Clinical Research

Reliability and Safety of Dobutamine Stress Echocardiography for Detection of Myocardial Ischemia-Viability: Experience From 802 Consecutive Studies

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Introduction: Dobutamine stress echocardiography (DSE) represents an important diagnostic modality for the evaluation of coronary artery disease (CAD). The aim of this study was to present our experience from the application of the method in routine clinical practice.

Methods: Eight hundred two DSE studies were performed in 418 patients (group A) with chest pain without a positive history of CAD and in 384 patients (group B) with a known history of CAD.

Results: Two hundred sixty six studies were diagnostic of reversible myocardial ischemia. In group A, 119 patients had evidence of reversible ischemia and underwent coronary angiography, whereas 147 patients in group B had evidence of inducible ischemia and 94 of them underwent coronary angiography. Sensitivity and specificity of the method were from 82% to 100%, and 80% to 100%, respectively, for the detection of significant disease in the main left coronary artery or left anterior descending artery, and for 2- or 3-vessel disease. In group A, patients with no inducible ischemia had clinical follow-up over 1-21 months. During the study period one patient developed an acute myocardial infarction, 5 patients experienced an episode of sustained ventricular tachycardia, and 6 patients had an episode of supraventricular tachycardia. Other adverse effects included nausea (21%) and discomfort (31%).

Conclusions: DSE is a reliable and safe method for the detection of myocardial ischemia.

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Stress echocardiography (pharmaceutical or exercise) represents an important diagnostic method for the evaluation of coronary artery disease (myocardial ischemia and/or viability)[1-4]. The commonest protocol applied in stress echocardiography is carried out with intravenous administration of dobutamine-atropine[5-7].

Although some adverse reactions may appear during this procedure, many studies have proved that it is exceptionally safe[8-11]. Disadvantages of the method include its limited use in patients with a poor acoustic window, the need for an echocardiographic device with special capabilities, and the fact that it is a subjective, qualitative method which is very dependent on the echocardiographer who performs the study. In spite of its many advantages, there are only a few hospitals in Greece where stress echocardiography is routinely used for the detection of myocardial ischemia and/or viability in everyday clinical practice.

The aim of this study was to present our experience from a large number of dobutamine stress echocardiographic studies performed in our laboratory for the detection of myocardial ischemia

and/or viability, focusing on sensitivity and specificity as well as the safety and predictive value of this method for major events.

Subjects-methods

Eight hundred two dobutamine stress echocardiography (DSE) studies were carried out in the Echo Laboratory of the Cardiology Department of the Athens Euroclinic during the 21 months from July 2001 to March 2003. All studies were performed by two cardiologists with extensive experience in dobutamine stress echocardiography, according to the criteria that have recently been approved and published by the American College of Cardiology (ACC), the American Heart Association (AHA)[12] and the American Society of Echocardiography[13]. Furthermore, two experienced and well trained nurses were responsible for preparing the patient, taking care of the dobutamine infusion rate, continuously monitoring the patient's vital signs and administering drugs, according to the sonographer's instructions, for the management of any complications that might take place during the procedure.

All studies were performed using a Philips ATL 5000, which has the capability of second harmonic imaging as well as digital video recording, grabbing cine-loops of some cardiac cycles and displaying captured cine loops before and during stress on a quad screen, side by side. All studies were recorded on an analog video recorder, while the last 55 were also digitally recorded and stored on the hard disk of a personal computer, after file compression using the program Div X. 5.0.2 codec.

Patients underwent DSE study without interrupting treatment with drugs with a negative chronotropic action (b-blockers, diltiazem, verapamil, etc.) and abstained from any oral intake for 3 hours before the procedure. Every patient was connected with an ECG recorder so that a 12-lead ECG could be recorded at any time during the DSE study. Lead V2 was positioned one interspace higher and leads V3-V6 one interspace lower than the standard positions, so that the chest would be as exposed as possible for better and easier echocardiographic imaging[14]. Additionally, the heart rate signal was captured through 3 more patches and recorded by the echocardiographic instrument (3-channel recording), so that the cardiac rhythm during the DSE study could also be watched by the sonographer and stored in the digital memory along with the corresponding echocardiographic videos and images. Patients were also connected with an automated noninvasive arterial blood pressure and a pulse oxymetry monitor. At baseline, and at 1-minute intervals during the study, ECG, arterial blood pressure and % hemoglobin saturation were recorded.

The DSE protocol that we applied was the same as that used in the University of Ohio, with some modifications[15]. The DSE study was performed in 4 stages for myocardial viability detection, and in 4 to 5 stages for myocardial ischemia detection. Each stage lasted 3 minutes. The starting dobutamine infusion rate was 5μg/kg/min for detection of myocardial viability, 10 μg/kg/min for myocardial ischemia detection in high risk patients and 20 μg/kg/min in low risk patients. Dosage doubling occurred in the second stage, followed by increasing doses by 10 μg/kg/min in each stage up to a total rate of 30 μg/kg/min for detection of myocardial viability and 50 μg/kg/min for detection of myocardial ischemia. The target heart rate was 90% of the predicted maximal heart rate according to age. If the target heart rate was not achieved after the 5th stage of the DSE study was complete, then atropine 0.5-2 mg was additionally given intravenously. In some cases the fifth stage of studies performed for myocardial ischemia detection was prolonged for 3 more minutes in order to achieve the target heart rate.

Dobutamine infusion was stopped[8,14,15] when one of the following criteria was met:

- Maximal heart rate reached 90% of the predicted maximal heart rate according to age.
- Abnormal myocardial thickening or motion appeared in new regions.
- Arterial blood pressure >240/120 mmHg or lowering of systolic blood pressure < 90 mmHg accompanied by severe symptoms.
- Sustained ventricular tachycardia, atrial flutter or atrial fibrillation.
- ECG changes indicative of myocardial ischemia (ST segment elevation ≥1mm or ST segment depression >2mm with horizontal or downward slope), with coexisting abnormal myocardial thickening or motion.

All DSE studies were carried out from 4 views per stage: parasternal long axis view, parasternal short axis view, apical 4-chamber view and apical 2-chamber view. The left ventricle was divided into 16 segments, which were further studied regarding their systolic thickening, according to the relevant guidelines approved by the American Society of Echocardiography[14]. Every segment studied was chara-

cterized as normal, hypokinetic, akinetic or dyskinetic. Myocardial ischemia was documented by the presence of either an ischemic (reduced systolic thickening of a segment with previously normal thickening in response to dobutamine infusion) or a biphasic response (improved systolic thickening of a previously hypokinetic/akinetic segment in response to initially low dosage, and following deterioration in response to higher rates of dobutamine infusion). Reduced systolic thickening of a previously hypokinetic segment and the absence of a hyperdynamic response (systolic thickening <75% of diastolic thickness) of a segment with previously normal thickening in response to dobutamine infusion were additional criteria indicative of myocardial ischemia. The assessment of myocardial viability was based on the presence of improvement of systolic thickening of a previously hypokinetic, akinetic, or dyskinetic segment in response to dobutamine infusion. It is well known that the first phase of a biphasic response to dobutamine infusion of a previously hypokinetic, akinetic or dyskinetic myocardial segment is also a sign of myocardial viability.

In all patients studied, Wall Motion Score Index (WMSI) was calculated both during baseline study and at maximal heart rate. All 16 segments of the left ventricle were scored according to the scale: normal thickening=1, hypokinesis=2, akinesis=3, and dyskinesis=4. WMSI was derived from the sum of all 16 segmental wall motion scores, divided by the total number of segments considered.

Sensitivity, specificity, positive and negative predictive value of dobutamine stress echocardiography were calculated in all DSE studied patients who had a coronary angiogram. Hemodynamically severe stenoses of coronary vessels were considered to be those with a demonstrated 50% reduction of internal lumen diameter (evaluated by quantitative coronary angiography) or with fractional flow reserve <75% present in borderline cases.

A detailed medical history was obtained from all patients undergoing the DSE study and the presence of any of the conventional coronary artery disease risk factors was recorded: age, diabetes mellitus, hypertension, hypercholesterolemia, smoking, family history of coronary artery disease and obesity.

- Diabetics were defined as patients with a known history of diabetes mellitus, with or without drug therapy.
- Patients were considered to have hypercholesterolemia if they had a known history of the disorder documented by previous biochemical analyses, or if they were already on a lipid-lowering drug therapy
- Patients were considered to have arterial hypertension if they had a known history of hypertension or if they were on anti-hypertensive therapy.
- Smokers were defined as patients who had smoked at least 5 cigarettes per day during the last year.
- Obesity was defined as evaluated body mass index >30kg/m^2.
- Family history of coronary artery disease was considered positive if there was a first degree relative (a parent, or a brother or a sister) with documented coronary artery disease at an age of <55 years in the case of males, and <65 years in the case of females.

Statistical analysis

Continuous variables are presented as mean value ± standard deviation. The continuous variables of our study were not of normal distribution, so comparisons of means and analyses of variance were performed with the use of the nonparametric Mann-Whitney test and Kruskall-Wallis test, respectively, while linear nonparametric correlations were calculated using Spearman's test. Categorical variables were compared using the χ^2 test. A dichotomous variable was checked for any relationship with other variables by applying logistic regression analysis. Statistical significance was assumed at a value of $p<0.05$. All statistical analysis was performed with SPSS software (version 10.0, SPSS Inc).

Results

Studies and population characteristics

During the 21 months from July 2001 to March 2003, 802 patients (age 54.1 ± 11.8 years, 601 [74.93%] males and 201 [25.07%] females) underwent a pharmaceutical stress echocardiographic study with administration of dobutamine and atropine. One (0.12%) out of 802 studies was carried out for evaluation of left ventricular inotropic reserve, 11 (1.3%) for detection of myocardial viability exclusively and the remaining 790 (98.5%) for detection of both myocardial ischemia and viability.

The study population was composed of two groups: group A, which included 418 (52.11%) patients without previous history of coronary artery disease, and group B, which included 384 (47.88%) patients with a pre-

Table 1. Characteristics of patients undergoing dobutamine stress echocardiography.

	GROUP A N=418	GROUP B N=384	
Sex	F=140 (33.4%) M=278 (66.6%)	F=72 (18.75%) M=312 (81.25%)	χ^2=22.3, p<0.0009
Age	54.7 ± 11.18	55.9 ± 11.08	p=NS
Smokers	132 (31.5)%)	319 (83.07%)	χ^2=215.6, p<0.0009
Hypercholesterolemia	132 (31.5%)	144 (37.5%)	χ^2=3.1, P=0.078
Family history of coronary artery disease	31 (7.4%)	55 (14.3%)	χ^2=10.6, P=0.001
Obesity	75 (17.9%)	127 (33.07%)	χ^2=24.3, p<0.0009
Hypertension	164 (39.2%)	144 (37.5%)	p=NS
Diabetes mellitus	25 (5.9%)	63 (16.4%)	χ^2=23.1, p<0.0009
Left ventricular ejection fraction	60.4% ± 4.6%	43.03% ± 10.2%	t=-5.5, p<0.0009
B-blocker	125 (29.9%)	326 (84.8%)	χ^2=226.5, p<0.0009
Left bundle branch block	10 (2,3%)	14 (3,6%)	p=NS
Abnormal Q wave on ECG	0 (0%)	115 (29.9%)	χ^2=147.6, p<0.0009
Permanent pacemaker	4 (0.09%)	6 (1.5%)	p=NS

existing history of coronary artery disease, with or without history of aortocoronary bypass surgery or percutaneous transluminal angioplasty (PTCA). There were a number of differences between these two groups (Table 1). Although age did not discriminate the two groups, group A included a greater number of females than group B (p<0.0009). Group B included more smokers (p<0.0009), more patients with a known family history of coronary artery disease (p=0.001), more obese (p<0.0009) and more diabetic patients (p<0.0009) (Table 1). The two groups were not different as regards the prevalence of hypertension. Patients of group B had a lower left ventricular ejection fraction compared to group A (43.03% ± 10.2% vs. 60.4% ± 4.6%, respectively, p<0.0009) and included a greater percentage of patients who were under b-blocker treatment (patients of group A were taking b-blockers as a hypertension treatment, while patients of group B did so as part of the standard drug treatment of coronary artery disease). We emphasize that an extremely small number of patients of both groups were under treatment with diltiazem. Only group B included patients with an abnormal Q wave on the ECG, while the frequencies of an existing left bundle branch block and presence of a permanent pacemaker were identical (Table 1). It should be noted that in our clinic most patients with either left bundle branch block or a permanent pacemaker undergo elective myocardial scintigraphy study for the detection of myocardial ischemia, and only in special cases is DSE applied.

From group A, 363 (86.8%) patients underwent DSE study for detection of myocardial ischemia, after an episode of chest pain similar to angina, but without ECG changes or serum markers indicative of myocardial necrosis. Of the rest, 30 (7.1%) patients underwent DSE study for detection of myocardial ischemia after a first episode of atrial fibrillation and 25 patients after an episode of syncope of unknown origin. The patients in the last two subgroups had more than two traditional risk factors for coronary artery disease. Patients with chest pain underwent their DSE study a few hours after admission to our department, while patients with atrial fibrillation underwent the

Table 2. Results of dobutamine stress echocardiography studies in the two groups of patients.

Group A (N=418)			Group B (N=384)	
Indications for the performance of DSE studies	Chest pain	363	Chest pain	298
	Episode of atrial fibrillation	30	Part of follow up program of coronary artery disease	86
	Episode syncope	25		
DSE study indicative of myocardial ischemia		119		147
Coronary angiogram		119		94
Ejection franction > 60%		418		78
Past history of a revascularization procedure		0	PTCA/STENT	325
			By-pass	59

study 24 hours after restoration of sinus rhythm. Out of 384 patients of group B, 298 (77.6%) underwent DSE study for detection of myocardial ischemia after an episode of chest pain, while in the remaining 86 (22.3%) the study was part of their follow-up program for known coronary artery disease. In group B, three hundred and six (79.6%) patients had a history of a previous transmural myocardial infarction, whereas the rest had intact contractility of the left ventricle. Moreover, 59 (15.3%) patients of the same group had a history of aortocoronary bypass surgery, whereas the remaining 325 (84.6%) patients had undergone percutaneous transluminal angioplasty, with or without implantation of a stent (Table 2).

In the 12 (1.4%) patients out of the whole study population who underwent DSE study for detection of myocardial contractile reserve (1) and myocardial viability (11) exclusively, the maximum rate of dobutamine infusion was 20 μg/kg/min. For the remaining patients the maximum rate of dobutamine infusion was 30 μg/kg/min in 16 (1.9%) patients and 50 μg/kg/min in 774 (96.5%) patients. The mean value of the maximum dobutamine dosage administered in the whole study population was 48.5±5.1 μg/kg/min. Regarding the dosage of atropine co-administration, 37 (4.6%) patients were not administered any atropine, while the remaining patients were given 0.83± 0.62 mg intravenously.

Although 79 (9%) patients had a poor acoustic window, the DSE study reached a clear diagnostic result. Moreover, in 25 (3%) patients of group B, the maximum heart rate achieved during the DSE study varied between 78-85% of the predicted heart rate according to age. In these cases, the DSE studies were considered non-diagnostic, although not indicative of myocardial ischemia.

Wall motion score index

The WMSI during baseline echocardiography and at peak DSE study, according to sex, age, presence of normal left ventricular ejection fraction, and the number and the identity of the diseased coronary vessels, is depicted in table 3. Paired analysis with the non-parametric Wilcoxon test revealed a statistically significant difference between WMSI at baseline and at peak of stress in the whole study population ($z=-4.2$ $p<0.0009$). Subgroup analyses using a paired Wilcoxon test revealed a statistically significant increase of WMSI at peak of DSE study in patients with 1-vessel disease ($p=0.04$), 2-vessel disease ($p=0.01$), 3-vessel disease ($p=0.02$), left main coronary artery disease ($p=0.001$), left anterior descending coronary artery disease ($p=0.001$), circumflex coronary artery disease ($p=0.002$) and right coronary artery disease ($p=0.002$). Applying a non-parametric Mann Whitney test, using as grouping variables sex, age >65 years and the presence of the conventional coronary artery disease risk factors, no statistically significant difference was identified regarding either

Table 3. Wall Motion Score Index (WMSI) during baseline and peak dobutamine stress echocardiography, in various subgroups of the study population (mean value±standard deviation).

	Baseline WMSI		Peak WMSI	
	+	–	+	–
Age>65 years	1.15±0.25	1.15±0.26	1.22±0.32	1.25±0.37
Sex (M=male, F=female)	M=1.15±0.23	F=1.15±0.31	M=1.25±0.33	F=1.23±0.43
Ejection fraction>55%	1.07±0.15	1.25±0.32	1.16±0.26	1.35±0.42
Coronary vessels with non-significant stenoses	1.06±0.14		1.11±0.24	
1-vessel disease	1.11±0.2		1.25±0.3	
2-vessel disease	1.21±0.24		1.36±0.35	
3-vessel disease	1.37±0.39		1.52±0.49	
Left main disease	1.62±0.3	1.14±0.25	1.63±0.42	1.24±0.36
Left anterior descending artery disease	1.28±0.34	1.08±0.16	1.42±0.42	1.15±0.28
Left circumflex artery disease	1.26±0.34	1.1±0.18	1.44±0.44	1,15±0.27
Right coronary artery disease	1.29±0.33	1.07±0.15	1.44±0.43	1.14±0.26

+ = presence of the characteristic of the dichotomous variable
– = absence of the characteristic of the dichotomous variable

baseline WMSI or peak WMSI (p=NS). Using non-parametric Spearman's correlation, we demonstrated that age, considered as a continuous variable, was not related to any WMSI, whereas left ventricular ejection fraction was negatively correlated with both baseline WMSI (r=-0.359, p=0.002) and peak WMSI (r=-0.274, p=0.02). Moreover, logistic regression analysis revealed that presence of a normal left ventricular ejection fraction (>60%) was related to both baseline WMSI (b=-3.2, p=0.008) and peak WMSI (b=-1.6, p=0.03). Logistic regression analysis also revealed that baseline WMSI and peak WMSI were both correlated with left descending coronary artery disease (b=3.15, p=0.005 and b=2.12, p=0.006, respectively), circumflex coronary artery disease (b=2.2, p=0.004 and b=2.3 p=0.02, respectively), right coronary artery disease (b=3.76, p=0.002 and b=2.4, p=0.002, respectively), and left main coronary artery disease (b=3.2, p=0.003 and b=2.2, p=0.004, respectively). Finally, Kruskall-Wallis non-parametric analysis of variance revealed that both baseline WMSI and peak WMSI were statistically different among the subgroups of patients, using as grouping variable the number of the diseased coronary vessels (p=0.002 and p=0.009 respectively). These differences were attributed to existing differences of baseline WMSI and peak WMSI between patients with multivessel disease (2 or 3 vessels) and patients with 1-vessel disease or non-significant coronary artery disease (Mann-Whitney, z=-2.9, p=0.003 and z=-3.1, p=0.001, respectively).

Reliability of DSE study

Only those patients in both groups A and B who had a DSE study either indicative of myocardial ischemia or negative regarding echocardiographic imaging and clinically positive (because of ischemic ECG

Table 4. Dobutamine stress echo studies, indicative of the presence or absence of myocardial ischemia, and the corresponding coronary angiograms, revealing the presence (+) or absence (–) of significant stenoses in coronary vessels.

	+	–	Total
DSE studies indicative of myocardial ischemia	139	4	143
DSE studies not indicative of myocardial ischemia	47	23	70
Total	186	27	213

changes and an angina-like clinical syndrome during maximal dobutamine infusion rate) underwent coronary angiography. Two hundred sixty six (33.1%) of the DSE studies were positive for myocardial ischemia –196 (73.6%) according to imaging criteria and 70 (26.4%) according to clinical criteria– while 536 (66.8%) were negative. One hundred nineteen (28.4%) patients of group A had a DSE study indicative of myocardial ischemia and all underwent coronary angiography. In group B 147 (38.2%) patients had a positive DSE study for myocardial ischemia, but only 94 (63.9%) of them underwent coronary angiography (Table 2). Thus, a total of 213 (26.5%) patients had a coronary angiogram, which resulted in demonstration of severe coronary vessel stenoses (>50% reduction of internal lumen diameter) in 186 (87.3%) patients. In 27 (12.7%) cases, coronary angiography either did not reveal any severe coronary vessel stenosis or restenosis inside implanted stents (N=23), or revealed coronary vessels without stenoses but with slow flow in one or more of them (N=4) (Table 4). Of the 186 patients with severe coronary vessel stenoses, 14 (7.5%) had left main coronary artery disease (% stenosis = 61.8±15.37%), 98 (45.69%) had left anterior descending artery disease (% stenosis of main left anterior descending artery = 76.75±23.8%, % stenosis of diagonal artery= 69.41±23.31%), 93 (50%) had circumflex coronary artery disease (% stenosis of main circumflex artery= 72.36±25.22%, % stenosis of obtuse marginal artery = 69.4±24.37%), and 46 (24.7%) patients had right coronary artery disease (% stenosis of right coronary artery = 88.85 ± 11.55%). One-, 2- and 3-vessel disease were present in 82 (44.08%), 58 (31.18%) and 32 (17.2%) patients, respectively, whereas 14 (7.5%) patients had left main coronary artery disease, as mentioned above. All patients found to have a significant coronary artery stenosis, 71 (38.1%) from group B and 116 (61.9%) from group A, subsequently underwent a revascularization procedure: 31 (16.6%) patients had aortocoronary bypass graft surgery, while 155 (83.3%) patients had PTCA with stent implantation.

As depicted in table 4, DSE had overall sensitivity 75% and specificity 85%. To be more precise, sensitivity, specificity, positive and negative predictive values of DSE in our study were related to both the number and the identity of the diseased vessels (Table 5). Interestingly, in the case of left

Table 5. Reliability of dobutamine stress echocardiography in our study.

	Sensitivity	**Specificity**	**Positive predictive value**	**Negative predictive value**
Left main disease	100%	100%	100%	100%
Left anterior descending artery disease	88%	80%	81%	87%
Left circumflex artery disease	65%	85%	81%	71%
Right coronary artery disease	75%	86%	85%	78%
1-vessel disease	65%			
2-vessel disease	82%			
3-vessel disease	85%			

main coronary artery disease, DSE had sensitivity, specificity, positive predictive and negative predictive value all 100%. For left anterior descending artery disease, DSE was found to have sensitivity 88%, specificity 80%, positive predictive value 81% and negative predictive value 87%. For left circumflex artery disease, the sensitivity was 65%, specificity 85%, positive predictive value 81% and negative predictive value 71%. Finally, in the case of right coronary artery disease, DSE had sensitivity 75%, specificity 86%, positive predictive value 85% and negative predictive value 78%. Moreover, the sensitivity of DSE for diagnosis of 1-, 2- and 3-vessel disease was 65%, 82%, and 85% respectively (Table 5).

Sex and age were not found to affect the sensitivity or specificity of DSE for detection of myocardial ischemia in our study. Although in the group of males DSE had lesser overall sensitivity, compared to the group of females (73% versus 78%, respectively), χ^2 test revealed that this difference was not statistically significant (p=0.21). Similarly, the specificity of DSE was similar in males and females in our study (82% versus 87%, respectively, p=0.32). Furthermore, using logistic regression analysis we demonstrated that age was not related to the sensitivity or specificity of DSE (b=0.03, p=0.1 and b=0.006, p=0.21, respectively).

Electrocardiographic changes during DSE revealing the presence of an "injury current" and thus indicative of myocardial ischemia, were either 1.5 mm ST segment depression or 1 mm ST segment elevation. ST segment depression during DSE studies was found to have low sensitivity and specificity (21% and 32% respectively). In contrast, ST segment elevation during DSE studies was found to have low sensitivity (37%) on the one hand, but an exceptionally high positive predictive value (90%) on the other. Furthermore, using logistic regression analysis, we demonstrated that the presence of ST segment depression during DSE studies was not related to the sensitivity and specificity of the method (p=0.3 and p=0.4, respectively). Similarly, applying the same statistical methodology, we found that the presence of ST segment elevation during DSE studies was not related to the sensitivity and specificity of the method either (p=0.3 and p=0.4, respectively).

The effect of left ventricular hypertrophy on the diagnostic accuracy of DSE was also evaluated. For the entire study population the thickness of the interventricular septum was 11.5±0.45 mm. Hypertrophy of the left ventricle was defined according to a cut off point 13 mm of interventricular septum thickness. Six hundred and sixty two (82.5%) patients were found not to have left ventricular hypertrophy, while the remaining 140 (17.5%) patients had myocardial hypertrophy. The sensitivity of DSE in patients with left ventricular hypertrophy was not statistically different to that in patients without hypertrophy (78% vs. 74%, respectively, χ^2=0.16, p=0.68). Logistic regression analysis revealed that the thickness of the interventricular septum was not related to the sensitivity of the method (b=-0.24, p=0.67). Similarly, the specificity of DSE was not statistically different between patients with and without left ventricular hypertrophy (83% vs. 87%, respectively, χ^2=0.88 p=0.34), nor was the thickness of the interventricular septum related to the sensitivity of the method (b=-0.21, p=0.19).

Regarding the diagnostic accuracy of DSE in detecting myocardial viability, that is to say, functional myocardial recovery following a revascularization procedure, it was evaluated in 86 patients of group B with known coronary artery disease who underwent a DSE study as a part of their follow up program after recent myocardial revascularization (PTCA with stent implantation). These patients had previously undergone a DSE study in our echo laboratory prior to the revascularization procedure, when the diagnosis of coronary artery disease was considered. (The DSE studies of the other 298 (77.6%) patients who had undergone a revascularization procedure were not suitable for the evaluation of the diagnostic accuracy of DSE in detecting myocardial viability, since there were no corresponding DSE studies prior to revascularization). DSE was found to have sensitivity 90%, specificity 100%, positive predictive value 100%, and negative predictive value 91% in the detection of myocardial viability.

All patients of group A with a DSE study negative for myocardial ischemia (N=299) were followed up for a period of 1-20 months with endpoints either a non-fatal acute coronary syndrome (unstable angina, acute myocardial infarction with and without ST segment elevation) or death of cardiovascular origin. Only 1 patient with a DSE study negative for myocardial ischemia was admitted to our department one month later with an acute myocardial infarction (negative predictive value 99.6%). Regarding patients with a DSE study positive for myocardial ischemia (N=266), 213 out of the total were followed up for the same period and no case of non-fatal acute coronary syndrome or death of cardiovascular origin was recorded. However it should be noted that, as stated above, 186 of these patients, with documented

Table 6. Major and minor adverse effects in patients during dobutamine stress echocardiography.

	Kind of complication	Number of events
Major complications	Acute myocardial infarction	1 (0.1%)
	Unstable angina	1 (0.1%)
	Acute pulmonary edema	1 (0.1%)
	Sustained ventricular tachycardia	5 (0.6%)
	Non-sustained ventricular tachycardia	7 (0.8%)
	Atrial fibrillation	3 (0.3%)
	Severe drop of arterial blood pressure	3 (0.3%)
Minor complications	Nausea-vomiting	168 (21%)
	Discomfort-anxiety	248 (31%)
	Urinary retention	1 (0.1%)
	Urinary urgency	25 (3%)
	Abdominal pain-tenesmus	3 (0.3%)

significant coronary artery stenoses on the coronary angiogram, subsequently underwent a revascularization procedure.

Safety of DSE

DSE proved to possess remarkable safety, both in patients with and in those without a previous history of coronary artery disease (Table 6). No case of death occurred during the DSE studies. In 1 (0.1%) case an acute pulmonary edema occurred during the DSE study. This was managed successfully and was later found to be due to 3-vessel disease and left main coronary artery disease. Also, during 1 (0.1%) DSE study we had to manage an acute coronary syndrome, with ST segment elevation followed by an episode of sustained ventricular tachycardia (idioventricular rhythm, Figure 1), in a 48-year-old male with a previous history of hypertension, dyslipidemia, and heavy smoking and a family history of coronary artery disease, who was admitted to our department complaining of episodes of retrosternal pain during effort (CCS I) and also at rest. The patient underwent a DSE study because of the presence of multiple coronary artery disease risk factors and the ominous symptoms above. During the DSE study, the patient experienced a significant increase of arterial blood pressure up to 220/120 mmHg and then complained of sudden retrosternal pain of great severity, expanding all over the chest, which was accompanied by ST segment elevation in the inferior leads of the ECG followed by an idioventricular rhythm. The patient was sent for a coronary angiogram right away and a dissection of the right coronary artery was identified (Figure 2). The patient was managed successfully according to a conservative strategy and a transmural myocardial necrosis was eventually averted. Although the existence of the dissection of the right coronary artery prior to the DSE study cannot be ruled out in this case, there are clear indications suggestive of a causal relationship between the DSE study and the dissection (the severe increase of arterial blood pressure during the DSE study that may have played a role in causing the dissection, the severe subsequent symptoms with simultaneous ECG documentation of myocardial ischemia). It is noteworthy that such a complication during DSE has never been mentioned in the lite-

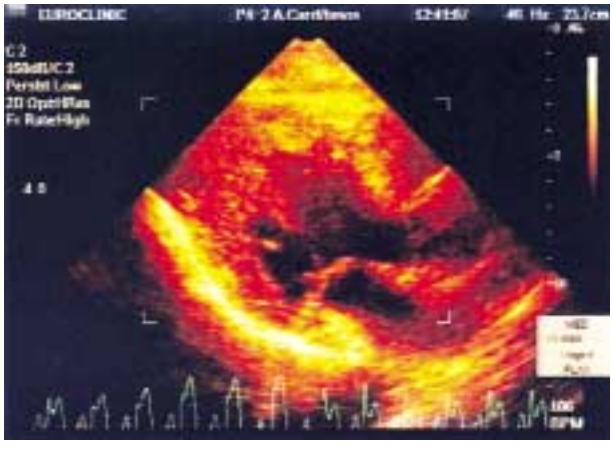

Figure 1. Long parasternal axis view after the onset of acute myocardial infarction with ST segment elevation during dobutamine stress echo study. At the bottom of the figure the simultaneous continuous rhythm monitoring is depicted, with ST segment elevation and the moment of the onset of sustained ventricular tachycardia.

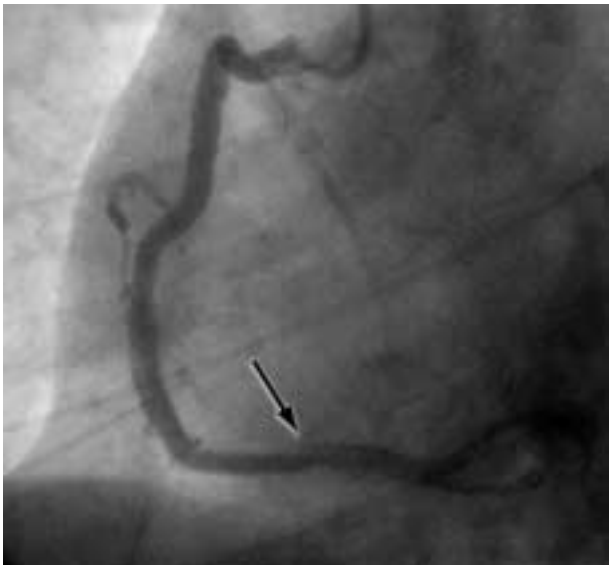

Figure 2. Dissection of the right coronary artery (arrow) in the same patient, accompanied by acute myocardial infarction with ST segment elevation during dobutamine stress echo study.

rature. During another 1 (0.1%) DSE study, the patient experienced prolonged myocardial ischemia, which was managed with PTCA and stent implantation. Regarding major arrythmiologic events, 5 episodes of sustained ventricular tachycardia (0.6%), 7 episodes of non-sustained ventricular tachycardia (0.8%), 3 episodes of atrial flutter (0.3%) and 3 episodes of atrial fibrillation (0.3%) occurred during all the DSE studies. The patients who experienced episodes of sustained ventricular tachycardia during the DSE studies were all sent for coronary angiogram. It was demonstrated that this arrhythmia during a DSE study is not related to the presence of coronary artery disease (3 patients had coronary artery disease while 2 did not, p=NS). Additionally, 2 of these patients underwent an electrophysiological study, while in 1 patient who had an implantable cardioverter defibrillator the arrhythmia was terminated with antitachycardiac pacing. Two more of these patients did not undergo an electrophysiological study because in the first case the arrhythmia episode was actually an idioventricular rhythm due to revascularization that took place during an acute coronary syndrome (which occurred during the DSE study as mentioned above), while the second patient suffered from dilated cardiomyopathy. All episodes of both sustained ventricular tachycardia and atrial flutter were terminated by administering atenolol intravenously. All episodes of atrial fibrillation occurred in the subgroup of patients without previous history of coronary artery disease, who underwent a DSE study as part of the diagnostic investigation for detection of myocardial ischemia after an episode of atrial fibrillation. In all these cases, sinus rhythm recovery took place. Three vagotonic episodes also occurred during the DSE studies, accompanied by a severe drop in arterial blood pressure (<80mmHg) which was managed with abrupt termination of the procedure and administration of fluids and atropine (0.3%).

Concerning minor complications of DSE, 168 (21%) patients experienced nausea and an urge to vomit and were administered metoclopropamide intravenously; 248 (31%) patients had severe discomfort, anxiety, numbness and a feeling of constriction in the head and chest; 1 (0.1%) patient experienced urine retention following the administration of 1 mg of atropine; 1 (0.1%) patient had abdominal pain and tenesmus with excessive gas production, and 25 (3%) patients experienced an urgent need to urinate (Table 6).

Logistic regression analysis revealed that the occurrence of an adverse effect during a DSE study was unrelated to sex (b=0.88, p=0.9), age (b=0.01, p=0.71), and the dosage of dobutamine (b=0.005, p=0.94) or atropine (b=0.28, p=0.66). This analysis did not include 12 cases where dobutamine administration was terminated when the stage of a drug infusion rate of 20μg/kg/min was reached. These patients did not experience a minor complication of DSE, but 2 of them had an episode of sustained ventricular tachycardia during the study. Furthermore, the occurrence of a minor adverse effect during DSE studies was also not related to sex (b=0.26, p=0.76), age (b=0.12, p=0.71), or dosage of dobutamine (b=0.005, p=0.94) and atropine (b=0.28, p=0.66).

Discussion

Since the first application of DSE in clinical settings in 1985, many papers have been published regarding the sensitivity and specificity of this method in comparison with other diagnostic methods[5,16-18] for the diagnosis of coronary artery disease, mainly with treadmill stress test and radionuclide myocardial perfusion imaging. Most of these studies demonstrated that DSE possesses a higher sensitivity and specificity compared to the former, but higher spe-

cificity and lower sensitivity than the latter. Furthermore, the high predictive value of DSE regarding major cardiac events has also been demonstrated, both in patients with known coronary artery disease and in patients with high clinical suspicion of coronary artery disease admitted because of an episode of chest pain[22-24].

The aim of this retrospective study was to present our experience from the routine application of DSE in clinical settings. In the Echo Laboratory of the Cardiological Department of our Hospital, 4-6 DSE studies are now performed every day (especially during the last 6 months). Most of these studies are performed for the detection of myocardial ischemia and viability, either in patients with known coronary artery disease or in patients admitted for chest pain when angina is suspected. Each DSE study is a short (1 hour total time), reliable and cheap procedure.

Concerning the organization of the Echo Laboratory, a well trained nurse and a well qualified echocardiographer with extensive experience in stress echocardiography are required. Although in Greece no criteria have been approved regarding the qualifications and experience of an echocardiographer who is to perform DSE, the relevant guidelines approved by the American College of Cardiology/ American Heart Association[12] and the American Society of Echocardiography[13] should be taken into consideration. According to these guidelines, training in stress echocardiography should include supervised performance (hands on) of 50 exercise stress echocardiographic studies and of 50 pharmaceutical stress echocardiographic studies in an Echo Laboratory Training Center where 40 such studies are performed each month. Furthermore, the American Society of Echocardiography[13] recommends that education in stress echocardiography should be continuing, and for the maintenance of competence 15 studies per month or 100 studies annually are required. In view of the large number of DSE studies performed in our Echo Laboratory (4-6 per day), the above mentioned recommendations are fulfilled.

Owing to the fact that the coronary angiogram constitutes the gold standard for the detection of significant coronary artery stenoses, the reliability of DSE in our Echo Laboratory was evaluated according to 213 coronary angiograms that were recorded following the DSE studies. It is worth noting that in this study we present our experience from applying DSE in everyday clinical practice. In consequence, the larger percentage of our study population, composed of 536 subjects with a DSE study negative for myocardial ischemia, did not undergo a coronary angiogram. However, 70 patients with a DSE study negative for myocardial ischemia according to imaging findings, but positive according to clinical criteria (mainly because of chest pain during the study indicative of angina) eventually underwent coronary arteriography. The reliability of DSE for the detection of myocardial ischemia according to our study is comparable with that reported by other previous studies[16-18]. The high sensitivity of the method for the detection of left main and/or left descending artery coronary artery disease, as well as for 2- or 3-vessel coronary artery disease, is remarkable. DSE has a lower sensitivity for the detection of 1-vessel coronary artery disease and for left circumflex and right coronary artery disease. The high specificity and the high positive predictive value of the method are also remarkable. An interesting conclusion that we reached in our study, which is in accordance with findings from other studies in the literature, is the fact that the specificity and sensitivity of DSE are not related to sex, age, or ECG changes occurring during the study. We demonstrated, as in previous studies[25,26], that the sensitivity and specificity of DSE are not affected statistically significantly by the presence of mild myocardial hypertrophy. Furthermore, it is important to note the high reliability of DSE for the detection of myocardial viability and functional myocardial recovery following PTCA that we found in our study, after investigating the results of DSE in a small group of 86 patients who had undergone a comparable pair of DSE studies (before and after PTCA).

Another interesting finding is the high negative predictive value of DSE regarding myocardial infarction and/or death in patients admitted with chest pain, without ECG changes suggestive of myocardial ischemia or a biochemical analysis indicative of myocardial necrosis. This finding is in accordance with other recently published studies[24] that have laid emphasis on the high negative predictive value of DSE. In addition, we must point out that the operation of a chest pain unit is both safe and feasible, and DSE may constitute a fundamental part of it, helping clinicians in making decisions according to relevant findings[22] in everyday clinical practice.

Our study demonstrated that DSE is a safe procedure. Interestingly, no death occurred during DSE in our study, which is in agreement with the conclusions reported in all previous published studies with

large numbers of patients[8-11]. As far as major events during DSE studies are concerned, myocardial infarction and sustained ventricular tachycardia were the most significant, but occurred with extremely low incidences, as in previous published studies[8-11]. Picano et al[10] reported 3 (0.1%) cases of myocardial infarction during 2800 DSE studies, whereas Secknus and Marwick8 reported just 1 case during 30[11] DSE studies, as in our study (0.1%). Concerning the occurrence of sustained ventricular tachycardia during DSE, Picano et al[10] reported 3 (0.1%) cases, and Secknus and Marwick[8] 5 (0.1%) cases, while in our study 5 (0.6%) episodes occurred.

An interesting major complication of DSE that occurred in our study and has never been reported before, was one case of an acute coronary syndrome that, as the subsequent coronary angiogram revealed, was caused by a type D dissection of the right coronary artery.

In our study we demonstrated that the development of an episode of sustained ventricular tachycardia during a DSE study is not evidence of myocardial ischemia. In all these cases, this life-threatening arrhythmia was terminated by the intravenous administration of atenolol, which actually confirms that activation of b1 receptors plays a significant role in the triggering of this arrhythmia during DSE.

Another notable finding of our study is that investigation for myocardial ischemia with DSE, as part of the diagnostic process of an episode of atrial fibrillation, can take place on the next day after restoration to sinus rhythm. These DSE studies can be performed without significant risk of recurrence (10% in our study). It is also interesting that in our study episodes of either non-sustained ventricular tachycardia or hypotension did not occur in significant frequencies, compared to previous published studies. Secknus and Marwick[8] reported 198 (7%) hypotensive events (systolic blood pressure<80 mmHg) which caused the termination of the procedure in 3.5%, whereas in our study only 3 (0.3%) patients experienced hypotension. Similarly, no significant events during DSE were attributed to atropine administration. Picano et al[10] reported 5 (0.1%) episodes of delusions, whereas no such event occurred in our study. It is remarkable, however, that there was one case of urine retention in our study.

In contrast, minor events –actually side effects– during DSE occurred in higher frequencies, so that many patients described their experience as quite an ordeal. Paradoxically, episodes of nausea, vomiting and discomfort occurred in higher percentages compared to those reported by previous studies[8,10]. Picano et al[10] reported that less than 12% of patients had nausea or headache, whereas Secknus and Marwick[8] reported less than 1%. In our study, episodes of nausea and vomiting occurred in 20% of DSE studies, while episodes of discomfort and anxiety were noted in 31%. It is notable that neither major nor minor events during DSE are related to age, sex, or the maximum dosage of dobutamine or atropine administration.

Finally, it should be noted that very few patients with either left bundle branch block or a permanent pacemaker were included in our study, as we prefer such patients to undergo myocardial scintigraphy. This policy has been followed with reference to the guidelines[27] for the diagnostic management of patients with chronic stable angina, approved by the American College of Cardiology/American Heart Association. However, it should be emphasized that evidence has been accumulating in the literature to support the view that DSE detects coronary artery disease with higher specificity and accuracy compared to myocardial scintigraphy in patients with either a permanent pacemaker[28] or left bundle branch block[29].

To conclude, with this study we aimed to describe our experience from a large number of DSE studies, performed as a routine in clinical settings for the detection of myocardial ischemia-viability in our Echo Laboratory. DSE represents a reliable method for the detection of myocardial ischemia, with high sensitivity and specificity in detecting left main and/ or left descending artery coronary artery disease, as well as 2- or 3-vessel coronary artery disease. The method is quite safe with a low frequency of occurrence of major events, suggesting that DSE could be a widely used diagnostic procedure in hospital, if not outside.

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