Exercise Echocardiography

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11.1 Historical Background

Many tests have been proposed in combination with echocardiography, but only a few have a role in clinical practice. For the diagnosis of organic coronary artery disease, exercise remains the paradigm of all stress tests and the first which was combined with stress echocardiography. In the early 1970s, *M*-mode recordings of the left ventricle were used in normal subjects [1] and in patients with coronary artery disease [2]. Subsequently, two-dimensional (2D) echocardiography was used to document ischemic regional wall motion abnormality during exercise [3]. The technique was at that time so challenging [4], that with the introduction of dipyridamole [5] and dobutamine [6] as pharmacological stressors many laboratories used pharmacological stress even in patients who were able to exercise. Large-scale, multicenter, effectiveness studies providing outcome data are in fact available only with pharmacological [7, 8] not with exercise echocardiography, offering a more robust evidence-based platform for their use in clinical practice. Exercise echocardiography was only really applied as a clinical tool in the early 1990s [4] and it is now increasingly used for the diagnosis of coronary artery disease, the functional assessment of intermediate stenosis, and risk stratification. A series of successive improvements led to a progressively widespread acceptance: digital echocardiographic techniques, allowing capture and synchronized display of the same view at different stages [9], improved endocardial border detection by harmonic imaging [10], and ultrasound contrast agents that opacify the left ventricle [11] (Fig. 11.1). In the USA, most laboratories use the posttreadmill approach with imaging at rest and as soon as possible during the recovery period [12, 13]. In Europe, a number of centers have implemented their stress echocardiography laboratory with a dedicated bed or table allowing bicycle exercise in a semisupine position and real-time continuous imaging throughout exercise [14, 15]. The diffusion of semisupine exercise

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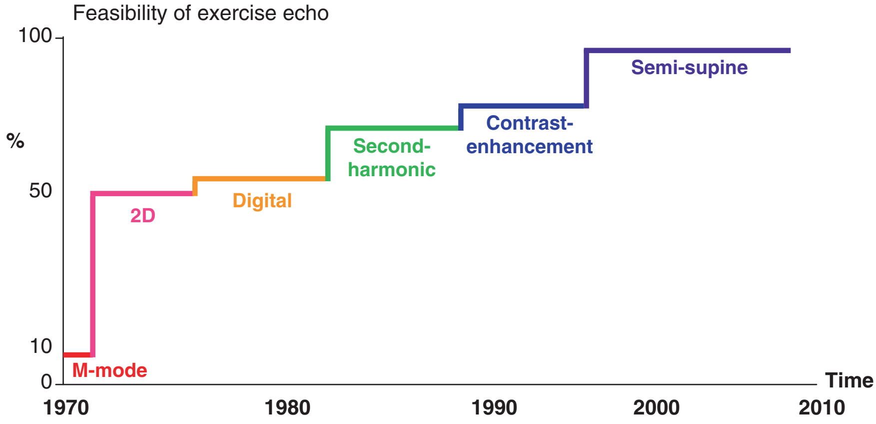

Fig. 11.1 The timeline of innovation in exercise echocardiography. The progressive increase in feasibility was linked to minor (digital acquisition) and major (2D, second-harmonic, contrast enhancement for border detection) technical improvements. Interestingly, the most important methodological improvement, i.e., the shift from posttreadmill to semisupine bicycle stress, is the most obvious, already clearly documented in the mid-1980s, and is still remarkably absent from US practice and the latest recommendations

imaging – much more user-friendly for the sonographer than the treadmill test – made image acquisition easier and interpretation faster [16–18]. Semisupine exercise gained its well-deserved role in the stress echocardiography laboratory for coronary artery disease diagnosis and, with growing frequency outside coronary artery disease, in the assessment of pulmonary hypertension, valve disease, cardiomyopathy, and heart failure [19, 20].

11.2 Pathophysiology

Exercise protocols are variable and include treadmill as well as upright and supine bicycle ergometry. All these forms of stress increase myocardial oxygen consumption and induce ischemia in the presence of a fixed reduction in coronary flow reserve [21] (Fig. 11.2). Of the determinants of myocardial oxygen demand, heart rate increases two- to threefold, contractility three- to fourfold, and systolic blood pressure by 50% (Fig. 11.2) [21]. End-diastolic volume initially increases to sustain the increase in stroke volume through the Frank–Starling mechanism, and later falls at high heart rates (Fig. 11.3). Coronary blood flow increases three- to fourfold in normal subjects, but the reduction in diastolic time (much greater than shortening in systolic time) limits mostly the perfusion in the subendocardial layer – whose perfusion is mainly diastolic, whereas the perfusion in the subepicardial layer is also systolic [22]. In the presence of a reduction in coronary flow reserve, the regional myocardial oxygen demand and supply mismatch determines myocardial ischemia and regional dysfunction. When exercise is terminated, myocardial oxygen demand gradually declines, although the time course of resolution of the wall

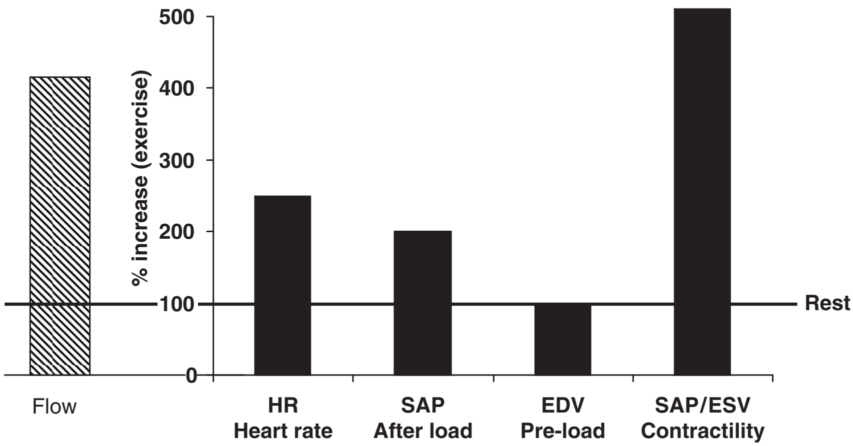

Fig. 11.2 The increase of main determinants of myocardial oxygen consumption in normal subjects referred for semi-supine exercise stress echo. Panel A: Heart rate (HR) increases two to threefold, the systolic arterial pressure (SAP) increases 1.5 to 2.5 fold, end-diastolic volume (EDV) 1.2 fold, and myocardial contractility (the most important determinant of myocardial oxygen consumption, measured as variation in elastance, i.e., the increase in end-systolic pressure divided for end-systolic volume) increases 4 to 8 fold versus baseline

motion abnormality is quite variable [23]. Some induced abnormalities may persist for several minutes, permitting their detection on postexercise imaging. However, wall motion usually recovers very rapidly, and postexercise imaging can easily miss wall motion abnormalities. Regional and global function, although closely linked, may behave differently during stress. For example, if a small wall motion abnormality develops as a result of limited ischemia, the remainder of the left ventricle may become hyperdynamic, and the ejection fraction will increase despite the presence of an ischemic wall motion abnormality. In such a case, a regional abnormality will be present in the absence of global dysfunction. Alternatively, severe exercise-induced hypertension in the absence of coronary artery disease may lead to an abnormal ejection fraction response without an associated wall motion abnormality. There are distinct advantages and disadvantages to exercise versus pharmacological stress, which are outlined in Table 11.1. The most important advantages of exercise are that it is a stress familiar to both patient and doctor; it adds echocardiography information on top of well-established and validated electrocardiographic and hemodynamic information, and it is probably the safest stress procedure. The disadvantages are the limited ability to perform physical exercise in many individuals, who are either generally deconditioned or physically impeded by neurologic or orthopedic limitations. In addition, stress echocardiography during physical exercise is certainly more technically demanding than pharmacologic stress because of its greater difficulty and tighter time pressure [23].

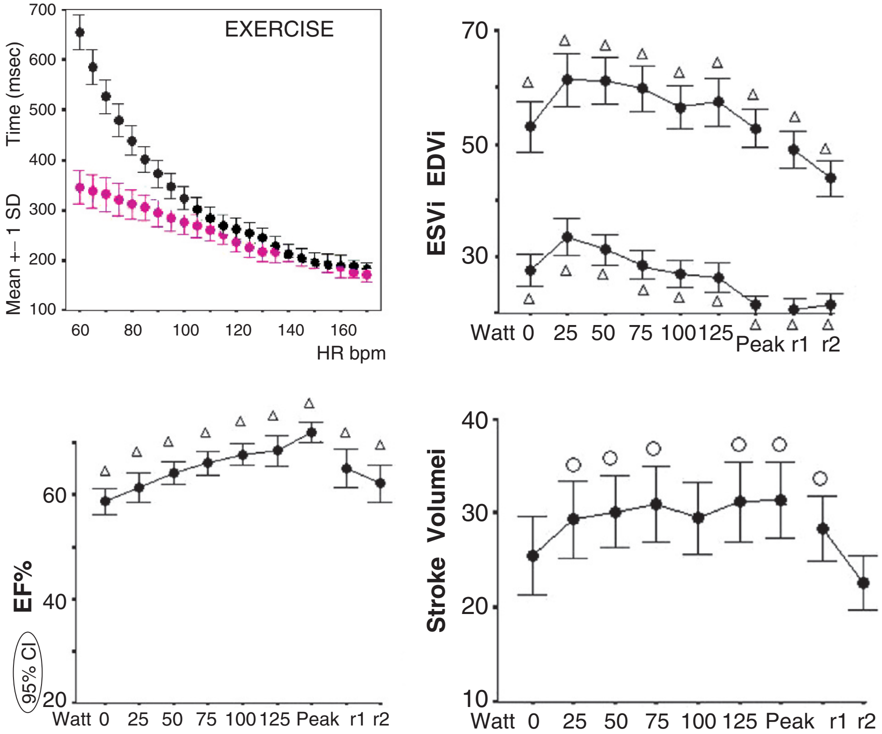

Fig. 11.3 The twofold increase in heart rate (*upper left panel*) is accompanied by a reduction of diastolic time, critical for subendocardial perfusion. The shortening of cardiological diastole is much more pronounced than shortening of cardiological systole, but the former is much more critical for subendocardial perfusion, even in the absence of coronary artery disease. (From [22])

Table 11.1 Exercise versus pharmacological stress

Parameter	Exercise	Pharmacological
Intravenous line required	No	Yes
Diagnostic utility of heart rate and blood pressure response	Yes	No
Use in deconditioned patients	No	Yes
Use in physically limited patients	No	Yes
Level of echocardiography imaging difficulty	High	Low
Safety profile	High	Moderate
Clinical role in valvular disease	Yes	No
Clinical role in pulmonary hypertension	Yes	No
Fatigue and dyspnea evaluation	Yes	No

11.3 Exercise Techniques

As a general rule, any patient capable of physical exercise should be tested with an exercise modality, as this preserves the integrity of the electrocardiogram (ECG) response and provides valuable information regarding functional status. Performing echocardiography at the time of physical stress also allows links to be drawn among symptoms, cardiovascular workload, and wall motion abnormalities. Exercise echocardiography can be performed using either a treadmill or bicycle protocol (Table 11.2). When treadmill exercise is performed, scanning during exercise is not feasible, and therefore most protocols rely on postexercise imaging [13]. It is imperative to complete postexercise imaging as soon as possible. To accomplish this, the patient is moved immediately from the treadmill to an imaging table and placed in the left lateral decubitus position so that imaging may be completed within 1–2 min. This technique assumes that regional wall motion abnormalities will persist long enough to be detected in the recovery phase. When abnormalities recover rapidly, false-negative results occur. The advantages of treadmill exercise echocardiography are the widespread availability of the treadmill system and the wealth of clinical experience that has accumulated with this form of stress testing. Information on exercise capacity, heart rate response, rhythm, and blood pressure changes are analyzed and, together with wall motion analysis, becomes part of the final interpretation. Bicycle exercise echocardiography is done with the patient either upright or recumbent (Fig. 11.4). The patient pedals against an increasing workload at a constant cadence (usually 60 rpm). The workload is escalated in a stepwise fashion while imaging is performed. Successful bicycle stress testing requires the patient's cooperation (to maintain the correct cadence) and coordination (to perform the pedaling action). The most important advantage of bicycle exercise is the chance to obtain images during the various levels of exercise (rather than relying on postexercise imaging). With the patient in the supine posture, it is relatively easy to record images from multiple views during graded exercise. With the development

Table 11.2 Exercise methods

Parameter	Treadmill	Upright bicycle	Supine bicycle
Ease of study for patients	Moderate	High	High
Ease of study for sonographer	Low	Moderate	High
Stage of onset of ischemia	No	Yes	Yes
Peak rate pressure product	High	High	High
Systolic blood pressure	Lower	Higher	Higher
Heart rate	Higher	Lower	Lower
Induction of coronary spasm	Higher	Lower	Lower
Preload increase	Lower	Lower	Higher
Ischemic strength	++ (+)	++ (+)	+++
Preferred modality in	USA	Europe	Echocardiography laboratory

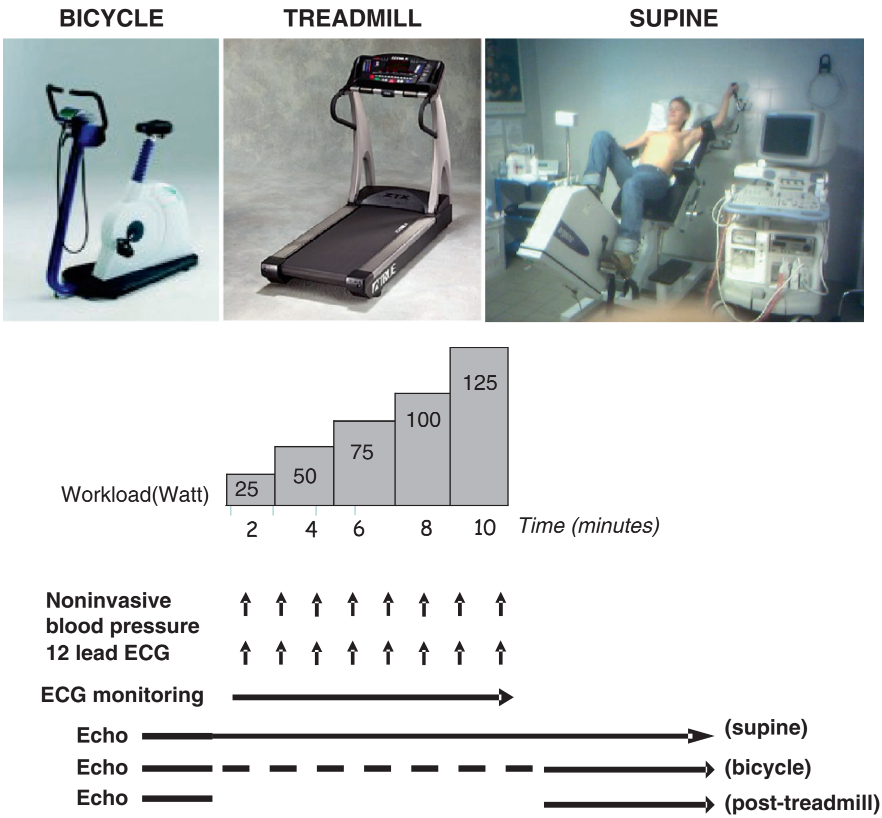

Fig. 11.4 Protocols of exercise stress echocardiography: upright bicycle (*left*); treadmill (*middle*); semisupine bicycle (*right*). Postexercise imaging is performed with treadmill only; at peak and postexercise with upright; and during, at peak, and after exercise with semisupine

of ergometers that permit leftward tilting of the patient, the ease of image acquisition has been further improved. In the upright posture, imaging is generally limited to either apical or subcostal views. By leaning the patient forward over the handlebars and extending the arms, apical images can be obtained in the majority of cases. To record subcostal views, a more lordotic position is necessary and care must be taken to avoid foreshortening of the apex. When considering the various forms of exercise, it is important to appreciate certain fundamental differences. For most patients, both duration of exercise and maximum achieved heart rate are slightly lower in the supine position [24, 25], due primarily to the development of leg fatigue at an earlier stage of exercise. The limitation is overcome in part by the occurrence of ischemia at a lower workload with supine exercise. The earlier development of ischemia is the result of both a higher end-diastolic volume and higher mean arterial blood pressure for a given level of stress in the supine position [25, 26]. These differences contribute to a higher wall stress and an associated increase in myocardial oxygen demand compared with an upright bicycle. Coronary spasms are provoked more frequently during treadmill than during bicycle exercise [27].

11.4 Safety and Feasibility

The safety of exercise stress is witnessed by decades of experience with ECG testing and stress imaging [28]. Also in exercise echocardiography registries collecting over 85,000 studies (25,000 in the international and 60,000 in the German registry), exercise echocardiography was the safest stress echocardiography test [29, 30]. Death occurs on average in 1 in 10,000 tests, according to the American Heart Association statements on exercise testing based on a review of more than 1,000 studies on millions of patients [28]. Major life-threatening effects (including myocardial infarction, ventricular fibrillation, sustained ventricular tachycardia, stroke) were reported in about 1 in 6,000 patients with exercise in the international stress echocardiography registry – fivefold less than with dipyridamole echocardiography, and tenfold less than with dobutamine echocardiography (Fig. 11.5). Although it is possible that patients referred for pharmacological stress are in general "sicker" than patients without contraindication to exercise, the available evidence suggests that while stress echocardiography is a safe method in the real world, exercise is safer than pharmacological stress [29], and dipyridamole [30] safer than dobutamine [31]. These conclusions are also in agreement with the preliminary results of the German Stress Echocardiography Registry, published only in abstract form, which recruited more than

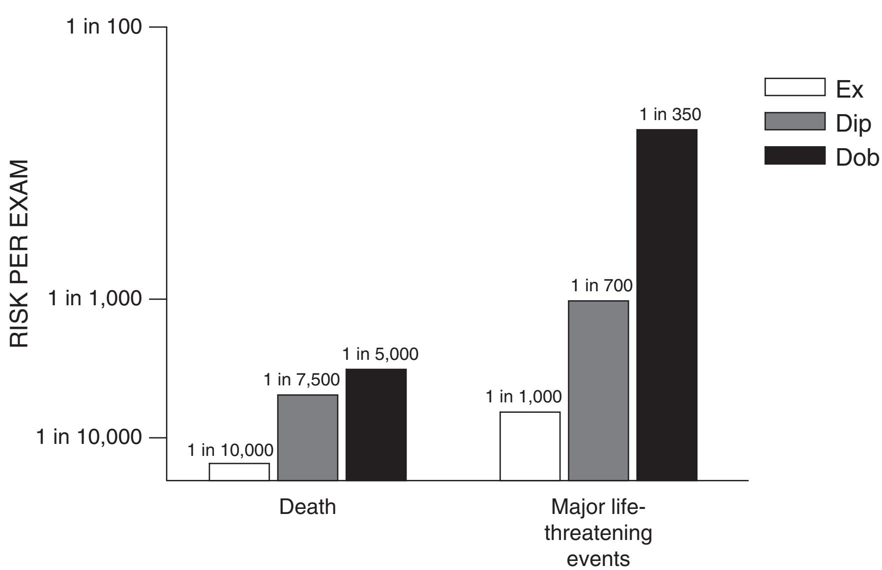

Fig. 11.5 Safety of stress echocardiography: highest for exercise, intermediate for dipyridamole, lowest for dobutamine stress. (Original data from [29–32], summarized in [15])

60,000 tests and reported a rate of complication of 0.6% with exercise, 3.6% with dobutamine, and 1.5% with dipyridamole [32].

The feasibility of obtaining interpretable studies of good quality – relatively unchanged versus baseline images – is sufficient with posttreadmill, good for upright, and almost excellent with semisupine testing which should be the test of choice for exercise stress echocardiography. From the perspective of the stress echocardiography laboratory, there is little question that semisupine exercise is easier, more feasible, and more informative than other forms of exercise stress. It is also undisputed that even semisupine exercise is more technically demanding than dobutamine and much more technically demanding than vasodilator stress.

11.5 Diagnostic Results for Detection of Coronary Artery Disease and Myocardial Viability

For the detection of angiographically significant coronary disease repeatedly assessed in a series of continuously updated meta-analyses [33–37], the overall sensitivity and specificity of exercise echocardiography has been reported to be 83 and 85%, respectively, according to the most updated meta-analysis of 55 studies with 3,714 patients (Table 11.3) [33–37]. The specificity of exercise echocardiography is similar to dobutamine echocardiography, lower than dipyridamole echocardiography, and higher for all forms of stress echocardiography compared to stress single-photon emission computed tomography (SPECT) [37]. The diagnostic accuracy is similar to other forms of stress imaging (dobutamine or dipyridamole stress echocardiography or stress SPECT) (Fig. 11.6). Although the available

Table 11.3 Sensitivity and specificity of exercise echocardiography (*echo*) according to meta-analysis of 55 studies with 3,714 patients (adapted from [37])

Test	No. of studies	Sensitivity % (95% CI)	Specificity % (95% CI)	lnDOR (95% CI)
Exercise echo	55	82.7 (80.2–85.2)	84.0 (80.4–87.6)[a]	3.0 (2.7–3.3)
Adenosine echo	11	79.2 (72.1–86.3)	91.5 (87.3–95.7)	3.0 (2.5–3.5)
Dipyridamole echo	58	71.9 (68.6–75.2)	94.6 (92.9–96.3)[a]	3.0 (2.8–3.2)
State of the art dipyridamole echo	5	81 (79–83)	91 (88–94)	3.1 (1.9–3.3)
Dobutamine echo	102	81.0 (79.1–82.9)	84.1 (82.0–86.1)[a]	2.9 (2.7–3.0)
Combined echo	226	79.1 (77.6–80.5)	87.1 (85.7–88.5)[a]	2.9 (2.8–3.0)
Combined SPECT	103	88.1 (86.6–89.6)[b]	73.0 (69.1–76.9)	2.8 (2.6–3.0)

CI confidence interval, *lnDOR* natural logarithmic of the diagnostic odds ratio

[a] Nonoverlapping confidence intervals indicating a statistically higher specificity than the corresponding SPECT test

[b] Nonoverlapping confidence intervals indicating a statistically higher sensitivity than all other tests, except for adenosine and dipyridamole SPECT and a statistically lower specificity than all other tests except for exercise SPECT

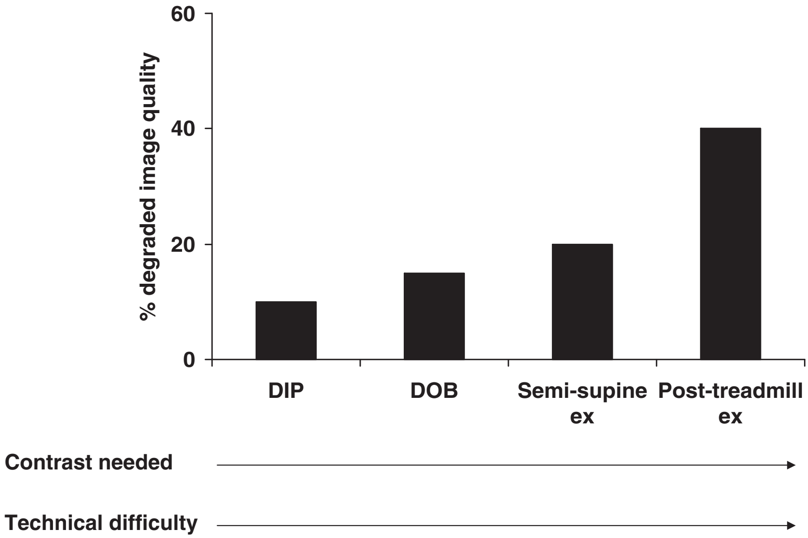

Fig. 11.6 The technical echocardiographic difficulty of different stresses. Factors polluting image quality are more frequent with posttreadmill, and least frequent with pharmacological stresses

information is only limited, exercise echocardiography can also be useful for detecting myocardial viability. Endogenous catecholamines produced during a low-level exercise test can also serve as a myocardial stressor to elicit contractile reserve in viable myocardium, with an accuracy comparable to low-dose dobutamine echocardiography [38, 39].

11.6 Prognostic Value

The presence, site, extent, and severity of exercise-induced wall motion abnormalities have a clearly proven prognostic impact, as shown by over 20 studies on 5,000 patients – ranging from patients with normal baseline function [40–43] to those evaluated early after an acute myocardial infarction [44–47], women [48], or hypertensive subjects [49]. The prognostic value of exercise stress echocardiography is high, comparable to other forms of pharmacological (dobutamine or dipyridamole) stress echocardiography and stress SPECT [49, 50] (Fig. 11.7).

Among patients who have a normal exercise echocardiogram, prognosis is favorable and the coronary event rate is quite low [40]. An abnormal stress echocardiogram, defined as a new or worsening wall motion abnormality, substantially increases the likelihood of a coronary event during the follow-up period. This finding, coupled with the presence or absence of resting left ventricular dysfunction and the exercise capacity of the patient, provides a great deal of prognostic information in an individual patient. The prognostic value is incremental over clinical and exercise electrocardiography variables [42, 50] (Fig. 11.8).

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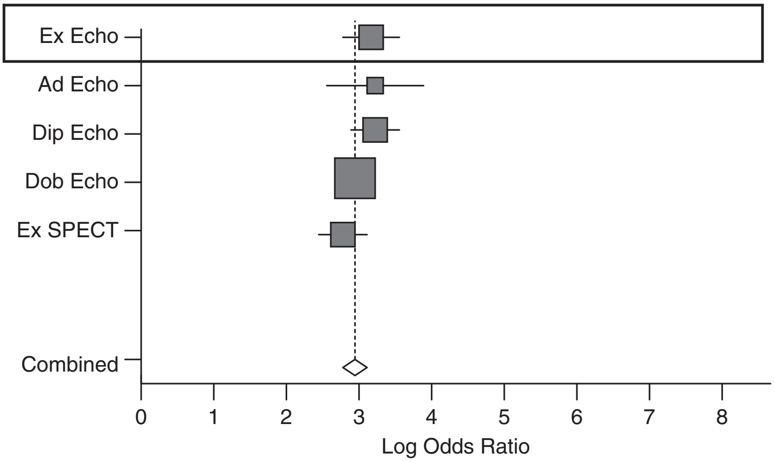

Fig. 11.7 The diagnostic accuracy of exercise echocardiography (*squared line*) versus other stress imaging test. The value of the log odds ratio is a measure of overall diagnostic accuracy. The size of the box is smaller for smaller sizes, with higher confidence intervals. (Modified from [37])

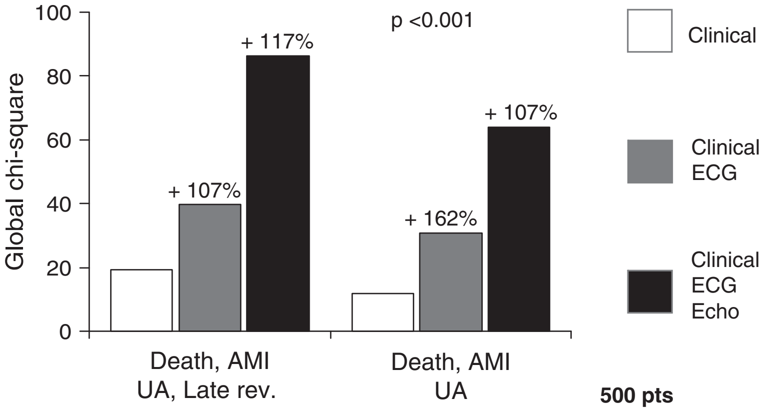

Fig. 11.8 The prognostic value of exercise echocardiography. (Modified from [42])

In patients evaluated for coronary artery disease, exercise echocardiography and exercise scintigraphy combined with the ECG variable provide comparable prognostic information and can be used interchangeably for risk stratification [50]. Other ancillary markers, beyond regional wall motion, can further stratify the prognosis during exercise echocardiography. In patients with a positive test result the prognosis is more malignant, and in patients with a negative test result the prognosis is less benign, with exercise-induced left ventricular cavity dilation [51] or severe mitral insufficiency [52, 53]. However, the systematic search of these ancillary markers of ischemia is unfeasible and technically challenging during exercise stress echocardiography, and may shift the focus of imaging away from wall motion, which remains the cornerstone of diagnosis. Their greatest clinical value is outside coronary artery disease, in patients with heart failure [20] or valvular heart disease [19].

11.7 Indications and Contraindications to Exercise Stress Echocardiography

Exercise is the most physiologic stressor of all and thus is preferable in patients who are capable of exercising (Table 11.4). For coronary artery disease diagnosis, exercise echocardiography is the appropriate first-line test, skipping the exercise electrocardiography test, in patients with conditions making the ECG uninterpretable, such as left bundle branch block or Wolf–Parkinson–White syndrome or ST-segment abnormalities on baseline resting ECG [54, 55, 56]. Exercise echocardiography is also the most suitable second-line stress test, when exercise ECG, performed as a first-line test reproduced ST-segment depression and/or angina or when the positive predictive value of these findings remains low (e.g., in women and/or hypertensive subjects) (Fig. 11.8). Exercise stress echocardiography is frequently performed inappropriately, as with all other stress imaging testing, as a first-line test in patients with low pretest probability of disease and in whom ECG is interpretable [57, 58]. There are contraindications to exercise echocardiography, such as the classical contraindications to exercise stress, including unstable hemodynamic conditions or severe, uncontrolled hypertension. Additional relative contraindications to exercise stress is the inability to exercise adequately, and – specifically for exercise echocardiography – a difficult resting echocardiogram. These conditions are not infrequent, especially in an elderly population, since out of five patients referred for testing, one is unable to exercise, one exercises submaximally [14], and one has an interpretable but challenging echocardiogram, which makes pharmacological stress echocardiography a more practical option. Exercise stress echocardiography has similar indications and contraindications to exercise SPECT, and similar diagnostic and prognostic accuracy as recognized by general cardiology guidelines [54, 55]. In a cost-conscious and radiation risk-conscious environment, this implies that stress echocardiography should be the obligatory choice [59, 60], even from a legal standpoint [61, 62], to avoid the environmental

Table 11.4 Indications to exercise stress echocardiography for diagnosis of coronary artery disease (adapted from [56])

	Appropriate	Uncertain	Inappropriate
Intermediate pretest probability of coronary artery disease	√		
ECG uninterpretable			
Prior stress ECG uninterpretable or equivocal	√		
Repeat stress echocardiography after 2 years, in asymptomatic stable symptoms		√	
Repeat stress echocardiography annually, in asymptomatic or stable symptoms		√	
Symptomatic, low pretest probability, interpretable ECG			√
Asymptomatic, low risk			√
Asymptomatic less than 1 year after percutaneous coronary intervention, with prior symptoms			√

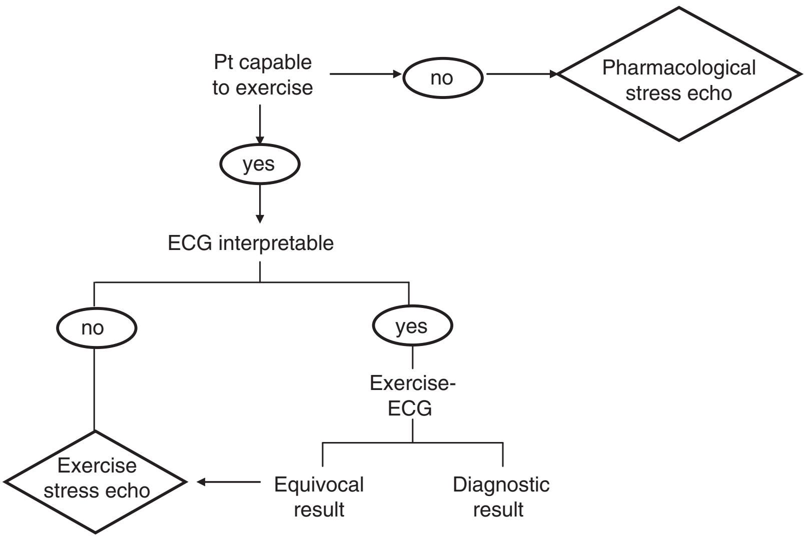

Fig. 11.9 The proposed algorithm for the use of exercise echocardiography

burden, radiological dose exposure (corresponding to 500–1,500 chest X-rays), and long-term risk (1 cancer in 500 exposed subsets) of stress scintigraphy [63, 64]. A unique advantage of exercise echocardiography over the other forms of stress is that it may offer helpful and tremendously versatile evaluation of valve function, of pulmonary hemodynamics, and of special subsets of patients, such as patients with heart failure, pulmonary hypertension, or valve disease (Table 11.4). In all these patients, the physiologic nature of exercise stress and the staggering versatility of the echocardiography technique allow one to tailor the most appropriate test to the individual patient in the stress echocardiography laboratory (Fig. 11.9).

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