Pharmacological Stress Echocardiography in Diabetic Patients

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Abstract

Background: Diabetes Mellitus substantially increases cardiovascular risk in individuals affected.

Objective: To evaluate the importance of pharmacological stress echocardiography (PSE) in risk stratification of diabetic patients with suspected myocardial ischemia.

Methods: Prospective cohort study. The patients underwent PSE according to the protocols of dipyridamole (0.84 mg/kg with up to 1.0 mg of atropine) or dobutamine (5-40 ug/kg/min associated with up to 2.0 mg/atropine). They were monitored through reference to medical records, phone calls or interview with the assistant physician. The clinical outcome was the combination of cardiovascular death, acute myocardial infarction, unstable angina and need for surgical or percutaneous myocardial revascularization.

Results: We evaluated 291 patients, 59.5% women, mean age of 65 ± 9.6 years. The symptoms were atypical precordial chest pain (60%), typical precordial chest pain in 12%, and 24% asymptomatic. The median follow-up time was 42 m (01-105). There were 66 events combined, 51 of them with positive EPS. Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive Value (NPV) compared to the outcomes were: 75%, 93.3%, 89%, 77.3% and 92.4%, respectively. The PSE positive result for ischemia, male gender, previous acute myocardial infarction (AMI), coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), systemic arterial hypertension (SAH), prior use of acetylsalicylic acid (ASA) and abnormal electrocardiography (ECG) were associated with the occurrence of events in the univariate analysis. In the multivariate analysis, only the positive result of PSE was an independent predictor of combined clinical outcomes (RR 25.26, 95% CI, 13.62 - 46.81 p <0.001).

Conclusion: The positive result for myocardial ischemia was the only independent predictor for the occurrence of combined clinical outcomes.(Arq Bras Cardiol: Imagem cardiovasc. 2015;28(2):73-79)

Keywords: Stress echocardiography; Myocardial Ischemia; Diabetes Mellitus.

Introduction

Coronary artery disease (CAD) is the leading cause of morbimortality in patients with Diabetes Mellitus (DM). Approximately 50% of mortality is related to CAD[1]. After acute myocardial infarction (AMI) the outcome is worse compared to non-diabetic patients[2]. However, the noninvasive diagnosis and risk stratification for CAD in these patients are important for the selection and optimization of therapeutic intervention, which may improve survival and reduce complications in this population[3,4]. The treadmill test (TT) is a noninvasive method most widely used for diagnosis and functional evaluation in CAD[5]. However, the value of this test is limited in this population due to the frequent impairment in exercise capacity, especially given the high prevalence of peripheral vascular disease or peripheral neuropathy[6,7].

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Pharmacologic stress echocardiography (PSE) has been shown to be safe and effective in myocardial ischemia evaluation, and several authors have used this imaging method for coronary risk stratification in this subgroup[8,9].

The purpose of this study was to evaluate the importance of PSE in risk stratification of diabetic patients with suspected myocardial ischemia.

Material and Methods

An observational and prospective study carried out from March 2003 to December 2011, in diabetic patients who had any impediment to undergo TT, or positive TT by change in ST segment without corresponding clinical manifestation, or inconclusive TT, and who underwent PSE for evaluation of myocardial ischemia. PSE was performed without suspension of medications.

The study was approval by the Ethics Committee on Clinical Research of the said center, and the patients agreed and signed the informed consent form.

The study excluded patients with poor echocardiographic window, known contraindications to dipyridamole or dobutamine, or those who refused to participate.

The protocol used consisted in the intravenous administration of a total dose of dipyridamole 0.84 mg/kg plus atropine[10], or increasing doses of dobutamine 5 - 40ug/Kg/min plus atropine[11].

A 12-lead conventional electrocardiogram (ECG) was performed before the beginning of the test. The ECG was considered abnormal when it presented changes in the ST segment and/or T wave, signs of left ventricular hypertrophy, pathological Q waves or disorders of intraventricular conduction of the stimulus (bundle-branch block). During the procedure, blood pressure and echocardiographic images were recorded at each stage of traditional cutting plans. Criteria for test interruption were: detection of segmental contraction abnormalities of the left ventricle (LV), precordial chest pain of moderate intensity at least, ventricular arrhythmias or side symptoms classified as important by the physician performing the test. The equipment used was the *Vivid 3 Pro - GE Medical Systems*, USA. According to current recommendations, the left ventricle (LV) was divided into 17 segments[12]. A 4-point score was given for each segment, as follows: 1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia.

Then the LV wall motion score index (LVWMSI) was calculated as the sum of scores of the LV 17 segments divided by the number of segments analyzed. Values greater than 1 were considered abnormal. Scores at rest (pre) and at the peak of drug infusion were determined for each patient. The test result was positive for ischemia with the occurrence of a change in LV's segmental contractility (hypokinesia, akinesia or dykinesia) or worsening of a pre-existing contractile change. Two independent examiners evaluated the tests offline.

The follow-up involved reference to medical records, phone calls to or interviews with the assistant physician.

Clinical events evaluated during the follow-up: death of cardiac origin, AMI, unstable angina (UA), and coronary artery bypass surgery (CABG) or percutaneous intervention (PCI).

Death was attributed to cardiac origin in events of significant arrhythmia, congestive heart failure (CHF) or AMI[13]. The diagnosis of DM, AMI and UA followed the diagnostic criteria defined by prevailing guidelines[14-16].

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, while qualitative variables were expressed in absolute and relative frequencies. Cumulative event probabilities were estimated by the Kaplan-Meier curves and the presence of differences by log-rank test. The Cox proportional hazards model was used to determine variables with independent prognostic value for the occurrence of events. All variables with value $p<0.20$ in univariate analysis were considered for the model. The significance level assumed was of 0.05. Data were analyzed using SPSS for Windows v.12.0.

Results

The PSE was performed in a total of 291 patients, 59.5% female, mean age of 65 ± 9.6 years (37 - 83 years). The clinical characteristics of patients are detailed in Table 1. The high number of patients with hypertension and dyslipidemia is noteworthy. On the other hand, the number of cardiac events characterized by a previous history of AMI, CABG or PCI was low.

Out of 291 diabetic patients, 60% had atypical chest pain, 12% typical pain (angina) and 24% were asymptomatic in their routine activities, of which 26% with TT characterized by: ischemic ST-T segment changes or angina. In this sample, 59.1% presented normal basal electrocardiogram (ECG), and 40,9% presented abnormal ECGs. The patients were reassessed for analysis of cardiac events in an average period of 42 months (minimum of one month and a maximum of 105 months). A total of 77 patients presented past history of CAD characterized by previous AMI, CABG, PCI or coronary angiography (CA) indicating the presence of obstructive coronary artery lesion of at least 50% of the vessel lumen.

As for medications, 38.1% were using beta-blockers, 26% used calcium blocker, 13% nitrate, 33% angiotensin-converting enzyme inhibitor, 23% angiotensinogen receptor blocker, 44% aspirin and 43% statin.

As for the PSE protocol, 71% were analyzed with dipyridamole and 29% with dobutamine. PSE showed myocardial ischemia in 66 (22.7%) patients. The result was negative in 225 (77.3%) patients. Of the 291 patients studied, 68 (23.4%) had combined cardiac events during the follow-up period.

As for the number of events, there was a significant difference between positive and negative tests. Out of the 66 events, 51 were positive and 15 negative. The probability of occurrence of events during follow-up with positive results was of 77% (Chart 1).

There were 17 CABG (5.8%); 41 PCI (14.1%), 6 (2.1%) UA, 2 (0.7) MI, 4 (1.4) deaths (Table 2). Thus, the sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of the test related to the clinical outcomes were: 75%, 93.3%, 89%, 77.3% and 92.4%, respectively.

As for the survival analysis of all clinical, electrocardiographic and echocardiographic variables analyzed, PSE positive result for myocardial ischemia, male sex, previous AMI, CABG and PCI, SAH, prior use of ASA, and abnormal ECG presented statistically significant association with the occurrence of events (Table 3).

With the Cox regression at a significance level of 5.0%, only the PSE variable was significant. Patients with positive PSE for ischemia were approximately 26 times more likely to have the event than patients with negative PSE (Table 4).

Discussion

It has long been known that DM increases the risk of cardiovascular disease[17]. Approximately 65% of deaths of

Table 1 – Sampling distribution of demographic and clinical characteristics

Characteristics	N	%
Females	173	59.5
Age ≥ 65 years	148	50.9
Obesity - BMI>30	89	30.6
SAH	244	83.6
Family History of CAD	91	31.3
Smoking	13	4.5
Dyslipidemia	187	64.3
Abnormal ECG	119	40.9
Previous CABG	26	8.9
Previous AMI	26	8.9
Previous PCI	25	8.6
Previous CA	15	5.2
Treadmill Test		
Not performed	188	64.6
Positive	82	28.2
Negative	11	3.8
Inconclusive	10	3.4
Abnormal LVWMSI	66	22.7

BMI: body mass index; SAH: Systemic arterial hypertension; CAD: coronary artery disease; ECG: electrocardiogram; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; AMI: acute myocardial infarction; CA: coronary angiography; LVWMSI: left ventricular wall motion score index.

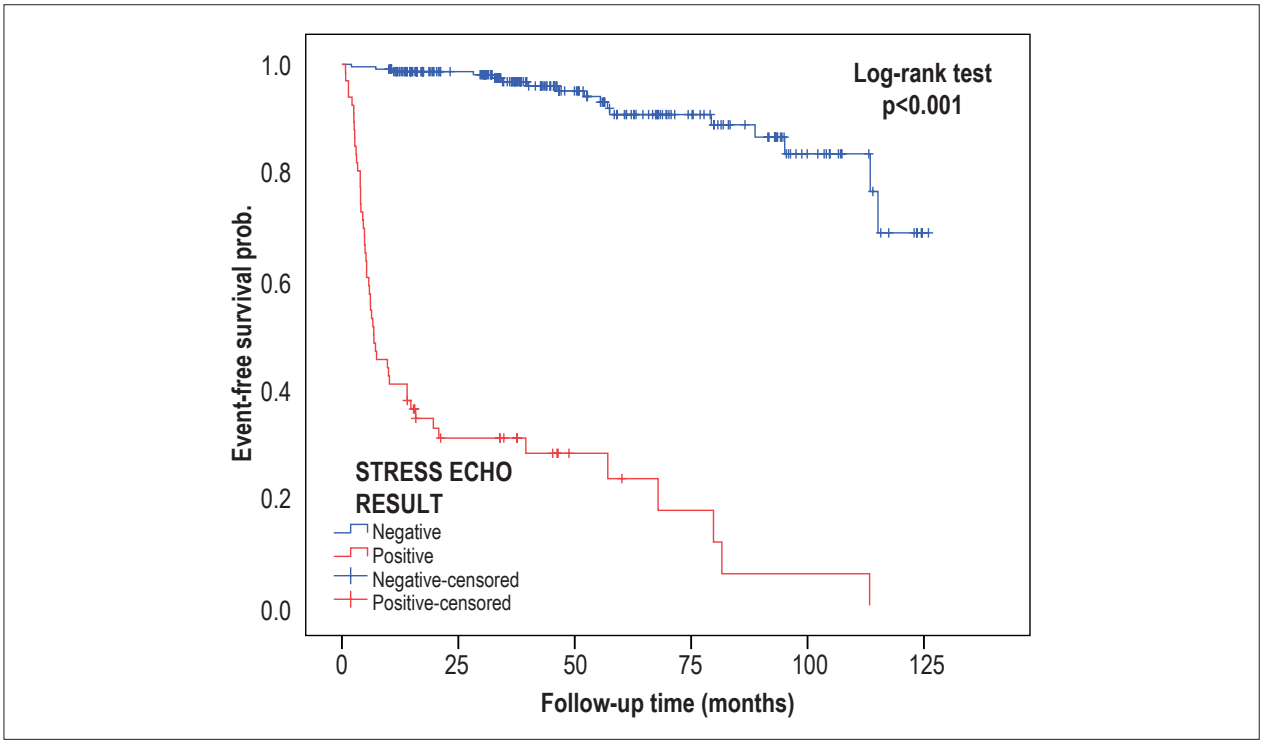

Chart 1 – *Event-free survival curve according to pharmacological stress echocardiography (PSE) result.*

Table 2 – Distribution of frequency according to evolution

Evolution	N	%
Combined event	68	23.4
PCI	41	14.1
CABG	17	5.8
Angina	6	2.1
AMI	2	0.7
Cardiovascular Death	4	1.4

AMI: acute myocardial infarction; UA: unstable angina; PCI: percutaneous coronary intervention; CABG: coronary artery bypass surgery coronary artery bypass grafting.

Table 3 – Results of COX univariate analysis - Predictors for event

Predictors	RR (CI 95%)	p-value
Male	1.43 (0.89 – 2.29)	0.145
Age ≥ 65 years	1.28 (0.79 – 2.08)	0.309
PSE positive result	26.18 (14.39 – 47.25)	< 0.001*
Previous coronary artery bypass grafting	1.58 (0.81 – 3.09)	0.182
Previous percutaneous coronary intervention	2.10 (1.12 – 3.93)	0.020*
Previous acute myocardial infarction	1.69 (0.86 – 3.32)	0.125
Left ventricular hypertrophy	1.24 (0.77 – 2.01)	0.377
Abnormal ECG	1.73 (1.07 – 2.78)	0.026*
Systemic arterial hypertension	2.67 (1.07 – 6.63)	0.035*
Family History of CAD	1.24 (0.75 – 2.05)	0.396
Smoking	1.31 (0.52 – 3.26)	0.568
Dyslipidemia	0.88 (0.54 – 1.45)	0.623
Prior use of beta-blocker	1.16 (0.71 – 1.87)	0.557
Use of acetylsalicylic acid	1.40 (0.87 – 2.26)	0.166*
Obesity (body mass index > 30)	0.92 (0.54 – 1.57)	0.760

*RR: relative risk; CI: confidence interval; PSE: pharmacological stress echocardiography; *: p<0.20.*

Table 4 – Results of the Cox Regression Model adjustment

Predictors	RR (CI 95%)	p-value
Male	1.47 (0.87 – 2.48)	0.154
PSE positive result	25.26 (13.62 – 46.81)	< 0.001
Previous CABG	1.21 (0.72 – 2.89)	0.783
Previous PCI	1.22 (0.59 – 2.52)	0.601
Previous AMI	0.82 (0.36 – 1.88)	0.633
Abnormal ECG	1.45 (0.85 – 2.48)	0.174
SAH	1.76 (0.69 – 4.48)	0.238
Use of ASA	0.80 (0.45 – 1.43)	0.454

RR: relative risk; CI: confidence interval; PSE: pharmacological stress echocardiography; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; AMI: acute myocardial infarction; ECG: electrocardiogram; SAH: systemic arterial hypertension; AAS: acetylsalicylic acid.

type 2 diabetes patients are from cardiovascular disease or stroke[18]. The risk is very high among diabetic patients that already had a first cardiovascular event, such as a AMI[19]. The population of this sample reliably reflects the daily cardiologic practice, where a high number of patients present at least another risk factor besides diabetes (that is a risk-raising factor by itself), thus requiring further assessment, regardless of symptoms. In fact, atypical precordial chest pain was the dominant symptom in symptomatic patients. Myocardial scintigraphy has been used as a prognostic marker in these patients[20], however its high cost, the use of ionizing radiation and prolonged time to perform the test are factors that limit its application on a large scale. Although important variables such as previous AMI, abnormal ECG, abnormal left ventricular wall motion index (LVWMSI), all of which well identified as predictors of events in the context of ischemic heart disease, were significantly associated with clinical outcomes, they are not independent predictors in multivariate analysis, possibly due to the small number of the majority of these variables in the sample studied.

The prognostic value of stress echocardiography in patients with known or suspected CAD disease is already well established[21,22]. A study evaluating prognosis in patients with unstable angina of low and moderate risk found sensitivity, specificity, accuracy, positive and negative predictive values similar to this series, although studying patients of higher risk levels, but evaluated in a shorter time period as for the onset of outcomes[23]. In this series, we found values consistent with the literature in terms of sensitivity and specificity compared to the clinical outcomes specified[24]. Only 4% of patients included in this sample with negative results presented events during follow-up period, which confirms the excellent negative predictive value of the method. A study with diabetic patients assessed by physical stress echocardiography presented events in 7% of negative tests for ischemia during follow-up[25].

In the series comprising 5,456 patients, including 749 diabetic patients, submitted to PSE and followed up for 31 months, where mortality and/or AMI occurrence was evaluated, the conclusion was that pharmacological echostress was an equally effective predictor of cardiac events in diabetic and non-diabetic patients regardless of age, although normal testing had a lower predictor value for adverse outcomes in diabetic patients when compared to non-diabetic patients[26]. In this study, reinforcing what was said above, the positive PSE result for myocardial ischemia was an independent predictor of combined clinical outcomes.

Limitations of the study

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

The post-test bias cannot be eliminated, since test results were available to the assistant physicians. Positive tests for ischemia may have influenced increased clinical treatment, as well as in the decision for myocardial revascularization, either surgical or percutaneous. Such fact might have reduced the probability of death and AMI in high-risk patients. Another noteworthy fact was the non-suspension of medications before the test. This may have contributed to a lower rate of abnormal tests, but the impact on prognosis was irrelevant, based on the good prognosis of patients with negative PSE.

Conclusion

The presence of myocardial ischemia detected by PSE was the only independent predictor of outcomes in this group of patients.

Authors' contributions

Research creation and design: Almeida MC, Markman-Filho B. Data collection: Almeida MC; Mota VG; Peregrino MA; Markman DL; Markman M; Markman AC; Markman-Filho B. Data analysis and interpretation: Almeida MC; Markman-Filho B. Statistical analysis: Almeida MC; Markman-Filho B. Manuscript drafting: Almeida MC; Markman-Filho B. Critical revision of the manuscript as for important intellectual content: Mota VG; Markman-Filho B. Database update: Peregrino MA; Markman DL; Markman M; Markman AC.

Potential Conflicts of Interest

No relevant potential conflicts of interest.

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Academic Association

This study is not associated with any graduate program.

References

1. Ford ES, DeStefano F. Risk factors for mortality from all causes and from coronary heart disease among persons with diabetes: Findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Am J Epidemiol. 1991;133(12):1220-30.
2. Eberly LE, Cohen JD, Prineas R, Yang L. The Multiple Risk Factor Intervention Trial Research Group: Impact of incident diabetes and incident nonfatal cardiovascular disease on 18-year mortality: the multiple risk factor intervention trial experience. Diabetes Care. 2003; 26(3):848-54.
3. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with sinvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. Lancet. 2003; 361(9374):2005-16.
4. American Diabetes Association. Clinical practice recommendations 2000. Diabetes Care. 2000; 23(Suppl 1): S1-116.
5. Meneghelo RS, Araújo CGS, Stein R, Mastrocolla LE, Albuquerque PF, Serra SM, et al; Sociedade Brasileira de Cardiologia. III Diretrizes da Sociedade

Brasileira de Cardiologia sobre teste ergométrico. Arq Bras Cardiol. 2010 (5 Supl.1): 1-26.

6. Akbari CM, LoGerfo FW. Diabetes and peripheral vascular disease. J Vasc Surg. 1999; 30(2):373-84.

7. May O, Arildsen H, Damsgaard EM, Mickley H. Cardiovascular autonomic neuropathy in insulin-dependent diabetes mellitus: prevalence and estimated risk of coronary heart disease in the general population. J Intern Med. 2000; 248(6):483-91.

8. Picano E, Bedetti G, Varga A, Cseh E. The comparable diagnostic accuracies of dobutamine-stress and dipyridamole-stress echocardiographies: a meta-analysis. Coron Artery Dis. 2000;11(2):151-9.

9. Senior R, Monaghan M, Becher H, Mayet J, Nihoyannopoulos P. Stress echocardiography for the diagnosis of patients with suspected or known coronary artery disease: a critical appraisal. Supported by the Bristish Society of Echocardiography. Heart 2005; 91(4): 427-36.

10. Picano E, Pingitore A, Conti U, Kozàkovà M, Boem A, Cabani E, et al. Enhanced sensitivity for detection of coronary disease by addition of atropine to dipyridamole echocardiography. Eur Heart J. 1993;14(9):1216-22.

11. McNeill AJ, Fioretti PM, El-Said ESM, Salustri A, Forster T, Roelandt JRTC. Enhanced sensitivity for detection of coronary disease by addition of atropine to dobutamine stress echocardiography. Am J Cardiol. 1992;70(1):41-6.

12. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the cardiac imaging committee of the council on clinical cardiology of the American Heart Association. Circulation. 2002; 105(4): 539-42.

13. Cortigiani L, Dodi C, Paolini EA, Bernardi D, Bruno G, Nannini E. Prognostic value of pharmacological stress echocardiography in women with chest pain and unknown artery disease. J Am Coll Cardiol. 1998;32(7):1975-81.

14. American Diabetes Association. Diagnosis and classification of Diabetes Mellitus. Diabetes Care. 2010; 33 (Suppl1): S62-S69.

15. Piegas LS, Feitosa G, Mattos LA, Nicolau JC, Rossi Neto JM, Timerman A, et al; Sociedade Brasileira de Cardiologia. Diretriz da Sociedade Brasileira de Cardiologia sobre tratamento do infarto agudo do miocárdio com supradesnível do segmento ST. Arq Bras Cardiol.2009;93(6 supl.2):e179-e264.

16. Nicolau JC, Timerman A, Piegas LS, Marin-Neto JA, Rassi A. Jr. Guidelines for unstable angina and non-st-segment elevation myocardial infarction of the Brazilian Society of Cardiology (II Edition, 2007). Arq Bras Cardiol. 2007; 89(4):89-e131.

17. Milicevic Z, Raz I, Beattie SD, Campaigne BN, Sarwat S, Gromniak E, et al. Natural history of cardiovascular disease in patients with diabetes: role of hyperglycemia. Diabetes Care. 2008: 31 (Suppl 2): S155-S160.

18. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. Diabetologia 2001; 44 (Suppl 2): S14-S21.

19. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and nondiabetic subjets with and without prior myocardial infarction. N Engl J Med. 1998; 339(4):229-34.

20. Wiersma JJ, Verberne HJ, ten Holt WL, Radder IM, Dijskman LM, van Eck-Smit BL, et al. Prognostic value of myocardial perfusion scintigraphy in type 2 diabetic patients with mild, stable angina pectoris. J Nucl Cardiol. 2009; 16(4):524-32.

21. Marwick T. Stress echocardiography. Heart. 2003; 89(1):113-8.

22. Armstrong W, Zoghbi WA. Stress echocardiography: current methodology and clinical applications. J Am Coll Cardiol. 2005;45(11):1739-47.

23. Markman Filho B, Almeida MC, Markman M, Chaves A, Moretti MA, Ramires, JAF, et al. Stratifying risk in Unstable Angina with Dobutamine Stress Echocardiography. Arq Bras Cardiol. 2006; 87(3):259-64.

24. Almeida MC, Markman Filho B. Valor prognóstico da ecocardiografia sob Estresse com Dipiridamol em Mulheres. Arq Bras Cardiol. 2011; 96(1): 31-7.

25. Oliveira JLM, Barreto-Filho JAS, Oliveira CRP, Santana TA, Anjos-Andrade FD, Alves EO, et al. Prognostic value of exercise echocardiography in diabetic patients. Cardiovasc Ultrasound. 2009; 7:24.

26. Cortigiani L, Bigi R, Sicari R, Landi P, Bovenzi F, Picano E. Prognostic value of pharmacological stress echocardiography in diabetic and nondiabetic patients with known or suspected coronary artery disease. J Am Coll Cardiol. 2006;47(3):605-10.