

Stress Echocardiography and Major Cardiac Events in Patients with Normal Exercise Test

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Abstract

Background: Exercise test (ET) is the preferred initial noninvasive test for the diagnosis and risk stratification of coronary artery disease (CAD), however, its lower sensitivity may fail to identify patients at greater risk of adverse events.

Objective: To assess the value of stress echocardiography (SE) for predicting all-cause mortality and major cardiac events (MACE) in patients with intermediate pretest probability of CAD and a normal ET.

Methods: 397 patients with intermediate CAD pretest probability, estimated by the Morise score, and normal ET who underwent SE were studied. The patients were divided into two groups according to the absence (G1) or presence (G2) of myocardial ischemia on SE. End points evaluated were all-cause mortality and MACE, defined as cardiac death and nonfatal acute myocardial infarction (AMI).

Results: G1 group was comprised of 329 (82.8%) patients. The mean age of the patients was 57.37 ± 11 years and 44.1% were male. During a mean follow-up of 75.94 ± 17.24 months, 13 patients died, three of them due to cardiac causes, and 13 patients suffered nonfatal AMI. Myocardial ischemia remained an independent predictor of MACE (HR 2.49; [CI] 95% 1.74-3.58). The independent predictors for all-cause mortality were male gender (HR 9.83; [CI] 95% 2.15-44.97) and age over 60 years (HR 4.57; [CI] 95% 1.39-15.23).

Conclusion: Positive SE for myocardial ischemia is a predictor of MACE in the studied sample, which helps to identify a subgroup of patients at higher risk of events despite having normal ET. (Arq Bras Cardiol. 2013;101(1):35-42)

Keywords: Coronary Artery Disease; Exercise Test; Echocardiography, Stress.

Introduction

Coronary artery disease (CAD) is the most common cause of morbidity and mortality in Western countries¹. The availability of effective treatment options from the medical, interventional and surgical point of view becomes important in identifying patients at increased risk of cardiovascular events². Thus, the assessment of prognosis is essential to select the appropriate management of patients with suspected or known CAD³. Although the gold standard for the diagnosis of CAD is coronary angiography, noninvasive techniques play an important role in directing invasive diagnostic and therapeutic procedures, and are associated with lower morbidity and cost⁴.

Exercise test (ET) plays an important role in the diagnosis and risk stratification of patients with known or suspected CAD⁵⁻⁸. Among noninvasive tests, it continues to be the most commonly used method for diagnostic and prognostic

evaluation of CAD, with recognized value particularly in patients with intermediate pretest probability⁹. However, it is established in the literature that left ventricle wall motion abnormalities detected by Stress Echocardiography (SE) appear earlier in the ischemic cascade than angina or ST segment changes¹⁰.

It has been well documented that ischemia resulting from coronary obstruction may occur without clinically recognizable signs, such as electrocardiographic changes or symptoms, such as angina^{11,12}, which underlines the need for early recognition and treatment, with the objective to reduce subsequent risk^{13,14}. Patients who do not develop angina or electrocardiographic abnormalities on ET may have a low risk for cardiac events and deaths; however, the lower sensitivity of this test in detecting obstructive CAD may potentially result in failure to identify patients at higher risk¹⁵.

Previous studies have clearly indicated the role of SE in predicting cardiovascular events and mortality in various clinical settings¹⁶⁻²³; however, there are no studies in the literature addressing the prognostic value of SE in patients with intermediate pretest probability for CAD and normal ET. The objective of this study is to assess the value of SE in predicting cardiac events and deaths from all causes in this subgroup of patients.

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Methods

Patients

A total of 397 consecutive patients with suspected CAD, normal ET and intermediate pretest probabilities of CAD were included. Pretest probability was estimated in accordance with Morise's score^{24,25}. These patients were referred to the Clinical Echocardiography Laboratory at Hospital São Lucas (Aracaju, Sergipe) to undergo SE in the period from January, 2001 to December, 2005. The exclusion criteria were defined as: a) low or high pretest probability of CAD; b) prior diagnosis of CAD; c) positive ET for myocardial ischemia; d) presence of left bundle branch block (LBBB) of the His bundle, e) refusal to participate in the research; and f) inability to establish telephone contact during follow-up. The ethical principles governing human experimentation were carefully followed and all patients signed an informed consent form. The study was approved by the Ethics and Research Committee of the Federal University of Sergipe (CAAE 1818.0.000.107-06).

The protocol consisted of complete clinical research, in which previous symptoms were recorded, such as chest pain or dyspnea, and risk factors for cardiovascular disease were evaluated, followed by 12-lead electrocardiogram (ECG) and resting echocardiogram. Also included was a physical exertion test using a treadmill and, following, we proceeded back to the acquisition of echocardiography images. Clinical and demographic data, as well as the results of the stress tests, were recorded in our database.

Exercise test

Patients were examined in the postprandial period after a light meal and were instructed to avoid any excessive physical activity on the day the examination was conducted. The investigation was conducted with the person breathing room air, with the testing room at a constant temperature (20° C to 24° C). Bruce protocol was followed in conducting the ET. During the test, the subjects were monitored continuously by a three-lead ECG and were encouraged to reach their peak physical effort.

The ET was considered positive for myocardial ischemia when ST segment elevation or horizontal or descending negative deflection equal to or higher than one millimeter for at least 60-80 milliseconds from the J^o point was noted.

Stress Echocardiography

Echocardiography was carried out with a Hewlett Packard/Phillips SONOS 5500, observing the technical aspects classically described by Schiller et al²⁶. The two-dimensional echocardiography images were obtained in the parasternal and apical acoustic windows during rest and immediately after exercise, with the patient in the left lateral decubitus position and electrocardiographic recordings captured simultaneously. The images were recorded on a VCR or digital video display (DVD).

The wall motion was assessed by experienced level III echocardiographers, as recommended by the American Society of Echocardiography. The segmental parietal thickening

of the LV (left ventricle) was quantitatively evaluated at rest and after exercise by using the 16-segment model, ranked at: 1, normal; 2, hypokinetic, 3, akinetic and 4, dyskinetic. The left ventricular wall motion score index (LVWMSI) was calculated at rest and during exercise as the sum of the scores given to each of the 16 segments, divided by the number of segments evaluated at a given time. An LVWMSI equal to one corresponds to normal, from 1.1 to 1.6 represents a mild disorder; from 1.61 to 2 indicates moderate dysfunction. Values greater than 2 represent significant dysfunction²⁶. The difference between the LVWMSI under stress and at rest is known as Δ LVWMSI. The development of new alterations in parietal motility or the worsening of existing dyssynergia (Δ LVWMSI \neq 0) was considered indicative of myocardial ischemia.

Follow-up and outcomes

Patient follow-up was performed through structured interviews obtained by telephone contact. Contact was also made with the assisting physician and a revision of medical records was performed. Deaths from all causes and major cardiac events (MACE), defined as cardiac death and non-fatal acute myocardial infarction, were considered as outcomes of the study.

Statistical Analysis

Categorical variables were presented as percentages and analyzed using the chi-square or Fisher's exact test. Continuous variables were represented as mean \pm SD and compared with the aid of the unpaired t test or Mann-Whitney U test, whichever was appropriate. The cumulative event curves were estimated by the Kaplan-Meier method and compared using the long-rank test. Patients were censored at the time of myocardial revascularization for analysis of major cardiac events, but not for general mortality.

To evaluate the risk factors for MACE and deaths from all causes, Cox regression was utilized (univariate and multivariate). The variables included in the multivariate model were all those with $p < 0.1$ in the univariate analysis. Multicollinearity problems were solved before variables were inserted into the model. The method used was forward variable selection. The variables that remained in the model were tested for possible interactions. The assumption of proportional risk was tested through waste by Schoenfeld for each of the variables that remained in the final model. The values of $p < 0.05$ were considered significant. The statistical analyses were processed by means of the *Statistical Package for the Social Sciences (SPSS)* program, version 17.0 (Chicago, IL).

Results

Clinical characteristics of the study population

Among the 397 patients with intermediate pretest probability of CAD and normal ET undergoing SE, 175 (44.1%) were male and the mean age was 57.4 ± 11 years. Group G1 was comprised of 329 (82.8%) patients with negative results and group G2 contained 68 (17.2%) patients who tested

positive for myocardial ischemia by SE. Group G2 had a higher average age, but there was no difference between groups in relation to gender and presence of precordialgia. The two groups (G1 and G2) showed similar frequencies of comorbidities such as dyslipidemia, systemic arterial hypertension, diabetes mellitus, and family history of CAD (Table 1).

Hemodynamic and echocardiography parameters

Patients with ischemia on SE had a lower mean double product when compared to the group without ischemia. In addition, the averages of the chronotropic rate and peak cardiac rate were also lower in Group G2. In terms of the average of the ejection fraction, Group G2 (0.62 ± 0.07) had a lower ejection fraction in relation to Group G1 (0.67 ± 0.05). It was noted that the patients from Group G2 were more prone to developing arrhythmias (Table 2).

Follow-up and Outcomes

During the mean follow-up of 75.94 ± 17.24 months, there were 13 deaths (nine in G1 and four in G2), including three deaths from cardiac causes (AMI), as well as 13 non-fatal AMIs. Of the 16 MACE, eleven occurred in G1 and five in G2. In the univariate analysis, the variables male gender, age, double product at peak exercise and positive SE for myocardial ischemia were associated with mortality. Variables associated with the development of MACE in the univariate analysis were age, double product at peak exercise, wall motion abnormalities at rest, positive SE for myocardial ischemia and Δ LWMSI (Table 3). In the final model of the multivariate analysis, only the Δ LWMSI continued to show significance as an independent predictor of MACE (HR 2.49; [CI] 95% 1,74-3,58). The variables predicting mortality from any cause were male gender

(HR 9,83; [CI] 95% 2,15-44,97) and age older than or equal to 60 years (HR 4,57; [CI] 95% 1,39-15,23) (Table 4). Kaplan-Meier curve for all-cause death and MACE are represented in Figures 1 and 2, respectively.

Discussion

This study shows that a significant proportion of patients with intermediate pretest probability of CAD and normal ET presents myocardial ischemia detected on SE. It was shown that one in six patients had changes indicative of myocardial ischemia on SE. The results reflect the limitations of the negative predictive value of ET when compared to SE in the population where ET has its value primarily recognized in the intermediate pretest probability of CAD.

For the diagnosis of myocardial ischemia, when interpreting the results of ET one should take into account the pretest probability of CAD, since the predictive values are related to the prevalence of the disease in the population considered. The clinical value of ET is recognized mainly in patients with intermediate pretest probability of CAD. This is due to the fact that many false positive results are expected in asymptomatic groups and a high rate of future cardiac events can already be expected in patients with high pretest probability of CAD, regardless of the outcome of ET⁹.

The variability of ET diagnostic accuracy was previously studied by two meta-analyses^{27,28}. In these studies, patients underwent both procedures (ET and coronary angiography). The approximate sensitivity and specificity of ST segment rectified or descending depression $> 1.0\text{mm}$ was 50% and 90%, respectively²⁹⁻³¹. The SE shows good accuracy in the detection of CAD, with higher sensitivity and specificity for diagnosis in relation to electrocardiogram ET and echocardiogram at rest, and presents additional value in the localization and quantification of myocardial ischemia³².

Table 1 - Clinical characteristics of patients with negative (G1) and positive (G2) SE for myocardial ischemia

Variables	G1 n=329 (82.8%)	G2 n=68 (17.2%)	p
Male	146 (44.4%)	29 (42.6%)	0.794
Age (years)	56.78 \pm 10.67	60.21 \pm 12.14	0.019
BMI (kg/m ²)	28.49 \pm 4.98	28.29 \pm 4.01	0.753
Hypertension	182 (55.3%)	40 (58.8%)	0.596
Diabetes mellitus	25 (7.6%)	9 (13.2%)	0.131
Dyslipidemia	224 (68.1%)	54 (79.4%)	0.063
Family history of CAD	165 (50.2%)	35 (51.5%)	0.843
Asymptomatic	54 (16.5%)	10 (14.7%)	0.720
Typical precordialgia	19 (5.8%)	8 (11.8%)	0.075
Atypical precordialgia	255 (77.7%)	48 (70.6%)	0.205
Dyspnea	0 (0%)	2 (2.9%)	0.029
Beta-blockers	59 (18%)	8 (11.8%)	0.213
Calcium channel blockers	31 (9.5%)	6 (8.8%)	0.871

G1 : Patients negative for ischemia on SE; G2 : Patients positive for ischemia on SE; BMI : Body mass index; CAD : Coronary artery disease.

Table 2 - Hemodynamic and echocardiography parameters and echocardiography findings of patients with negative SE (G1) who were positive (G2) for myocardial ischemia

Variables	G1 n=329 (82.8%)	G2 n=68 (17.2%)	P
SBP (mmHg)			
Rest	127.26 ± 12.98	128.32 ± 12.68	0.515
Peak	184.52 ± 18.97	180.60 ± 23.55	0.202
DBP (mmHg)			
Rest	82.16 ± 5.90	83.09 ± 6.58	0.284
Peak	86.68 ± 9.65	87.57 ± 8.53	0.479
HR (bpm)			
Rest	76.52 ± 13.85	76.84 ± 13.24	0.861
Peak	150.68 ± 23.76	136.74 ± 21.82	< 0.001
Double product. x 10³ mmHg bpm			
Rest	9.76 ± 2.151	9.85 ± 1.191	0.744
Peak	27.88 ± 5.503	24.91 ± 6.038	< 0.001
Arrhythmia	80 (24.3%)	33 (48.5%)	< 0.001
WMA	0	29 (42.6%)	< 0.001
EF (%)	0.67 ± 0.05	0.62 ± 0.07	< 0.001
LVWMSI			
Rest	1.0 ± 0.0	1.08 ± 0.21	< 0.001
Peak	1.0 ± 0.0	1.17 ± 0.22	< 0.001
Δ LVWMSI	0.0 ± 0.0	0.08 ± 0.08	< 0.001

G1 : Patients negative for ischemia on SE; G2 : Patients positive for ischemia on SE; SBP : systolic blood pressure; DBP : diastolic blood pressure; HR : heart rate; WMA : wall motion abnormalities; EF : ejection fraction; LVWMSI : Left ventricular wall motion score index; Δ LVWMSI : Difference between LVWMSI with exertion and at rest.

Furthermore, the extent of ischemia and severity of myocardial wall motility disorders, measured at the peak of the SE exercise protocol, are considered independent and cumulative predictors of prognosis in patients with known or suspected CAD, providing additional prognostic information to the standard ET¹⁹. Studies show that the extent and severity of ischemia induced by exercise are strong predictors of AMI and cardiac death^{18,33,34}, which confirms the results of this study in which myocardial ischemia, estimated by ΔLVWMSI, has been a predictor of adverse cardiac events.

It is clear, therefore, that echocardiography variables that reflect the extent and severity of CAD are superior for risk assessment of subsequent events, as observed by Arruda and colleagues. In a cohort of 5,798 patients with known or suspected CAD, the LVWMSI had significant prognostic value for MACE and was more reliable than the variable ischemia, defined in the study as the development of a new change in parietal motility or worsening of existing dyssynergia.

The presence of myocardial ischemia detected by SE was previously described as a predictor of adverse cardiac events and mortality from any cause in patients with normal ET. In the study of a Spanish cohort that included 4004 patients, of whom 16.7% had ischemia on SE, the ΔLVWMSI was an independent predictor of mortality and MACE¹⁵. In the

present study, ΔLVWMSI was able to predict the development of adverse cardiac events; however, it was not a predictor of mortality from all causes. Importantly, the Spanish cohort included patients at high risk for CAD who were excluded from the study in order to evaluate a population that typically generates doubts in terms of the diagnostic approach.

The importance of SE in predicting mortality and adverse cardiac events overcomes the limitations inherent in the ET, and can even be observed in patients with inconclusive tests, just as in patients with LBBB. During the follow-up of 609 patients with LBBB (average follow up of 4.6 ± 3.4 years), five-year mortality and cardiac events were twice as high in patients who had ischemia on SE³⁵. In a study of a Brazilian population with LBBB, the SE was also a predictor of major cardiac events³⁶.

In this study, it was observed that SE confers a good prognosis in patients with normal results on echocardiography. This evidence was first described by Sawada et al³⁷ and was later confirmed by other studies. In a cohort of 1,325 patients whose coronary status was unknown, the prognosis after a normal SE was considered excellent. The rate of survival free of cardiac events over one, two and three years was 99.2%, 97.8% and 97.4%, respectively, with a favorable prognosis even in patients with intermediate pretest or high³⁸ probability. According to a study involving 437 patients with angina and

Table 3 - Univariate analysis for predictors of mortality and major cardiac events

	General Mortality		Major cardiac events	
	RR (95% CI)	p	RR (95% CI)	p
Male	7.95 (1.76-35.94)	0.007	1.97 (0.75-5.18)	0.169
Age (60 years or older)	3.87 (1.19-12.64)	0.025	2.88 (1.07-7.80)	0.037
Hypertension	0.89 (0.30-2.65)	0.831	1.47 (0.55-3.98)	0.445
Diabetes	0.92 (0.20-7.10)	0.936	1.46 (0.33-6.38)	0.616
Dyslipidemia	0.73 (0.24-2.23)	0.582	1.52 (0.49-4.67)	0.463
Obesity	0.37 (0.08-1.68)	0.198	1.13 (0.42-3.05)	0.811
Precordialgia	1.01 (0.22-4.57)	0.990	0.45 (0.16-1.27)	0.131
Dyspnea	1.12 (0.15-8.68)	0.908	1.75 (0.40-7.65)	0.459
Family history of CAD	1.07 (0.36-3.20)	0.902	1.83 (0.68-4.95)	0.234
SAH (peak exercise)	0.50 (0.07-3.83)	0.503	0.83 (0.19-3.64)	0.806
Double product (rest)	0.96 (0.72-1.29)	0.790	1.11 (0.87-1.42)	0.414
Double product (peak exercise)	0.88 (0.80-0.96)	0.003	0.92 (0.85-0.99)	0.032
CI	2.94 (0.96-9.00)	0.059	1.98 (0.76-5.12)	0.161
Arrhythmia	1.68 (0.55-5.13)	0.365	1.10 (0.39-3.10)	0.869
WMA at rest	1.15 (0.98-1.34)	0.078	1.15 (1.01-1.31)	0.029
Positive SE	3.61 (1.06-12.28)	0.040	3.82 (1.39-10.56)	0.010
Ejection fraction	1.98 (0.78-5.03)	0.153	0.94 (0.46-1.94)	0.869
LVWMSI (rest)	0.40 (0.001-152.27)	0.764	1.17 (0.83-1.64)	0.373
Δ LVWMSI	1.58 (0.86-2.89)	0.140	2.52 (1.76-3.62)	< 0.001

CAD : coronary artery disease, SAH: Systolic arterial hypertension ; CI : chronotropic incompetence; WMA: wall motion abnormalities; SE: Stress echocardiography; LVWMSI: left ventricular wall motion score index; Δ LVWMSI : Difference between LVWMSI with exertion and at rest.

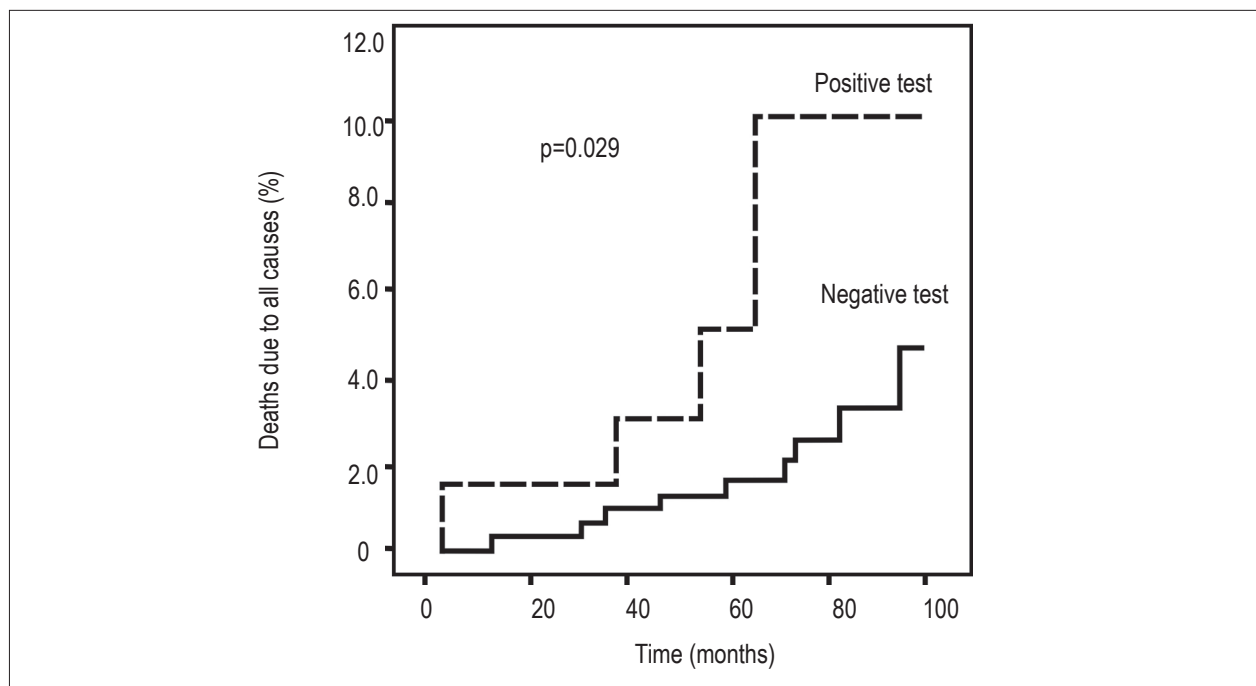


Figure 1 - Kaplan-Meier curve for all-cause death in patients with negative (G1) and positive (G2) SE for myocardial ischemia. (Log-rank, $p = 0.029$).

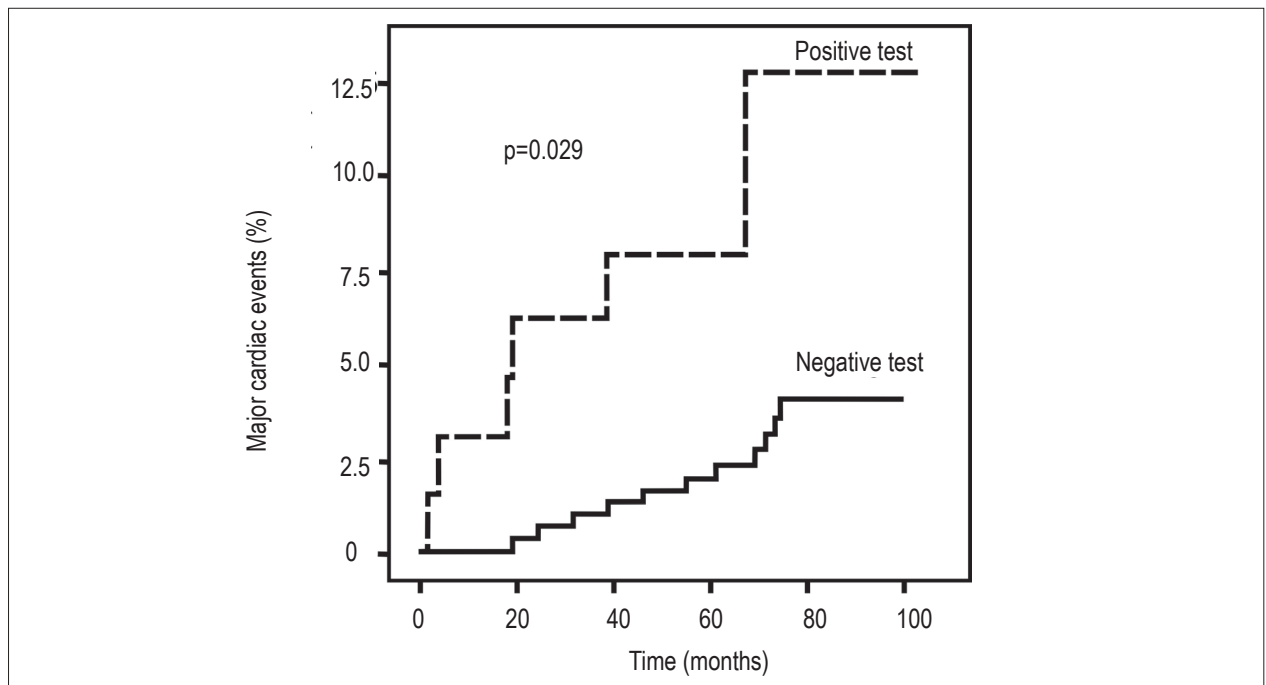


Figure 2 - Kaplan-Meier curve for major cardiovascular events in patients with negative (G1) and positive (G2) SE for myocardial ischemia. (Log-rank, $p = 0.005$).

no previous history of AMI or myocardial revascularization, patients with normal tests have a low rate of occurrence of events and may be exempted from invasive procedures for three years following a normal test¹⁹.

The favorable prognostic implications of negative SE for myocardial ischemia are consistent with a recent published meta-analysis in which the negative predictive value of SE for AMI and cardiac death was 98.4% ([95% CI] 97.9 to 98.9) over 33 months of follow-up, a value similar to that of myocardial perfusion scintigraphy, which was found to be 98.8% ([CI 95%] 98.5 – 99.0), over 36 months of follow-up³⁹.

With regard to the limitations of the study, we highlight the limitation inherent in observational studies, in which non-measured variables can corroborate the difference in prognosis between groups.

Although currently recommended as the initial test for evaluation of CAD compared to SE, ET has limitations regarding its negative predictive value. Through SE it was possible to identify a subgroup of patients at higher risk for developing adverse cardiac events, although they presented with a normal

ET. However, additional studies of cost-effectiveness are needed to determine whether the increase in prognostic value provided by SE justifies its use as an initial test. This strategy could involve reducing potential costs through the proper selection of therapeutic strategies to enable appropriate referral for coronary angiography for patients at higher risk.

Conclusion

A positive SE for myocardial ischemia is a predictor of MACE in the sample studied, which helps to identify a subgroup of patients at higher risk of adverse events, despite presenting a normal ET.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript, Critical revision of the manuscript for intellectual content: Calasans FR, Santos BFO, Silveira DCR, Araújo ACP, Melo LD, Barreto-Filho JA, Sousa ACS, Oliveira JLM.

Potential Conflict of Interest

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

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There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

Table 4 - Multivariate analysis results for overall mortality

	RR (95% CI)	p
Age		
60 years or older	4.57 (1.39-15.23)	0.014
Male	9.83 (2.15-44.97)	0.003
Positive SE	3.36 (0.97-11.66)	0.057

SE : Stress Echocardiography.

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