

Analysis of the Safety and Feasibility of Dobutamine Stress Echocardiography in Ten Thousand and Six Tests of a General Population

Análise da Segurança e Exequibilidade do Ecocardiograma sob Estresse com Dobutamina em Dez Mil e Seis Exames de uma População Geral

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Abstract

Background: Adverse effects and inconclusive results may occur on dobutamine stress echocardiography.

Objective: To assess the safety and feasibility of dobutamine stress echocardiography in a large general population.

Methods: A total of 10,006 dobutamine stress echocardiographies were performed between July 1996 and September 2007. Dobutamine was administered in four stages (10, 20, 30, and 40 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) to research myocardial ischemia starting with 5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to analyze myocardial viability. Atropine was started according to the protocols used in the period. Clinical, hemodynamic, and adverse effect data associated with dobutamine stress echocardiography findings were verified.

Results: Typical angina (8.9%), hypertensive peak (1.7%), isolated ventricular ectopias (31%), supraventricular tachyarrhythmia (1.89%), atrial fibrillation (0.76%), and non-sustained ventricular tachycardia (0.6%) occurred during dobutamine stress echocardiography. The adverse effects occurred more frequently in patients with positive dobutamine stress echocardiography findings for ischemia than in those with negative findings. Paradoxical sinus deceleration (0.16%) did not occur in cases of positive dobutamine stress echocardiography findings. Three severe complications occurred in cases that tested positive for ischemia on dobutamine stress echocardiography: two (0.02%) of ventricular fibrillation and one of acute coronary syndrome (0.01%). There were no cases of sustained ventricular tachycardia, cardiac rupture, asystole, or death. Compared to those with complete tests, patients with inconclusive results used less atropine (81.5% versus 49.9%, $p < 0.001$) and more beta-blockers (4.7% versus 19%, $p < 0.001$) and more commonly presented with a hypertensive peak (1.1% versus 14.2%, $p = 0.0001$) or non-sustained ventricular tachycardia (0.5% versus 2.2%, $p < 0.001$).

Conclusion: When properly performed, dobutamine stress echocardiography is safe and has high feasibility.

Keywords: Dobutamine; Side Effects; Echocardiography, Stress.

Resumo

Fundamento: Durante o ecocardiograma sob estresse com dobutamina, podem ocorrer efeitos adversos e exames inconclusivos.

Objetivo: Avaliar em uma grande população geral a segurança e a exequibilidade do ecocardiograma sob estresse com dobutamina.

Métodos: Estudo de 10.006 ecocardiogramas sob estresse com dobutamina realizados no período de julho de 1996 a setembro de 2007. A dobutamina foi administrada em quatro estágios (10, 20, 30 e 40 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) para pesquisa de isquemia miocárdica e iniciada com 5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ apenas na análise de viabilidade miocárdica. A atropina foi iniciada conforme os protocolos vigentes. Foram verificados dados clínicos, hemodinâmicos e efeitos adversos associados ao ecocardiograma sob estresse com dobutamina.

Resultados: Durante os ecocardiogramas sob estresse com dobutamina, ocorreu angina típica (8,9%), pico hipertensivo (1,7%), ectopias ventriculares isoladas (31%), taquiarritmia supraventricular (1,89%), fibrilação atrial (0,76%) e taquicardia ventricular não sustentada (0,6%). Os efeitos adversos citados foram mais frequentes nos pacientes com ecocardiogramas sob estresse com dobutamina positivos para isquemia. A desaceleração sinusal paradoxal (0,16%) não ocorreu em ecocardiogramas sob estresse com dobutamina positivo. As três complicações graves ocorreram em ecocardiogramas sob estresse com dobutamina positivos para isquemia. Foram dois casos (0,02%) com FV e um caso de síndrome coronariana aguda (0,01%). Não houve caso de taquicardia ventricular sustentada, ruptura cardíaca, assistolia ou óbito. Comparados

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aos exames concluídos, nos inconclusivos, os pacientes usaram menos atropina (81,5% versus 49,9%; $p < 0,001$) e mais betabloqueador (4,7% versus 19%; $p < 0,001$), apresentando mais pico hipertensivo (1,1% versus 14,2%; $p = 0,0001$) e taquicardia ventricular não sustentada (0,5% versus 2,2%; $p < 0,001$).

Conclusão: O ecocardiograma sob estresse com dobutamina realizado de forma apropriada é seguro e apresenta elevada exequibilidade.

Palavras-chave: Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Ecocardiografia sob Estresse; Dobutamina.

Introduction

Dobutamine stress echocardiography (DSE) is an accurate and well-established method of assessing coronary artery disease (CAD). Its wide use led to continuously improving safety of this important methodology in different sex and age groups. Thus, publications showing the adverse effects of DSE resulted in the development of more appropriate examination protocols and, consequently, provided strategies to reduce potential complications.¹⁻⁸

Studies available in the literature describe the use of dobutamine as being more susceptible to being associated with adverse effects and severe complications than the use of exercise or vasodilators as stressors. Thus, the occurrence of death, ventricular rupture, acute myocardial infarction, complex ventricular and supraventricular arrhythmias, among other events, is verified under different expressions.⁹⁻¹⁵ However, modifications in examination protocols and the accumulated experience avoid or reduce the occurrence of adverse effects, showing greater safety and feasibility of DSE over time, particularly by analyzing a large population.

Thus, this study aimed to assess DSE safety in a large general population, identify its adverse effects and complications, and verify conditions that affect its feasibility.

Methods

The present retrospective study included patients undergoing DSE whose data on clinical information, adverse effects, and severe complications were prospectively collected between July 1996 and September 2007. The patients were referred by their attending physicians with the diagnostic hypothesis of known or probable CAD. The examination was initiated only after the patients understood the information regarding the purpose of the DSE and its potential adverse effects and complications, and provided verbal consent. Regarding the use of atropine, it was mandatory that the ophthalmologist confirmed the absence of glaucoma contraindicating its use; in patients prone to urinary retention, this drug was avoided. The suspension of beta-blockers was requested within 48–72 hours prior to the examination except in cases in which the attending physician requested therapy maintenance. Following the service routine, all of the necessary conditions for effective cardiopulmonary resuscitation were checked and reviewed regularly.

An Apogee CX 200 and Vingmed System Five was used with a quadruple screen to enable the comparative analysis of the four stages of DSE and visualization of the heart in the parasternal (long- and short-axis) and apical (four- and two-chamber) views.

Blood pressure (BP) was measured at the beginning of each stage and at the end of the test. Electrocardiographic monitoring was continuous, and 12-lead electrocardiography was performed before and during the procedure.

Dobutamine was administered in a peripheral vein in four stages at increasing doses of 10, 20, 30, and 40 $\mu\text{cg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at three-minute intervals. The DSE was considered complete when at least 85% of the maximum heart rate (HR) was reached (220 minus age in years) and/or myocardial ischemia was determined through the occurrence of a contractile abnormality in a previously normal myocardium or the worsening of a pre-existing abnormality.

In cases referred for a myocardial viability assessment, only the presence of viable muscle was investigated as evidenced by increased or impaired contractility at rest. The initial dose of dobutamine was 5 $\mu\text{cg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, with increases at increments of 2.5 or 5 $\mu\text{cg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and the final dose reaching up to 20 $\mu\text{cg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, if necessary, to complete the examination but without the use of atropine.

Following the initial and current DSE protocol, atropine was initiated at the end of the fourth stage, while the dobutamine infusion could be extended during the administration of atropine.^{16,17} As the protocol progressed, atropine was administered during the fourth stage or after half of the third stage depending on the HR achieved or by the examiner's decision.^{18,19} Atropine was administered in a bolus of 0.25/0.50 mg/min and reaching the maximum cumulative dose of 2 mg. An infrequent and important situation in which atropine would be administered earlier would be the need to interrupt sinus deceleration in some specific cases.

At the end of the test, 5 to 10 mg of intravenous metoprolol could be administered to control the ischemia and/or HR reduction.^{1,3,5,9,16,18-23} As a routine service, after the DSE, the patient waited in the attached room for at least 20 minutes regardless of the test results.

Adverse effects and complications

Chest pain, when present, was defined as typical or atypical angina. The hypertensive peak was identified when the BP reached or exceeded 230/120 mmHg, while hypotension was identified when the systolic BP decreased to less than 100 mmHg. Arrhythmias were classified as supraventricular tachyarrhythmia (SVTA), atrial fibrillation (AF), sustained ventricular tachycardia (SVT) lasting > 30 seconds, non-sustained ventricular tachycardia (NSVT), and ventricular fibrillation (VF). The possible occurrence of paradoxical sinus deceleration, acute coronary syndrome, acute myocardial infarction, ventricular rupture, asystole, or death was also investigated. Even if not complete, DSE was stopped in cases of adverse effects that identified intolerance to the examination or were life-threatening.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, while categorical variables are expressed as absolute frequency and percentage. The descriptive analysis of data by group was performed using contingency and descriptive measure tables. The association between groups and categorized variables was analyzed using Fisher’s exact test. The normality of the distribution of quantitative variables by group was evaluated using the Shapiro-Wilk test. Levene’s test was used to analyze group homogeneity in relation to variance. Student’s *t*-test was used to analyze group homogeneity in relation to the normal distribution of quantitative variables, while the non-parametric Mann-Whitney *U* test was used for non-normally distributed variables. The analyses were performed using Statistical Package for Social Science software version 20.0 (SPSS Inc., Chicago, IL, USA). Values of *p* < 0.05 were considered statistically significant in all analyses.

Results

A total of 10,006 DSE procedures performed between July 1996 and September 2007 were analyzed, including negative tests for myocardial ischemia (79.68%), positive tests for myocardial ischemia (14.41%), myocardial viability tests (1.19%), and inconclusive tests (4.78%). However, of the 478 inconclusive DSE procedures, 27 were excluded from the statistical analysis due to inadequate image quality during the test without any adverse effects.

Table 1 presents the clinical data, which showed a predominance of female patients (56.7%), a 52.4% incidence of hypertension, a 43% incidence of dyslipidemia, a 16% incidence of diabetes, and a 18.9% incidence of known CAD. Of the 2,153 patients using beta-blockers, 25% did not follow the recommendation to discontinue the drug.

The fourth stage of the DSE protocol was reached in 86% of the tests, with the use of atropine in 80% and the registration of the maximum HR for age in 38.3% of the cases. The adverse effects occurring during DSE included chest pain including typical angina (8.9%), hypertensive peak (1.7%), paradoxical sinus deceleration (0.16%), isolated ventricular ectopias (31%), SVTA

(1.89%), AF (0.76%), NSVT (0.6%), acute coronary syndrome (0.01%), and VF (0.02%). There were no cases of SVT, Takotsubo cardiomyopathy, ventricular rupture, asystole, or death.

Analysis of the association between clinical variables at rest and the test results (positive or negative) revealed a greater association with male, older, hypertensive, and diabetic patients with known CAD in whom beta-blockers were used or suspended and who had a positive DSE result for myocardial ischemia (Table 2).

Table 2 - Analysis of the association between variables and positive or negative stress echocardiography results for myocardial ischemia.

Variable	Positive n (%)	Negative n (%)	P value
Sex			
Male	803 (55.7)	3,234 (40.6)	< 0.001
Female	638 (44.3)	4,734 (59.4)	< 0.001
Age, years			
≤ 65	860 (59.7)	5,112 (64.2)	0.001
> 65	581 (40.3)	2,856 (35.8)	0.001
Arterial hypertension	842 (58.4)	4,129 (51.8)	< 0.001
Dyslipidemia	710 (49.3)	3,400 (42.7)	< 0.001
Diabetes mellitus	349 (24.2)	1,183 (14.8)	< 0.001
Coronary artery disease	580 (40.2)	1,177 (14.8)	< 0.001
Beta-blocker			
Used	105 (7.3)	333 (4.2)	< 0.001
Suspended	306 (21.2)	1,234 (15.5)	< 0.001
Reached DSE stage 4	1,269 (88.1)	6,871 (86.2)	0.065
Used atropine	1,138 (79.0)	6,626 (83.2)	< 0.001
Reached HRmax during DSE	591 (41.0)	3,242 (40.7)	0.816
Typical angina	543 (37.7)	330 (4.1)	< 0.001
Hypertensive peak	36 (2.5)	67 (0.8)	< 0.001
Paradoxical sinus deceleration	0	14 (0.2)	0.148
Isolated ventricular ectopias	495 (34.4)	2,478 (31.1)	0.016
Supraventricular tachyarrhythmia	38 (2.6)	144 (1.8)	0.047
Atrial fibrillation	18 (1.2)	58 (0.7)	0.048
Non-sustained ventricular tachycardia	27 (1.9)	23 (0.3)	< 0.001

DSE, dobutamine stress echocardiography; HR, heart rate; HRmax, maximum HR.

Table 1 - Descriptive analysis of clinical data from stress echocardiography.

Variable	Negative for ischemia n (%)	Positive for ischemia n (%)	Myocardial viability n (%)	Inconclusive n (%)
Sex				
Male	3,234 (40.6)	803 (55.7)	82 (68.9)	216 (45.2)
Female	4,734 (59.4)	638 (44.3)	37 (31.1)	262 (54.8)
Arterial hypertension	4,129 (51.8)	842 (58.4)	29 (24.4)	242 (50.6)
Dyslipidemia	3,400 (42.7)	710 (49.3)	21 (17.6)	177 (37.0)
Diabetes mellitus	1,183 (14.8)	349 (24.2)	10 (8.4)	65 (13.6)
Smoking	539 (6.8)	105 (7.3)	3 (2.5)	33 (6.9)
Coronary artery disease	1,177 (14.8)	580 (40.2)	46 (38.7)	84 (17.6)
Beta-blocker				
Used	333 (4.2)	105 (7.3)	8 (6.7)	87 (18.2)
Suspended	1,234 (15.5)	306 (21.2)	5 (4.2)	75 (15.7)
Unused	6,401 (80.3)	1,030 (71.5)	106 (89.1)	316 (66.1)

The analysis of the association between variables occurring during stress and test results (positive or negative) also showed no intergroup difference in reaching the fourth stage of the protocol (reached in more than 86% of cases) or in maximum or submaximal HR during DSE. A positive DSE result for ischemia showed a stronger association with the occurrence of typical angina, hypertensive peak, SVTA, AF, and NSVT. Paradoxical sinus deceleration occurred only in patients with negative DSE findings, although atropine was more commonly used in this group (Table 2).

The comparative evaluation of DSE results in terms of clinical and hemodynamic variables showed that the patients who tested positive for ischemia were older, used less atropine, and had higher systolic BP at rest and under stress. On the other hand, patients with negative results for ischemia showed higher HR both at rest and under stress (Table 3). There was no intergroup difference in diastolic BP at rest or under stress.

The DSE stratification by results considering the comparison between the sexes and the distribution of the variables showed that women were older than men, used less atropine, and had a higher HR at rest despite positive or negative DSE results for ischemia. Women had a higher systolic BP, but only in negative tests for ischemia and at rest.

During stress, HR and diastolic BP were higher in male patients, but only in those who tested negative DSE for ischemia. However, systolic BP during stress was higher in male patients despite positive or negative DSE results. The other hemodynamic comparisons did not differ between the sexes despite positive or negative DSE results for ischemia (Table 4).

The comparison between complete and incomplete DSE results showed no intergroup differences in mean age (61 ± 11.7 versus 60 ± 11.9 years, $p = 0.23$). Inconclusive tests presented a lower occurrence of patients reporting chest

Table 3 - Comparison of stress echocardiogram negative or positive results for ischemia depending on the distribution of clinical and hemodynamic variables.

Variable	n	Mean	SD	Median	P value
Age, years					
Negative	7,968	60.603	11.874	61.0	< 0.001
Positive	1,441	62.353	10.767	63.0	
Atropine dose, mg					
Negative	6,502	0.67	0.34	0.5	0.003
Positive	1,097	0.63	0.25	0.50	
HR at rest, bpm					
Negative	7,968	76.591	13.415	75.0	< 0.001
Positive	1,441	74.056	12.907	72.0	
HR during DSE, bpm					
Negative	7,968	150.335	13.234	151.0	< 0.001
Positive	1,441	145.175	18.281	148.0	
SBP at rest, mmHg					
Negative	7,968	134.687	18.842	140.0	<0.001
Positive	1,441	136.998	20.223	140.0	
SBP during DSE, mmHg					
Negative	7,968	150.249	24.321	150.0	< 0.0001
Positive	1,441	153.380	26.942	150.0	

DSE, dobutamine stress echocardiography; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation.

pain, reaching the fourth stage, or using atropine in addition to having a lower incidence of isolated ventricular ectopias. However, inconclusive tests showed a higher percentage of patients using beta-blockers, with hypertensive peaks, and with NSVT (Table 5).

Table 4 - Stratification of stress echocardiography negative or positive results for ischemia: Comparison of sexes by distribution of variables.

Variable	Sex	n	Mean	SD	Median	P value
Age, years						
Positive	Male	803	61.740	10.866	62.0	0.017
	Female	638	63.125	10.598	63.0	
Negative	Male	3,234	59.235	12.506	59.0	< 0.001
	Female	4,734	61.538	11.328	61.0	
Atropine dose, mg						
Positive	Male	617	0.68	0.38	0.50	< 0.001
	Female	480	0.57	0.31	0.50	
Negative	Male	2,777	0.79	0.42	0.75	< 0.001
	Female	3,725	0.59	0.33	0.50	
HR at rest, bpm						
Positive	Male	803	73.269	12.705	72.0	0.012
	Female	638	75.045	13.100	74.0	
Negative	Male	3,234	74.401	12.674	73.0	< 0.001
	Female	4,734	78.087	13.700	77.0	
HR during DSE, bpm						
Negative	Male	3,234	151.711	13.256	153.0	< 0.001
	Female	4,734	149.395	13.138	150.0	
SBP at rest, mmHg						
Negative	Male	3,234	133.578	17.857	130.0	< 0.001
	Female	4,734	135.445	19.452	140.0	
SBP during DSE, mmHg						
Positive	Male	803	155.181	28.206	160.0	0.020
	Female	638	151.113	25.100	150.0	
Negative	Male	3,234	153.789	25.286	150.0	< 0.001
	Female	4,734	147.830	23.336	140.0	
SBP during DSE, mmHg						
Negative	Male	3,234	76.670	11.786	80.0	< 0.001
	Female	4,734	75.514	10.598	80.0	

DBP, diastolic blood pressure; DSE, dobutamine stress echocardiography; HR, heart rate; SBP, systolic blood pressure.

Table 5 - Comparison of complete and inconclusive stress echocardiography results.

Variable	Complete n (%)	Inconclusive n (%)	P value
Total	9,550 (100)	451 (100)	-
Dyslipidemia	4,135 (43.3)	165 (36.6)	0.005
Beta-blocker usage	446 (4.7)	86 (19.1)	< 0.001
Reached the fourth stage of DSE	8,189 (85.7)	356 (78.9)	< 0.001
Used atropine	7,785 (81.5)	225 (49.9)	< 0.001
Hypertensive peak	104 (1.1)	64 (14.2)	0.0001
Absent chest pain	7,838 (82.1)	423 (93.8)	< 0.001
Isolated ventricular ectopias	3,002 (31.4)	119 (26.4)	0.026
Non-sustained ventricular tachycardia	51 (0.5)	10 (2.2)	< 0.001

DSE, dobutamine stress echocardiography; *No difference in mean age (61 ± 11.7 versus 60 ± 11.9 years, $p = 0.23$).

Discussion

This study included a general population of 10,006 individuals who were subjected to DSE procedures, and analyzed several aspects related to clinical data resulting from dobutamine and atropine action. The adequacy of the different protocols used according to observations reported in the literature resulted in excellent feasibility to conclude the tests in this study associated with the use of atropine in 80% of the DSE procedures since some studies reported a variation of 32–41%, with inconclusive results occurring in 9–17% of procedures.^{1,3,9,17}

The occurrence of conclusive DSE has varied over the years among the studied populations, examination protocols, and technological development of echocardiography equipment with the second harmonic multifrequency transducers and the use of microbubble contrast, among other factors, that may influence their accuracy and feasibility. The 27 cases with an inadequate echocardiography window for analysis in this study could probably have been better visualized.^{24,25}

In this study, the association between positive DSE findings for myocardial ischemia and male sex, CAD risk factors, and a history of CAD was quite evident and within expectations. There was no difference between positive and negative results for ischemia in the proportion of cases in which the fourth stage of the test or target HR (maximum or submaximal) was reached; however, the patients with ischemia required less atropine, which could be compatible with the fact that the objective of the test had already been fulfilled.

Considering the diagnosis of myocardial ischemia using the contractile abnormality criterion, 14.41% of cases had positive DSE findings. This percentage may vary in the literature according to the sample characteristics, and some authors verified a progressively decreased percentage of positive DSE findings.²⁶

Typical pain was more frequently present in positive cases and was unquestionably related to the ischemic contractile abnormality. However, in cases in which the contractile abnormality was less expressed, bias for the positive diagnosis of ischemia may have been created. The occurrence of typical angina in positive cases may have been favored by the CAD itself as well as by suspending the use of beta-blockers, a condition that may also have caused, in this group, a higher incidence of hypertensive peak, which occurred in a low percentage of patients than that reported in previous studies.^{27,28}

The paradoxical deceleration of the sinus rhythm may be secondary to the ischemic or mechanical process; however, in the population studied here, it did not occur in a case with positive DSE findings for ischemia. This information suggests that these episodes must have resulted from mechanical stimulation of the left ventricular posterior wall and/or from an arterial baroreceptor compatible with Bezold-Jarisch syndrome.²⁹⁻³¹

Ventricular ectopias not presenting to be paired are common during DSE but are not relevant in this condition. A positive DSE for ischemia and the presence of associated comorbidities would infer the greater occurrence of SVTA, AF, and NSVT. However, the incidence of adverse effects was within the range of results published in other studies. This study detected a 1.89% incidence of SVTA, while the studies by Mathias et al.²² and Elhendy et al.³ reported rates of 1% and 4%, respectively.

The 0.76% incidence of AF during DSE in this present study was lower than the 0.86% incidence of AF observed in the meta-analysis by Mansecal et al.³² NSVT occurred in 0.6% of the DSE procedures performed in this present study, whereas De Sutter et al.¹⁴, evaluating 1,685 patients, reported the occurrence of 3.3% NSVT but did not provide information on the dose or percentage of patients using atropine, a condition that could have influenced this result.

The most severe adverse effects occurred only in patients with a positive DSE result for ischemia. The two cases of VF were resolved and later revascularized, subsequently progressing without sequelae. There was a case of acute coronary syndrome characterized by strong typical angina, contractile abnormality, and inferior wall ST-segment elevation without arrhythmia or hemodynamic disorders. After the ischemia improved with beta-blockers and coronary vasodilators, the patient was referred for a hemodynamic study. Coronary angiography showed significant right coronary stenosis, and full reperfusion was promptly achieved after angioplasty without complications. There were no serious complications such as SVT, Takotsubo cardiomyopathy, asystole, ventricular rupture, or death.

The comparison of the DSE results by distribution of clinical, hemodynamic, and sex variables showed that a lower percentage of women needed atropine in addition to concluding the test with a lower cumulative dose regardless of positive and negative DSE results for ischemia, which could be explained by the fact that women have a higher HR at rest. Another justification would be the lower body surface area of women, but this variable was not analyzed in this study. These characteristics in female patients have been reported previously.^{17,19}

Systolic BP at rest and under stress conditions was higher in cases of positive DSE results for ischemia, a finding that is compatible with the higher incidence of hypertension in this group. As for sex, males presented higher systolic BP both at rest and under stress. Diastolic BP differed between the sexes only in cases of negative DSE results for ischemia and was also higher in males. The other hemodynamic comparisons showed no difference between the sexes regardless of positive or negative DSE results for ischemia.

When associated with dobutamine, atropine causes cardiovascular response changes due to increased inotropic and chronotropic effects and cardiac work.^{33,34} Abram et al.³⁵ analyzed 2,968 cases of negative DSE results for ischemia to verify the typical pressure response in patients without known cardiovascular disease. During dobutamine administration, systolic BP increased, and diastolic BP decreased according to sex and age, that is, in males and in younger patients. These pressure changes became even more significant when atropine was administered during DSE. This atropine effect occurred in both men and women and was more evident in younger people. These data show how complex it is to analyze the simultaneous effects of dobutamine and atropine on cardiovascular dynamics.

The occurrence of 4.78% inconclusive examinations in this study was low compared to those of other publications, with neither age nor a positive result for myocardial ischemia

being causal factors. A lower proportion of inconclusive tests reached the fourth stage of the protocol concomitantly to the low use of atropine, with greater occurrence of adverse effects such as hypertensive peak and NSVT. Better BP control before the test using adequate beta-blocker replacement may reduce the most frequent limiting adverse effects to achieve more complete DSE procedures. NSVT is a more difficult problem to solve, but fortunately, it presents low risk when not progressing to SVT.

The present study did not aim to register minor manifestations such as a feeling of palpitations, heart acceleration, or nausea, for example, as these are tolerable and present no risk, which was explained to the patient before the test to assure them of the immediate reversibility of discomfort should it occur. No specific statistical analysis was performed of patients referred to verify the viability due to the absence of a relevant adverse effect in this group.

The use of atropine during DSE as proposed by McNeil et al.²⁰ showed increased sensitivity without losing specificity in the diagnosis of myocardial ischemia. Ling et al.¹⁶ analyzed a large sample and confirmed these findings, particularly for vessel damage and in patients treated with beta-blockers, making the association with atropine after the fourth stage routine in this diagnostic methodology without increasing the adverse effects. However, Santiago et al.³⁶ showed no difference in sensitivity, specificity, or positive predictive value with a mean dobutamine infusion of 30 and 40 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. In this context, Dyle et al.³⁷ evaluated dobutamine pharmacokinetics and reported sufficient serum levels of the drug at the dose of 30 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and concluded that atropine could be started in inadequate inotropic responses with dobutamine at doses of up to 20 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$.

The study by Tsutsui et al.²⁸ demonstrated the advantages of starting atropine after the second stage since it maintained its accuracy using less dobutamine and with shorter test duration, a decreased occurrence of minor adverse effects, and more diagnostic tests than the conventional protocol. However, consensus on a definitive protocol is still lacking since recent guidelines recommend the use of atropine in the third and fourth stages but with different total cumulative doses of 2 mg and 1.2 mg, respectively.^{7,8}

One of the important objectives of stress echocardiography is to reduce the occurrence of adverse effects, especially severe complications. Varga et al.¹⁵ conducted the largest review in the echocardiographic context that included 85,997 patients. However, it is important to note that the authors received data even from centers with experience performing only 20 tests, which would increase the possibility of severe complications. On the other hand, the authors found that no severe adverse effect was verified in 25 of the 75 participating centers. The largest study evaluating

cardiovascular complications during exercise, published by Stuart and Ellestad³⁸, included 518,448 stress tests with exercise. These authors reported 8.86 complications considered severe per 10,000 tests. This evaluation included 0.5 deaths, 3.58 acute myocardial infarctions, and 4.78 arrhythmias, considered severe by the authors (requiring venous therapy or cardioversion), per 10,000 tests.

Severe complications can be unpredictable in physical or pharmacological stress conditions; however, with the more frequent and early use of atropine in DSE, the patient's exposure to the adverse effects of dobutamine decreases, favoring the use of DSE.

Limitations

Although this study was a retrospective analysis, the data were prospectively collected. The exact transition period for the DSE protocols was not determined. Hemodynamic studies were not analyzed to assess DSE accuracy at diagnosing significant CAD; however, this was not the objective of this study. Another limitation of our study is its single-center design. As suggested by Armstrong et al.,³⁹ multicentric publications or meta-analyses would be more compatible and representative of the real world. However, this study was rigorous regarding its safety aspects and the progression of protocols essential for this excellent methodology.

Conclusion

When properly performed, DSE is safe and has high feasibility.

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Authors' contributions

Research creation and design: Abreu JS. Data acquisition: Abreu JS, Pinheiro TCD, Farias AGLP. Data analysis and interpretation: Abreu JS, Pinheiro TCD, Abreu MEB. Statistical analysis: Abreu JS. Manuscript writing: Abreu JS, Abreu MEB, Carneiro MM. Critical revision of the manuscript for important intellectual content: Abreu JS, Farias AGLP, Carneiro MM.

Conflict of interest

The authors have declared that they have no conflict of interest.

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