Prognostic Value of Myocardial Perfusion Scintigraphy with IQ·SPECT Technology in Patients with Suspected or Known Coronary Artery Disease

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Abstract

Background: **IQ·SPECT is a collimator design coupled with a cardio-centric acquisition orbit and specific reconstruction algorithm that increases camera efficiency. However, there is no prognostic data derived from IQ·SPECT exams.**

Objectives: **To evaluate the prognostic value of IQ·SPECT myocardial perfusion scintigraphy (MPS) in patients with suspected or known coronary artery disease (CAD).**

Methods: **The study population consisted of 734 consecutive patients with suspected or known CAD submitted to MPS with IQ·SPECT. Adequate follow-up was obtained in 625 patients. We retrospectively analyzed imaging and clinical data. The follow-up was obtained for no less than 12 months after the MPS study. Statistical significance was taken at $p < 0.05$.**

Results: **Normal IQ·SPECT compared to abnormal IQ·SPECT had lower annualized incidence of hard events (0.2% and 1.1%, respectively, $p = 0.02$), late combined events (1.1% and 5.5%, respectively, $p = 0.008$), and revascularization (1% and 14%, respectively, $p < 0.001$). Left ventricular ejection fraction ≤ 45% was found to be the only clinical predictor of hard events ($p < 0.0003$, confidence interval [CI] = 5.25 to 129.02). However, for combined events, abnormal MPS ($p < 0.0001$, CI = 3.39 to 11.13, hazard ratio [HR] = 6.14) and dyspnea/fatigue ($p = 0.013$, CI = 1.28 to 8.4, HR = 3.3) obtained statistical significance. In contrast, ischemic burden ≥ 5% ($p < 0.0001$, HR = 30.3) was the most relevant parameter for revascularization, followed by thoracic pain ($p = 0.002$, HR = 2.4).**

Conclusion: **Our study demonstrates that IQ SPECT MPS has significant prognostic capabilities with very low risk of adverse events in patients with normal findings.**

Keywords: **Prognosis; Myocardial Perfusion Scintigraphy; Coronary Artery Disease.**

Introduction

Cardiovascular diseases are still the leading cause of mortality worldwide, and ischemic heart disease is responsible for 8.9 million deaths, accounting for 16% of global deaths.[1] The diagnostic approach for coronary atherosclerosis and significant myocardial ischemia is a multistep process with diagnostic testing being offered to selected patients.[2] Quantitative assessment of the extension, severity, and reversibility of perfusion defects through myocardial perfusion scintigraphy (MPS) plays a crucial role in predicting future cardiac events such as cardiac death or nonfatal myocardial infarction.[3] It has been demonstrated that patients with negative ischemic scintigraphy have a lower risk of cardiac events in the long-term compared to those with ischemia-negative stress echocardiography.[4] Some studies indicate that severity of myocardial ischemia is associated with negative outcomes and that relieving ischemia might improve prognosis.[5]

In this context, the role of MPS in significant obstructive coronary artery disease (CAD) has driven advancements in nuclear cardiology on efficiency, patient radiation safety, and reducing costs. While professional societies have developed criteria to reduce overutilization,[6,7] technologies and procedures have been developed to promote fast, high-count imaging associated with low dose protocols.[6,7] MPS improvements brought the possibility to scan patients with half time, half dose, better image quality, and new types of quantification such as myocardial blood flow reserve.[8–12]

Compared to conventional NaI(Tl), solid-state SPECT scanners using semiconductor detectors such as cadmium zinc telluride (CZT) have increased the sensitivity and

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Central Illustration: **Prognostic Value of Myocardial Perfusion Scintigraphy with IQ□SPECT Technology in Patients with Suspected or Known Coronary Artery Disease**

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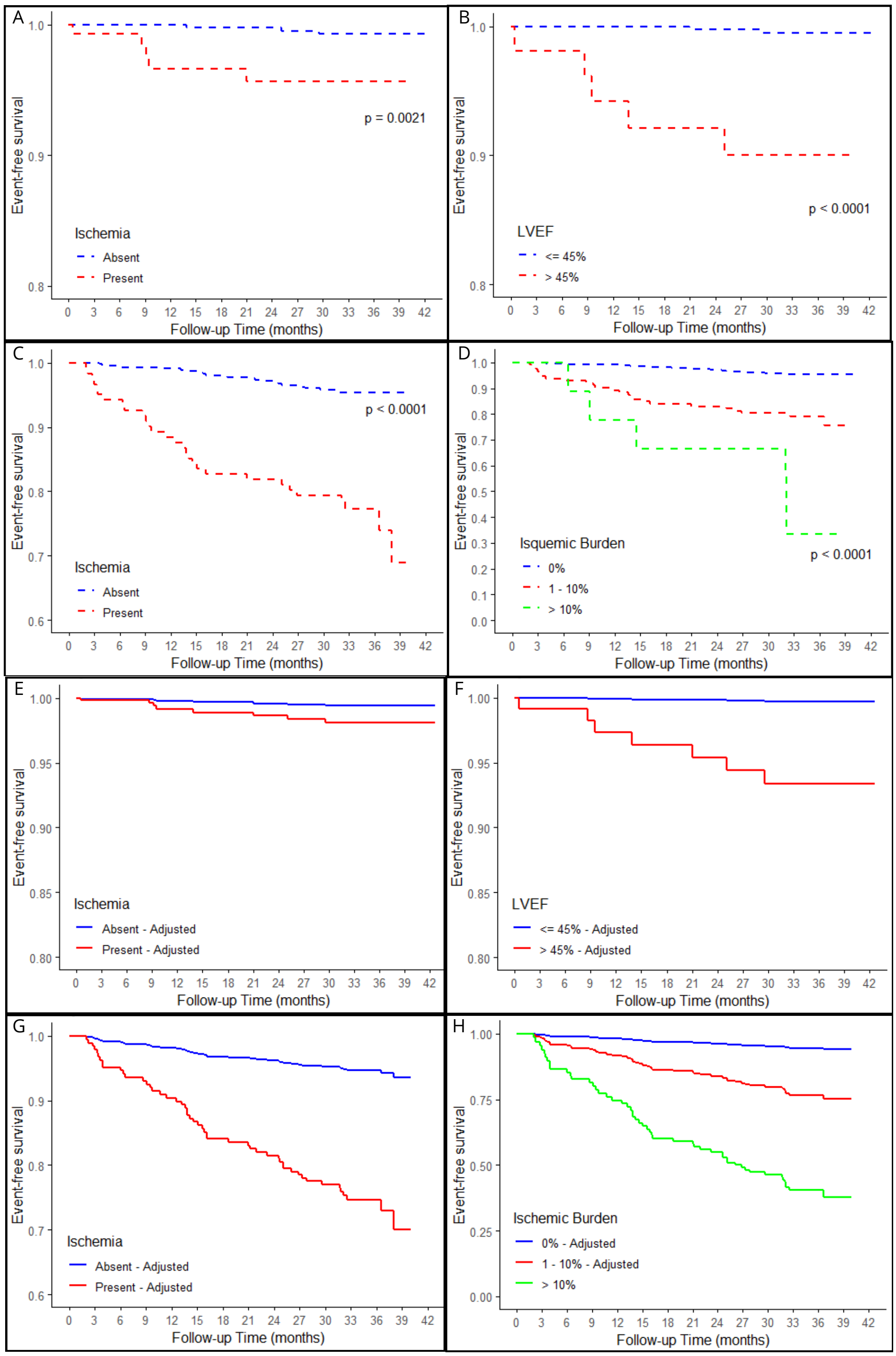

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Survival curves for hard events according to presence of ischemia (A) and LVEF < 45 % (B). Combined events analysis according to presence of ischemia (C) and ischemic burden (D). Adjusted curves for hard events according to ischemia (E) and LVEF < 45% (F). Adjusted curves for combined events according to ischemia (G) and ischemic burden (H). LVEF: left ventricular ejection fraction.

the image quality due to superior energy resolution, geometric efficiency, and simpler direct photon detection.[13] Furthermore, the cardiofocal collimator significantly increases photon detection from the area of interest while maintaining spatial resolution.[13,14] Resolution recovery and noise regulation algorithms in iterative reconstruction methods have emerged as software enhancements to reduce dose and acquisition times.[15,16] These algorithms compensate for collimator-related losses and enhance image quality.[17] Iterative reconstruction also simplifies the routine use of attenuation and scatter corrections.[17]

Despite its global utilization, IQ SPECT technology lacks prognostic validation data. Although many authors have demonstrated its utility, new possibilities, pitfalls, artifacts, and standard values must be considered.[18,19] Therefore, the well-known value of MPS for risk assessment, patient management, and risk stratification must be reevaluated considering these advancements.[20] Therefore, this investigation aims to assess the prognostic value of IQ·SPECT MPS.

Methods

Study population

An analysis of consecutive patients submitted to gated IQ·SPECT/CT myocardial perfusion scintigraphy was retrospectively performed between December 2011 and October 2012. Patients were selected from the nuclear medicine department database of a tertiary hospital. We included for analysis studies performed in patients aged 18 years or older with suspected or known CAD, referred for 99mTc-sestamibi MPS. The follow-up was obtained by phone calls or hospital registry access for not less than 12 months after the MPS study. The study protocol was approved by our local ethics committee (CAAE number: 07022212.6.0000.5533). We excluded patients younger than 18 years old or patients lost to follow-up.

Clinical information

Clinical characteristics, including sex, age, weight, history of diabetes, hypertension, dyslipidemia, sedentarism, smoking, family history of CAD, previous history of CAD or revascularization, and symptoms, were collected during time of examination by the clinical staff of the nuclear medicine department and stored in data records.

Cardiac stress procedure and tracer injection

Regarding stress protocol, the European guideline was applied to decide between physical or pharmacological induction.[21] In the physical exercise test, patients followed the Bruce protocol, increasing treadmill inclination and speed in 3-minute stages, with continuous monitoring of ECG and blood pressure, aiming to reach 85% of the predicted maximum heart rate, defined as 220 minus the patient's age. Alternatively, ST-segment depression, severe chest pain triggered by progression of stress, or significant arrhythmia were considered as criteria for injection. Decisions regarding suspension of aminophylline, beta blockers, calcium blockers, and nitrates were left to the attending clinician. However, foods or beverages with caffeine and chocolate components were suspended for 24 hours. Pharmacological stress with dipyridamole was the option of choice when treadmill exercise was not feasible or indicated. A standard dose of 0.56 mg/kg diluted in 20 ml of NaCl 0.9% solution was administered to the patient for 4 minutes, followed by radiopharmaceutical injection 2 to 4 minutes later. Aminophylline was started 3 to 4 minutes after the radioactive material administration to stop any side effects. Patients unable to do treadmill and dipyridamole contraindication (allergy, arterial hypotension, xanthine use, or severe bronchospasm) were stressed with dobutamine. Dobutamine test was done by intravenous infusion started at 5 to 10 mcg/kg/min, increasing every 3 minutes to 20, 30, and 40 mcg/kg/min, with atropine administration up to a maximum of 2 mg when necessary to reach 85% of the predicted maximum heart rate. The radiopharmaceutical used was 2-methoxy-isobutyl-isonitrile (99mTc-sestamibi; RPH-MIBI®). The standard tracer activity in each phase for two-day protocols was 555 MBq (15 mCi) except for those with more than 100 kg, who received 925 MBq (25 mCi). On other hand, for one-day protocols, an activity of 296 to 444 MBq (8 to 12 mCi) was prescribed for the first phase and 888 to 1332 MBq (24 to 36 mCi) for the second phase.

Myocardial perfusion image acquisition

Four different 99mTc–sestamibi gated SPECT/CT acquisition protocols were performed according to the department's routine practice, as follows: a two-day protocol, a one-day rest/stress protocol, a protocol involving rest injection during acute chest pain, and a stress-only protocol. All images were acquired in a two-detector SPECT/CT camera (Symbia T2, Siemens Medical, Erlangen, Germany) with IQ·SPECT technology that encompass a cone-beam collimator (Smartzoom®), cardio-centric acquisition, and a proprietary implementation of a conjugate-gradient iterative reconstruction algorithm with geometric correction. The standard acquisition protocol consisted of 34 projections in a 208° heart-centered orbit, 20 seconds per projection, 128 × 128 matrix, and no zoom factor. Low-dose CT attenuation map and two energy window scatter corrections were applied. The cardiac volumes were obtained with an iterative reconstruction algorithm (CardioFlash), 8 iterations and 4 subsets, and a gaussian filter. QGS Cedars Sinai software was used to obtain reorientations in short axis, vertical long axis, and horizontal long axis, as well as quantification of volumes, ejection fraction, and contractility analysis.

Image interpretation and perfusion imaging variables

Images were reviewed by two experienced nuclear medicine physicians. Each physician had access to entire clinical data and previous MPS recorded in our department. The 17 standardized cardiac segmentation model were used for regional characterization of the findings.[22] Each segment was rated from 0 (normal perfusion) to 4 (absence of uptake) and integrated in the summed stress score (SSS), summed rest score (SRS), and then subtracted to obtain summed difference score (SDS), as previously described.[23] We subsequently calculated a percentage from the estimated score dividing by 68, quantifying the ischemic defect. Discrepancies were resolved through consensus discussions among the physicians.

Follow-up

The follow-up was obtained by phone calls or hospital registry access for not less than 12 months after the MPS study in order to evaluate the main outcomes. Death and nonfatal myocardial infarction were considered hard events, whereas death, nonfatal myocardial infarction myocardial, or revascularization (surgical or percutaneous) 60 days or more after the MPS were defined as combined events. Myocardial infarction was defined by symptoms, troponin T levels, and electrocardiographic variations.

Statistical analysis

For numerical variables, we evaluated data normality using the Shapiro-Wilk test and expressed them as mean and standard deviation or median and interquartile range, as appropriate. For categorical variables, frequencies and percentages were calculated. Univariate associations between clinical variables, symptoms, previous pathological history, stress test result, and MPS results were analyzed using chi-squared test or Fisher's exact test for categorical data and the Mann-Whitney test for numerical data, in comparison to hard events and major cardiac events. The Kaplan-Meier method with log-rank and Cox regression was applied to survival analysis, and curves were adjusted by sex, age, and presence of clinical factors. Statistical significance was taken at $p < 0.05$. All tests were two-sided. All statistical analyses were performed using the SPSS statistical software package, version 20.0 (SPSS, Chicago, Illinois, United States) or SAS®, version 6.11 (SAS Institute, Inc., Cary, North Carolina, United States).

Results

Study population

A total of 734 patients were submitted to MPS in the nuclear medicine department between December 2011 and October 2012. Adequate follow up was obtained in 625 (85%) patients with a mean period of 1,041 ± 90 days. The mean age was 64 ± 12 years, and 415 (66.4%) patients were male. Chest pain evaluation was the main indication for MPS (28.6%). Patients were asymptomatic (47.5%) in most cases; 33.1% had chest pain; and 16.7% had dyspnea or fatigue. Other characteristics are displayed in Table 1.

SPECT results and follow-up

Treadmill exercise was the main stress test option, used in 65.3% (405) of patients. In contrast, 32.6% (202) had dipyridamole stress, and 1.9% (12) had dobutamine stress. There was no statistical significance between stress types. Only one patient had a pacemaker stimulus. Symptoms were observed in 8.7% of the patients submitted to physical stress. Ischemia was observed in 26.7% of the patients, as shown in Table 2.

Table 1 – Clinical characteristics of the study population

Clinical characteristics	N	%
Sex (male)	249	34.0
Age, mean (SD)	63.72 (12.4)	-
SAH	430	68.8
Dyslipidemia	392	62.7
Familial history for CAD	289	46.2
Smoking	284	45.4
Sedentarism	253	40.5
Diabetes	195	31.2
Obesity	195	31.2
Previous PTCA	190	30.4
Previous AMI	114	18.2
Previous CABG	108	17.2
Previous stroke	17	2.7
Definitive pacemaker	15	2.4

AMI: acute myocardial infarction; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; PTCA: percutaneous transluminal coronary angioplasty; SAH: systemic arterial hypertension; SD: standard deviation.

Table 2 – Scintigraphy variables

Variable	N	%
Stress type		
Physical exercise	407	65.1
Dipyridamole	205	32.8
Dobutamine	12	1.9
Pacemaker stimulus	1	0.2
Physical stress symptoms	35	8.7
Presence of ischemia	167	26.7
Ischemic burden		
0%	458	73.3
1% to 10%	142	22.7
> 10%	25	4.0
Resting LVEF ≤ 45%	70	11.8
Stress LVEF ≤ 45%	77	11.8

LVEF: left ventricular ejection fraction.

Revascularization MPS was observed in 13.1% (82) of patients (Supplementary Table 1). Major cardiac combined events were noted in 6.9% (43), and hard events in 1.4% (9) cases. Table 3 compares the annualized incidence of hard events, late combined events, and revascularization between patients with normal and abnormal MPS findings in IQ SPECT imaging, showing a significant increase in adverse events in patients with abnormal images. Supplementary Tables 2 to 5 compare types of tests, ischemia burden by group, and presence of revascularization and late combined events.

Table 3 – Annualized incidences

Variable	IQ SPECT normal	IQ SPECT abnormal	p
Hard events	0.2%	1.1%	0.02
Combined events	1.1%	5.5%	0.008
Revascularization	1%	14%	0.0001

Discussion

Based on the results obtained in our study, we can state that patients with normal MPS, performed using IQ·SPECT, have a low annualized risk of adverse events compared to patients with abnormal study. The rates of hard events, combined events, and myocardial revascularization at any time after the examination were significantly higher for patients with abnormal myocardial scintigraphy. Our findings demonstrated that IQ·SPECT can be a useful tool to assess the prognosis of patients with suspected or known CAD, which translates into potential clinical benefit given the need for shorter imaging time and reduced radiation exposure.

Despite the relevant number of prognostic studies published considering MPS, to our knowledge, this is the first study to evaluate the prognostic value of IQ·SPECT technology.[20,24] As already demonstrated, the new collimator design, specific acquisition protocol, and proprietary reconstruction method imply qualitative and quantitative differences on perfusion images when compared to conventional SPECT MPS.[14,19,25,26] IQ·SPECT improves time acquisition and reduces radiation exposure when compared to conventional SPECT cameras, maintaining image quality and diagnostic accuracy.[22] Other authors have demonstrated the prognostic capacity of MPS with diverse perspectives.[27–31] For these reasons, it is crucial to validate and evaluate the prognostic capacity of new technology.

By multivariate analysis, the independent variable with the highest weight to predict hard events was LVEF ≤ 45% at rest, with HR equal to 26.02. Similarly to the literature, Sharir et al. demonstrated that changes in stress LVEF contributed to a worse prognosis when compared to isolated perfusion information.[32] Another study documented that stress LVEF was the strongest predictor of mortality, whereas altered myocardial scintigraphy was the predictor of nonfatal infarction.[33]

Regarding combined events, the scintigraphy variable with the highest weight to predict the event was abnormal scintigraphy, with a relative risk of 6.14. Our findings agree with prognostic value studies of myocardial scintigraphy, which have shown that altered examination has independent predictive value for major cardiac events (death or myocardial infarction). The population with abnormal examination has a risk of serious adverse events 3 to 5 times higher than the population with normal examination, and the average rate of events in the population with altered examination is 5.9% per year.[34] Shaw et al. found in 4,728 patients that the rate of serious adverse events, death, or acute myocardial infarction was 0.6% per year when they had normal myocardial scintigraphy, followed for a period of 3 years.[35] Compared to recent studies with CZT technology, our results demonstrate the same magnitude of discrimination of prognosis with an IQ SPECT system.[12,36]

For myocardial revascularization at any time, multivariate analysis showed that the variable that best predicted the event was the myocardial ischemia burden, with a relative risk equal to 9.4 and 30.3, when the ischemic load was 1% to 4% and ≥ 5% respectively, similar to the literature. Shaw et al. showed event rates of 1.2%, 8%, and 10% for patients with normal scintigraphy (0%) and myocardial ischemia of 1% to 4% and ≥5%, respectively.[37] Chavoshi et al. showed similar results, and the rate of cardiac events was significantly higher in patients with higher ischemic loads (4.4% in normal scintigraphy compared to 14% in ischemic scintigraphy).[38]

Furthermore, our results agree with prior studies regarding attenuation correction. Niu et al. showed this technique tends to reduce false-positive myocardial perfusion studies.[39] A comparative study between SPECT with and without attenuation correction has consistently demonstrated that the use of attenuation correction increases the accuracy of the examination.[6] Pazhenkottil et al. demonstrated that patients with normal scintigraphy using attenuation correction with computed tomography have an excellent prognosis, with a period of at least 4 years of disease-free survival.[40] Bom et al. demonstrated an excellent negative predictive value of SPECT with attenuation correction in a population without previous CAD (negative predictive value = 98.5% in 2 years of follow-up).[41] Our data also point to a good accuracy for detecting low-risk patients, because in almost 3 years of follow-up, patients with normal examinations had a 0.2% rate of hard events. The possibility to reduce acquisition time of IQ·SPECT allows for improved throughput with no loss in diagnostic accuracy as previously demonstrated in obese patients, as IQ·SPECT was shown comparable to conventional SPECT.[42]

In the updated Brazilian Nuclear Cardiology guideline, myocardial SPECT was demonstrated to be cost-effective compared to anatomical methods in Brazilian public health systems, and the incorporation of IQ SPECT could make nuclear medicine investigation even more cost-effective, because it can increase the number of exams performed with SPECT equipment.[43]

Limitations

This study has some limitations. It was an observational retrospective study. Data were obtained through database analysis, and we did not compare standard and IQ·SPECT technology. The follow-up was obtained by phone call; therefore, it presented a loss of information, mainly regarding follow-up, where we were not able to contact 109 patients (approximately

15% of our sample). Additionally, a small number of events was found in our participants, which reduces the discriminatory capacity in multivariate analysis. Additionally, we did not subgroup patients with suspended medication in our analysis, and this may have influenced some of the results. It is also worth noting that the data presented in this study were originally submitted for publication shortly after data collection was completed. However, at that time, the manuscript did not receive editorial priority. With the recent and growing interest in accelerated acquisition techniques in myocardial perfusion imaging, the authors were newly motivated to resubmit this work. This context highlights the current clinical and operational relevance of the findings presented here.

We suggest that future prognostic research focusing on specific groups can show additional value for IQ·SPECT technology. For instance, women usually have smaller ventricles than men, most likely suffering partial volume effects, in addition to breast attenuation; they consequently have more false-positive and false-negative results. Obese patients who pose challenges for CZT technologies may also be a group of interest.

Conclusion

Our study demonstrates that IQ SPECT MPS has significant prognostic capabilities with very low risk of adverse events in patients with normal imaging. This system might be a significant alternative for MPS, as it seems to improve the patient throughput with half-time acquisitions, half-dose administration, and excellent image quality.

Author Contributions

Conception and design of the research: Rezende MF, Mesquita CT; acquisition of data: Rezende MF, Fernandes FA, Azevedo J, Mesquita CT; analysis and interpretation of the data: Rezende MF, Yahiro DS, Fernandes FA, Azevedo J, Mesquita CT; statistical analysis: Rezende MF, Yahiro DS, Mesquita CT; writing of the manuscript: Yahiro DS, Fernandes FA; critical revision of the manuscript for intellectual content: Azevedo J, Mesquita CT.

Potential Conflict of Interest

Claudio Tinoco Mesquita has received Research/Grant from Alnylam, Alexion pharmaceuthicals, Astrazeneca that are not relevant to the contents of this paper, and speakers fee from Servier, Pfizer, Eckert Ziegler. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Study Association

This article is part of the thesis of master submitted by Maria Fernanda Rezende, from Universidade Fedaral Fluminense.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital Pró-Cardíaco under the protocol number 07022212.6.0000.5533. 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.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

All datasets supporting the results of this study are available upon request from the corresponding author.

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*Supplemental Materials

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