Dobutamine Stress Echocardiography

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Ana Cristina Camarozano and Eugenio Picano

Keywords

Beta-receptors · Heart rate · Myocardial contractility · Safety · Viability

18.1 Historical Background

Dobutamine infusion is suitable pharmacological stress to induce regional wall motion abnormalities in presence of critical coronary artery stenosis, as shown by experimental studies at the beginning of the clinical applications of pharmacological stress echo (SE) in 1987 [1]. All major general cardiology guidelines recommend exercise SE over pharmacological SE since exercise provides a simultaneous physiologic assessment of functional capacity and symptom onset. However, many patients are unable to exercise on a treadmill or a bicycle due to rheumatologic, orthopedic, pulmonary, or neurological problems. For these patients, pharmacologic stress should be pursued [2].

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A. C. Camarozano (✉)
Medicine Department, Hospital de Clinicas UFPR, Federal University of Paraná, Curitiba, Brazil

E. Picano
Institute of Clinical Physiology of the National Research Council, Pisa, Italy
e-mail: stressecho007edition@gmail.com

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Dobutamine stress echocardiogram (DSE), like exercise and dipyridamole echo, has found its primary application in ischemic heart disease. Dobutamine is the prototype of pharmacological adrenergic and inotropic stress. It was initially proposed for the diagnosis of coronary artery disease in combination with perfusion imaging [3] and later with two-dimensional echocardiography by the Liège group of Luc Pierard [4]. Performing SE with a pharmacologic agent like dobutamine allows simulation of heart rate and increases myocardial oxygen demands like exercise echocardiography. Other sympathomimetic agents have been proposed for SE, including isoproterenol [5] and epinephrine [6], but these drugs often bring more pronounced side effects. The evolution of dobutamine stress paralleled that of other pharmacological stresses. With echocardiography, it began at relatively "low" doses (20 μg/kg/min), which gave low sensitivity values; later, more aggressive doses were adopted (up to 40 μg/kg/min), and finally it was coadministered with atropine [7], which overcame the limitation of moderate sensitivity to minor forms of coronary artery disease. Low-dose dobutamine is also used as a test of myocardial viability. It was the first [8] and still the most common way to assess myocardial viability using the contractile reserve.

In addition, DSE can help in the evaluation of valvular heart disease by helping to assess the effects of mitral and aortic stenosis, as well as in differentiating true-severe valvular aortic stenosis from pseudostenosis that may occur in the setting of left ventricular systolic dysfunction [9].

DSE can be performed with state-of-the-art ABCDE (Asynergy, B-lines, Contractile reserve, Doppler flow reserve, and Heart rate reserve) protocol validated in SE2020 Multicenter Study [10], with a slightly lower success rate than vasodilator stress for step D of coronary flow velocity reserve.

18.2 Pharmacology and Pathophysiology

The drugs that affect adrenergic transmission, also called catecholamines, can be endogenous (produced by the body itself) such as noradrenaline, adrenaline, and dopamine, or synthetic (produced in the laboratory) such as dobutamine. These drugs act on adrenergic receptors that are divided into alpha (1 and 2) and beta (1 and 2) [11, 12] (Table 18.1).

Dobutamine acts on adrenergic receptors, and acetylcholine (blocked by atropine) on muscarinic receptors, with a variety of different effects on myocardial cells (Fig. 18.1).

Table 18.1 Pharmacodynamics of dobutamine

	Receptor populations		
	α_1	β_1	β_2
Myocardium	Increased inotropy	Increased chronotropy Increased inotropy	–
Vasculature	Vasoconstriction	–	Vasodilation

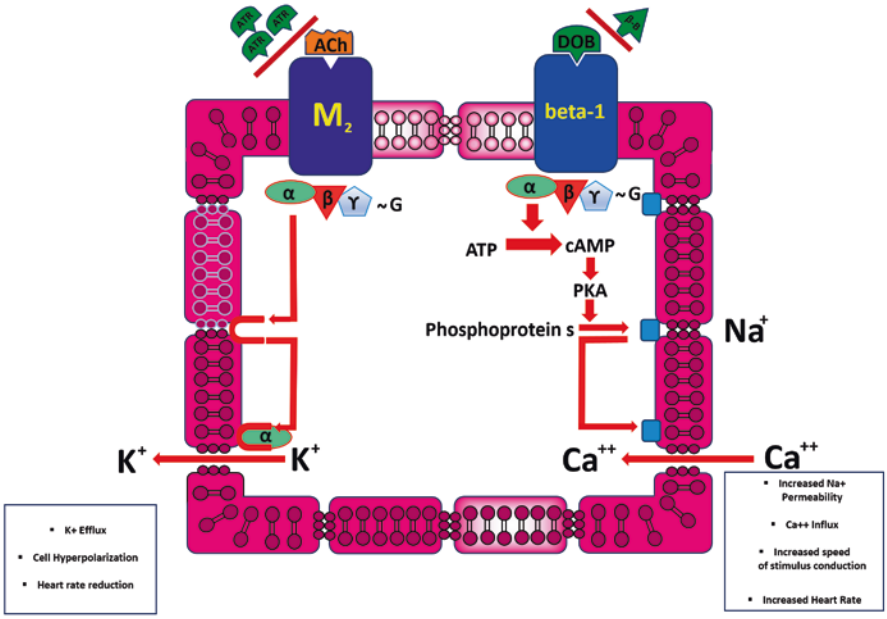

Fig. 18.1 The main cardiovascular receptor targets and physiologic effects of dobutamine, beta-blockers, atropine, and acetylcholine in the cardiac cell

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 with relatively weak beta-2 and alpha-1 activity [11] (Fig. 18.2).

Its mechanism consists, through beta-1 action, of primarily increasing the force of contraction and secondarily the heart rate and blood pressure, having as a final product the increase in cardiac output and the increase in myocardial oxygen consumption (Fig. 18.3). Heart rate increases twofold, and myocardial contractility increases two- to threefold at the peak versus baseline [12].

The dobutamine dose usually employed for SE testing causes a two- to threefold increase in coronary blood flow [13]. The extent of the increase in myocardial oxygen demand is similar to exercise, and in this sense, it has been called an "exercise-simulating agent," but in many ways, it differs from exercise. During exercise, stroke volume increases also through a Frank-Starling mechanism with an increase in end-diastolic volume at intermediate stages of stress, while the end-diastolic volume decreases with dobutamine with more marked hyperkinesis [14]. Dobutamine is different from exercise stress also for other important aspects since the response to antiischemic therapy does not parallel the response to exercise [15]. For applications beyond coronary artery disease, the pattern of changes in pulmonary

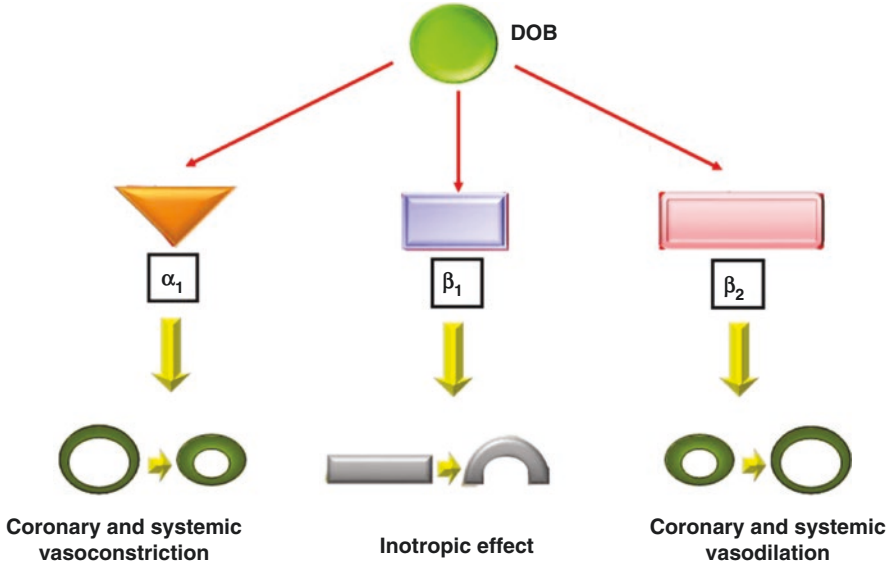

Fig. 18.2 The main cardiovascular physiologic effects of dobutamine

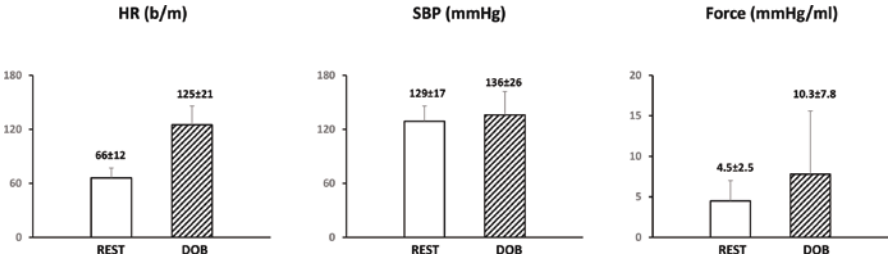

Fig. 18.3 Major determinants of myocardial oxygen consumption in resting conditions (*left*) and during peak dobutamine stress (*right*). The relative contributions of heart rate, systolic blood pressure, and force (an index of the inotropic state) are represented. During dobutamine, there is a marked increase in heart rate and inotropic state. The increase in systolic pressure is milder in populations under beta-blockers. (Redrawn and modified from Ciampi et al. [12])

hemodynamics, venous return, mitral regurgitation, and intraventricular obstruction induction is completely different from exercise and limits the applications of dobutamine stress beyond coronary artery disease.

Alpha-adrenergic activity can mediate systemic vasoconstriction, an increase in blood pressure, and increased coronary 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 enhanced alpha-adrenergic tone contribute to the loss of dobutamine-induced vasodilation in coronary atherosclerosis [16]. The effect of normally increased coronary

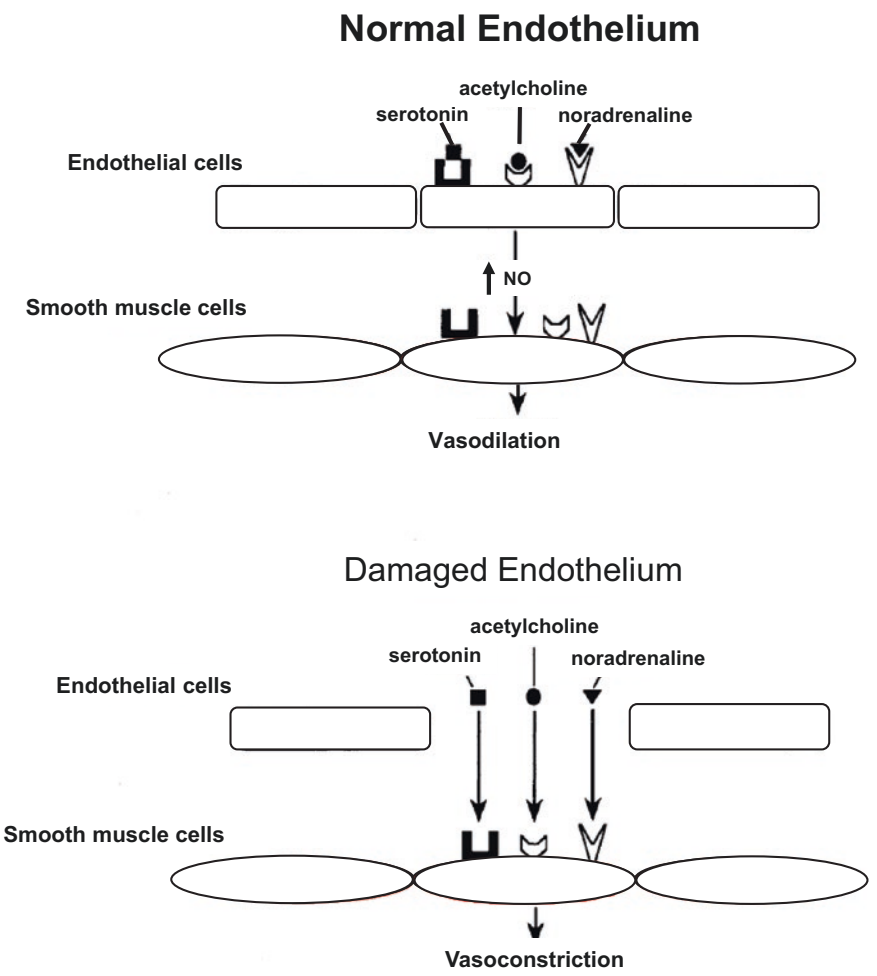

Fig. 18.4 *Top*: endothelial and smooth muscle cells in coronary vessels in the presence of intact endothelium. Mediators such as serotonin, acetylcholine, noradrenaline or exogenous dobutamine acting on noradrenaline receptors stimulate the corresponding receptors present on the endothelial surface, which induce smooth muscle cell relaxation and vasodilation via nitric oxide release. *Bottom*: when the endothelium is damaged, the same mediators act directly on the corresponding receptors present on the smooth muscle membrane, causing vasoconstriction

flow in normal vessels can become paradoxical coronary vasoconstriction in coronary vessels with abnormal, damaged endothelium (Fig. 18.4).

Dobutamine is an adrenergic agonist traditionally used in the intensive care unit for the treatment of decompensated heart failure. The onset of action of dobutamine is 1–2 min and the plasma half-life is approximately 2 min. Dobutamine is metabolized hepatically and in peripheral tissues, but there is no set dose reduction for those patients with hepatic or renal dysfunction. The short half-life of dobutamine

allows rapid resolution of its effects once the intravenous infusion is discontinued. However, the alpha-mediated coronary constrictive and platelet-aggregating effects are not reversed and may be potentiated by a beta-blocker. These undesired effects peak at 30–45 min after the end of dobutamine infusion, and therefore the patient must remain in the waiting room for at least half an hour after the test, even if the result was negative.

Dobutamine provokes ischemia mainly through the inotropic and chronotropic response to stimulation of myocardial beta-1 receptors determining temporarily an increase in myocardial oxygen demand.

Other mechanisms are the flow maldistribution mediated by beta-2 receptors of coronary arterioles and coronary vasospasm mediated by alpha-adrenoreceptors present on smooth muscle cells of epicardial arteries [16] (Fig. 18.5).

Tests inducing vasospasm (ergonovine infusion and hyperventilation) explore the functional component. Tests trying to unmask coronary stenosis (exercise, dipyridamole, adenosine, dobutamine, pacing) mostly explore the coronary reserve due to fixed, organic stenosis (Fig. 18.6). Some of these stressors (such as exercise or dobutamine) may also induce variations in coronary tone which can be superimposed on the organic factors, thus blurring the correlation between coronary anatomy and test positivity.

On top of dobutamine, atropine is usually given in refracted doses up to a cumulative dose of 1 mg, sometimes 2 mg. Atropine is a naturally occurring antimuscarinic drug consisting of an alkaloid of the belladonna plants. During the time of the Roman Empire, the plant was frequently used to produce poison. This prompted Linnaeus to name the shrub *Atropa belladonna*, after Atrops, the eldest of the Three Fates, who cuts the thread of life. The name belladonna (i.e., "beautiful woman") derives from the alleged use of this preparation by Italian women to dilate their

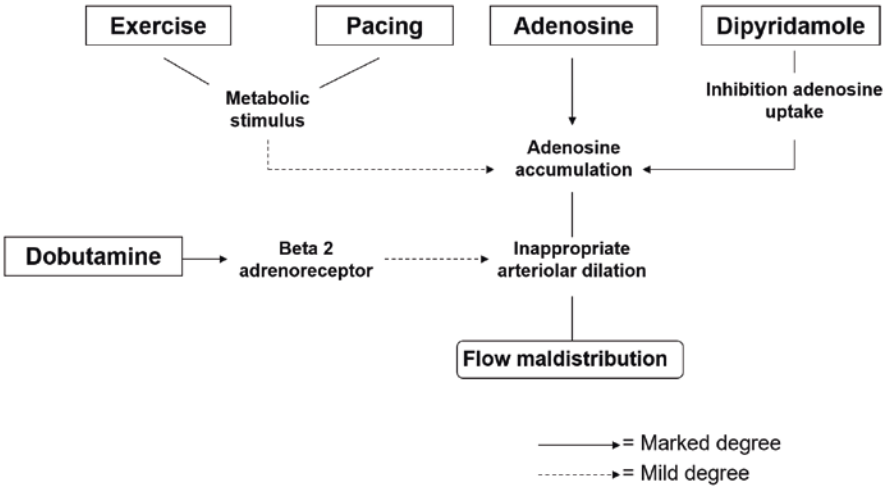

Fig. 18.5 The biochemical pathways leading to inappropriate arteriolar vasodilation under different stresses

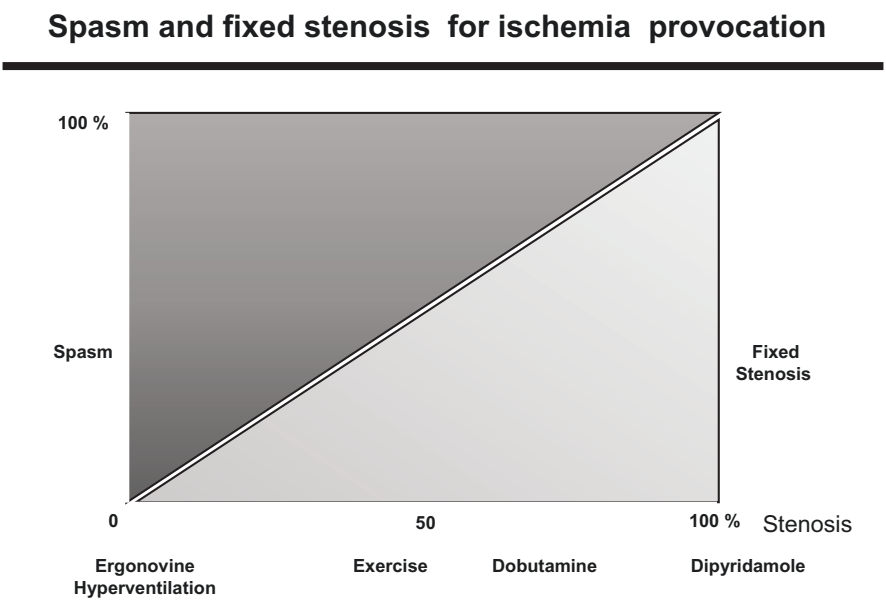

Fig. 18.6 Conceptual allocation of the tests employed in combination with echocardiography to induce ischemia via coronary vasospasm (*left*), coronary stenosis (*right*), or both mechanisms

pupils [17]. Atropine is the prototype of antimuscarinic drugs, which inhibit the actions of acetylcholine on anatomical effectors innervated by postganglionic cholinergic nerves. The main effect of atropine on the heart is to induce tachycardia by blocking vagal effects on the M2 receptors in the sinoatrial nodal pacemaker. Atropine also enhances atrioventricular conduction. Atropine-induced mydriasis may occasionally raise intraocular pressure in patients with glaucoma, which is, therefore, a contraindication to atropine administration. Atropine also decreases the normal amplitude of bladder contraction, and severe prostatic disease is thus another contraindication to atropine administration. Not surprisingly, however, the risk of resistant ischemia increases with atropine, along with nonischemic side effects. Nonischemic side effects described after DSE with atropine coadministration include atropine intoxication, consisting of restlessness, irritability, disorientation, hallucinations, or delirium, usually disappearing spontaneously over a few hours.

18.3 Methodology, Protocol, and Performance of DSE

A graded dobutamine infusion is given typically at a starting dose of 5 μg/kg/min. The goal of the dobutamine infusion is to achieve a heart rate of 85% of the maximal predicted heart rate for the patient's age. Accordingly, the dobutamine dose is increased every 3–5 min (usually 3 min) to doses of 10, 20, 30, and finally to 40 μg/kg/min.

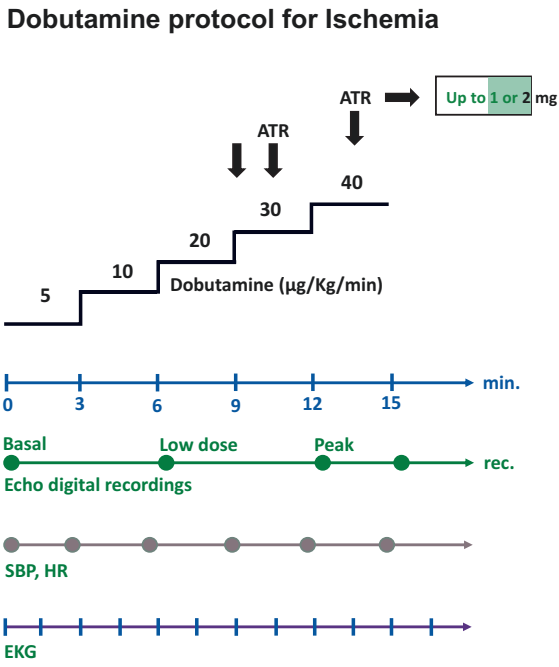

Fig. 18.7 The standard dobutamine-atropine protocol for detection of coronary artery disease and induction of ischemia

Figure 18.7 shows the most used protocol in patients with known or suspected coronary artery disease. It has been endorsed as the state-of-the-art protocol by both the European [18] and American [19] recommendations. Lower doses are associated with insufficient sensitivity, while higher doses are associated with a high rate of side effects [20].

In the standard protocol, the addition of atropine demonstrated great value at the end of this protocol, but if administered early in the test is faster, with a decrease in the number of inconclusive tests with a similar rate of adverse effects [21–23].

In DSE, the images can be obtained in the parasternal (or apical) long axis, parasternal short axis (mid ventricle), and apical four- and two-chamber views. During a DSE, images of the left ventricle from each projection are obtained during rest, low-dose dobutamine, peak-dose dobutamine, and poststress (at the same plane and the same depth). When the heart rate is lower than 100 beats or close to baseline levels, the acquisition of images corresponding to the recovery phase is suitable. In addition, metoprolol or short-acting esmolol can be used to antagonize the effects of dobutamine. Esmolol is administered 500 µg/kg IV followed by 250 µg/kg every 5 min until symptoms are relieved, or to a maximum of 1000 µg/kg. Another possibility is to administer metoprolol 5 mg intravenous push over 2 min and repeat every 5 min up to a total of three doses.

For viability assessment, the protocol is a little different by searching for the "biphasic response" where a myocardial territory with resting severe hypokinesia or akinesia augments its contraction at a low dose but later becomes hypokinetic or

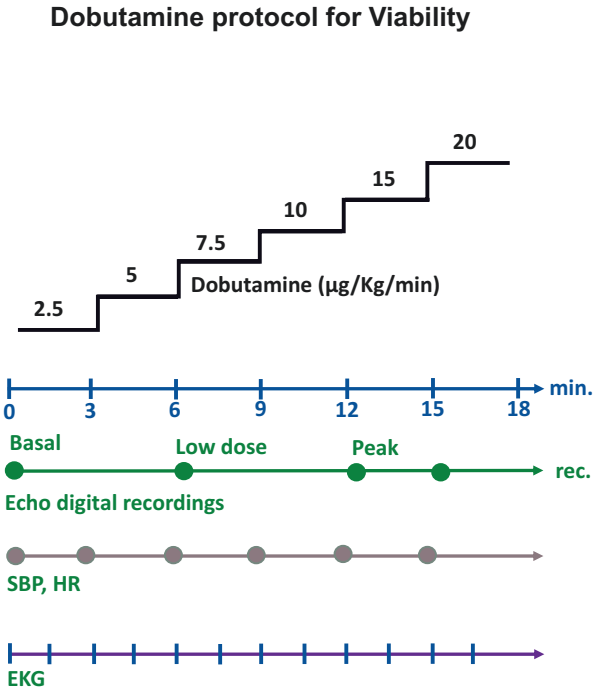

Fig. 18.8 The dobutamine protocol for myocardial viability analysis

akinetic at higher dobutamine doses. Steps of 5 min can be used starting from 5 up to 20 μg [20]. The worsening phase of the biphasic response usually occurs with doses ≥20 μg/kg/min (Fig. 18.8) [20]. If the aim is viability and ischemia assessment, after 20 μg/kg/min without myocardial ischemia demonstrated, the protocols can continue with the ischemia protocol up to 40 μg/kg/min plus atropine [20].

As DSE depends on reaching the endpoint of 85% of the maximum heart rate for the age when the dobutamine-atropine protocol manages to reach this endpoint, the test becomes diagnostic and can be stopped. With beta-blockers, a fast and significant increase in blood pressure can occur.

DSE is also influenced by therapy with calcium channel blockers and nitrates, although to a lesser extent than with beta-blockers [19]. Because of this, the beta-blocker therapy needs to be suspended at least 24 h before the exam, and ideally 3–4 days before the test, if the sensitivity of the test is the main diagnostic goal. This is not always feasible, practical, or safe in real-life conditions.

DSE response is affected by antiischemic drugs such as beta-blockers, calcium channel blockers, and nitrates in a matter different from exercise, and beta-blockers cause a rightward shift in the dose-response curve to dobutamine which cannot help to predict the response of exercise to the same drugs [7, 15].

For application beyond coronary artery disease, no atropine is recommended. In patients who are receiving beta-blocker therapy in the ischemia investigation, high doses (up to 40 μg/kg/min), with atropine, are often required [20]. For the specific application in patients with low-dose, low-gradient aortic stenosis and reduced ejection fraction, a lower dose (until 20 μg/kg/min) is recommended for safety reasons [20].

Patients need to be fasting for 4 h before the test. In all cases, the patients need to sign the informed consent. The endpoints of the DSE protocol include achievement of the target heart rate (at least 85% of maximum predicted heart rate for age, 220-age), detection of moderate wall motion abnormalities in at least two segments, symptomatic or sustained arrhythmias, hypotension, or severe hypertension (systolic pressure ≥220–240 mmHg or diastolic pressure ≥120 mmHg), or if a patient develops intolerable symptoms.

18.4 Myocardial Response and Testing Interpretation

The responses resulting from DSE may be: normal (contractile improvement with dobutamine), ischemic (contractile worsening during stress echocardiogram), viable sustained (a segment with resting akinesia or marked hypokinesia showing a gradual functional improvement with a low and high dose of dobutamine), viable biphasic (improvement at a low dose and worsening at the high dose of dobutamine), and fibrosis or scarring (akinesia or dyskinesia with no improvement in regional function during DSE) [20] (Fig. 18.9). Resting akinesia that becomes dyskinesia during stress should not be considered true active ischemia. It reflects a purely passive mechanical phenomenon, due to increased intraventricular pressure developed by normally contracting walls.

The normal response pattern is a marked increase in regional and global left ventricular function with a marked increase in heart rate and reduction of left ventricular end-systolic volume during stress. The entity of contractile and chronotropic response is comparable to exercise (Fig. 18.10).

The abnormal response pattern is a regional wall motion abnormality, often with preserved global left ventricular function (Fig. 18.11).

The typical SE report should comment both on global left ventricular function and regional function [19, 20]. Ischemia at DSE is based on decreased wall thickening in two or more contiguous segments (Fig. 18.12).

Contrast enhancement should be considered to augment endocardial definition when two or more left ventricle segments cannot be visualized in apical view at rest. This occurs in approximately 10% of stress echocardiograms [19, 20].

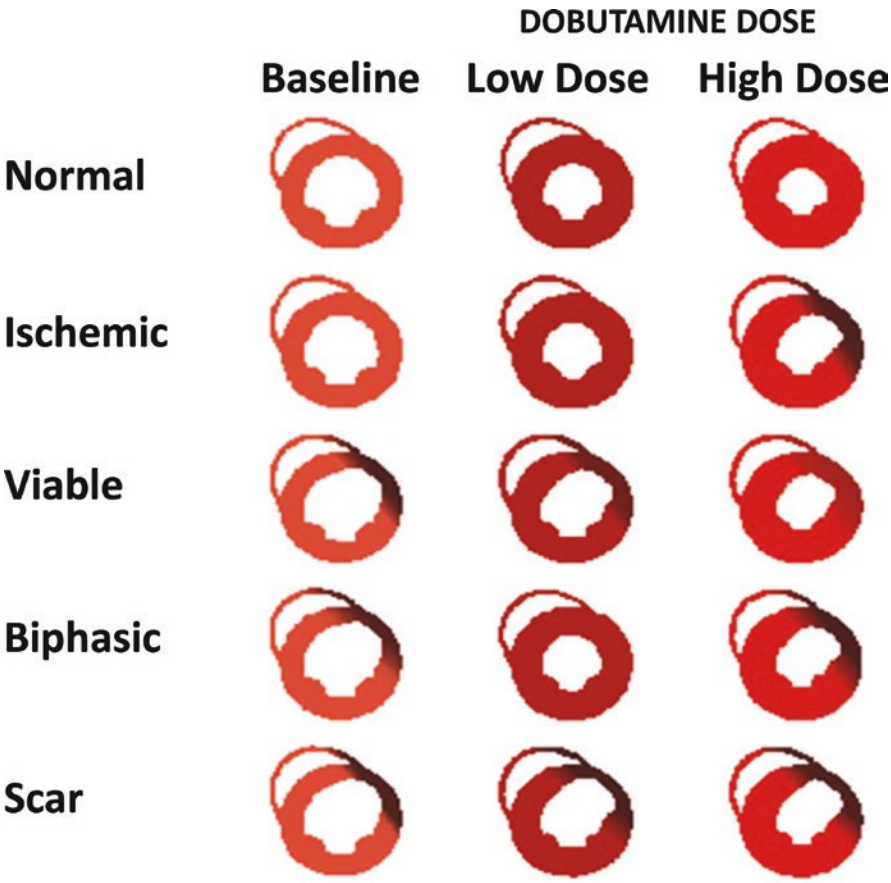

Fig. 18.9 Myocardial responses induced by dobutamine stress echocardiogram

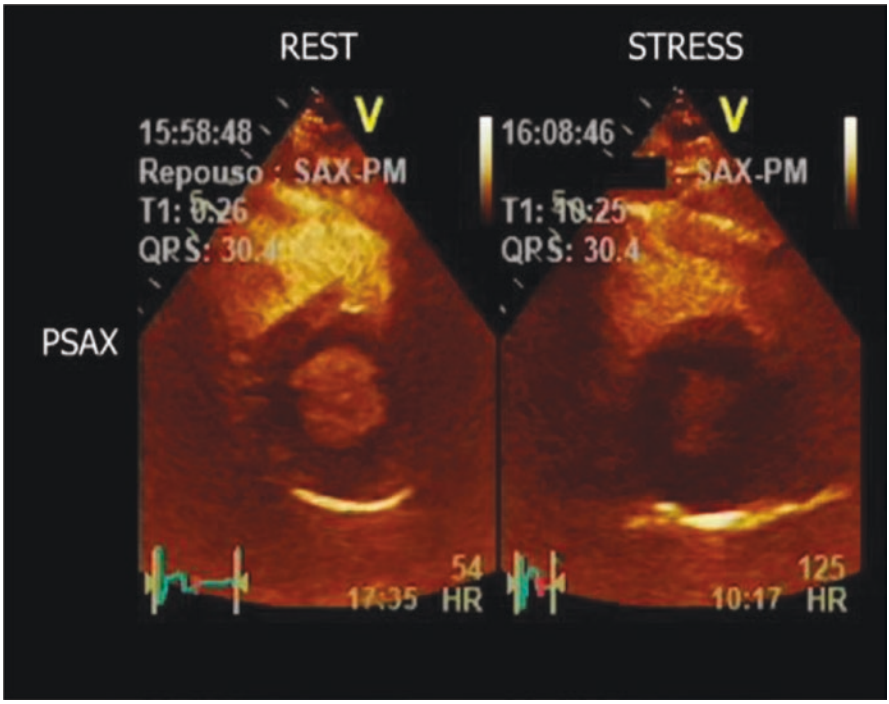

Fig. 18.10 Parasternal short-axis view at the mid-ventricular level showing a normal DSE response, with regional and global hyperkinesis and reduction of left ventricular end-systolic volume during stress, with the normal increase in heart rate. See accompanying Video 18.1 with more projections: apical four-chamber, apical two-chamber, parasternal long-axis, and short-axis. (Video images courtesy of Dr. José Luis Pretto, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

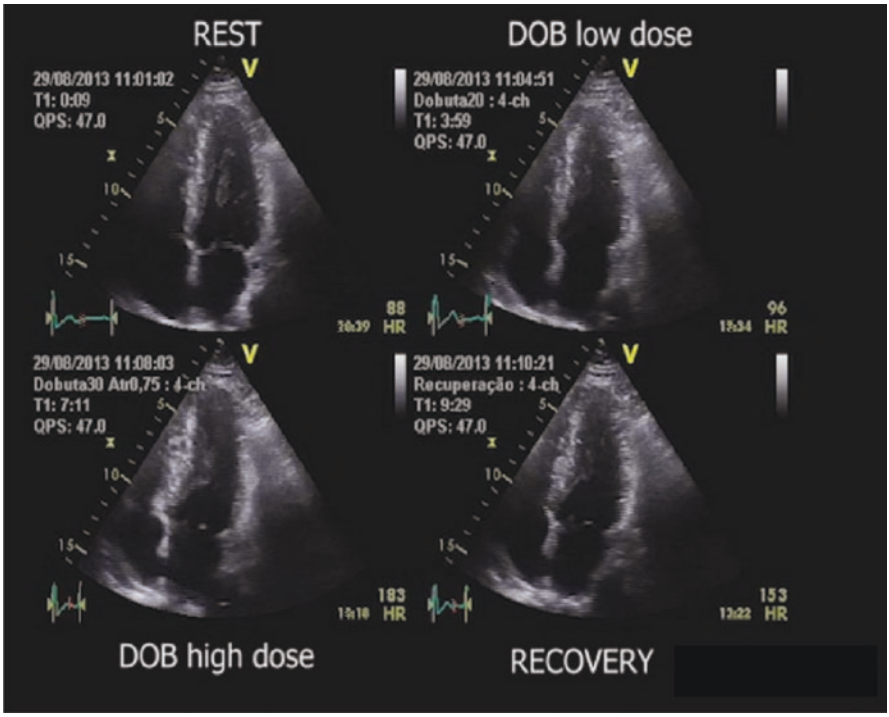

Fig. 18.11 Apical four-chamber view showing a normal regional and global wall motion at rest (left upper panel) with a normal hyperkinetic response after the intermediate dose (right upper panel), and abnormal apical akinesia at peak stress (left lower panel). There is full recovery after discontinuation of dobutamine infusion and beta-blocker administration (right lower panel). See corresponding Video 18.2. (By courtesy of Dr. José Luis Pretto, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

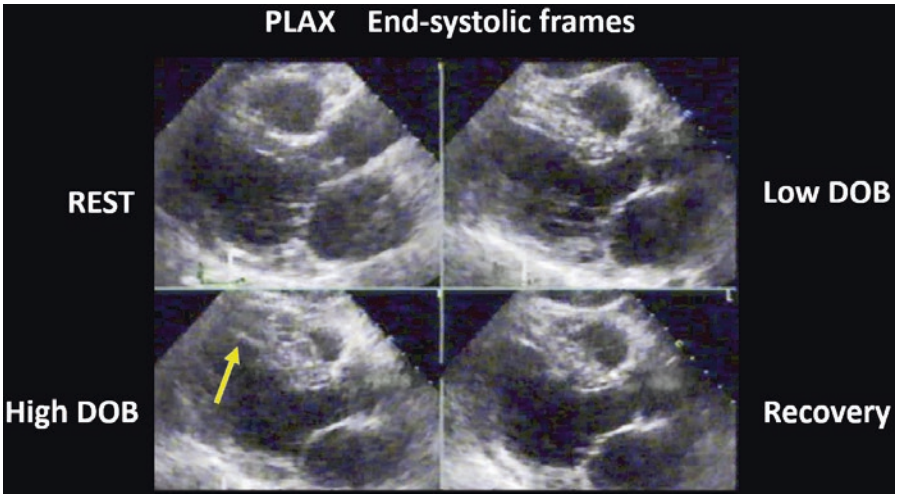

Fig. 18.12 Parasternal long-axis view showing an abnormal regional wall motion in the inferolateral wall at rest (left upper panel), with akinesia in the anterior septal wall at peak stress (left lower panel). See the corresponding Video 18.3, with the parasternal long- and short-axis view, apical four-chamber, and two-chamber views. (By courtesy of Dr. Ana Cristina Camarozano, Curitiba, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

18.5 Feasibility and Safety

Centers that perform a high volume of DSE procedures have the highest diagnostic yield and the lowest rate of complications [20]. Minor but limiting side effects preclude the achievement of maximal pharmacological stress in about 10% of patients [19, 20]. These side effects are complex ventricular tachyarrhythmias (frequent, polymorphic, premature ventricular beats, couplets, triplets, nonsustained ventricular tachycardia); nausea and/or headache; hypotension (>30 mmHg drop in blood pressure) and/or bradycardia; supraventricular tachyarrhythmias; and hypertension. Limiting side effects are more often asymptomatic with dobutamine, and more often symptomatic with dipyridamole [19]. Side effects usually disappear upon interruption of drug infusion, due to the short half-life. When symptoms or ischemia persist, intravenous beta-blockers are given, unless coronary vasospasm is suspected.

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 single-center experiences [24–30] and multicenter registries [31–34], major side effects occur in 1 of 300–350 cases (Table 18.2).

Tachyarrhythmias are the most frequent complication occurring during DSE. In some cases, they are associated with an ischemic regional wall motion abnormality. The mechanism of their onset can be attributed to the direct adrenergic

Table 18.2 Life-threatening complications in early single-center large experience (>1000 patients), and multicenter registries for DSE

Author, year	Patients	Complications(s)
Single institution experience		
Mertes et al., 1993 [24]	1118	None
Poldermans et al., 1994 [25]	1000	1 AMI, 4 VT, 1 prolonged ischemia
Zahn et al., 1996 [26]	1000	2 VF, 1 seizure
Seknus et al., 1997 [27]	3011	5 VT, 1 AMI, 1 prolonged ischemia, 1 hypotension
Bremer et al., 1998 [28]	1035	1 VF, 1 VT
Mathias et al., 1999 [29]	4033	1 VF 8 VT, 1 MI; 5 atropine intoxication
Kane, 2008 [30]	6755	6 major complications (0.09%)
Multicenter registry		
Picano et al. (EDIC), 1994 [31]	2949	2 VF, 2 VT, 2 AMI,
Pezzano (RITED), 1994 [32]	3041	2 VF, 1 asystole
Beckmann, 1999 [33]	9354	324 (2 VF)
Varga, 2006 [34]	35,103	63 (5 deaths)

AMI acute myocardial infarction, *VT* ventricular tachyarrhythmia, *VF* ventricular fibrillation, *MI* myocardial infarction

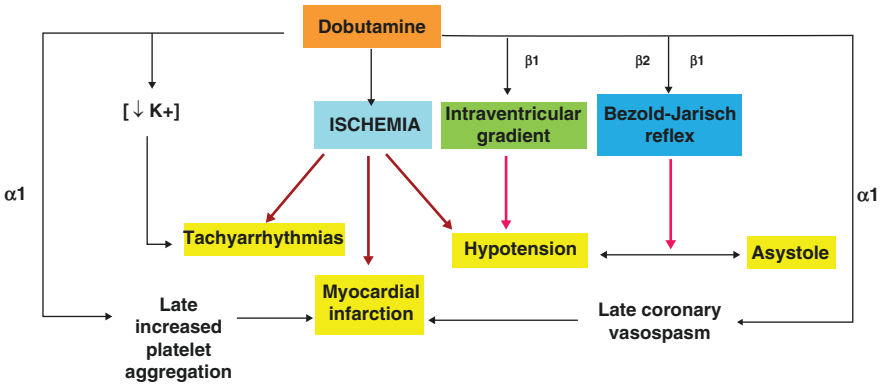

Fig. 18.13 The main myocardial, coronary, and hemodynamic effects of dobutamine. Complications may occur through ischemia-dependent and ischemia-independent pathways

arrhythmogenic effect of dobutamine, through myocardial β-receptor stimulation, which is particularly evident in patients with ischemic heart disease. However, in some cases, they are independent of ischemia and can also develop at low dobutamine doses. 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 [35, 36].

Side effects and complications can occur via ischemia-dependent and ischemia-independent pathways (Fig. 18.13). Ventricular and atrial tachyarrhythmias are more frequent when baseline (pretest) levels of potassium are low. The occurrence of atrial fibrillation during dobutamine stress is about 1%, especially in elderly patients (4% in those >80 years and those with a previous history of paroxysmal

atrial fibrillation) [37]. Significant hypotension is another adverse reaction during DSE. In some cases, this finding has been attributed to dynamic intraventricular obstruction provoked by the inotropic action of dobutamine [38], especially in hypertrophic hearts. Beta-blockers can reverse this situation. A vasodepressor reflex triggered by left ventricular mechanoreceptor stimulation (Bezold–Jarisch reflex) due to excessive inotropic stimulation may be an alternative mechanism for hypotension [39].

In very rare situations, dobutamine can induce increased delayed coronary occlusion through coronary vasospasm and platelet aggregation, possibly provoking prolonged myocardial ischemia, and acute myocardial infarction on the anatomic substrate of a vulnerable, possibly noncritical, plaque unable to induce ischemia during the stress [40]. In these cases, the patient is admitted to the intensive care unit.

Due to anticholinergic properties, the atropine may cause urinary retention, increased intraocular pressure, delirium (in high doses), dry mouth, weakness, and constipation [41].

However, in the universe of exams with appropriate indications that are performed with dobutamine, the benefits largely outweigh the risks, the number of major complications are acceptable, and often occur when the exam is performed under unfavorable conditions (such as in the first days after myocardial infarction, patient with the arrhythmogenic substrate or little experience of the examiner who does not identify ischemia initially).

In the general context, DSE is a safe and well-tolerated method, even when applied to the elderly, patients with left ventricular dysfunction, or more aggressive protocols.

18.6 Diagnostic Results for Detection of Coronary Artery Disease

The accuracy in detecting angiography-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 [42]. The diagnostic accuracy is similar to other forms of stress testing, such as exercise echocardiography, high-dose dipyridamole echocardiography, or stress scintigraphy [43]. In particular, the diagnostic accuracy, sensitivity, and specificity are identical to dipyridamole SE when state-of-the-art protocols are used for both stresses [44–48] as shown by meta-analyses including five studies on 435 patients (Fig. 18.14) [49].

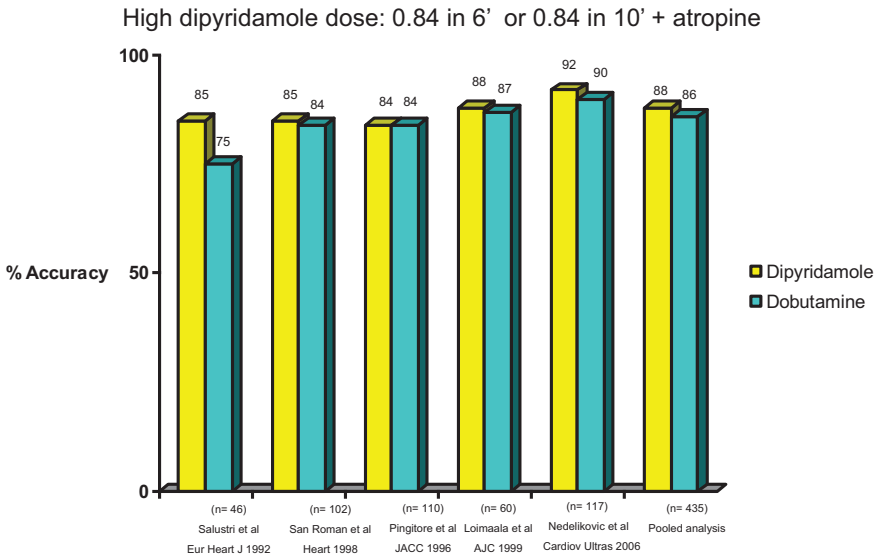

Fig. 18.14 The diagnostic accuracy of dobutamine echocardiography versus dipyridamole echocardiography for the detection of angiographically assessed coronary artery disease. (Redrawn from the meta-analysis of Picano et al. [49])

18.7 Dobutamine as a Test of Coronary Vasospasm by Serendipity

Coronary vasospasm can be elicited by dobutamine stress through stimulation of alpha-1 adrenergic receptors [50, 51]. This effect can occur during dobutamine infusion or when beta-blockers are administered at the end of testing since beta-blockers remove possible beta-2 receptors coronary vasodilation and leave vasoconstrictive alpha tone unopposed. Although dobutamine testing is targeted at the diagnosis of coronary artery disease, the unmasking of a coronary vasospastic mechanism by serendipity is not infrequent and should be recognized for its important clinical implications.

Coronary vasospasm may contribute to increasing the sensitivity of dobutamine (when the increase of coronary tone is superimposed on significant coronary artery stenosis) and is also a frequent cause of false positivity, due to true ischemia induced by coronary vasospasm. Dobutamine-induced coronary vasospasm can go unrecognized and progress to myocardial infarction when treated with beta-blockers. It is also possible that true ischemia is induced by coronary vasospasm with a direct action on small coronary vessels, with patent epicardial coronary arteries and a reversible Takotsubo-like effect with regional (most frequently apical) wall motion abnormality in absence of epicardial artery stenosis [52–54]. In this case, the likely cause is a severe diffuse coronary vasospasm in vessels too small to be imaged by coronary angiography.

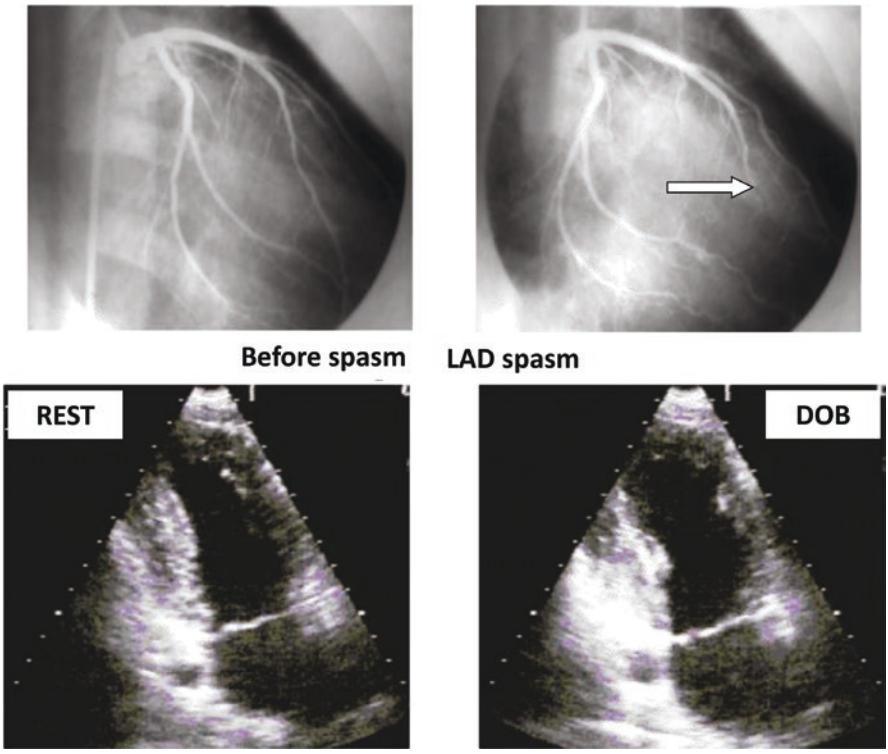

Fig. 18.15 Normal coronary angiogram (left upper panel) and spontaneous spasm of the left anterior descending coronary artery (indicated by arrow) during coronary angiography (right upper panel). In the lower panels, end-systolic frames from the apical two-chamber view showing normal thickening at rest (left lower panel) and akinesia of the anterior wall and inferior-apical segments during peak dobutamine dose. (Modified from Varga et al. [50])

Three positivity patterns are highly suggestive of coronary vasospasm. Coronary vasospasm can be elicited by dobutamine stress through stimulation of alpha-1-adrenergic receptors [55–66]. Consequently, DSE becomes positive during dobutamine for coronary vasospasm (Fig. 18.15).

This effect can occur during dobutamine infusion or when beta-blockers are administered at the end of testing since beta-blockers remove possible beta-2 receptors-mediated coronary vasodilation and leave vasoconstrictor alpha tone unopposed (Fig. 18.16).

Another possible vasospastic pattern is that a mildly positive test becomes markedly positive, with more extensive and severe ischemia after metoprolol administration (Fig. 18.17).

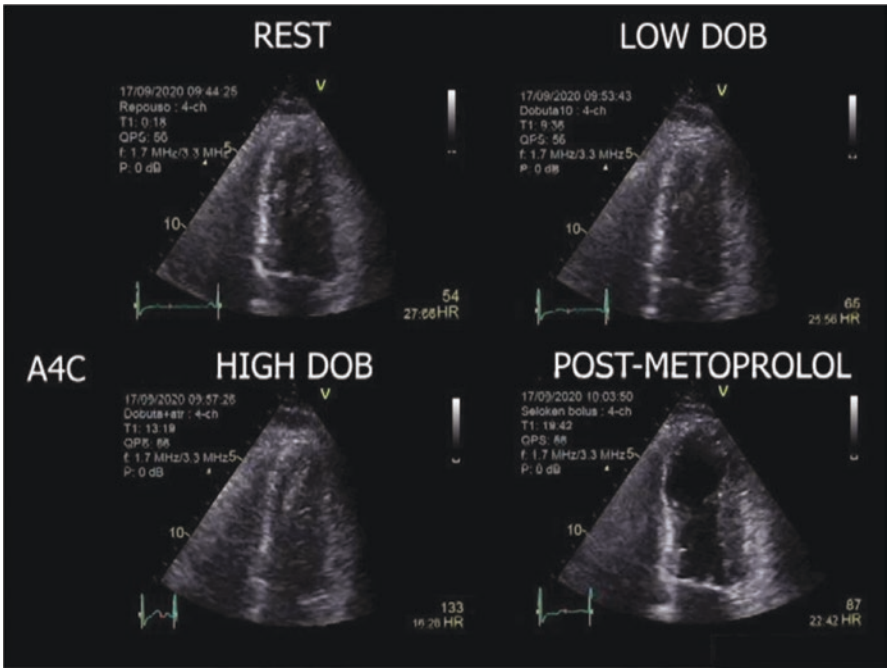

Fig. 18.16 Apical four-chamber view showing end-systolic frames with normal wall thickening at rest (left upper panel), intermediate dose (right upper panel), and peak dose (left lower panel), with reduced thickening of the mid-septal, septoapical, apical, and middle lateral segments after metoprolol, in presence of left ventricular end-systolic cavity dilation. Apical four-chamber view (A4C) is shown at end-systole. See corresponding Video 18.4, inclusive of apical four-chamber, two-chamber, and three-chamber views. (By courtesy of Dr. José Luis Pretto, Passo Fundo, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

In each of the three conditions, coronary artery stenosis can be either absent or present but is not responsible for the induction of ischemia. The dominant mechanism of epicardial artery vasospasm should be recognized to be effectively treated. Patient with ischemia is usually given beta-blockers. But if the cause of the worsening effect of beta-blockade is recognized, further beta-blockers should be put on hold, and i.v. nitrates should be given. If the vasospastic origin is not recognized, catastrophes may occur.

The recognition of coronary vasospasm is not a pathophysiological curiosity but has very practical implications. In all these cases, the vasospastic origin must also be incorporated into decision-making since chronic therapy with beta-blockers is contraindicated. In coronary vasospastic disorders superimposed on organic coronary stenosis, coronary revascularization gives unsatisfactory results.

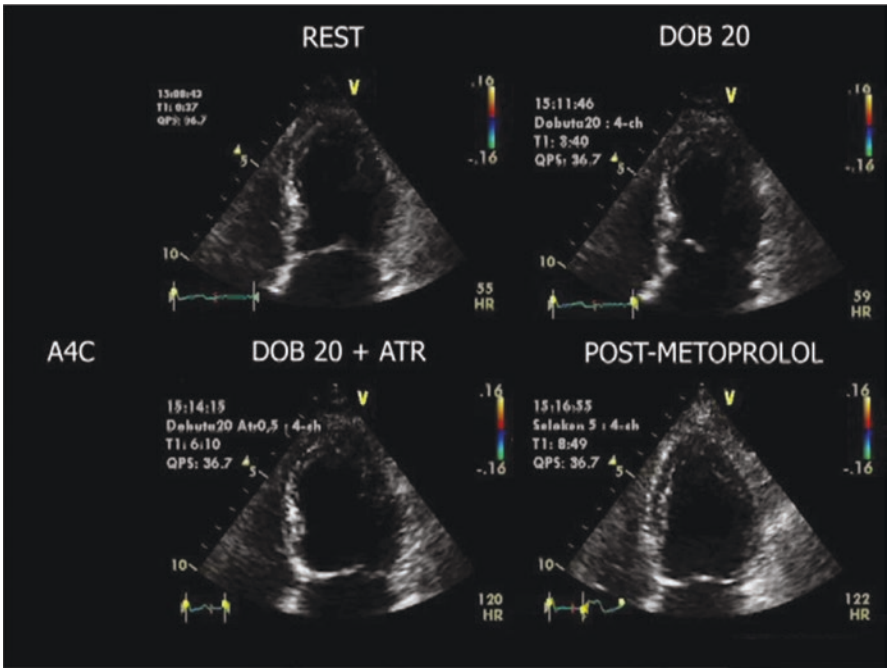

Fig. 18.17 End-systolic frames showing normal wall motion at rest in the apical four-chamber view (left upper panel). DSE is positive in the lateral and latero-apical segments during the dobutamine administration (right upper panel) and more positive after atropine (left lower panel) and beta-blocker (right lower panel) administration. See the corresponding Video 18.5. (By courtesy of Dr. Dimitrios Soulis, Athens, Greece. The video is available under the chapter's "Supplementary Material" on Springer Link)

18.8 Identification of Myocardial Viability

"Hibernating" myocardium refers to viable but under-perfused myocardial tissue that regains functionality after revascularization. Stunned myocardium is a normally perfused myocardium with a depressed function that regains functionality over time. Hibernating or stunned myocardium is viable and must be separated from necrotic myocardium, with a scar and irreversible damage, that will not improve and will not respond to any revascularization, electrical or medical therapy. At low-dose, dobutamine recognizes myocardial viability through the regional contractile reserve with high specificity and good sensitivity, with excellent diagnostic [55] and prognostic values. A contractile reserve is associated with a mild degree of myocardial damage and can predict functional recovery with higher specificity than other diagnostic markers of myocardial viability, such as thallium uptake by SPECT or fluorodeoxyglucose uptake by PET or myocardial scar at the delayed enhancement with cardiac magnetic resonance (Fig. 18.18).

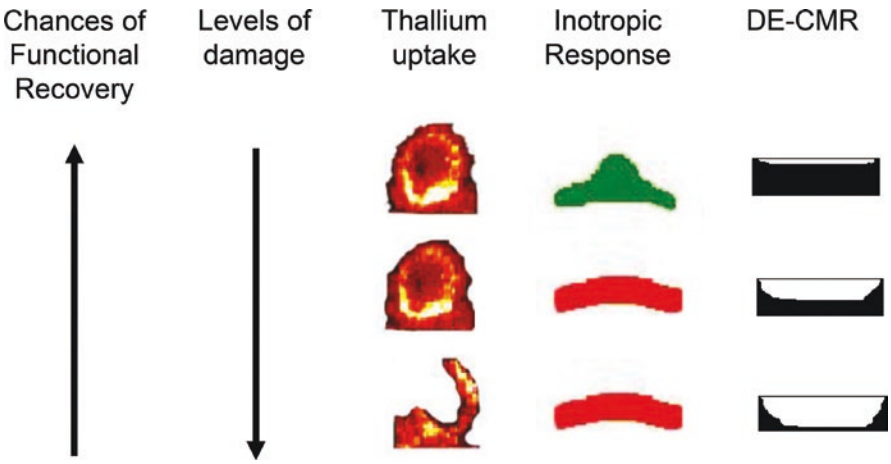

Fig. 18.18 The viability cascade. Higher cellular damage corresponds to a progressive loss of cellular function. Mild damage is associated with preserved inotropic response. Severe damage is expressed by loss of contractile response. *DE-CMR* delayed enhancement with cardiac magnetic resonance

There are three possible response patterns with dobutamine testing for myocardial viability.

In the viable response, an akinetic segment shows inotropic reserve and improves to hypokinesis or normokinesis. In the fixed response, an akinetic segment remains unchanged during stress and this response is indicative of a scar. In the biphasic response, an akinetic segment improves at the intermediate dose and worsens at the high dose. This response is indicative of viability and ischemia.

In patients with severe resting left ventricular dysfunction, a large amount of myocardial viability identified by low-dose DSE is associated with better survival in very different clinical settings, both in the presence and absence of underlying coronary artery disease. The better outcome associated with a contractile reserve with dobutamine has been observed in revascularized patients studied after chronic myocardial infarction (a model of hibernating myocardium) [56], medically treated patients studied early after acute myocardial infarction (a model of stunned myocardium) [57], with nonischemic dilated cardiomyopathy [58], and in patients treated with cardiac resynchronization therapy [59].

When compared to optimal medical therapy, viability is not related to better outcomes following either coronary artery bypass surgery or percutaneous coronary intervention, as shown by the large-scale, multicenter, randomized Surgical Treatment of Ischaemic Heart Failure (STICH) and REVIVED-BCIS2 trials [60, 61] . However, in patients with reduced resting ejection fraction, a significant (≥5 segments) left ventricular contractile reserve assessed with dobutamine stress identifies patients more likely to improve resting EF and to develop a favorable LV remodeling with end-systolic volume reduction at follow-up, with a lower rate of cardiovascular events.

18.9 Prognostic Value

In a meta-analysis of 36 studies including over 100,000 patients, a normal baseline and stress echocardiogram gives an annual risk for death of <1%, the same as for a normal stress myocardial perfusion scan [62]. The prognostic value of DSE is excellent and comparable to dipyridamole echocardiography in various patients' subsets, from chronic coronary syndromes [63, 64] to preoperative evaluation of patients before major vascular surgery [65, 66] and dilated cardiomyopathy [67].

However, as happened with all functional tests based on regional wall motion abnormalities or perfusion defects, the predictive value of a negative DSE declined in the last decades, probably due to the policy to study patients under antiischemic and plaque-stabilizing therapy and the proliferation of referral of patients with atypical symptoms [62]. Therefore, DSE was remodeled to capture the multiple prognostic vulnerabilities of the patient beyond coronary stenoses, such as the diastolic, contractile, coronary microcirculatory, and cardiac autonomic reserve [68]. The prognostic value of dobutamine is expanded with a comprehensive approach integrating regional wall motion abnormalities, B-lines, global left ventricular contractile reserve, coronary flow velocity reserve in the left anterior descending coronary artery, and heart rate reserve, each step adding a new variable with independent and incremental value over the others [10]. There is great potential to incorporate this protocol into routine practice.

18.10 Pitfalls and Specific Considerations

The limitations of DSE are related to feasibility, safety, technical difficulty of echocardiographic interpretation, sub-optimal possibility to combine coronary flow reserve and wall motion information, and inability to predict physiologic therapy-induced changes in exercise stress results. Minor but limiting side effects occur in 5–10% of tests, and submaximal results with nontarget heart rate have limited diagnostic, and prognostic, power [69].

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, and coronary flow velocity assessment less easy and feasible than with vasodilators [10, 70]. New technologies such as strain deformation imaging [71], real-time three-dimensional echocardiography [72], and artificial intelligence for regional wall motion assessment can be combined with DSE [73], but the reliability may be challenged by the high heart rate and image quality degradation.

Patients with a history of complex atrial arrhythmias (paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia) or complex ventricular arrhythmias (such as non-sustained ventricular tachycardia) or with moderate to severe

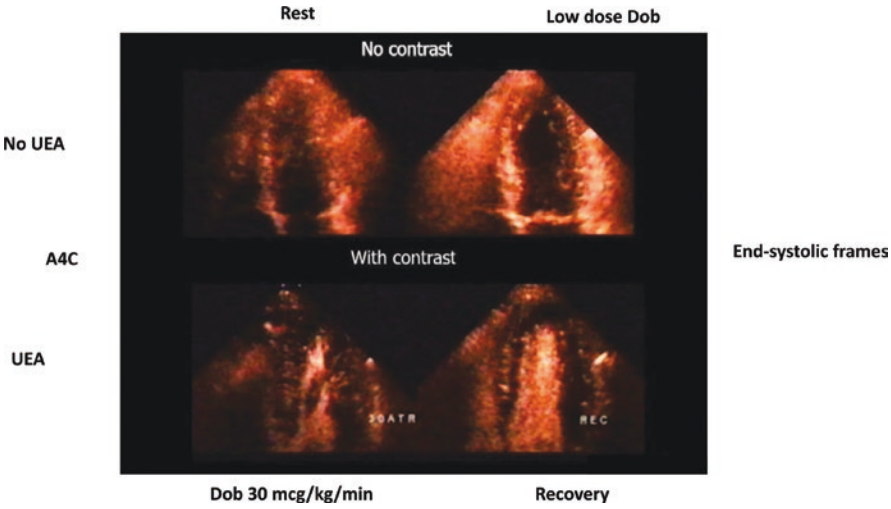

Fig. 18.19 Apical four-chamber at rest (left upper panel) and after low dose (right upper panel) without contrast, and at peak dose (left lower panel) and the recovery phase (right lower panel) following ultrasound-enhancing agents, with the improvement of image quality and endocardial border delineation in a negative test without wall motion abnormalities. See the corresponding Video 18.6. (By courtesy of Dr. Ana Cristina Camarozano, Curitiba, Brazil. The video is available under the chapter's "Supplementary Material" on Springer Link)

hypertension should probably not undergo dobutamine stress testing and be referred for safer vasodilator stress [19, 20].

The use of ultrasound-enhancing agents to analyze the endocardial border is able to improve the accuracy and reading reproducibility for regional wall motion and left ventricular volume measurements if two or more segments are not well visualized in the apical view (Fig. 18.19) [19, 20].

The proliferating anecdotal reports of catastrophes during DSE also contribute to assessing the safety of the test. Cardiac rupture [74–79], papillary muscle rupture [80], ventricular fibrillation [81–83] which may occur also 15 min after a negative test, refractory coronary vasospasm [84, 85], myocardial infarction [86, 87], cardiac asystole [88, 89], and acute Takotsubo syndrome [90] have all been described during dobutamine testing.

Ventricular arrhythmias can occur during dobutamine stress, and more frequently with the induction of myocardial ischemia. An example of torsade de point is shown in Fig. 18.20.

Ventricular fibrillation can occur also with low ("viability") doses, in patients with severe left ventricular dysfunction, when the search viability is indicated, and sometimes even low doses elicit an ischemic response. An example of ventricular fibrillation is shown in Fig. 18.21.

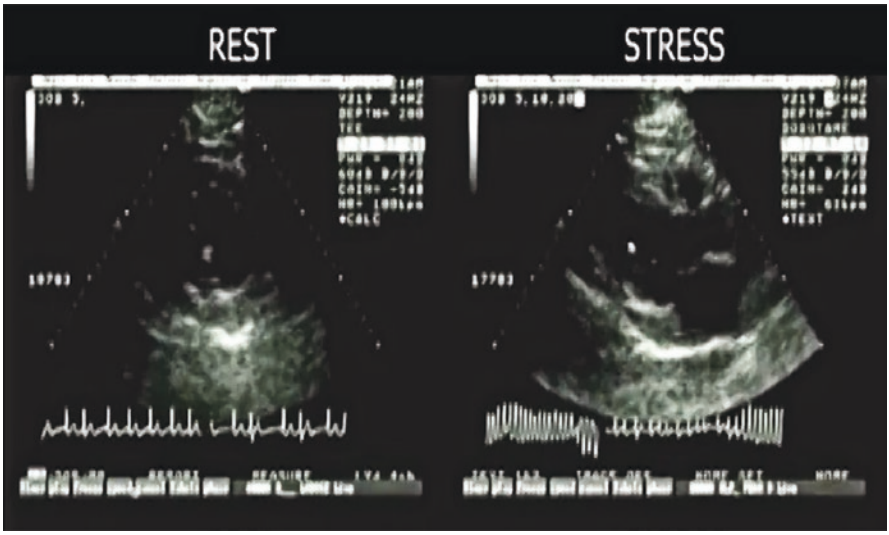

Fig. 18.20 Parasternal short axis (left, resting conditions) and long-axis (right, dobutamine 20 μg/kg/min) views of a patient with frequent ventricular ectopic beats suddenly evolving in torsade de point simultaneously with the development of septal akinesis. See the corresponding Video 18.7. (By courtesy of Dr. Rafael Payà, Valencia, Spain. The video is available under the chapter's "Supplementary Material" on Springer Link)

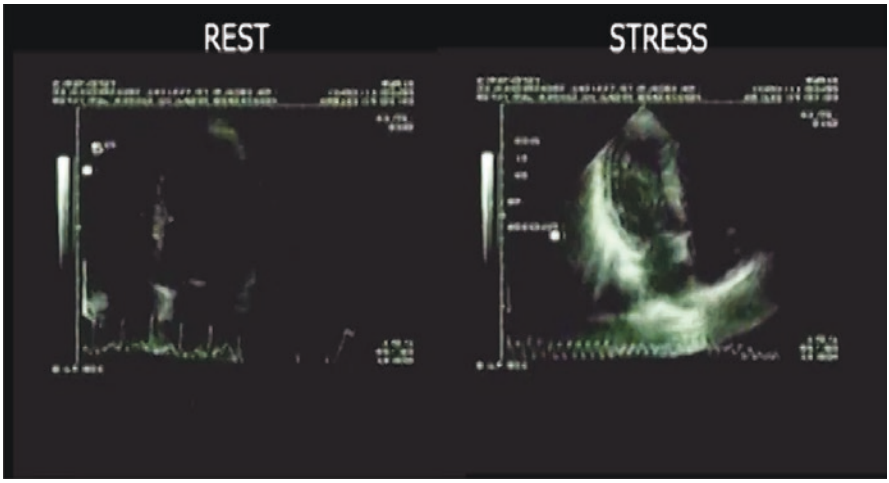

Fig. 18.21 Apical views at rest (left) and during stress (right, dobutamine 10 μg/kg/min) of a patient with global left ventricular dysfunction and tested for myocardial viability with low-dose dobutamine. The frame on the right captures the ventricular fibrillation in presence of left ventricular cavity dilation, spontaneous contrast in the left ventricular cavity, and comet-like B-lines departing from the pericardial line. See the corresponding Video 18.8. (By courtesy of Professor Albert Varga. Szeged, Hungary. The video is available under the chapter's "Supplementary Material" on Springer Link)

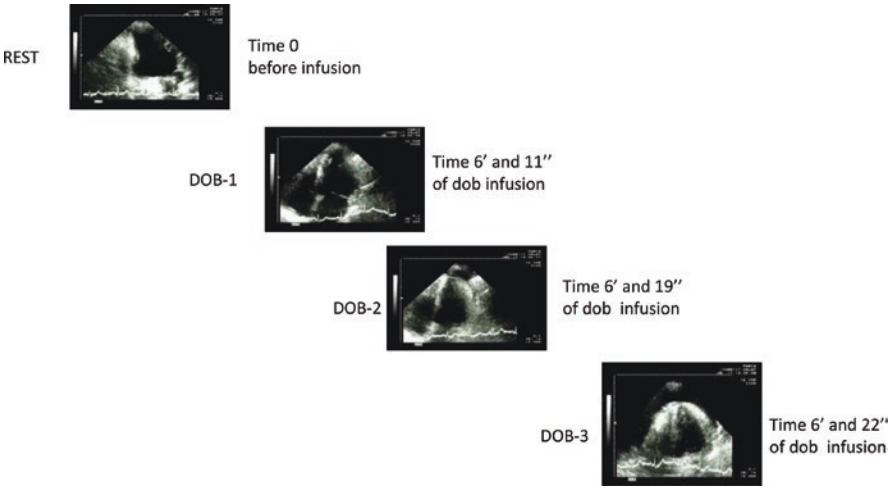

Fig. 18.22 Apical view at rest (left) and during stress (right, dobutamine 30 μg/kg/min) in a patient with recent (7 days) inferior myocardial infarction with wall thinning and dyskinesia of the inferobasal segment at rest. The frame on the right captures the rapidly developing pericardial effusion for cardiac wall rupture or fissuration. See the corresponding Video 18.9. (By courtesy of Dr. Barbara Reisenhofer, Pontedera, Italy. The video is available under the chapter's "Supplementary Material" on Springer Link)

The catastrophic event of cardiac rupture has been reported with dobutamine early after an acute myocardial infarction with thinned aneurysmatic inferobasal wall. An example of cardiac rupture is shown in Fig. 18.22.

Every stress test carries a risk, and probably dobutamine stress test is less safe than other forms of physical or pharmacological stresses, such as exercise, dipyridamole, or adenosine [91]. A tenfold rise in high-sensitivity troponin T suggestive of subclinical myocardial injury occurs in 13% of patients after negative high-dose dobutamine, especially when atropine is administered in elderly patients, and in 0% of patients after high-dose dipyridamole [92].

It is necessary to perform dobutamine stress, even at low doses, with a cardiologist attending and with personnel and facilities always ready for resuscitation. This is true for all forms of SE in all patients, and especially true for dobutamine stress even at low doses and particularly in patients with reduced global left ventricular function. A regional wall thinning in resting conditions increases the risk of rupture during testing. In all cases, recommended protocols should be followed, and careful monitoring by the physician with immediate access to resuscitation facilities is warranted. Finally, both the patient and the physician should be fully aware of the rate of complications during dobutamine infusion [93].

18.11 Contraindications

The contraindications of the exam help must be considered to minimize adverse effects [19]. In addition to usual contraindications to all forms of stress testing for clinical or hemodynamic instability, specific contraindications to dobutamine are severe arterial hypertension (>180 mmHg systolic blood pressure or 110 mmHg diastolic blood pressure), uncontrolled tachycardia (heart rate >110 bpm), and hypertrophic cardiomyopathy or significant left ventricular outflow obstruction (resting peak late gradient ≥30 mmHg).

Specific contraindications to atropine coadministration are known glaucoma and severe prostatic disease.

Caution is warranted in patients with recent inferior wall myocardial infarction, especially with wall thinning and resting dyskinesia, and in large aortic aneurysms at risk of rupture. Patients with severe left ventricular dysfunction should be studied with doses not exceeding 20 μg/kg/min. In patients with uncontrolled arterial hypertension, a history of atrial fibrillation, or significant ventricular arrhythmias, a safer vasodilator test may be considered. Formal contraindications to stress testing, dobutamine, and specifically atropine coadministration are listed in Table 18.3.

Table 18.3 Dobutamine and atropine main contraindications, and diagnostic criteria

	Contraindication to dobutamine	Contraindication to atropine	Premature termination	Diagnostic end point
Unstable coronary syndromes	x (all stresses)			
Uncontrolled cardiac arrhythmias	x (all stresses)			
Allergy/hypersensitivity to Dobutamine	x			
HR >110 b/m	x			
SBP >180 mmHg	x			
LVOTG >30 mmHg	x			
Untreated acute narrow-angle glaucoma		x		
Untreated severe urinary retention		x		
SBP <90 mmHg			v	
SBP >240 mmHg			v	
AV block ≥2			v	
PSVT, AF, VT			v	
Intolerable symptoms			v	
New RWMA (any dose)				v
HR >85% max predicted HR (any dose)				v
Maximal doses				v

AF atrial fibrillation, *HR* heart rate, *LVOTG* left ventricular outflow tract obstruction, *SBP* systolic blood pressure, *RWMA* regional wall motion abnormality, *VT* ventricular tachycardia, *PSVT* paroxysmal supraventricular tachycardia, *AV* atrioventricular

18.12 Guidelines and Recommendations

DSE based on the analysis of wall motion and thickening is recommended (class 1, must be considered) in general cardiology guidelines as an alternative to exercise for myocardial ischemia and prognosis of patients with chest pain or dyspnea [94, 95], or before high-risk surgery in patients with more than two clinical risk factors and poor functional capacity (<4 METs). It is also recommended as the test of choice for myocardial viability assessment in patients with severe or moderate left ventricular dysfunction [20]. Beyond coronary artery disease, DSE is recommended ("may be useful," class 2a) by the International Society of Heart and Lung Transplantation Guidelines for the detection of cardiac allograft vasculopathy in heart transplant recipients, since following denervation heart rate response is often inadequate with exercise [96, 97]. DSE is recommended by the American College of Cardiology/American Heart Association 2020 and European Society of Cardiology 2021 general cardiology guidelines in valvular heart disease in patients with suspected low-flow, low-gradient severe aortic stenosis with reduced ejection fraction for differentiating true-severe from pseudo-severe aortic stenosis, and in patients with mitral stenosis or valve prostheses with a mismatch between symptoms and resting echo findings who cannot exercise [98, 99]. Specialty recommendations also suggest its use in nonischemic dilated cardiomyopathy to assess the contractile reserve, a marker of response to medical therapy, and—in patients with indication based on clinical and electrocardiographic criteria—to cardiac resynchronization therapy [21]. The use of dobutamine is discouraged in hypertrophic cardiomyopathy due to the nonphysiological mechanism of induction of gradients, and nonpredictive of exercise-induced gradients (Table 18.4) [100].

Table 18.4 The most common DSE indications

	Appropriate	Uncertain	Inappropriate
Diagnosis of CAD in a patient unable to exercise	√		
Diagnosis of viability in ejection fraction <35%	√		
High-risk noncardiac surgery in an intermediate-risk patient	√		
Low-flow, low-gradient aortic stenosis for gradients and flow reserve	√		
Before cardiac resynchronization therapy for contractile reserve	√		
Dilated cardiomyopathy for contractile reserve	√		
Need to evaluate antianginal therapy efficacy		√	
Intermediate-risk noncardiac surgery in an intermediate-risk patient		√	
Evaluation of dynamic gradient in hypertrophic cardiomyopathy			√
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

With the last-generation comprehensive SE protocol, DSE can be performed with simultaneous assessment also of B-lines, contractile reserve, coronary flow reserve, and heart rate reserve to capture the many vulnerabilities of the patient beyond coronary artery stenosis. The large-scale validation of ABCDE DSE is ongoing in the prospective, international, multicenter SE 2030 study [101].

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