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Prognostic Value of Dobutamine Stress Echocardiography in Predicting Major Cardiac Events in Patients with Metabolic Syndrome

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ABSTRACT

Background: The metabolic syndrome increases cardiovascular mortality. We report the mid-term prognostic value of dobutamine echocardiography for metabolic syndrome. **Patients and methods:** A dobutamine echocardiography protocol was performed in patients aged 18 years of age or older who suffered from chest pain and who were followed-up for two years. The patients were divided in two groups, with and without metabolic syndrome. Statistical analyses were performed using ROC curves and survival analysis; the Begg-Greenes method was used to correct for verification bias. We included 128 patients, 66 with metabolic syndrome and 62 without. **Results:** Forty-one patients with metabolic syndrome and 36 without had positive dobutamine echocardiography test results (p = 0.77). Coronary artery disease was found in 27 patients with metabolic syndrome and in 29 without metabolic syndrome; percutaneous revascularization was required in 24 and 26 patients, respectively (p = 0.29). Cardiovascular events occurred in 28 patients during follow-up (19 in metabolic syndrome vs. 9 in non-metabolic syndrome; p = 0.17). The odds ratio of major cardiovascular events in the metabolic syndrome group was 5.8 (95% CI: 1.74-19.60); in the control group it was 8.6 (95% CI: 2.53-29.59). **Conclusion:** Dobutamine echocardiography for metabolic syndrome has high sensitivity but is not a determining factor for mid-term prognosis. (REV INVES CLIN. 2015;67:199-206)
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BACKGROUND

The increased prevalence of ischemic heart disease in recent decades mainly affects the economically active population, in which there is a high prevalence of risk factors such as dyslipidemia, diabetes, and hypertension, and obesity takes a prominent place. Cardiovascular diseases represent one of the most common causes of morbidity and mortality worldwide[1,2].

Many recent studies have demonstrated the relationship between the metabolic syndrome (MS) and cardiovascular mortality, even though it is difficult to compare them due to differences in cohorts studied and diagnostic criteria for MS[3]. Coronary mortality is three-times higher in patients with MS, even in the absence of diabetes mellitus or previous cardiovascular disease. The components of MS account for 18% of the risk of cardiovascular disease[4,5], and this risk increases exponentially when more than three MS components are associated[6].

Stress echocardiography has demonstrated its usefulness in the evaluation of coronary artery disease. Dobutamine echocardiography (dobutamine echo) is used for the diagnosis of ischemic heart disease[7], identifying patients with a poor prognosis after myocardial infarction[8] and medically treated angina[9]. It also has an adequate sensitivity and specificity in detecting myocardial viability[10]. However, it is not known whether its performance is different in MS patients and in patients with suspected ischemic heart disease. We report on the performance and medium-term prognostic value of dobutamine echo in patients with MS and patients with suspected ischemic heart disease.

MATERIAL AND METHODS

Patient selection

Between January 2010 and February 2013, stress echocardiography was performed in patients over 18 years of age, regardless of gender, who had experienced typical chest pain (functional class II or III of the Canadian Cardiovascular Society) within the past three months, with or without electrocardiographic changes. We did not include patients with unstable angina, electrocardiogram changes suggestive of acute myocardial infarction (ST-segment elevation of more than 2 mV or presence of Q wave), high creatine kinase-MB enzyme flow curve, history of acute myocardial infarction, positive stress test, revascularization or catheterization, diagnosis of heart failure, cardiomyopathy or uncontrolled hypertension. All patients underwent pharmacological stress echocardiography with dobutamine (dobutamine echo), with follow-up of two years after the study. The end points were major adverse cardiac events (MACE): angina, heart failure, stroke, need for revascularization, or death. The patients who were candidates for a dobutamine echo test were divided into two groups depending on their status as carriers of MS. For MS diagnosis, we used the definition of the National Cholesterol Education Program Adult Treatment Panel III (NCAP ATP-III). According to this definition, MS is present if three or more of the following five criteria are met: waist circumference > 90 cm (men) or 80 cm (women), blood pressure > 130/85 mmHg, fasting triglyceride level > 150 mg/dl, fasting high-density lipoprotein cholesterol levels < 40 mg/dl (men) or 50 mg/dl (women), and fasting blood sugar > 100 mg/dl[11].

In those patients with positive stress echo, cardiac catheterization was performed within 30 days. The study design and data collection were planned prospectively once the project was approved by the Ethics and Research Committee of the National Commission of Scientific Research. All patients gave written informed consent before the protocol began.

Dobutamine echocardiography

All echocardiographic studies were performed using a Philips Sonos 7500 (Bothell, Washington), before cardiac catheterization, by two echocardiography experts with over 10 years of experience in this area and unaware of the research hypothesis. Dobutamine echo was performed according to a standard protocol[12,13], starting with a dose of 10 µg/kg for three minutes, and increasing the dose by 10 µg/kg every three minutes until reaching 85% of the theoretical maximum heart rate (220 minus age in years), without exceeding 40 µg/kg. If the expected heart rate was not achieved, we added 1 mg of atropine. The electrocardiogram and blood pressure were monitored continuously during the study at each stage of the test and five minutes post-drug administration. The analyzed images were acquired from apical 4-chamber and short-axis parasternal views, with the patient in left lateral

position, allowing comparison of the different views at different stages. Left ventricular regional contractility was assessed according to the recommendations of the American Society of Echocardiography[14]; each of the 16 segments was classified according to regional mobility: normal, hypokinetic, akinetic, and dyskinetic. We considered the following criteria for terminating the dobutamine stress echo test before completing the infusion protocol: (i) unequivocal presence of abnormal regional contractility, (ii) decrease in absolute or relative systemic blood pressure > 30 mmHg, and (iii) any of the circumstances listed as criteria for terminating the stress test. The test was considered positive for ischemia if there was a new regional anomaly in a segment with normal contractility, and/or deterioration with respect to the degree of dyssynergia in a segment with abnormal baseline, provided it was not akinetic or dyskinetic[15].

Cardiac catheterization

The indication for coronary angiography was in accordance with the clinical criteria used by our group: angina and heart failure or the presence of myocardial ischemia or viability demonstrated by dobutamine echo. The invasive study was performed in a General Electric Cath Lab Advantx (Wisconsin, USA) by the Judkins technique, with selective angiography and left ventriculography in conventional projections. The degree of stenosis in each major coronary artery was estimated using the measurements obtained with an automated caliper using at least two projections. We considered as significant those lesions ≥ 70% of vessel diameter and ≥ 50% of the left main trunk.

All images were stored in digital media (CD) and were interpreted by hemodynamic experts with over 10 years of experience who were unaware of the research hypothesis.

Follow-up

Monitoring of patients was performed monthly or bimonthly by their respective clinical cardiologists in the outpatient cardiology hospital where the study was conducted. Those patients who did not attend their appointment or who had negative results on dobutamine echo were referred to their primary care unit, contacted by telephone by medical personnel involved in the project, and given an appointment at the research unit for cardiovascular clinical evaluation, which was repeated bimonthly until at least 18 months of follow-up. For analysis purposes, we considered as MACE during follow-up any of the following: cardiac death, hospitalization for heart failure, nonfatal myocardial infarction or unstable angina, and need for revascularization (angioplasty or surgery). In all cases, the event was confirmed by clinical evaluation of the patient and/or review of his clinical history. All events were considered in patients with more than one event. This study was approved by the Ethics and Research Committee and all the patients signed an informed consent.

Statistical analysis

We performed an exploratory analysis of all numeric variables to determine the characteristics of the distribution curve. Using 2 × 2 tables, we obtained the level of inter- and intra-observer agreement in 20 subjects who were not included in the study.

The comparison of qualitative variables between patients with and without MS was done by chi-square test, while the quantitative variables were compared using Student's *t* test for independent samples with normal distribution, or the Mann-Whitney *U* test for samples with non-normal distribution.

Bayesian analysis was used to estimate sensitivity, specificity, positive predictive value, and negative predictive value of the test in patients with and without MS; the comparison of proportions between the two groups was done using chi-square test.

The comparison of the diagnostic performance between one group and another was done using ROC curves, while the area under the ROC curve was calculated through Wilcoxon test, and the Begg and Greenes method was used to correct for verification bias[16].

To evaluate the occurrence of MACE in the group with MS and in the group without MS, we used the Kaplan-Meier method and compared the groups by log rank analysis.

We obtained the likelihood of MACE by analyzing the risk factors in patients with and without MS with positive stress test results.

All inferential statistical analyses were considered significant when $p < 5\%$.

Table 1. Baseline clinical characteristics and comparison between patients with and without metabolic syndrome*

Variable	With metabolic syndrome (n = 66)	Without metabolic syndrome (n = 62)	Statistic t/z	P value
Age	63.15 ± 10.17	60.73 ± 10.98	1.3	0.21
Gender				
– Male	39 (59%)	43 (69%)	1.46	0.22
– Female	27 (41%)	19 (31%)		
Coronary risk factors				
– Smoking	31 (47%)	45 (72%)	7.64	0.005
– Obesity	42 (63%)	18 (29%)	20.26	0.001
– Diabetes	52 (78%)	10 (16%)	47.78	0.001
– Hypertension	64 (96%)	31 (50%)	34.44	0.001
– Dyslipidemia	57 (86%)	32 (51%)	16.62	0.001
– Sedentary	40 (61%)	37 (59%	0.005	0.94
Number of risk factors	5 (4-6)†	3 (2-4)†	6.74	0.001
Current functional				
– Class II	38 (58%)	43 (69%)	1.91	0.16
– Class III	28 (42%)	19 (31%)		
Angiographic findings				
– One vessel	6	9	4.69	0.19
– Two vessels	16	10		
– Three vessels	8	14		

*Metabolic syndrome criteria according to NCEP-III. According to the NCEP ATP III definition, metabolic syndrome is present if three or more of the following five criteria are met: waist circumference > 90 cm (men) or 80 cm (women), blood pressure > 130/85 mmHg, fasting triglyceride level > 150 mg/dl, fasting high-density lipoprotein cholesterol level < 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar > 100 mg/dl. †Values are expressed as median and interquartile range. The inferential analysis by Mann-Whitney *U* considered as significant p values < 5%.

We calculated the power of the test by considering the proportion of event-free patients in each group with negative stress echocardiography test results (42.9% in the control group vs. 59.8% in the MS group). For the bilateral hypothesis, the power of the test was 88.07% and for the unilateral assumption, the power was 93.29%. Thus, we believe that our results are reliable and that the equality of the groups with respect to the presence of MACE was not due to the sample size.

The statistical software used for analysis was SPSS 22.0 and Med Calc 13.1.

RESULTS

Clinical features

A total of 133 patients met the selection criteria, 63 without and 70 with MS; of them, one patient in the first group and four patients in the second were excluded because of inconclusive stress echocardiogram. There were no significant differences between groups with respect to the clinical variables of interest, except for those that by definition are part of the MS (Table 1).

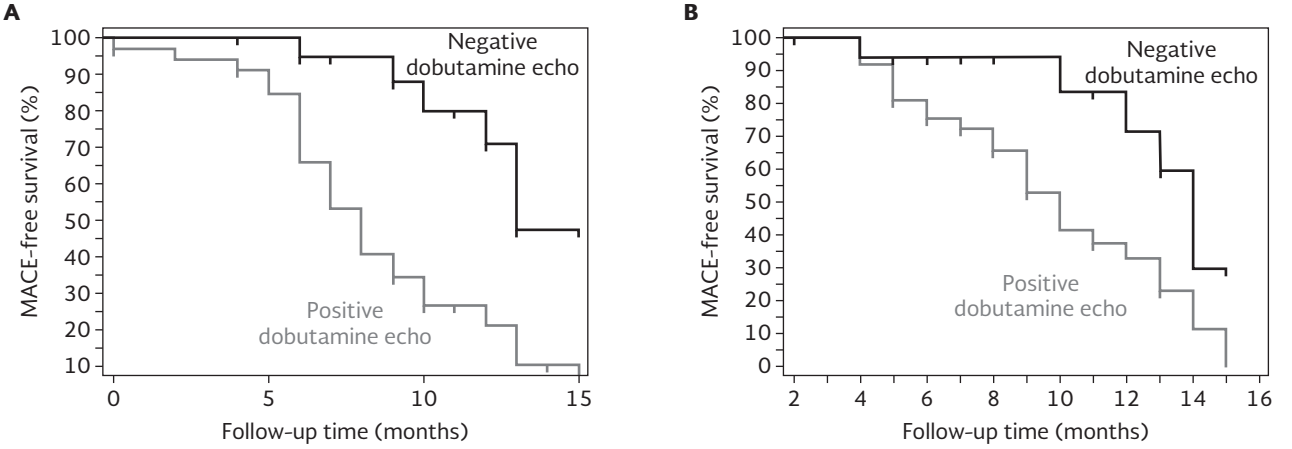
Diagnostic performance of dobutamine echocardiography

The adequate levels of inter- and intra-observer agreement for diagnosis in the case of positive dobutamine stress test were k = 0.81.

Forty-one patients with MS and 36 without MS had positive pharmacological stress echo, with no significant differences between groups (p = 0.77).

Cardiac catheterization revealed significant coronary artery disease (blockage of ≥ 50% of the lumen) in at least one of the coronary segments in 27 patients with MS and 29 patients without the syndrome; percutaneous revascularization was necessary in 24 and 26 of those patients, respectively; there was no statistical difference between groups (p = 0.29).

Figure 1. Follow-up of patients according to metabolic syndrome. **A:** with metabolic syndrome. **B:** without metabolic syndrome



Five patients with MS and six without the syndrome with positive dobutamine echo did not accept coronary angiography; however, all were followed up to assess the occurrence of any major cardiovascular event.

For analysis purposes, we considered the findings on selective coronary angiography as a gold standard or reference test for those patients with positive results in dobutamine echo. To correct for verification bias in subjects with negative results in the stress test, and therefore not catheterized, we used the Bayesian method developed by Begg-Greenes. According to our results, the sensitivity and negative predictive value of dobutamine echo was significantly higher in patients with MS (sensitivity 0.81 vs. 0.63 with MS and without MS, respectively, p = 0.03; specificity 0.57 vs. 0.53 with MS and without MS, respectively, p = 0.7; positive predictive value 0.66 vs. 0.73 with MS and without MS, respectively, p = 0.5; negative predictive value 0.75 vs. 0.41 with MS and without MS, respectively, p = 0.0003). However, there were no differences between groups when comparing the areas under the ROC curve (AUC: 0.60; 95% CI: 0.41-0.73 for the group without MS vs. AUC: 0.70; 95% CI: 0.50-0.80 for the MS group; p = 0.47)

Follow-up

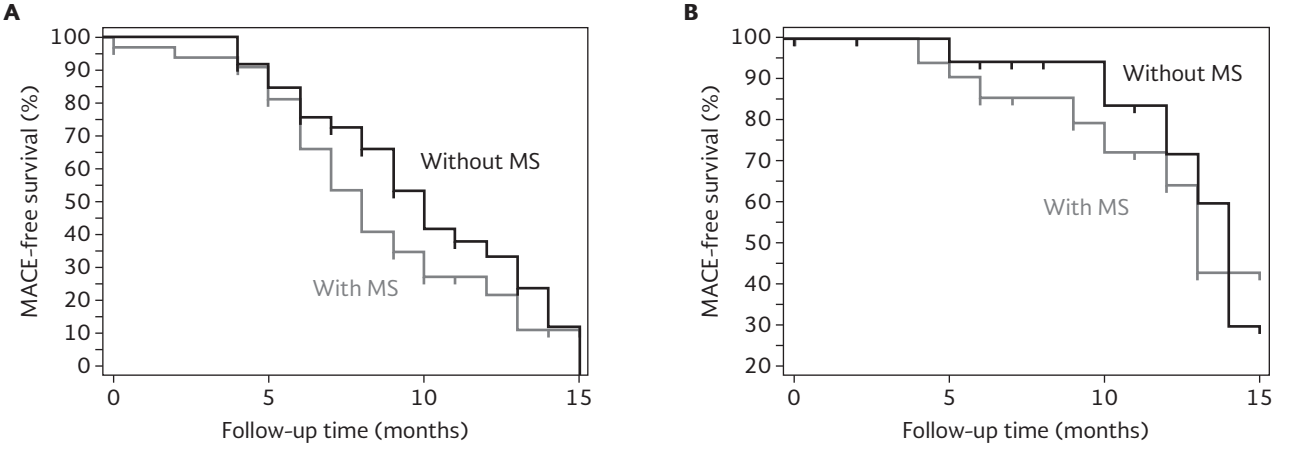
Loss to follow-up for the entire cohort was 5.4%, three for the group with MS and four for the control group, with no significant differences (p = 0.09). There were no differences between groups regarding the follow-up time (8.53 ± 3.9 months for the MS group vs. 8.24 ± 3.86 months for the group without MS; p = 0.69).

We recorded at least one cardiovascular event during follow-up in 28 patients; although there were more adverse events in patients with MS, there were no significant differences between groups (19 in MS group vs. nine in control group; p = 0.17). In the group with MS, 11 patients had angina, five needed revascularization, one had heart failure and two died; none had a documented heart attack. In the control group, the events were: three patients with angina, two with documented myocardial infarction and two who needed revascularization, one with heart failure and one death.

We compared the occurrence of MACE in patients with positive results in dobutamine echo to look for evidence of the predictive power of the test for each group. In the MS group, 47.7% of patients with negative results for myocardial ischemia or viability on the stress echocardiogram were event-free during follow-up compared with 16.1% of those with positive results, and the difference was statistically significant (p = 0.0004; Fig. 1 A). In addition, there was a statistically significant difference between the results of dobutamine echo in patients without MS; of those without MS and negative dobutamine echo, 29.9% were event-free during follow-up, compared with 17% of those with positive dobutamine echo test results (p = 0.0087; Fig. 1 B).

Furthermore, we analyzed whether there were differences in the proportion of event-free patients between carriers of MS and the control groups according to the results of echocardiography: 23.6% of carriers of MS were event-free during follow-up, compared to 10.7% of the control patients with positive results for stress

Figure 2. Follow-up of patients according to dobutamine echocardiography test result. **A:** positive dobutamine echo test. **B:** negative dobutamine echo test



echocardiography, with no significant differences (p = 0.28; Fig. 2 A). There were no significant differences between groups when the test result was negative (59.8% event-free in the MS group vs. 42.9% in the control group; p = 0.67; Fig. 2 B).

Finally, we calculated the risk of MACE in patients with positive results in dobutamine echo. According to our results, the overall risk for the control group was 8.6 (95% CI: 2.53-29.59) and 5.8 for those with MS (95% CI: 1.74-19.60).

DISCUSSION

The results obtained in our study showed that pharmacological stress echocardiography with dobutamine (dobutamine echo) is a useful test for diagnosis of ischemic heart disease in MS patients in whom there is a high suspicion of cardiovascular disease, with a high sensitivity and negative predictive value compared with those obtained in patients without MS, for whom the results are similar to those obtained by other investigators. The findings obtained from the analysis of the ROC curves confirmed that the test is useful in both groups[17]. Kamelesh, et al. reported similar findings, but they used stress-imaging studies to assess the prevalence of CAD, they did not perform cardiac catheterization, and only 4% of their patients were women[18].

Diabetic patients have increased morbidity and higher rates of cardiovascular events such as silent ischemia and myocardial infarction compared to non-diabetics[19]. The presence of MS (combined with central obesity, hypertension, and hyperglycemia) contributes to the increased risk of cardiovascular events and death from these causes[20] since MS affects mainly large-to-medium caliber vessels[21]. In our study, the occurrence of major cardiovascular events was more frequent in carriers of MS, most of whom also had an established diagnosis of diabetes mellitus.

During follow-up, there was a lower proportion of event-free patients among those with positive dobutamine echo test results, and even among those with MS and negative dobutamine echo.

Patients with and without MS behaved in a similar manner, independently of having positive or negative stress test results, with no statistically significant differences. This effect has already been observed and is consistent with that reported by other authors in patients with diabetes mellitus, in whom it was observed that using the results of dobutamine echo test to plan their management could be confusing due to the propensity of the patients to experience mural abnormalities in the absence of a previous infarction, the presence of microvascular ischemia, and the accelerated rate of progression that can limit the long-term negative predictive value of normal dobutamine echo test in these patients[22]. This is known by coronary angiography in patients who were considered candidates for dobutamine echo, or through subsequent monitoring and analysis of the stress test results corrected for verification bias with the Begg and Greenes method, which has proven useful in other studies[23].

The MS is considered a marker of cardiovascular disease; Al Badarin, et al. found, in a cohort of patients with abnormal dobutamine echo test results, that the presence of MS slightly increases the prevalence of coronary artery disease, but not significantly, compared to patients without MS. These findings are similar to ours, where no significant difference was observed between patients with and without MS with positive test results; perhaps the number of diabetic patients included influenced the test result because patients with diabetes and/or glucose intolerance are more likely to have coronary artery disease[24].

Other studies with diabetic patients have found that when these patients are candidates for dobutamine echo, they usually have other comorbidities that make them candidates for it and that favor an increased prevalence of stroke, peripheral vascular disease, and neuropathy. Thus, the dobutamine echo test can predict a greater number of cardiac events in this group of patients, who are at a higher risk compared to those who are not candidates for the test and have fewer comorbidities[22]. The inability to perform exercise in patients with diabetes mellitus and the indication of dobutamine echo test constitute a marker not only of a high pretest probability of coronary heart disease, but also generally of poor prognosis, which may be true for the group of patients with MS in this study because about 80% of them had diabetes mellitus[25,26].

The results of this study support the diagnostic use of dobutamine echo test in patients with MS in the study protocol for coronary heart disease due to its high sensitivity compared to that reported in the general population, although it is not a determining factor in establishing the mid-term prognosis of these patients. Patients with extensive abnormalities in multivessel distribution according to dobutamine echo, which are more frequent in patients with MS, are at increased risk of death from myocardial infarction, which may justify the need for coronary angiography and myocardial revascularization.

DECLARATION OF INTEREST

The authors declare no conflicts of interest.

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