Dobutamine Stress Echocardiography

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12.1 Historical Background

Among exercise-independent stresses, the most popular are dobutamine and dipyridamole. Dobutamine is the prototype of pharmacological adrenergic or inotropic stress. It was initially proposed for the diagnosis of coronary artery disease in combination with perfusion imaging [1] and later with two-dimensional (2D) echocardiography by the Liège group [2]. Other sympathomimetic agents have been proposed for stress echocardiography, including isoproterenol [3] and epinephrine [4], but these drugs often bring more pronounced arrhythmogenic side effects. Following the demonstration of low-dose dobutamine as a test of myocardial viability in 1990 [5], in the subsequent decade dobutamine has been extensively adopted in pharmacological stress echocardiography. The evolution of dobutamine stress paralleled that of other pharmacological stresses. With echocardiography, it began at relatively "low" doses (20 μg kg^{-1} min^{-1}), which gave low sensitivity values [6]; later, more aggressive doses were adopted (up to 40 μg kg^{-1} min^{-1}) [7, 8], and finally it was coadministered with atropine [9], which overcame the limitation of less than ideal sensitivity to minor forms of coronary artery disease.

12.2 Pharmacology and Pathophysiology

Dobutamine is a synthetic catecholamine resulting from the modification of the chemical structure of isoproterenol. It acts directly and mainly on beta-1 adrenergic receptors of the myocardium, producing an increase in heart rate, enhancement of atrioventricular conduction, and increased contractility (Fig. 12.1). In fact, alpha-adrenergic activity can mediate systemic vasoconstriction and an increase in blood pressure and – at the coronary level – increased constriction up to coronary vasospasm, especially when the alpha-mediated vasoconstriction is enhanced by chronic or acute beta-blockade. Stimulation of beta-2 receptors on coronary arterioles may induce coronary arteriolar vasodilation. However, endothelial dysfunction and

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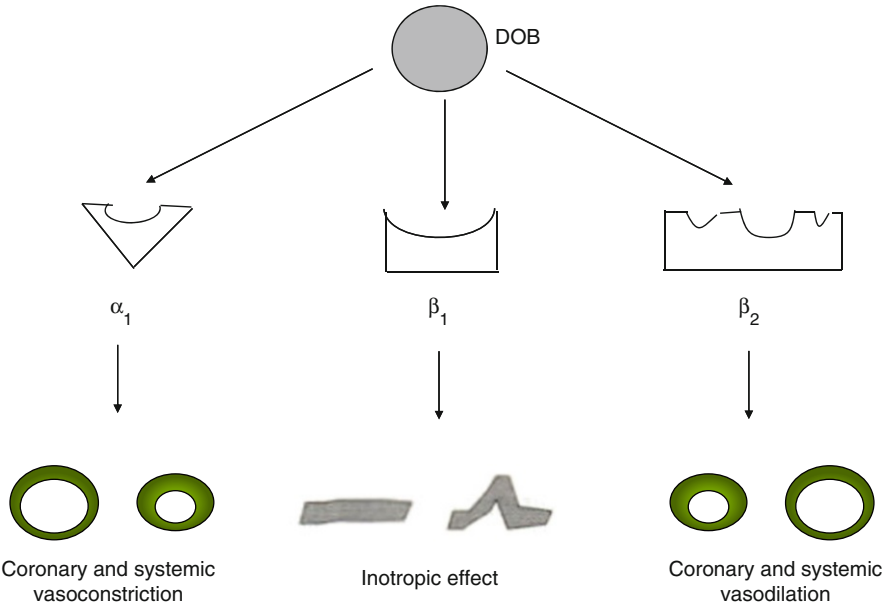

Fig. 12.1 The main cardiovascular receptor targets and physiologic effects of dobutamine

enhanced alpha-adrenergic tone contribute to the loss of dobutamine-induced vasodilation in coronary atherosclerosis [10]. The short half-life (2 min) of dobutamine allows rapid resolution of its effects once the intravenous infusion is discontinued. However, the alpha-mediated coronaro-constrictive and platelet-aggregating effects are not reversed, and may be potentiated, by beta-blockers and peak at 30–45 min after the end of infusion.

Dobutamine provokes ischemia mainly through the inotropic and chronotropic response to stimulation of myocardial beta-1 receptors determining an increase in myocardial oxygen demand (see Fig. 5.4 in Chap. 5). Heart rate increases two- to threefold, systolic arterial pressure increases 1.5- to twofold, and myocardial contractility increases four- to eightfold versus baseline. Other proischemic mechanisms are the flow maldistribution mediated by beta-2 receptors of coronary arterioles [11] and coronary vasospasm mediated by alpha-adrenoreceptors present on smooth muscle cells of epicardial arteries. The dobutamine dose usually employed for stress echocardiography testing causes a two- to threefold increase in coronary blood flow [12].

12.3 Methodology

The protocol displayed in Fig. 12.2 is the most widely used, the only one validated in a large-scale multicenter prospective trial [13], and it has been recently proposed as the state-of-the-art protocol by both the American [14] and European [15] recommendations. Doses lower than those shown in Fig. 12.2 are associated with

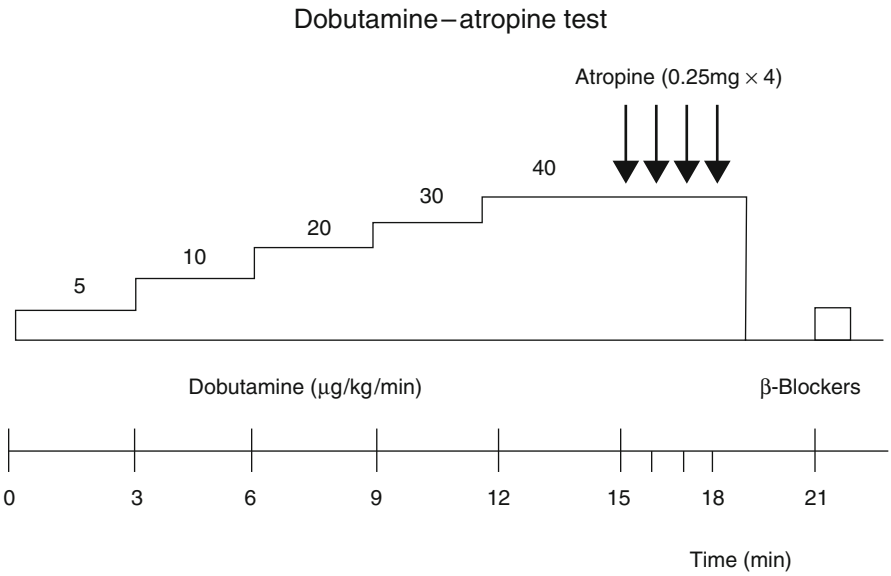

Fig. 12.2 Protocol of the dobutamine–atropine stress test. For viability detection in patients off beta-blockers, a 5-min step from 5 to 10 mcg is suggested

insufficient sensitivity, while higher doses are associated with an unacceptable high rate of side effects. For viability assessment, steps of 5 min are used, starting from 5 up to 10 mcg [5]. However, to fully recruit the inotropic reserve in patients with heart failure and usually with beta-blocker therapy, high doses (without atropine) are required [16].

Alternatively, on the pharmacology basis that atropine may take up to 3 min to achieve maximum effect, there are studies suggesting that an early administration of atropine, at a starting dose of up to 20 μg kg^{-1} min^{-1}, is more effective and equally accurate and may even be safer than a late atropine injection [17–20] and is also included in the American recommendations [14].

12.4 Feasibility and Safety

Minor but limiting side effects preclude the achievement of maximal pharmacological stress in about 10 % of patients [13, 21]. In order of frequency, these side effects are complex ventricular tachyarrhythmias (frequent, polymorphic, premature ventricular beats, couplets and triplets, nonsustained ventricular tachycardia), nausea and/or headache, hypotension (>30 mmHg drop in blood pressure) and/or bradycardia, supraventricular tachyarrhythmias (supraventricular tachycardia or atrial fibrillation), and hypertension. Limiting side effects are more often asymptomatic with dobutamine and more often symptomatic with dipyridamole [21]. Side effects usually disappear upon interruption of drug infusion, since the half-life is 2–3 min.

When symptoms or ischemia persist, IV beta-blockers – usually the short-acting drug esmolol – are given.

Both the patient and the physician should be aware of the rate of major complications that may occur during dobutamine stress. As concordantly shown by meta-analysis [22], single-center experiences [23–28], multicenter studies [13], and retrospective registries [29–31], major life-threatening side effects occur in 1 of 300–350 cases (Table 12.1).

The proliferating anecdotal reports of catastrophes also contribute in assessing the safety of the test. Cardiac rupture [32–35], ventricular fibrillation [36, 37], refractory coronary vasospasm [38, 39], myocardial infarction [40, 41], cardiac asystole [42, 43], and acute Tako-tsubo syndrome [44] have all been described during dobutamine testing. Tachyarrhythmias are the most frequent complication occurring during dobutamine stress echocardiography. In some cases they are subsequent to pharmacologically induced myocardial ischemia during the test and therefore are associated with a transient wall motion abnormality. However, in many cases they are independent of ischemia 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 ischemic heart disease. Dobutamine infusion can also lower the blood potassium level, thereby contributing to the genesis of ventricular ectopy through a depolarizing effect on the cell membrane [45] (Fig. 12.3).

Significant hypotension, sometimes associated with bradyarrhythmias, including asystole, is another frequent adverse reaction during dobutamine echocardiography.

Table 12.1 Life-threatening complications in early single center large experiences, multicenter studies (EDIC), and multicenter registries for dobutamine stress echocardiography

Author, year	Patients	Complications (s)
Single institution experience		
Mertes et al. 1993 [23]	1118	None[a]
Zahn et al. 1996 [25]	1000	1 VF, 1 LVF, 1 seizure
Secknus and Marwick 1997 [26]	3011	5 VT, 1 AMI, 1 prol ischemia, 1 hypo
Bremer et al. 1998 [27]	1035	1 VF, 1 VT
Poldermans et al. 1994 [24]	650	1 VF, 3 sustained VT
Mathias et al. 1999 [28]	4033	1 VFm 8 VT, 1 MI; 5 atropine intoxications
Multicenter registry		
Picano et al. (EDIC), 1994 [13]	2949	2 VF, 2 VT, 2 AMI, 1 prol ischemia, 1 hypo
Pezzano et al. (RITED) 1998 [29]	3041	2 VF, 1 asystole
Beckmann, 1999 [30]	9354	324 (2 VF)
Varga, 2006 [31]	35,103	63 (5 deaths)

AMI acute myocardial infarction, *VT* ventricular tachyarrhythmia, *VF* ventricular fibrillation, *LVF*, *VFm*, *MI* myocardial infarction, *prol* prolonged, *hypo* hypotension

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

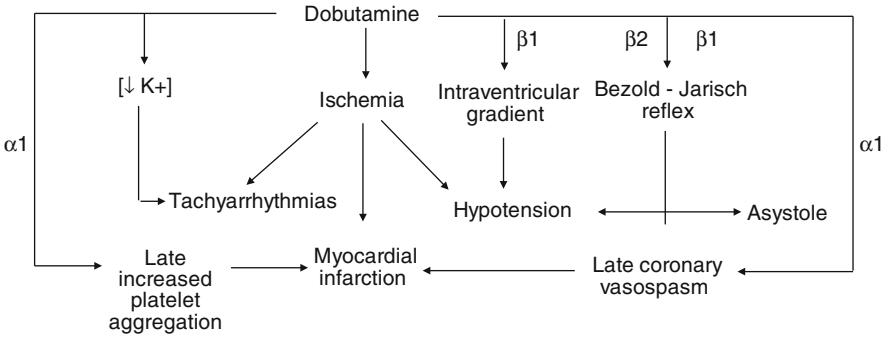

Fig. 12.3 Ischemia-dependent and ischemia-independent pathways of complications during dobutamine stress

In some cases this finding has been attributed to dynamic interventricular obstruction provoked by inotropic action of dobutamine, especially in hypertrophic hearts [46]. A vasodepressor reflex triggered by left ventricular mechanoreceptor stimulation (Bezold–Jarisch reflex) due to excessive inotropic stimulation may be an alternative mechanism [47]. These effects can be almost abolished if atropine is injected earlier.

Late and long-lasting transmural myocardial ischemia, with persistent ST segment elevation, is probably due to the coronary vasoconstrictive effect of dobutamine, through α-receptor stimulation, sometimes involving multiple coronary segments. Moreover, dobutamine can induce increased platelet aggregation, possibly provoking coronary occlusion, prolonged myocardial ischemia, and acute myocardial infarction on the anatomic substrate of a vulnerable, possibly noncritical, plaque unable to induce ischemia during stress [13, 48].

12.5 Diagnostic Results for Detection of Coronary Artery Disease

The accuracy in detecting angiographically assessed coronary artery disease has been consistently reported to be high, with sensitivity and specificity of 81 and 84 %, respectively, in a meta-analysis of 102 studies with over 7900 patients [49]. The diagnostic accuracy is similar to other forms of stress testing, such as exercise echocardiography [49, 50], dipyridamole echocardiography [49, 50], or stress SPECT [49]. In particular, the sensitivity and accuracy are identical to dipyridamole stress echocardiography when state-of-the-art protocols are used for both stresses (Fig. 12.4), as shown by two meta-analyses including 5 studies on 435 patients [50, 51].

One of the strategies in order to improve sensitivity of dobutamine stress echocardiography is a rapid injection of (5 mg in 1 min) metoprolol at peak stress with the acquisition of post-metoprolol images in a maximum interval of 3 min after the

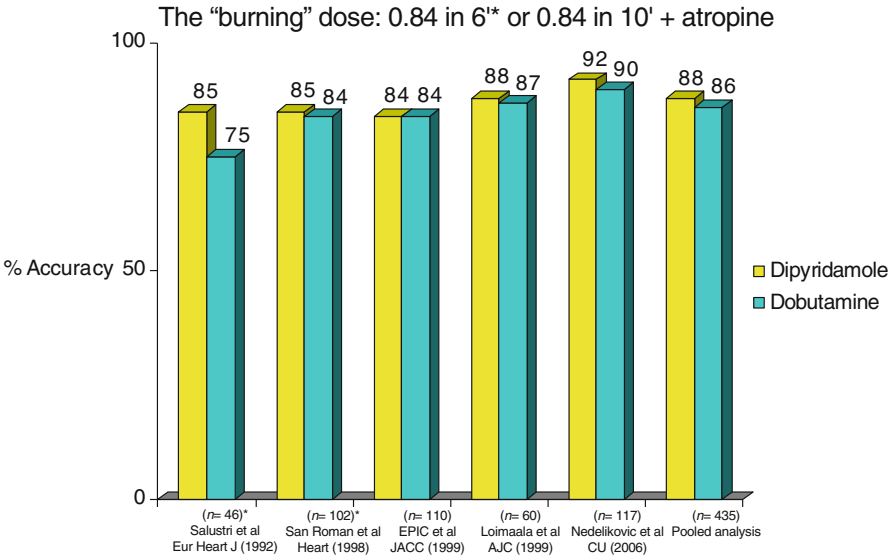

Fig. 12.4 The diagnostic accuracy for noninvasive detection of coronary artery disease of dobutamine echocardiography versus dipyridamole echocardiography (all protocols) and state-of-the-art (high dose with atropine or fast high dose) dipyridamole echocardiography (From meta-analysis of Noguchi et al. [50] and Picano et al. [51])

end of dobutamine infusion in negative studies where patients are not hypertensive at peak stress. This strategy may increase the sensitivity (mainly in single-vessel disease patients) up to 92 % without loss in specificity (Fig. 12.5) [52]. A possible mechanism is the unmasking of coronary vasospasm mediated by unopposed alpha-adrenoreceptors.

12.6 Identification of Myocardial Viability

Low-dose dobutamine recognizes myocardial viability with high specificity and good sensitivity, with excellent diagnostic [53] and prognostic [54] value. In patients with preserved global left ventricular function, myocardial viability identifies a greater risk to subsequent development of ischemia and nonfatal reinfarction early after acute myocardial infarction [55]. In patients with severe resting left ventricular dysfunction, a large amount of myocardial viability identified by low-dose dobutamine echocardiography is associated with a better survival [56]. This finding has been consistently described both in medically treated patients studied early after acute myocardial infarction [56] (a model of stunned myocardium) (Fig. 12.6) and in revascularized patients studied after chronic myocardial infarction (a model of hibernating myocardium) [57–59]. A contractile reserve identified by high-dose dobutamine (up to 40 mcg) identifies patients with dilated cardiomyopathy and better response to medical therapy and cardiac resynchronization therapy [60, 61].

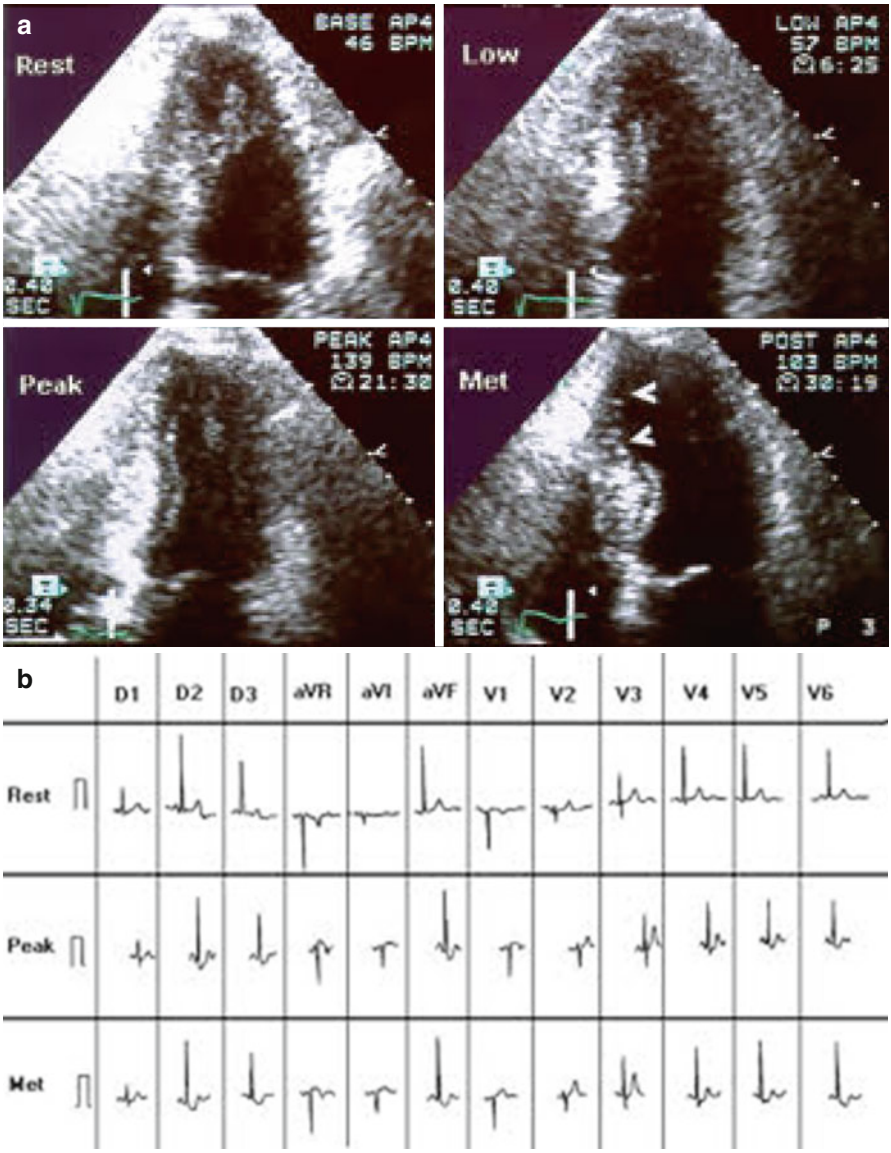

Fig. 12.5 (**a**) Example of a patient with a 90 % LAD stenosis without NWMA at peak developed only after metoprolol. Apical four-chamber view at end-systole with normal thickening at rest (HR of 46 beats min^{-1}, rate-pressure product of 6578 mmHg min^{-1} and LVESVI 15.7 ml m^{-2}) and low doses. At peak, HR was 139 beats min^{-1}, rate-pressure product was 20,850 mmHg min^{-1}, and LVESVI was 12.8 ml m^{-2}. After metoprolol (Met), there is a lack of thickening in the apical septum (*white arrows*) (HR of 103 beats min^{-1}, rate-pressure product of 15,450 mmHg min^{-1}, and LVESVI 33.3 ml m^{-2}). (**b**) EKG from patient in (a) demonstrating ST changes in leads D1, D2, aVF, V5, and V6 only during metoprolol

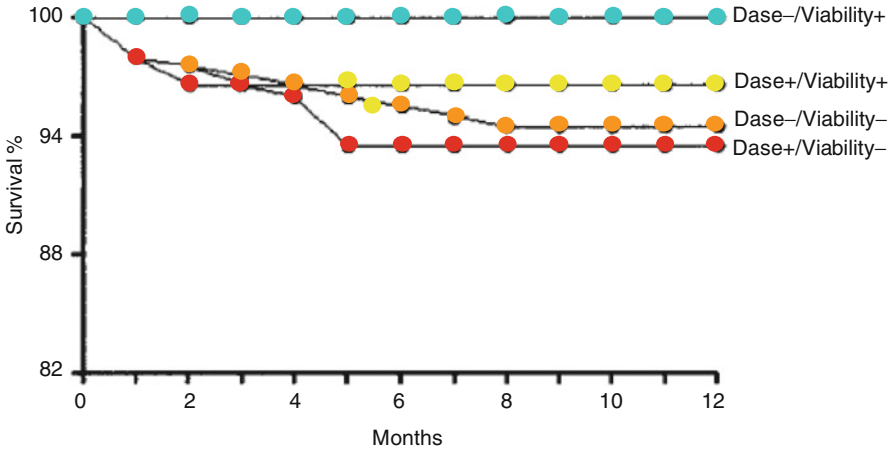

Fig. 12.6 Kaplan–Meier survival curves (considering only death as an end point) in patients stratified according to presence or absence of echocardiographically assessed viability and ischemia at low and high doses of dobutamine, respectively. Best survival is observed in patients with low-dose viability and no inducible ischemia; worst survival, in patients without viability and with inducible ischemia. *Viability* + and *viability* – indicate the presence or absence of myocardial viability at low-dose dobutamine, respectively; *Dase* + and *Dase*–, the presence or absence of myocardial ischemia at high-dose dobutamine, respectively (From Picano et al. [56])

Although the results of the STICH (Surgical Treatment for Ischemic Heart Failure) trial have cast doubt on the role of dobutamine stress echocardiography and other imaging modalities for the assessment of viability, the results are still predictive of a positive outcome [61]. When these are taken into consideration with previous studies [52–58], it becomes reasonable to recommend viability assessment when treating patients with coronary artery disease and left ventricular dysfunction [62].

12.7 Prognostic Value

The presence, site, timing, extent, and severity of dobutamine-induced wall motion abnormalities have a clear prognostic impact, as shown by over 50 studies on over 10,000 patients, including patients with or suspected coronary artery disease [63–72], evaluated early after acute myocardial infarction [73–77], and patients undergoing major noncardiac vascular surgery [78–85]. These studies concordantly show that dobutamine stress echocardiography results predict subsequent death, on the basis of coexistent fixed resting wall motion abnormalities, dobutamine dose required to induce ischemia (Fig. 12.7), and peak wall motion score index (Fig. 12.8). The prognostic value of dobutamine stress echocardiography is independent and additive to resting echocardiography and exercise electrocardiography and comparable to dipyridamole echocardiography [68, 86, 87] and stress SPECT [82, 88].

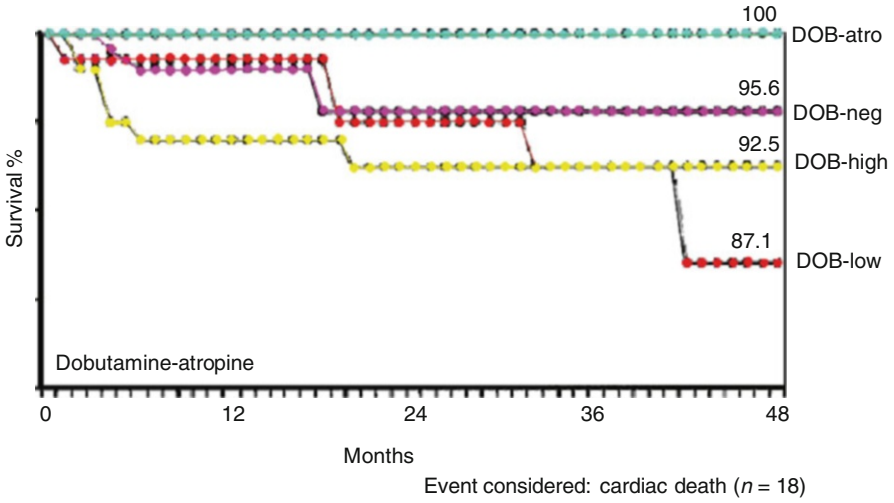

Fig. 12.7 Kaplan–Meier survival curves event-free of cardiac death in patients with negative and positive dobutamine echocardiography test results (*DOB*). Survival is worse in patients with positive DOB. In patients with positive DOB, a progressively worse survival is identified with positivity after atropine, high and low dose (From Pingitore et al. [68])

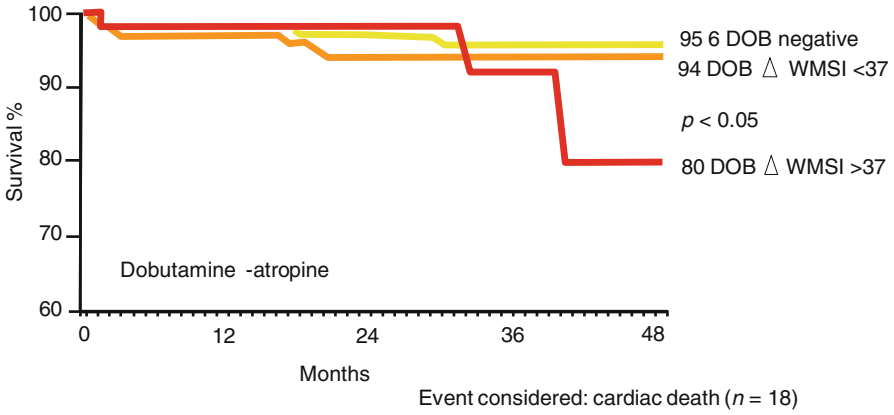

Fig. 12.8 Kaplan–Meier survival curves event-free of cardiac death in patients with negative and positive dobutamine echocardiography test results (*DOB*). In patients with positive DOB, a progressively worse survival is identified for patients with higher changes in peak wall motion score index (*WMSI*) (From Pingitore et al. [68])

12.8 Pitfalls

The limitations of dobutamine stress are related to feasibility, safety, technical difficulty of echocardiographic interpretation, suboptimal possibility to combine coronary flow reserve and wall motion information, and inability to predict physiologic

therapy-induced changes on exercise stress results. Minor but limiting side effects occur in 5–10 % of tests, and submaximal results have limited diagnostic and prognostic power. The test is less safe than other pharmacological stresses, such as vasodilators, and much less safe than exercise, with major life-threatening complications being 2–3 times more frequent with dobutamine than with dipyridamole and 4–5 times more frequent than with exercise. The echocardiographic image degradation during stress is less than with exercise, but significant, since high heart rate and hypercontractility make the wall motion interpretation more challenging. Changes exerted by anti-ischemic therapy (especially beta-blockers) on dobutamine stress are unrelated to physiologic effects of that same therapy on exercise, and therefore the test cannot be used to monitor pharmacological interventions in ischemic heart disease [89].

12.9 Indications and Contraindications

High-dose dobutamine is an appropriate choice for pharmacological stress echocardiography used for the detection of coronary artery disease, especially in patients with inability to exercise or contraindications to exercise [90] or with resting images of borderline quality which may make the more technically difficult exercise stress echocardiography a challenging task [91] (Table 12.2). It is also appropriate in intermediate-risk patients undergoing elective high-risk noncardiac surgery. Low-dose dobutamine is the first choice for identification of myocardial viability in patients with severe left ventricular dysfunction [90]. It is also appropriate in low-flow, low-gradient aortic stenosis to separate true from pseudosevere aortic stenosis [92]. Appropriateness is uncertain in intermediate-risk patients undergoing

Table 12.2 Appropriate and inappropriate indications to dobutamine stress echocardiography

	Appropriate	Uncertain	Inappropriate
Diagnosis of CAD in patient unable to exercise	√		
Diagnosis of viability in ejection fraction <35 %	√		
High-risk noncardiac surgery in intermediate-risk patient	√		
Low-flow, low-gradient aortic stenosis	√		
Need to evaluate antianginal therapy efficacy		√	
Intermediate-risk noncardiac surgery in intermediate-risk patient		√	
Prediction of CRT efficacy		√	
First-line test in patients able to exercise			√
Severe hypertension, malignant ectopy, inferior wall aneurysm early after AMI			√
Low-risk noncardiac surgery in low-risk patient			√

AMI acute myocardial infarction, *CAD* coronary artery disease, *CRT* cardiac resynchronization therapy

intermediate-risk noncardiac surgery [90, 93]. In women who cannot exercise, dobutamine stress echocardiography may be preferred than other modalities [93, 94]. Patients with a history of complex atrial (paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia) or ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation) or with moderate to severe hypertension should probably not undergo dobutamine stress testing and be referred for safer vasodilator stress [95].

12.10 Emerging and Promising Technologies

12.10.1 Coronary Flow and Microvascular Measurements

Dobutamine allows a combined dual imaging of wall motion and coronary flow reserve with either coronary flow velocity reserve, myocardial contrast echocardiography, or deformation parameters of left ventricular function. In a recent study, the outcomes of 651 patients with normal wall motion response during stress echocardiography with dobutamine or dipyridamole stress to evaluate coronary flow velocity reserve (CFVR) were evaluated in diabetic patients. CFVR was calculated simultaneously in the distal territory of the left anterior descending coronary artery. Diabetes increased risk only in patients with abnormal CFVR (<2.0) independently of the pharmacological stress technique used [96]. The use of CFVR was also evaluated in 20 patients with Tako-tsubo cardiomyopathy. The authors demonstrated that hyperemic CFVR increased significantly after recovery leading to a greater CFVR (2.9 + 0.3 vs. 2.1 + 0.4) and concluded that there was a transient impairment of CFR at the acute phase of TTC, which was due to a reduced vasodilating capacity [97]. Dynamic changes in microcirculatory blood flow at each stage of DASE can also be detected using real-time myocardial contrast echocardiography. The best parameter for detecting CAD in all stages was β reserve, which could highly accurately separate patients with from without coronary artery disease [98].

12.10.2 Myocardial Function and Deformation Parameters

The need for a more quantitative method for the interpretation of stress echocardiography depended on the development of new imaging modalities. Tissue Doppler and myocardial strain derived from Doppler measurements, or two-dimensional (strain and strain rate), has been considered an important alternative to better quantify regional contraction at rest or during stress [99, 100].

Tissue Doppler is feasible during stress tests, however is limited by the need of a high frame rate of at least 140 (s-1), and is angle dependent. These constraints limit the accurate deformation analysis of apical segments [101].

Classically, myocardial ischemia is defined as the transient reduction of myocardial thickening during induction of stress through pharmacological or exercise stress. However, myocardial ischemia can also cause early and late systolic

thickening, which unfortunately cannot be detected subjectively by the human eye, which has poor temporal resolution (30 frames per second), but can easily be measured by two-dimensional speckle tracking, a technique that is able to define deformation parameters known as Strain (fiber shortening) and Strain rate (fiber shortening over time) that are angle independent, making it more suitable for clinical practice. The results have been excellent in the experimental setting [102] and encouraging in the clinical realm [103], although some limitations do exist – as discussed in Chap. 23.

Real-time three-dimensional echocardiography during dobutamine stress has also been proposed to evaluate the extent and severity of CAD with good results and better specificity in multislice compared to multiplanar mode [104].

Table of Contents Video Companion

See stress echo primer, cases 8, 9, 10, 11, and 12.
See also, in the section illustrative cases, cases 11 (coronary artery disease), 32 to 35 (valvular heart disease), and 36 (heart transplant).
See also in the section "Nuovo Cinema Paradiso Remastered" the 2 short movies: Myocardial viability, a moonlight serenade, and Rocky Horror stress echo picture show.
See also in the section "Selected presentations: Angels in the stress echo lab."
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