LEADING ARTICLE

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Dobutamine Stress Echocardiography

Safety in Diagnosing Coronary Artery Disease

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Abstract

Dobutamine stress echocardiography is considered a relatively well-tolerated diagnostic modality, effective in the management of patients with known or suspected coronary artery disease. Adverse effects during testing are relatively frequent, precluding the achievement of a diagnostic end-point in about 5 to 10% of tests. These adverse effects, mostly tachyarrhythmias and arterial hypotension, are usually minor and self limiting. However, severe life-threatening complications, as well as death, also occur.

By analysing Medline-quoted literature up to March 1999, we found 35 original studies from a single institution with more than 100 patients, as well as 2 multicentre studies, concerning the feasibility and safety of dobutamine stress echocardiography. In a cumulative total of 26 438 tests performed, 79 life-threatening complications (such as acute myocardial infarction, asystole, ventricular fibrillation, sustained ventricular tachycardia or severe symptomatic hypotension) have been reported, giving an incidence of 1 severe adverse reaction per every 335 examinations. In addition, 29 isolated case reports have been published describing life-threatening complications during dobutamine echocardiography. In case reports, 2 deaths have been described, both due to acute cardiac rupture in patients with recent inferior myocardial infarction. Severe adverse reactions during dobutamine echocardiography can be ischaemia independent, and are independent of operator experience and are unpredictable; some complications can be late occurring and long lasting. As a consequence, the procedure must be clearly indicated, written informed consent has to be obtained from the patient, an attending physician must be present during testing, and long term observation of outpatients is useful in order to manage late complications.

In conclusion, while the safety of dobutamine stress echocardiography was reported to be outstanding in early reports, further experience presents a substantially more worrying picture. This must be taken into account by both physicians and patients when assessing the risk–benefit profile of the procedure.

Dobutamine is a synthetic catecholamine, resulting from modification of the chemical structure of isoproterenol, with particular affinity for cardiac muscle α- and β-receptors.[1] Through β_1-adrenergic receptor stimulation, dobutamine produces an increase in myocardial contractility, atrioventricular conduction and heart rate. α-Adrenergic activity can mediate systemic vasoconstriction and raise blood pressure, as well as increase the inotropic state of the myocardium; stimulation of vascular β_2-receptors may induce coronary and peripheral arteriolar vasodilation.[2]

The various actions of dobutamine are dose dependent, with the inotropic effect predominating at low doses and positive chronotropic action developing at high doses. The drug has a short half-life (2 minutes) requiring continuous intravenous infusion to maintain haemodynamic modifications and allowing rapid resolution of effects once the infusion is discontinued.[3]

1. Dobutamine Stress Echocardiography

Dobutamine administration, at an adequate dosage, can provoke myocardial ischaemia mainly through an increase in myocardial oxygen demand. Coronary flow heterogeneity and maldistribution may occur as well,[3] as a consequence of β2-receptor–mediated vasodilation or, indirectly, as a result of an increase in myocardial oxygen demand.

For this reason, dobutamine infusion, associated with cardiac imaging techniques, has been used as an exercise-independent diagnostic tool in the evaluation of coronary artery disease. Since the first data on the diagnostic use of dobutamine stress imaging were reported in 1984,[4] the clinical application of the test with nuclear or ultrasound techniques[5] has dramatically increased, due to ease of use and diagnostic accuracy of the procedure. Initially used as an alternative diagnostic tool in patients unable to exercise, the indications for dobutamine stress have expanded to include risk stratification in patients with previous myocardial infarction, chronic ischaemic heart disease and undergoing major vascular surgery.[6] Due to the effects of the drug on cardiac contractility and coronary flow, dobutamine stress imaging is also effective for the detection of myocardial viability[7] of regions with resting dysfunction.

Echocardiographic techniques easily fit alongside diagnostic pharmacological stress protocols, since myocardial function, both regional and global, is continuously monitored and evaluated on-line in real time during the test. Therefore, dobutamine stress echocardiography has become, in the last few years, one of the most widely employed noninvasive imaging method for diagnostic evaluation and prognostic stratification in patients with suspected or known coronary artery disease.[8,9] A positive test for myocardial ischaemia is linked to the development of a transient left ventricular regional dyssynergy of contraction, which is absent or less extensive in the resting echocardiographic evaluation.

The standard dobutamine stress test protocol usually adopted in echocardiography laboratories consists of continuous intravenous infusion of dobutamine in 3-minute increments, starting with 5 μg/kg/min and increasing to 10, 20, 30 and 40 μg/kg/min. If no end-point is reached, atropine (in doses of 0.25mg up to a maximum of 1mg) is added to the 40 μg/kg/min dobutamine infusion (fig. 1). This test, dobutamine-atropine stress echocardiography, is widely used in the clinical setting and demonstrates high diagnostic accuracy, averaging 80 to 85%, for angiographically assessed coronary artery disease.[8,9]

Other more conservative protocols – with longer duration of steps and peak dobutamine dosage of 20 or 30 μg/kg/min[10,11] – have been proposed, but they are limited by unsatisfactory sensitivity. More aggressive protocols – with higher peak dosage of dobutamine up to 50 or 60 μg/kg/min, and atropine up to 2mg[12] – have also been proposed. These should to be used with extreme caution, since, as we will discuss, even the 'standard dose' (40 μg/kg/min, with 1mg of atropine) raises safety concerns.

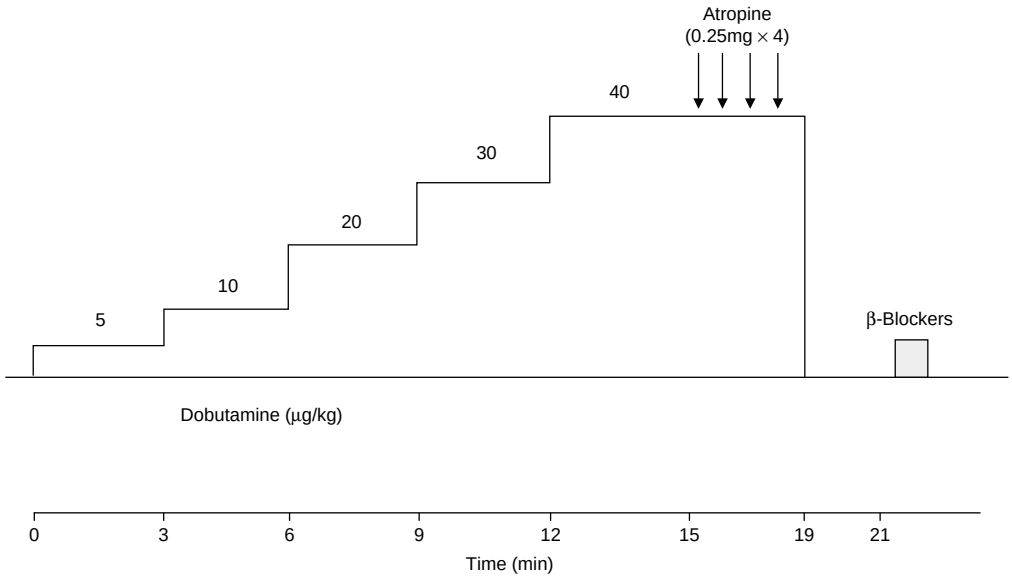

Fig. 1. Drug infusion protocol of standard dobutamine stress echocardiography with atropine addition.

2. Contraindications and Minor Adverse Effects

Contraindications to dobutamine stress echocardiography are a documented history of complex atrial (paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia) or ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation); severe or uncontrolled hypertension can be a contraindication to testing.

Minor but significant clinical adverse effects occur during the test in about 30% of patients. Most are self-limiting, but in about 5 to 10% of patients they preclude completion of the test.

Nausea, headache, tremors, shortness of breath, palpitations, and anxiety are noncardiac adverse effects. Chest pain is usually linked to dobutamine-induced myocardial ischaemia, which is the diagnostic end-point of the test.

Minor cardiac adverse effects mainly consist of nonsustained tachyarrhythmias, hypotension (>30mm Hg drop in blood pressure), short-lasting bradyarrhythmias and hypertension. Tachyarrhythmias are frequent during the test (10 to 30% incidence rate). In order of frequency, arrhythmias are represented by frequent polymorphic premature ventricular beats, couplets, nonsustained ventricular tachycardia, supraventricular premature beats, nonsustained supraventricular tachycardia and paroxysmal atrial fibrillation.[9]

The incidence of cardiac and noncardiac minor adverse effects is positively correlated with dobutamine dose, being lower at initial stages and higher at maximal drug dose. Atropine addition at maximal dobutamine dose further increases the rate of adverse effects, considering also that atropine poisoning can occur.

Adverse effects usually disappear upon interruption of drug infusion, due to the short half-life of dobutamine. If symptoms or ischaemia persist, intravenous β-blockers (propranolol, esmolol) are given.

3. Major Adverse Effects and Life-Threatening Complications

We describe separately the evidence from initial large series arising from early use of the procedure from single centres with patient populations larger

than 100, then we examine the results of prospective multicentre trials and, finally, we review the evidence from anecdotal case reports.

From Medline-quoted literature, up to March 1999, we found 35 original studies from single institutions with more than 100 patients (for an overall sample of 20 448 tests), specifically mentioning the occurrence of eventual adverse effects or complications, and 2 multicentre registries (globally collecting information on 5990 tests) [table I]. In addition, 28 isolated case reports describing complications during dobutamine stress echocardiography have been detected, some published as abstracts or in other Medline-transparent literature. To our knowledge, none of the single case reports were reported in the multicentre registries.

3.1 Single Centre Reports

The results of single centre reports are shown in table I.

Mertes et al.[13] in 1993 reported the initial experience in 1118 consecutive patients undergoing dobutamine stress echocardiography (with addition of atropine in 420 patients). No major adverse effects occurred in this population; there were only minor complications (such as 40 instances of nonsustained ventricular tachycardia). In 1995, Pellikka et al.[14] presented the initial experience of the Mayo Clinic in 1000 consecutive dobutamine echocardiography tests: 1 extension of myocardial infarction, 1 transient ischaemic attack and 4 sustained ventricular tachycardias were reported as serious complications. In 1996, Zahn et al.[15] reported 1 case of ventricular fibrillation, 1 case of acute pulmonary oedema and a focal cerebral seizure in a caseload of 1000 dobutamine-atropine echocardiography tests performed. In the same experience, 10 new atrial fibrillations, 3 supraventricular tachycardias and 25 decreases in blood pressure (>20mm Hg) were evidenced among other minor adverse effects during the test. Lewis et al.[16] observed 2 cases of acute myocardial infarction in a series of 650 patients performing dobutamine-atropine echocardiography.

Table I. Occurence of life-threatening complications in published experience with studies of >100 patients undergoing dobutamine stress echocardiography

Reference	Patients	Complication(s)
Single institution experience		
Marcovitz & Armstrong[28]	141	none[a]
Mertes et al.[13]	1118	none[a]
Takeuchi et al.[29]	120	none[a]
Baudhuin et al.[30]	136	none[a]
Boccanelli et al.[31]	109	none[a]
Beleslin et al.[32]	136	none[a]
Fetiveau et al.[33]	373	none[a]
Gordon et al.[34]	127	none[a]
Dagianti et al.[35]	100	none[a]
Pellikka et al.[14]	1000	1 AMI, 4 VT, 1 prol. ischaemia
Chan et al.[36]	137	none[a]
Bigi et al.[25]	109	1 VF, 1 VT
Anthopulos et al.[37]	120	none[a]
Pingitore et al.[38]	360	none[a]
Cladellas Capdevila et al.[20]	141	2 VT
Zahn et al.[15]	1000	1 VF, 1 LVF, 1 seizure
San Roman et al.[18]	102	2 VT, 1 LVF, 2 hypo
Cornel et al.[27]	318	1 VT
Wu et al.[39]	104	none[a]
Williams et al.[40]	136	none[a]
Ling et al.[41]	1968	none[a]
Van Damme et al.[42]	156	none[a]
Lamisse et al.[26]	600	4 VT
Smart et al.[43]	232	none[a]
Hennessy et al.[19]	474	1 VT, 1 LVF, 1 hypo
Lewis et al.[16]	650	2 AMI
Seknus & Marwick[17]	3011	5 VT, 1 AMI, 1 prol. ischaemia, 1 hypo
Paventi et al.[44]	256	none[a]
Hiro et al.[45]	732	none[a]
Pinton et al.[46]	735	none[a]
Elhendy et al.[21]	1164	7 VT
Bremer et al.[22]	1035	1 VF, 1 VT
Cortigiani et al.[23]	368	1 VT
Elhendy et al.[47]	1446	none[a]
Poldermans et al.[24]	1734	3 VF, 13 VT, 6 hypo
Multicentre registry		
Picano et al.[48] (EDIC)	2949	2 VF, 2 VT, 2 AMI, 1 prol. ischaemia, 1 hypo
Pezzano et al.[49] (RITED)	3041	2 VF, 1 asystole
Total	26 438	79 (1/335)[b]

a No life-threatening complications reported; however, minor and self limiting adverse effects were documented.

b Incidence (number of complications/number of tests).

AMI = acute myocardial infarction; **EDIC** = Echo-Dobutamine International Cooperative study; **hypo** = severe symptomatic arterial hypotension; **LVF** = left ventricular failure with acute pulmonary oedema; **prol. ischaemia** = prolonged myocardial ischaemia with ST segment elevation; **RITED** = Registro Italiano Test Eco-Dobutamina; **VF** = ventricular fibrillation; **VT** = sustained ventricular tachycardia.

Recently, Seknus and Marwick[17] reviewed the experience of their institution with dobutamine stress echocardiography, reporting safety and the incidence of adverse effects in 3011 tests performed in 2871 patients over 5 years, using evolving protocols (atropine addition in last examinations) and indications. Neither death nor ventricular fibrillation were observed, but serious complications occurred in 9 patients, including 5 sustained ventricular tachycardia, 1 myocardial infarction and other 3 conditions requiring in-hospital admission (sustained supraventricular tachycardia, hypotension, suspected myocardial infarction with ST segment elevation and left ventricular dysfunction).

San Roman et al.,[18] in a sample of 102 consecutive patients with suspected coronary artery disease, reported a high incidence (7%) of serious complications: 1 case of left-sided heart failure, 2 cases of severe hypotension requiring pharmacological support, 2 sustained ventricular tachycardias, 2 hypertensive reactions (systolic blood pressure to 250mm Hg). Hennessy et al.,[19] from a case-load of 474 patients, reported the occurrence of 1 acute pulmonary oedema and 1 sustained ventricular tachycardia during dobutamine stress echocardiography. Caldellas Capdevila et al.[20] observed 2 cases of sustained ventricular tachycardia in 141 patients with chest pain or who were candidates for vascular surgery. Elhendy et al.,[21] studied hypertensive patients with dobutamine echocardiography, and reported 7 episodes of sustained ventricular tachycardia among 1164 examinations.

In 1998, Bremer et al.[22] analysed the experience with dobutamine stress echocardiography performed by trained sonographers and found 1 episode of ventricular fibrillation and 1 of sustained ventricular tachycardia in a overall sample of 1035 patients. Cortigiani et al.,[23] describing the stress test case-load in a primary care centre, reported 1 instance of sustained ventricular tachycardia in 368 tests.

Very recently, Poldermans et al.[24] collected the 9-year experience of the Thoraxcenter, Rotterdam, The Netherlands, in 1734 patients who had undergone dobutamine-atropine stress echocardiography: 3 episodes of ventricular fibrillation, 13 of sustained ventricular tachycardia and 6 of severe symptomatic hypotension occurred during the examinations. In addition, further studies[25-27] described the occurrence of sustained complex ventricular arrhythmias during dobutamine echocardiography tests.

In contrast, other studies[28-47] performed in large populations did not report any life-threatening complication during dobutamine stress echocardiography but documented only minor and self-limiting adverse effects, such as nonsustained ventricular arrhythmias, atrial arrhythmias or moderate hypotension. From the screened studies, 68 life-threatening complications in 20 448 dobutamine stress echocardiography tests were observed overall, with a complication rate of 1 in every 301 tests.

3.2 Multicentre Studies

Only 2 multicentre studies, concerning the feasibility and safety of dobutamine stress echocardiography, were found from the literature search (table I).

The Echo-Dobutamine International Cooperative (EDIC) study,[48] presented in 1994, collected the experience of 24 laboratories which performed dobutamine-atropine stress echocardiography. In an overall sample of 2949 diagnostic tests (performed in 2799 patients) life-threatening complications events occurred in 9 patients. These were 3 ventricular tachycardias, 2 ventricular fibrillations, 3 acute myocardial infarctions and 1 prolonged myocardial ischaemia resistant to β-blockers. In addition, atropine poisoning with long-lasting hallucinations was observed in 5 patients.

More recently, the Registro Italiano Test Eco-Dobutamina (RITED)[49] presented the findings of 63 Italian laboratories on complications and adverse effects during the test. Among the 63 centres entering the registry, only 7 submitted more than 100 case studies. Of the 3041 examinations collected, about 17% of tests were low dose procedures assessing myocardial viability, possibly

leading to an underestimation the incidence of severe adverse reactions during testing. Three severe adverse effects were reported: 2 ventricular fibrillations and 1 asystole.

Considering both multicentre studies and the experience of single institutions, an incidence was reported of 1 life-threatening complication per 355 examinations (79 per 26 438 tests), but no deaths. From these data, the test appears to be reasonably well tolerated. However, a definite risk for major complications must be considered. The complication incidence is not trivial, especially when compared with the safety of the exercise stress test (about 1 major complication per every 3000 tests) or with that of pharmacological stress testing using such vasodilator agents as dipyridamole (1 complication per 1400 tests).[50]

3.3 Anecdotal Case Reports

In the medical literature there were several case reports of major complications, including death, during dobutamine stress echocardiography. Most of these single experiences are reported without mentioning the cumulative number of dobutamine tests performed in that centre, thereby making the evaluation of incidence of complications impossible. However, these data can contribute to the knowledge and objective evaluation of the safety of the dobutamine test when applied in everyday clinical practice.

In the last 3 years (table II), 28 case reports concerning life-threatening adverse effects during dobutamine stress echocardiography have been reported, sometimes in minor and Medline-transparent literature.[51-76] In particular, 4 acute myocardial infarctions, 6 ventricular fibrillations, 2 syncopes due to asystole, 6 persistent transmural myocardial ischaemias with ST segment elevation and 1 haemorrhagic stroke (associated with an increase in blood pressure) have been reported by different centres during diagnostic tests.

Finally, dramatic fatal complications were reported. Two cardiac deaths have been described during dobutamine echocardiography (using a low dose in 1 patient), which was performed for prognostic stratification.[67,71] Both deaths were due to acute cardiac rupture with pericardial tamponade, occurring in patients with recent myocardial infarction involving the inferior wall of the left ventricle (a-dyskinetic at resting echocardiographic examination). In both patients no ischaemic variations in wall motion could be detected before the complication occurred. Two other cases of nonfatal late cardiac rupture of the interventricular septum, in patients with recent myocardial infarction, have been observed.[66,75] Very recently, a death subsequent to persistent ventricular fibrillation during

Table II. Life-threatening complications during dobutamine stress echocardiography published as case reports

Reference	Complication
Di Giovambattista et al.[51]	VF
Cohen et al.[52]	Prol. ischaemia
Mathew et al.[53]	Prol. ischaemia
Pontillo et al.[54]	VF
Lanzarini et al.[55]	Asystole
Kardaras et al.[56]	Prol. ischaemia
Madu et al.[57]	VT
Shaheen et al.[58]	VF
Deligonul et al.[59]	Prol. ischaemia
Ferreira et al.[60]	AMI
Daniels & Orsinelli[61]	Cardiac rupture[a]
Weidmann et al.[62]	AMI
Takeuchi et al.[63]	AMI
Salustri et al.[64]	Asystole
Falsini et al.[65]	Stroke
Giunta et al.[66]	Cardiac rupture
Borziani et al.[67]	Cardiac rupture[a]
Tio et al.[68]	Prol. ischaemia
Pinton et al.[69]	Asystole
Yamagishi et al.[70]	Prol. ischaemia
Reisenhofer et al[71]	Cardiac rupture[a]
Breithardt et al.[72]	1 AMI, 1 VF[b]
Andrade et al.[73]	1 VF, 1 VT
Poldermans et al.[74]	VF
Bianchi et al.[75]	Cardiac rupture
Varga et al.[76]	VF[a]
Orandini et al.[77]	Cardiac rupture

a Subsequent death.

b With AMI.

AMI = acute myocardial infarction; **prol. ischaemia** = prolonged myocardial ischaemia with ST segment elevation; **VF** = ventricular fibrillation; **VT** = sustained ventricular tachycardia.

dobutamine echocardiography has been reported.[76] A further case of fatal cardiac rupture of the inferior wall during dobutamine testing performed early after myocardial infarction has been reported by Orandini et al.[77]

From these fragmentary reports, we can conclude that, although dobutamine echocardiography has an acceptable safety profile overall, serious, even fatal, adverse effects may occur and should be considered when evaluating the indications for and risk-benefit ratio of the test.

4. Multicentre Stress Echocardiography Complications Registries

The safety of the dobutamine test is a major issue in deciding its practicability and cost effectiveness – yet, the seed of efficacy (safety under ideal conditions such as those of initial feasibility studies) is often strikingly different from the fruit of effectiveness (safety under real life conditions populated by real patients, real doctors and real problems).[48]

For this reason, a German stress echocardiography registry has recently been started. Preliminary data, presented at the November 1999 meeting of the American Heart Association,[78] censored 9354 dobutamine stress tests, with an overall incidence of 3.6% for serious adverse effects and 0.02% (2 cases) for ventricular fibrillation. In this same registry, adverse effects occurred in 1.5% (with no ventricular fibrillation) of the 1245 dipyridamole tests.

Using a similar approach, at the Clinical Physiology Institute in Pisa, Italy, a scientific survey of severe complications during stress echocardiography (exercise, dobutamine and dipyridamole) is currently ongoing. The organisers of the stress complications registry distribute to all laboratories known to perform stress echocardiography a cover letter summarising the rationale of the survey. As well, a very simple Case Report Form is sent; only 1 form is to be filled out for every stress echocardiography laboratory, in order to minimise the time taken by physicians to summarise the entire experience of the laboratory. To date (January 2000) preliminary information on >80 000 tests (>23 000 using dobutamine) has been collected and data analysis – still in progress – shows a rate of complications of 1 out of 400 tests for dipyamole and 1 out of 1200 tests for dobutamine.[79] Interestingly, these 2 independent registries – involving different investigators, different geographical distribution (one German, the other international) and different patient numbers (more than 60 000 examinations for the German, and more than 80 000 examinations for the last update of the international registry) – reached very similar conclusions. Beckmann and Haug[78] concluded that bicycle and dipyridamole stress showed significantly less serious adverse effects compared with dobutamine and arbutamine and should therefore be the methods of first choice in clinical routine. Varga et al.[79] also concluded that exercise is safer than pharmacological stress and dipyridamole is safer than dobutamine.

5. Clinical Lesson Learned from Complications

'What we call experience is often a dreadful list of ghastly mistakes.'

John Chambers Da Costa, 1863-1933

From the experience of the last 10 years of intensive and increasing dobutamine use, some lessons can be learned.

1. Severe complications (sustained ventricular arrhythmias, myocardial infarction, death) can be sudden and unpredictable. These may not be preceded by symptoms or linked to the development of dobutamine-induced myocardial ischaemia (which is possibly detectable using echocardiographic or electrocardiographic markers). As a consequence, occurrence of severe complications is largely independent of the operator's experience with the test (that is, experience in the early identification of ischaemic wall motion abnormalities which leads to timely interruption of the test when the test is obviously positive).

2. Some major complications due to dobutamine administration for diagnostic purpose can oc-

cur in a late or very late period after stress test termination. This is especially true for ischaemic complications such as acute myocardial infarction or transmural myocardial ischaemia. Occasionally, these can occur as late as 1 hour after test termination (e.g. 1 of the 2 cases of acute myocardial infarction described by Lewis et al.,[16] occurred 1.5 hours after test termination, while the patient was in the hospital cafeteria), and can be resistant to the specific antidote of administering a β-blocker. Therefore, although this outcome is the exception, an adequate patient observation period of about 1 hour after dobutamine stress echocardiography is warranted. This is the current policy in our stress echocardiography laboratory for all outpatients.

3. The early (3 to 12 days) post-infarction period seems to be particularly risky for dramatic complications such as acute cardiac rupture. All of these events described to date occurred during pre-discharge examination, in patients hospitalised with recent acute myocardial infarction.[61,66,67,71,75,77] All tests associated with cardiac rupture occurred in patients with a dyskinetic and thinned inferior wall in resting conditions. It may be wise to exclude patients with such features during resting echocardiography examination from dobutamine testing in the early phase after myocardial infarction.

6. Mechanisms of Dobutamine-Induced Adverse Reactions

Tachyarrhythmias are the most frequent complication occurring during dobutamine stress echocardiography. In some cases they are subsequent to pharmacologically induced myocardial ischaemia during the test, and so are associated with a transient wall motion abnormality. However, in most cases they are independent of ischaemia and can also develop at low dobutamine doses. The mechanism of their onset can be attributed to the direct adrenergic arrhythmogenic effect of dobutamine, through myocardial β-receptor stimulation, which is particularly evident in patients with ischaemic heart disease. Dobutamine infusion can also lower the blood potassium level, thereby contributing to the genesis of ventricular ectopy through a depolarising effect on the cell membrane.[80]

Significant hypotension, sometimes associated with bradyarrhythmias, including asystole, is another frequent adverse reaction during dobutamine echocardiography. In some cases this finding has been attributed to dynamic interventricular obstruction provoked by inotropic action of dobutamine, especially in hypertrophic hearts.[81] An alternative mechanism may be a vasodepressor reflex triggered by left ventricular mechanoreceptor stimulation (Bezold-Jarish reflex) due to dobutamine-induced excessive inotropic stimulation, with peripheral vasodilatation and negative chronotropic effects.[81]

Late and long-lasting transmural myocardial ischaemia, with persistent ST segment elevation, is probably due to coronary vasoconstrictive effect of dobutamine, through α-receptor stimulation, sometimes involving multiple coronary segments.[53,56,59,68] Moreover, some evidence demonstrated that dobutamine can induce platelet aggregation, possibly provoking coronary occlusion, prolonged myocardial ischaemia and acute myocardial infarction.[82]

No definite data can be obtained to explain the occurrence of cardiac rupture during the dobutamine test. However, once again the global inotropic mycardial stimulation can significantly increase the wall stress and provoke rupture of a zone with lowered resistance, such as a necrotic and thinned ventricular wall.

Atropine addition at the end of a negative test, in order to reach maximal heart rate, can be responsible for noncardiac serious adverse effects due to atropine intoxication.[48,83]

7. Safety of Dobutamine Stress Testing: Medicolegal Implications

Since in many countries (including the US) dobutamine has not been approved for pharmacological stress echocardiography, it is wise to obtain written consent by the patient after he or she has been informed in detail about the rate of complications. Similar to what has been described for exer-

cise stress testing, the best medicolegal protection is to perform the test according to published standards and guidelines.[84] The written informed consent form should explicitly state the rate of complications for the tests (approximately 1 major complication out of 400 tests); this is the best way of informing the patient and the physician that every test carries a risk and that different tests carry different risks (higher for inotropic agents than for vasodilators).

Although a few reports[22] have implied that the incidence of complications is low during dobutamine stress echocardiography performed only by trained sonographers (as happens in some instances in the US), we firmly believe that stress echocardiography must be always performed with the attending physician present. When complications occur, the physician should be able to prove that indications for testing were appropriate, the protocol followed standard guidelines, the patient was aware before testing of the inherent risk of the procedure, and that standard treatment was provided for the complication in a timely fashion by personnel with adequate knowledge.

Dobutamine stress testing can therefore be performed in the echocardiography laboratory, but:

- not in patients in whom it is contraindicated, such as patients with severe uncontrolled hypertension and with a history of significant arrhythmias
- not at dosages exceeding 40 μg/kg plus 1mg of atropine (the standard protocol), since no diagnostic gain has been conclusively demonstrated, while no definite data are available about safety, when using very high doses
- only after the patient signed the informed consent form
- always with an attending physician present who has the knowledge and facilities available for basic and advanced life support to manage life-threatening complications
- after testing, outpatients should remain in the waiting room for about 60 minutes, because late complications may occur.

Last but not least, the indication for the test should be class I (of proven value) according to the recommendations of the American College of Cardiology and the American Heart Association[6]: a complication occurring in an inappropriate test has a high medicolegal potential.

8. Conclusion

Dobutamine stress echocardiography is a relatively well tolerated diagnostic modality, effectively used in the management of patients with known or suspected coronary artery disease. Adverse effects during testing are relatively frequent, precluding the achievement of a diagnostic endpoint in 5 to 10% of tests; these adverse effects are usually minor and self-limiting. However, the occurrence of severe life-threatening complications, including death, is possible. In fact, although the safety of dobutamine stress echocardiography was reported to be outstanding in early reports from single centres, even when high dosages and atropine coadministration were used, later larger scale multicentre trials and expanded experience from single centres present a substantially more worrisome picture, with life-threatening complications occurring in about 1 of 350 tests. This must be taken into account when assessing the risk-benefit profile of the procedure. Both the physician recommending the procedure and patients submitted to it should be aware of this information. Finally, due to the presence of life-threatening complications, dobutamine stress tests should be always be performed with an attending physician present, which does not appear to be the case in some institutions in the US.[22,85]

In our laboratory, after 10 years' experience, dobutamine stress echocardiography is now a first choice test when the low dosage (≤10 μg/kg/min) is used for viability assessment in patients with ischaemic severe left ventricular dysfunction (ejection fraction ≤30%). We use the high dose (up to 40 μg/kg/min plus atropine 1mg) in patients with a class I indication for pharmacological echocardiographic testing, in whom the dipyridamole test – which has similar diagnostic accuracy but a

more reassuring safety record than dobutamine[86] – is contraindicated or gives nondiagnostic results.

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