Exercise Echocardiography

11

Luc A. Piérard and Eugenio Picano

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 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]. In the USA, most laboratories use the post-treadmill 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 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

E. Picano, *Stress Echocardiography*, DOI 10.1007/978-3-319-20958-6_11

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]. Of the determinants of myocardial oxygen demand, heart rate increases two- to threefold, contractility three- to fourfold, and systolic blood pressure by 50 % [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. 11.1).

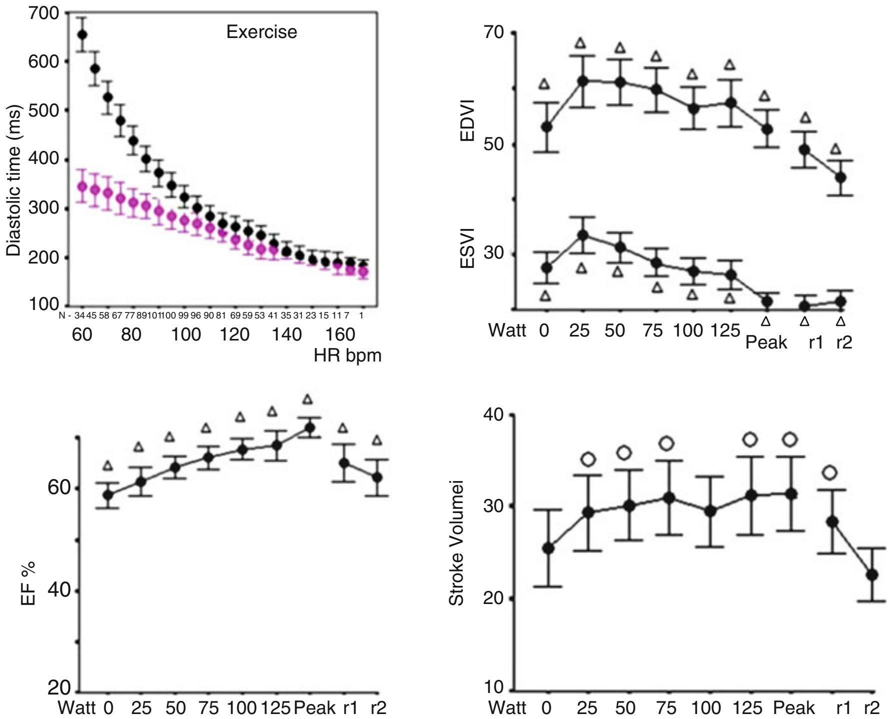

Fig. 11.1 The twofold increase in heart rate (*upper left panel*) is accompanied by a reduction of diastolic time. The shortening of diastole (*black dots*) is much more pronounced than shortening of systole (*purple dots*), but the former is much more critical for sub-endocardial perfusion, even in the absence of coronary artery disease. The trends of end-diastolic volume index (EDVI) and end-systolic volume index (ESVI), ejection fraction (EF) and stroke volume index (Svi) are shown in right upper panel, left lower panel and right lower panel respectively. (From Bombardini et al. [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

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 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 can 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 echocardiographic 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 more technically demanding than pharmacologic stress because of its greater difficulty and tighter time pressure [23].

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. 11.2).

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 possibility to obtain images during the various levels of exercise (rather than relying on postexercise

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

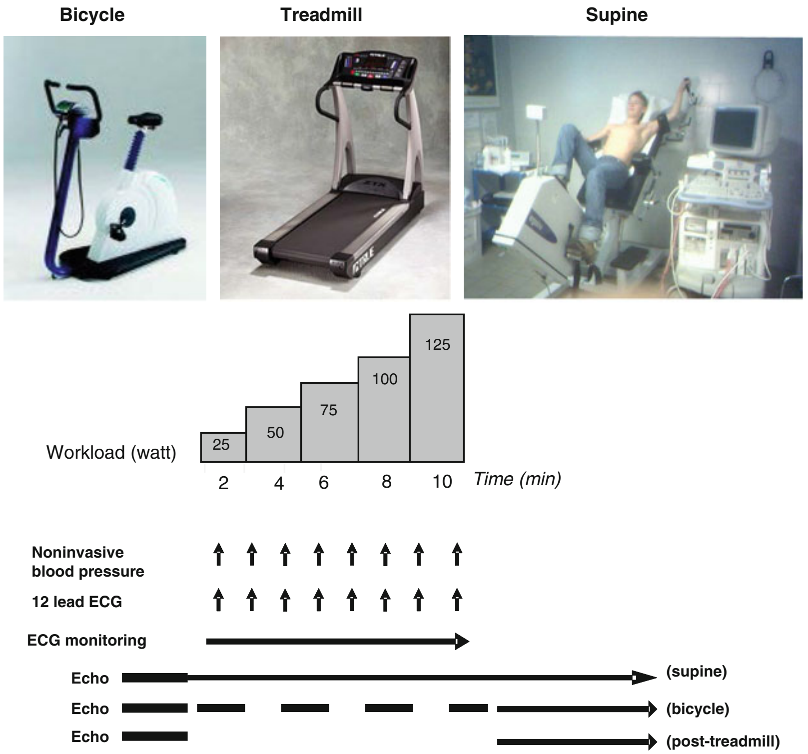

Fig. 11.2 Protocols of exercise stress echocardiography: upright bicycle (*left*); treadmill (*middle*); semisupine bicycle (*right*). Postexercise imaging is performed with treadmill only; at peak and postexercise with upright; and during, at peak, and after exercise with semisupine

imaging). With the patient in the supine position, it is relatively easy to record images from multiple views during graded exercise. With the development 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 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]. 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 1000 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 6000 patients with exercise in the international stress echocardiography registry – fivefold less than with dipyridamole echocardiography and tenfold less than with dobutamine echocardiography (Fig. 11.3). 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

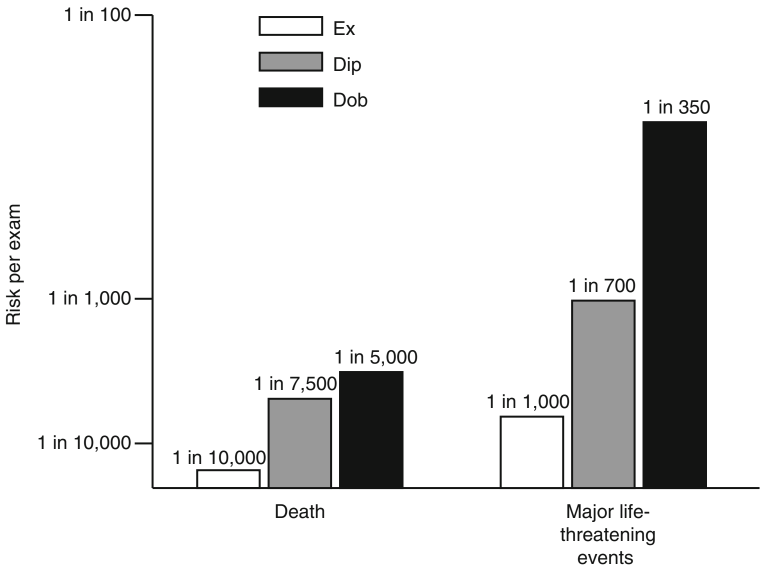

Fig. 11.3 Safety of stress echocardiography: highest for exercise, intermediate for dipyridamole, lowest for dobutamine stress (Original data from [29–32], summarized in [15])

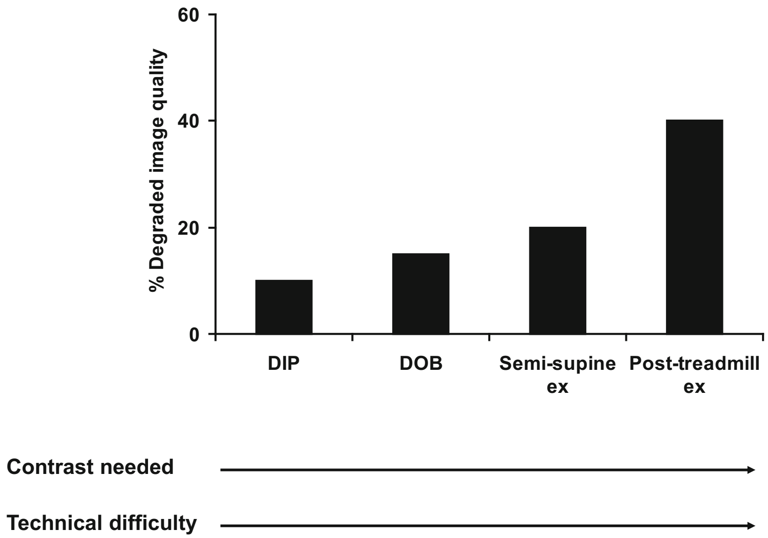

Fig. 11.4 The technical echocardiographic difficulties of different stresses. Factors polluting image quality are more frequent with post-treadmill and least frequent with pharmacological stresses

Stress Echocardiography Registry, published only in abstract form, which recruited more than 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 post-treadmill, 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 evidence that semisupine exercise is easier, more feasible, and more informative than the other forms of exercise stress. It is also undisputed that semisupine exercise is more technically demanding than dobutamine and much more technically demanding than vasodilator stress (Fig. 11.4).

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

For the detection of angiographically significant coronary artery disease repeatedly assessed in a series of continuously updated meta-analyses [33–37], the overall sensitivity and specificity of exercise echocardiography have been reported to be 83 and 85 %, respectively, according to the most updated meta-analysis of 55 studies with 3714 patients (Table 11.3) [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

Table 11.3 Sensitivity and specificity of exercise echocardiography (*echo*) according to meta-analysis of 55 studies with 3714 patients

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)

Adapted from Heijenbrok-Kal et al. [37]
CI confidence interval, *lnDOR* natural logarith 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

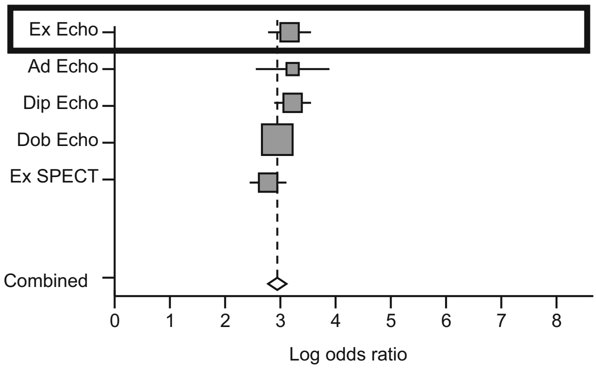

Fig. 11.5 The diagnostic accuracy of exercise echocardiography (*squared line*) versus other stress imaging tests. The value of the log odds ratio is a measure of overall diagnostic accuracy. The size of the box is smaller for smaller sizes, with higher confidence intervals (Modified from Heijenbrok-Kal et al. [37])

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. 11.5).

Although the available 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]. A maximum exercise test can also identify a biphasic response suggesting the presence of viable myocardium at jeopardy [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 5000 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 [50].

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 the individual patient. The prognostic value is incremental over clinical and exercise electrocardiographic variables [42, 50] (Fig. 11.6).

In patients evaluated for coronary artery disease, exercise echocardiography and exercise SPECT combined with the ECG variables 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 regurgitation [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].

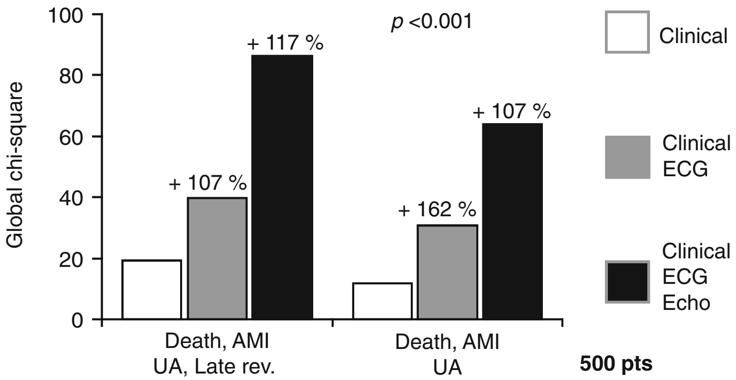

Fig. 11.6 The prognostic value of exercise echocardiography (Modified from Marwick et al. [42])

11.7 Exercise Echocardiography Outside Coronary Artery Disease

The baseline transthoracic echocardiogram performed at the time of SE permits recognition of many causes of cardiac symptoms in addition to ischemic heart disease, including dilated cardiomyopathy or hypertrophic cardiomyopathy, pulmonary hypertension, and valvular heart disease. As with CAD, also in these diseases, the application of exercise stress under controlled conditions can unmask structural defects which – although occult in the resting or static state – may occur under real-life loading conditions and lead to dysfunction detected by echocardiography.

Nowadays, in the SE laboratory, we can assess a variety of parameters beyond left ventricular function: valvular gradients and regurgitant flows and left and right heart hemodynamics including pulmonary artery systolic pressure, ventricular volumes, and extravascular lung water (see Fig. 1.6 in Chap. 1). From a practical viewpoint, it is not feasible to do everything in all patients, since there is little time during stress and there are so many things to see [54]. Therefore, the variables of potential diagnostic interest should be strategically tailored and prioritized to the individual patient based on the perceived incremental value of each (Table 11.4). Exercise is the test of choice for most applications – and bicycle semisupine exercise is technically easier than upright bicycle or post-treadmill, as it allows continuous monitoring and recording of the desirable parameters.

In general, many parameters used in stress echo applications beyond CAD can be more difficult to acquire but are easier to measure and more amenable to quantification than regional wall motion assessment; therefore, these applications may be less dependent upon the subjectivity of interpretation and operator experience [54]. The application of exercise stress echo is useful in many different conditions, from valvular (see Chap. 36) to congenital heart disease (see Chap. 37) to hypertrophic cardiomyopathy (see Chap. 34), to optimize risk stratification and timing of intervention [55], as discussed in detail in other chapters of this book.

11.8 Pitfalls

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. Difficult echocardiograms can often be salvaged by contrast echocardiography for border enhancement of unreadable left ventricular segments at baseline and during stress.

Table 11.4 Applications of exercise stress echo beyond coronary artery disease

	A	U	I	Source	Cutoff values (ref)	Class rec/lev evidence
Dilated cardiomyopathy						
Contractile reserve	√			ESC 2012, EAE 2009	WMSI >0.25	EC
Symptomatic HCM						
Resting peak gradient <50 mmHg	√			ACCF/AHA 2011	>50 mmHg	IIa, B
Asymptomatic VHD						
Severe	√			ACCF/AHA 2011	PASP >60 mmHg	II, C
Severe MS	√			ACCF/AHA 2011	MG >15 mmHg, PASP >60 mmHg	I, C
Severe AR	√			ACCF/AHA 2011	LV reserve PASP increase	EC
Severe AS, normal EF		√		ACCF/AHA 2011	MG increase >20 mmHg	IIb, C (30)
Moderate AS, AR, MR, MS		√		ACCF/AHA 2011	Increase in degree of insufficiency/gradient Increase in PASP	EC
Mild MS, MR, AS, AR			√	ACCF/AHA 2011	Increase insufficiency/gradient Increase in PASP	EC
Symptomatic VHD						
Moderate MS	√			ACCF/AHA 2011	MG >15 mmHg, PASP >60 mmHg	I, C
Low flow, low gradient AS	√			ACCF/AHA 2011	True stenosis: SV >20 %, MG >40 mmHg, AVA <1.0 cm^2 and increase ≤0.3 cm^2	IIa, C
Moderate MR	√			ACCF/AHA 2011	Increase in MR severity, increase in PASP	EC
Mild MS, MR		√		ACCF/AHA 2011	Increase insufficiency/gradient Increase in PASP	EC
Severe AS, MS, MR			√	ACCF/AHA 2011	Increase in PASP	EC

(continued)

Table 11.4 (continued)

	A	U	I	Source	Cutoff values (ref)	Class rec/lev evidence
Pulmonary hypertension						
Suspected PAH in normal resting TTE		√		ACCF/AHA 2011	No accepted cutoff	EC
Reevaluation of exercise-induced PH on therapy		√		ACCF/AHA 2011		EC
Proven resting PH			√	ACCF/AHA 2011		EC
Suspected diastolic heart failure						
Symptoms, normal EF, inconclusive resting TTE		√		ESC 2012	E/e' >15	EC
Pediatric age group						
Isolated subaortic stenosis Aortic coarctation	√			ACC/AHA 2008	Increase in LVOT MG >30 mmHg Coarctation MG >20 mmHg and diastolic runoff	IIa, C
Heart transplant recipients						
Detection of cardiac allograft vasculopathy	√			ISHLT 2010	WMA	IIa, B

Modified from Ref. [54]

A Appropriate, *U* *u*ncertain, *I* *i*nappropriate, *EC* *e*xpert consensus, *As* aortic stenosis, *MG* mean gradient, *MS* mitral stenosis, *MR* mitral regurgitation, *PG* *p*eak gradient, *PAH* pulmonary arterial hypertension, *VHD* valvular heart disease

11.9 Clinical Guidelines

Exercise is the most physiologic stressor of all and thus is preferable in patients who are capable of exercising (Table 11.5). 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 Wolff–Parkinson–White syndrome or ST-segment abnormalities on baseline resting ECG [56, 57]. 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).

Exercise stress echocardiography is frequently performed inappropriately, as with all other stress imaging tests, as a first-line test in patients with low pretest probability of disease and in whom ECG is interpretable [56, 57]. Exercise stress echocardiography has similar indications and contraindications to exercise SPECT, and similar diagnostic and prognostic accuracy as recognized by general cardiology guidelines [56, 57]. In a cost-conscious and radiation risk-conscious environment, this implies that stress echocardiography should be the preferred choice [58]. 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. In all these patients, the physiologic nature of exercise stress and the staggering versatility of the echocardiographic technique allow one to tailor the most appropriate test to the individual patient in the stress echocardiography laboratory (Fig. 11.7).

Table 11.5 Indications to exercise stress echocardiography for diagnosis of coronary artery disease [56]

	Appropriate	Uncertain	Inappropriate
Intermediate pretest probability of coronary artery disease	√		
ECG uninterpretable	*v*		
Prior stress ECG uninterpretable or equivocal	√		
Repeat stress echocardiography after 2 years, in asymptomatic or 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			√

Adapted from Montalescot et al. [56]

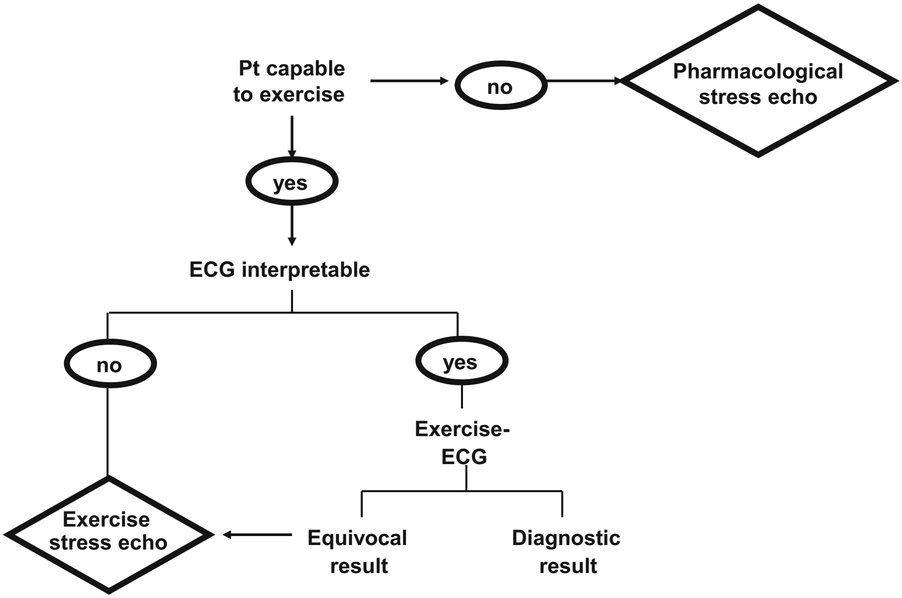

Fig. 11.7 The proposed algorithm for the use of exercise echocardiography

Table of Contents Video Companion

See also in the section illustrative cases: case number 9 (by Jesus Peteiro, La Coruna, Spain) and 10 (by Bogdan Popescu, MD, Bucarest, Romania); cases 29, 30, and 31 (by Maria Joao Andrade, Lisbon, Portugal)

Springer Extra Materials available at http://extras.springer.com/2015/978-3-319-20957-9

References

1. Kraunz RF, Kennedy JW (1970) An ultrasonic determination of left ventricular wall motion in normal man. Studies at rest and after exercise. Am Heart J 79:36–43
2. Mason SJ, Weiss JL, Weisfeldt ML et al (1979) Exercise echocardiography in detection of wall motion abnormalities during ischemia. Circulation 59:50–54
3. Wann LS, Faris JV, Childress RH et al (1979) Exercise cross sectional echocardiography in ischemic heart disease. Circulation 60:1300–1308
4. Bairey CN, Rozanski A, Berman DS (1988) Exercise echocardiography: ready or not? J Am Coll Cardiol 11:1355–1358
5. Picano E, Distante A, Masini M et al (1985) Dipyridamole-echocardiography test in effort angina pectoris. Am J Cardiol 56:452–456
6. Berthe C, Pierard LA, Hiernaux M et al (1986) Predicting the extent and location of coronary artery disease in acute myocardial infarction by echocardiography during dobutamine infusion. Am J Cardiol 58:1167–1172

7. Picano E, Landi P, Bolognese L et al (1993) Prognostic value of dipyridamole echocardiography early after uncomplicated myocardial infarction: a large-scale, multicenter trial. The EPIC Study Group. Am J Med 95:608–618
8. Picano E, Sicari R, Landi P et al (1998) Prognostic value of myocardial viability in medically treated patients with global left ventricular dysfunction early after an acute uncomplicated myocardial infarction: a dobutamine stress echocardiographic study. Circulation 98: 1078–1084
9. Feigenbaum H (1994) A digital echocardiographic laboratory. J Am Soc Echocardiogr 7: 105–106
10. Caidahl K, Kazzam E, Lidberg J et al (1998) New concept in echocardiography: harmonic imaging of tissue without use of contrast agent. Lancet 352:1264–1270
11. Laskar R, Grayburn PA (2000) Assessment of myocardial perfusion with contrast echocardiography at rest and with stress: an emerging technology. Prog Cardiovasc Dis 43:245–258
12. Armstrong WF, Ryan T (2008) Stress echocardiography from 1979 to present. J Am Soc Echocardiogr 21:22–28
13. Pellikka PA, Nagueh SF, Elhendy AA et al; American Society of Echocardiography (2007) American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 20:1021–1041
14. Pierard LA (2007) Echocardiographic monitoring throughout exercise better than the post-treadmill approach? J Am Coll Cardiol 50:1864–1866
15. Sicari R, Nihoyannopoulos P, Evangelista A et al (2008) Stress echocardiography consensus statement of the European Association of Echocardiography. Eur J Echocardiogr 9:415–437
16. Picano E, Lattanzi F, Masini M et al (1987) Comparison of high-dose dipyridamole-echocardiography test and exercise 2-D echocardiography for diagnosis of coronary artery disease. Am J Cardiol 59:539–542
17. Hecht HS, DeBord L, Sho WR et al (1993) Digital supine bicycle stress echocardiography: a new technique for evaluating coronary artery disease. J Am Coll Cardiol 21:950–956
18. Park TH, Tayan N, Takeda K et al (2007) Supine bicycle echocardiography improved diagnostic accuracy and physiologic assessment of coronary artery disease with the incorporation of intermediate stages of exercise. J Am Coll Cardiol 50:1857–1863
19. Piérard LA, Lancellotti P (2007) Stress testing in valve disease. Heart 93:766–772
20. Tumminello G, Lancellotti P, Lempereur M et al (2007) Determinants of pulmonary artery hypertension at rest and during exercise in patients with heart failure. Eur Heart J 28: 569–574
21. Bombardini T, Gemignani V, Bianchini E et al (2007) Cardiac reflections and natural vibrations: force-frequency relation recording system in the stress echo lab. Cardiovasc Ultrasound 5:42
22. Bombardini T, Nevola E, Giorgetti A et al (2008) Prognostic value of left-ventricular and peripheral vascular performance in patients with dilated cardiomyopathy. J Nucl Cardiol 15:353–362
23. Beleslin BD, Ostojic M, Stepanovic J et al (1994) Stress echocardiography in the detection of myocardial ischemia. Head-to-head comparison of exercise, dobutamine, and dipyridamole tests. Circulation 90:1168–1176
24. Thadani U, West RO, Mathew TM et al (1977) Hemodynamics at rest and during supine and sitting bicycle exercise in patients with coronary artery disease. Am J Cardiol 39:776–783
25. Poliner LR, Dehmer GJ, Lewis SE et al (1980) Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine positions. Circulation 62:528–534
26. Currie PJ, Kelly MJ, Pitt A (1983) Comparison of supine and erect bicycle exercise eletrocardiography in coronary artery disease: accentuation of exercise-induced ischemic ST segment depression by supine posture. Am J Cardiol 52:1167–1173
27. Yamakado T, Kasai A, Masuda T et al (1996) Exercise-induced coronary spasm: comparison of treadmill and bicycle exercise in patients with vasospastic angina. Coron Artery Dis 7:819–822

28. Fletcher GF, Balady GJ, Amsterdam EA et al (2001) Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 104:1694–1740
29. Varga A, Garcia MA, Picano E et al (2006) Safety of stress echocardiography (from the International Stress Echo Complication Registry). Am J Cardiol 98:541–543
30. Picano E, Marini C, Pirelli S et al (1992) Safety of intravenous high-dose dipyridamole echocardiography. The Echo-Persantine International Cooperative Study Group. Am J Cardiol 70:252–258
31. Picano E, Mathias W Jr, Pingitore A et al (1994) Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Echo Dobutamine International Cooperative Study Group. Lancet 344:1190–1192
32. Beckmann S, Haug G (1999) National registry 1995–1998 on 150,000 stress echo examinations side effects and complications in 60,448 examinations of the registry 1997–1998. Circulation 100(Suppl):3401A
33. Fleischmann KE, Hunink MG, Kuntz KM et al (1998) Exercise echocardiography or exercise SPECT imaging? A meta analysis of diagnostic test performance. JAMA 280:913–920
34. Albuquerque de Fonseca L, Picano E (2001) Comparison of dipyridamole and exercise stress echocardiography for detection of coronary artery disease (a meta-analysis). Am J Cardiol 87:1193–1196
35. Kim C, Kwok YS, Heagerty P et al (2001) Pharmacologic stress testing for coronary disease diagnosis: a meta-analysis. Am Heart J 142:934–944
36. Noguchi Y, Nagata-Kobayashi S, Stahl JE et al (2005) A meta-analytic comparison of echocardiographic stressors. Int J Cardiovasc Imaging 21:189–207
37. Heijenbrok-Kal MH, Fleischmann KE, Hunink MG (2007) Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. Am Heart J 154:415–423
38. Hoffer EP, Dewe W, Celentano C et al (1999) Low-level exercise echocardiography detects contractile reserve and predicts reversible dysfunction after acute myocardial infarction: comparison with low-dose dobutamine echocardiography. J Am Coll Cardiol 34:989–997
39. Lancellotti P, Hoffer EP, Piérard LA (2003) Detection and clinical usefulness of a biphasic response during exercise echocardiography early after myocardial infarction. J Am Coll Cardiol 41:1142–1147
40. Sawada SG, Ryan T, Conley M et al (1990) Prognostic value of a normal exercise echocardiogram. Am Heart J 120:49–55
41. Olmos LI, Dakik H, Gordon R et al (1998) Long-term prognostic value of exercise echocardiography compared with exercise 201Tl, ECG, and clinical variables in patients evaluated for coronary artery disease. Circulation 98:2679–2686
42. Marwick TH, Case C, Vasey C et al (2001) Prediction of mortality by exercise echocardiography: a strategy for combination with the Duke treadmill score. Circulation 103:2566–2571
43. Arruda-Olson AM, Juracan EM, Mahoney DW et al (2002) Prognostic value of exercise echocardiography in 5,798 patients: is there a gender difference? J Am Coll Cardiol 39:625–631
44. Jaarsma W, Visser C, Funke Kupper A (1986) Usefulness of two-dimensional exercise echocardiography shortly after myocardial infarction. Am J Cardiol 57:86–90
45. Applegate RJ, Dell'Italia LJ, Crawford MH (1987) Usefulness of two-dimensional echocardiography during low level exercise-testing early after uncomplicated myocardial infarction. Am J Cardiol 60:10–14
46. Ryan T, Armstrong WF, O'Donnel JA et al (1987) Risk stratification following acute myocardial infarction during exercise two-dimensional echocardiography. Am Heart J 114:1305–1316
47. Quintana M, Lindvall K, Ryden L et al (1995) Prognostic value of predischarge exercise stress echocardiography after acute myocardial infarction. Am J Cardiol 76:1115–1121
48. Heupler S, Mehta R, Lobo A et al (1997) Prognostic implications of exercise echocardiography in women with known or suspected coronary artery disease. J Am Coll Cardiol 30: 414–420

49. Marwick TH, Case C, Sawada S et al (2002) Prediction of outcomes in hypertensive patients with suspected coronary disease. Hypertension 39:1113–1138
50. Shaw LJ, Marwick TH, Berman DS et al (2006) Incremental cost-effectiveness of exercise echocardiography vs. SPECT imaging for the evaluation of stable chest pain. Eur Heart J 27:2448–2458
51. Yao SS, Shah A, Bangalore S et al (2007) Transient ischemic left ventricular cavity dilation is a significant predictor of severe and extensive coronary artery disease and adverse outcome in patients undergoing stress echocardiography. J Am Soc Echocardiogr 20:352–358
52. Lancellotti P, Gérard PL, Piérard LA (2006) Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation. Eur Heart J 27:187–192
53. Peteiro JC, Monserrat L, Bouzas A et al (2006) Risk stratification by treadmill exercise echocardiography. J Am Soc Echocardiogr 19:894–901
54. Picano E, Pellikka PA (2014) Stress echo applications beyond coronary artery disease. Eur Heart J 35:1033–1040
55. Henri C, Pierard L, Lancellotti P et al (2014) Exercise testing stress imaging in valvular heart disease. Can J Cardiol 30:1012–1016
56. Montalescot G, Sechtem U, Achenbach S et al (2013) 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 34:2949–3003
57. Wolk MJ, Bailey SR, Doherty JU et al; American College of Cardiology Foundation Appropriate Use Criteria Task Force (2014) ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol 63:380–406
58. Picano E, Vañó E, Rehani MM et al (2014) The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC Associations of Cardiovascular Imaging, Percutaneous Cardiovascular Interventions and Electrophysiology. Eur Heart J 35: 665–672