

Prognostic Value of Dipyridamole Stress Echocardiography in Women

Maria Celita de Almeida¹ e Brivaldo Markman Filho^{1,2}

Procardio Diagnósticos¹; Universidade Federal de Pernambuco², Recife, PE - Brazil

Abstract

Background: Stress echocardiography is an important diagnostic and prognostic tool in ischemic heart disease.

Objective: To evaluate the role of dipyridamole stress echocardiography (DSE) in the investigation of myocardial ischemia in women and its ability to predict combined events (cardiovascular death, acute myocardial infarction [AMI], unstable angina, coronary artery bypass grafting [surgery or percutaneous intervention] at an average follow-up of 16 months.

Methods: A prospective study using the protocol of dipyridamole at 0.84 mg in 10 minutes, associated with atropine (0.25 mg/min up to 1.0 mg).

Results: This study evaluated 147 women. DSE was positive in 14 patients (9.5%), negative in 128 (87.1%) and inconclusive in 5 (3.4%). Events occurred in 8 patients, 7 had positive DSE. The other 138 did not present any events. Our of these, 128 had negative DSE. The sensitivity, specificity, accuracy, the positive and negative predictive values of the test before the events were respectively: 83%, 95%, 94%, 42% and 99%. The event-free survival for patients with negative DSE was 99.2% compared with 58% for positive DSE ($p < 0.001$). Univariate analysis identified the DSE result, basal electrocardiogram (ECG), LV ejection fraction, dyslipidemia, wall motion score index at rest and peak, history of AMI, coronary artery bypass grafting, as prognostic predictors related to outcomes. The results of DSE and ECG remained significantly associated with outcomes in the multivariate analysis ($p < 0.001$).

Conclusion: The baseline ECG and positive DSE were independent variables for the occurrence of outcomes. The DSE showed excellent negative predictive value, confirming its usefulness in evaluating prognosis in such patients. (Arq Bras Cardiol 2011; 96(1): 31-37)

Keywords: Echocardiography, stress; myocardial ischemia; diagnostic techniques and procedures; dipyridamole; prognostic; women.

Introduction

In developed countries, atherothrombotic disease, including coronary artery disease (CAD) and cerebrovascular accident (CVA), is the leading cause of death among women¹. However, in women, CAD is presented differently related to men. The onset of symptoms is late (5-10 years), the group of symptoms is more atypical and there is a greater prevalence of comorbidities such as hypertension (HBP), diabetes mellitus (DM) and dyslipidemia (DLP). Besides this, there is a poor specificity of routine diagnostic tests, and increased mortality during percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)².

The treadmill test (TT) is associated with a high rate of false-positive results and a huge number of variables may change the accuracy of such test in women. The combination of imaging

tests significantly increases the diagnostic accuracy for CAD and several authors have used stress echocardiography (EE) in this subgroup patients³⁻⁵.

In dipyridamole stress echocardiography (DSE), this drug works by causing myocardial ischemia through the mechanism of coronary "flow steal", as previously explained⁶⁻⁷. Concomitant administration of atropine, increasing heart rate, enhances the effects described.

This study was intended to evaluate the prognostic value of DSE in women with suspected myocardial ischemia.

Methods

Prospective observational study conducted from Mar/2005-Jun/2007 in women with some contraindication to ET or ET positive for ST-segment alteration without clinical manifestation of CAD or inconclusive ET, who underwent DSE for evaluation of myocardial ischemia. The DSE was performed without discontinuation of drug therapy.

The study was approved by the Ethics Committee on Clinical Research of the said center and the patients signed an informed consent.

Mailing address: Brivaldo Markman Filho •

Av. Visconde de Jequitinhonha, 2544/1902 - 51130-020 - Recife, PE - Brazil

E-mail: brivaldomarkman@uol.com.br

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Patients with improper echocardiographic window, previously known contraindication to dipyridamole or those who had used xanthine products in the 24 hours preceding the examination were excluded.

The protocol used consisted of intravenous administration of a total dipyridamole dose of 0.84 mg/kg in 10 minutes, as follows: 0.56 mg/kg in four minutes, four minutes of observation, and if no criterion of positivity was evidenced, an additional dose of 0.28 mg/kg were infused in two minutes⁸. If no criteria for test interruption arose, atropine was administered at a dose of 0.25 mg every minute, totaling 1.0 mg. The test was completed with the infusion of aminophylline, to reverse the effects of dipyridamole (maximum dose of 240 mg for three minutes) in the 16th minute.

During the procedure, blood pressure and echocardiographic images were recorded at each stage. Criteria for test interruption were: onset of segmental abnormalities in left ventricular contraction, chest pain of at least moderate intensity, ventricular arrhythmias or side effects deemed important by the physician who performed the examination.

The equipment used was a Vivid 3 Pro – GE Medical Systems⁴. According to current recommendations, the left ventricle (LV) was divided into 17 segments⁹. A score of 4 points was given for each segment, as follows: 1 = normal, 2 = hypokinesia, 3 = akinesia, 4 = dyskinesia^{7,10}.

Then, the LV wall motion score index (LVWMSI) was calculated, considering the sum of the points of the 17 LV segments divided by the number of segments analyzed. Values greater than one were considered abnormal. For each patient, the scores at rest (pre) and at the peak of drug infusion were determined.

The test was considered positive for ischemia with the onset of a change in the LV segmental contractility (hypokinesia, akinesia or dyskinesia) or worsening of a pre-existing contractile change. The studies were evaluated off-line by two independent examiners.

Follow-up was through medical records, telephone interview or an interview with the attending physician.

The clinical events assessed during follow-up were: death of cardiac origin, acute myocardial infarction (AMI), unstable angina (UA) and coronary artery bypass surgery (CABG) or percutaneous intervention (PCI), occurring three months after the DSE.

Death was attributed to cardiac origin when the following was documented: significant arrhythmia, congestive heart failure (CHF) or AMI¹¹. The diagnosis of AMI and UA followed the diagnostic criteria defined by current guidelines^{12,13}.

Clinical follow-up of each patient was closed after the occurrence of any event. Therefore, only the first event was considered.

Statistical analysis

The results were expressed as mean, median and standard deviation for quantitative variables. Qualitative variables were expressed in absolute and relative frequencies. Faced with clinical outcomes, we calculated the sensitivity, specificity,

accuracy, positive predictive value (PPV) and negative predictive value (NPV) of the DSE.

The cumulative probabilities of events were estimated by the Kaplan-Meier curves and the presence of differences by the log rank test. The COX proportional hazards model was used to determine the variables with independent prognostic value for occurrence of events. For the model, we considered all variables that, in the univariate analysis, showed statistical significance ($p < 0.20$).

The significance level was 0.05. Data were analyzed with SPSS (Statistical Package for Social Science) - IBM™ for Windows version 12.0.

Results

A total of 147 patients whose mean age was 62 years (37-87 years) was assessed by DSE. Five tests were stopped early due to disabling symptoms (two cases of intense dyspnea, two cases of important chest pain with no significant alteration of myocardial contractility and one case of bronchospasm), which were excluded from the analysis of results. Clinical characteristics of patients are shown in Table 1. Noteworthy is the high number of patients with hypertension and dyslipidemia. On the other hand, the number of coronary events characterized by history of AMI was low, as well as the number of coronary revascularisation procedures.

Out of 147 women, 66.0% had atypical chest pain, 7.5% typical chest pain (angina) and 26.8% were asymptomatic, of which 51.3% with TT characterized by: ischemic ST-T segment changes or angina. In this sample, 72.8% presented normal basal electrocardiogram (ECG) and 27.2%, ECG with abnormalities. Abnormalities were considered: changes in left ventricular repolarization, left bundle branch block (LBBB), electrically inactive area and left ventricular hypertrophy. Regarding ventricular function, only 08 patients (5%) had lowered EF

Table 1 - Distribution of sampling frequency according to clinical characteristics

Clinical characteristics	Yes	
	n	%
DM	28	19,0
Family history of CAD	53	36,1
Smoking	10	6,8
HBP	116	78,9
Dyslipidemia	82	55,8
Previous CABG	9	6,1
Pre PCI	8	5,4
TT	46	31,3
Scintigraphy	5	3,4
Previous CA	4	2,7
Previous AMI	10	6,8

DM - diabetes mellitus; HBP - high blood pressure, CABG - coronary artery bypass grafting; PCI - percutaneous coronary intervention; TT - treadmill test; CA - coronary angiography; AMI - acute myocardial infarction, CAD - coronary artery disease.

(<0.56) at baseline Doppler echocardiography. History of CAD, previous AMI, CABG or PCI, or prior coronary angiography indicating the presence of obstructive coronary artery lesion of at least 50.0% of the vessel lumen was present in 27 patients.

As for medications, 42.0% were using beta-blockers, 22% used calcium blocker, 16% nitrate, 39% angiotensin-converting enzyme inhibitors, 35% aspirin and 32% statins. There were 5.0% of patients using beta-blocker and nitrate combination, 5% with beta-blocker and calcium blocker and only 3% under combined use of beta-blocker, calcium blocker and nitrate.

The average follow-up for events was 16 months (minimum of two months and a maximum of 27 months).

The DSE showed myocardial ischemia in 14 (9.5%) patients. The result was negative in 128 (87.1%) and inconclusive in 5 (3.4%) patients. Out of 147 patients analyzed, eight (5.4%) had cardiac events during follow-up period. Out of the 8 events, 7 occurred among the 14 positive tests for myocardial ischemia, of which two events occurred earlier than three months of the examination and, therefore, were excluded from the analysis, and one among patients with negative test. Among the 7 patients with positive test without events, 4 were patients with CAD.

Regarding the number of events, there was significant difference between positive and negative tests. The probability of occurrence of events during follow-up for women with positive test was 42% and for women with negative test was 0.8% ($p < 0.0001$) (Chart 1).

We observed 4 CRM (2.7%), three PCI (2.0%) and one patient (0.7%) had UA. No AMI or death occurred during follow-up (Table 2).

Thus, the sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the test related to clinical outcomes were respectively 83.0%, 95.0%, 94.0%, 42.0% and 99.0%.

Regarding the survival analysis of all clinical, electrocardiographic and echocardiographic variables analyzed, DSE positive for previous ischemia, acute myocardial infarction, PCI and CABG, increased LVWMSI, abnormal ECG and ejection fraction (EF) <0.56 presented statistically significant association with the occurrence of events (Table 3).

With the Cox regression at a significance level of 5.0%, only the variables DSE and abnormal baseline ECG were significant. It was found that patients with positive DSE for ischemia were roughly 57 times more likely to have the event than patients with negative DSE. Patients with abnormal baseline ECG were 13 times more likely to present the event than those with normal ECG (Table 4).

Table 2 - Distribution of sampling frequency according to event

	n	%
Event	8	5,4
CABG	4	2,7
PCI	3	2,0
UA	1	0,7

CABG - coronary artery bypass grafting, PCI - percutaneous coronary intervention; UA - unstable angina.

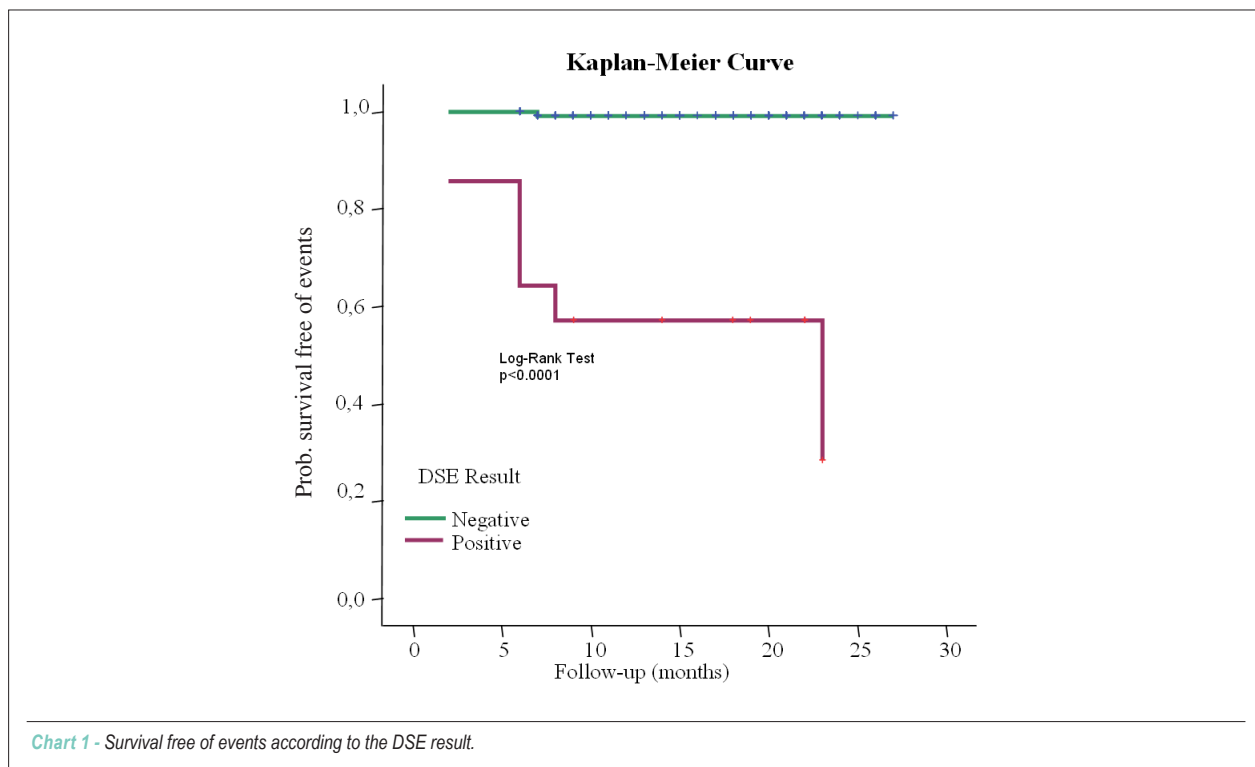


Chart 1 - Survival free of events according to the DSE result.

Table 3 - Results of univariate analysis of Cox - Predictors for event

Predictors	RR (CI 95.0%) 95.0%	p-value
Positive result in DSE	75.25 (9.23 – 213.66)	< 0.001*
Previous AMI	4.43 (1.02 – 21.36)	0.0416*
Previous CABG	7.99 (1.98 – 32.24)	0.005*
Previous PCI	13.71 (3.22 – 58.50)	0.001*
Increased LVWMSI	81.67 (10.19 – 254.42)	< 0.001*
Abnormal ECG	10.31 (2.14 – 49.73)	0.003*
EF <0.56	4.96 (0.58 – 42.48)	0.203*
TT	0.60 (0.13 – 2.91)	0.523
Age ≥ 65 years	2.17 (0.58 – 8.08)	0.235
HBP	2.37 (0.29 – 19.03)	0.399
DM	2.25 (0.56 – 9.01)	0.238
Family history of CAD	1.67 (0.44 – 6.29)	0.443
Dyslipidemia	2.93 (0.61 – 14.12)	0.158
Smoking	1.97 (0.243 – 16.05)	0.515
Obesity (BMI > 30)	0.71 (0.15 – 3.41)	0.664

* Statistically significant ($p < 0.005$), RR - relative risk, CI - confidence interval, AMI - acute myocardial infarction, CABG - coronary artery bypass grafting; PCI - percutaneous coronary intervention; LVWMSI - left ventricular wall motion score index, ECG - electrocardiogram; EF - ejection fraction; TT - treadmill test; HBP - high blood pressure, DM - diabetes mellitus, BMI - body mass index, CAD - coronary artery disease.

Table 4 - Results of the adjustment of the Cox regression model

Predictors	RR (CI 95%)	p-value
Positive DSE	56.59 (6.74 – 174.87)	< 0.001
Abnormal baseline ECG	12.68 (1.51 – 86.42)	0.019

RR - relative risk; CI - confidence interval; DSE - dipyridamole stress echocardiography; ECG - electrocardiogram.

Table 5 - Distribution of sampling frequency of side effects

Side effect	n	%
Ventricular extrasystole	8	5.4
Headache	7	4.8
Chest pain	4	2.7
Dyspnea	2	1.4
Bronchospasm	1	0.7

As to the DSE safety profile, the side effects observed in the sample are shown in Table 5. There were no major complications and all the side effects were reversed with the administration of aminophylline.

Discussion

The concept that CAD is a universal disease was confirmed by the INTERHEART study¹⁴. In this evaluation, nine risk

factors were associated with more than 90.0% of the risk attributable to a first AMI. Dyslipidemia, smoking, diabetes and hypertension were the most important ones. In our study, more than three quarters of the patients were hypertensive, and approximately half of them had dyslipidemia.

Among the clinical variables of interest, history of AMI, CABG and PCI proved to be independent predictors for cardiac events¹⁵. In a study using the pharmacological stress echocardiography to stratify the risk of AMI, previous AMI, CABG or PCI were adverse prognostic factors in univariate analysis¹⁶. History of AMI, CABG or PCI were predictive risk factors by univariate analysis, but did not reach statistical significance in multivariate analysis due to the size of the sample.

The LV systolic function is a determinant factor of prognosis in patients with ischemic heart disease¹⁷. Left ventricular ejection fraction (LVEF) is the measure most used in clinical practice, and is extremely valuable for risk stratification¹⁸. Only 5.0% of women analyzed presented LVEF <0.56. Out of these patients, 20.0% had events. There was a statistically significant association between LVEF and events, although the magnitude of such association has been jeopardized by the small number of patients with reduced EF.

Abnormal baseline ECG was significantly associated with future events. Literature data show that normal ECG is a favorable prognostic factor in patients with suspected CAD or CAD defined, as it suggests preserved left ventricular function¹⁹. On the other hand, conduction disturbances, most often BRE and left anterior fascicular block, may occur in patients with chronic CAD, are more associated with left ventricular dysfunction and may reflect multiarterial disease and previous myocardial damage²⁰. Left ventricular hypertrophy on ECG is an independent predictor of events in patients with chronic CAD²¹.

Regarding the results of DSE, significant difference was observed between patients with negative and positive tests in relation to the occurrence of cardiac events during follow-up. Cortigiani et al²² reported that DSE on women has specificity of 93.0% and diagnostic accuracy of 87.0%, better than the TT for diagnosis of CAD. These results were also observed in two reviews: an American review²³ and an English one²⁴.

This study showed that out of eight events, only one happened among 128 women with negative tests for ischemia (0.8%), highlighting the difference.

This sample of women with negative tests shows the high negative predictive value of the test in the study group (99.0%). The positive predictive value found (42.0%) is consistent with the sample studied, especially when compared with patients with higher cardiovascular risk²⁵. Consistently with our results, Marwick et al²⁶ reported that normal stress echocardiography (SE) corresponds to low risk for cardiac events (<1.0% per annum) under analyses of 4-5 year of follow-up. Similar data were also found in the American recommendations of non-invasive tests in the clinical evaluation of women with suspected CAD²⁷.

The negative test in which an event occurred was of a diabetic and smoker patient. Some studies show that false negatives are more frequent in submaximal tests, single-vessel lesions or moderate lesions (stenosis between 50

to 70.0%)^{28,29}. Diabetic patients may present more rapid progression of CAD³⁰ and the patient underwent coronary angiography after 6 months of testing. This fact could explain the false-negative result.

Among the patients with positive tests with no events during the follow-up period (7 patients), 4 had proven CAD. This indicates the possibility that, at the option of the medical team, clinical treatment has been enhanced, rather than proposed coronary artery revascularisation procedures (surgical or percutaneous). One patient had normal coronary arteries and had her test considered ischemic due to abnormalities found on the inferior wall contractility, a common cause of false-positive tests³¹. The presence of typical chest pain may suggest microcirculation disease, more common in women than in men³². From the other two patients with positive test, one had a coronary spasm during angiography and coronary arteries free of significant atheromatous disease and the other presented aneurysmal segment in left anterior descending artery, which may have contributed to the positive test³³.

The analysis of clinical, electrocardiographic and echocardiographic variables by logistic regression analysis showed that positive DSE for ischemia and abnormal baseline ECG were independent predictors for cardiac events during follow-up. We observed a clear superiority of the DSE over the electrocardiography variable in the multivariate analysis, which is consistent with other studies^{34,35}. These data are corroborated by the findings reported by Shaw et al, who evaluated 4,234 women who underwent Dobutamine Stress Echocardiography (DoSE) or stress echocardiography with exercise (SEE) for five years, concluding that the SE is a strong independent predictor of long-term cardiac events in women³⁶.

Biagini et al evaluated the overall mortality in women with suspected CAD or with known CAD undergoing DoSE, and observed that the presence of myocardial ischemia during DoSE had an independent association with increased overall mortality risk after adjustment with clinical data³⁷. This study, once again, further demonstrates the superiority of SE on the ECG findings as a prognostic factor.

Some studies have assessed the safety of DSE in patients with chronic coronary artery disease or under investigation, delivering good results^{38,39}. Mathias Jr et al⁴⁰, evaluating the safety profile of DoSE in a prospective study in 4,033 patients, found significant adverse effects related to the examination in 10 patients (0.25%), with no record of death. A multicenter study evaluated the safety profile of DSE in 10,451 examinations. Significant side effects occurred in 113 patients (1.2%), including 7 major adverse events (0.07%): one death, one cardiac arrest of short duration, readily reversed, two AMI, one pulmonary edema and an episode of prolonged ventricular tachycardia⁴¹.

In our study, the occurrence of side effects was small, which were promptly reversed after the infusion of

aminophylline, with no record of serious complications, corroborating the literature data.

Study limitations

This study was observational and there was no interference in the conduct of assistant physicians.

The post-test bias cannot be eliminated, since the results of DSE were available to the assistant physicians. Positive tests for ischemia may have influenced the indication for coronary angiography and therefore the decision for revascularization, either surgical or percutaneous. This fact contributed for patients with higher risk to have reduced chances of death and AMI. Similarly, the positive test result may have influenced the enhancement of the clinical treatment, reducing the possibility of occurrence of events.

On the other hand, failure to suspend antianginal medications prior to testing may have contributed to the decrease in sensitivity even in terms of outcome. However, as to the prognosis, based on the excellent negative predictive value against clinical outcomes at follow-up, the impact was not relevant.

Even in the realm of hypotheses, only patients with more extensive coronary disease could have positive DSE, and this fact could have influenced the positive predictive value of the test.

Conclusions

Abnormal baseline ECG and a positive DSE for myocardial ischemia were independent predictors for the occurrence of clinical outcomes combined. DSE is a safe, feasible and effective method in the evaluation of women with clinical suspicion of myocardial ischemia. The test presented excellent negative predictive value, confirming its usefulness in prognostic evaluation in this group of patients.

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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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