

Safety and Predictors of Complications with a New Accelerated Dobutamine Stress Echocardiography Protocol

José Alberto San Román, MD, PhD, FESC, Ricardo Sanz-Ruiz, MD, José Ramón Ortega, MD, Matías Pérez-Paredes, MD, PhD, María Jesús Rollán, MD, PhD, Ana Cristina Muñoz, MD, Federico Segura, MD, Diego Jimenez, MD, PhD, Andres Carnero, MD, Marta Pinedo, MD, Roman Arnold, MD, Itziar Gómez, MD, and Francisco Fernández-Aviles, MD, PhD, FESC, FACC, *Valladolid, Las Palmas de Gran Canaria, and Murcia, Spain*

Background: This study sought to document the safety of a new accelerated dobutamine-atropine stress echocardiography protocol and to analyze its complications.

Methods: Dobutamine-atropine stress echocardiography studies were performed using an incremental dobutamine infusion protocol from 20 to 40 $\mu\text{g}/\text{kg}/\text{min}$ in 3-minute stages and followed by atropine.

Results: A total of 962 patients were included. Mean age was 64 ± 11 years and 584 were male (61%). Mean ejection fraction was $62 \pm 10\%$. Complications included hypertensive responses in 66 patients (7%), arrhythmias in 26 (2.7%), and symptomatic hypotension in 16 (1.7%). No patient developed heart failure, acute myocardial infarction, ventricular fibrillation, or died. The independent predictors of hypertensive responses were age, baseline systolic blood pressure, and treatment with nitrates. The independent predictors of arrhythmias were history of hypertension, previous coronary artery disease, and baseline heart rate.

Conclusions: This accelerated dobutamine-atropine stress echocardiography protocol is safe in a low-risk population and has a rate of complications similar to that reported for the standard protocol.

The evaluation of patients without known coronary artery disease (CAD) who have chest pain is still a challenge for clinicians. Moreover, an accurate risk stratification of patients with chest pain who have already been given the diagnosis of CAD is mandatory. For these purposes, electrocardiographic (ECG) monitoring during exercise is the stress technique most frequently used. Exercise stress testing is of no value, however, in patients who are unable to exercise, are poorly motivated, or have baseline electrical abnormalities.¹ These limitations explain that pharmacologic stress tests combined with imaging techniques to detect myocardial ischemia are highly demanded. Dobutamine-atropine stress echocardiography (DSE) has become widely accepted as a very useful tool in this setting.

Given the increasing demand of this technique, and the burden of work and long waiting lists in echocardiography laboratories, we designed an accelerated DSE protocol that shortens dobutamine infusion

time from 15 to 6 minutes, thus improving the cost-effectiveness of the test.^{2,3} To be universally accepted, this protocol must fulfill 4 requirements: (1) high diagnostic accuracy; (2) capability of grading the severity of the ischemic response; (3) comparable safety profile; and (4) prognostic power. The first two requirements were already addressed by our group.^{2,4} However, its safety is still unsettled. Thus, the aim of this study was to assess the safety of this accelerated DSE protocol and to analyze the predictors of complications derived of its use.

METHODS

Study Population

This was a prospective, multicenter safety study, performed in 4 tertiary hospitals between January 2001 and August 2004. After approval by the institutional review committee, all patients who were referred to our laboratories for CAD diagnosis (symptom evaluation) or for prognostic studies (risk assessment) were included. Exclusion criteria were the diagnosis of acute coronary syndrome in the previous 15 days, significant aortic stenosis, atrial fibrillation with uncontrolled ventricular response, and uncontrolled hypertension (systolic blood pressure > 180 mm Hg and/or diastolic blood pressure > 110 mm Hg). All patients included in the study provided signed informed consent.

Accelerated Dobutamine-Atropine Infusion Protocol

Dobutamine was administered intravenously at an initial dose of 20 $\mu\text{g}/\text{kg}/\text{min}$ during 3 minutes and then was increased to 40 $\mu\text{g}/\text{kg}/\text{min}$ during 3 minutes more. If the test result was still negative and

From the Institute of Heart Sciences (ICICOR), Clinic University Hospital of Valladolid, Valladolid, Spain; Cardiology Department, Dr. Negrín University Hospital of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain (J.R., F.S.); Cardiology Department, José M. Morales-Messeguer University Hospital of Murcia, Murcia, Spain (M.P.-P., D.J., A.C.); and Cardiology Department, Pio del Río Hortega University Hospital of Valladolid, Valladolid, Spain (M.J.R., A.C.M.). Reprint requests: José Alberto San Román, MD, PhD, FESC, Institute of Heart Sciences (ICICOR), Clinic University Hospital, C/Ramon y Cajal 3, 47005 Valladolid, Spain (E-mail: asanroman@secardiologia.es).

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heart rate was under 85% of the age- and sex-predicted maximum heart rate, 1 mg of atropine was infused.

Situations that led to premature termination of dobutamine infusion were as follows: achievement of greater than 85% of the age-predicted maximal heart rate; severe angina; S-T depression more than 3 mm or elevation more than 2 mm; new wall-motion abnormalities; systolic blood pressure greater than 220 mm Hg; diastolic blood pressure greater than 120 mm Hg; symptomatic hypotension; and sustained ventricular arrhythmias.

Monitoring

Blood pressure and a 12-lead ECG were obtained at rest and every 3 minutes up to 10 minutes after finishing the infusion or recovery of contractility if the test result was positive. A positive ECG result was considered when a downsloping or horizontal S-T segment depression of more than 0.1 mV from baseline at 0.08 seconds from the J point was visualized.

Echocardiographic Examination

Two-dimensional echocardiographic monitoring was performed during and up to 10 minutes after the end of the test from the long and short parasternal, apical 4-, 2-, and 3-chamber views. For purposes of analysis, the left ventricle (LV) was divided in 16 segments as already described and recommended by the American Society of Echocardiography.⁵ Each segment was graded according to contractility and wall-motion score index was derived as previously described elsewhere. Ejection fraction was calculated by the Simpson's rule. Stress echocardiography results were considered positive for CAD when new or worsening regional wall-motion abnormalities were induced by drug infusion. Image acquisition was gated with ECG signal and was digitalized. Patients were receiving β -blocker treatment on the day of the examination when it was indicated by their referring physicians and was not withdrawn before the study (studies done with a prognostic purpose only).

Side Effects and Complications

We defined as side effects the following: palpitations, nausea, headache, anxiety, tremor, urgency, dyspnea, dizziness, and frequent premature supraventricular or ventricular complexes ($\geq 6/\text{min}$). Any of them in such a range that forced us to stop dobutamine infusion before ending the protocol were considered as severe.

We considered as complications the following: hypertension (defined as systolic blood pressure > 220 mm Hg or diastolic blood pressure > 120 mm Hg), hypotension (defined as >30 -mm Hg decrease with symptoms), arrhythmias (including second- or third-degree atrioventricular blockade, atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation), acute pulmonary edema, acute myocardial infarction, and death.

Statistical Analysis

Qualitative variables are expressed as percentages and were compared with the χ^2 method. The Fisher exact test was used when indicated. Quantitative variables are expressed as mean value \pm SD (or median and interquartile range with not-normally distributed variables) and were compared by Student *t* test. The Wilcoxon test was used when data were not normally distributed. Independent predictors of complications were obtained by backward stepwise logistic regression analysis. Variables with a *P* value less than .10 in the univariate analysis and those considered clinically relevant were included in the multivariable model. We calculated adjusted odds ratio (OR) with 95% confidence interval (CI) for each variable. Statistical significance was set at a *P* value of less than .05. All data

Table 1 Baseline characteristics of the patients included in the study

Clinical characteristics	All patients (n = 962)
Age, y	64 \pm 11
Male	584 (61%)
Risk factors	856 (89%)
Hypertension	586 (61%)
Diabetes mellitus	282 (29%)
Hyperlipidemia	445 (46%)
Smokers	223 (23%)
Baseline rhythm	
Sinus rhythm	913 (95%)
Atrial fibrillation	38 (4%)
Pacemaker rhythm	19 (2%)
History of CAD	478 (49%)
Previous myocardial infarction	263 (27%)
Previous anterior myocardial infarction	75 (8%)
Previous revascularization	298 (31%)
PTCA	253 (26%)
CABG	45 (5%)
Medications	
β -Blockers	519 (54%)
Calcium antagonists	224 (23%)
Nitrates	327 (34%)
Echocardiographic characteristics	All patients (n = 962)
Left ventricular hypertrophy	217 (22%)
Left ventricular ejection fraction $< 45\%$	51 (5%)
Median baseline WMSI	1.14 \pm 0.27
Wall-motion abnormalities	308 (32%)

CABG, Coronary artery bypass grafting; CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty; WMSI, wall-motion score index.

A patient was considered to have history of CAD when any of the following was present: (1) history of stable or unstable angina; (2) history of myocardial infarction; (3) angiographic demonstration of coronary artery disease.

Data are presented as mean \pm SD or n (%).

were analyzed with software (Statistical Package for Social Sciences, Version 11.0, SPSS Inc, Chicago, IL).

RESULTS

Among all the patients referred for DSE, 962 entered the study. Baseline characteristics of the population are depicted in Table 1. The study was performed with diagnostic purposes in 484 patients (50.3%) and for prognostication in patients with known CAD in 478 cases (49.7%).

Response to Dobutamine Infusion

Hemodynamic behavior of our patients is shown in Table 2. Atropine was used in 678 patients (70%), 395 of whom (58%) were on β -blockers. The target heart rate ($>85\%$ of the age- and sex-predicted maximum) was achieved by 454 patients (47%), in 221 before ending the protocol (23%), and in 233 after atropine infusion (24%). Angina appeared in 113 patients during dobutamine infusion (12%) and 118 patients developed ECG changes (12%). Table 3 describes the characteristics of the 262 studies with positive results, that is, in which wall-motion score index increased (27%).

Table 2 Baseline and maximum stress hemodynamic characteristics

	Baseline	Maximum stress	P*
Heart rate, beat/min	66 ± 12	129 ± 21	<.001
Systolic blood pressure, mm Hg	135 ± 22	155 ± 31	<.001
Diastolic blood pressure, mm Hg	74 ± 12	77 ± 15	<.001
Rate-pressure product, beat/min × mm Hg	8918 ± 2306	20,049 ± 5415	<.001

Data are presented as mean ± SD.

*Student *t* test for paired samples.

Table 3 Characteristics of the positive studies (n = 262)

Typical angina	113 (43%)
Angina free-time, min	7.2 ± 2.4
ECG abnormalities	118 (45%)
ECG abnormalities free-time, min	7.7 ± 2.5
Ischemia free-time, min	6.5 ± 1.9
WMSI, mean ± SD	
Baseline	1.25 ± 0.31
Maximum stress	1.60 ± 0.36
Δ WMSI	0.35 ± 0.21

ECG, Electrocardiogram; WMSI, wall-motion score index.

Data are presented as n (%) or mean ± SD.

Safety

The protocol was completed (dobutamine plus atropine) in 678 patients (70%) and 221 patients (23%) achieved the target heart rate before ending the protocol (in other words, not needing atropine).

Premature termination of the test was decided in the remaining 63 patients. In 31 patients it was a result of complications (3.2%): arrhythmias in 9 (3 ventricular tachycardia) (0.9%), hypertensive responses in 15 (1.5%), and symptomatic hypotension in 7 patients (0.7%). In 17 patients the test was interrupted because of severe side effects (1.8%). Other reasons for interruption of the study (n = 15) included: 9 patients with severe echocardiographic positivity, 2 patients with severe angina, 1 with symptomatic LV outflow tract obstruction, 1 with atypical chest pain, 1 with agitation, and 1 with asymptomatic hypotension.

Side effects appeared in 158 patients (16%) and are described in Table 4. Complications occurred in 106 patients (11%) and are depicted in Table 5. A more detailed description of the arrhythmic complications can be found in Table 6. Asymptomatic hypotension, which was not regarded as a complication, was observed in 15 patients (1.6%). There were no severe complications such as death, myocardial infarction, ventricular fibrillation, acute pulmonary edema, or congestive heart failure.

Because of the high proportion of patients on β-blocker treatment, a subanalysis comparing the presence of side effects and complications in patients with β-blockers versus patients without β-blockers was performed. No differences were found between these two groups of patients, neither in side effects (off β-blockers 2.5%, on β-blockers 1.2%, *P* = not significant) nor in complications (off β-blockers 3.4%, on β-blockers 3.1%, *P* = not significant).

Predictors of Complications

Hypertensive responses. Univariate analysis showed as related variables age, baseline systolic blood pressure, use of nitrates, history of

Table 4 Frequency of side effects (total: 178 side effects in 158 patients, 16% of the population)

	No of cases	Percent
Palpitations	61	6.3
Nausea	31	3.2
Headache	18	1.9
Tremor	16	1.7
Anxiety	14	1.5
Dyspnea	9	1.1
Premature atrial complexes	7	0.7
Premature ventricular complexes	22	2.2

Table 5 Frequency of complications (total: 108 complications in 106 patients, 11% of the population)

	No of cases	Percent
Hypertensive responses	66	7
Arrhythmias	26	2.7
Symptomatic hypotension	16	1.7

Table 6 Arrhythmias caused by dobutamine infusion

	n (%)
Supraventricular tachycardia	12 (1.2)
Spontaneous termination	10 (1)
β-Blocker therapy required	2 (0.2)
Atrial fibrillation	6 (0.6)
Spontaneous termination	6 (0.6)
β-Blocker therapy required	0 (0)
Ventricular tachycardia	8 (0.8)
Nonsustained	7 (0.7)
Sustained*	1 (0.1)

*Terminated after intravenous β-blockers and nitroglycerin.

CAD, echocardiographic positivity, baseline wall-motion score index, baseline end-diastolic LV volume, and baseline end-systolic LV volume (Table 7).

Multivariable analysis with logistic regression confirmed as independent predictors of hypertensive responses age (OR = 0.93, 95% CI 0.91-0.96), baseline systolic blood pressure (OR = 1.04, 95% CI 1.03-1.06), and treatment with nitrates (OR = 0.41, 95% CI 0.20-0.86). Age and use of nitrates were found to be protective variables (Figure 1).

Arrhythmias. Variables that correlated with the presence of arrhythmias were the history of hypertension, previous CAD, and baseline heart rate (Table 8). All of them were included in the multivariable analysis and all were confirmed as independent predictors of arrhythmias (OR = 1.96, 95% CI 1.03-3.79; OR = 0.40, 95% CI 0.22-0.75; OR = 0.96, 95% CI 0.93-0.99, respectively), being known CAD and higher baseline heart rate protective variables (Figure 2).

Symptomatic hypotension. We found no variables related to the development of hypotension.

DISCUSSION

The main finding of our study was that the new accelerated DSE protocol herein described is safe in the general population. The most

Table 7 Variables associated with hypertensive responses

	No hypertensive responses	Hypertensive responses	P
Age, y	64 ± 11	57 ± 12	<.001
Baseline systolic blood pressure, mm Hg	134 ± 21	152 ± 19	<.001
Patients on nitrates, %	36	15	<.001
Patients with history of CAD, %	52	35	.009
Patients with positive DSE, %	28	14	.01
Baseline WMSI	1.15 ± 0.28	1.05 ± 0.13	<.001
Baseline end-diastolic left ventricular volume, mL	93 ± 38	80 ± 23	.01
Baseline end-systolic left ventricular volume, mL	38 ± 24	31 ± 11	.01

CAD, Coronary artery disease; DSE, dobutamine stress echocardiography; WMSI, wall-motion score index.

Data are presented as mean ± SD or as percentage when indicated.

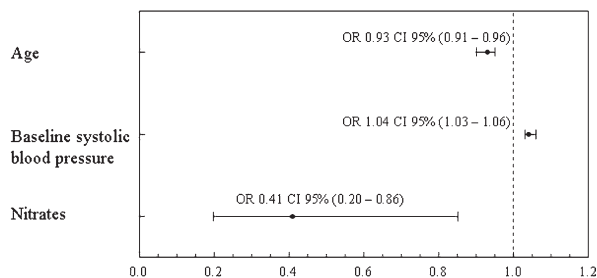


Figure 1 Independent predictors of hypertensive responses with accelerated dobutamine-atropine stress echocardiography protocol. Multivariate analysis (logistic regression).

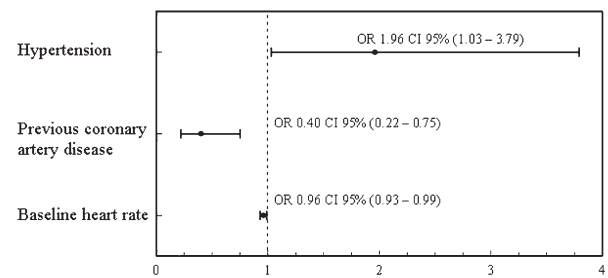


Figure 2 Independent predictors of arrhythmias with accelerated dobutamine-atropine stress echocardiography protocol. Multivariate analysis (logistic regression).

Table 8 Variables associated with arrhythmias

	No arrhythmias	Arrhythmias	P
Patients with history of hypertension, %	60	75	.04
Patients with history of CAD, %	52	35	.02
Baseline heart rate, beat/min	66 ± 12	62 ± 10	.03

CAD, Coronary artery disease.

Data are presented as mean ± SD or as percentage when indicated.

frequent complications of this protocol were hypertensive responses (7%), and its independent predictors were age, baseline systolic blood pressure, and treatment with nitrates. Other complications such as arrhythmias and hypotension were unusual.

Our population showed similar baseline characteristics and hemodynamic response to dobutamine infusion to that reported on previous studies with DSE.⁶⁻⁸

Studies using the standard protocol have shown a very variable incidence of side effects ranging from 2.8%⁷ to 26%.⁸ Only two studies have been published with a one-stage ("accelerated") dobutamine infusion protocol (using 40 μg/kg/min⁹ and 50 μg/kg/min¹⁰ perfusions). In these protocols an incidence of side effects of 27% and 38%, respectively, was reported, somewhat higher than our results (16%), which is likely related to a more gradual increment of dobutamine dosage in our protocol by using two stages. Besides, they infused the drug for a longer period of time (10 minutes instead of 6).

Regarding complications with DSE, Picano et al⁶ reported a high incidence of complications (17% hypotension, 7% hypertensive responses, and 17% arrhythmias) probably because of the fact that 43% of their patients have had a recent myocardial infarction (<15 days). Poldermans et al¹¹ and Secknus and Marwick⁷ had a low rate

of hypertensive responses (0.1% and 2.7%, respectively), hypotension (5% and 7%, respectively), and arrhythmias (3.7% and 3.6%, respectively). Mertes et al⁸ reported an incidence of atrial fibrillation of 0.6% and of nonsustained ventricular tachycardia of 3.5%, not analyzing hypertensive or hypotensive responses.

Regarding complications in the two accelerated DSE protocols aforementioned, Lu et al⁹ showed a rate of atrial fibrillation and nonsustained supraventricular tachycardia of 10%, and a rate of nonsustained ventricular tachycardia of 2%, both higher than in our protocol. Burger et al¹⁰ reported a lower rate of hypertensive responses (1%), but higher rate of hypotension and arrhythmias than in our series: 5% of hypotensive responses and 10% of arrhythmias.

In our series we have a high incidence of hypertensive responses (7%). By contrast, we report a low incidence of hypotension (1.7%) because we only included symptomatic hypotension as a complication. The rate of atrial fibrillation and nonsustained supraventricular tachycardia (1.8%) is lower than in the other two accelerated protocols and similar to those in the standard protocol. We report a very low incidence of nonsustained ventricular tachycardia (0.7%) and a similar incidence of sustained ventricular tachycardia to the remaining series (0.1%).

The fact that CAD is protective against arrhythmias is an unexpected finding. It may be explained by chance and results could be equivocal as a result of the small number of events. Another explanation could be that patients with known CAD are patients in most cases already revascularized and, thus, they have a lower risk for ischemia-induced arrhythmias. Finally, therapy could be a confounding factor: a high proportion of our patients were on β-blocker treatment (54%), because of the fact that 49% of the population had history of CAD. Nevertheless, and in concordance with previous results published by our group,¹² no differences in side effects and complications were observed between patients on β-blockers and patients off β-blockers.

Stress echocardiography is nowadays considered as a safe option in cardiac stress testing: a recently published registry with 85,997 patients reported a rate of one life-threatening event every 1000 examinations.¹³ Keeping this rate of complications in perspective, it can be affirmed that the dobutamine infusion protocol herein described has a safety profile comparable with that for the standard protocol. Hypertensive response is the most frequent complication, and is predicted by baseline systolic blood pressure. History of hypertension is also a predictor of arrhythmias. Therefore, we have to be cautious when using this protocol in patients who are hypertensive as they may develop hypertensive responses and arrhythmias.

We are aware of several limitations. Firstly, our study is nonrandomized. Thus, we cannot affirm that the novel protocol is as safe as the standard one. Nonetheless, our results support that the former is safe in a group of patients at low risk. Secondly, our population has a low-risk profile and, therefore, the results of this study cannot be applied to patients at high risk. Until its safety is proven in patients at higher risk, it seems reasonable to recommend the standard DSE protocol in these patients. Finally, and although low LV ejection fraction was not an exclusion criteria, only 5% of patients had an ejection fraction of 45% or less. Patients with severe LV dysfunction are more often referred to our laboratory for viability assessment. Indeed, myocardial viability studies, which require lower doses of dobutamine (5, 10, and 20 $\mu\text{g}/\text{kg}/\text{min}$), cannot be performed with this protocol.

Conclusion

The two-stage DSE protocol is safe and well tolerated in a low-risk population. This study supports the routine use of this protocol in the echocardiography laboratory with diagnostic and prognostic intentions, which should translate into saving time without diminishing diagnostic accuracy.

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