Analyzing the Safety and Predictors of Arrhythmias during Dobutamine-Atropine Stress Echocardiography in a Non-Hospital Setting

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Abstract

Background: **Dobutamine-atropine stress echocardiography (DASE) is an accessible and important test, especially in patients under investigation for coronary artery disease. However, it is necessary to evaluate its safety, as it is used in patients with increasingly complex and serious conditions and in seniors.**

Objective: **To confirm the safety of DASE and evaluate the predictors of arrhythmias in a non-hospital setting.**

Methods: **DASE was performed to evaluate ischemia using the standard protocol of dobutamine infusion of 5 to 40 mcg/kg/min associated with atropine.**

Results: **From September to November 2010, 227 patients were evaluated prospectively. The mean age was 60.7 +/- 12.5 years old and 60.8% were females. Mean ejection fraction was 67.9 +/- 9. Among the adverse events, 12 patients presented hypertensive response, 466 had arrhythmia, 58 had headaches and 57 had precordial pain. No patient had acute myocardial infarction, ventricular fibrillation, cardiac rupture, asystole or death. As for the onset of significant arrhythmia, three patients had atrial fibrillation, 16 had sustained supraventricular tachycardia, 19 had non-sustained ventricular tachycardia and 2 had sustained ventricular tachycardia. In these patients, age (OR = 1.0559, p = 0.0002) and segmental contractility index at rest (SCIr) > 1 (OR 2.5039, p = 0.0354) were independent predictors for the onset significant arrhythmia during the test.**

Conclusion: **DASE was proven safe in this group of patients in a non-hospital setting. Age and SCIr > 1 were independent predictors for the onset of significant arrhythmia during the test. (Arq Bras Cardiol: Imagem cardiovasc. 2018;31(3):168-174)**

Keywords: **Echocardiography, Stress/adverse effects; Safety; Dobutamine; Heart Failure; Arrhythmias, Cardiac.**

Introduction

Stress echocardiography is well consolidated, widely established and disseminated throughout the world. Nowadays, all over Brazil, many hospitals and clinics use this diagnostic resource. It is a low-cost, fast, quite accurate, radiation-free, tolerable and safe method.[1,2]

Despite these advantages, the method raises concerns as to its safety, as a vasopressor arrhythmogenic drug is used.[3] "Stress" may occur with patients, who are very frightened by the name of the test, and with the requesting physicians, as they do not know the details of the technique, and with the echocardiographers who, when unfamiliar with the method, are concerned about the complications and unwanted effects.

This study proposes to reinforce the safety of dobutamine-atropine stress echocardiography, providing information to the requesting physicians and encouraging echocardiographers to get acquainted with it, thus spreading the word on the method, which can be performed safely in a non-hospital setting.

Dobutamine is a well-tolerated synthetic catecholamine resulting from the chemical modification of isoproterenol, synthesized for the first time in 1975. It has a half-life of 2 to 3 minutes and is among those that most increase myocardial oxygen consumption and may, therefore, cause ischemia. These characteristics made it ideal to cause cardiac stress, being the drug mostly used in the vast majority of services that do stress echocardiography. This method was first used in the mid-1980s. Since then, many other studies have demonstrated its high diagnostic accuracy and the importance of adding atropine to dobutamine to increase the diagnostic power of the test, especially in patients taking beta-blockers.[4,5] Atropine is a substance with parasympatholytic activity, used to achieve higher heart rates and greater double-products and, consequently, provide greater chronotropic power.[6]

Recommendations of stress echocardiography have rapidly expanded. In addition to its use for diagnosing coronary artery disease, the test is recommended for stratification of patients undergoing vascular surgery, evaluation of patients with chronic kidney disease, recent acute myocardial infarction, heart valve disease and evaluation of viable myocardium in patients with significant systolic dysfunction. Besides, dobutamine has been

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increasingly used in older patients with increased cardiovascular risk. Also, the protocol has been established with shorter duration and with larger doses of the medication.[3,7,8] Although it is known to be a safe test, serious complications may occur, but with a very small incidence which, in a way, reassures the patient, the requesting physician and the echocardiographer doing the test.

Methods

Patient selection and study setting

This is a prospective study for evaluation of safety and analysis adverse effects during the stress echocardiography protocol. A population of consecutive patients with suspected coronary artery failure was evaluated. The patients were referred to stress echocardiography from September to November 2010 in a single echocardiography laboratory. The sample size was limited to the study's operational capacity.

Echocardiography, safety analysis and arrhythmia

Before the dobutamine-atropine stress echocardiography (DASE), the patients were asked to report any previous cardiovascular diseases, which cardiac procedures they had undergone and which drugs they were taking on a regular basis.

The echocardiography was performed using a HD-11 echocardiograph (Philips Ultrasound Systems, Andover, MA USA). The tests were performed systematically on all patients.

The patients were initially submitted to a baseline echocardiographic study, with linear measures of cardiac structures and valvular flows. To evaluate ejection fraction, the Teichholz or Simpson method was used depending on the extent of the segmental contractility abnormality. When the latter method was used, measurement of the final systolic diameter was not taken. Once standard baseline four- and two-chamber views on the longitudinal parasternal, transverse and apical planes were taken, intravenous infusion of dobutamine at an initial dose of 5 μg/kg/min was started, with increments of 10, 20, 30 and 40 μg/kg/min every three minutes. If the patient had no echocardiographic signs of myocardial ischemia and had not reached a heart rate of at least 100 bpm at the 20 μg/kg/min stage, atropine was administered at doses of 0.25 mg/min every 1 minute up to the maximum cumulative dose of 2 mg.

Patients were maintained under continuous clinical, electrocardiographic and pressure monitoring, and measurements of blood pressure, heart rate and 12-lead electrocardiography were taken at baseline, at the end of each stage and during the recovery stage. Patient symptomatology was recorded according to direct questioning or direct patient complaint at any time of the study.

DASE was considered effective when the study achieved one of the following objectives: at least 85% of maximum heart rate (referred to as submaximal heart rate), predicted for age, calculated according to the Karvonem equation (220 — age = maximum heart rate)[9] or presence of ischemic echocardiographic signs (worsening of left ventricular segmental contractility).

The criteria for interrupting the test, then considered non-diagnostic, were: intolerable symptoms, limiting side effects including hypertension (systolic blood pressure > 230 mmHg or diastolic blood pressure > 120 mmHg), relative or absolute hypotension (drop of systolic blood pressure > 30 mmHg at rest or systolic arterial pressure 80 mmHg, supraventricular arrhythmia (sustained supraventricular tachycardia and atrial fibrillation) and ventricular arrhythmia (non-sustained and sustained ventricular tachycardia).[10]

The safety criteria for the DASE test included absence of serious, life-threatening complications defined in the meta-analysis performed by Geleijnse et al.,[11] such as cardiac rupture, acute myocardial infarction, stroke, asystole, fibrillation ventricular and sustained ventricular tachycardia.[11]

As for the events of cardiac arrhythmia seen during the test, sustained ventricular tachycardia was determined as well-defined, regular narrow QRS complexes (< 120 ms) in the absence of conduction disorders; atrial fibrillation in the absence of P wave, associated with irregular rhythm, narrow QRS complexes (< 120 ms) in the absence of conduction disorders; frequent ventricular extrasystoles in the presence of premature ventricular complexes, with frequency greater than 6 complexes per minute; ventricular bigeminism in the presence of ventricular extrasystoles alternating with normal QRS complexes; unstable ventricular tachycardia defined as in the presence of more than three premature complex ventricular beats lasting less than 30 seconds, with heart rate greater than 100 beats per minute and sustained ventricular tachycardia in the presence of more than three premature complex ventricular beats lasting longer duration than 30 seconds and with heart rate greater than 100 beats per minute.[12]

The left ventricle was divided into 17 myocardial segments, as recommended by the American Society of Echocardiography (ASE).[13] Qualitative analysis of myocardial segmental contractility was based on the visual evaluation of myocardial thickening and on the degree of wall mobility in a segmental contractility index (SCI), giving each segment the following score: 1 - normal; 2 - hypokinesia; 3 - akinesia; and 4 - dyskinesia. The normal value of this index is 1 (17 points/17 segments). Any value greater than 1 was considered an index of abnormal segmental contractility. Worsening of myocardial segmental motility in one or more left ventricular segments during pharmacological stress was considered segmental myocardial contractility positive for ischemia.[13,14]

Statistical analysis

Given the reduced proportion of events observed (< 2%) in the binary response variables, we considered using exact inference for binary logistic regression instead of a conventional asymptotic method in order to avoid inaccuracies in parameter estimates and p values. Initially, univariate binary logistic regression analyses were conducted to identify factors associated with the occurrence of arrhythmias.

Then, considering the covariates that presented a p value smaller than or equal to 0.10 (in univariate regression analyses), a multiple binary logistic regression model was determined or the Monte Carlo method was used with 10,000 replications when the exact inference was shown to be computationally inapplicable.

The presence of multicollinearity between these covariates was evaluated by estimating variance inflation factors (VIF) as described in Allison PD (2001). VIF values greater than 2.5 served as indicators of considerable multicollinearity in a multiple logistic regression model. When advisable, covariates were excluded from the multiple regression model due to multicollinearity.

The linearity assumption between each quantitative covariant and the log-odds of the binary response variable in binary logistic regression models was evaluated using the fractional polynomial method and smoothed scatter plots. When this assumption was not satisfied, quantitative variables were categorized to be used in logistic regression according to the median distribution.

Odds ratios and their 95% confidence intervals were estimated. When advisable, a non-biased median estimate of the odds ratio was calculated.

Quantitative variables were described as mean ± standard deviation except when there was considerable asymmetry in the distribution. In these cases, they were described as median (interquartile range). Normality was assessed by visual inspection of histograms. Categorical variables were described as counts (percentages).

All probabilities of significance (p values) are bilateral and values smaller than 0.05 are considered statistically significant. The software applications SAS 9.2 (Statistical Analysis System, Cary, NC), LogXact 9.0 (Cytel Software Corporation, Cambridge MA, USA), Stata 9.2 (Stata Corporation, College Station, TX) were used in the statistical analysis of data.

Results

A total of 2,227 dobutamine stress echocardiography tests were performed during the study period. The clinical characteristics and echocardiographic data are described in Tables 1 and 2, respectively.

Data on the drug treatment of these patients are described in Table 3.

The adverse effects and arrhythmia induced during stress echocardiography are shown in Table 4.

The mean SCIr value of the group without significant arrhythmia and with significant arrhythmia during the test was 1.05 (± 0.19) and 1.26 (± 0.42), respectively.

Negative results for myocardial ischemia were the most frequent ones, with 1,894 (85.1%) tests. There were 127 (5.7%) and 205 (9.2%) tests considered inconclusive and positive for ischemia, respectively.

Submaximal heart rate was reached in 1,994 (89.5%) patients. The causes for discontinuing the test at an early stage included: severe chest pain in 5 patients, severe increase in blood pressure (greater than 230/120 mmHg) in 8 patients and severe headache in 18 patients. The onset of arrhythmia was responsible for discontinuing the protocol in 40 patients. Most of the arrhythmias presented were dose-dependent and occurred at the peak of pharmacological stress. The protocol was discontinued in the presence of significant arrhythmia (atrial fibrillation, sustained supraventricular tachycardia, non-sustained ventricular tachycardia and sustained ventricular tachycardia). Under no circumstances there was hemodynamic instability or the need for electrical cardioversion. When necessary, metoprolol, amiodarone or lidocaine were administered for reversal of arrhythmia (19, 3 and 1 patient, respectively), with all arrhythmias reversed in less than two minutes after termination of the protocol. Routine observation was performed on all patients.

No patient presented severe adverse events such as acute myocardial infarction, ventricular fibrillation, asystole, stroke, cardiac rupture or death.

The variables that correlated with the arrhythmia onset in the univariate analysis were use of amiodarone, age, ejection fraction and segmental contractility index at rest (SCIr) >1 and at peak stress (Table 5). Age and SCIr >1 were confirmed as independent predictors for arrhythmia onset in multivariate analysis (Table 6). The use of amiodarone showed a tendency for arrhythmia to appear during the test in the latter analysis. SCI at peak stress was excluded in the multivariate analysis due to multicollinearity of this variable.

Table 1 – Clinical characteristics of the total group

Clinical characteristics	Total group (n = 2227)
Age	60 ± 12
Women	1354 (60.8%)
Hypertension	1429 (64.2%)
Dyslipidemia	627 (28.2%)
Diabetes mellitus	399 (17.9%)
Smokers	226 (10.1%)
History of acute myocardial infarction	80 (3.6%)
Chagas' Disease	23 (1%)
PTA	127 (5.7%)
Coronary artery bypass grafting	78 (3.5%)
Contraindication to the use of atropine	120 (5.4%)
Pacemaker	7 (0.3%)
Atrial fibrillation at rest	8 (0.4%)

PTA: percutaneous angioplasty.

Table 2 – Echocardiographic data of the total group

Echocardiographic data	Total group (n = 2227)
Left atrium (mm)	36.7 ± 5.4
Septum (mm)	9.1 ± 1.9
Posterior wall (mm)	8.86 ± 1.56
LVEDD (mm)	48 ± 6.10
LVESD (mm)	28.85 ± 4.77
Ejection fraction (%)	67.85 ± 8.01

LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter.

Table 3 – Drug treatment of the total group

Drug treatment	Total group (n = 2227)
Beta-blocker	245 (11.0%)
Beta-blocker discontinued	253 (11.4%)
ACEI	289 (13.0%)
Calcium channel blocker	171 (7.7%)
ASA	188 (8.4%)
Nitrate	84 (3.8%)
ARB	330 (14.8%)
Amiodarone	58 (2.6%)

ACEI: angiotensin-converting 1 enzyme inhibitor; ASA: acetylsalicylic acid; ARB: angiotensin II receptor blocker.

Table 4 – Adverse effects and arrhythmias presented by the total group

Adverse effects	General group (n = 2227)
Hypertensive response	12 (0.5%)
Arrhythmias	466 (21.1%)
Headache	58 (2.8%)
Chest pain	57 (2.6%)
Anxiety	27 (1.2%)
Tremors	72 (3.2%)
Lumbar pain	32 (1.4%)
Nausea	10 (0.4%)
Arrhythmias	**General group (n = 2227)**
Atrial fibrillation	3 (0.1%)
Supraventricular extrasystoles	77 (3.5%)
Isolated ventricular extrasystoles	213 (9.6%)
Frequent ventricular extrasystoles	111 (5%)
Bigeminism	17 (0.8%)
Bradycardia	4 (0.2%)
SSVT	16 (0.7%)
NSVT	19 (0.9%)
SVT	2 (0.1%)

SSVT: sustained supraventricular tachycardia; NSVT: non-sustained ventricular tachycardia; SVT: sustained ventricular tachycardia.

Discussion

The use of dobutamine stress echocardiography for the diagnosis of coronary artery disease in patients with exercise limitation has increased over the years. In addition, the use of protocols with high doses of dobutamine and with early use of atropine has been applied more often.[15-17]

Despite the potential risk of complications, especially arrhythmogenic complications, the method was safe when performed on 2,227 patients. No patient presented severe complications such as death, acute myocardial infarction, cardiac rupture, stroke, ventricular fibrillation or asystole. Most previous safety studies reported very low incidence of these events, as in the meta-analysis published by Geleijnse et al.,[11] with 55,071 patients, where mortality, cardiac rupture and stroke had an incidence lower than 0.01%, acute myocardial infarction of 0.02%, with an incidence rate of major complications of 1: 475 (adding sustained ventricular tachycardia, asystole, and ventricular fibrillation). This number is also consistent with the complications found in the International Stress Echo Complication Registry,[18] where this rate was 1:595, in the evaluation of 35,103 patients.

The population studied by us is in the same age group compared to the different safety studies of stress echocardiography.[11] A study recently conducted by O'Driscoll et al.[19] with 550 octogenarian patients demonstrated that dobutamine stress echocardiography was a safe test capable of identifying individuals at high risk for cardiovascular events.

The risk factors for coronary artery disease in our group had a lower prevalence compared to other cohorts, except for systemic arterial hypertension.[20-22] The most prevalent risk factors reported were hypertension, dyslipidemia and diabetes. These were the ones that most related to the populations already studied, such as the group evaluated by San Roman et al.,[23] where the prevalence of hypertension was 61%, diabetes mellitus 29%, dyslipidemia 46%, smoking 23%, history of infarction 23% and coronary artery bypass grafting 31%.

Regarding drug treatment, our group of patients used, less frequently, antianginal therapy such as beta-blockers, nitrates and calcium channel blockers, compared with previous studies.[20-23]

The positive result for ischemia in our study population was less frequent than in other studies, perhaps because of the lower number of risk factors reported for CAD.[19-22] A cohort of 4,033 patients conducted by Mathias et al.[24] presented a positive result for ischemia in 37% of the patients and an inconclusive result in 10%. Sicari et al.,[25] in their cohort of 7,333 patients, had a positive result for ischemia in 39% of the tests.

As for arrhythmias, supraventricular and ventricular extrasystoles were the most frequent ones, as in the safety studies performed and analyzed in the meta-analysis published by Geleijnse et al.[11] However, the incidence was lower than in most studies. NSVT occurred in 19 (0.9%) patients. This incidence occurred following the average of the studies published (average of 2.19%, ranging from 0.2% to 7.3%).[11] Sustained ventricular tachycardia occurred in only 2 (0.1%) patients, and this incidence followed the average of previous studies (average of 0.15%, ranging from 0.0% to 0.78%). As for atrial fibrillation, the incidence in our group was lower than in the other studies, where this arrhythmia had an average incidence of 0.9%.[11]

Although our study is a prospective one, in a population of consecutive patients, the mean preserved ejection fraction in our patients favors the occurrence of fewer arrhythmias, particularly ventricular arrhythmias. In previous safety studies of stress echocardiography, ventricular fibrillation occurred almost exclusively in patients with ventricular dysfunction and with induction of extensive ischemia.[11]

Table 5 – Univariate analysis of arrhythmia predictors

Covariate	Events	OR	95% CI	p value
Amiodarone	58	5.74	1.68 – 15.55	0.006
Age		1.06	1.03 – 1.09	< 0.001
EF > 69% *	1015	0.56	0.23 – 1.03	0.066
SICr > 1	213	3.72	1.65 – 7.81	0.063
Peak SIC > 1	289	2.27	0.98 – 4.67	0.055

**Covariate obtained through the ROC curve. OR: odds ratio; CI: confidence interval; EF: ejection fraction; SICr: segmental contractility index at rest.*

Table 6 – Multivariate analysis of arrhythmia predictors

Covariate	OR	95% CI	p value
Amiodarone	3.35	0.94 – 9.48	0.060
Age	1.05	1.02 – 1.08	< 0.001
EF > 69% *	0.60	0.27 – 1.29	0.225
SCIr > 1	2.45	1.03 – 5.43	0.041

** Covariate obtained through the ROC curve. OR: odds ratio; CI: confidence interval; EF: ejection fraction; SCI: segmental contractility index.*

Undesirable adverse effects such as precordial pain had a lower incidence than in previous studies, such in as those conducted by Mathias et al.,[24] San Roman et al.,[23] and Mertes et al.,[20] where precordialgia occurred in 12.6% 8.5% and 12.7%, respectively. Headache occurred similarly as in other studies, as reported by Mathias et al.,[24] Mertes et al.,[20] and San Roman et al.,[23] with an incidence of 1.9%, 4% and 1.9%.

The incidence of hypertensive response and hypotension was also lower than in the safety studies evaluated in the meta-analysis published by Geleijnse et al.,[11] where the mean incidence of hypertension as a cause of protocol discontinuation was 1.3% and hypotension, as a criterion for discontinuing the test, was 1.7%. A recent retrospective analysis published by Abram et al.,[26] with 2,968 patients, without cardiovascular disease and normal stress echocardiography, showed that blood pressure variation during the test depends on age, gender, and use of atropine. There was a greater increase in systolic pressure in men and young people, with a more pronounced atropine effect in the young people.

In the attempt to identify an independent predictor for the emergence of significant arrhythmia events, clinical and echocardiographic data were evaluated in the univariate and multivariate model. The variables that correlated independently with the onset of significant arrhythmia events (atrial fibrillation, sustained supraventricular tachycardia and sustained and non-sustained ventricular tachycardia) were age and SCI greater than 1.

Abnormal DASE correlated independently with mortality outcome in many studies published in the literature.[20,27-30] Studies have shown that an increased value of this index at rest, low doses and high doses, especially in those with reduced ejection fraction, correlated with the mortality outcome, with values ranging from 1.4 to 1.7 to identify high-risk patients. [20]

In a study conducted by San Roman et al.,[23] with 962 patients, which evaluated the safety of stress echocardiography in a fast-track protocol, patients who had a history of systemic arterial hypertension, no history of coronary artery disease and baseline heart rate had cardiac arrhythmias more frequently. SCIr was not an independent predictor for arrhythmia in this study.[23]

Our study included a significant number of patients with stable clinical characteristics. Dobutamine-atropine stress echocardiography demonstrated safety and only 2 patients had significant adverse effects (SVT) without any hemodynamic instability. This data is important to corroborate and stimulate the use of dobutamine-atropine stress echocardiography in a non-hospital setting.

Finally, it should be emphasized that for the prevention of complications during the test, it is important to recognize the contraindications and identify high-risk patients, especially those with history of acute myocardial infarction or with systolic dysfunction. The risk-benefit of each complementary test should always be considered in clinical practice.

Limitations of the study

It was not possible to analyze the intra and interobserver variation of the echocardiogram data since the digital images were not archived. However, the examinations are performed in a systematic way, by the same medical and nursing team, trained and with great experience in performing this type of examination.

Conclusion

Dobutamine-atropine stress echocardiography was safe, reinforcing its use as a diagnostic method for coronary artery disease in a non-hospital setting.

No patient presented significant adverse events, such as acute myocardial infarction, ventricular fibrillation, asystole, stroke, cardiac rupture or death. Only two patients had SVT, but with no hemodynamic instability.

Age and abnormal segmental contractility at rest (SCIr greater than 1) were independent predictors for significant arrhythmia during the test.

Authors' contributions

Research creation and design: Rassi DC, Furtado RG, Turco FP, Melato LH, Dourado CN, Rassi Jr. L; Data acquisition: Rassi DC, Furtado RG, Turco FP, Melato LH, Dourado CN, Rassi Jr. L; Data analysis and interpretation: Rassi DC, Furtado RG, Turco FP, Melato LH, Dourado CN, Rassi Jr. L; Statistical analysis: Rassi DC, Furtado RG; Funding: Rassi DC, Furtado RG, Turco FP, Melato LH, Dourado CN, Rassi Jr. L; Manuscript drafting: Rassi DC, Furtado RG, Turco FP, Melato LH, Oliveira ACR, Dourado CN, Rassi Jr. L; Critical revision of the manuscript as for important intellectual content: Rassi DC, Furtado RG, Turco FP, Melato LH, Oliveira ACR, Dourado CN, Rassi Jr. L.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

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