirely appropriate.

This study aims at providing information about PCI's effectiveness in a real-world population by assessing short-, medium- and long-term survival rates of IHD patients treated with one single PCI, from 1999 to 2010, and paid by the Brazilian public healthcare system (*Sistema Único de Saúde – SUS*) in the state of Rio de Janeiro (RJ).

Mailing Address: Christina Grüne de Souza e Silva •
Rua Professor Rodolpho Paulo Rocco, 225 - 8º andar - Cidade Universitária. Postal Code 21941-913, Ilha do Fundão, RJ - Brazil
E-mail: christina.g.dss@gmail.com
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Methods

Study population and data collection

Data on PCI obtained at administrative databases of the state of RJ were analyzed retrospectively. The *DATASUS* administrative database of Authorization for Hospital Admission (*Autorização de Internação Hospitalar - AIH*) was consulted to gather data on PCI performed in public or private hospitals paid by the *SUS* between 1999 and 2010.

SUS is the Brazilian public healthcare system. It is funded from general government revenues, it is single, universal, hierarquical and integrated.[14] *DATASUS* contains data of the Department of Healthcare Information of the Brazilian Ministry of Health, and it manages *SUS*' healthcare and financial information.[15] *AIH* is a registry system[16] for any admissions that occurs in any public or private hospital that maintain a convenant with the *SUS*.

Patient inclusion criteria**:** people who lived in the state of RJ, ≥ 20 years old, submitted to one single PCI between 1999 and 2010. Patient exclusion criteria: individuals submitted to coronary artery bypass grafting during the study period.

From the *AIH* database were obtained patients' name, date of birth, hospital admission and discharge, sex, address, mother´s name and type of PCI.

PCI procedures were classified according to the *AIH* database codes as described in a previous study[9] as follows: a) PCI without stent placement (PCI-WS); b) PCI with stent placement (PCI-S); and c) primary PCI (PCI-P). During the study period the *SUS* would not pay for drug-eluting stents; therefore, PCI-S refers to the use of bare-metal stents.

The post-procedure outcome was death from any cause, and information on patients' death was obtained at the death database of the state of RJ from 1999 to 2014. In order to match information from both databases, *AIH* and deaths, Stata®14 probabilistic record linkage (Reclink) was used, once there is no common identification field between these two databases, and this essentially consists of a fuzzy merge. This method allows matching weights for each pre-defined variable, thus creating a new variable to hold the matching score in a zero-to-one scale, which indicates the probability that the pairs formed refer to the same patient. The pre-defined variables were patient´s name, date of birth and sex.

Pairs that scored = 1.00 (perfect matches) were considered the same patient. Pairs that scored ≥ 0.99 and < 1.00 were considered possible matches and were manually reviewed using mother´s name and address to define whether or not they were going to be considered the same patient. Pairs with lower scores were considered a "non-match".

In order to test the sensitivity and specificity of the probabilistic linkage method used, in-hospital deaths found at the *AIH* database were compared to the matching information from the death database. Out of a total of 357 in-hospital deaths found at the *AIH* database, 307 were found with the linkage process with the death database, and no false positives were detected. Therefore, the estimated sensitivity and specificity were 86% and 100%, respectively.

After the linkage process, patients were classified according to sex and the age groups 20-49, 50-69 and ≥ 70 years old. Underlying causes of death were obtained at the death database and classified according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[17] as IHD (codes I20 to I25) or non-IHD (any other code).

As the *AIH* database contains no information about the exact date of the PCI procedure, only the date of the patients` hospital admission and discharge, and as the average stay of these patients was 2 days,[9] to analyze the survival rate the discharge date was considered day one. Short- and medium-term survival rates were defined as the probability of survival until day 30 and one year after discharge, respectively. As there are two possible discharge types at the *AIH* database – hospital discharge or death - short-term outcomes included in-hospital mortality rates. Long-term survival was defined as the probability of survival up to 10 or 15 years after hospital discharge for comparisons among types of PCI or between age groups and sex, respectively.

The study was approved by the ethics committee of *Hospital Universitário Clementino Fraga Filho* (*Faculdade de Medicina – UFRJ*) on 10/18/2012 (1148/12).

Statistical analysis

Statistical analysis was performed based on data distribution. As the Shapiro-Wilk and Kolmogorov-Smirnov tests showed that age was not normally distributed, age distributions were described as median and interquartile ranges (P25-P75). Distribution of categorical variables was described as relative frequencies. The differences among groups were analyzed with the Kruskal-Wallis test for continuous variables or chi-square test for categorical variables. Probabilities of short-, medium- and long-term survival rates were estimated with the Kaplan-Meier survival method. Survival models were estimated with Cox proportional hazards regression to compare risks among age groups, sex and type of PCI; 95% confidence intervals (CI) were calculated to express the degree of uncertainty associated with the statistics for all analyses of subgroups. Stata 14® was used for all analyses. Test results with a p-value < 0.05 were considered statistically significant.

Results

Out of 22,735 patients, 3,472 were excluded and 19,263 were selected (63.6% men). Median (P25-P75) ages for men and women were 60 (52-68) and 62 (54-70) years, respectively ($p < 0.05$). The frequency distribution of the age groups 20-49, 50-69 and ≥70 years old for men and women was 16.2% and 13.1%, 63.9% and 60.1%, and 19.9% and 26.8%, respectively ($p < 0.05$).

Minimum and maximum follow-up were 4.0 and 15.0 years, respectively, and 5,433 patients (65.1% men) died during follow-up. Probabilities of survival and 95% CI for men and women were, respectively, short-term: 97.3% (97.0-97.6%) and 97.1% (96.6-97.4%), medium-term: 93.6% (93.2-94.1%) and 93.4% (92.8-94.0%), and long-term: 55.7% (54.0-57.4%) and 58.1% (55.8-60.3%). Men aged 20-49 years tended to have higher probability of survival in a 9-year follow-up, after which this tendency would reverse (Table 1). Men and women aged 50-69 years had the same probability of survival in a 180-day follow-up, after which women tended to have a higher

Table 1 – Suvival proprabilities of patients submitted to a single percutaneous coronary intervention in the state of Rio de Janeiro paid by *SUS* between 1999-2010 according to age group and sex

Follow-up	20-49 years old		50-69 years old		≥70 years old	
	Men	Women	Men	Women	Men	Women
	(n = 1,987)	(n = 917)	(n = 7,819)	(n = 4,224)	(n = 2,435)	(n = 1,881)
	[% (95%CI)]	[% (95%CI)]	[% (95%CI)]	[% (95%CI)]	[% (95%CI)]	[% (95%CI)]
1 day	98.9 (98.3–99.3)	98.6 (97.6–99.2)	98.5 (98.2–98.8)	98.5 (98.1–98.9)	96.8 (96.0–97.4)	96.4 (95.4–97.1)
30 days	98.2 (97.5–98.7)	98.0 (96.9–98.8)	97.7 (97.3–98.0)	97.7 (97.2–98.1)	95.3 (94.4–96.1)	95.2 (94.1–96.0)
180 days	97.1 (96.3–97.8)	95.8 (94.2–96.9)	96.1 (95.7–96.5)	96.1 (95.5–96.6)	91.2 (90.0–92.3)	91.1 (89.7–92.3)
1 year	96.2 (95.3–97.0)	95.0 (93.4–96.2)	94.5 (94.0–95.0)	94.7 (94.0–95.4)	88.7 (87.3–89.9)	89.6 (88.2–90.9)
2 years	94.4 (93.3–95.3)	93.2 (91.4–94.7)	92.3 (91.6–92.8)	92.7 (91.9–93.5)	83.0 (81.5–84.4)	86.2 (84.6–87.7)
3 years	92.9 (91.7–94.0)	91.7 (89.7–93.3)	89.7 (89.0–90.3)	90.7 (89.8–91.6)	77.7 (76.0–79.3)	82.6 (80.8–84.3)
4 years	91.1 (89.8–92.3)	90.1 (88.0–91.8)	87.4 (86.6–88.1)	88.4 (87.4–89.4)	73.7 (71.9–75.4)	79.2 (77.3–80.9)
5 years	89.4 (87.9–90.7)	88.4 (86.2–90.3)	84.9 (84.0–85.6)	85.9 (84.8–86.9)	69.5 (67.7–71.3)	75.8 (73.8–77.7)
6 years	87.8 (86.2–89.2)	86.7 (84.2–88.8)	82.4 (81.5–83.2)	83.5 (82.3–84.6)	64.1 (62.1–66.0)	71.9 (69.8–74.0)
7 years	85.7 (84.0–87.2)	84.9 (82.3–87.1)	79.9 (79.0–80.9)	81.4 (80.2–82.6)	59.9 (57.8–62.0)	68.5 (66.2–70.7)
8 years	83.5 (81.6–85.1)	82.8 (79.9–85.2)	76.7 (75.6–77.7)	79.4 (78.0–80.7)	55.5 (53.2–57.6)	65.4 (63.0–67.7)
9 years	81.9 (80.0–83.7)	81.7 (78.7–84.2)	73.7 (72.5–74.8)	77.4 (76.0–78.8)	51.6 (49.3–53.9)	61.8 (59.3–64.3)
10 years	79.3 (77.1–81.3)	79.3 (76.1–82.1)	70.6 (69.3–71.8)	74.6 (73.0–76.1)	47.9 (45.5–50.3)	55.8 (53.0–58.5)
11 years	77.5 (75.2–79.6)	78.2 (74.9–81.2)	67.8 (66.4–69.1)	71.8 (70.0–73.5)	44.3 (41.8–46.8)	51.8 (48.9–54.7)
12 years	75.9 (73.4–78.1)	77.3 (73.9–80.4)	64.7 (63.1–66.1)	68.8 (66.9–70.7)	42.3 (39.6–44.9)	47.9 (44.7–51.0)
13 years	73.8 (71.1–76.3)	75.5 (71.7–78.9)	61.4 (59.7–63.1)	66.5 (64.3–68.6)	39.1 (39.6–42.0)	45.8 (42.4–49.0)
14 years	71.4 (68.2–74.4)	73.2 (68.6–77.3)	59.7 (57.8–61.6)	64.2 (61.7–66.6)	35.6 (32.3–39.0)	44.6 (41.1–48.0)
15 years	69.6 (65.8–73.1)	72.3 (67.3–76.7)	57.7 (55.4–60.0)	61.9 (58.9–64.9)	35.6 (32.3–39.0)	42.0 (37.5–46.4)

CI: confidence interval; SUS: Sistema Único de Saúde - Brazilian Public Healthcare System

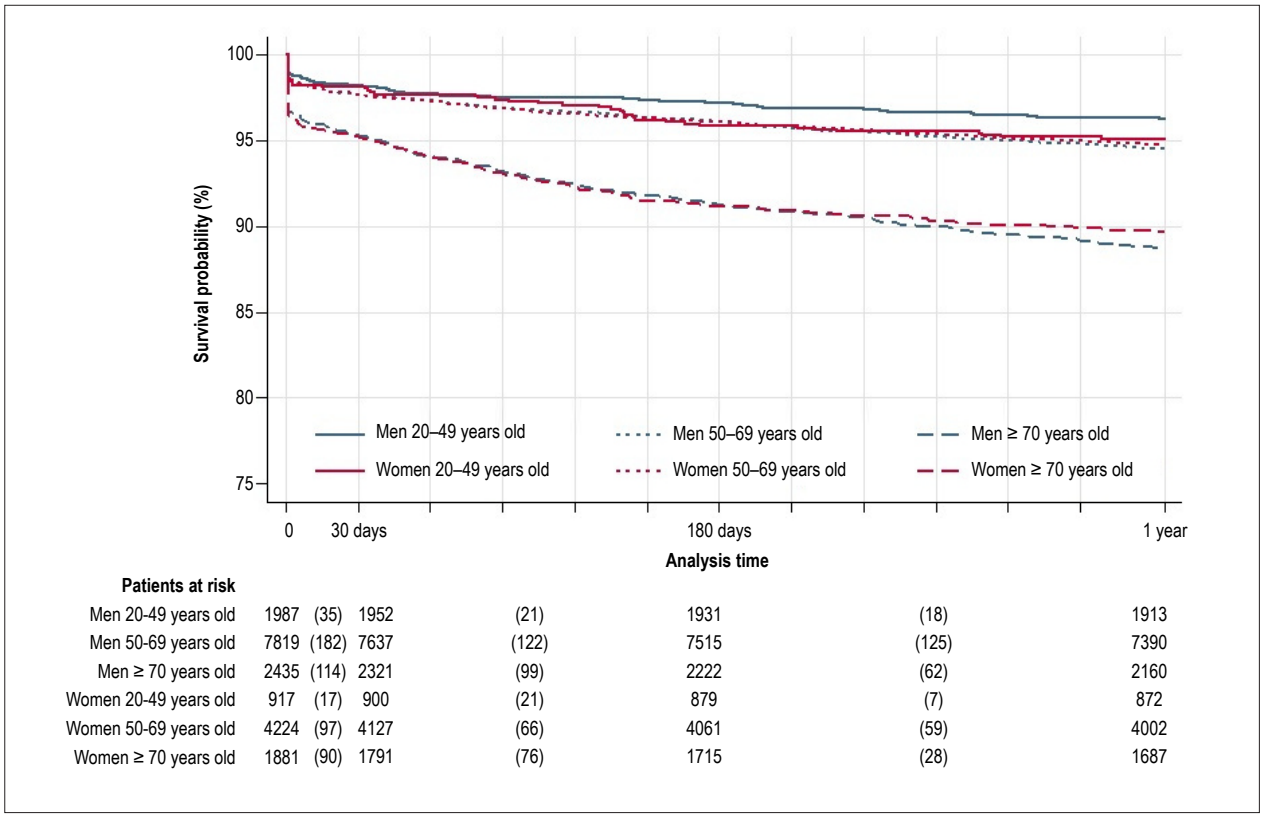
probability of survival (Table 1). In the oldest age group men tended to have higher probability of survival, up to 180 days, after which that tendency would also reverse (Table 1). Figures 1 and 2 show Kaplan-Meier curves and estimates of survival according to sex and age group in one-year and 15-year follow-up, respectively. Table 2 shows Cox proportional hazards risks and 95% CI referring to age group and sex.

Concerning the type of PCI, patients who underwent PCI-P, PCI-WS and PCI-S were aged 61 ± 11, 60 ± 11, and 61 ± 10 years old, respectively ($p < 0.05$). A total of 175, 2,652 and 2,606 deaths occurred among patients submitted to PCI-P, PCI-WS, and PCI-S, respectively. Short-, medium- and long-term probabilities of survival for PCI-WS (n = 6,967) were 96.9% (96.5-97.3%), 93.4% (92.7-93.9%) and 68.6% (67.4-69.6%), respectively; for PCI-S (n = 11,600) were 97.8% (97.5-98.1%), 94.2% (93.7-94.6%) and 68.4% (67.0-69.7%), respectively; and for PCI-P (n = 696) were 89.8% (87.3-91.8%), 85.2% (82.3-87.6%) and 59.7% (49.8-68.2%), respectively. As PCI-S and PCI-P started to be paid by *SUS* in 2000 and 2004, respectively, long-term survival for the three procedures were measured in a 10-year follow-up for comparison purposes. Figure 3 shows Kaplan-Meier curves and estimates of survival and Table 2 presents Cox proportional hazards risks and 95% CI according to the type of PCI. In short- and medium-term follow-up, patients submitted to PCI-S had higher probability of survival than those submitted to PCI-WS, but after 2 years of follow-up their probabilities of survival became similar (HR 0.91, 95% CI 0.82-1.00, p = 0.062).

IHD was considered the underlying cause of death of 66.7%, 44.1% and 26.9% of the deaths that occured within 30 days, one year and 15 years after hospital discharge, respectively. During the entire follow-up period, PCI-P had the higher percentage of deaths due to IHD (49.1%) compared to PCI-WS (25.9%) and PCI-S (26.4%), $p < 0.05$.

Discussion

This study has led to some important findings: 1) women tended to have slightly lower short- and medium-term probability of survival, but better long-term survival rates; 2) older patients had lower probabilities of survival; 3) differences in probability of survival changed slightly over time when PCI-P was compared to PCI with and without stent placement because the difference in the probability of survival was concentrated in the immediate period after the procedure; 4) although short- and medium-term survival rates were higher for patients submitted to PCI-S than for those submitted to PCI-WS, no difference was observed in the long-term survival rates between them; 5) the probabilities of survival observed were lower than those observed in RCTs.



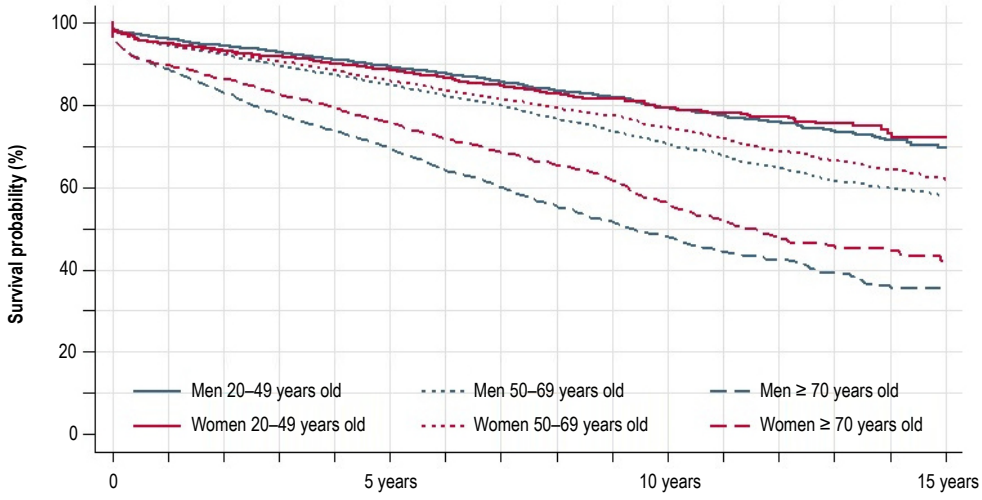
Patients at risk							
Men 20-49 years old	1987	(35)	1952	(21)	1931	(18)	1913
Men 50-69 years old	7819	(182)	7637	(122)	7515	(125)	7390
Men ≥ 70 years old	2435	(114)	2321	(99)	2222	(62)	2160
Women 20-49 years old	917	(17)	900	(21)	879	(7)	872
Women 50-69 years old	4224	(97)	4127	(66)	4061	(59)	4002
Women ≥ 70 years old	1881	(90)	1791	(76)	1715	(28)	1687

Figure 1 – *Kaplan-Meier survival estimates of patients submitted to one single percutaneous coronary intervention paid by SUS between 1999 and 2010 according to sex and age group in a one-year follow-up.*

Additionally, this study has some major strengths. First, it addressed a large number of patients (19,263) accompanied for more than 15 years, thus enabling the observation of important outcomes of interest in the future. Second, although only data from PCI paid by *SUS* were analyzed and, therefore, they could not mirror those observed with PCI paid exclusively with private resources, in the state of RJ the PCI paid by *SUS* accounts for the majority of the PCI procedures performed. Only about 25,3% and 33,5% of the population of the state of RJ in 2000 and 2010, respectively, had private health insurance,[18] so at least 7 out of 10 of the PCI procedures performed in the state of RJ between 1999 and 2010 were certainly paid by *SUS*. Third, the data analyzed were from the third most populous Brazilian state and from 23 hospitals in the state of RJ, enabling the assessment of a broad range of patients and a high number of hospitals, which represent patients treated in a regular medical practice.

As to sex, former studies have examined the differences in survival or mortality rates between sex after a PCI. Although most agree that women present a higher prevalence of clinical risk factors and comorbidities when submitted to a PCI,[19] there is conflicting evidence as to whether being a woman faces an independent risk of survival or mortality after a PCI. Data collected from German hospitals on PCI with or without stent placement in stable and acute coronary syndromes show that, after adjusting for age, women had higher in-hospital mortality rates than men only when the PCI was performed in the setting of ST-elevation myocardial infarction.[20] In the CLARIFY study,[21] similar rates of death for all causes after a one-year follow-up were observed for men and women with stable coronary artery disease submitted to PCI, after adjustment for baseline characteristics. On the other hand, data from the United Kingdom and Sweden[22] showed that, when adjusting for age, being a woman was an independent predictor for all-cause mortality at 30 days and at one year after PCI performed for stable or acute coronary syndromes. In this study, even when clinical differences at baseline were not adjusted, women aged ≥50 years old tended to have lower survival rates than men the same age group in a 180-day follow-up, and in the youngest age group, women tended to have a lower survival probability even after over a 1-year follow-up.

As to long-term survival rates, most of the studies have shorter follow-up periods compared to those in this study. Berger et al.[23] followed 4,284 patients in New York City for 3 years on average. Although men and women had the same in-hospital mortality rates, being a woman was independently associated with a reduction in hazards of long-term mortality. Similarly, the BARI study[24] showed that when adjusting for baseline risk status, women had higher survival rates in a 5-year follow-up when treated with PCI for multivessel coronary artery disease. In the present study women also tended to have higher long-term survival rates, even though for the youngest age group this tendency only occurred after a 10-year follow-up.



Patients at risk

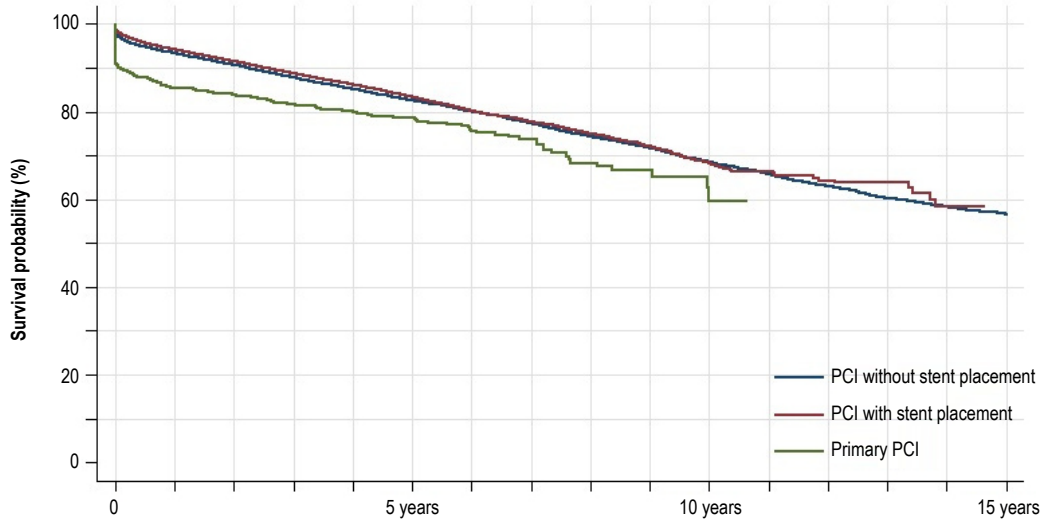
Men 20-49 years old	1987	(208)	1582	(133)	732	(46)	75
Men 50-69 years old	7819	(1165)	5577	(642)	2026	(202)	142
Men ≥ 70 years old	2435	(734)	1451	(330)	457	(71)	26
Women 20-49 years old	917	(104)	701	(56)	338	(15)	30
Women 50-69 years old	4224	(587)	3081	(282)	1217	(112)	98
Women ≥ 70 years old	1881	(452)	1241	(223)	423	(66)	31

Figure 2 – *Kaplan-Meier survival estimates of patients submitted to one single percutaneous coronary intervention paid by SUS between 1999 and 2010 according to sex and age group until 15 years of follow-up.*

Table 2 – Cox proportional hazards risks and 95% confidence interval after short, medium and long-term follow-up in patients submitted to a single percutaneous coronary intervention in the state of Rio de Janeiro paid by *SUS* between 1999-2010 according age group, sex and type of procedure

	Short-term	Medium-term	Long-term
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age group			
(50-69 years)/(20-49 years)	1.30 (0.97–1.75)	1.33 (1.09–1.61)	1.45 (1.32–1.58)
(≥70 years)/(20-49 years)	2.67 (1.97–3.62)	2.74 (2.24–3.35)	2.87 (2.61–3.16)
(≥70 years)/(50-69 years)	2.05 (1.71–2.46)	2.07 (1.84–2.33)	2.01 (1.89–2.13)
Sex*			
Women/Men - 20-49 years old	1.05 (0.59–1.88)	1.32 (0.91–1.92)	0.99 (0.83–1.19)
Women/Men - 50-69 years old	0.99 (0.78–1.27)	0.96 (0.81–1.13)	0.87 (0.81–0.94)
Women/Men - ≥70 years old	1.03 (0.79–1.36)	0.91 (0.76–1.10)	0.78 (0.71–0.86)
Type of PCI†			
(PCI-S)/(PCI-WS)	0.71 (0.59–0.85)	0.87 (0.77–0.98)	0.98 (0.92–1.04)
(PCI-P)/(PCI-WS)	3.34 (2.55–4.37)	2.32 (1.87–2.87)	1.32 (1.13–1.55)
(PCI-P)/(PCI-S)	4.72 (3.62–6.15)	2.68 (2.18–3.30)	1.38 (1.18–1.60)

CI: confidence interval; PCI-P: primary percutaneous coronary intervention; PCI-S: percutaneous coronary intervention with stent placement; PCI-WS: percutaneous coronary intervention without stent placement; Medium-term: until 1 year of follow-up; Short-term: until 30 days of follow-up; (*) Long-term: until 15 years of follow-up; (†) Long-term: until 10 years of follow-up



Patients at risk							
PCI without stent placement	6967	(1210)	5684	(947)	4526	(490)	492
PCI with stent placement	11600	(1892)	7614	(692)	647	(22)	0
Primary PCI	696	(148)	335	(27)	20	(0)	0

Figure 3 – *Kaplan-Meier estimates of survival for patients submitted to one single percutaneous coronary intervention (PCI) paid by SUS between 1999 and 2010 according to PCI type.*

The 2015 life table shows that in the general population in the state of RJ, women´s live expectancy is higher than men´s at the age groups addressed in this study: 22.6 and 18.8 years for women and men aged 60 years old, respectively, and 9.1 and 8.0 years for women and men aged ≥ 80 years old, respectively.[25] However, it is not known if the survival of Brazilian men and women with coronary artery disease differ. In a study conducted in Norway with patients admitted to a hospital who had suffered a first episode of acute myocardial infarction, no age-adjusted sex-specific differences were observed in 28-day, one-year or 10-year case-fatality rate for patients aged <60 years.[26] However, in patients aged ≥60 years, for the same periods, a lower case-fatality rate was evidenced in women. In Sweden, women that presented myocardial infarction, whether or not admitted to a hospital, over a 23-year period showed a 9% higher survival rate.[27] Several attempts have been made in order to explain these conflicting results, such as biological attributes and social behaviors; however, those explanations are largely speculative. Regardless the causes, based on our results it seems that PCI reduces the gap in survival rates favoring women over men mainly among the cases involving younger patients (<50 years), and after some years following the intervention women have again a better probability of survival as observed in the general population.

As in other studies, here also older individuals had lower probabilities of survival than younger ones. The New York State Angioplasty Registry's data of patients submitted to emergency or elective PCI showed that when stratified by age group, overall in-hospital mortality rate in patients aged ≥ 80 years old was threefold higher than in patients aged 60-79 years, and sevenfold higher than in patients aged <60 years.[28] A collaborative analysis from ten randomized trials,[29] with a median follow-up of surviving patients of 5.9 years showed a 16% overall mortality rate of patients submitted to PCI done with balloon angioplasty or with bare-metal stents. As by age group, mortality rate in patients aged <55, 55-64 and ≥ 65 years old was 8%, 14% and 20%, respectively, showing a gradual effect of age in mortality.

Regarding the differences in outcomes after PCI with or without stent placement, while there is no doubt that bare-metal stent placement reduces the rate of restenosis and revascularization,[30] most RCTs have failed to show any advantage as to mortality rates of bare-metal stent placement over simple balloon angioplasty. The BENESTENT group has found no differences in in-hospital mortality and mortality rates at 7 months, one year and 5 years, in patients with stable angina submitted to PCI-S or simple balloon angioplasty.[31,32] A meta-analysis of RCTs comparing both procedures in the setting of non-acute coronary artery disease have shown just a small benefit in overall mortality rates with the routine use of stent, corresponding to an average of three, five and six additional lives saved per 1,000 patients treated at 30 days, 6 months and 12 months, respectively.[33] However, it was not possible to guarantee that this small additional benefit related to mortality rates was due to stent placement instead of to unbalanced co-interventions once more aggressive post-intervention therapy was observed in the stent group. As for acute myocardial infarction, Suryapranata et al.[34] showed

that in a follow-up of 24 months the rates of reinfarction and of subsequent target-vessel revascularization were higher in patients submitted to simple balloon angioplasty, but no difference was observed in mortality rates between the stent group and the balloon group.

As for observational studies, the analysis of the New York State´s Coronary Angioplasty Reporting System data[35] showed that in-hospital mortality rates were not different between PCI with and without stent placement, but the gap between the mortality rates in the two procedures widened about six months after the procedure, favoring PCI-S, and after that the gap remained constant for a two-year follow-up. Our study also observed a higher survival rate for patients submitted to PCI-S; however, the survival rate gap between the two procedures was larger at the beginning of the follow-up, getting narrower in longer follow-up periods and, finally, from 2 to 10 years no more differences in the survival rates were observed. Therefore, after these results, future studies should be conducted to address whether PCI using drug-eluting stents shows different results when compared to bare-metal stent or simple balloon angioplasty, and whether stent placement is cost-effective against simple balloon angioplasty for the public healthcare system in the state of RJ.

Finally, the death rates observed in this study are higher than those in RCTs. In a RCT conducted in the United States and in Canada with patients with stable or unstable coronary artery disease,[36] 0.4% and 1.2% of the patients submitted to PCI-S and simple balloon angioplasty died, respectively, compared to 4.3% and 5.2%, respectively, in our study at 6 months of follow-up. Boden et al.[37] showed a 7.6% cumulative death rate in 4.6 years of follow-up in patients with stable coronary artery disease submitted to PCI, (~3% with drug-eluting stent), while in our study 16.3% of the patients submitted to PCI-S died until 5 years of follow-up. In a continued follow-up of 53% of the original population from the former study, Sedlis et al.[38] showed that 25% of the patients submitted to PCI died within 15 years against 28.2% of deaths observed in this study. These discrepancies are likely to be explained by the problematic extrapolation of RCTs' findings to the general population because of their restrictive inclusion and exclusion criteria. Therefore, this observational study is more likely to provide an indication of what is being achieved in the daily medical practice with a population of patients assisted by the Brazilian public healthcare system and, thus, observational studies should be deemed complementary to RCTs' results. So, indications of PCI, especially in cases of stable IHD and in older patients, have to be questioned once the survival rates observed in such cases were lower than those expected when just clinical treatment has been used. We have to stress that the cases selected were submitted to one single procedure during the study period and they probably represent cases of better prognosis in the large spectrum of clinical presentations of IHD.

Some limitations inherent to observational studies should be highlighted. The data provided were limited to those included in the *AIH* database. The *AIH* database was created for administrative purposes and hence it does not include some important clinical information such as comorbidities, medications prescribed, number of vessels affected and patients' socioeconomic status, which might have influenced our results. Furthermore, these secondary databases did not follow strict data collection protocols and may be considered of lower quality in comparison to the data collected in RCTs. Yet, today the *AIH* database is the best tool available in Brazilian´s public healthcare system for this type of study due to its comprehensiveness and accessibility.

Conclusion

This study reports the probability of survival in 30 days, one year and 15 years of follow-up of a large number of patients submitted to one single PCI procedure paid by the Brazilian public healthcare system in the state of Rio de Janeiro. Women were prone to have a slightly lower survival probability than men in 30-day and one-year follow-up, but women had a higher survival probability within 15 years, especially when they were older. Additionally, patients submitted to PCI procedures without stent placement had a lower probability of survival within 30 days and one year, although no difference was observed after a two-year follow-up regarding the use of stents. These findings, which mirror the medical practice performed in a real-world population may help physicians make decisions regarding indicating the PCI considering the questions raised about the true benefits of this procedure.

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Author contributions

Conception and design of the research and Analysis and interpretation of the data: de Souza e Silva CG, Klein CH, Godoy PH, Salis LHA, de Souza e Silva NA; Acquisition of data: Klein CH, Godoy PH, de Souza e Silva NA; Statistical analysis: de Souza e Silva CG, Klein CH; Writing of the manuscript: de Souza e Silva CG; Critical revision of the manuscript for intellectual content: Klein CH, Godoy PH, Salis LHA, de Souza e Silva NA.

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 Hospital Universitário Clementino Fraga Filho (Faculdade de Medicina – UFRJ) under the protocol number 1148/12. 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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Effects of Rosuvastatin on Apolipoprotein J in Balloon-Injured Carotid Artery in Rats

Ning Yang, Bo Dong, Jinyu Yang, Yang Li, Lu Kou, Yue Liu, Qin Qin

Department of Cardiovascular, Tianjin Chest Hospital, Tianjin - China

Abstract

Background: Restenosis after percutaneous coronary intervention in coronary heart disease remains an unsolved problem. Clusterin (CLU) (or Apolipoprotein [Apo] J) levels have been reported to be elevated during the progression of postangioplasty restenosis and atherosclerosis. However, its role in neointimal hyperplasia is still controversial.

Objective: To elucidate the role Apo J in neointimal hyperplasia in a rat carotid artery model *in vivo* with or without rosuvastatin administration.

Methods: Male Wistar rats were randomly divided into three groups: the control group (n = 20), the model group (n = 20) and the statin intervention group (n = 32). The rats in the intervention group were given 10mg /kg dose of rosuvastatin. A 2F Fogarty catheter was introduced to induce vascular injury. Neointima formation was analyzed 1, 2, 3 and 4 weeks after balloon injury. The level of Apo J was measured by real-time PCR, immunohistochemistry and western blotting.

Results: Intimal/medial area ratio (intimal/medial, I/M) was increased after balloon-injury and reached the maximum value at 4weeks in the model group; I/M was slightly increased at 2 weeks and stopped increasing after rosuvastatin administration. The mRNA and protein levels of Apo J in carotid arteries were significantly upregulated after rosuvastatin administration as compared with the model group, and reached maximum values at 2 weeks, which was earlier than in the model group (3 weeks).

Conclusion: Apo J served as an acute phase reactant after balloon injury in rat carotid arteries. Rosuvastatin may reduce the neointima formation through up-regulation of Apo J. Our results suggest that Apo J exerts a protective role in the restenosis after balloon-injury in rats. (Arq Bras Cardiol. 2018; 111(4):562-568)

Keywords: Coronary Artery Dsease; Percutaneous Coronary Intervention; Rosuvastatin Calcium; Apolipoprotein J; Coronary Reestenosis; Rats.

Introduction

Coronary heart disease (CHD) is one of the most common cardiovascular diseases with high morbidity and mortality. Major effective techniques for myocardial revascularization are percutaneous coronary intervention (PCI) and coronary bypass surgery. Percutaneous transluminal coronary angioplasty (PTCA) is an effective treatment for CHD, but its effect in long-term is influenced by a high restenosis rate. Although drug eluting stents (DES) combined with dual antiplatelet therapy greatly reduce the occurrence of restenosis, the incidence rate still exceeds 10%.[1, 2] The mechanism underlying restenosis after PCI has been widely studied worldwide, but effective cellular or molecular targets for the treatment of restenosis after PCI urgently needs to be identified.

Mailing Address: Qin Qin •
N°. 261 Taierzhuang South Road, Jinnan District, Tianjin. 300222, Tianjin – China
E-mail: qinqintj@163.com
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Clusterin (CLU), or Apolipoprotein (Apo) J, is a heterodimeric glycoprotein, which is composed of α and β subunits linked by disulfide bond.[3,4] The coding gene of Apo J is located on chromosome 8p21-p12, mainly encoding two isoforms – secretory CLU (sCLU) and nuclear CLU (nCLU).[5] Apo J has been reported to be induced during the progression of postangioplasty restenosis and atherosclerosis.[6-9] However, the role of Apo J in neointimal hyperplasia is still controversial. It has been reported that Apo J could stimulate the proliferation and migration of vascular smooth muscle cell (VSMC) in CLU-knockout mice by inhibiting the expression of p53 and p21, and promote restenosis.[10,11] On the contrary, Kim et al.[12] revealed that the overexpression of sCLU can inhibit the migration and proliferation of VSMC and inhibit the apoptosis of cells. In view of existing paradoxical findings, we aimed to elucidate the role Apo J in neointimal hyperplasia in a rat carotid artery model *in vivo* with or without rosuvastatin intervention.

Methods

Animals

Male Wistar rats weighing 350-400 g were randomly divided into three groups: control group (n = 20), model group

(n = 20) and intervention (statin) group (n = 32). All animals were then randomly divided into 4 groups – to be evaluated at 1, 2, 3 or 4 weeks after balloon injury. The study was approved by the Ethics Committee of Tianjin Chest Hospital.

Balloon injury

The rats were weighed on the day of operation, and randomly divided into three groups. The rats in the intervention group were given 10 mg/kg dose of rosuvastatin. A 2F Fogarty catheter was introduced to induce vascular injury as previously reported.[13] Briefly, the rats were anesthetized after intraperitoneal injection of 10% chloral hydrate at a dose of 0.3 mL/100 g body weight. A 2F balloon catheter was inserted into aortic outlet of carotid artery. The balloon was then inflated and pulled back 3 times to denude the endothelium.

At 1, 2, 3 and 4 weeks after surgery, rats were anesthetized by intraperitoneal injection of 10% chloral hydrate at a dose of 0.3 ml/100 g body weight. Then, the animals were sacrificed by intravenous administration of 2-3 mL of potassium chloride solution *via* subclavian vein; 0.3 cm of the right carotid artery was fixed in 10% neutral formalin for pathological examination, and the other part was frozen immediately in liquid nitrogen and stored at -80°C for further use.

Hematoxylin-eosin (HE) staining

Vascular specimens were fixed in 10% formaldehyde solution for 3-4h. Routine dehydration and paraffin embedding were performed. The sections were cut evenly and the thickness was 4 μm. The injury of blood vessels was observed under light microscope.

Immunohistochemistry (IHC) assay

The level of Apo J was assessed by IHC in rat carotid artery. The primary antibody (polyclonal rabbit anti-human Apo J IgG) was purchased from Santa Cruz, Inc. (Cat No. sc-8354). The secondary antibody (labeled goat anti-rat/rabbit IgG polymer) was purchased from Maixin BioTech (Fuzhou, China). All photos were captured and saved using the ISCapture system, and data collection and analysis are performed using the Image Pro Plus 6 image processing software.

Enzyme-linked immunosorbent assay (ELISA)

Venous blood was collected and centrifugated at 3000r/min for 10 min. The supernatant was collected using a micropipette and stored in the refrigerator at -20°C for use. The samples were then thawed at room temperature for ELISA. ELISA was performed using a commercial kit (Rat Competitive ELISA for Apolipoprotein J A 252 SC), following the manufacturers' instructions.

Real-time polymerase chain reaction (PCR)

The mRNA level of Apo J was detected by real-time PCR in rat carotid artery. RNA was extracted by Trizol one-step extraction method, and reverse transcription was performed. Primers used for amplification for Apo J were as follows: Forward, TAA GGA GAT TCA GAA CGC CG; reverse, ATC CCT GGT GTC ATC TAG AG. Primers for the control GAPDH were as follows: Forward, GTG ATG CTG GTG CCG AGT AG; reverse, GGT GGC AGT GAT GGC GTG C. Real-time PCR reactions were prepared following the instructions of SYBR®*Premix Ex Taq*™ system (Perfect Real Time). The mRNA levels in each sample were calculated by $2^{-\Delta\Delta Ct}$.

Western blotting

Proteins were extracted from 30 mg of rat carotid artery. Briefly, proteins were separated using SDS-PAGE with 10% separation gel and 5% concentrated gel. Then the separated proteins were transferred into polyvinylidene difluoride (PVDF) membranes. The membranes were blocked and incubated with antibodies. Relative levels of Apo J were analyzed using Image Lab analysis software. β-actin was used as inner control. Bands were quantified using QUANTITY ONE software (Bio-Rad, Hercules, CA, USA).

Statistical analysis

Statistical analysis was performed using SPSS 20.0. Quantitative data were expressed by mean ± standard deviation (SD). The difference between two groups was compared using independent-samples *t* test; comparisons between three groups were analyzed using one-way ANOVA (analysis of variance). $P < 0.05$ was considered statistically significant.

Results

Survival and success rates of rat carotid artery model

Among the 52 rats of the model group and the intervention group, 2 died during operation by suffocation, and 2 died for arterial hemorrhage 12h after operation. Therefore, 47 rats survived with approximately 90% survival rate. The pathological examination showed intimal hyperplasia and thickening in the experimental group, suggesting that the model was successfully constructed. The mean operation time was 34.19 ± 6.09 min. The feasibility and success rate of this model can be highly reproducible if surgical procedures are properly performed.

Level of serum Apo J

There was no significant difference in serum Apo J level before and after operation in the intervention group (Table 1). There was no significant difference in the level of serum Apo J at 1, 2, 3 and 4 weeks before ($F = 1.002$, $p = 0.408$) of after ($F = 0.189$, $p = 0.903$) operation.

Statin intervention inhibited intimal hyperplasia

Results of pathological examination showed that no intimal hyperplasia was observed in the control group (Figure 1). In the model group and intervention group, the intima was slightly thickened 1 week after operation, and further thickened 2 weeks after operation. During 3 weeks after operation, the degree of intimal hyperplasia was further aggravated in the model group; however, this change was not as marked as at 2 weeks after operation, and the cells gradually became paralleled. During 4 weeks after operation, the degree of intimal hyperplasia was further aggravated in the model group, but no significant changes were observed regarding the degree of intimal hyperplasia as compared with week 3 (Figure 2 and 3).

Table 1 – Serum levels of apolipoprotein J (Apo J) before and after operation in the statin intervention group

Time points	Pre-operation		Post-operation		t*	p#
	n	Apo J	n	Apo J		
1	7	13.498 ± 3.015	7	10.317 ± 3.567	1.802	0.097
2	7	14.062 ± 4.538	7	11.516 ± 1.762	1.383	0.192
3	8	11.234 ± 2.740	8	11.117 ± 3.104	0.08	0.937
4	8	14.143 ± 4.609	8	11.205 ± 3.579	1.424	0.176
F§		1.002		0.189		
P#		0.408		0.903		

*t test used to compare the differences between the two groups; §F one-way ANOVA (analysis of variance) to compare the difference between all four groups. #p value < 0.05 was considered statistically significant.

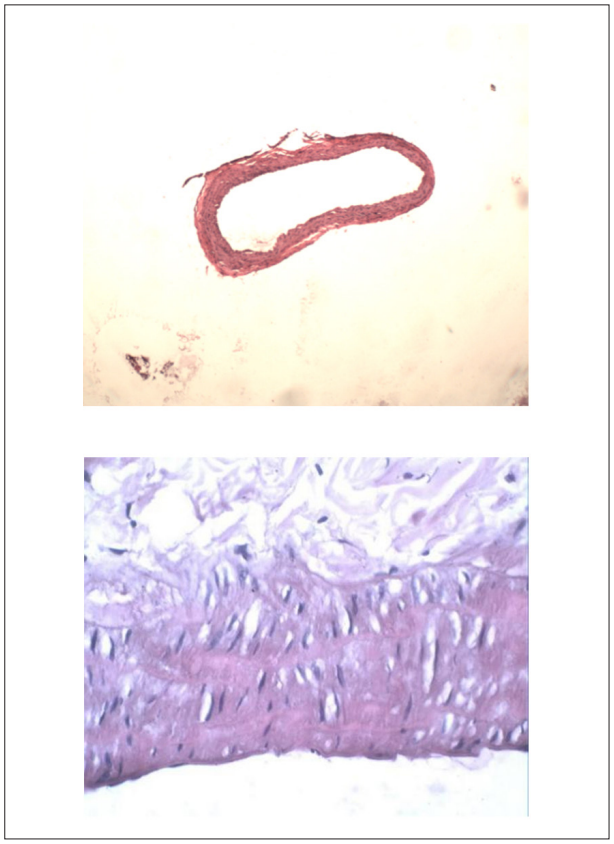

Figure 1 – *Hematoxylin-eosin (HE) staining in the control group. Upper, magnification 40×; lower, magnification 400×.*

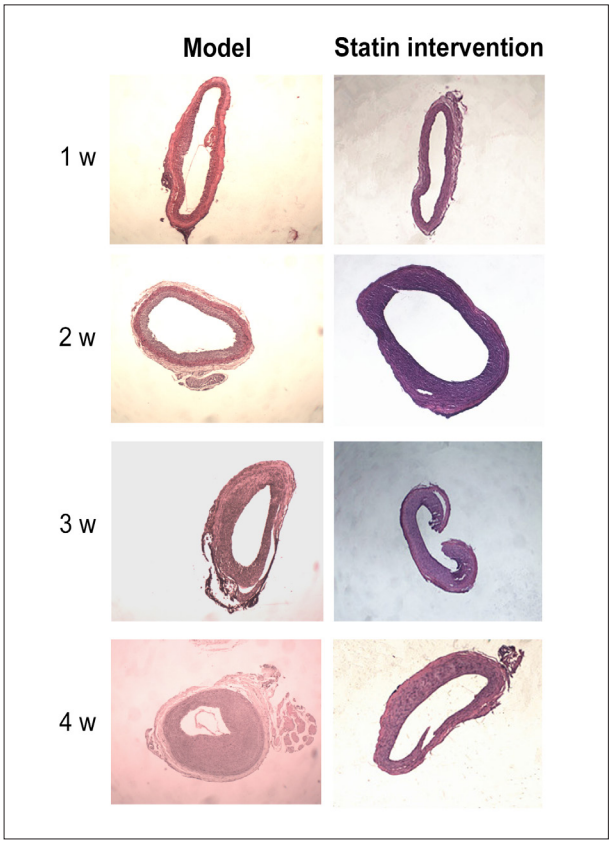

Figure 2 – *Hematoxylin-eosin (HE) staining in the model group and in intervention group 1 week (w), 2 weeks, 3 weeks and 4 weeks after balloon injury of rat carotid arteries; magnification 40×.*

Intimal and medial membrane areas were measured using Image Pro Plus 6, and intimal/medial area ratio (intimal/medial, I/M) was used to indicate the degree of intimal hyperplasia. As shown in Table 2, the I/M was close to 0 in the control group and was significantly different from that in the model group and the intervention group at all time points (1, 2, 3 and 4 weeks). There were significant differences of I/M between different time points in the model group, and I/M reached the maximum at the fourth week. No significant difference of I/M was observed between 2, 3 and 4 weeks post-surgery in the intervention group, and I/M in the intervention group was significantly lower than that in the model group (Table 2). Taken together, our results suggest that rosuvastatin could significantly inhibit intimal hyperplasia in rats.

Level of Apo J in carotid arteries

The mRNA levels of Apo J were measured by real-time PCR. Our results showed that the Apo J mRNA level was strikingly increased 2 weeks after operation, reached to a peak at the 3rd week, and decreased at the 4th week post-surgery in the model group. In intervention group, the Apo J mRNA level was strikingly increased and reached to a peak at the 2nd week, and decreased at the 3rd and 4th week post-surgery in the intervention group. In addition, the mRNA level of Apo J was higher in the intervention group than in the model group at the 1st week after operation. At the 2nd week post-surgery, the mRNA level of Apo J was strikingly increased in both groups and was significantly higher in the stain-intervention group than the model group (Table 3). Similar results have been observed in the protein levels of Apo J as shown in Figure 4. Our results showed that rosuvastatin could significantly increase the expression level of Apo J in balloon-injured rat carotid arteries.

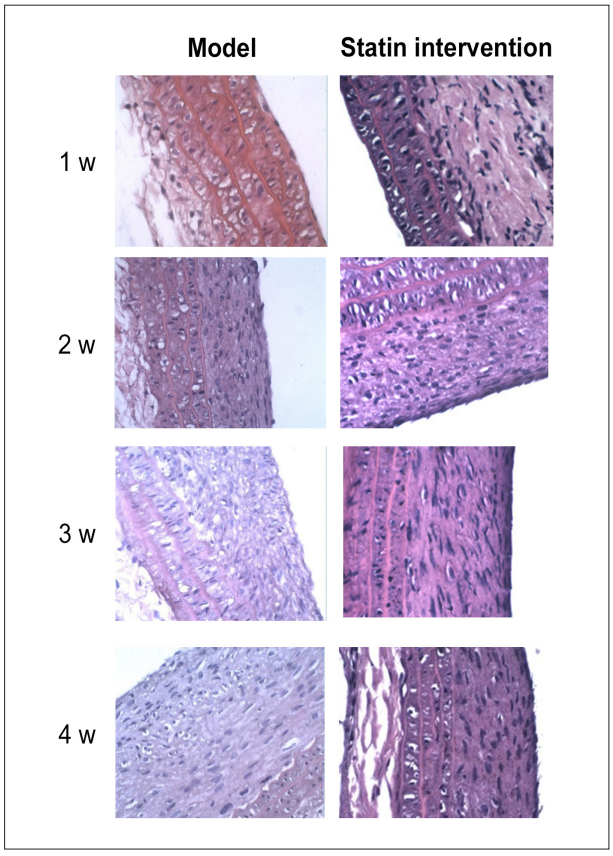

Figure 3 – *Hematoxylin-eosin (HE) staining in the model group and in intervention group 1 week (w), 2 weeks, 3 weeks and 4 weeks after balloon injury of rat carotid arteries; magnification 400×.*

Discussion

In the present study, we found that I/M increased after balloon-injury and reached the maximum at 4w in the model group; also, I/M was slightly increased at 2w and stopped increasing after rosuvastatin administration. Our results suggest that rosuvastatin could significantly reduce the degree of intimal hyperplasia in balloon-injured carotid arteries in rats. The levels of Apo J mRNA and protein in carotid arteries were significantly upregulated after rosuvastatin administration as compared with the model group, and reached to maximum at 2 weeks, which was earlier than the in the model group. Our results suggest that rosuvastatin may inhibit intimal hyperplasia through upregulation of Apo J after balloon-injury in rats.

Apo J has been reported to be closely related to cardiovascular diseases, such as atherosclerosis and restenosis after angioplasty.[14,15] Ishikawa et al.[7] revealed the distribution of Apo J in the extracellular matrix of endarterium in human atherosclerotic aorta, and its potential protective role against human atherosclerosis by cholesterol transport from the aortic wall to the liver. It has been reported that ApoJ is increased in tissue injury and cell stress, and plays vital role in protection against oxidative stress, cell lysis and apoptotic cell death.[16-21] Additionally, ApoJ could be observed in active tissue remodeling. These findings indicate that ApoJ may act as an acute phase reactant. In the present study, we observed a marked neointimal thickening 2 weeks post-surgery, with proliferation and migration VSMCs observed by HE staining in the model group. The proliferation and migration of VSMC were the most active at week 3, and decrease at week 4. In the meantime, the mRNA and protein levels of Apo J were significantly increased at week 2, reached a peak at 3 weeks after operation, and then decreased at 4 weeks. The results showed high expression of Apo J in the phase of active proliferation and migration of VSMCs. Consistent with other studies, our results suggest that Apo J may be an acute phase reactant after balloon-injury in rat carotid arteries.

Table 2 – Intimal/medial (I/M) area ratio in the study groups

Time points	Control group		Model group		Statin intervention group		t*	p#
	n	I/M	n	I/M	n	I/M		
1	5	0.04 ± 0.07	5	0.63 ± 0.40$^{\gamma}$	5	0.42 ± 0.04$^{\gamma}$	10.066	< 0.001
2	5	0.01 ± 0.02	4	1.08 ± 0.29$^{\blacktriangle}$	4	1.29 ± 0.31$^{\Delta\blacktriangle}$	39.639	< 0.001
3	5	0.03 ± 0.03	4	1.81 ± 0.11$^{\alpha\beta}$	4	1.47 ± 0.54$^{\Delta\beta}$	37.142	< 0.001
4	5	0.05 ± 0.04	4	2.61 ± 1.12$^{\alpha b\theta}$	4	1.50 ± 0.26$^{\Delta\theta c}$	20.287	< 0.001
F$		0.741		9.432		21.393		
P#		0.543		< 0.001		< 0.001		

**t test used to compare the differences between the two groups. $F one-way ANOVA (analysis of variance) to compare the difference between all four groups. #p value < 0.05 was considered statistically significant*

Table 3 – Relative (2-ΔΔCt) levels of apolipoprotein J mRNA

Time points	Control group		Model group		Statin intervention group		t*	p#
	n	2-ΔΔCt	n	2-ΔΔCt	n	2-ΔΔCt		
1	5	0.958 ± 0.251	5	0.641 ± 0.296	6	1.275 ± 0.468[a]	4.212	0.039
2	5	0.948 ± 0.090	4	7.804 ± 1.328[a▲]	6	10.040 ± 2.086[Δb]	52.279	< 0.001
3	5	1.004 ± 0.196	4	8.011 ± 2.306[aβ]	6	7.327 ± 2.869[Δ*β]	15.31	< 0.001
4	5	1.048 ± 0.349	4	3.429 ± 1.119[abcθ]	6	2.413 ± 0.492[*#θ]	14.212	0.001
F§		0.182		29.266		31.336		
P#		0.907		< 0.001		< 0.001		

*t value was calculated using independent-samples t test to compare the difference between two groups. §F value was calculated using one-way ANOVA (analysis of variance) to compare the difference among the four groups. #p value (probability value) < 0.05 is considered to be statistically significant.

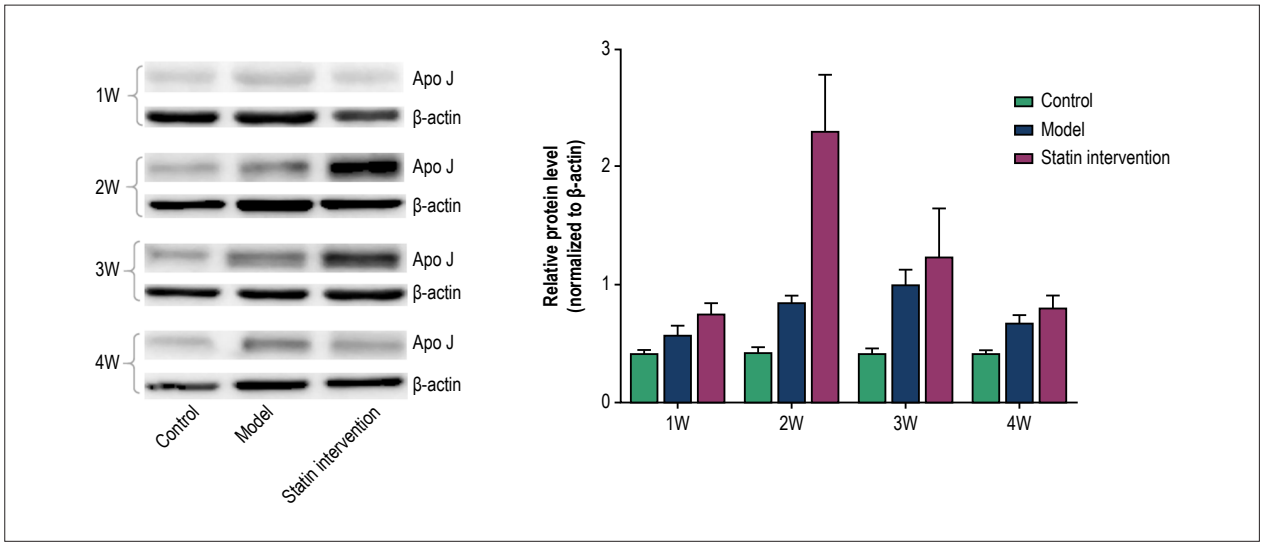

Figure 4 – *Western blotting of apolipoprotein J (Apo J) protein levels 1 week (w), 2 weeks, 3 weeks and 4 weeks after balloon injury of rat carotid arteries.*

In-stent restenosis after interventional procedures has become one of the most urgent problems to be solved worldwide. Rosuvastatin, a potent hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, has been reported to reduce neointimal thickening after vascular endothelial injury in rats[13] In the present study, the rats in the intervention group received intragastric administration of rosuvastatin (10 mg/kg/d). In accordance with other studies,[22-24] we found that rosuvastatin significantly reduced the neointima formation.

It has been reported that secreted isoform of Apo J (sCLU) could inhibit the proliferation and migration of VSMCs.[12,25] Kim et al.[12] also found that Apo J could significantly inhibit neointimal hyperplasia using adenovirus-mediated overexpression of Apo J in rats. In the present study, we found that the mRNA and protein levels of ApoJ in carotid arteries were significantly upregulated after rosuvastatin administration as compared with the model group. Moreover, Apo J reached a maximum at week 2 after rosuvastatin administration, and that was earlier than the model group which reached peak expression at the third week. These results suggest that rosuvastatin may increase the level of Apo J in the balloon-injured carotid arteries, which indirectly indicates a protective role of Apo J against restenosis after balloon-injury in rats.

Conclusion

Our results showed that Apo J served as an acute phase reactant after balloon-injury in rat carotid arteries. Rosuvastatin may reduce the neointima formation through further up-regulation of Apo J. Our findings suggest that Apo J exerts a protective role against restenosis after balloon-injury in rats.

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Author contributions

Conception and design of the research and Writing of the manuscript: Yang N, Qin Q; Acquisition of data: Yang N, Dong B, Yang J, Li Y, Kou L, Liu Y; Analysis and interpretation of the data: Yang N, Dong B, Yang J, Li Y, Kou L; Statistical

analysis: Yang N, Dong B; Critical revision of the manuscript for intellectual content: Yang N, Dong B, Yang J, Li Y, Qin Q.

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 on Animal Experiments of the Tianjin Chest Hospital under the protocol number 2015-006-05

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Original Article

Rosuvastatin Decreases the Formation of Neointima by Increasing Apo J, Reducing Restenosis after Balloon Injury in Rats

Paulo Magno Martins Dourado

Faculdade de Medicina da Universidade de São Paulo - Instituto do Coração (InCor) - Laboratório de Hipertensão Experimental, São Paulo, SP - Brazil

Short Editorial regarding the article: Effects of Rosuvastatin on Apolipoprotein J in Balloon-Injured Carotid Artery in Rats

The study by Yang et al.[1] brings new light on the action of Apolipoprotein (Apo) J, also called clusterin (CLU), a heterodimeric glycoprotein consisting of α and β subunits linked by disulfide bond.[2,3] The coding gene of Apo J is located on chromosome 8p21-p12, encoding two main isoforms, including secreted (sCLU) and nuclear (nCLU)[4] on restenosis following balloon percutaneous transluminal carotid angioplasty (PTCA) in an experimental model in rats; this was published in this edition of the Brazilian Archives of Cardiology, because there is a controversy in the literature whether Apo J, which is elevated in atherosclerosis and post-angioplasty, plays a protective or promoting role for restenosis. Apo J is involved in several important pathological processes in the transport of lipids, and in the differentiation of vascular smooth muscle cells (VSMC), including cell death by apoptosis, cell cycle regulation, cell adhesion, tissue remodeling, regulation of the immune system and oxidative stress, playing a role in the development of clinical atherosclerosis.[5,6] In the process of attenuating atherosclerosis, Apo J can promote the export of cholesterol and phospholipids from foam cells of macrophages,[7] and show cytoprotective and anti-inflammatory actions interacting with many known inflammatory proteins that may act in the initial phase of clinical cardiovascular events, and may play an important role in mediating atherosclerotic disease, such as C-reactive protein, paraoxonase and leptin.[8] There are studies reporting that Apo J can stimulate the proliferation and migration of VSMC, and promote restenosis,[9,10] and there have been studies showing that overexpression of CLUs can inhibit migration and proliferation of VSMC, and inhibit cellular apoptosis.[11] In view of these controversial results, the authors sought to elucidate the role of Apo J in neointimal hyperplasia, using the rat carotid artery in vivo, with or without rosuvastatin.

The results of the study published here suggest that rosuvastatin can inhibit intimal hyperplasia due to the high expression of Apo J in the active proliferation and migration phase of VSMC, after balloon injury in rats. In the present study, the authors evidenced an increase in the intimal/media (I/M) area rate after the balloon injury that reached the maximum value in the fourth week in the model group; in addition, I/M was increased at week 2, and such increase ceased after the administration of rosuvastatin. These results suggest that rosuvastatin can significantly reduce the degree of intimal hyperplasia in the balloon-injured carotid arteries in rats. The levels of Messenger Ribonucleic Acid (mRNA) and Apo J were increased in the carotid arteries in the group using rosuvastatin, when compared to the model group, reaching the maximum in the second week, earlier than in the model group, suggesting that rosuvastatin can inhibit intimal hyperplasia by increasing Apo J after balloon injury in rats. Therefore, Apo J has been identified as having a central role in the migration, adhesion and vascular proliferation process, and that it can contribute significantly to restenosis after vascular injury.

The results of this study showed that Apo J can be an acute phase reagent after balloon injury in the carotid arteries of rats; therefore, it plays a favorable role, decreasing the development of restenosis, which in spite of all existing interventions remains as a challenge to be overcome. Rosuvastatin, a potent inhibitor of the HMG-CoA (hydroxymethylglutaryl-CoA) reductase enzyme, seems to reduce neointimal thickening after vascular endothelial injury in rats.

This study opens new perspectives by highlighting possible mechanisms involved in the genesis of restenosis after percutaneous interventions, opening the way for clinical studies researching the action of Apo J as a new predictor and a therapeutic target for the protection of the vessel after PTCA.

Keywords

Clusterin/genetic; Rats; Carotid Arteries; Angioplasty; Percutaneous Coronary Intervention/trends; Coronary Restenosis

Mailing Address: Paulo Magno Martins Dourado •
Rua Apinajes, 969, apto. 21. Postal Code 05017-000, Perdizes, São Paulo, SP – Brazil
E-mail: pmdourado@terra.com.br, pmagno@cardiol.br

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Genetic Testing and Pregnancy Outcome Analysis of 362 Fetuses with Congenital Heart Disease Identified by Prenatal Ultrasound

Shiyu Luo, Dahua Meng, Qifei Li, Xuehua Hu, Yuhua Chen, Chun He, Bobo Xie, Shangyang She, Yingfeng Li, Chunyun Fu

Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region,[1] Guangxi - China

Abstract

Background: **Congenital heart defects (CHD), as the most common congenital anomaly, have been reported to be associated with chromosomal abnormalities. Currently, patients with CHD are routinely offered karyotyping and chromosomal microarray (CMA) testing, but the genotype-phenotype relationship has not yet been fully established.**

Objective: **To determine the type and frequency of chromosomal abnormalities in fetuses with CHD and to analyze pregnancy outcomes of fetuses with heart abnormalities caused by different genetic factors.**

Methods: **A total of 362 cases of CHD were enrolled from 2009 to 2016. Detailed ultrasound and laboratory examinations, including karyotyping and CMA, were performed. Outcome was obtained from discharge summaries.**

Results: **Of the 362 fetuses, 220 were found with an isolated CHD, and 142 had CHD with extracardiac anomaly. Among these 362 fetuses, 140 were identified with a genetic cause, including 111 cases with aneuploidy, 10 cases with abnormality of chromosomal structure by karyotyping and 19 cases with pathogenic or likely pathogenic copy-number variations (CNVs) by CMA. The detection rate is close to 38.7%. Only one (identified as trisomy 18 syndrome) in 140 positive cases resulted in perinatal death, with the others being induced. The remaining 222 cases had negative results for both genetic testing and of these cases, 56 resulted in induced labor, and 77 had natural childbirth or caesarean births. The pregnancy outcome of the remaining 89 cases was uncertain.**

Conclusions: **Karyotyping and CMA are effective and accurate prenatal genetic techniques for identifying fetal chromosomal abnormalities associated with cardiac defects, and this can assist clinical doctors to perform appropriate genetic counselling with regard to the etiology and outcome of CHD. (Arq Bras Cardiol. 2018; 111(4):571-577)**

Keywords: **Heart Defects, Congenital; Chromosome Disorders; Spectral Karyotyping; Pregnancy; Fetus; Ultrasonography.**

Introduction

Congenital heart disease (CHD), one of the most common birth defects, affecting approximately 1 in 100 live births.[1-3] With the availability of advanced surgical techniques, normal or near normal cardiac function can be restored after surgical treatment of most types of CHDs ranging from simple ventricular septal defects (VSD) to more complex cardiovascular abnormalities. However, the long-term prognosis of a small, but significant number of CHD fetuses is usually complicated by severe extracardiac abnormalities, such as developmental delay and mental retardation. There is increasing evidence that genetic factors influence the development of most types of CHD,[4-6] but the precise genetic basis of most CHD cases remains not fully understood. Current ultrasound technologies are able to detect most of CHD. However, it is difficult for physicians to make a comprehensive assessment of fetuses with CHD merely based on the evidence of prenatal ultrasound, as well as to manage the course of established pregnancy.[7] Therefore, genetic testing is now highly recommended for fetuses with CHD.

Karyotyping has been the mainstream diagnostic method for detecting chromosomal abnormalities associated with CHD.[8] For CHD cases in prenatal diagnosis, chromosomal anomalies are estimated to be as high as 22.[9,10] Now, chromosomal microarray (CMA) has become the first tier technique in fetal structural anomalies detected by ultrasonography.[11,12] The advent of CMA technology has allowed genome-wide searches of submicroscopic chromosomal deletions or duplications in the genome, known as copy-number variations (CNVs). CNV is a form of structural variation in the genome: specifically, it is a type of duplication or deletion that has an influence in the base pairs,[13] and CNVs play an important role in generating necessary variation in the population and disease phenotypes.[14] Recent studies have shown that a substantial proportion of CHD patients were detected with pathogenic CNVs,[15, 16] and the syndromic or isolated CHD patients were found with multiple recurrent CNV loci, such as 22q11.2 (the DiGeorge syndrome region), 7q11.23, 8p23.1, 9q34.3, and 1q21.1.[17-19]

Mailing Address: Chunyun Fu •
N°.59 Xiangzhu Road, Nanning, Guangxi – China
E-mail: fuchunyun2008@sina.com, 948178849@qq.com
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At present, only a few studies have reported genetic testing among large groups of fetuses with CHD in China,[20-24] the genotype-phenotype relationship has not yet been fully established. The Laboratory of Genetics and Metabolism from the Maternal and Child Health Hospital in Guangxi is one of the largest Perinatal Diagnostic centers in South China. This study aimed to analyze the chromosomal abnormalities and pregnancy outcomes in 362 fetuses with CHD.

Methods

Subjects

Fetal ultrasound anatomy scans were routinely performed for pregnant women at the Prenatal Diagnosis Center of Guangxi Zhuang Autonomous Region in China. The anatomy scans were conducted between 20 and 28 weeks of gestation by senior sonographers using GE E8 ultrasound machines (General Electric Healthcare, USA). If CHD was suspected, the echocardiography was subsequently performed for confirmation.

A total of 8,430 pregnancies between June 2012 and June 2016 were screened for fetal cardiac defects, and 362 fetuses were identified with CHD. The Medical Ethics Committee of the Guangxi Maternal and Child Health Hospital approved the study protocol (Approval no.160220), and the parents of all selected fetuses with CHD gave their written consent.

Testing of SNP microarray

All samples of amniotic fluid or fetal cord blood were collected from the pregnant women, and genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the manufacturer's protocol. SNP (Single Nucleotide Polymorphism) microarray testing was performed using Illumina HumanCytoSNP-12 v2.1 BeadChip (Illumina, USA). The laboratory policy at the time of testing was not to report well-established polymorphisms, CNVs that do not contain genes and CNVs smaller than 0.20 Mb. However, stretches of homozygosity larger than 10 Mb were reported.

Karyotyping

All samples of amniotic fluid or fetal cord blood were used to perform G-banding according to the standard procedure as described previously.[25]

Results

Clinical data

Among the 8,430 pregnancies, 362 cases of CHD were diagnosed using fetal echocardiography, for a frequency of 4.2%. The mean age of the pregnant women was 31.1 ± 5.1 years, and the mean gestational week at diagnosis was 24.4 ± 3.8 weeks.

The 5 most common types of CHD were, in order, ventricular septal defect (51.9%, 188/362), persistent left superior vena cava (13.0%, 47/362), endocardial cushion defects (0.9%, 33/362), single umbilical artery (0.9%, 32/362) and right-sided aortic arch (0.8%, 29/362).

Etiology

In total, 362 fetuses were diagnosed with CHD. The genetic tests found 111 cases with aneuploidy, 10 cases with abnormality of chromosome structure, and 19 cases with pathogenic or likely pathogenic CNVs (Table 1). The remaining 222 cases showed no abnormal genetic findings. The abnormalities of chromosome numbers consisted of trisomy 18 syndrome (61 cases), trisomy 21 syndrome (31 cases) and trisomy 13 syndrome (19 cases). CMA identified 19 CNVs, including DiGeorge syndrome (8 cases), Jacobsen syndrome (2 cases), Angelman/Prader-Willi syndrome (1 case), 16p11.2-p12.2 microdeletion syndrome (1 case), 16q24-triplication syndrome (1 case), Thrombocytopenia-absent radius (TAR) syndrome (1 case), 3q29 microduplication syndrome (1 case), 22q11 duplication syndrome (1 case), Cri du chat syndrome (1 case) and 2 likely pathogenic CNVs (Table 2).

Occurrence of fetal cardiac malformations

Of the 362 CHD, 181 fetuses were found with single cardiac malformations, and 181 were found with multiple cardiac abnormalities; 220 were found with an isolated CHD; and 142 had CHD with extracardiac anomaly. Table 3 lists the etiology of the various types of fetal cardiac malformations observed.

Pregnancy Outcomes

Among all 140 cases with a positive genetic testing result, only one woman chose to continue her pregnancy, and the rest of them chose to induce labor. The fetus was diagnosed with trisomy 18 syndrome, presenting difficulties in feeding, and died 4 days after birth. Among the remaining 222 negative cases, 56 were subjected to labor induction, and most of these cases were deemed incurable or had poor prognostic cardiac malformations (including single ventricle, left or right ventricular dysplasia and tetralogy of fallot) or were complicated with extracardiac anomalies (Figure 1).

Mothers of 77 fetuses with mild or curable cardiac malformations chose to maintain their pregnancies. Of these cases, 66 were found with no abnormality after birth, 8 cases needed surgery, one presented delayed development, one was found with clubfoot, one was identified with hypomyotonia, and the pregnancy outcomes of the remaining 89 cases were uncertain (Figure 1).

Discussion

In this study, 362 cases of fetal CHD were identified in a total of 8,430 pregnancies at a single Maternal and Children's hospital from the Southern region of China from June 2012 to June 2016, with an incidence of 4.2%. This incidence was similar to that reported in Xi'an, in Northwestern China,[26] and higher than the rate of 2.3% reported in Guangzhou, In southern China.[23] Among the 362 CHD fetuses, ventricular septal defect (51.9%, 188/362) and persistent left superior vena cava (13.0%, 47/362) were the most prevalent cardiac abnormalities detected by ultrasound scans.

Many factors such as genetic factors (including chromosomal abnormalities and gene mutations) and risk factors associated

Table 1 – Genetic testing of 362 fetuses with congenital heart defects

Etiology	Classifications	Numbers
Aneuploidyn(111, 30.7%)	Trisomy 18	61
	Trisomy 21	31
	Trisomy 13	19
Abnormality of chromosome structure (10, 2.8%)	46,X,i(X)(q10)	1
	46,der(18)dup(18)(q11q22)del(18)(q22q23)	1
	46,XY,r(13)(p13q34)	1
	46,XY,der(21;21)(q10;q10),+21	1
	46,XX,der(9)t(9;18)(p22;q21)mat	1
	46,XY,del(10)(q11q22)dn	1
	46,XY,6q-dn	1
	46,XY,der(18)t(7;18)(q22;q23)mat	1
	46,XX,del(5)(p13)	1
	46,XY,der(5)t(5;12)(p13;p12)mat	1
CNVs (19, 5.2%)	15q13.2q13.3(30940398-32515681)x1	1
	arr16p11.2(29614976-30199805)x1~2	1
	arr16q21q24.3(63,863,382-90,130,136)x2~3	1
	arr1q21.1q21.2(146,501,348-147,828,939)x1	1
	arr3q21.1q29(123031042-198022430)x2~3	1
	arr22q11.21(18877787-21458625)x1	1
	arr22q11.21(18889490-21460220)x1	1
	arr22q11.21(18895703-21928916)x1	1
	arr 22q11.21(18844632-21462353)x1	1
	arr 11q24.1q25(123615329-1349444006)x1	1
	arr10q26.13q26.3 (126254468-135430043)x3, arr11q24.1q25(122805910-134944006)x1	1
	arr 10p15.1p12.31(6085312-21544231)x1	1
	arr 5q11.2q12.1(56368573-61428613)x1	1
	arr21q11.2 q21.1(14687571-18341062)x1	1
	arr22q11.21(21050552-21811991)x1	1
	arr22q11.21(20740778-21445064)x1	1
	arr22q11.21(18895703-21452237)x1	1
	arr11q23.3q25(116728277-134944006)x3, arr22q11.1q11.21(16079545-20306993)x3	1
	arr5p15.33p15.1(354051-17484038)x1, 5q34q35.3(165731079-180705539)x3	1

CNVs: copy-number variations.

with mothers (including the rubella virus, other infections, radiation, drug use and environmental pollution) are reported to be associated with CHD.[5-7,27-29] However, the causes of most types of CHD are still poorly understood. In our study, 140 of 362 CHD fetuses were identified with clinically significant chromosomal abnormalities by karyotyping and CMA, with a detection rate of up to 38.7%. The positive rates of genetic testing in this study is far higher than previous reports in Chongqing, China[24] and the Netherlands.[30] This rate is similar to that of Brazilians.[31]

Among the 140 chromosomal abnormalities, 111 (79.3%) were aneuploidy, of which trisomy 18 was the most common; 10 (7.1%) cases were abnormality of chromosome structure; and 19 (13.6%) cases were pathogenic or likely pathogenic CNVs. It is suggested that aneuploidy is the leading genetic cause of fetuses with CHD in our population. Given that G-banding can only reliably detect structural abnormalities > 10 Mb in size, 11 pathogenic CNVs may be missed by karyotyping but detected by CMA. On this basis, we estimate that the incremental yield of reportable CNVs with less than 10 Mb achieved by CMA was 3.0%.

Complex multiple cardiac malformations have poor prognosis and heavily affect the quality of life of surviving infants, but cases such as mild tetralogy of fallot have

Table 2 – Copy-number variations (CNVs) in 362 fetuses with congenital heart disease (CHD)

Patient	Cardiac defect	Extra-cardiac defect	CNVs	Size (Mb)	Known syndrome/candidate genes related to CHD	Classification
1	persistent left superior vena cava	Intrauterine growth retardation	15q13.2q13.3(30940398-32515681)x1	10.0	Angelman/Prader-Willi syndrome	pathogenic
2	persistent left superior vena cava, single umbilical artery		arr16p11.2(29614976-30199805)x1~2	0.5	16p11.2-p12.2 microdeletion syndrome	pathogenic
3	pulmonary stenosis		arr16q21q24.3(63,863,382-90,130,136)x2~3	26.3	16q24-triplication syndrome	pathogenic
4	complete-type endocardial cushion defect		arr1q21.1q21.2(146,501,348-147,828,939)x1	1.3	Thrombocytopenia-absent radius (TAR) syndrome	pathogenic
5	ventricular septal defect	Short limbs	arr3q21.1q29(123031042-198022430)x2~3	75.0	3q29 microduplication syndrome	pathogenic
6	tetralogy of fallot		arr22q11.21(18877787-21458625)x1	2.6	DiGeorge syndrome	pathogenic
7	tetralogy of fallot		arr22q11.21(18889490-21460220)x1	2.6	DiGeorge syndrome	pathogenic
8	right aortic arch, persistent left superior vena cava		arr22q11.21(18895703-21928916)x1	3.0	DiGeorge syndrome	pathogenic
9	tetralogy of fallot, absent pulmonary valve		arr 22q11.21(18844632-21462353)x1	2.6	DiGeorge syndrome	pathogenic
10	single umbilical artery		arr 11q24.1q25(123615329-1349444006)x1	11.3	Jacobsen syndrome	pathogenic
11	endocardial cushion defect, single atrium		arr10q26.13q26.3 (126254468-135430043)x3, arr11q24.1q25(122805910-134944006)x1	9.2; 12.1	Jacobsen syndrome	pathogenic
12	Atria septal defect		arr 10p15.1p12.31(6085312-21544231)x1	15	CACNB2	likely pathogenic
13	ventricular septal defect		arr 5q11.2q12.1(56368573-61428613)x1	5.1		likely pathogenic
14	ventricular septal defect, atrial septal defect		arr21q11.2q21.1(14687571-18341062)x1	3.7	DiGeorge syndrome	pathogenic
15	ventricular septal defect	fetal cystic hygroma	arr22q11.21(21050552-21811991)x1	0.7	DiGeorge syndrome	pathogenic
16	ventricular septal defect		arr22q11.21(20740778-21445064)x1	0.7	DiGeorge syndrome	pathogenic
17	tetralogy of fallot, thymic hypoplasia	Intrauterine growth retardation	arr22q11.21(18895703-21452237)x1	2.6	DiGeorge syndrome	pathogenic
18	pulmonary valve stenosis, aortic coarctation ventricular septal defect		arr11q23.3q25(116728277-134944006)x3; arr22q11.1q11.21(16079545-20306993)x3	18	22q11 duplication syndrome	pathogenic
19	ventricular septal defect, Small left heart	Intrauterine growth retardation	arr5p15.33p15.1(354051-17484038) x1,5q34q35.3(165731079-180705539)x3	17.1; 15.0	Cri du chat syndrome	pathogenic

Table 3 – Genetic detection in different categories of fetuses with congenital heart disease (CHD)

Classification of CHD	Aneuploidy	Abnormality of chromosome structure	CNVs	Other
Single cardiac malformation (n = 181)	40	4	9	128
Multiple cardiac abnormalities (n = 181)	71	6	10	94
Isolated CHD (n = 220)	26	8	14	172
CHD with extracardiac anomaly (n = 142)	85	2	5	50

CNVs: copy-number variations.

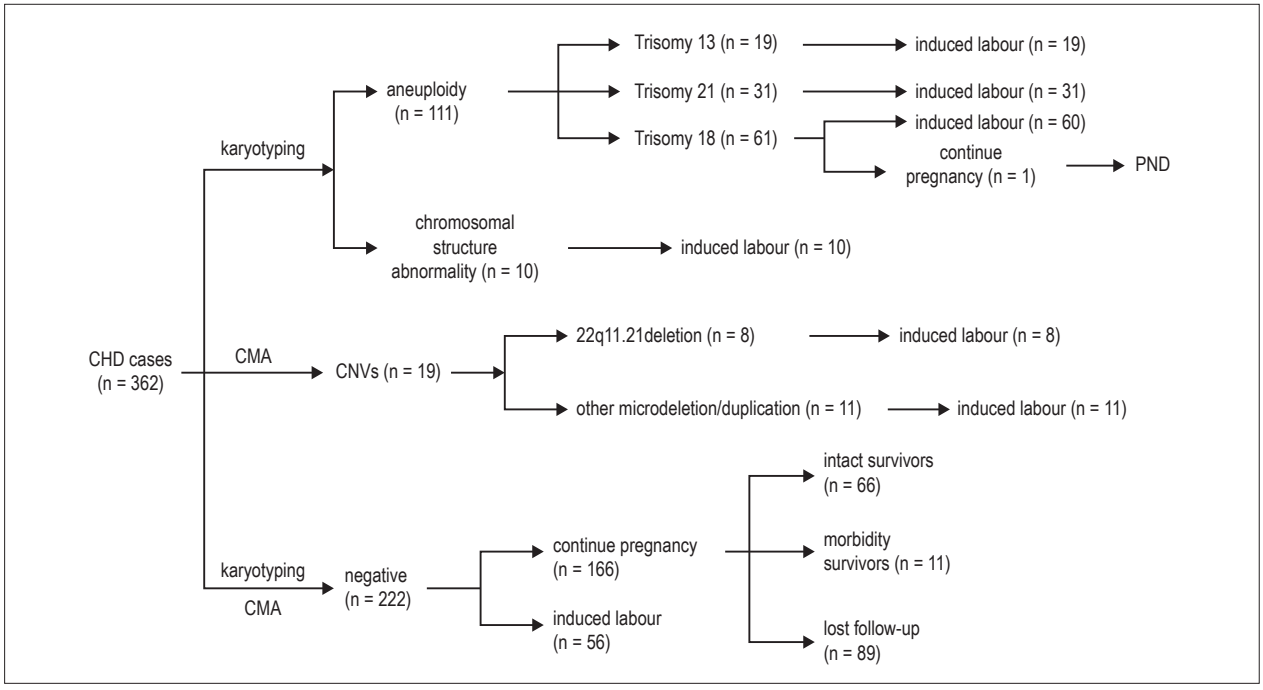

Figure 1 – *The patient pathway in the current study. PND: perinatal deaths. CMA: chromosomal microarray; CNVs: copy-number variations; CHD: congenital heart defects.*

a reasonable outcome after surgery, as well as a good prognosis. In our study, ultrasonic results of some fetuses with CHD caused by aneuploidy only displayed mild cardiac malformations, although complex CHD combined with extra cardiac defects were more common in these cases. Besides, some symptoms such as mental disability cannot be found by prenatal ultrasound. In these cases, the results of genetic testing is of great importance, because this situation is easily ignored by patients and clinicians. However, several negative cases featured complex CHD and extra cardiac defects after karyotype and CMA testing, and these cases provide an important clue for the study of other factors that lead to CHD.

Several limitations should be considered in the study when reviewing these findings. Firstly, a comprehensive analysis of all known CHD associated genes was not carried out. Secondly, the inheritance of CNVs in some cases with likely pathogenicity was not identified.

Conclusion

Karyotyping and CMA analysis was conducted in 362 CHD fetuses, and it was found that 38.7% of CHD fetuses had a positive genetic testing result. Aneuploidy is the major cause of CHD fetuses in our population. The combination of ultrasonic detection and genetic testing can effectively diagnose fetuses with cardiac malformations and extra cardiac defects, thus providing valuable information to the clinician and patients.

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Author contributions

Conception and design of the research: Fu C; Acquisition of data: Meng D, Hu X, Xie B; Analysis and interpretation of the

data: Luo S, Li,Q, Chen Y, He C, Xie B, She S, Li Y; Statistical analysis: Meng D, Chen Y, He C; Obtaining financing: Meng D; Writing of the manuscript: Luo S, Li,Q; Critical revision of the manuscript for intellectual content: She S, Li Y, Fu C.

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 Guangxi Maternal and Child Health Hospital under the protocol number 160220. 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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Predictors of Family Enrollment in a Genetic Cascade Screening Program for Familial Hypercholesterolemia

Pãmela Rodrigues de Souza Silva,[1] Cinthia Elim Jannes,[1] Theo G. M. Oliveira,[1] Luz Marina Gómez Gómez,[1] José E. Krieger,[1] Raul D. Santos,[2] Alexandre Costa Pereira[1]

Laboratório de Genética e Cardiologia Molecular do Instituto do Coração (InCor) da Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP – Brazil

Clínica de Lípides do Instituto do Coração (InCor) da Faculdade de Medicina da Universidade de São Paulo,[2] São Paulo, SP – Brazil

Abstract

Background: Genetic cascade screening is the most cost-effective method for the identification of individuals with familial hypercholesterolemia (FH), but the best strategies for the enrollment of at-risk individuals in a FH screening program are not fully known.

Objective: The aim of this study is to identify the best predictors of familial enrollment into genetic screening, using features derived from tested probands.

Methods: One hundred and eighty-three index-cases (ICs) with a positive genetic result that had relatives screened from 01/2011 to 07/2015 were included. The response variable was the number of relatives for each enrolled IC. All variables in the study were based on ICs' derived clinical and socioeconomical features. The effect size of predictor variables were obtained through a general linear model using a negative binomial regression link function. Significance was considered with a $p < 0.05$.

Results: Mean IC age when enrolling into the program was 50 years old; 78.1% of individuals reported knowledge of relatives with dyslipidemia. Mean baseline LDL-cholesterol level was 316 ± 90 mg/dL. Referral origin through the cascade program website vs. tertiary care, IC LDL-cholesterol and familial history of high LDL-cholesterol levels were independent predictors associated with a higher number of enrolled relatives.

Conclusions: Our data suggest that FH cascade screening programs can predict family enrollment based on IC features. This information may be useful for devising better and more effective screening approaches for at-risk individuals. (Arq Bras Cardiol. 2018; 111(4):578-584)

Keywords: Hypelipoproteinemia Type II/genetics; Mass Screening; Dyslipidemias/genetics; Hypercholesterolemia; Genetic Testing; Cholesterol.

Introduction

Familial hypercholesterolemia (FH) is a genetic disease characterized by elevated blood LDL cholesterol (LDL-C) levels. FH is usually caused by mutations in the gene encoding the LDL receptor (*LDLR*) and less frequently (~5% of cases) by mutations in genes coding for apolipoprotein-B (*APOB*) or proprotein convertase subtilisin/kexin type 9 (*PCSK9*). Individuals carrying these mutations are exposed to high lipid levels and, thus, have a higher risk of developing early atherosclerotic cardiovascular disease and mortality.[1,2]

The worldwide prevalence of heterozygous FH ranges between 1:200 and 1:500 individuals, varying in a few countries.[3,4] FH is an underdiagnosed disease and, therefore, most affected individuals do not have access to proper treatment until later in life.[5]

FH diagnosis usually involves the identification of typical clinical signs of the disease such as high levels of LDL-C (> 190 mg/dL), tissue cholesterol deposition (e.g. tendon xanthomas and corneal arcus when detected in individuals less than 45 years old), a family history of high blood cholesterol and or early atherosclerotic disease.[6]

In many instances, a typical FH index case (IC) is clinically diagnosed after the onset of an atherosclerotic cardiovascular event. Due to its autosomal dominant transmission, FH can and must be diagnosed early in asymptomatic relatives to start LDL-C lowering treatment with the aim of preventing cardiovascular disease onset. Genetic testing is important not only for diagnostic confirmation of index cases and in relatives, but also as a prognostic tool since recent evidence confirmed that the presence of FH-causing mutations implicates in higher cardiovascular risk even in comparison with other hypercholesterolemic individuals.[7,8]

Mailing Address: Pãmela Rodrigues de Souza Silva •
Av. Dr. Enéas de Carvalho Aguiar, 44. Postal Code 05403-900, Cerqueira César, São Paulo, SP – Brazil
E-mail: pam_r_s@usp.br, pam_r_s@hotmail.com
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Currently, cascade genetic screening is the most cost-effective method for FH diagnosis.[9–12] The screening begins with the clinical and genetic diagnosis of an IC, of which all first-degree relatives are screened for the same mutation. After the identification of all affected relatives, the cascade gives sequence to all 2nd-degree relatives, and then successively. Most importantly, the higher the number of screened relatives, the more cost-effective the cascade becomes.[13,14]

Interestingly, despite being recognized as the most cost-effective strategy for population-wide FH identification, little is known about the best strategies for maximizing the enrollment of at-risk individuals in a cascade screening program. One can argue that this information is even more important than devising ways to identify index-cases to be tested from the overall population.. Therefore, the aim of this study is to identify the main predictors of family enrollment into cascade screening using the IC as a starting point.

Methods

The Brazilian FH screening program (HipercolBrasil) is performed by the Laboratory of Genetics and Molecular Cardiology at the Heart Institute (InCor) of the University of São Paulo Medical School Hospital. This study was approved by the institutional ethics committee (CAPPesq 3757/12/013). All participants read and signed an informed consent form authorizing the study.

Participants included in our analysis were previously registered in the HipercolBrasil Program and were referred to the program by institutional physicians or by other collaborators. Individuals that spontaneously contacted the program by phone or website were also included. Once the inclusion criteria were met, participants were referred to molecular genetic testing.

Study population and inclusion criteria

The inclusion criterion for program enrollment was the presence of a baseline LDL-C value ≥ 210 mg/dL. However, some individuals with LDL-C < 210 mg/dL were also enrolled when suggestive signs of FH were detected by the physicians. All genetic positive ICs (individuals in which a pathogenic or likely pathogenic mutations were identified) who authorized the screening of relatives from January 2011 to July 2015 were included in the present study.

Whole blood was collected after a physical exam was performed and a standardized questionnaire was applied by trained personnel from the HipercolBrasil team. In case of a positive genetic result, the IC was contacted and informed about the importance of the genetic results and the possibility of free family screening. After a comprehensive explanation of the disease risks and early diagnosis benefits, the IC was asked to provide information on all at-risk first-degree relatives. These were then contacted by phone and invited to join the cascade program by trained specialized health professionals. The screening in relatives is restricted to the same mutation found in the IC, despite the presence or not of FH clinical features. All relatives also signed the informed consent form and were submitted to the same standardized questionnaire application.

Study variables

Possible predictor variables from ICs were obtained before the genetic test results were available**.** The standardized questionnaire consisted of socioeconomic, clinical and biochemical variables.

Information regarding employment status consisted of three categories: employed (working age, individual currently working); unemployed (working age, individual not currently working) and inactive (students, elderly and/or retired individuals and those with special needs unable to work). Educational level was defined as: illiterate, elementary education, high-school education, and college/university.

IC origin was defined according to whom or from where the patient was referred to the program. ICs could have been referred by physicians from the Lipid Clinic of the Heart Institute (the lipids referral center closely associated with the HipercolBrasil program); from partner centers located at other tertiary care institutions; from private physicians; by the patient itself through the program website (www.hipercolesterolemia.com.br); or by a primary health care unit. Enrollment criteria were the same for all ICs regardless of origin. The participation of other partner centers in the study was approved by the institutional ethics committee (CAAE 00594212.0.0000.0068/nº:1.213.994).

Required clinical information was: occurrence of atherosclerotic or familial history of early atherosclerotic cardiovascular disease and/or altered lipid levels; clinical stigmata such as corneal arcus, xanthelasmas or xanthomas. Biochemical exams were obtained from medical records or from previous exams brought by the patient. The following values were recorded: total cholesterol (TC), LDL-C, HDL-C, triglycerides (TG) and fasting glucose. The Dutch Lipid Clinic Network (DLNC) score and Simon Broome criteria were calculated using the available information at the baseline visit. Whenever possible, the baseline value of LDL-C was used. In case of a patient receiving lipid-lowering treatment with unavailable baseline LDL-C values, the current value was used to calculate the score. Those clinical scores were applied only with the intention of collecting and storing data and were not used as criteria for program enrollment.

Genetic testing

IC samples were sequenced for six FH-related genes: *LDLR*, *APOB*, *PCSK9*, *LDLRAP1*, *LIPA* and *APOE*. Target regions were considered as coding exons plus 10bp of introns up and downstream and captured using a specially designed enrichment reagent. Templates were prepared on Ion One Touch System and sequenced in Ion Torrent PGM® platform, with 32 samples per run in a 316v2 Ion Chip. Bioinformatics analyses were performed in CLC Genomics Workbench 9.5 (QIAGEN) in a custom pipeline. Minimum quality requirements for variant call were: Base quality of PhredQ ≥ 20; Target-region coverage ≥ 10x; Frequency of variant allele ≥ 20% and bidirectional presence of variant allele.

After filtering for a MAF ≤ 0.002 with control populations (NHLBI-ESP6500, AbraOM, ExAC and 1000Genomes), all potential mutations were consulted for previous description

in ClinVar, Human Genome Mutation Database (HGMD), British Heart Foundation and Jojo Genetics databases. Functional impact prediction was performed with SIFT, PROVEAN and PolyPhen-2 and mutations without a previous description should be indicated as damaging in at least two algorithms to be considered as potentially pathogenic. Individuals with negative results were also screened for large insertions and deletions via MLPA (MRC-Holland). Point mutations found in ICs were screened in relatives through Sanger sequencing, and large insertions/deletions via MLPA.

Statistical analysis

The response variable of this study consisted in the number of family members enrolled in the program by each family, starting from a positive IC. The response variable consists of count data, which would suggest the application of a Poisson model. However, as the dependent variable variance was higher than the mean value, the most adequate model in this situation was the negative binomial model, due to data overdispersion (Figure 1). Predictive variables were based on the IC's clinical and socioeconomic characteristics. We initially performed a distribution analysis on the response variable and the model that appropriately fit this variable was one using a negative binomial distribution. Thus, the estimate for predictor variables for the number of enrolled relatives was derived through a general linear model using a negative binomial regression link function. The following variables were included in the initial model: age, family history of high cholesterol levels, DLNC score, Simon Broome Score, baseline lipid-lowering treatment, employment situation, baseline LDL-C or highest level during treatment, educational level and origin. The mean and standard deviation were calculated for continuous variables. Significance was considered at a $p < 0.05$. Statistical analyses were performed with SPSS v19.0 (IBM) and R software (Package gamlss, version 3.3.1).

Results

A total of 183 ICs were analyzed, of which 2316 relatives were contacted and 1605 agreed to enroll in the program (overall enrollment rate of 69.3%). Eighty-seven families were excluded from the study after model adjustment for multiple regression analysis. These were related to 87 ICs that had missing data in at least one of the variables included in the final model. Clinical characteristics of the ICs are shown in Table 1.

Regarding the educational level, 30.6% of ICs had college, 25.1% high-school, 22.4% elementary education and 4.9% were illiterate. The greatest percentage of ICs is currently employed (41.0%). Most of ICs were referred by local physicians (81.4%), followed by 7.7% of patients that reached the program via the website. The other 5% were referred from partner centers located at other tertiary care institutions and 3.3% from private physicians.

Table 2 shows the univariate negative binomial regression calculated for all the variables in the study. Only family history of altered lipid levels and referral of patients via the website were significantly associated with the number of relatives brought into the program.

Table 1 – Clinical characteristics of Index cases

Variables	n	
Age (Mean ± SD)	183	47 ± 18
Male sex (%)	84	45.9
Tendon xanthomas (%)	26	14.2
Corneal Arcus (%)	49	26.8
Early coronary disease (%)*	54	29.5
Family history of early coronary disease (%)†	72	39.3
Family history of increased LDL-C levels(%)‡	98	53.6
Current pharmacological treatment (%)§	145	79.2
DLCN Score (%)		
Definitive	74	40.4
Probable	48	26.2
Possible	33	18.0
Simon Broome (%)		
Definitive	29	15.8
Probable	124	67.8
Baseline TC// mg/dL (Mean ± SD)	104	405 ± 112
TC mg/dL (Mean±SD) highest level during treatment	64	305 ± 124
Baseline LDL-C mg/dL (Mean ± SD)	104	326 ± 111
LDL-C mg/dL (Mean ± SD) highest level during treatment	64	238 ± 122
Baseline HDL-C mg/dL (Mean ± SD)	102	47 ± 15
HDL-C mg/dL (Mean±SD) highest level during treatment	64	43 ± 10
Baseline TG¶ mg/dL (Mean ± SD)	99	144 ± 63
TG mg/dL (Mean ± SD) highest level during treatment	32	132 ± 77

**Coronary disease in men aged < 55 years or women aged < 60 years. † Family history of coronary disease (e.g.. heart attack) in first or second degree relatives (men aged < 55 years and women < 60 years).‡ First or second degree relatives with TC > 260 mg/dl or LDL > 160 mg/dL in children (> 16 years old) or TC > 290 mg/dL or LDL > 190 mg/dL in adults (pre-treatment levels or the highest level during treatment).§ Current use of lipid-lowering drugs (e.g. statins). // TC: total cholesterol; TG: triglycerides. SD:standard deviation; DLCN: Dutch Lipid Clinic Network; HDL-C: high-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.*

Results after model adjustment are outlined in Table 3. Family history of high LDL-C levels was an independent predictor associated with a higher number of enrolled relatives, with an increasing estimate of 1.76-fold when comparing ICs with and without family history of dyslipidemia. IC baseline LDL-Cvalues were also associated with a higher number of enrolled relatives.

The IC referral origin also significantly influenced the number of relatives in the program. When comparing the origin of ICs, for those enrolled via website the expected number of relatives decreased by 0.42-fold when compared to ICs referred from inside a referral center.

Discussion

The present study is, to the best of our knowledge, the first to assess the predictors that might influence enrollment of

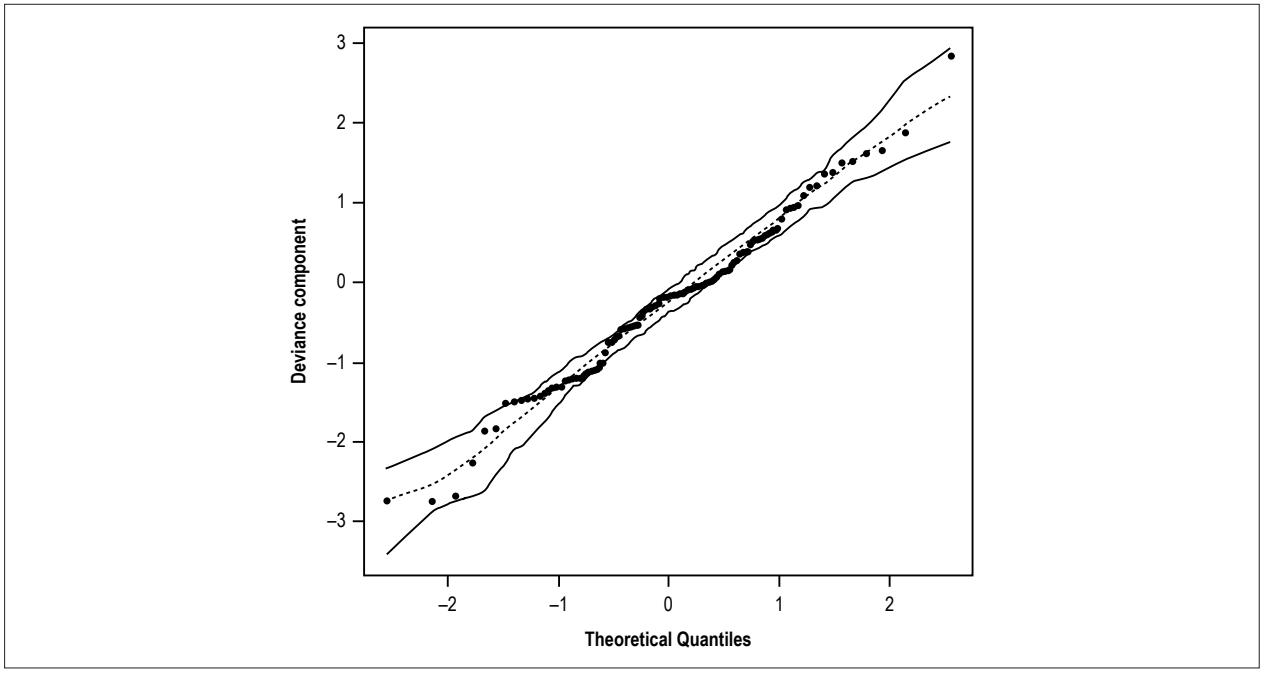

Figure 1 – *QQ Plot for the general linear model using a negative binomial distribution.*

Table 2 – Parameters associated with relatives' inclusion in the cascade screening according to univariate negative binomial regression analysis

Predictors	Estimate	Std. Error	p value*
Age (years)	0.005	0.003	0.141
Early coronary disease†	-0.024	0.143	0.867
DLCN‡ Score (Probable)	0.117	0.415	0.777
DLCN Score (Possible)	-0.158	0.600	0.792
Family history of early coronary disease	0.136	0.171	0.425
Family history of increased LDL-C levels	0.395	0.201	0.048
Educational level (Elementary)	0.460	0.326	0.159
Educational level (High School)	0.355	0.324	0.273
Educational level (College)	0.219	0.320	0.494
Employment Situation (Unemployed)	-0.175	0.247	0.479
Employment Situation (Inactive)	-0.204	0.150	0.174
Origin§ (Rio de Janeiro)	-0.751	0.400	0.060
Origin (website//)	-0.745	0.245	0.002
Current pharmacological treatment	0.179	0.190	0.346
LDL-C	0.001	0.000	0.112

**p value < 0.05. † Coronary disease in men aged < 55 years or women aged < 60 years. ‡ DLCN: Dutch Lipid Clinic Network. § IC origin was defined according to whom or from where the patient was referred to the program. // Website: by the patient itself via the program website. LDL-C: Low-density lipoprotein cholesterol.*

relatives in a genetic FH cascade screening program, considering clinical, demographic and socioeconomic features of ICs as the main source. Currently, for every IC with a pathogenic variant identified by molecular genetic testing, around 69.3% of eligible relatives are enrolled in our cascade screening program. For each positive IC we identified 1.8 affected relatives.[13]

Based on ICs' characteristics, the factor that most influences the inclusion of relatives in the program is a reported family history of dyslipidemia. High levels of LDL-C in ICs also contributed to the enrollment of relatives in the cohort, suggesting that some measure of the IC dyslipidemia severity also modulates the relatives' willingness to enroll in disease screening.

Table 3 – Parameters associated with relatives' inclusion in the cascade screening according to multiple negative binomial regression analysis

Predictors	Estimate	Std. Error	p value*
Origin (website)†	-0.846	0.339	0.012
Family history of increased LDL-C levels	0.565	0.210	0.007
LDL-C	0.002	0.000	0.004

** p value < 0.05. † IC origin was defined according to whom or from where the patient was referred to the program. Website: by the patient itself via the program website. LDL-C: Low-density lipoprotein cholesterol.*

Once enrolled in the program, ICs are provided with systematic recommendations about the importance of family screening, mainly due to the possible identification of at-risk individuals, which makes genetic testing of great importance. Genetic testing not only confirms the ICs' clinical diagnosis, but also elucidates the family history of dyslipidemia and the existence of at-risk relatives.[15]

Relatives frequently underestimate the disease risks and are not aware of their condition, increasing the chance of early atherosclerotic cardiovascular event onset.[16–18] Sometimes, even though embodied with knowledge of the importance of genetic testing, they remain reluctant to participate due to the lack of motivation.[19]

The cascade effectiveness depends on the ICs' agreement to recruit relatives through the program and on the actual enrollment of these relatives, so that the ideal scenario is the enrolment of all eligible individuals.[20,21] To find the best strategy for familial enrollment in a cascade screening program is relevant and impacts the overall cascade's cost-effectiveness. The Dutch FH cohort reported the obstacles in recruiting relatives after 5 years of cascade screening,[22] even with a relatively efficient rate of enrollment. Some of the most important raised points are the social and ethical questions surrounding genetic testing, but also the fact that many participants died before having the chance to enroll in the cascade. Many countries have already implemented this form of detection, revealing its feasibility[9,13,14,22] which is considered the gold-standard method referred by the NICE guidelines.[16]

Recruiting ICs via website was a factor that decreased the chance of familial enrollment when compared to ICs referred from the Lipid Clinic of the Heart Institute, a tertiary referral center. This result is probably related to both the amount of information that ICs receive and the severity of the ICs' condition. Those recruited by specialists of tertiary health centers are more conscious about their risks as well as for their relatives. On the other hand, those recruited via website are only guided by the screening program. Therefore, the amount of information delivered by the screening program only might not be enough for the ICs to understand the importance of family enrollment, suggesting that awareness should be emphasized even after several visits.

Unexpectedly, we did not observe a significant effect of the educational level on family enrollment prediction. This observation deserves further study, since it may suggest new ways for educational and awareness programs to be developed.

One limitation of our study is that it is based on a genetic-screening cascade and that the identified predictors may not apply to biochemical-based cascades, since the genetic cascade is only performed for those individuals with a pathogenic variant of FH.

Conclusions

Early diagnosis through cascade screening is important for the prevention of risk factors, because over time individuals would be diagnosed early in their lives or even in childhood, thus allowing adequate treatment and prevention of additional risks. With cascade screening, the relatives are diagnosed at a younger age, which is the main factor that characterizes the effectiveness of this diagnostic method. We conclude that after four years of screening, family history of dyslipidemia, as well as high LDL-C levels are the factors that most influenced the inclusion of relatives in the genetic cascade. A professional approach certainly plays an important role in family adherence and our results laid the foundations for the planning of specific intervention trials designed to test new approaches for increasing family enrollment.

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Author contributions

Conception and design of the research: Souza Silva PR, Gómez LMG, Krieger JE, Santos RD, Pereira AC; acquisition of data and obtaining financing: Souza Silva PR, Jannes CE, Krieger JE, Santos RD, Pereira AC; analysis and interpretation of the data: Souza Silva PR, Oliveira TGM, Gómez LMG, Santos RD, Pereira AC; statistical analysis: Souza Silva PR, Gómez LMG, Pereira AC; writing of the manuscript: Souza Silva PR, Jannes CE, Oliveira TGM, Santos RD, Pereira AC; critical revision of the manuscript for intellectual contente: Souza Silva PR, Jannes CE, Oliveira TGM, Krieger JE, Pereira AC.

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 Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo under the protocol CAPPesq 3757/12/013. 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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Predictors of Family Recruitment in a Program of Genetic Cascade Screening for Familial Hypercholesterolemia

Maria Cristina de Oliveira Izar and Francisco Antonio Helfenstein Fonseca

Disciplina de Cardiologia - Escola Paulista de Medicina - Universidade Federal de São Paulo, São Paulo, SP – Brazil

Short Editorial regarding the article: Predictors of Family Enrollment in a Genetic Cascade Screening Program for Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a common inherited disease affecting lipid metabolism; it is associated with lifelong exposure to high levels of LDL-cholesterol, and premature atherosclerotic cardiovascular disease. FH imposes an enormous burden on patients and their relatives, due to years of life lost, and particularly, for not being diagnosed as an entity.[1]

In spite of the high LDL-cholesterol and even after an atherosclerotic event, a large proportion of individuals with FH remains undiagnosed.[2,3] Criteria for diagnosing FH are based on clinical findings, family history, LDL-cholesterol levels, and genetic testing (Simon Broome or Dutch Lipid Clinic Network), or on the LDL-cholesterol levels alone (US MED PED).[4] However, FH phenotypes can vary, and the lack of physical signs (15-30% of patients with genetic diagnosis of FH present xanthomas or corneal arcus, and 5% have xanthelasma) can contribute for the underdiagnosis of FH. [5-7]

Genetic testing using a panel that includes FH-causing genes (*LDLR*, *APOB*, *PCSK9*, and *LDLRAP-1*) is the best approach to identify probands.[1,4] When cascade screening is proposed to a family with a confirmed genetic case of FH, the costs for this screening program are much lower and are considered a cost-effective intervention, enabling early diagnosis and treatment of the affected relatives. One problem with cascade screening is how to have a high proportion of relatives adhering to the screening program.[8-11]

Silva-Souza, et al.,[12] in the article entitled *Predictors of Family Recruitment in a Program of Genetic Cascade Screening for Familial Hypercholesterolemia* identified the best predictors of genetic family screening, using characteristics derived from their probands.[12] From January 2011 to July 2015, 183 probands (confirmed for FH by genetic testing) had their 1st degree family members recruited for the cascade program. The response variable was the number of relatives that adhered to the recruitment.[13] Study variables were derived from clinical and socioeconomic characteristics of the index cases. A linear negative binomial regression model was used to test predictors. Reference origin from the *site* of cascade screening vs. tertiary prevention, LDL-cholesterol in the proband, and family history were independent predictors for a higher number of recruited subjects.

There are a number of reasons that would reinforce the need and the importance to adhere to a genetic cascade screening program. The costs are lower than when a proband is diagnosed,[10] it is a predictor of coronary disease,[14] adherence to lipid-lowering drugs can be enhanced, and the treatment can be initiated earlier in life.[14] A structured follow-up of the screened individuals should be performed to assure early and continuous treatment. Most concerns related to lack of adherence to screening are related to patient/relatives education, and physician inertia. Strategies to address these issues and mitigate the burden of atherosclerotic disease in this population should be developed.

Keywords

Hyperlipoproteinemia Type II/genetic; Lipid Metabolism Disorders; Hyperlipoproteinemia/prevention &control; Family Health Strategy

Mailing Address: Maria Cristina de Oliveira Izar •
Rua Loefgren, 1350. Postal Code 04040-001, Vila Clementino, São Paulo, SP – Brazil
E-mail: mcoizar@terra.com.br; mcoizar@cardiol.br

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Independent Predictors of Late Presentation in Patients with ST-Segment Elevation Myocardial Infarction

Juliane Araujo Rodrigues, Karina Melleu, Márcia Moura Schmidt, Carlos Antonio Mascia Gottschall, Maria Antonieta Pereira de Moraes, Alexandre Schaan de Quadros

Instituto de Cardiologia / Fundação Universitária de Cardiologia – IC/FUC, Porto Alegre, RS – Brazil

Abstract

Background: In patients with acute ST-segment elevation myocardial infarction (STEMI), the time elapsed from symptom onset to receiving medical care is one of the main mortality predictors.

Objective: To identify independent predictors of late presentation in patients STEMI representative of daily clinical practice.

Methods: All patients admitted with a diagnosis of STEMI in a reference center between December 2009 and November 2014 were evaluated and prospectively followed during hospitalization and for 30 days after discharge. Late presentation was defined as a time interval > 6 hours from chest pain onset until hospital arrival. Multiple logistic regression analysis was used to identify independent predictors of late presentation. Values of $p < 0.05$ were considered statistically significant.

Results: A total of 1,297 patients were included, with a mean age of 60.7 ± 11.6 years, of which 71% were males, 85% Caucasians, 72% had a mean income lower than five minimum wages and 66% had systemic arterial hypertension. The median time of clinical presentation was 3.00 [1.40-5.48] hours, and approximately one-quarter of the patients had a late presentation, with their mortality being significantly higher. The independent predictors of late presentation were Black ethnicity, low income and diabetes mellitus, and a history of previous heart disease was a protective factor.

Conclusion: Black ethnicity, low income and diabetes mellitus are independent predictors of late presentation in STEMI. The identification of subgroups of patients prone to late presentation may help to stimulate prevention policies for these high-risk individuals. (Arq Bras Cardiol. 2018; 111(4):587-593)

Keywords: ST Elevation Myocardial Infarction; Emergency Medical Services; First Aid; Time Factors.

Introduction

In patients with acute ST-segment elevation myocardial infarction (STEMI), the time interval between symptom onset and hospital arrival (delta T) is one of the most consistent predictors of mortality.[1] Most deaths occur at the start of disease manifestation, and in the 40% to 65% of the cases, death occurs within the first hour, and in 80%, within the first 24 hours.[2] The benefit of myocardial reperfusion is time-dependent, and the earlier the coronary flow is restored, the better the clinical evolution of the patient.[3]

Although many advances have occurred in the last two decades, resulting in an important impact on morbidity and mortality, the postponing of treatment due to the delay in seeking medical attention is still a major problem in daily clinical practice.[4] Evidence in the literature indicates that female gender, marital status, Diabetes Mellitus (DM), Systemic Arterial Hypertension (SAH), atrial fibrillation, and age are predictors of hospital arrival delay.[5-10]

However, there are few contemporary studies evaluating the predictors of late presentation in patients with AMI in the Brazilian setting. The identification of high-risk subgroups of late presentation in the general population could contribute to optimize strategies to reduce the time to access the health care system, with the potential to decrease adverse cardiac outcomes. The aim of this study was to identify predictors of late presentation in patients with STEMI that are representative of daily clinical practice.

Methods

Design and population

All patients with STEMI treated at our institution from December 2009 to November 2014 were consecutively and prospectively included. Patients who arrived at the hospital more than 12 hours after symptom onset, those transferred from another health care service and those who refused to participate in the study were excluded.

Mailing Adress: Alexandre Schaan de Quadros •
Avenida Princesa Isabel, 370. Postal Code 90620-000, Santana, Porto Alegre, RS – Brazil
E-mail: quadros.pesquisa@gmail.com, editoracap-pc@cardiologia.org.br
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The study was carried out in accordance with the Guidelines and Norms Regulating Research Involving Human Subjects and was approved by the Institution's Research Ethics Committee.

Logistics

All patients were interviewed at the time of admission and followed during hospital stay, with clinical, angiographic and laboratory data being collected through a standard questionnaire. The occurrence of cardiovascular events was evaluated by the investigators in up to 30 days after the index event.

Definitions

STEMI was defined as typical chest pain at rest associated with ST-segment elevation of at least 1 mm of two contiguous leads of the frontal plane or 2 mm in the horizontal plane, or typical pain at rest in patients with a new, or presumably new, left bundle-branch block.[11]

Late presentation was defined as a time interval until hospital arrival of more than 6 hours after the onset of the first STEMI related symptom. Previous heart disease was defined as prior STEMI or previous Percutaneous Coronary Intervention (PCI) or myocardial revascularization surgery (CABG).

Major cardiovascular events (MCVE) were defined as a combination of all-cause mortality, new STEMI or stroke.[11] New STEMI was defined as recurrent chest pain, elevation of biological markers after the initial natural curve decline, with ST-segment elevation or new Q waves, according to the universal definition of myocardial infarction. Stroke was defined as a new focal neurological deficit with sudden onset, of presumably cerebrovascular cause, irreversible (or resulting in death) within 24 hours and not caused by another readily identifiable cause. The stroke was classified as ischemic or hemorrhagic.[11]

Patient treatment

The patients were treated according to the institution's routines, and the researchers did not interfere with any of the applied treatments. All patients with STEMI were referred to coronary angiography and primary PCI (PCIp) as reperfusion therapy, when appropriate, as recommended by the guidelines.[12] Our institution is a tertiary referral center in cardiology, and the Hemodynamics department operates 24 hours/day, 7 days a week, performing approximately 3,000 coronary angioplasties/year. The emergency department is open to patients who spontaneously seek the hospital, whereas patients who are transferred from other health institutions in the city, the metropolitan region and the countryside of the state are also accepted. In our study, the decisions regarding patient referral from the emergency service to the Hemodynamic laboratory and the percutaneous therapy were left to the attending physicians. Decisions related to the procedure, such as access route, administration of glycoprotein IIb/IIIa inhibitors, aspiration thrombectomy, direct stenting, post-dilatation, models and number of stents used, were made at the discretion of the operators.

The medications used in the initial care followed an institutional routine: aspirin (300 mg), clopidogrel (300 to 600 mg) and anticoagulant (heparin 70 to 100 U/kg) administered at the emergency department immediately after admission.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 22.0, and the level of significance of $p < 0.05$ was considered for all the tests. The Kolmogorov-Smirnov test was used to evaluate data normality. Continuous variables were expressed as mean and standard deviation for those with normal distribution, or as median and 25-75 percentiles. Categorical variables were described as absolute (n) and relative (%) numbers.

The baseline characteristics of patients with late presentation were compared to those who arrived within the first 6 hours using the t-test for independent samples and chi-square test, as appropriate. Univariate and multivariate analyses were performed using the multiple logistic regression method, with late presentation as the dependent variable, and the variables with a p value ≤ 0.20 in the univariate analysis being included in the multivariate analysis.

The WINPEPI program, version 11.43, was used to calculate the sample size, which was calculated as 1,076 patients considering a statistical power of 90%, significance level of 5%, proportion of late presentation of 40% and odds ratio of 1.5 for the female gender as a risk factor.[13] An addition of 10% was made to control possible losses and refusals, and the final sample size consisted of 1,200 patients.

Results

Between December 2009 and November 2014, 1,297 individuals met the eligibility criteria and were included in the study. For 302 patients (23%), the time of arrival at the hospital since the chest pain onset was > 6 hours, being considered as late presentation according to the criteria defined in the study protocol.

Table 1 shows the baseline characteristics of the population, according to the presence or not of late presentation. The median time of presentation was 3.0 [1.4-5.5] hours, being significantly higher in those considered as late presentation (8.5 [7.0-11.9] hours vs. 2.2 [1.0-3.7] hours). There was no statistically significant difference in relation to the mean age in the two groups. On the other hand, patients with late presentation were more often women of Black ethnicity with low income and lower educational level, when compared to those who arrived within the time window of the first 6 hours from pain onset.

The two groups were overall similar regarding the presence of risk factors for coronary artery disease (CAD), but the percentage of patients with DM was significantly higher among those with late presentation. Regarding the comparisons between pre-hospitalization diagnoses, we observed that patients with late presentation less often had a prior diagnosis of CAD (STEMI or myocardial revascularization) and chronic renal failure, and the frequency of other comorbidities was not statistically different. Regarding the atherosclerotic disease burden, we did not observe statistically significant differences between the groups related to the time of clinical presentation.

Table 1 – Basal characteristics of patients

Characteristic	Total n = 1.297	< 6 hours n = 995	≥ 6 hours n = 302	p Value
Sociodemographic data				
Female gender	29	26	37	0.001
Age	60 .7 ± 11.6	60 ± 11.7	62 ± 11.5	0.82
Black ethnicity	15	13	19	0.009
Income < 5 minimum wages	72	69	82	< 0.001
Schooling ≤ 8 (years)	52	50	60	0.008
Delta T (hours)	3. 00 [1.40-5.48]	2.16 [1.00-3.70]	8.50 [7.00-11.87]	
Risk factors for CAD				
Arterial hypertension	66	65	68	0.37
Active smoking	54	54	56	0.95
Dyslipidemia	37	37	35	0.66
Family history	33	34	33	1.00
Diabetes mellitus	25	23	32	0.001
Previous medical history				
Previous CAD*	29	31	23	0.004
Depression	19	18	22	0.19
Stroke	6.1	5.9	6.6	0.75
Heart failure	5.5	3.2	3.6	0.86
Chronic kidney disease	3.3	6.3	2.7	0.02
Killip III/IV	7	6.9	7.6	0.75

*Statistical tests: t-test, Mann-Whitney and chi-square test. Results expressed in %, mean ± standard deviation, and median and 25-75 percentiles. *Previous CAD, acute myocardial infarction or prior myocardial revascularization. CAD: coronary artery disease.*

Table 2 – Uni- and multivariate analysis of characteristics associated with late presentation

Variables	OR (95%CI)	p value	Adjusted OR (95%CI)	p value
Female gender	1,42 (1,16-1,74)	< 0,001	1,13 (0,90-1,42)	0,28
Age	1,00 (0,99-1,01)	0,99	1,00 (0,99-1,01)	0,99
Black ethnicity	1,41 (1,10-1,79)	0,005	1,43 (1,11-1,84)	0,005
Income < 5 minimum wages	1,81 (1,37-2,40)	< 0,001	1,60 (1,19-2,15)	0,001
Schooling ≤ 8 years	1,33 (1,08-1,65)	0,007	1,05 (0,84-1,31)	0,66
Depression	1,17 (0,92-1,48)	0,19	1,15 (0,90-1,47)	0,25
Diabetes mellitus	1,42 (1,15-1,74)	0,001	1,37 (1,10-1,71)	0,005
Previous CAD *	0,70 (0,55-0,89)	0,004	0,72 (0,55-0,94)	0,02
Heart failure	0,47 (0,24-0,91)	0,02	0,54 (0,26-1,13)	0,10

** Previous CAD, acute myocardial infarction or prior myocardial revascularization. OR: odds ratio; 95% CI: 95% confidence interval; CAD: coronary artery disease.*

Most patients with late presentation had lesions in one vessel (48%), 31% had lesions in two vessels and 19% in three vessels – similar rates to those without late presentation (49%, 31% and 18%, respectively; p = 0.72).

Table 2 shows the odds ratios of the clinical characteristics and late presentation, before and after adjustment by multiple logistic regression analysis. The independent predictors of late presentation were Black ethnicity, income less than five minimum wages and DM, whereas prior CAD was a protective factor.

Figure 1 shows the median time of presentation in the patients' subgroups, according to different combinations of predictors of late presentation, showing a large difference in time regarding a certain combination of predictors. For instance, patients with all predictors of late presentation (Black ethnicity, low-income, DM patients, and no previous cardiovascular disease) had the highest median time of presentation, while those with none of the predictors (Caucasian ethnicity, high income, no DM and previous cardiovascular disease) had the lowest median time of presentation (p < 0.001), as shown in figure 1.

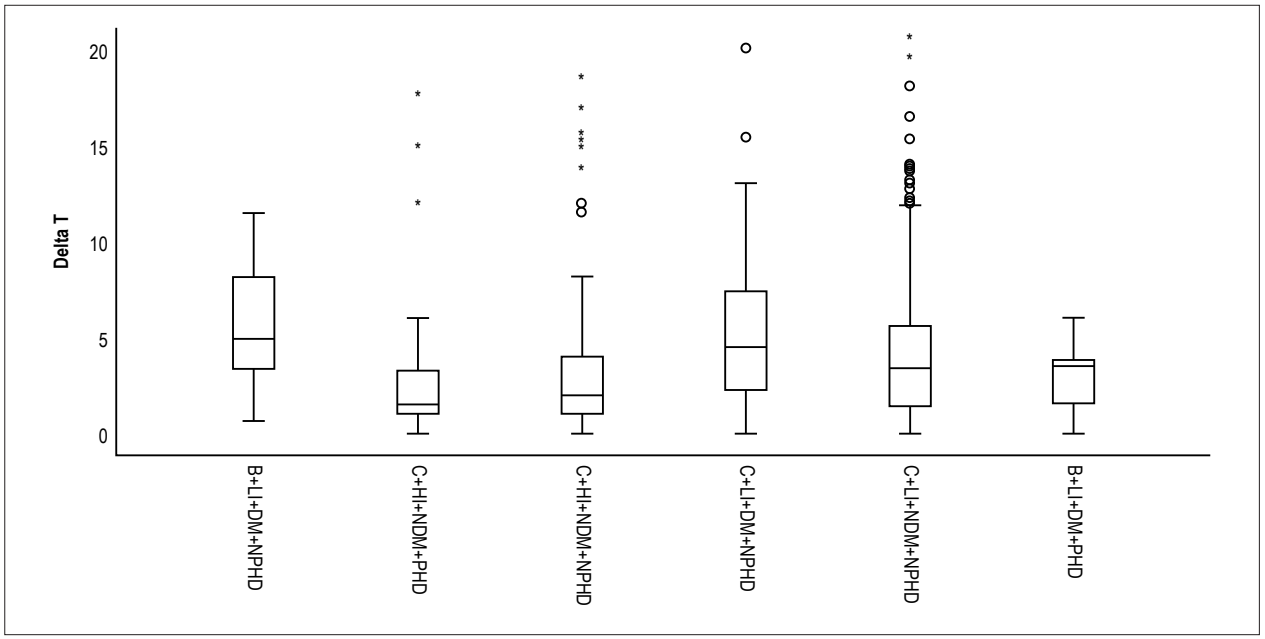

Figure 1 – *Median time of presentation, according to different combinations of late presentation predictors. C: caucasian; B: black; LI: low income (< 5 minimum wages); HI:high income (= 5 minimum wages); DM: diabetes mellitus; NDM: does not have diabetes mellitus; PHD: previous heart disease; NPC: does not have previous heart disease.*

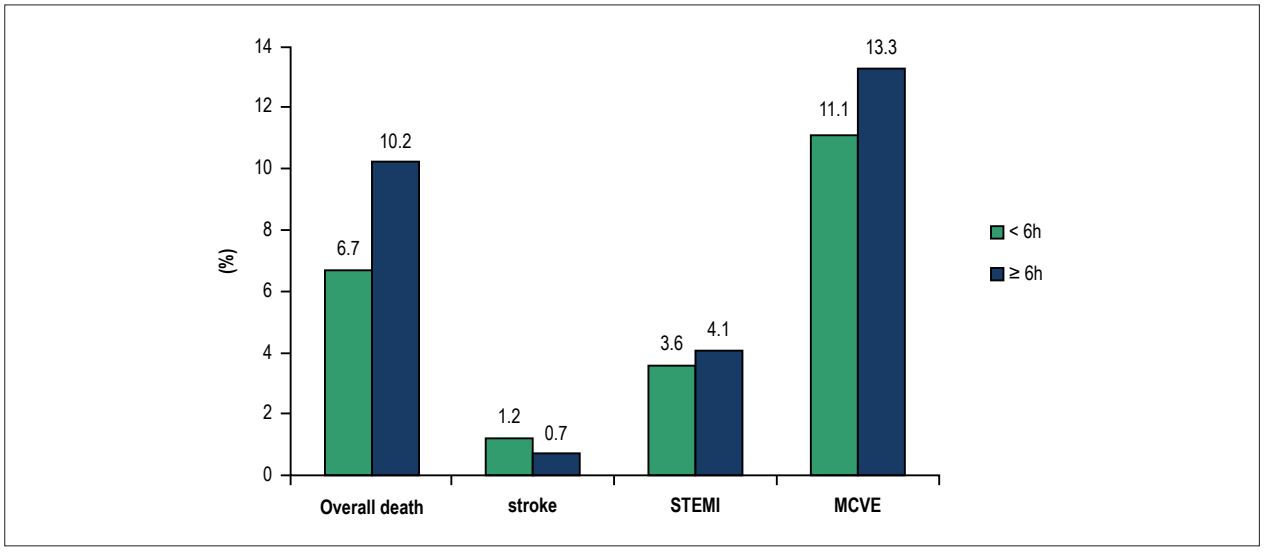

Figure 2 – *Clinical outcomes in 30 days. STEMI: acute ST-segment elevation myocardial infarction; MCVE: major cardiovascular events.*

Figure 2 shows the rates of cardiovascular events in 30 days in patients with late presentation or without. Patients with late presentation had significantly higher mortality rates ($p < 0.05$), and comparisons between groups, considering the occurrence of other clinical outcomes, did not show statistically significant differences.

Discussion

This study showed that the main predictors of hospital arrival delay in patients with STEMI, treated at a referral hospital in Cardiology in the Southern Region of Brazil, were Black ethnicity, low income and DM, whereas the presence of prior heart disease was associated with earlier arrival. Individuals with all predictors of late presentation had mean time of hospital arrival more than two-fold higher than those who had none of these characteristics. These findings are important, since the time from symptom onset to hospital arrival is one of the main determinants of mortality in STEMI,[3] as also demonstrated in our study.

Black ethnicity was one of the independent predictors of late presentation in patients with STEMI in the present study.

This finding is compatible with data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation) registry, which showed that Caucasians arrive earlier than Blacks while studying a population of more than 100,000 patients (Odds Ratio – OR -2.2; 95% Confidence Interval: 95%CI -4.2 - -0.3; p = 0.03).[14] On the other hand, a large study involving more than 43,000 consecutive patients with STEMI from the ACTION-GWTG database showed that there is no significant difference regarding time of arrival between Black and Caucasian patients.[15] Racial differences could be explained by genetic or socioenvironmental characteristics, and we are unaware of studies that have showed differences in pain threshold according to ethnicity. On the other hand, individuals of Black ethnicity in Brazil show unfavorable socioeconomic and cultural status when compared to those of White ethnicity, which could explain our findings.

From this perspective, low-wage income was also identified as an independent predictor of late presentation in our study. Nguyen et al.[8] performed a systematic review that also showed that patients with low socioeconomic status seek medical attention later.[8] Low income may be associated with the patient's recognition of their symptoms and pathology, inferring that people with better level of schooling seek emergency services earlier.[8] On the other hand, Qian et al.[1] analyzed 100 patients with STEMI in China, with no association of low wage income with late presentation.[1]

In our study, the diagnosis of DM was also an independent predictor of late presentation, which is compatible with the evidence available in the literature.[16-21] Patients with DM more frequently have silent ischemia, which may be explained by the presence of diabetic neuropathy and a higher pain threshold.

Previous heart disease was considered a protective factor for late presentation, and the association between this characteristic and the time of presentation varied according to the studies. Kuno et al.[22] demonstrated that patients who had been previously submitted to a percutaneous coronary intervention procedure had a shorter time of presentation.[22] In a cross-sectional study that included 335 patients and considered late presentation arriving at the hospital within 12 hours of pain onset, previous STEMI and revascularization did not show a statistically significant association with time of presentation.[23] Our study did not include analyses of the associated mechanisms between the presence of predictors and the occurrence of late presentation, but it could be speculated that patients who had previous cardiac events or were submitted to myocardial revascularization procedures would be more familiarized and conscious about the disease and the need to seek medical attention quickly.

Women showed significantly longer time until hospital arrival than men, but female gender did not remain an independent predictor of late presentation in the multivariate analysis. The association between female gender and hospital arrival delay after chest pain onset has also been reported in other studies, and it has been found that women more often have atypical symptoms than men.[24-26]

Limitations

In this study, we did not have available information regarding the distance between the patients and the hospital when they had the chest pain onset, a fact that may have an influence on hospital arrival delay. However, most of the patients who come spontaneously to our institution are city residents. Because it is located downtown, travel time does not exceed 30 minutes in most cases. It is important to emphasize that patients transferred from other hospitals and health institutions were excluded from our study, since the objective was to analyze the factors that influence spontaneous delay in search for medical care of patients with infarction, and not to analyze factors that have an impact on medical transfer time.

We considered analyzing the association between the distance from the patients' home to our institution, but many patients were not at home at the time of pain onset, but at work or another location, and therefore this analysis was not included in the present report.

We did not have available ventricular function information from all patients, because left ventriculography is not routinely performed during catheterization and primary percutaneous coronary intervention (pPCI) to minimize contrast volume. However, the percentage of patients with previous CHF who presented with Killip III/IV class at the time of STEMI was similar, suggesting that left ventricular function in both groups was not significantly different. This was a single-center study in a large tertiary cardiology hospital, and the results shown herein may not be valid for populations that are significantly different from ours.

Conclusions

The independent predictors for late presentation to the hospital in patients with acute ST-segment elevation myocardial infarction were Black ethnicity, low-income and DM, whereas a history of previous heart disease was a protective factor. Approximately one-fourth of the patients in this sample were late arriving at the hospital, and their mortality rate was significantly higher than those who arrived early. Patients who had all of the characteristics associated with late presentation showed a two-fold delay related to hospital arrival when compared to those without these characteristics, which illustrates the potential opportunity to decrease the mean time of arrival if public health interventions focused on these high-risk subgroups are carried out.

Author contributions

Conception and design of the research: Rodrigues JA, Quadros AS; Acquisition of data: Melleu K; Analysis and interpretation of the data: Rodrigues JA, Schmidt MM, Quadros AS; Statistical analysis: Rodrigues JA, Schmidt MM; Writing of the manuscript: Rodrigues JA; Critical revision of the manuscript for intellectual content: Gottschall CAM, Moraes MAP, Quadros AS.

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 Instituto de Cardiologia do Rio Grande do Sul under the protocol number 466/12. 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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The Importance of the Prehospital Phase in ST Elevation Myocardial Infarction

Gláucia Maria Moraes de Oliveira and Paolo Blanco Villela

Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ – Brazil

Short Editorial regarding the article: Independent Predictors of Late Presentation in Patients with ST-Segment Elevation Myocardial Infarction

Notwithstanding the decline which has been observed in recent years, circulatory diseases continue to be the leading cause of death in Brazil.[1] In spite of recent advances in clinical and interventional treatment,[2,3] ischemic heart disease (IHD) was responsible for 116,333 deaths in 2016, of which 80% were due to acute manifestations, principally in the form of acute myocardial infarction (AMI).[4]

In treating AMI patients, especially those with ST-segment elevation, the pre-hospital phase of care plays a crucial role in short- and long-term prognosis. Two data related to this phase deserve our attention. First, we may observe delays in reaching healthcare services. In 80% of cases, these delays last for more than two hours starting from the moment symptoms begin to manifest.[2,3] Second, it stands out that 50% of deaths resulting from AMI were recorded precisely during the pre-hospital phase.[2,3]

Whether these delays in reaching pre-hospital care are predominantly patient-related, including, among other factors, difficulties in recognizing and interpreting symptoms owing to socioeconomic status and/or cultural factors, or whether they are associated with a lack of efficiency within the healthcare system, for example in transporting patients from the place where symptoms onset to the final destination, i.e. the hospital, has yet to be established in the literature.[4] It is also important to highlight that a recent study indicated that there are sex-specific differences, with greater delays being observed in women, mainly owing to atypical symptoms which lead to delays in the decision to seek healthcare.[5]

Several factors have been associated with delays during the pre-hospital phase, including non-white ethnicity; low socioeconomic status; cultural factors; previous history of angina, diabetes, or hypertension; sociodemographic and situational factors, for example, distance to treatment centers or medical consultation conducted by spouses or relatives; lack of knowledge regarding the meaning of symptoms; anxiety caused by symptoms; access to public and private healthcare systems; the time of day/night when symptoms onset; previous infarction, and associated symptoms, such as profuse sweating, arterial hypotension, and intensity of precordial pain severity.[6-8]

In Brazil, Rodrigues et al. published a study on predictors of late presentation in 1,297 patients with AMI in a referral center in the country's South Region, which is able to perform primary angioplasty 24 hours a day, seven days a week.[9] Approximately 25% (n = 302) of the total patients attended between December 2009 and November 2014 presented a delay of more than six hours, with a significantly higher mortality rate. The independent predictors of late presentation were: black ethnicity, low income level (less than five times minimum wage), and diabetes mellitus. The following variables lost statistical significance after adjusting for multiple logistic regression analysis: female sex, less than eight years of schooling, and occurrence of chronic renal failure. Patients with all of the independent predictors of late presentation took twice as long to reach the hospital as other patients. History of previous heart disease, AMI, or myocardial revascularization were protective factors,[9] likely owing to the early recognition of a new event and, thus, to reduced delays in seeking medical treatment.

Unfortunately, the authors of this study did not record the distance between the place where symptoms onset and the referral center; they also excluded transfer patients in order to evaluate spontaneous demand.[9] These two factors also influence mortality related to the pre-hospital phase, even though they are dependent on the healthcare system. On the other hand, they also did not analyze the following confounding factors which are related both to distance between place of symptoms onset and referral center and to transfer patients: ventricular function, time taken to implement mechanical or drug reperfusion therapy, reperfusion therapy success rate, associated procedures, and implementation of adjuvant therapy recommended in the guidelines.[2,3]

It is also noteworthy that overall mortality differed significantly between the two groups studied, there being no differences observed regarding subgroups, even with major cardiovascular events. This leads us to suppose that other factors that were not analyzed influenced 30-day mortality rate, for instance, mortality related to the performance of highly complex procedures.

One recent study suggests that higher mortality in women due to delays during the pre-hospital phase may be due to the fact that women appear to be more vulnerable to prolonged untreated ischemia.[10] The longest delays in this study were related to the healthcare system. The authors stress that

Keywords

Cardiovascular Diseases/mortality; Epidemiology; Emergency Medical Services; Healthcare Inequality; Patient Acceptance of Healthcare; Patient Transportation

Mailing Address: Gláucia Maria Moraes de Oliveira •
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – 8°. andar - Sala 6, UFRJ. Postal Code 21941-913, Cidade Universitária, RJ – Brazil
E-mail: glauciam@cardiol.br, glauciamoraesoliveira@gmail.com

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mortality was even higher in those who arrived at the hospital with more than twelve hours' delay, as they did not receive any form of reperfusion therapy. In the study carried out by Rodrigues et al., these patients were excluded, thus making it impossible to establish a comparison.[9]

Cultural differences regarding attitudes toward AMI symptoms are also relevant patient-dependent factors. A recent study carried out in Japan showed that patients who were men, were elderly, had lower levels of schooling and had lower self-confidence regarding their understanding of AMI would present delays in seeking medical treatment.[11] These patient-related factors were also absent from Rodrigues et al.[9]

It is important to highlight that the results of the study carried out by Rodrigues et al. come from a single center whose conditions are quite rare in Brazil, which demonstrates that the continuous availability of mechanical reperfusion therapy was not sufficient to reduce the 30-day AMI mortality rate of about 10% in patients who arrived at the hospital with more than six hours' delay following onset of symptoms. This is an additional conclusion to the data presented by the authors.

It is necessary to invest not only in the availability of excellent mechanical reperfusion therapy, but also in equal access to healthcare systems, both by improving the population's socio-economic and cultural conditions and by implementing thrombolytic therapy close to the place where the patient is located during the onset of symptoms or in pre-hospital transport. Only then will we be able to make the mortality rates we observe in our clinical practice match the ones described in the clinical trials of the guidelines.

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Factors Associated with Inadequate Management of Antiplatelet Agents in Perioperative Period of Non-Cardiac Surgeries

Juliana Maria Dantas Mendonça Borges,[1,2] Pamella de Assis Almeida,[1] Mariana Martins Gonzaga do Nascimento,[3] José Augusto Soares Barreto Filho,[1,4,5] Mario Borges Rosa,[3] Antonio Carlos Sobral Sousa[1,4,5]

Universidade Federal de Sergipe,[1] Aracaju, SE – Brazil

Universidade Tiradentes,[2] Aracaju, SE - Brazil

Instituto Para Práticas Seguras no Uso de Medicamentos,[3] Belo Horizonte, MG – Brazil

Centro de Ensino e Pesquisa da Fundação São Lucas,[4] Aracaju, SE – Brazil

Departamento de Medicina da Universidade Federal de Sergipe (UFS),[5] Aracaju, SE - Brazil

Abstract

Background: The current guidelines dispose recommendations to manage antiplatelet agents in the perioperative period; however, the daily medical practices lack standardization.

Objectives: To asses factors associated with inadequate management of antiplatelet agents in the perioperative period of non-cardiac surgeries.

Methods: Cross-sectional Study conducted in hospital from October 2014 to October 2016. The study dependent variable was a therapy that did not comply with the recommendations in the Brazilian Association of Cardiology (SBC) guidelines. The independent variables included some characteristics, the people in charge of the management and causes of lack of adherence to those guidelines. Variables were included in the multivariate model. Analysis was based on the odds ratio (OR) value and its respective 95% confidence interval (CI) estimated by means of logistic regression with 5% significance level.

Results: The sample was composed of adult patients submitted to non-cardiac surgeries and who would use acetylsalicylic acid (aspirin) or clopidogrel (n = 161). The management failed to comply with the recommendations in the guidelines in 80.75% of the sample. Surgeons had the highest number of noncomplying orientations (n = 63). After multivariate analysis it was observed that patients with a higher level of schooling (OR = 0.24; CI95% 0.07-0.78) and those with a previous episode of acute myocardial infarction (AMI) (OR = 0.18; CI95% 0.04-0.95) had a higher probability of using a therapy complying with the guidelines.

Conclusion: Positive association between patients' schooling level, or those with a history of previous AMI, with management of the use of aspirin and clopidogrel in the perioperative period of non-cardiac surgeries. However, diverging conducts stress the need of having internal protocol defined. (Arq Bras Cardiol. 2018; 111(4):596-604)

Keywords: Surgery/perioperative care; Intraoperative Care; Platelet Aggregation; Adults; Myocardial Infarction; Educational Status.

Introduction

A study published in 20018 by the World Health Organization (WHO) informed that in 2012 313 million surgeries had been performed worldwide, thus evidencing a 38% increase in eight years. During that period in Brazil approximately 6 thousand surgeries per 100.000 inhabitants were performed, summing up about 10 to 13 million surgical procedures in 2012,[1] and the rate of non-cardiac surgeries was estimated at 3 million per year.[2] These figures still are bound to increase due to several factors, such as the growing and ageing population.[3]

In 2014, Botto et al.,[4] stated that cardiac complications are the main cause of post-operation deaths of patients submitted to non-cardiac surgeries. These are alarming data once in the world over 10 million adults every year have at least one cardiac complication in the first 30 days following a non-cardiac surgical procedure.[4,5] Among the cardiac complications arising from these types of procedure the most common is acute myocardial infarction (AMI),[4,6,7] which is also associated with long-term mortality, although often enough it is detected earlier during clinical screening.[8]

Due to the key role performed by platelets in pathogenesis of atherothrombotic events, using antiplatelet agents is of the essence for primary and secondary prevention of cardiovascular events.[9] However, although the use of antiplatelet agents has increased cardiovascular safety of many

Mailing Address: Juliana Maria Dantas Mendonça •
Rua Poeta Vinicius de Moraes, 60, apt 704. Postal Code 49037-490, Aracaju, SE – Brazil
E-mail: jumariapharma@gmail.com, judantas20@hotmail.com
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patients,[10] when they need a non-cardiac surgery, surgeons and anesthesiologists frequently have to face the decision of whether to interrupt or not antiplatelet therapy in those patients during the perioperative period considering the risks of the occurrence of thrombi or bleedings, respectively.[11-13]

Thus, in order to help physicians make decisions in the perioperative period referring to antiplatelet therapy, the recommendations of the American association of thorax physicians (2012) and of the Brazilian (2013), European and American cardiology societies of cardiology (2014) are supposed to serve as basis of clinical evidence to help perioperative conducts and, consequently, to guarantee more safety to patients.[5,14-16]

In this sense, this study is an attempt to assess the factors associated with inadequate management of antiplatelet agents in the perioperative period of non-cardiac surgeries based on the existing Brazilian guidelines.

Methods

Study outline, sample and data collection

This is a cross-sectional study conducted in a high-complexity hospital, which is reference in cardiology and has internal hospital accreditation. That hospital unit contains 150 beds and, during the study period, 650 non-cardiac surgeries per month were performed on average.

In the study patients submitted to non-cardiac surgeries and who previously and regularly used at least one platelet agent for primary or secondary prevention were included, which composed a sample obtained by convenience instead of probabilistic, composed of adult patients (18 years old or older).

Data were collected from October 2014 to October 2016 by means of interviews with patients, or with their companions, before they were submitted to surgical procedures, using a questionnaire specific to obtain data. The interviews were held by a team of professionals and academics previously trained who attended the Departments of Pharmacy and Medicine of a public university and the Department of Pharmacy of a private university.

Variables and data analysis

Descriptive analysis of the variables was done by determining absolute and relative frequencies for qualitative variables, and the means for quantitative variables. In the univariate and multivariate analyses the preoperative therapy with aspirin or clopidogrel was defined the dependent variable, which is inadequate according to the SBC recommendations (yes or no), once the study was conducted in Brazil. For this variable firstly was determined whether the patients had used antiplatelet agent for primary and secondary prevention, and then whether the recommendations disposed in the SBC guidelines referring to antiplatelet agents and anticoagulants in cardiology had been met, those adopted by the institution as reference at the time of the study, as presented in Box 1.

Independent variables are described in Table 1. Patients were deemed to have a history of revascularization procedure if they had already been submitted to percutaneous coronary intervention or surgical revascularization. Patients were deemed dyslipidemic when they used medicines such as statins, resins, ezetimibe or fibrates, which the V Brazilian Guideline of Dyslipidemia and Atherosclerosis Prevention (2013) deems treatments of choice for dyslipidemia,[17] additionally, patients were deemed hypertensive when at their medical records there was this information and because they used anti-hypertensive medicines, as described in the 7th Brazilian Guideline of Arterial Hypertension (2016).[18] For the Body Mass Index (BMI), patients who had 18.5- 24.9 Kg/m^2 BMI[19] were considered having normal weight. As to a surgery' intrinsic risk of cardiac complications, the 3rd SBC Guideline of Perioperative Cardiovascular Assessment[20] was adopted as reference[20].

We conducted univariate analyses using the Pearson chi-square test or Fisher exact test with expected frequency equal or lower than five. All variables were included in the multivariate model which, on its turn, was done with logistic regression. Multivariate analysis was based on the odds ratio (OR) value and its respective 95% confidence interval (CI$^{95\%}$), estimated by logistic regression. A 5% level of statistical significance was the criterion adopted to identify characteristics independently associated with the dependent variable. The likelihood-ratio test was used to compare the models, and the final models' properness was assessed with the Hosmer-Lemeshow test. All statistical analyses were done with the Stata® statistic software package, version 12.

Ethical aspects

This investigation was registered in the National Council of Ethics in Research – CONEP with the Certificate of Submission for Ethical Appreciation – CAAE no. 33899914.2.0000.5546,

Box 01 – SBC recommendation (2013) as to using aspirin and clopidogrel in the preoperative period of non-cardiac surgery

Indications	References
Patients using aspirin for secondary prevention in schedule of non-cardiac operations should keep using aspiring in a smaller dose (75 to 100 mg/day), except in neurosurgeries and transurethral resection of the prostate.	25,28
Patients using aspirin for primary prevention should suspend it 7 days before the procedure.	
For patients using clopidogrel as primary prevention, its use should be suspended 5 days before the surgical procedure.	26
For patients using clopidogrel for secondary prevention, the bleeding risk should be considered. When the bleeding risk is moderate or high, clopidogrel should be suspended 5 days before the procedure, but when the bleeding risk is low, the antiplatelet agent should be maintained.	29

ASPIRIN: acetylsalicylic acid.

Table 1 – Sample characteristics (n = 161). High-complexity hospital, Aracaju, Sergipe, Brazil, 2014-2016

Characteristics	Total n(%)	Noncomplying with recommendations*		Value p§
		No(%)	Yes (%)	
Gender				
Male	73(45.3)	23.3	76.7	
Female	88(54.7)	15.9	84.1	0.237
Age				
40-69 years	85(52.8)	15.3	84.7	0.178
70-99 years	76(47.2)	23.7	76.3	
Schooling				
Up to high-school	65(40.4)	12.3	87.7	
Primary School – complete – incomplete	40(24.8)	25.0	75.0	0.180
University –complete or incomplete	56(34.8)	23.2	76.8	
Married				
No	63(39.1)	20.6	79.4	0.722
Yes	98(60.9)	18.4	81.6	
Works				
No	126(78.3)	23.0	77.0	0.022
Yes	35(21.7)	5.7	94.3	
Has children				
No	10(6.2)	10.0	90.0	0.443
Yes	151(93.8)	19.9	80.1	
Body Mass Index†				
Up to 29	115(71.3)	20.2	79.8	0.687
30 or more	46(28.7)	17.4	82.6	
Number of diseases‡				
0-2	120(74.5)	20.8	79.2	0.385
3-4	41(25.5)	14.6	85.4	
Previous revascularization procedure#				
No	124(77.0)	19.4	80.6	0.953
Yes	37(23.0)	18.9	81.1	
Acute Myocardial Infarct				
No	132(82.0)	15.9	84.1	0.022
Yes	29(18.0)	34.5	65.5	
Stroke				
No	152(94.4)	18.4	81.6	0.270
Yes	9(5.6)	33.3	66.7	
Dyslipidemia				
No	94(58.4)	25.5	74.5	0.017
Yes	67(41.6)	10.5	89.5	
Systemic Arterial Hypertension				
No	43(26.7)	16.3	83.7	0.563
Yes	118(73.3)	20.3	79.7	

Continuation

Time using aspirin or clopidogrel				
1-4 years	72(44.7)	19.4	80.6	0.956
5 years or more	89(55.3)	19.1	80.9	
Surgeon expertise				
General or digestive system	67(41.6)	80.6	19.4	0.770
Urologist	11(6.8)	16.1	83.2	
Orthopedist	24(14.9)	83.3	16.7	
Other	59(36.7)	78.0	22.0	

ASPIRIN: acetylsalicylic acid; SBC: Brazilian Society of Cardiology; (*) Therapy according or noncomplying with the use of aspirin or clopidogrel therapy in the preoperative period, according to the SBC; (†) Body Mass Index = (weight in Kg) : (height in meters²); (‡) Number of diseases documented in the medical records and confirmed by patients on the date they were admitted for surgery; (#) history of percutaneous coronary intervention or surgical revascularization; (§) Obtained with Pearson chi-square test, significant when < 0.05.

in compliance with the norms for scientific research involving human beings in Brazil. All individuals included in the study agreed to participate in the research by signing a free and informed consent (FIC).

Results

Out of the total number of patients interviewed (n = 1,200), 161 were included in this study because they reported using at least one antiplatelet agent: Aspirin (156) and clopidogrel (5). Among those, 48 used antiplatelet agent for primary prevention (29.8%) and 113 for secondary prevention (70.2%). The patients were 69.5 years old on average (minimum = 42; maximum = 99; SD = ±10.5) and the majority was female (54.7%), in addition to having an average AMI of 27.8 kg/m² (minimum = 17.3; maximum = 46.3; SD = ±5.5) and number of diseases 1.8 on average (minimum = 0; maximum = 4; SD = ±0.9). The majority had schooling up to high-school (40.4%) and the mean time of daily use of aspirin and/or Clopidogrel was 6.3 years (minimum = 1; maximum = 40; SD = ±6.8). Table 1 shows the characteristics of the sample in detail:

Out of the whole sample, 80.7% of the sample failed to comply with the SBC cardiology guidelines. As to types of noncomplying therapies, most of them occurred in cases where platelet agents was suspended as recommended, but within a longer period of time to that recommended in the guidelines, as detailed in Table 2.

As to the people in charge of rendering orientation for the management of antiplatelet agents, 85.1 % of the surgeons who rendered instructions to patients, in addition to 63.2% of the cardiologists, did it in disagreement with the recommendations in the SBC guidelines as to the use of aspirin or clopidogrel in the preoperative period of non-cardiac surgeries. As to the cardiac risks in surgical procedures to which the patients were submitted, according to the SBC[20] guidelines for perioperative cardiovascular assessment, the majority (58%) of the procedures was classified as low cardiac risk (<1%), and none was classified high risk in this study.

Table 3 presents the results of multivariate analyses of the characteristics associated to the therapy lacking compliance with the recommendations for using aspirin or clopidogrel in preoperative period according to the SBC. After multiple adjustments, schooling up to university, complete or incomplete (OR 0.24; CI95% 0.7-0.78), and previous history of AMI (OR 0.18: CI95% 0.04-0.95) remained independently associated with the therapy lacking compliance with the SBC. .

Discussion

The rather expressive frequency of therapies with aspirin and clopidogrel lacking compliance with the SBC guidelines' recommendations (2013) in the perioperative period of non-cardiac surgeries was not observed in other studies once, as far as we are aware, this is the first one conducted in Brazil on this subject. However, the lack of organization of standardization of medical conducts in the management of antiplatelet agents is well known, i.e., there are groups of physicians who advocate the suspension of those medicines before surgeries in order to avoid bleedings, while others advocate their maintenance in order to avoid thrombotic events.[11-13,21-24]

The Brazilian guidelines say that in cases where aspirin or clopidogrel is used for primary prevention of cardiovascular diseases, they should be suspended, respectively seven and five days before a non-cardiac surgical procedure. However, in this study, the majority of the noncompliance with the Brazilian guidelines happened due to their suspension for periods longer than those disposed for aspirin and clopidogrel. This conduct can potentially expose patients to cardiac complications in the perioperative period once the literature evidences that those medicines, after being suspended for 8-10 days, lose their antiplatelet agent's effect.[25,26] Cases where the conduct of suspending the drug was correct were also observed, but for a period shorter than that recommended in the guidelines and, so, the goal of losing the pharmacological effect of the antiplatelet agent is never reached once that effect at platelet level is irreversible, and the time they remain active is approximately 10 days.[26]

Therefore, although the conduct of suspending the antiplatelet agent was correct, it is possible to infer that the suspension of the antiplatelet agent for longer or shorter periods than those recommended by the guidelines occurred because the hospital does not have its own assistance protocols focused

Table 2 – Results of noncompliance with the SBC recommendations for using aspirin and clopidogrel in preoperative periods of non-cardiac surgeries (n = 161) in high-complexity Hospital, Aracaju, Sergipe, Brazil, 2014-2016

Therapy*		Frequency n(%)
Compliance		31(19.3)
Non compliance	It was not suspend; it was supposed to be suspended	30(18.6)
	It was suspended; it was not supposed to be suspended	37(23.0)
	It was suspended; it was supposed to be suspended, but for a period longer than recommended	42(26.1)
	It was suspended; it was supposed to be suspended, but for a period lower than recommended	21(13.0)
Total		161(100)

ASPIRIN: acetylsalicylic acid; SBC: Brazilian Society of Cardiology; (*) Therapy according or noncomplying with the use recommended by the SBC for using aspirin or clopidogrel in preoperative periods according to the SBC.

on this matter, and, as such, diverging conducts strengthen the need of defining internal conducts, more divulgation of the guidelines used as reference at that institution, and continued education. Double checking conducts according to internal protocols of an institution can also be an important choice to ensure patients' safety.

Other important datum in this study, and one that draws attention, is that a significant number of noncomplying therapies occurred resulting from having patients oriented to suspend antiplatelet agents when the Brazilian guidelines state the opposite for cases where patients use aspirin and clopidogrel for secondary prevention of cardiovascular diseases,[24,27] except for clopidogrel, which depends of the procedure's bleeding risk;[28] but in this case, all 5 patients who had been using this drug were submitted to low bleeding-risk surgeries. According to some authors, an increased bleeding risk related to the effect of the antiplatelet action of those drugs is well known,[29,30] mainly in the ageing population,[31] which stands for the majority in this study.

However, other studies, as much as the SBC orientations (2013), except for neurosurgeries and transurethral resection of the prostate, advocate that the benefits of secondary prevention substantially exceeds the bleeding risks those drugs may cause[13,24,27] once the AMI is the main cause of death in old patients after non-cardiac surgeries.[32]

A successful surgery depends on the aptitude and technical skills of the surgeon, on the indication and previous preparation, on the perioperative period management and care dimensioning the risks, on preventing and treating complications.[33] In other words, a surgeon operates trying to avoid surgical complications during the procedure as much as possible, and among them one can be highlighted among general complications, whose universal example is hemorrhage.[34] Those statements can justify the results of this study because the medical expertise representing the majority of the results noncomplying with the guidelines was surgery.

As to the association with patients' characteristics, it was observed that patients with more schooling and those who at some moment had an AMI episode have more chance of using antiplatelet therapy in the preoperative period of non-cardiac surgeries according to the SBC (2013). No studies with this type of association were found in the literature.

However, on this matter, in a research done in the United States, its findings strongly suggest that the level of schooling is able to affect the risk of an individual developing cardiovascular diseases, regardless of any cardiovascular risk factor defined, i.e., patients with less than 12-year schooling ran significantly higher risk of AMI than those with 12-year or more schooling.[35] As much as other authors, we understand that a higher schooling level enables patients to understand better the doctor's orientations as to managing medicines and their health condition, as much as to have more access to information,[36] once nowadays patients would rather participate more and more in the decision-making process with their doctors.[37]

As to patients who already had an AMI episode and are in the group where the antiplatelet therapy complies more with the guidelines in the perioperative period, one can understand that surgeons and doctors in charge of this medicine management look for avoiding reinfarction, and so they instruct their patients not to suspend aspirin or clopidogrel in the preoperative period of non-cardiac surgeries, thus abiding by the recommendations in the guidelines and advocated by other authors.[15,24,25,27,38]

This study has some limitations once the information obtained about management of antiplatelet therapy was rendered by the very patients, or by their companions, who in some situations said that opinions diverged between surgeon and cardiologist, or between surgeon and anesthetist, for instance, which would lead the very patients, or their companions, to decide which orientations should be followed. Additionally, the answers were written down on the patients' reports, and physicians did not have the opportunity of confirming them. In addition, the study is limited to assessing simultaneously the two types of revascularization procedures (angioplasty and coronary revascularization) referring to the management of the antiplatelet agents, and it just does not assess the clinical impact of the antiplatelet therapy after the preoperative period. Therefore, we suggest that future studies address this prospective approach in order to size up the occurrence of thrombotic or hemorrhagic events during and after surgery.

Conclusion

General surgeons stand for a group of physicians which follows the least the guidelines for managing antiplatelet agents in perioperative periods of non-cardiac surgeries.

Table 3 – Results of the multivariate analysis of the characteristics associated with the therapy lacking compliance with the recommendations of use of aspirin or clopidogrel in preoperative periods according to SBC (n = 161) in high-complexity Hospital, Aracaju, Sergipe, Brazil, 2014-2016

Characteristic	OR ($CI^{95\%}$)*	Value p†
Gender		
Male	1.00	-
Female	2.22(0.74-6.68)	0.155
Age		
40-69 years	1.00	-
70-99 years	0.63(0.24-1.65)	0.354
Schooling		
Up to high school	1.00	-
Primary school complete or incomplete	0.46(0.13-1.66)	0.237
University complete incomplete	0.24(0.07-0.78)	0.018
Married		
No	1.00	-
Yes	1.28(0.47-3.48)	0.631
Work outside the home		
No	1.00	-
Yes	4.80(0.92-25.11)	0.063
Has children		
No	1.00	-
Yes	0.60(0.06-5.73)	0.655
Body Mass Index‡		
Up to 29	1.00	-
30 or more	1.24(0.43-3.54)	0.689
Number of diseases§	1.72(0.65-4.56)	0.279
Previous revascularization procedure#		
No	1.00	-
Yes	2.08(0.58-7.49)	0.261
Acute Myocardial Infarction		
No	1.00	-
Yes	0.18(0.04-0.95)	0.043
Stroke		
No	1.00	-
Yes	0.21(0.03-1.66)	0.138
Dyslipidemia		
No	1.00	-
Yes	1.00(0.24-4.17)	0.999
Systemic Arterial Hypertension		
No	1.00	-
Yes	0.22(0.04-1.27)	0.090
Time using aspirin or clopidogrel		
1-4 years	1.00	-
5 years or more	0.90(0.35-2.36)	0.837
Surgeon expertise		
General or digestive system	1.00	-
Urologist	3.30(0.33-33.09)	0.310
Orthopedist	1.38(0.32-5.88)	0.665
Other	0.75(0.28-2.03)	0.578

ASPIRIN: acetylsalicylic acid; SBC: Brazilian Society of Cardiology; (*) Odds Ratio ($CI^{95\%}$) estimated with the logistic regression method; (†) Logistic regression significant when < 0.05; (‡) Body Mass Index = (weight in Kg) : (height in meters)^2; (#) History of Percutaneous Coronary Intervention or surgical revascularization; (§) Number of diseases documented in medical records and confirmed by patient on the date they were admitted for surgery – continuous variable.

Divergences in conducts seem to stress the need of defining internal protocols, to divulge guidelines and continued education to ensure patients' safety. Additionally, it was concluded that patients with more schooling, or a previous history of AMI, agree more with the cardiology guidelines, i.e., patients who have less schooling should be better accompanied in the management of the medicine therapy, and also to have more access to information about their health condition. However, fear of the possibility of a new infarction in a patient leads physicians no to hesitate to suspend the antiplatelet agent in non-cardiac surgical procedures when they are not neurosurgeries or transurethral resection of the prostate.

Author contributions

Conception and design of the research: Borges JMDM, AlmeidaPA, Nascimento MMG, Barreto Filho JAS, Rosa MB, Sousa ACS; Acquisition of data: Borges JMDM, Almeida PA; Analysis and interpretation of the data: Borges JMDM, Nascimento MMG, Barreto Filho JAS, Rosa MB, Sousa ACS; Statistical analysis: Borges JMDM, Nascimento MMG, Barreto Filho JAS, Sousa ACS; Obtaining financing: Borges JMDM, Sousa ACS; Writing of the manuscript: Borges JMDM, Nascimento MMG, Rosa MB, Sousa ACS; Critical revision of the manuscript for intellectual content: Borges JMDM, Nascimento MMG, Barreto Filho JAS, Rosa MB, Sousa ACS.

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 Sergipe under the protocol number 33899914.2.0000.5546. 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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From Journals to Bedside: We Must Improve the Compliance with Practice Guidelines

Barbara Kumagai and Bruno Caramelli

Unidade de Medicina Interdisciplinar em Cardiologia, InCor, HCFMUSP, São Paulo, SP - Brazil

Short Editorial regarding the article: Factors Associated with Inadequate Management of Antiplatelet Agents in Perioperative Period of Non-Cardiac Surgeries

In this issue of "Arquivos Brasileiros de Cardiologia", Borges et al.[1] described the rate of non-compliance with practice guidelines in a Hospital-based study regarding the use of antiplatelet agents in the perioperative setting of non-cardiac surgery.[1] The authors found an extremely high non-compliance rate of 80.75%, and depicted a significant negative association among non-compliance, patient education level, and the presence of previous myocardial infarction. The authors concluded that local procedures and protocols must be urgently defined.

Perioperative care underwent profound changes in the past decades. Initially, evaluation was limited to issues related to the anesthetic procedures, or to the cancellation of interventions for patients at high risk of complications. Eventually, population aging, the improvement in surgical techniques, and the development of less invasive procedures brought to operation theaters patients at an increased risk of complications, especially cardiovascular ones. Perioperative care specialists had to develop new and interdisciplinary skills to deal with several aspects of medicine, kindly deserving the nickname *Chameleon doctor*.[2-4]

Among perioperative complications, cardiovascular are the most feared and strongly related to mortality and morbidity. Myocardial infarction complicating non-cardiac surgery represents a big challenge, especially after the elegant demonstration that almost half of the events involves coronary thrombosis in the pathophysiology, and are not a simple consequence of increased oxygen demand or decreased supply.[5] This latter issue, in a scenario of an increasing number of coronary Stenting procedures, requires recommendations for physicians working at the point-of-care. Elaborated by experts and frequently supported by medical associations, practice guidelines serve also as a reference for public and private health systems approval and reimbursement.[6] Previous authors have also found elevated non-compliance rates in different areas of medicine both at local and country level. However, the non-compliance rate regarding the management of antiplatelet agents in the perioperative setting, has not been previously studied. Despite analyzing a small sample size and one Hospital, the study by Borges et al. is very welcome, and stands out because of the astonishing high non-compliance rate of more than 80%.

At a closer look, however, two other aspects came out and must be highlighted:

1. Treatment delivered without evidence-based support

The most worrying aspect is the finding that almost 30% of the patients were taking antiplatelet agents for primary prevention of cardiovascular diseases. Unfortunately, this treatment is not fully supported by clinical data, even for patients at high cardiovascular risk.

2. Underrepresentation of some surgical specialties

According to clinical practice guidelines, there are only two specific conditions where antiplatelet agents are not safe and must be suspended before non-cardiac surgery: intracranial and transurethral resection of the prostate because of the limited possibility for local compression in order to stop bleeding. In Borges et al.'s study, however, urological interventions represent only 6.8% of the group, and neurological interventions were not included. This finding leads us to conclude that observed interruptions (or not) of the antiplatelet agent refers, most of the times in the present study, to their use as a primary prevention drug.

3. Is it correct to consider some aspects related to the use of non-evidence-based treatment as non-compliance?

Taking in account aspects 1 and 2 above, one can depict that, indeed, most patients in the present study did not interrupt or incorrectly interrupt the antiplatelet drug that was incorrectly prescribed (18.6 + 26.1 + 13 = 57.7% on Table 2). Despite the importance of the finding in Borges et al.'s study, we think that their results could be contained in two major findings:

- Antiplatelet agents are frequently overprescribed, and this issue can have consequences for patients that may be submitted to surgery in the future.
- Interrupting an antiplatelet agent, going against practical guidelines recommendations, is frequent and can have consequences for patients at an increased cardiovascular risk in the perioperative period.

In conclusion, the interesting study by Borges et al. tells us that training is urgently needed to improve perioperative care and cardiovascular primary prevention.

Keywords

Practice Guidelines as Topic; Myocardial Infarction; Perioperative Care; Platelet Aggregation Inhibitors/therapeutic use; Medication Adherence; Treatment Refusal.

Mailing Address: Bruno Caramelli •
Av. Dr. Enéas C. de Aguiar,44. Postal Code 05403-000, Pinheiros, São Paulo, SP - Brazil
E-mail: bcaramel@usp.br

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Relationship of Electromechanical Dyssynchrony in Patients Submitted to CRT With LV Lead Implantation Guided by Gated Myocardial Perfusion Spect

Erivelton Alessandro do Nascimento,[1,2] Christiane Cigagna Wiefels Reis,[2] Fernanda Baptista Ribeiro,[3] Christiane Rodrigues Alves,[2] Eduardo Nani Silva,[3] Mario Luiz Ribeiro,[3] Claudio Tinoco Mesquita[2]

Instituto Estadual de Cardiologia Aloysio de Castro,[1] Rio de Janeiro, RJ - Brazil

Programa de Pós-graduação em Ciências Cardiovasculares da Universidade Federal Fluminense (UFF),[2] Niterói, RJ - Brazil

Hospital Universitário Antônio Pedro - Universidade Federal Fluminense,[3] Niterói, RJ – Brazil

Abstract

Background: **Heart failure (HF) affects more than 5 million individuals in the United States, with more than 1 million hospital admissions per year. Cardiac resynchronization therapy (CRT) can benefit patients with advanced HF and prolonged QRS. A significant percentage of patients, however, does not respond to CRT. Electrical dyssynchrony isolated might not be a good predictor of response, and the last left ventricular (LV) segment to contract can influence the response.**

Objectives: **To assess electromechanical dyssynchrony in CRT with LV lead implantation guided by GATED SPECT.**

Methods: **This study included 15 patients with functional class II-IV HF and clinically optimized, ejection fraction of 35%, sinus rhythm, left bundle-branch block, and QRS ≥ 120 ms. The patients underwent electrocardiography, answered the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and underwent gated myocardial perfusion SPECT up to 4 weeks before CRT, being reassessed 6 months later. The primary analysis aimed at determining the proportion of patients with a reduction in QRS duration and favorable response to CRT, depending on concordance of the LV lead position, using chi-square test. The pre- and post-CRT variables were analyzed by use of Student t test, adopting the significance level of 5%.**

Results: **We implanted 15 CRT devices, and 2 patients died during follow-up. The durations of the QRS (212 ms vs 136 ms) and the PR interval (179 ms vs 126 ms) were significantly reduced ($p < 0.001$). In 54% of the patients, the lead position was concordant with the maximal delay site. In the responder group, the lateral position was prevalent. The MLHFQ showed a significant improvement in quality of life ($p < 0.0002$).**

Conclusion: **CRT determines improvement in the quality of life and in electrical synchronism. Electromechanical synchronism relates to response to CRT. Positioning the LV lead in the maximal delay site has limitations. (Arq Bras Cardiol. 2018; 111(4):607-615)**

Keywords: **Heart Failure; Cardiac Resynchronization Therapy; Eletrodes,Implanted;, Stroke Volume; Radionuclide Imaging.**

Introduction

Heart failure (HF) affects more than 5 million individuals in the United States. Approximately 550,000 new cases are diagnosed annually, and decompensated HF accounts for over 1 million hospital admissions per year.[1] Projections show that HF prevalence will increase by 46% from 2012 to 2030, resulting in more than 8 million individuals with HF aged 18 years and older.[2] As a consequence of this epidemiological transition, of the advances in healthcare and of population aging, the prevalence of coronary artery disease, systemic arterial hypertension, obesity and diabetes mellitus is increasing and will have a significant impact on HF incidence in developing countries.[3]

Cardiac resynchronization therapy (CRT) has become an option to treat advanced symptomatic HF with: (A) left ventricular dysfunction; (B) electrical dyssynchrony; and (C) optimized clinical therapy. The technique has shown a significant improvement in *New York Heart Association* functional class (NYHA FC) and in left ventricular ejection fraction (LVEF) of individuals with severe ventricular dysfunction and left bundle-branch block (LBBB).[4] However, a significant group of patients does not respond favorably to CRT.[5-7] Patients with coronary artery disease and previous acute myocardial infarction are less likely to respond, because of the presence of fibrosis. The selection criteria for CRT currently used do not seem ideal, because previous studies on CRT using those criteria have found a significant percentage of patients (20% to 40%) who did not benefit from the therapy.[6,7]

Electrocardiogram has been used to detect patients with dyssynchrony due to the correlation of the QRS complex prolongation (electrical dyssynchrony) with the presence

Mailing Address: Erivelton Alessandro do Nascimento •
Rua Gil Ferreira, 182. Postal Code 27283-570, Jardim Primavera, Volta Redonda, RJ - Brazil
E-mail: hpcrates7@gmail.com, hpcrates@cardiol.br
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of mechanical dyssynchrony. Thus, it is worth studying the ventricular synchronism before CRT to estimate the patient's response, because the procedure involves high costs. Phase analysis to assess left ventricular (LV) dyssynchrony has been incorporated into gated myocardial perfusion SPECT (GATED SPECT).[8] In addition to the synchronism parameters and in a highly reproducible way, phase analysis provides the assessment of the last ventricular segment to contract. Patients with LBBB tend to begin LV mechanical contraction earlier in the cardiac cycle in the septal wall, and later in other myocardial regions because of the deceleration of the nervous impulse propagation along the conduction system, causing late activation, the most common last site of contraction being located in the posterolateral wall.[9]

The present study aimed at assessing the ability to analyze LV synchronism by use of GATED SPECT to predict the response to CRT and guide LV lead implantation.

Methods

The present study contains national data that are part of the international multicenter project VISION CRT, which assesses the value of phase analysis by use of GATED SPECT in patients who will be submitted to CRT, coordinated in multiple countries by the International Atomic Energy Agency. It is a non-blind clinical trial that included consecutive patients, who underwent 12-lead electrocardiogram at rest immediately before undergoing GATED SPECT and speckle-tracking echocardiography. In addition, the patients answered the Minnesota Living with Heart Failure Questionnaire (MLHFQ) within 4 weeks before the implantation of the CRT device and 6 ± 1 months after that implantation for comparison. Thus, the scintigraphic parameters of ventricular function [LVEF, end-diastolic volume (EDV), end-systolic volume (ESV), LV mass] were assessed, as were the parameters to assess dyssynchrony by use of phase analysis. The analysis of GATED SPECT with the software ECT Synctool, version 3.0, used the following parameters for mechanical dyssynchrony: standard deviation (SD) > 43° and histogram bandwidth (HBW) > 135°.

The inclusion criteria were as follows: patients stable and older than 18 years, in NYHA FC ≥ II, with LVEF ≤ 35% of ischemic or non-ischemic cause, sinus rhythm, QRS duration ≥ 120 ms, LBBB morphology, being followed up at or referred to two tertiary institutions of the Brazilian Unified Health System. Patients with cardioverter-defibrillator implanted for primary or secondary prevention of sudden cardiac death were included.

Patients with any of the following characteristics were excluded: severe disease and life expectancy shorter than 1 year; right bundle-branch block; pregnancy or breastfeeding; acute coronary syndromes; coronary artery bypass grafting or percutaneous coronary intervention within 3 months from study entrance and up to 6 months after CRT.

The definition of 'responder to CRT' considered the presence of two of the following findings: 1. improvement of at least one NYHA FC; 2. improvement of at least 5 points in the MLHFQ; 3. improvement of LVEF ≥ 5%; 4. reduction in ESV ≥ 15%; 5. reduction in HBW < 51°. The categorical variables were presented in nominal and ordinal forms.

The LV pacing lead position was classified as follows: 1. concordant, when positioned in the maximally delayed segment; 2. adjacent, when located in up to one segment away from the maximal delay site; and 3. remote, when located more than one segment away from the maximal delay site.

This project was approved by the Ethics Committee in Research of the Antônio Pedro University-affiliated Hospital/ Fluminense Federal University (No 884844).

Statistical analysis

Statistical analysis was performed with EXCEL (2010, Microsoft Corporation) and SPSS software, version 21.0 (2012, IBM Corporation), and data were shown as means and standard deviations. The categorical variables were compared by use of Fisher exact and chi-square tests, while paired Student *t* test was used for numerical variables. The Kolmogorov-Smirnov test showed the normal distribution of the continuous variables. Pearson's linear correlation coefficient was calculated for the continuous variables. The significance level adopted in the statistical analysis was 5%.

Results

From July 2014 to August 2016, 15 patients were included in the study and 2 patients were lost to follow-up because of death (Table 1). Mean follow-up was 193 ± 16 days.

All QRS intervals had a duration longer than 150ms and LBBB morphology. After CRT, a significant reduction was observed in the duration of QRS intervals (212 ms *vs* 136 ms; $p < 0.001$) and of PR intervals (179 ms *vs* 126 ms; $p < 0.001$). No change was observed in the QT interval after CRT.

The impact of CRT on the quality of life was recorded by use of the MLHFQ, with significant response ($p=0.0002$) when comparing the mean score before and after CRT (Figure 1).

Analysis with HBW (Figure 2) showed that the longer the QRS duration, the higher the HBW value, showing that HBW and SD also have a direct relationship, because their linear correlation coefficient is good (Figure 3).

The group of patients with a significant improvement in LVEF 6 months after CRT (6 patients) had a lower pre-CRT LVEF than that of non-responders (7 patients) (Figure 4).

When assessing the electrocardiographic parameters associated with clinical response to the CRT device, the responder group showed a significant reduction in the PR interval in ms ($p < 0.0001$), which did not reach significance in the non-responder group ($p = 0.09$). This is influenced by the need for constant ventricular stimulation in CRT, which normally leads to more reduced PR intervals.

When classifying the patients as responders and non-responders, the SD and HBW values were higher in responders than in non-responders. The HBW difference between the groups showed statistical significance by use of Student *t* test (Figure 5).

During follow-up, 2 patients without mechanical dyssynchrony before the CRT device implantation became non-responders in the reassessment 6 months after CRT. Thus, we deduced that patients with exclusive electrical

Table 1 – General baseline characteristics of the patients submitted to cardiac resynchronization device implantation

Demographic characteristics	N or mean ± SD
Total of patients	15
Age (years)	63.21 ± 7.7
Body mass index (kg/m^2)	26.92 ± 5.4
Male sex	4
Diabetes mellitus	6
Hypertension	9
Dyslipidemia	8
Smoking	0
Previous coronary artery disease	7
Previous infarction	7
Coronary artery bypass grafting	2
Percutaneous coronary intervention	0
NYHA functional class II	1
NYHA functional class III	7
NYHA functional class IV	5
Beta-blocker	13
Angiotensin-converting-enzyme inhibitor	8
Angiotensin-receptor blocker	7
Acetylsalicylic acid	2
Diuretics	8
Statin	5
Aldosterone antagonist	8
Digoxin	4

dyssynchrony do not respond to CRT on GATED SPECT because they have no change suggestive of mechanical dyssynchrony on baseline tests. Likewise, patients with severe mechanical dyssynchrony and changes on baseline tests show a marked improvement in the GATED SPECT parameters after CRT, mainly HBW.

Of the group of responders, 77.7% had the pacing lead implanted in the lateral region, 11.1% in the posterolateral region, and 11.1% in the posteroseptal region (Figure 6).

When assessing synchronism by use of myocardial perfusion imaging, concordant LV lead positioning was achieved in 54% of the cases (Figure 7 illustrates a concordant implantation), the major reason for not reaching concordance being the anatomical variability of the veins related to coronary sinus, as well as the absence of tributaries reaching the site determined by myocardial perfusion imaging. One of the patients had an aneurysmal coronary sinus, which prevented the lead from being anchored. Thus, the LV lead implantation was converted to the epicardial pathway, in the maximally delayed site.

Discussion

In our study, we observed that CRT led to patients' clinical improvement and to a reduction in electrical and mechanical dyssynchrony. Although CRT is associated with the improvement of several clinical parameters, not every patient benefited from that, and longer QRS duration on the electrocardiogram and increased SD and HBW on GATED SPECT were markers of higher likelihood of clinical response. In addition, we observed that GATED SPECT could identify the last myocardial segment to contract, the ideal LV lead implantation site on CRT. However, because of anatomical limitations, that identification led to concordant implantation in only 54% of the cases.

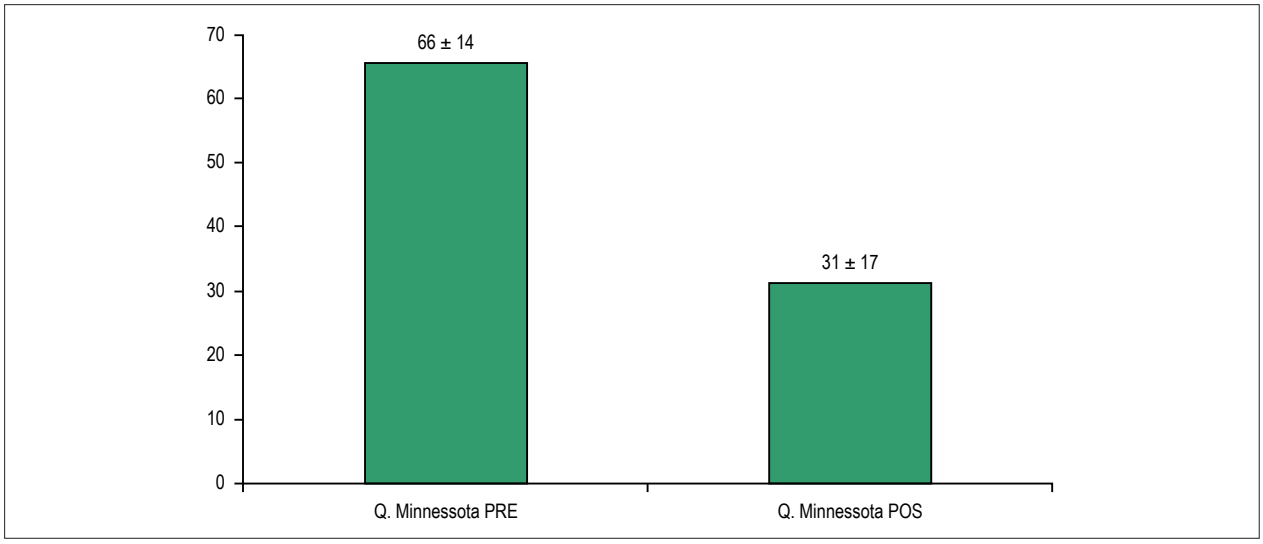

Figure 1 – *Comparison of the mean score of the Minnesota Living with Heart Failure Questionnaire before and after cardiac resynchronization therapy, using Student t test.*

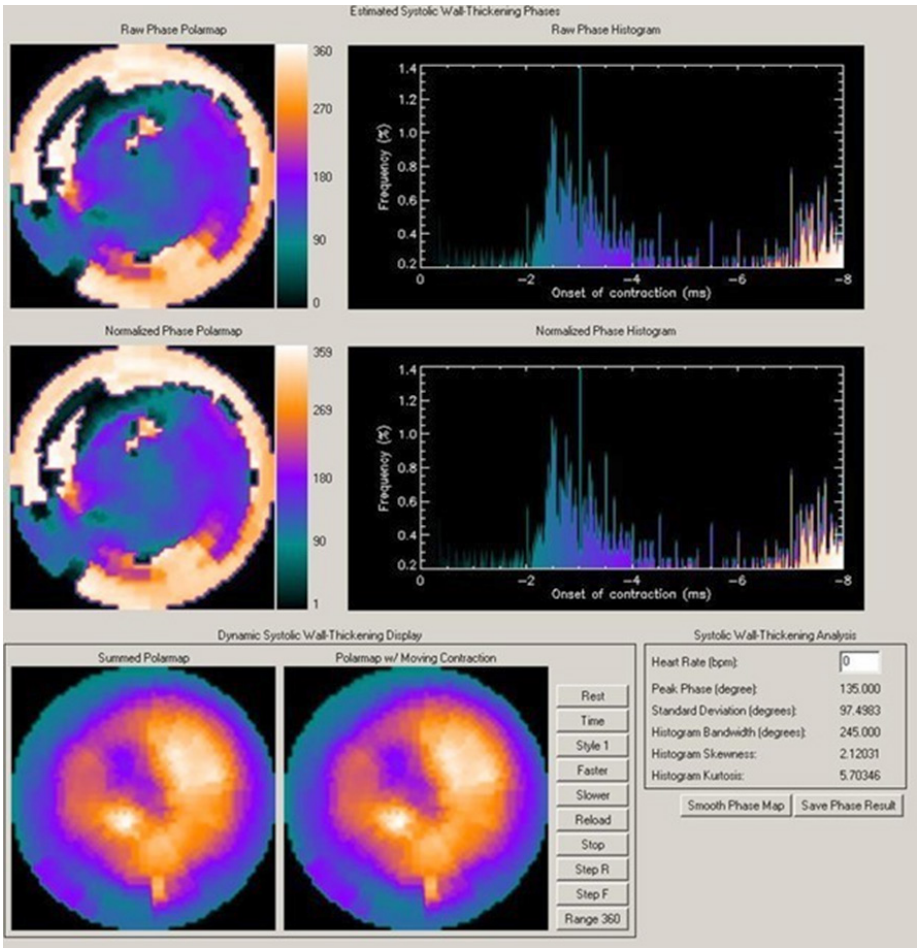

Figure 2 – *Gated myocardial perfusion SPECT with analysis of ventricular synchronism in a patient with dilated cardiomyopathy and left bundle-branch block, showing marked dyssynchrony with HBW of 245° and SD of 97°.*

The population of the present study reflects the profile of patients normally treaded at high-complexity hospitals, and most of them had coronary artery disease. As shown in previous studies, most of our patients had NYHA FC III or IV at the time of CRT.[10] The clinical-functional assessments of the present study, NYHA FC and MLHFQ, confirmed the benefit of CRT reported previously.[10-13] In this study, 77.8% of the patients had a reduction of at least one NYHA FC and a significant improvement in their quality of life, as shown on the MLHFQ after CRT. Although the MLHFQ assesses subjective data, it refers to the patients' perception of their symptoms, which is aligned with the results of a previous study.[4]

In most patients, CRT is associated with clinical benefits. Some electrocardiographic parameters are considered predictors of a higher chance of response to treatment, such as the longer QRS duration, and the benefit increases even more when QRS duration is > 150 ms, as reported by Poole et al.[14] In our study, all patients had QRS duration > 150 ms (mean QRS duration, 212 ms), which increased the likelihood of response. Supporting such data, the COMPANION study has shown no benefit of CRT for patients with QRS duration < 147 ms[12] when assessing the primary outcome of death or hospitalization due to any cause. However, the RAFT study,[13] assessing the primary outcome of death or hospitalization due to HF, has found a higher benefit of CRT in individuals with QRS duration > 150 ms.

Our sample did not include patients with non-LBBB morphology, nonspecific intraventricular conduction disorders and/or right bundle-branch block, which might have led to the clinical benefit observed. Those findings have also been reported in several recent studies,[7,15] which have shown a reduction or even absence of CRT benefit in that group of patients. It is worth noting that our study, even recruiting all patients with LVEF < 35%, QRS duration > 150 ms and LBBB morphology, identified 27% of them as non-responders (clinical criteria/death). Those figures are aligned with those reported in the literature.[6,15]

We could not demonstrate that patients with higher PR interval had higher benefit, which might be due to the small size of our sample. However, the responder group showed a significant reduction in the PR interval (from 178 ms before CRT to 125 ms 6 months after).

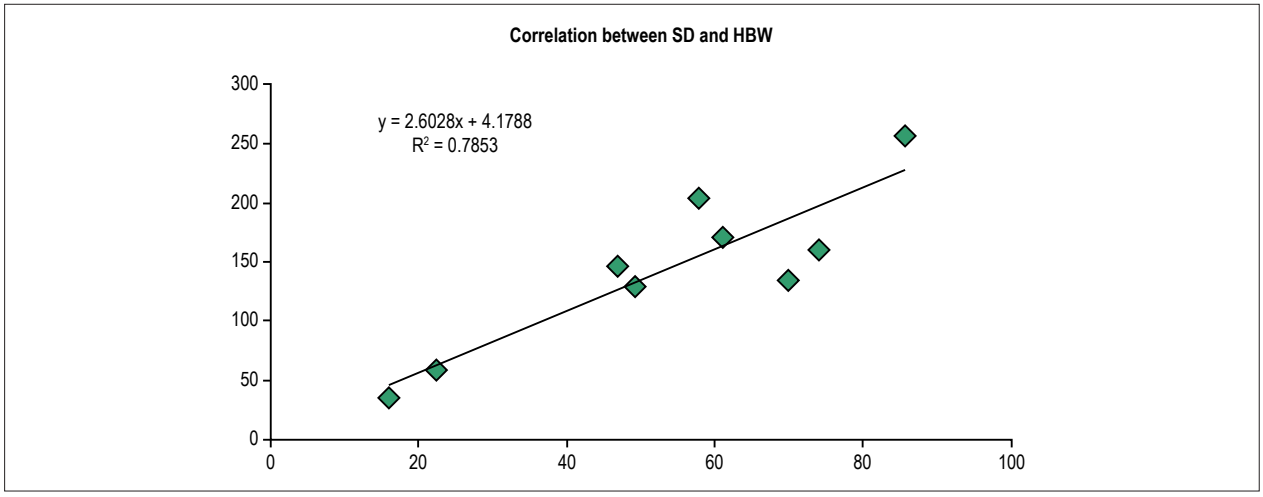

Figure 3 – *Correlation between SD and HBW before cardiac resynchronization therapy (R^2: 0.78)*

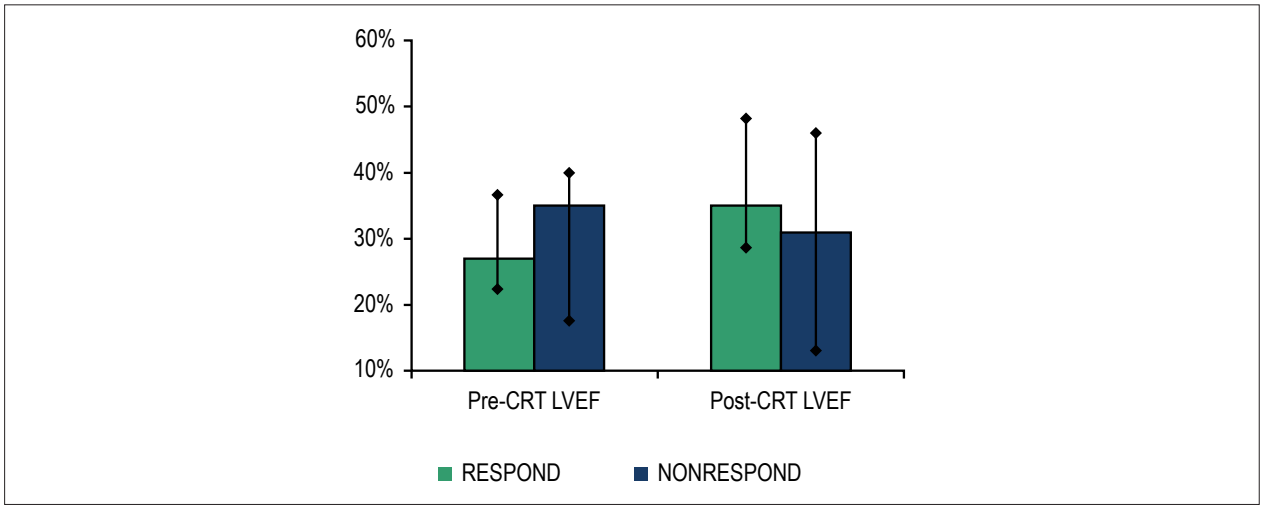

Figure 4 – *Distribution of the mean pre- and post-cardiac resynchronization therapy left ventricular ejection fraction according to clinical response to implantation. Pre-CRT LVEF PRE: pre-cardiac resynchronization therapy left ventricular ejection fraction; Post-CRT LVEF: post-cardiac resynchronization therapy left ventricular ejection fraction; RESPOND: responder group; NONRESPOND: non-responder group. (Student t test).*

On GATED SPECT, SD and HBW could assess mechanical dyssynchrony before CRT. On the assessment 6 months after CRT, those variables showed no significance, probably because not all patients had the LV lead positioned in the maximally delayed segment. On GATED SPECT, the significant cardiac function data were LV ESV and LV mass, probably due to reverse remodeling determined by CRT.

In the search for a relationship between responders to CRT and the presence of mechanical dyssynchrony on myocardial perfusion imaging, responders had higher SD and HWB values as compared to non-responders (HBW of 177° *vs* 76°, and SD of 62° *vs* 36°, respectively). Such findings are aligned with those reported by Henneman et al.,[16] whose study showed significantly higher values of dyssynchrony parameters in responders as compared to non-responders (HBW of 175° *vs* 117°, and SD of 56° *vs* 37°, respectively). In addition, responders had longer QRS duration than non-responders, supported by the finding of the direct relationship between them.

When assessing the maximal delay site of LV activation, the presence of fibrosis in the site and adjacent to it can be determined, which can influence the response to CRT. Daoulah et al.[17] have shown that the presence of transmural fibrosis in the posterolateral region before CRT is associated with a 75% lower chance of echocardiographic or clinical response to that therapy. In our study, 11.1% of the patients had the lead implanted in the posterolateral region; however, no fibrosis was reported in that region in our sample, and 7 patients had history of previous myocardial infarction.

The LV lead implantation in the viable maximal delay site could increase the frequency of reverse remodeling and decrease symptoms.[18,19]

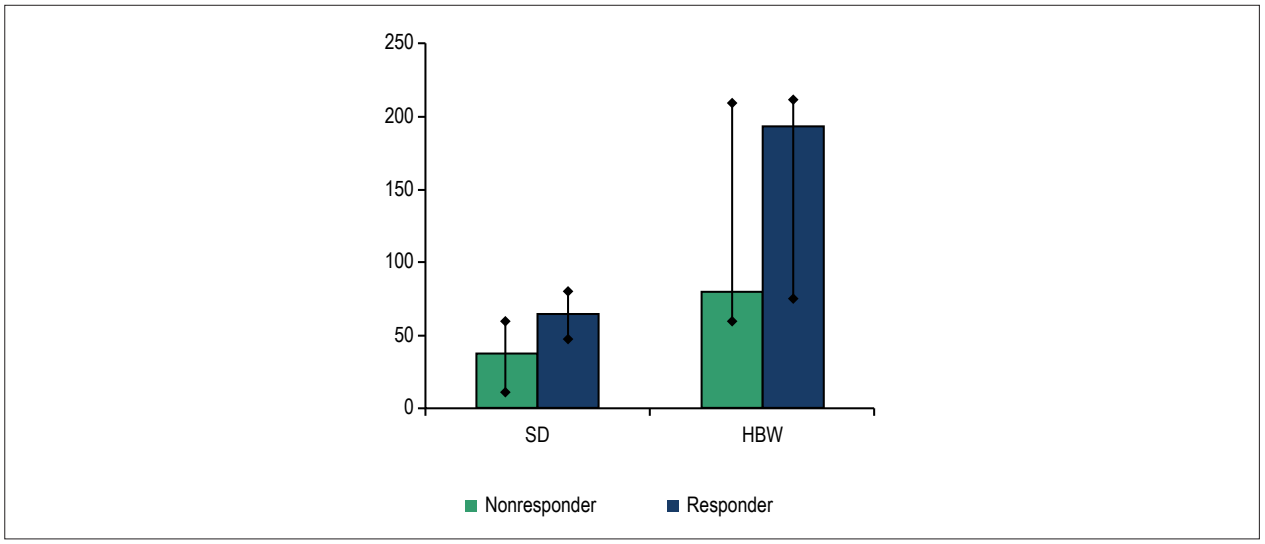

Figure 5 – *Distribution of the mean pre-cardiac resynchronization therapy SD and HBW according to clinical response. SD: standard deviation; HBW: histogram bandwidth (Student t test).*

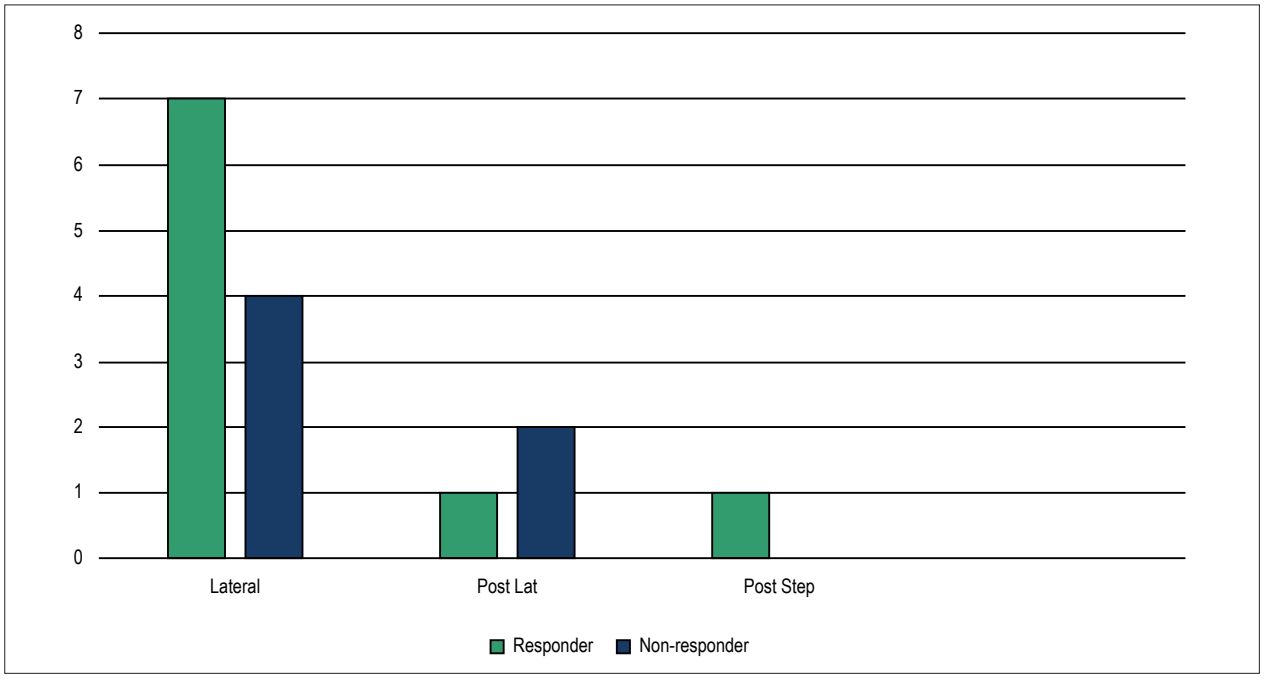

Figure 6 – *Response to cardiac resynchronization therapy according to the left ventricular lead implantation site. Post Lat - posterolateral region; Post Sep - posteroseptal region.*

Despite the limitation of LV lead positioning in the last activation site, the vascular technique has some benefits: 1. less invasive procedure with smaller peri- and postoperative complications; 2. lower chronic stimulation thresholds; and 3. shorter hospital length of stay. One strategy to overcome the limitation of stimulating the maximal delay site in LV contraction is the possibility of using multipoint pacing. This stimulation has been made possible with the development of technologies of multipolar leads that stimulate the left ventricle in several sites, generating several possibilities of stimulating vectors.[20] In addition, GATED SPECT can identify the last LV activation site at the same time it identifies if the area has fibrosis, contributing, thus, to select patients for CRT.

Of the limitations of our study, we highlight the small number of patients assessed and the lack of quadripolar LV leads, which increase the likelihood of LV resynchronization as compared to the use of unipolar leads.

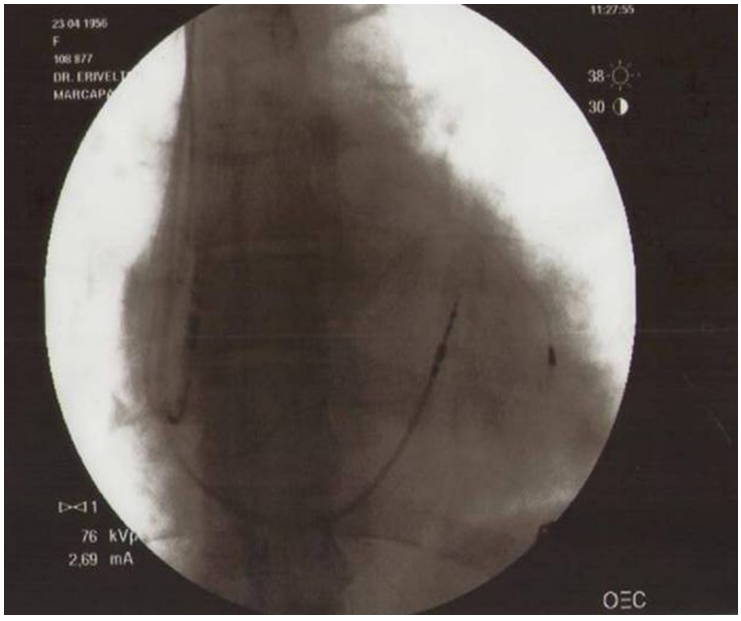

Figure 7 – *Fluoroscopy during implantation of the cardiac resynchronization device with left ventricular lead implanted in the maximal delay site determined on GATED SPECT.*

Considering the present study's findings, it seems that the use of electrocardiography in isolation, based on QRS duration and its morphology to select patients for CRT, is not a good isolated preditor; however, the association of the duration and morphology criteria with the imaging criteria of mechanical dyssynchrony can provide a better response to CRT.

The benefit of using imaging techniques, especially GATED SPECT with phase analysis, to detect mechanical dyssynchrony and to guide lead positioning in the site of maximal conduction delay should increase the number of responders, but larger studies with LV lead positioning guided by imaging techniques are required to draw definite conclusions.

Conclusion

1) Patients submitted to CRT have a good clinical response, with a reduction in electrical dyssynchrony assessed on electrocardiography and a reduction in mechanical dyssynchrony assessed on GATED SPECT.
2) Responders to CRT have longer QRS duration before the implantation of the CRT device as compared to non-responders. In addition, responders had a significant reduction in the PR interval duration as compared to non-responders.
3) Electrical dyssynchrony is not necessarily associated with mechanical dyssynchrony, as shown on GATED SPECT.
4) The phase analysis of GATED SPECT showed that the parameters SD and HBW are associated with higher likelihood of responding to CRT.
5) Although GATED SPECT indicates the last myocardial segment to contract for the LV lead positioning in this site, that is not always possible because of anatomical variability (tributaries) and caliber of the coronary sinus.

Author contributions

Conception and design of the research and Statistical analysis: Nascimento EA, Reis CCW, Mesquita CT; Acquisition of data and Critical revision of the manuscript for intellectual content: Nascimento EA, Reis CCW, Ribeiro FB, Alves CR, Silva EN, Ribeiro ML, Mesquita CT; Analysis and interpretation of the data and Writing of the manuscript: Nascimento EA, Reis CCW, Silva EN, Mesquita CT; Obtaining financing: Mesquita CT.

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 Hospital Universitário Antônio Pedro under the protocol number 884.844. 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 Cardiac Dyssynchrony – An Unsolved Issue! How to improve selection and response to Cardiac Resynchronization Therapy?

Eduardo Arrais Rocha

Hospital das Clínicas da Universidade Federal do Ceará, Fortaleza, CE - Brazil

Short Editorial regarding the article: Relationship of Electromechanical Dyssynchrony in Patients Submitted to CRT With LV Lead Implantation Guided by Gated Myocardial Perfusion Spect

The authors Nascimento et al.,[1] published an important work demonstrating the value of myocardial perfusion scintigraphy (SPECT-Gated) to identify cardiac dyssynchrony (CD) and with posterior implantation of left ventricle (LV) electrode in the area with higher dyssynchrony, with favorable correlation with clinical results and cardiac function. The study rises important issues in the attempt to reduce non-respondent rate (30-40%). These high rates are due to implants in very advanced or irreversible phases of the disease or to positioning of the LV electrode in areas with fibrosis or due to absence of dyssynchrony.

All the current directives take the indication of cardiac resynchronization therapy (CRT) in consideration, based on electrical dyssynchrony criteria, in detriment of mechanical dyssynchrony criteria. The Echo CRT[2] study confirmed the unfavorable results in patients submitted to CRT in absence of CD, minding it may be a deleterious therapy.

Occurrence of CD is the pathophysiological base of CRT. Over 1/3 of patients with left branch blockade (LBB) may not suffer from CD, particularly those with QRS < 150 ms.[3] That number is higher in the other intraventricular conduction disorders. Thus, new techniques which may improve the selection of those patients and allow for implanting electrodes in the regions with a with higher level of contraction delay are welcome.

However, several aspects deserve special attention. This work encompasses a subgroup of patients, from an ongoing multicentric VISION-CRT global study, which must bring a definitive answer on the value of perfusion scintigraphy in the selection of patients for CRT, thus helping to select the location to position the electrode in the coronary sinus.[4]

Several imaging methods were and have still been described as important ones to identify and quantify CD. All of them show both advantages and disadvantages, and their studies, are mostly unicentric and performed with small populations and show non-reproducible results, with no direct correlation with relevant outcomes, such as mortality or, even, substitutive outcomes, such as response to CRT.

Keywords

Myocardial Perfusion Imaging, Diagnostic Imaging; Cardiac Resynchronization Therapy; Cardiac Resynchronization Therapy Devices; Eletrodes

Mailing Address: Eduardo Arrais Rocha •
Av. Padre Antônio Tomás, 3535 / 1301. Postal Code 60192-120, Cocó, Fortaleza, CE – Brazil
E-mail: eduardoa@cardiol.br, eduardoarraisrocha@gmail.com

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Echocardiogram has classically become the standard and most used method, given its low cost, easy accessibility and repetition, when necessary for pacemaker (PC) reprogramming, however, in virtue of the lack of standardization of the best methodology, of the high intra- and inter-observer variability, of the need for a proper acoustic window and, mainly, due to the lack of favorable results in multicentric studies, such as PROSPECT trial, its trustworthiness and applicability were caused to decrease.[5]

New echocardiographic techniques emerged and have evolved in that sense, such as Speckle-tracking, the Septal Flash, the Apical Rocking and the 3D-echocardiogram, some of which already showing initial evidence of correlation with better prognosis after CRT, as shown in the study by Hoke and Bax JJ,[6] on PREDICT –CRT[7] and on TARGET[8] studies. As disadvantages, they are always dependent observers and, up to the moment, have not show favorable results in large series.

Myocardial perfusion scintigraphy has appeared in the last decade, with the phase analysis technique, as an additional method for CD analysis. Its advantage lies on lower intra- and inter-observer variability, on high reproducibility and on allowing three-dimensional LV contraction analysis, also having the possibility of joint analysis of ischemia and fibrosis, however, it adds more costs than echocardiogram, radiation, higher acquisition time, lower possibility of repetitions for PC comparisons and reprogramming. Also, the benefits of its use in large series still require confirmation. Variations on protocols and cut-off values related to better evolution are also under discussion.[9] This method may present difficulty of analysis in cardiac segments with poor tissue perfusion, overestimating areas with extensive scarring, mainly, in dilated hearts and hearts with fine walls.[9-11]

Magnetic resonance imaging has allowed a good assessment of CD and an excellent analysis of the cardiac function and its areas with fibrosis, the disadvantage being the long time of the exam, auditory noises, difficulty for claustrophobia, impossibility of use for patients with old PC who are going to be submitted to "up-grading", high costs, lower availability and analyses of results achieved only in small series.[10,11]

Imaging exams such as cardiac tomography arise as a perspective of combined use of several methods, aiming, besides CD analysis, at the identification of the anatomy of the coronary sinus, allowing to opt for the best surgical technique, such as lateral mini-thoracotomy, video-thoracoscopy or endocardial LV electrode implantation by transeptal puncture when necessary, due to the absence of tributary veins proper for its positioning in the regions with the highest degree of delay.

Some issues seem defined: the importance of cardiac dyssynchrony as a first therapeutic target in cardiac resynchronization, the need for its identification, quantification and localization, the relevance of an ideal electrode positioning in the LV, in fibrosis-free areas with higher ventricular contraction delay. Confirmation for the data mentioned previously in multicentric studies, correlated with better prognosis outcomes, should clarify an effervescent area in artificial heart stimulation and it may cause such techniques to become widespread in medical guidelines and implemented in clinical practice. Thus, the study at hand shows positive perspectives in search for better results in cardiac resynchronization therapy.

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Risk-Benefit Assessment of Carotid Revascularization

Pedro Piccaro de Oliveira, José Luiz da Costa Vieira, Raphael Boesche Guimarães, Eduardo Dytz Almeida, Simone Louise Savaris, Vera Lucia Portal

Instituto de Cardiologia - Fundação Universitária de Cardiologia (IC/FUC), Porto Alegre, RS - Brazil

Abstract

Severe carotid atherosclerotic disease is responsible for 14% of all strokes, which result in a high rate of morbidity and mortality. In recent years, advances in clinical treatment of cardiovascular diseases have resulted in a significant decrease in mortality due to these causes.

To review the main studies on carotid revascularization, evaluating the relationship between risks and benefits of this procedure.

The data reviewed show that, for a net benefit, carotid intervention should only be performed in cases of a periprocedural risk of less than 6% in symptomatic patients. The medical therapy significantly reduced the revascularization net benefit ratio for stroke prevention in asymptomatic patients. Real life registries indicate that carotid stenting is associated with a greater periprocedural risk. The operator annual procedure volume and patient age has an important influence in the rate of stroke and death after carotid stenting. Symptomatic patients have a higher incidence of death and stroke after the procedure. Revascularization has the greatest benefit in the first weeks of the event.

There is a discrepancy in the scientific literature about carotid revascularization and/or clinical treatment, both in primary and secondary prevention of patients with carotid artery injury. The identification of patients who will really benefit is a dynamic process subject to constant review.

Introduction

Carotid endarterectomy was introduced in 1954 for stroke prevention, but it wasn`t until the 90`s that the first randomized clinical trials (RCTs) evaluated its effectiveness. The first published RCTs on the subject were NASCET (1991), VACS (1991) and ECST (1993), all of which demonstrated benefit of surgical intervention in secondary prevention setting.[1-3] Regarding primary prevention, a small RCT was published in 1993[4] followed by two larger ones (ACAS, 1995; ACST, 2004)[5,6] that demonstrated a greater benefit of surgical intervention when compared to optimal medical treatment.

Several studies comparing carotid angioplasty and stenting (CAS) and carotid endarterectomy (CEA) were published in the 2000's, leading to a recommendation for routine use of embolic protection devices. Five clinical trials (SAPPHIRE,[7] EVA-3S,[8] SPACE,[9] CREST[10] and ACT I[11]) found that percutaneous intervention is an alternative to surgical intervention in both symptomatic and asymptomatic patients. On the other hand, the ICSS trial found a higher risk of stroke and death after CAS in symptomatic patients.[12] Paraskevas et al.[13] compiled data from several "real-world" registries in a systematic review and found that percutaneous procedures resulted in higher rates stroke and death when compared do CEA, albeit with conflicting results from each registry.[13]

While many studies have focused on comparing the two modalities of intervention, the definition of optimal medical treatment (OMT) has evolved and currently reduces relative risk of stroke related to extracranial atherosclerosis by up to 70%.[1,2,10,14]

Ascertaining risk-benefit ratio between CAS and CEA is challenging. There are thirty-four international guidelines on the subject, with significant variability regarding choice of carotid revascularization procedure.[15] This review aims to provide an updated risk-benefit assessment across the different treatment options (CEA, CAS and OMT) for symptomatic and asymptomatic carotid stenosis.

Keywords

Carotid Artery Diseases; Atherosclerosis; Endarterectomy, Carotid; Stroke; Indicators of Morbidity and Mortality; Risk Assessment

Mailing Address: Vera Lucia Portal •
Rua Luciana de Abreu, 471 sala 603. Postal Code 90570-080, Moinhos de Vento, Porto Alegre, RS – Brazil
E-mail: veraportal@cardiol.br, editoracao-pc@cardiologia.org.br, veraportal.pesquisa@gmail.com
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Methods

This article was based on a literature review carried out through an online search of the main articles and guidelines published in the last 30 years, aiming to evaluate the relationship between risk and benefit of carotid revascularization. Due to the differences in the indexing processes in the bibliographic databases, we opted for the search for free terms, without the use of controlled vocabulary (descriptors).

Results

Stroke is the third cause of death in the Western world and the leading cause of permanent neurological disability.[16] About 85% of strokes are ischemic in origin and 80% of non-hemorrhagic strokes affect brain areas irrigated by carotid arteries. Most strokes are due to thromboembolism of atherosclerotic lesions in internal carotid arteries. Usually, these occur in smaller carotid plaques with lower than 50% stenosis, considered non-surgical stenosis. The remaining cases are considered stenotic plaques that should be evaluated for surgical treatment.[14]

Evolution of optimal medical treatment

Pivotal studies on the incidence of stroke in patients with severe symptomatic carotid stenosis, without carotid

revascularization, were published in the beginning of the 1990's.[1-3] At that time, acetyl salicylic acid was the cornerstone of OMT. In NASCET study, two year stroke incidence was 26% in OMT group, compared to 9% in CEA group.[1] In 1995, primary prevention study ACAS[5] found a much lower (17.5%) five-year stroke incidence in its OMT group. In 2004, ACST[7] reported a further drop of stroke risk to 11.8% (2.4% annually), and by the time 10-year results were reported, in 2010,[17] there was an even greater reduction in OMT group (7.2% in the last five years of follow-up). ACST also showed that in those cases of stroke with untreated severe ipsilateral carotid stenosis, OMT reduced stroke risk by almost 70%, resulting in an annual stroke incidence of 0.7% in the last five years of follow-up[17] (Table 1).

Stroke risk reduction was followed by a large reduction in myocardial infarction incidence during the same period, which is largely attributable to improvement of OMT and risk factor control.[18]

A reduction of almost 30% in mortality from atherosclerotic coronary artery disease was reported in Brazil between 1990 and 2009.[19] Between 2003 to 2013, mortality rates due to coronary heart disease fell by 38% and the actual number of deaths decreased by 22.9% in the United States.[18]

Studies with angiotensin-converting enzyme inhibitors (ACE inhibitors) have proved the benefit of this class of drugs on ventricular remodeling, showing also a reduction of 20% in cardiovascular events.[20,21] A meta-analysis of more than 30,000 patients demonstrated a protective effect of ACE inhibitors against ischemic events, even in patients without ventricular dysfunction.[22] Currently, several guidelines acknowledge the role of these drugs in preventing cardiovascular disease.[23-25]

Nevertheless, routine use of statins is considered the greatest landmark in OMT. A meta-analysis of 26 RCTs (over 170,000 subjects), published in 2010, demonstrated the efficacy and safety of statins, as well as the correlation between the dose used and the protective effect.[26] Two randomized clinical trials reported in 2016 reinforced these findings. The *Effect of Statin Treatment on Modifying Plaque Composition* (STABLE) study tested high-dose rosuvastatin through a follow-up with intravascular imaging. Besides stabilizing the atherosclerotic plaque, rosuvastatin could also induce some reversal of the atherosclerotic process.[27] A second study, *Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease* (HOPE 3), demonstrated that routine use of statin in primary prevention subjects with intermediate risk of cardiovascular diseases resulted in 24% reduction in outcomes, including stroke.[28]

Risks and benefits of intervention

Several international societies indicate carotid intervention in symptomatic patients, ipsilateral stroke or TIA within the previous 6 months, presenting at least 50% extracranial carotid stenosis.[15] Considering the great advances in clinical treatment in the last decades, the most important guidelines postulate that the intervention should only be performed when the periprocedural risks are smaller than 6%.[15,29-31] (Table 2)

Table 1 – Evolution of Clinical Treatment[23-24]

Trial	Publication Year	Annual incidence of stroke in the clinically treated group
ACAS[5]	1995	3,5%
ACST first 5 years[6]	2004	2,4%
ACST last 5 years[17]	2010	1,4%

Table 2 – Management of patients with Symptomatic extracranial carotid stenosis[23-24]

Carotid Stenosis	Recommendations (Class and Evidence Level)*	Periprocedural Risk to maintain clinical benefit
< 50%	OMT (IA)	
50-59%	CEA + OMT (IIaB)	< 6%
	CAS + OMT (IIbB)	
60-69%	CEA + OMT (IIaB)	< 6%
	CAS + OMT (IIbB)	
70-99%	CEA + OMT (IA)	< 6%
	CAS + OMT (IIaB)	
Occlusion	OMT (IA)	

*OMT: Optimized medical therapy; CEA: Carotid endarterectomy, CAS: Carotid angioplasty and stenting. (Classes of Recommendation: I - The benefit is greater than the risk and the treatment/procedure should be performed or administered; IIa - The benefit is greater than the risk, but further studies are needed, so that it reasonable to perform procedure or administer treatment; IIb - the benefit is equal to or greater than the risk and treatment/procedure may be considered. Levels of Evidence: A - Data derived from multiple randomized clinical trials or meta-analyses; B - Data derived from a single randomized clinical trial or multiple non-randomized studies.) * For all patients: When procedure is indicated, CAS should only be performed if there is a high risk for CEA.*

In cases of severe asymptomatic carotid stenosis, the joint guideline of the American Heart Association and American Stroke Association for primary prevention of stroke, published in 2014,[30] and the guideline of the European Society of Cardiology, published in 2017,[31] recommend that the periprocedural risk should be less than 3% for a net benefit in the revascularization process. (Table 3)

The risks associated with carotid intervention are heterogeneous, which makes it necessary to separate the patients into subgroups. (Table 4) The first important criterion in the definition of these subgroups is the presence or absence of symptoms, defined by the occurrence of a stroke or a transient ischemic attack (TIA) within the previous six months, affecting the territory supplied by the affected carotid artery.[1] The second criterion is based on the definition of high-risk patients for carotid endarterectomy: congestive heart failure, ischemic cardiopathy, the need for associated cardiac surgery, severe pulmonary disease, contralateral carotid artery occlusion, paralysis of recurrent laryngeal nerve, carotid restenosis after procedure, cervical radiotherapy, prior cervical surgeries or age greater than 80 years.[32]

A systematic review published in 2015 examined the rates of stroke and death after CAS and CEA in twenty-one international records, which together represent more than 1,500,000 procedures performed between 2008 and 2015.[13] In asymptomatic patients not at high risk for endarterectomy, carotid stenting had a periprocedural risk lower than 3% in 43% of the cases, and a risk greater than 5% in 14% of the registries. For surgical revascularization in the same group, 95% of the registries reported risks lower than 3%. (Figure 1) In the group of symptomatic patients not at high risk, 72% of the registries after carotid angioplasty showed a greater than 6% incidence of stroke and death in 30 days. On the other hand, only 11% of the registries showed a risk above 6% among the patients submitted to endarterectomy. (Figure 2) Only three of the twenty-one registries analyzed reported data regarding patients with high risk for carotid endarterectomy. In one of them, the rate of events was greater than 3% in asymptomatic patients, for both CAS and CEA. In the group of symptomatic patients, all registries reported rates of stroke and death greater than 6% after CAS and two records showed rates above 6% after carotid endarterectomy.

Carotid stenting: the age and operator effect

The elderly population usually presents vessel tortuosity and a large burden of atherosclerosis, characteristics that increase complications after angioplasty procedures. Age has been associated with periprocedural stroke and death after CAS, this same finding was not reported after CEA.[33] A Cochrane meta-analysis of 16 randomized clinical trials[34] and a subanalysis of the CREST trial[35] described an association of age ≥ 70 years and increased periprocedural risk after CAS. A meta-analysis of four randomized trials (EVA-3S, SPACE, ICSS and CREST) found that the periprocedural risk of stroke or death after CAS were 3% for patients younger than 60 years and 12% for those older than 70 years, whereas the periprocedural stroke and death risk remained stable at 5% across the entire age spectrum in the CEA group.[33]

The possibility that the operator is a crucial factor for the good result of the carotid percutaneous intervention was

Table 3 – Management of patients with Asymptomatic extracranial carotid stenosis[23-24]

Carotid Stenosis	Recommendations (Class and Evidence Level)*	Periprocedural Risk to maintain clinical benefit
< 60%	OMT (IA)	
60-69%	OMT (IA); CEA + OMT (IIaB) ou CAS + OMT (IIbB)	< 3%
70-99%	OMT (IA) CEA + OMT (IIaB) ou CAS + OMT (IIbB)	< 3%
Occlusion	OMT (IA)	

OMT: Optimized medical therapy; CEA: Carotid endarterectomy, CAS: Carotid angioplasty and stenting. (Classes of Recommendation: I - The benefit is greater than the risk and the treatment/procedure should be performed or administered; IIa - The benefit is greater than the risk, but further studies are needed, so that it reasonable to perform procedure or administer treatment; IIb - the benefit is equal to or greater than the risk and treatment/procedure may be considered. Levels of Evidence: A - Data derived from multiple randomized clinical trials or meta-analyses; B - Data derived from a single randomized clinical trial or multiple non-randomized studies.)
** For all patients: When procedure is indicated, CAS should only be performed if there is a high risk for CEA.*

Table 4 – Risk Subgroups for Carotid Intervention

Subgroup	Definition
Symptomatic	Occurrence of a stroke or a transient ischemic attack (TIA) within the previous six months, affecting the territory supplied by the affected carotid artery
High-risk for Carotid Endarterectomy	Congestive heart failure, ischemic cardiopathy, the need for associated cardiac surgery, severe pulmonary disease, contralateral carotid artery occlusion, paralysis of recurrent laryngeal nerve, carotid restenosis after procedure, cervical radiotherapy, prior cervical surgeries or age greater than 80 years

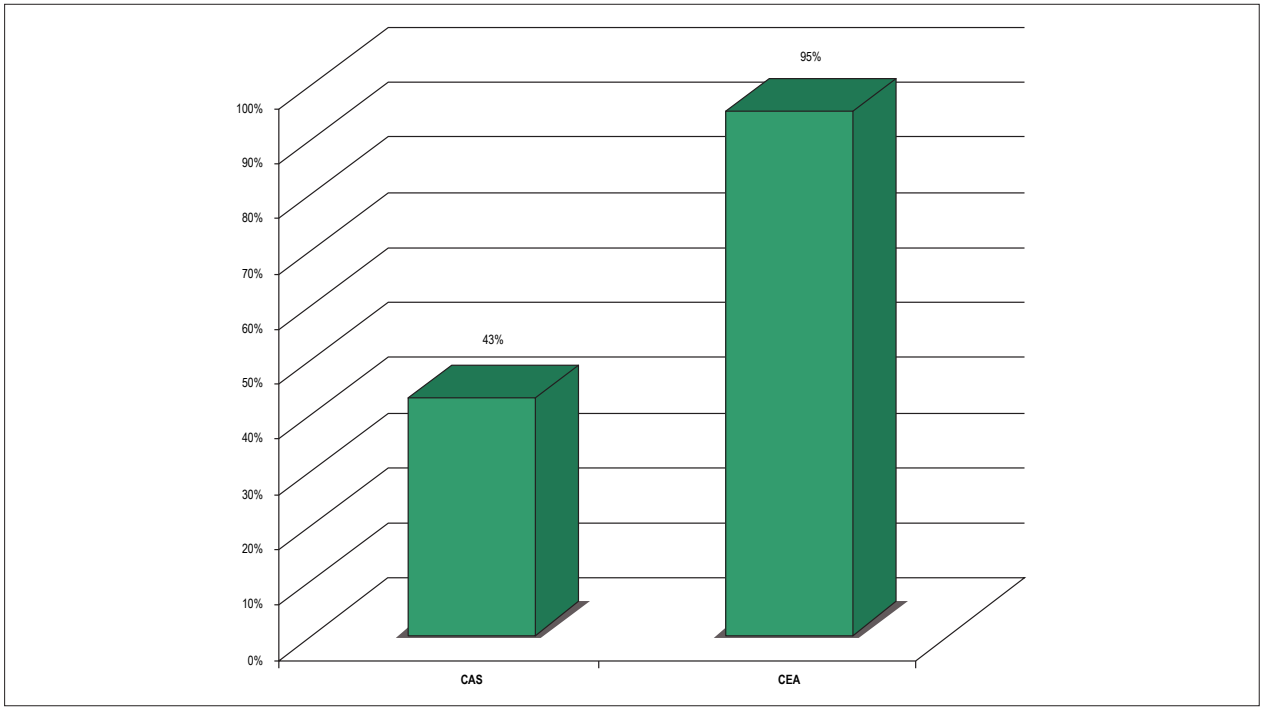

Figure 1 – *Percentage of Registries with a Lower than 3% Incidence of Stroke and Death in 30 days after Asymptomatic Carotid Intervention. CAS: Cardiotid angioplasty and stenting; CEA: Carotid endarterectomy. Paraskevas KI, Kalmykov EL, Naylor AR. Stroke/Death Rates Following Carotid Artery Stenting and Carotid Endarterectomy in Contemporary Administrative Dataset Registries: ASystematic Review. Eur J Vasc Endovasc Surg. 2015;51(1):3-12.*

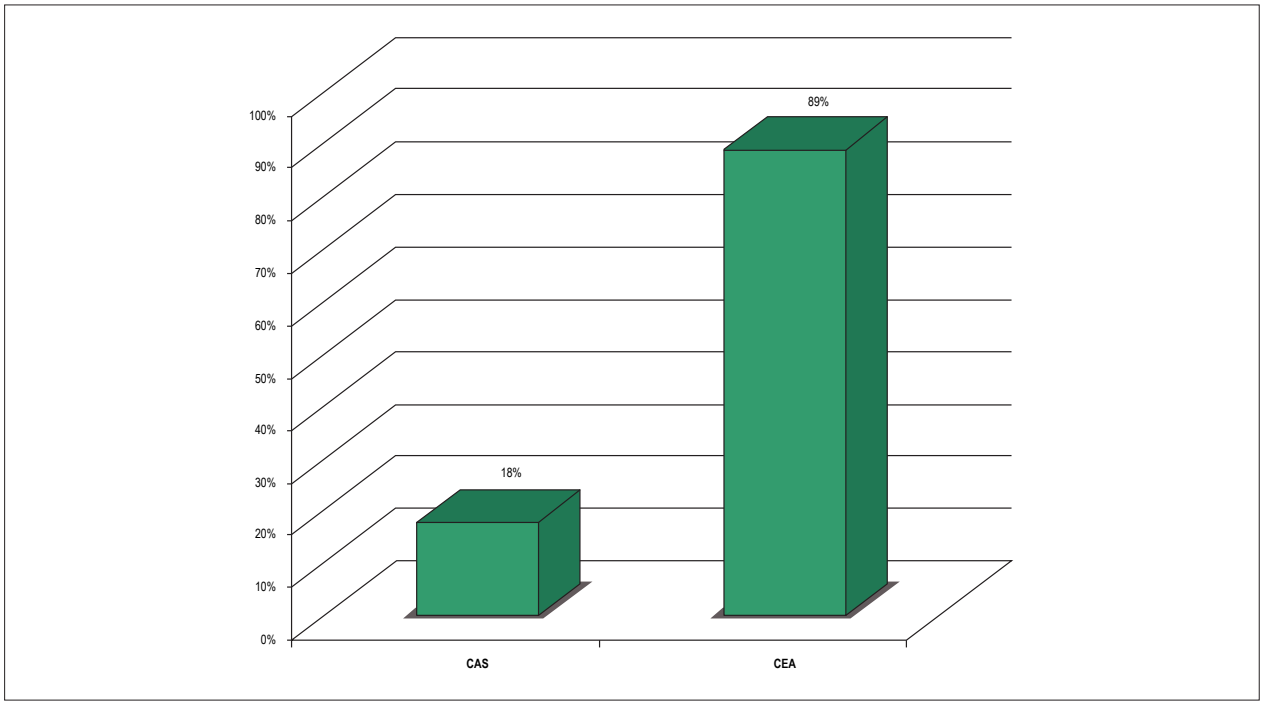

Figure 2 – *Percentage of Registries with a Lower than 6% Incidence of Stroke and Death in 30 days after Symptomatic Carotid Intervention. CAS: Cardiotid angioplasty and stenting; CEA: Carotid endarterectomy. Paraskevas KI, Kalmykov EL, Naylor AR. Stroke/Death Rates Following Carotid Artery Stenting and Carotid Endarterectomy in Contemporary Administrative Dataset Registries: ASystematic Review. Eur J Vasc Endovasc Surg. 2015;51(1):3-12.*

taken into account in the design of the protocols of clinical trials involving CAS. In an attempt to standardize the group of operators, the EVA-3S study[8] included only interventionists with a minimum of 12 carotid angioplasties performed previously. The SPACE study[9] required a minimum of twenty and five previous procedures. Although most studies report the total volume of procedures performed by the operator, the few ones that specifically addressed this point were not able to show an association between the operator's prior experience and lower rates of complications.[36-38]

The combined analysis of three large randomized trials (EVA-3S, SPACE and ICSS), published in 2012,[39] showed great differences in the incidence of death or stroke when the operators were stratified by annual volume of procedures. Procedures performed by operators with at least six carotid angioplasties per year had an incidence of stroke and death in 30 days of 5.1%, while the procedures performed by those with three or less, showed a 10.1% incidence. It is important to observe that all operators included in the analysis had already performed a minimum number of procedures, i.e., had already surpassed the learning curve. Unlike the annual volume, the total volume of carotid procedures performed during the life of the operator had no association with an increase of complications such as stroke and death, in concordance with other previously published studies.[40]

Symptomatic patients revascularization – a time sensitive benefit

The results of the main studies with symptomatic patients demonstrate that the greatest benefit of intervention occurs in the first weeks after the index event.[41-43] After the first 14 days, there is a rapid decrease in the benefit of the intervention, and more than 70% of the protective effect is seen within the first 30 days; after two years, the symptomatic patient presents the same risk level as the asymptomatic patient.[41-43] However, this recommendation has been poorly implemented with less than 20% undergoing revascularization within two weeks the onset of the stroke or TIA.[44] A Danish nationwide initiative was able to increase the percentage of CEA within the recommended timeframe from 13% in 2007 to 47% in 2010.[45] The evidence of the early procedure safeness is more robust for CEA than for CAS which has conflicting results in different studies.[46-48]

Secondary prevention is indicated in cases of transient ischemic accident or small strokes, due to the high risk of intracranial hemorrhage when performing carotid intervention in the first few weeks after a major ischemic stroke and to the questionable clinical benefit in the long term.[49]

Patient with asymptomatic severe carotid lesion

The ACAS study, published in 1995,[5] showed that the adjusted risk of stroke and death associated with the intervention was 2.3%, with the endarterectomy preventing 59 cerebral vascular accidents in five years for every 1,000 procedures performed. Despite the very low risk as compared to that observed in practice and to those of the old pharmacological practices, 94% of the CEA were unnecessary. With an adjustment of the periprocedural risk to 0%, eighty-two cerebral vascular accidents would be prevented for every thousand endarterectomies, but still 92% of the patients would be submitted to a procedure without benefits. The same principle can be applied to the 10-year results of the ACST which showed that, with a reduction of the periprocedural risk to 0%, 74 cerebral vascular accidents would be prevented for every thousand endarterectomies, meaning that 93% of the procedures would have been unnecessary.[17]

The large clinical trials currently conducted have been limited to the comparison between carotid angioplasty and surgery. The lack of a clinical therapy group in the ACT I study, published in 2016, was strongly criticized.[50] The new editions of the studies SPACE, SPACE-2 (ISRCTN78592017), CREST and CREST-2 (NCT02089217) planned the inclusion of a third group in clinical therapy, but the SPACE-2 study was suspended by a low rate of inclusions. Presently, the CREST-2 trial has included more than 780 of the 2,480 patients referred.

The current guidelines of the European Society of Cardiology for asymptomatic patients with severe lesions and a moderate surgical risk recommend endarterectomy (Class IIa) in the presence of clinical characteristics and/or imaging results suggestive of an increased risk of late ipsilateral stroke. Angioplasty should be considered (Class IIa) for patients with high risk for endarterectomy, provided that the rates of periprocedural death or stroke are < 3% and the patient's life expectancy is greater than five years, for any one of the groups.[31]

The population with severe asymptomatic carotid stenosis is not homogeneous. Some lines of research try to identify patients with higher risk through more detailed imaging studies to locate markers of vulnerable plaques and microembolization.[51,52] That would allow a more cost-effective carotid revascularization in patients currently classified as asymptomatic.

Discussion

The present review focuses on the primary and secondary prevention of ischemic stroke through carotid revascularization, which could impact 14% of all cerebral vascular accidents.[16]

The first studies on this subject were published in the beginning of the 1990's. From the year 2000, studies have focused on the comparison between angioplasty and carotid endarterectomy, without the inclusion of a clinical therapy group for comparison. In this period, there has been significant improvement of clinical treatment and better control of risk factors. The use of acetylsalicylic acid for cardiovascular prevention was already routine decades before a decline in rates of cardiovascular events was observed, suggesting that other classes of drugs are responsible for this change. In the last decades, several studies have shown the impact of statins on cardiovascular outcomes, with a reduction in incidence of up to 50%.[26]

The data reviewed in the present study show that, for a net benefit of the procedure, carotid intervention should only be performed in cases of a periprocedural risk of less than 6% in symptomatic patients or 3% in asymptomatic patients. A systematic review published in 2015 showed that carotid revascularization is more efficient in symptomatic patients but is associated to a higher incidence of death and stroke. In addition, the results did not show a trend to improved

outcomes after carotid stenting between 2008 and 2015, suggesting that this modality of intervention, although less invasive, has higher rates of complications even in patients with high surgical risk.[13]

The data concerning the effect of operator in CAS show that prior experience is important and can influence the rate of serious complications. A difference of almost 100% in the incidence of 30-day stroke and death outcomes between different groups of operators has already been observed in clinical trials.[40] The annual volume of carotid procedures performed by the operator is the factor that best correlated with lower rates of complications.[40]

The indication for carotid intervention in symptomatic patients showed a greater benefit in the first weeks of the event. In this context, the joint guideline of the American Heart Association and American Stroke Association for prevention of stroke in symptomatic patients, published in 2014, recommends as class IIa that carotid revascularization occurs within two weeks of the index event, if there are no complications that contraindicate the procedure.[30] The 2017 guideline of the European Society of Cardiology (*ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial diseases, in collaboration with the European Society for Vascular Surgery*), maintained this recommendation.[31]

The indication for carotid intervention is still questionable in the case of asymptomatic patients, since the studies published up to now have shown a high rate of unnecessary procedures.[53] Currently, some studies try to identify asymptomatic patients with higher risk who could undergo a more cost-effective carotid revascularization procedure.

Conclusion

Severe lesion of the extracranial carotid artery is responsible for 14% of all cerebral vascular accidents. Carotid revascularization has been performed for over 50 years, and several studies have proven that the intervention is capable of preventing this outcome, but with a not inconsiderable risk of serious complications. More recently, carotid angioplasty procedures have broadened the range of invasive options, but the expected reduction in periprocedural risk was not observed. Additionally, the increased incidence of atherosclerosis resulted in a great heterogeneity of patients who are possible candidates for endarterectomy or stenting, and the evolution of pharmacological therapy changed the risk-benefit ratio of intervention in many cases of atherosclerotic disease. Concerning patients treated with the current best medical therapy, carotid intervention should only be performed when it is documented a periprocedural risk of less than 6% in symptomatic patients. Although major guidelines endorse intervention in asymptomatic patients provided that the periprocedural risk is less than 3%, the narrow magnitude of the absolute stroke prevention places carotid intervention as a questionable procedure in an unselected asymptomatic population.

Author contributions

Conception and design of the research: Oliveira PP, Vieira JLC, Portal VL; Acquisition of data: Oliveira PP, Guimarães RB; Analysis and interpretation of the data: Oliveira PP, Portal VL; Writing of the manuscript: Oliveira PP, Vieira JLC, Guimarães RB, Almeida ED, Savaris SL, Portal VL; Critical revision of the manuscript for intellectual content: Oliveira PP, Vieira JLC, Almeida ED, Savaris SL, Portal VL.

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Internationalization is Necessary, But is it Enough?

Gláucia Maria Moraes de Oliveira,[1] Andrea De Lorenzo,[2] Fernanda Marciano Consolim Colombo,[3] Eduardo Back Sternick,[4] Andréa Araujo Brandão,[5] Sergio Emanuel Kaiser,[6] Alexandre Schaan de Quadros,[7] Renato Abdala Karam Kalil,[7] Christianne Brêtas Vieira Scaramello,[9] Francisco Rafael Martins Laurindo,[8] Ludhmila Abrahão Hajjar[8]

Programa de Pós-Graduação em Cardiologia da Universidade Federal do Rio De Janeiro (UFRJ),[1] Rio de Janeiro, RJ – Brazil
Programa de Pós-Graduação em Ciências Cardiovasculares do Instituto Nacional de Cardiologia (INC),[2] Rio de Janeiro, RJ – Brazil
Programa de Pós-Graduação em Medicina da Universidade Nove de Julho (UNINOVE),[3] São Paulo, SP – Brazil
Programa de Pós-Graduação em Ciências da Saúde da Faculdade Ciências Médicas de Minas Gerais,[4] Belo Horizonte, MG – Brazil
Programa de Pós-Graduação em Ciências Médicas Universidade do Estado do Rio de Janeiro (UERJ),[5] Rio de Janeiro, RJ – Brazil
Programa de Pós-Graduação em Fisiopatologia Clínica e Experimental da Universidade Estadual do Rio de Janeiro (UERJ),[6] Rio de Janeiro, RJ – Brazil
Programa de Pós-Graduação do Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia (IC/FUC),[7] Porto Alegre, RS – Brazil
Programa de Pós-Graduação em Cardiologia da Universidade de São Paulo (USP),[8] São Paulo, SP – Brazil
Programa de Pós-Graduação em Ciências Cardiovasculares da Universidade Federal Fluminense (UFF),[9] Rio de Janeiro, RJ – Brazil

Globalization has left its mark on the 21st century. One of the many ways of defining globalization is as the integration of information, communication, and economy on a worldwide scale, with a direct influence on all levels of higher education. In this manner, the internationalization of postgraduation may be seen as a response to globalization, taking shape in the form of programs and policies put in place by academic institutions and governments in order to increase student and faculty exchanges and to stimulate and strengthen partnerships in research, among other actions. Universities and research centers have, in fact, been practicing these actions for a long time, but they have expanded significantly, particularly during this century.

Various studies[1-3] have repeatedly shown that collaborative research that involves authors from multiple institutions and/or countries have an identifiably greater impact than research involving only one group or institution. In Brazil, the internationalization of postgraduation has been highly valued by the Coordination for the Improvement of Higher Education Personnel (CAPES), generating immense efforts on the part of postgraduate programs (PGPs) to achieve the goals defined. In a study conducted with PGPs ranked 6 or 7 by CAPES, Ramos[1] observed that internationalization in these PGPs encompasses everything from international mobility, international cooperation networks, academic output (international publications, international co-authorships, presentation of academic work in international scientific conferences and meetings), to access to resources through the sharing of research facilities and international funding. In Brazilian PGPs, the most popular internationalization strategies were international mobility of faculty, researchers, and students and international research collaboration, implemented mainly through international cooperation agreements. This study, nevertheless, detected inequalities between institutions in the provision of adequate conditions for internationalization. The availability of financial resources, the existence of regulatory frameworks, and organizational support were considered important requisites for achieving this goal.[1]

Thus, due to the demands of CAPES, the need to internationalize has led to an institutional "race" between PGPs in search of partners, with or without government support, and often in a competitive manner. The strategies adopted by each institution vary in accordance with their "scope" (based on professors and researchers' contacts or previously established partnerships) and their level of resources and complexity capable of influencing international visibility and competitiveness. This "academic entrepreneurship"[2] may or may not be considered positive, given that more well known institutions often have a head start in the competition for funds, to the detriment of other academic centers. The existence of national policies that support internationalization, including the publication of national journals, is extremely important, as can be seen in the example of countries that have successfully invested in this form of support.[3]

In order to meet the demands imposed by CAPES, PGPs and medical societies are faced with the challenge of making a joint effort to provide all academic institutions with access to opportunities and to allow the scientific output that originates from these PGPs to be disseminated by their national and international peers. In this context, the Brazilian Society of Cardiology (SBC) has held "Postgraduate Meetings in Cardiovascular Sciences." The theme of the fourth meeting, in 2018, was "The Internationalization of Brazilian Postgraduate Programs."

During this meeting, the international guest speaker Professor Fausto J. Pinto, the Director of the Faculty of Medicine of the University of Lisbon, spoke about partnerships between European and Brazilian universities and announced the signing of a recent agreement between the Portuguese institution and the Federal University of Rio de Janeiro's School of Medicine for the bilateral recognition of diplomas

Keywords

Scientifcs Periodicals/internacionalization; International Cooperation; Researcher Performance Evaluation System; Journal Impact Factor; Databases, Bibliographics; Citation Databases

Mailing Address: Gláucia Maria Moraes de Oliveira •
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – Prédio do HU 8º andar – sala 6, UFRJ. Postal Code 21941-913, Cidade Universitária, RJ – Brazil
E-mail: glauciam@cardiol.br, glauciamoraesoliveira@gmail.com
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and dual degrees. He emphasized the importance of reinforcing contacts between universities in Brazil and Europe, especially in Portugal, in order to make the dissemination and adaptation of existing models possible by establishing a network of Portuguese-language medical schools as an element to facilitate exchange, in addition to the creation of an "Erasmus-like" program for the Community of Portuguese Language Countries (CPLP).

The visibility of national research is another important aspect of internationalization. It is of the utmost importance to disseminate research carried out by the Brazilian scientific community in the area of cardiovascular disease (CVD), which is recognized as the leading cause of mortality in Brazil and worldwide. The SBC has two journals indexed in SciELO: the *Arquivos Brasileiros de Cardiologia (ABC Cardiol)* and the *International Journal of Cardiovascular Sciences*. The *ABC Cardiol*, which is indexed in the main databases, including ISI Web of Science, Index Medicus, MEDLINE, PubMed Central, EMBASE, Scopus, SciELO and LILACS, obtained an Impact Factor (IF) of 1.318 from Journal Citation Reports (JCR), as well as a B2 rating from the CAPES Qualis System in its most recent evaluation.[4]

The *ABC Cardiol* is Latin America's main journal for the publication of research in the area of Cardiology and Cardiovascular Sciences and it has an important and increasing degree of internationalization, as more than 20% of its articles are of international origin. It is worth emphasizing that Portuguese language countries (PLCs) have access to the bilingual version of the *ABC Cardiol*, which is published in all Lusophone countries by the Portal of the Federation of Cardiology Societies of Portuguese Language Countries (http://www.fsclp.org), representing approximately 245 million people. In PLCs, the large differences, related mainly to socioeconomic conditions, in the relative impact of CVD burden are noteworthy.[5] The highest quality of scientific output published in the *ABC Cardiol* continues to originate from Brazilian postgraduate programs, which are increasingly exposed, in the meanwhile, to international competition to find publishing space in the *ABC Cardiol*, added to the lower incentive to publish in this journal as a direct result of its current CAPES ranking. It is also very important to valorize the publication of science and knowledge, which are public goods, in open science journals such as the ABC Cardiol and other journals in the SciELO network.

CAPES values the social involvement of PGPs, with the objective of promoting improvements in the population's living conditions. However, Brazilian studies focusing on populations with peculiar socioeconomic characteristics rarely receive the interest of the international community; their dissemination would need to be driven by CAPES' evaluation system in order to strengthen a national exchange network that included PLCs. The innovative scientific contributions that result from PGPs and their mission for civil society are also worth highlighting. In this sense, it would be desirable for this regulatory agency to create a system, mediated by Qualis, for valuing the leading journal in the fight against the CVD epidemic in a manner that makes it possible to share successful experiences in fighting CVD with these countries.

An unprecedented academic revolution is taking place in higher education, leading to a real need for the internationalization of PGPs. Internationalization offers new opportunities for study and research that are limited neither by national boundaries nor by boundaries to knowledge. However, "internationalization is not a goal in itself, but rather a means to accomplish improvements in teaching, research, and innovation,"[6] as well as to promote the development of a more just and equitable society through improvements in the living conditions of the population; this, upon final analysis, is the main objective of research undertaken by PGPs. The recognition of national research must also occur ethically and meritocratically through the valuing of the means responsible for its dissemination. The growth of Brazilian journals will have to be the fruit of intellectual investment on the part of researchers who produce quality science and internationalization through international partnerships, as well as stimulation and valorization through better rankings in CAPES' evaluation system.

Author contributions

conception and design of the research: Oliveira GMM; acquisition of data and analysis and interpretation of the data: Oliveira GMM, Lorenzo AD; writing of the manuscript and critical revision of the manuscript for intellectual contente: Oliveira GMM, Lorenzo AD, Colombo FMC, Sternick EB, Brandão AA, Kaiser SE, Quadros AS, Kalil RAK, Scaramello CBV, Hajjar LA.

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Case 5 / 2018 - Acute Respiratory Failure and Cardiogenic Shock in a Patient in the First Trimester of Pregnancy with Mechanical Mitral Valve Prosthesis Implant

Walkíria Samuel Ávila, Vinícius Araújo de Freitas Chagas Caldas, Daniel Valente Batista, Paulo Sampaio Gutierrez
Instituto do Coração (InCor) HC-FMUSP, São Paulo, SP - Brazil

This case describes a 36-year-old female patient born in the state of Alagoas, and residing in the municipality of Guarulhos, state of São Paulo, Brazil, married, illiterate, admitted at the Gynecology and Obstetric Service after clinical diagnosis of upper airway infection at the 9th week of the 1st pregnancy.

She was followed up at the outpatient clinic specialized in congenital heart defects due to complex congenital heart disease, which included interatrial defect associated with patent ductus arteriosus and interventricular septal defect, as well as a left atrioventricular septal defect. She underwent surgery at the age of eight, consisting of atrioseptoplasty, ventriculoseptoplasty and mitral valve replacement by a mechanical prosthesis. She had paroxysmal atrial fibrillation, with a previous thromboembolic event, left hemisphere ischemic stroke, without neurological sequelae, being asymptomatic from the cardiovascular point of view, in functional class I (NYHA classification) at the last consultation in April 2018. She used only warfarin, undergoing regular follow-up of prothrombin time control/INR, having maintained it between 2-3 in the last controls.

During hospitalization in the Obstetrics Service, warfarin was replaced by enoxaparin 1mg / kg, subcutaneously, every 12 hours, and during the evolution she had atrial fibrillation with high ventricular response accompanied by dyspnea at rest and orthopnea, being subsequently referred to the Emergency Service of the Cardiology Hospital.

The physical examination at admission (May 30, 2018) showed regular overall health status, normal skin color, hydrated, anicteric, conscious, oriented, without alterations at the neurological examination. Cardiovascular examination showed regular heart rhythm, with heart rate at 115 beats per minute, holosystolic murmur, with prosthesis profile, at the superior left sternal border 2 + / 6 +, good peripheral perfusion. The respiratory system showed crackling rales on the left lung base, and mild dyspnea at rest. Gravid abdomen, with no signs of hepatic congestion. Extremities without edema, with no discomfort or pain in the calves.

The laboratory results at admission (May 30, 2018) were: hemoglobin 12.4 g / dL; leukocytes 13,050/mm^3 (band cells 1%, segmented 79%, eosinophils 1%); platelets 120,000/mm^3; C-reactive protein: 74.6mg / dL; Urinalysis: Leukocytes 16,000/mL, negative nitrite test, bacteria 1+/4+, Urinary culture at the hospital of origin with multisensitive *E.coli*.

The admission electrocardiogram (May 30, 2018) (Figure 1) showed sinus rhythm, heart rate of 115 bpm, indirect signs of right atrial overload.

The admission chest x-ray (May 30, 2018) (Figure 2) disclosed indirect signs of pulmonary congestion ("cottony" infiltrate, predominantly bibasal), peri-hilar air bronchogram on the right and image compatible with mechanical prosthesis in the mitral position.

The initial diagnosis at hospitalization was bronchopneumonia, pulmonary congestion, atrial fibrillation with high ventricular response, and a single, nine-week non-ectopic pregnancy, and she was prescribed: Ceftriaxone, Clarithromycin, Oseltamivir, Furosemide and Sotalol. The requested exams included blood culture, H1N1 virus screening, transthoracic echocardiography, and Anti-Xa factor.

During the evolution she showed signs and symptoms of pulmonary infectious disease (cough, dyspnea, leukocytosis with left shift, high PCR, with negative H1N1), and it was decided to discontinue Oseltamivir and implement empirical antibiotic therapy with Meropenem.

Compared with the patient's last transthoracic echocardiogram, the transthoracic echocardiogram carried out on June 4, 2018 disclosed a marked increase in the mitral transvalvular gradient (maximum diastolic gradient of 39mmHg and mean of 25mmHg), in addition to an increase of pressures in the right chambers, with right ventricular systolic pressure of 75 mmHg, with no evidence of thrombi or vegetation (Table 1).

Furosemide and metoprolol were added to the antibiotics aiming at heart rate control, in addition to anticoagulation maintenance with enoxaparin with adequate levels of Anti-Xa factor (between 0.8 and 1U/mL) with improvement of clinical status. A transesophageal echocardiogram was requested for a more adequate assessment of the valve prosthesis (June 14, 2018). This examination showed the reduction in the mobility of the mitral prosthesis components, with a high mean transvalvular gradient (30 mmHg and a hypoechogenic image occupying the central region of the atrial face of the prosthesis, compatible with a thrombus). Its measurements,

Keywords

Respiratory Insufficiency; Heart Defects, Congenital; Heart Valve Prosthesis; Shock, Cardiogenic; Pregnancy.

Section Editor: Alfredo José Mansur (ajmansur@incor.usp.br)

Associated Editors: Desidério Favarato (dclfavarato@incor.usp.br)
Vera Demarchi Aiello (anpvera@incor.usp.br)

Mailing Address: Vera Demarchi Aiello •
Avenida Dr. Enéas de Carvalho Aguiar, 44, subsolo, bloco I, Cerqueira César. Postal Code 05403-000, São Paulo, SP – Brasil
E-mail: demarchi@cardiol.br, anpvera@incor.usp.br
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Anatomopathological Correlation

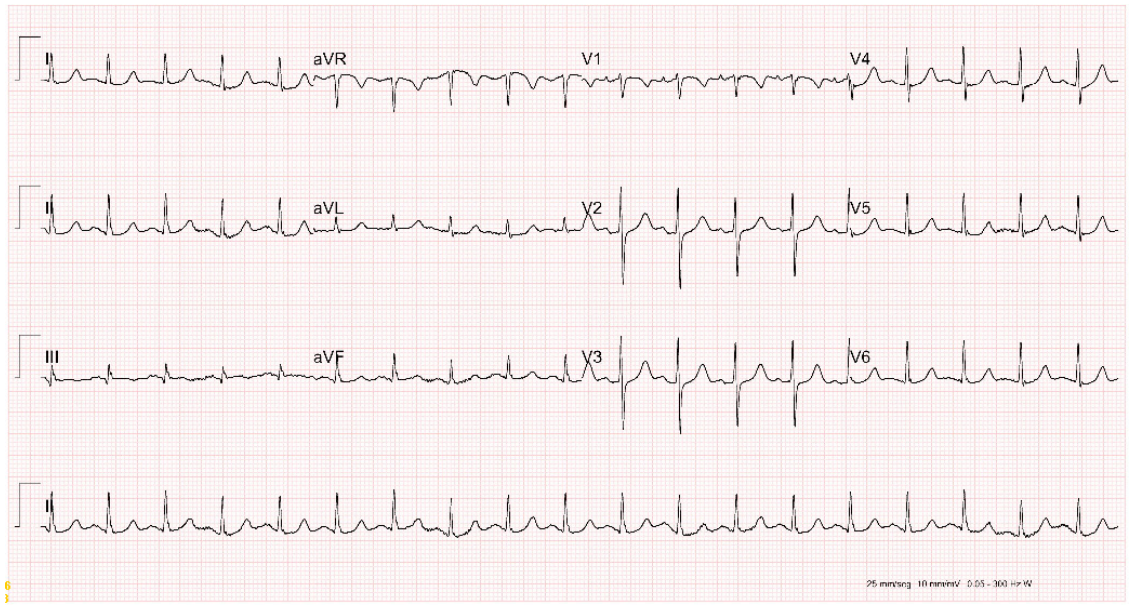

Figure 1 – *Admission ECG: sinus rhythm with indirect signs of left atrial overload and right atrial overload (Peñaloza-Tranquesi).*

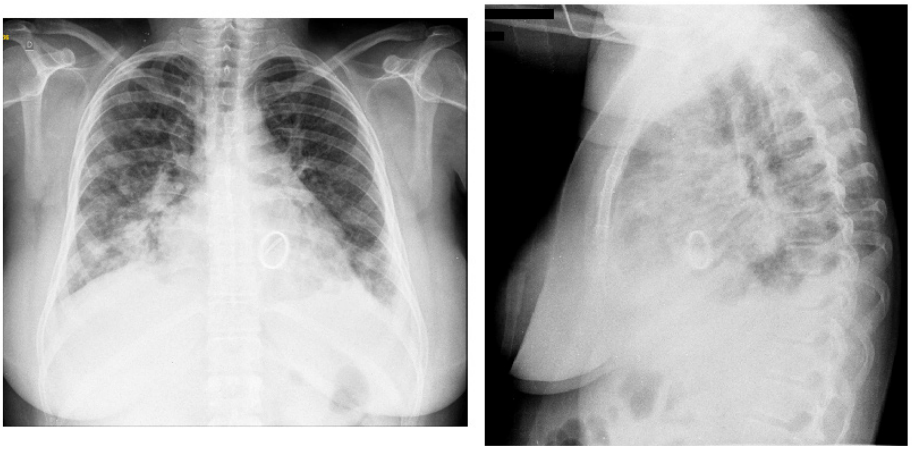

Figure 2 – *Admission chest x-ray: signs of congestion and pulmonary infection (air bronchogram).*

even underestimated, since it was difficult to determine its full extent using the two-dimensional methodology, reached values of 0.9 x 1.3 cm, resulting in an area of 1.17 cm^2 (important when > 0.8 cm^2) and, thus, the surgical intervention was indicated, since it was available at the service (Table 1). Given the echocardiographic diagnosis of mitral valve prosthesis thrombosis, surgical treatment of the mitral valve was indicated, despite the gestational age, due to the high risk of maternal death. Intravenous unfractionated heparin was then started in an infusion pump while awaiting the surgical procedure.

During this period, the patient developed a new picture of marked dyspnea, with marked congestion (Figure 3), tachycardia, and fever, requiring invasive ventilatory support with orotracheal intubation, and hypotension requiring vasopressor agent (noradrenaline). She went into cardiorespiratory arrest for 6 minutes, with spontaneous circulation and frank shock, requiring high doses of noradrenaline, adrenaline and vasopressin. She remained in shock and, despite the measures, presented with bradycardia and asystole and died (7h22; June 18, 2018). (Dr. *Walkíria Samuel Ávila)*

Table 1 – Echocardiographic evolution

Echocardiographic measures	Date		
	Pre-admission	June 04, 2018	June 14, 2018
Aorta (mm)	24	28	28
Left atrium (mm)	45	55	57
Right ventricle (mm)	24	26	41
Septum (mm)	10	9	9
Posterior wall (mm)	9	10	9
Left Ventricle Diast./Syst. (mm)	53/33	40/28	40/25
LVEF (%)	Normal	Normal	Normal
Max. trans-mitral gradient (mm Hg)	16	39	45
Mean trans-mitral gradient (mm Hg)	6	25	30
Mitral prosthesis (mobility)	Good	Low	Low
Thrombus	No	No	Yes
RV Syst pressure (mm Hg)	46	75	73

Diast.: diastolic; Syst.: systolic; LVEF: left ventricular ejection fraction; RV: right ventricle.

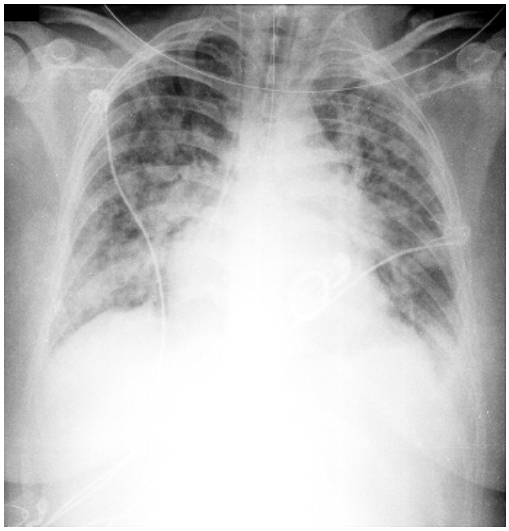

Figure 3 – *Chest X-ray showing significant pulmonary congestion.*

Clinical aspects

The case reported is of a 36-year-old pregnant woman with repaired complex congenital heart disease, with a mechanical mitral valve prosthesis implanted 28 years before, paroxysmal atrial fibrillation, and a history of thromboembolism, a triad that characterizes a high thromboembolic risk.[1]

Notwithstanding, the patient maintained the adequate anticoagulation goal (INR = 3) until the pregnancy diagnosis, when the anticoagulation regimen of warfarin was replaced by enoxaparin due to the risk of fetal warfarin syndrome, which occurs between the 6th and 12th weeks of gestation (characterized by nasal hypoplasia, dysplasia of the bony epiphyses, limb deformities, neurological and respiratory problems).[1] However, there is less evidence of the erratic bioavailability and distribution of enoxaparin during pregnancy,[2] although it constitutes a current challenge to define the best anticoagulation strategy in this population with high thromboembolic risk.

As a therapeutic option for the treatment of prosthesis thrombosis, the thrombolysis with streptokinase or alteplase, guided by serial transesophageal echocardiography, was shown to be safe and effective.[3] However, considering the clinical situation of the patient, such as NYHA functional class IV, the need for intensive care, mechanical mitral prosthesis with a thrombus size > 0.8 cm^2, the surgical treatment was chosen.[4-6]

Anatomopathological Correlation

Despite the established supportive care, while waiting for the previously indicated definitive surgical therapy, the patient showed clinical deterioration and died, alerting us to the potential severity of a prosthesis thrombosis picture, which requires an emergency procedure (surgical or thrombolysis), regardless of aggravating factors such as the pregnancy itself or associated infections. (Dr. Vinícius Araújo de Freitas Chagas Caldas and Dr. Daniel Valente Batista)

Diagnostic hypotheses: cardiogenic shock, acute pulmonary edema, thrombosis of the mechanical mitral prosthesis, systemic inflammatory response syndrome with possible pulmonary infectious focus. (Dr. Vinícius Araújo de Freitas Chagas Caldas and Dr. Daniel Valente Batista)

Necropsy

The gravid uterus contained an apparently well-formed fetus. The mother had a mild degree of pulmonary emphysema and significant alterations in the cardiovascular system, with a patent ductus arteriosus (Figure 4) measuring 2 mm in diameter; small interventricular septal defect (Figure 5); surgical sutures in the atrial septum, possibly corresponding to the defect closure; embolism (or thrombosis) of the left subclavian vein; and mechanical valve prosthesis in the mitral position, occluded by the presence of a thrombus-like mass in the two faces (Figure 6). Microscopic study confirmed the nature of this mass, with absence of microorganisms (Figure 7). There were small infarcts in the right kidney, possibly due to embolism caused by the prosthesis thrombus, and in the subendocardial region of the left ventricle. The lungs showed many alterations, almost in their entirety, with a histopathological pattern of organizing pneumonia (Figure 8). Furthermore, demonstrating congestion, there were macrophages containing hemosiderin, but not in large numbers; and dilation of lymphatic vessels. (Paulo Sampaio Gutierrez)

Anatomopathological diagnoses: Congenital heart disease with interatrial defect, interventricular defect, patent ductus arteriosus, and thrombosis of the mechanical mitral valve.

Cause of death: Mitral valve obstruction / organizing pneumonia (Dr. Paulo Sampaio Gutierrez)

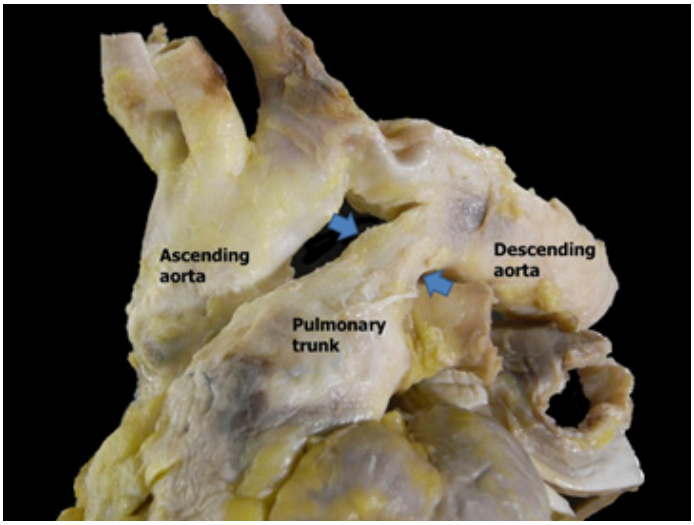

Figure 4 – *Great arteries of the heart showing patent ductus arteriosus (between the arrows).*

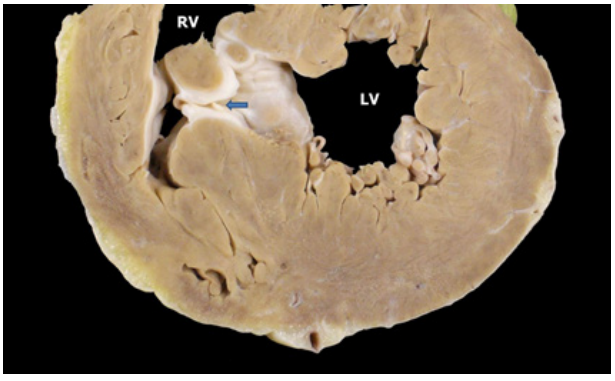

Figure 5 – *Transversal section of the heart at the region of the ventricles showing a muscular ventricular septal defect (arrow). RV- right ventricle; LV- left ventricle.*

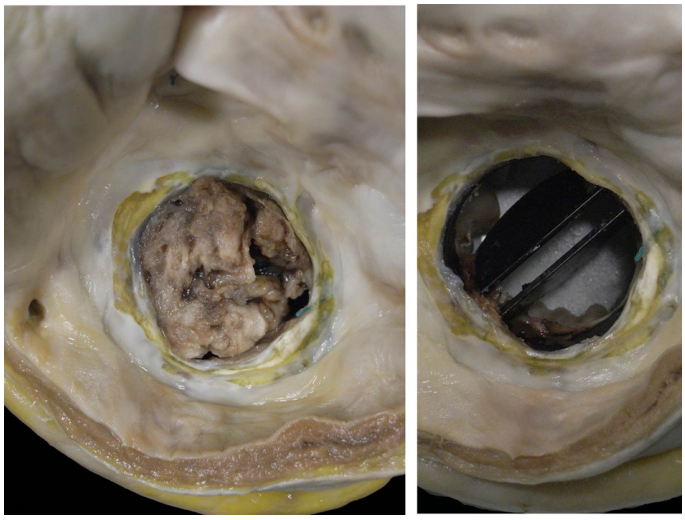

Figure 6 – *The mechanical valve prosthesis is seen from the opened left atrium. The left panel shows a massive thrombus occluding almost completely the valvar orifice. After removal of the thrombus, (right panel), it is demonstrated that the prosthesis shows adequate opening.*

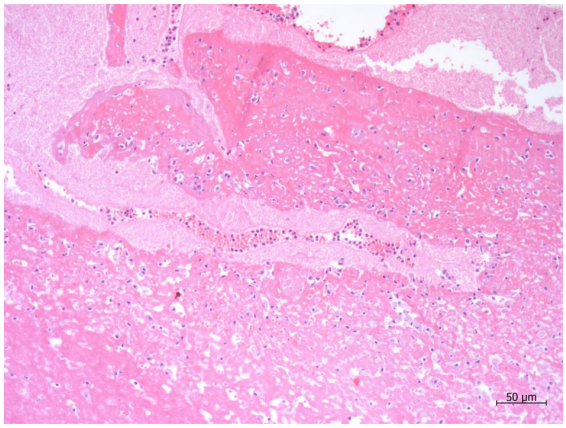

Figure 7 – *Histological section of the mass adhered to the valve prosthesis, constituted by thrombus, with fibrin and moderate amounts of inflammatory cells, without microorganisms. Hematoxylin & eosin staining; objective magnification: 10x.*

Comment

Although the main problem that led to the death of the patient was thrombosis of the mitral valve prosthesis – emphasizing the difficulty of managing the coagulation system during pregnancy – it is worth mentioning that the lungs were also very affected, with a pattern of organizing pneumonia. It is important to emphasize that the diagnosis of "organizing pneumonia" refers to a picture that may follow not only classical bacterial pneumonia, but also several other situations, such as viral infections, exposure to toxic inhalants and others.[7] However, marked congestion, albeit sudden, is not listed among the possible causes of this process. Therefore, in the present case, organizing pneumonia must have been due to the respiratory picture, possibly an infectious one, whether viral or bacterial, which was already present when the patient was admitted at the institution.

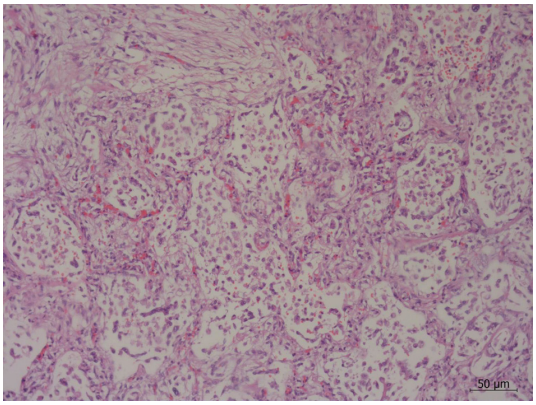

Figure 8 – *Histological section of the lung showing alveoli filled by mononuclear cells and presence of collagen. Hematoxylin & eosin staining; objective magnification: 10x.*

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Quantification of Coronary Flow Reserve with CZT Gamma Camera in the Evaluation of Multivessel Coronary Disease

Ana Carolina do Amaral Henrique de Souza,[1] Bernardo Kremer Diniz Gonçalves,[1] Angelo Tedeschi,[1] Ronaldo de Souza Leão Lima[1,2]

Universidade Federal do Rio de Janeiro (UFRJ),[1] Rio de Janeiro, RJ - Brazil

Clínica de Diagnóstico por Imagem,[2] Rio de Janeiro, RJ - Brazil

Introduction

Evaluating patients with multivessel coronary disease using myocardial perfusion scintigraphy (MPS) remains a challenge as the extent and severity of the disease can be underestimated. This phenomenon occurs in part due to balanced ischemia and inaccuracy of traditional devices to identify small changes in coronary flow in the stress phase.[1,2] New gamma cameras with cadmium and zinc telluride (CZT) detectors that are already commercially available have shown higher temporal and spatial resolution,[3-5] theoretically enabling dynamic acquisition of images and calculation of myocardial blood flow (MBF) and coronary flow reserve (CFR) in an absolute way.[6,7] This tool, whose use with positron emission tomography (PET) is already well established,[8-10] may be promising to non invasively access three-vessel obstructive coronary artery disease (CAD) using scintigraphy and its conventional radiotracers. The objective of this case report is to describe the quantification of CFR upon diagnosis of a patient with multivessel disease whose myocardial perfusion image showed a defect not compatible with coronary angiography.

Clinical case

A 58-year-old patient was seen for the first time in an outpatient Cardiology clinic presenting with dyspnea on medium exertion and improvement with rest. His medical history included hypertension, dyslipidemia, and positive family history. The patient was not under regular clinical follow-up or on optimized medication. Transthoracic echocardiogram performed nine months showed no alterations and patient was referred for myocardial perfusion scintigraphy in a specialized service. A one-day protocol was performed, with rest phase followed by pharmacological stress phase using dipyridamole and ^{99m}Tc-sestamibi as radiotracer at 10 and 30 mCi at rest and stress, respectively. Images were obtained in a CZT gamma camera (Discovery 530, GE Healthcare), with MBF and CFR quantified in a context of clinical research, coupled with the perfusion imaging protocol. The protocol was initiated by intravenous injection of 1 mCi of ^{99m}Tc-sestamibi to place the heart within the gamma camera field of vision. The rest phase included the acquisition of dynamic images during eleven minutes, immediately followed by the perfusion images during five minutes. While the patient was still positioned in the gamma camera, pharmacological stress phase was initiated with dipyridamole (0.56 mg/kg) so that stress dynamic images could be obtained during eleven minutes and perfusion images, for three minutes. Images showed a small area of inferolateral ischemia, with no contractile alterations. Reduced CFR values were identified in all coronary territories, as well as absolute flow (ml/min/g), on rest and stress (Figure 1). After scintigraphy, symptoms persisted despite therapeutic optimization, so the patient was referred for coronary angiography, which revealed three-vessel obstructive CAD, with a 90% segmental lesion of the proximal third in anterior descending artery; 75% proximal lesion in the second diagonal branch; 75% ostial lesion in the first and third marginal branches of the circumflex; 75% segmental lesion in the posterior ventricular branch. In the right coronary artery, a long lesion of 50% was found in the middle third, in addition to a 75% lesion in the posterior descending and ventricular branches (PD/VP), with 90% impairment of the PV branch.

Discussion

This is the first quantification report of CFR in a CZT gamma camera in our country. The protocol for image acquisition was proven safe and adequate to generate good-quality data. This case clearly represents a situation in which MPS is not able to identify the extent of ischemia due to multivessel disease. This phenomenon is in accordance with the literature, which has already described low prevalence of perfusion defects in populations of patients with three-vessel coronary obstructive disease.[1] One of the reasons of this event is balanced ischemia. Considering that MPS only evaluates relative flow, it is based on the comparison of a myocardial wall with another whose radiotracer uptake is greater, and in situations like these an overall flow reduction occurs, generating little or no heterogeneity and, therefore, a possibly normal image.

In this context, determining myocardial flow and quantifying CFR is useful to identify high-risk patients, as they present absolute and non-relative results, like in conventional MPS. CFR can be defined as the magnitude of increased myocardial blood flow secondary to stress of any nature compared to resting flow. It is thus possible to describe not only the effects of focal epicardial obstructions, but also diffuse atherosclerosis and microvascular dysfunction, both of which are quite common

Keywords

Fractional Flow Reserve, Myocardial; Coronary Artery Disease; Coronary floe reserve/methods; Diagnostic Imaging; Myocardial Perfusion Imaging.

Mailing Addressa: Ana Carolina do Amaral Henrique de Souza •
Av. Jornalista Alberto Francisco Torres, 67 apto 601, Postal Code 24230-000, Icaraí, Niterói, RJ – Brazil
E-mail: ana_carolina_amaral@hotmail.com
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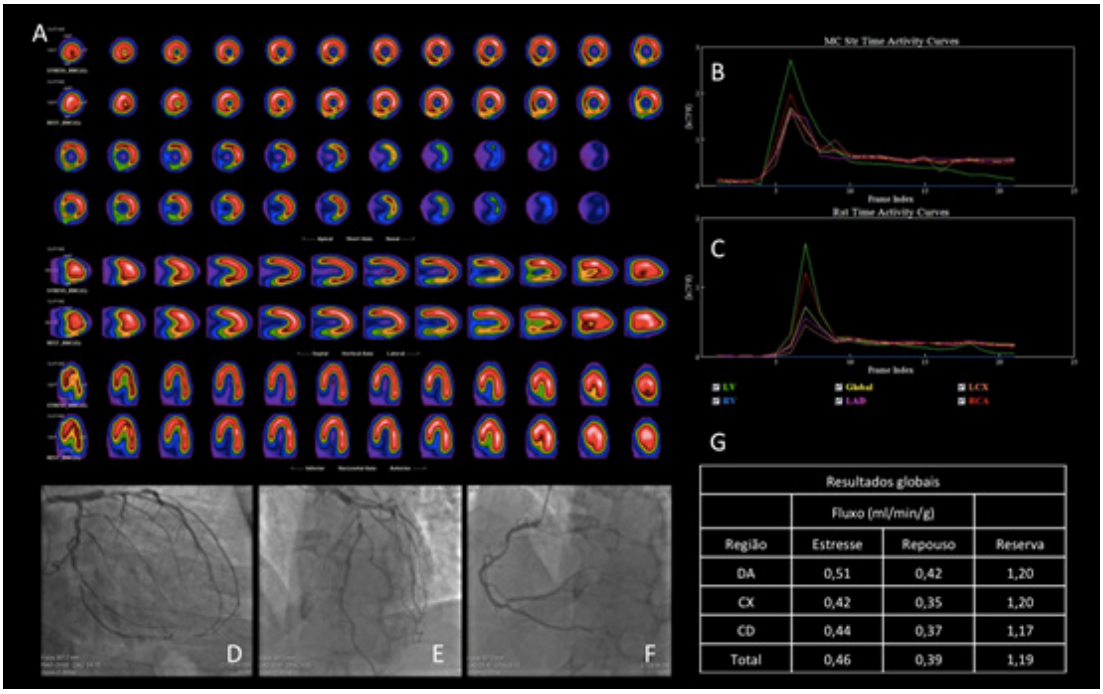

Figure 1 – *Evaluation of patient with suspected CAD. A) MPS showing small area of inferolateral ischemia. B and C) Time-activity curves in stress and rest phases, respectively, derived from the dynamic acquisition in CZT gamma camera. D, E, and F) Angiographic images showing 90% lesion in anterior descending artery, 75% lesion in circumflex artery and 50% in the middle third of right coronary artery, with 90% obstruction in posterior ventricular branch. G) Overall results of MBF quantification (in ml/min/g) and CFR in coronary territories (anterior descending artery, circumflex artery, and right coronary artery, respectively), followed by total values (last line). Reduced values of MBF and CFR are seen in all territories, which is compatible with the obstructive lesions found in coronary angiography. CAD: coronary artery disease; MPS: myocardial perfusion scintigraphy; MBF: myocardial blood flow; CFR: coronary flow reserve.*

in women and patients with metabolic syndrome. Previous PET studies have shown that CFR measurement can classify patients at low and high risk for cardiovascular events[9] and therefore be used as a new tool for risk stratification.

New gamma cameras with solid and stationary CZT detectors have advantages when compared to traditional ones, with sodium-iodide detectors, as they allow for dynamic tomographic images and, theoretically, CFR quantification. Wells et al.[6], in a pioneering work, have demonstrated a precise CFR quantification in a porcine model of resting and transitory occlusion upon stress using CZT gamma camera, paving the way for new possibilities of pilot studies with humans. Bouallègue et al.[7] evaluated CFR in 23 patients in comparison to their angiographic data, including fractional flow reserve (FFR), and found a good correlation between CFR and the number of obstructed vessels and reduced CFR values in obstructed territories.

As seen in the present report, CFR quantification and the new methods of dynamic acquisition of myocardial blood flow constitute a current field of research that could generate knowledge about new applications of scintigraphy and bring improvements to diagnosis and management of coronary disease patients, including those with multivessel disease.

Author contributions

Conception and design of the research: Lima RSL; Acquisition of data: Souza ACAH, Gonçalves BKD, Tedeschi A, Lima RSL; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Souza ACAH; Critical revision of the manuscript for intellectual content: Tedeschi A, Lima RSL, Gonçalves, BKD.

Potential Conflict of Interest

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Study Association

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Takayasu Arteritis: From Diagnosis to a Life-Threatening Complication

Filipa Cordeiro, Sofia Silva Carvalho, Fernando Salvador, Alberto Ferreira, J. Ilidio Moreira

Centro Hospitalar de Trás-Os-Montes e Alto Douro, Hospital de Vila Real, Portugal

A fifty-two-year-old Caucasian woman was admitted for severe epigastric pain irradiating to the back. Physical examination and electrocardiogram were normal. Laboratory tests showed leucocytosis (11100 cells/uL) and increased levels of C-reactive protein (15.6 mg/dl). Due to the suspicion of acute aortic syndrome (AAS), she underwent computed tomography (CT), which showed a low attenuation circumferential mural thickening of the aorta (43 Hounsfield units (HU)), which enhanced (73 HU) after contrast administration (Figures 1 A-C), suggestive of aortitis.[1] Transesophageal echocardiogram also revealed thickened thoracic aorta (Figure 1 D). Cardiovascular magnetic resonance imaging confirmed the diagnosis of aortitis and excluded intramural hematoma (mural thickening hypointense on T1-weighted images and hyperintense on T2-weighted images)[1,2] (Figures E-F). Infectious serologies were negative.

The patient was diagnosed with Takayasu arteritis (TA) at initial inflammatory phase and initiated treatment with high-dose steroids. There was a reduction of serum inflammatory markers and aortic wall inflammation. Positron emission tomography after fifteen days of therapy showed a discrete tracer uptake in the thoracic aorta (Figure G). After six weeks of treatment, the patient initiated severe back pain. CT angiography showed type A aortic dissection (Figure H). She underwent emergent cardiac surgery, which included resection of ascending aorta, replacement with an artificial graft and obliteration of distal false lumen. Postoperative period was uneventful.

TA is a rare, large-vessel vasculitis characterized by an inflammatory phase followed by a pulseless phase.[3,4] Multimodality imaging is useful for diagnosis, which can be challenging due to the similarities with AAS, and follow-up.[1,2] Aortic dissection is an exceptionally rare complication.[5]

Keywords

Takayasu Arteritis/surgery; Aortitis/physiopathology; Takayasu Arteritis/diagnostic imaging; Vasculitis.

Mailing Address: Filipa Cordeiro •
Rua da Pena, nº420. 4750-693, Barcelos, Braga – Portugal
E-mail: filipabritocordeiro@gmail.com
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Author contributions

Writing of the manuscript: Cordeiro F; Critical revision of the manuscript for intellectual content: Cordeiro F, Carvalho SS, Salvador F, Ferreira A, Moreira JL.

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Study Association

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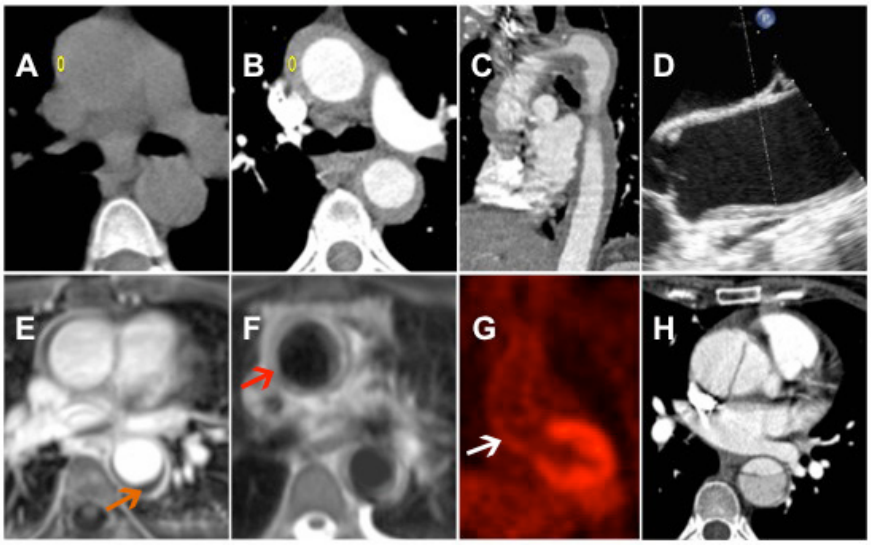

Figure 1 – *A) Non-contrast computed tomography showing low-attenuation concentric mural thickening of the thoracic and abdominal aorta (43 HU). B and C) Computed tomography angiography revealing enhancement of the mural thickening of the thoracic and abdominal aorta (73 HU). D) Transesophageal echocardiogram presenting thickening of the thoracic aorta after the Valsalva sinus. E and F) Cardiovascular magnetic resonance imaging demonstrating that mural thickening was hypointense on T1-weighted images (E, orange arrow) and hyperintense on T2-weighted images (F, red arrow), consistent with aortitis. G) Positron emission. Tomography after fifteen days of steroid therapy showing a discrete tracer uptake in the thoracic aorta (white arrow). H) Computed tomography angiography revealing type A aortic dissection six weeks after the initial diagnosis of Takayasu arteritis.*

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Body Mass Index May Influence Heart Rate Variability

Thalys Sampaio Rodrigues[1] and Levindo José Garcia Quarto[2]

University of Melbourne Department of Medicine Austin Health,[1] Heidelberg, Victoria - Austrália

Hospital Regional Norte,[2] Sobral, CE - Brazil

We read with interest the article by Bassi et al.,[1] titled "Effects of Coexistence Hypertension and Type II Diabetes on Heart Rate Variability and Cardiorespiratory Fitness", published in the issue of July 2018. The authors investigated the influence of systemic hypertension on cardiac autonomic modulation in patients with type 2 diabetes mellitus (T2DM) and assessed the heart rate variability (HRV) on exercise capacity in these patients. They concluded that hypertension negatively affects cardiac autonomic function, with greater impairment in HRV, when compared to normotensive patients with T2DM.

Keywords

Hypertension/prevalence; Diabetes Mellitus, Type 2; Risk Factors; Cardiovascular Diseases; Autonomic Nervous Systems; Heart Rate.

Mailing Address: Thalys Sampaio Rodrigues •
145 Studley road. 3084, Heidelberg, Victoria – Australia
E-mail: thalys.sampaiorodrigues@unimelb.edu.au
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Several aspects of this study require discussion. As previously reported, numerous factors may have impact on HRV indices, including sex, insulin resistance, body mass index (BMI), hyperlipidemia, hypertension, ischemic and non-ischemic cardiomyopathy, and smoking status.[2-4] For instance, increased BMI can independently decrease HRV, particularly when central adiposity is present.[5] Indeed, the hypertensive group had a higher BMI when compared to the normotensive group (28 ± 4.4 vs 31 ± 3.8, $p = 0.031$). Given the lack of control for BMI between the two groups, the conclusions made by the authors should be regarded cautiously.

Finally, it is known that subclinical myocardial dysfunction is highly prevalent in diabetic patients and is independently associated with cardiac autonomic neuropathy.[6] However, the authors only considered medical history consistent with ischemic heart disease for stratification/exclusion of patients for analysis. We believe that a more detailed cardiovascular assessment, including echocardiography to determine left ventricular mass and left ventricular diastolic dysfunction, would be important to better stratify the patients and strengthen their conclusions.

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Reply

Dear Editor,

We appreciate the authors' interest towards our article, "Effects of Coexistence Hypertension and Type II Diabetes on Heart Rate Variability and Cardiorespiratory Fitness". We also appreciate the opportunity to respond to their comments. Their critique of our study mainly focused on 3 issues: 1) lack of methodological attention in relation to the participants' gender, BMI and insulin resistance; 2) lack of methodological details about the study population, regarding smoking habits and hyperlipidemia; and 3) lack of consistent investigation on ischemic and non-ischemic cardiomyopathy. We appreciate the authors' concerns; however, we do not agree with many of their comments.

The first issue was clearly acknowledged in our paper. Since cardiac variability dynamics differ between genders, with higher parasympathetic activity and overall complexity for women, gender distribution must be considered when investigating heart rate dynamics.[1] However, in our study, gender

distribution is not significantly different for the investigated groups (Diabetes Mellitus (DM) and DM + Hypertension Systemic arterial hypertension (SAH), p = 0.464). In relation to insulin resistance, we agree with the authors' comments about differences possibly influencing HRV indices. However, we believe that the difference found between groups could be attributed to different weight and BMI. We kindly invite the authors to read a recent study from our group, demonstrating that obesity *per se* impairs aerobic-hemodynamic responses to exercise but that, however, metabolic syndrome (obesity, DM and hypertension) in young adults negatively impacts overall HRV, parasympathetic activity and HRV complexity, corroborating our findings.[2] In the present study, differences were observed between groups for BMI and weight, with patients in the DM group being overweight and patients in the DM + Hypertension group presenting grade 1 obesity; however, we would like to emphasize that, after age, sex and BMI adjustments, we concluded that these variables did not influence our results.

As for the second issue, current smokers were excluded from our study, as previous evidence showed that tobacco use represents an important cardiovascular risk and leads to HRV impairment.[3] Even though it was not detailed in the exclusion criteria section, Table 1 clearly shows that none of the participants were current smokers. As for dyslipidemia, we agree with the authors that it may influence HRV; however, after adjustments for this variable, we concluded that dyslipidemia did not significantly influence our results (p = 1.000).

The last issue is related to the lack of consistent investigation on ischemic and non-ischemic cardiomyopathy in the present study. The authors have criticized that a simple clinical evaluation may not be sufficient to determine the presence of ischemic conditions; however, clinical investigation may indicate the need for further exams, aimed at detecting ischemic and non-ischemic heart disease. In addition, the absence of effort-induced ischemic signs was evident during the cardiopulmonary test. Even though this was not clearly stated in the text, we emphasized that all participants underwent a thorough clinical evaluation, consisting of physical examination, resting electrocardiogram and maximal incremental exercise. We kindly invite the authors to read a relevant study about screening procedures for this kind of patients.[4] Our patients presented no signs or symptoms of suspected ischemic disease, neither at rest, nor during effort. Thus, according to the most recent guidelines for investigation of ischemic patients with DM,[5] no further examination was needed through echocardiography or other exams to investigate the presence of myocardial dysfunction.

Finally, it is well known that hypertension *per se* negatively affects HRV;[6] however, no previous studies investigated linear and non-linear HRV indices in DM + SAH coexistence. Thus, we believe that our article provides a relevant contribution to the understanding of HRV alterations in pathological conditions.

In consideration of the fact that HRV is highly influenced by a number of variables, including demographic and anthropometric characteristics, the presence of obesity, associated comorbidities and cardiovascular risk factors, future, robust studies are needed to further investigate the influence of specific variables on linear and non-linear HRV indices, in order to confirm the preliminary findings of our study.

Daniela Bassi
Ramona Cabiddu
Audrey Borghi-Silva

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Erratum

September issue of 2017, vol. 109 (3), Suppl. 1, pages 1-104

In "3rd Guideline for Perioperative Cardiovascular Evaluation of the Brazilian Society of Cardiology", consider Marcondes-Braga FG as the correct form for the name of the author Fabiana Goulart Marcondes Braga.

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