Exercise Echocardiography

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Keywords

Exercise · Ischemia · Semi-supine bike · Viability · Treadmill · Valvular heart disease

17.1 Historical Background

For the diagnosis of organic coronary artery disease, exercise remains the fundamental stress test and the first which was combined with stress echocardiography (SE). In the early 1970s, M-mode echocardiography of the left ventricle was used in normal subjects [1] and patients with coronary artery disease [2]. Subsequently, two-dimensional echocardiography was employed to document ischemic regional wall motion abnormality during exercise [3]. The technique was at that time so challenging, that many laboratories used pharmacological stress even in patients who were able to exercise. 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

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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 [5], improved endocardial border detection by harmonic imaging [6], and ultrasound-enhancing agents [7]. In the United States, the Bruce protocol with the treadmill is used by 70% of centers [8], and therefore, most SE laboratories use the post-treadmill approach with imaging at rest and as soon as possible during the recovery period. Peak treadmill imaging is however feasible, in expert hands, and improves the diagnostic accuracy of postexercise imaging [9]. In Europe, bicycle exercise is frequently used, and several centers have implemented their SE laboratory with a dedicated bed or table allowing bicycle exercise in a semi-supine position and real-time continuous imaging throughout the exercise [10]. The diffusion of semi-supine exercise imaging—much more user-friendly for the sonographer than the treadmill test—made image acquisition easier and interpretation faster. Semi-supine exercise gained its well-deserved role in the SE 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 [11].

17.2 Pathophysiology

Exercise protocols are variable and include treadmill tests 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 [12]. The mechanism of exercise-induced ischemia can be easily fitted into the familiar concept framework of ischemia as a supply-demand mismatch, deriving from an increase in oxygen requirements in the presence of a fixed reduction in coronary flow reserve (Fig. 17.1).

During exercise, heart rate increases two- to threefold, contractility three- to fourfold, and systolic blood pressure by 50%. Exercise is a strong chronotropic, inotropic, and hemodynamic stress and, therefore, a powerful inducer of ischemia, when exercise level is maximal in a patient with underlying coronary artery disease (Fig. 17.2).

Coronary blood flow increases three- to fourfold in normal subjects, but the reduction in diastolic time (much greater than the 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 [13]. In the presence of a reduction in coronary flow reserve, the regional myocardial oxygen demand and supply mismatch determines myocardial ischemia and regional dysfunction, with reduced regional wall motion and impaired regional thickening. When exercise is terminated, myocardial oxygen demand gradually declines, although the time course of resolution of the wall motion abnormality is quite variable [14]. Some induced abnormalities may persist for several minutes, permitting their detection on postexercise imaging. However, wall motion and thickening usually recover very rapidly, and postexercise imaging can easily miss wall motion

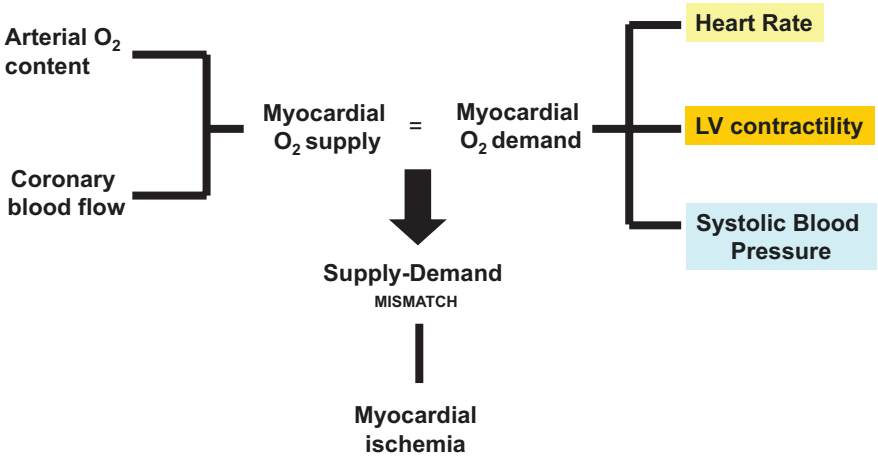

Fig. 17.1 The hemodynamic mechanism of myocardial ischemia. Myocardial ischemia develops when there is a mismatch between myocardial oxygen supply and demand. The main determinants of myocardial oxygen demand are heart rate, systolic blood pressure, and the contractile state of the myocardium. (From Picano [12])

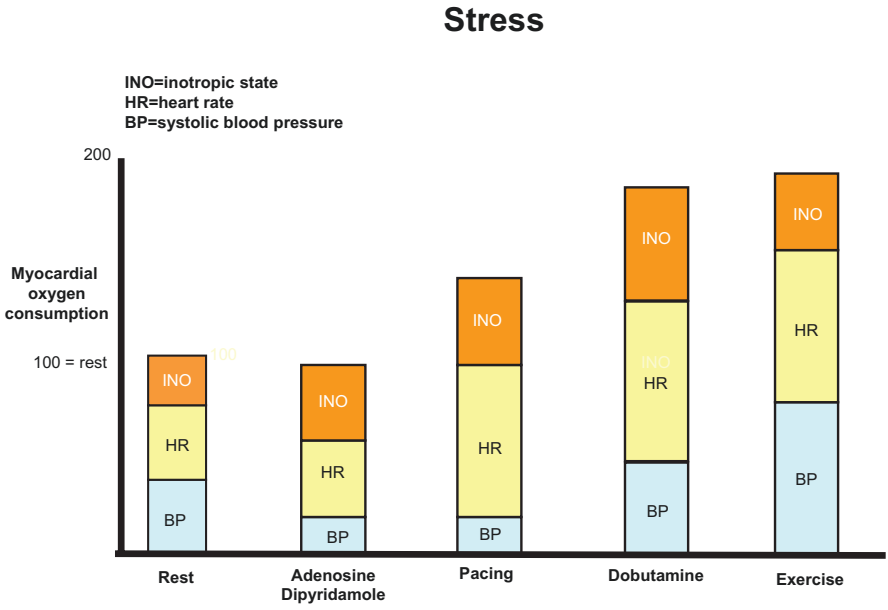

Fig. 17.2 Determinants of the increase in myocardial oxygen consumption during stress. Exercise determines a more pronounced increase in myocardial oxygen consumption compared to pacing or dobutamine. The increase is mild with vasodilators which however achieve the same ischemic strength through a different mechanism of inappropriate coronary arteriolar vasodilation. (From Picano [12])

Table 17.1 Exercise versus pharmacological stress

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

abnormalities. Regional and global functions, although linked, may behave differently during stress. For example, if a small wall motion abnormality develops because 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 regional wall motion abnormality. There are distinct advantages and disadvantages to exercise versus pharmacological stress (Table 17.1).

The most important advantages of exercise are that it is familiar to both patient and doctor; it adds echocardiographic information on top of well-established and validated electrocardiographic and hemodynamic information, and it is 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, SE during physical exercise is more technically demanding than pharmacologic stress because of its greater difficulty and tighter time pressure [15].

17.3 Exercise Techniques

As a rule, any patient capable of physical exercise should be tested with an exercise modality, as this preserves the integrity of the electrocardiogram 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, with modest differences in hemodynamic response (Table 17.2).

The treadmill is performed with the patient upright. Bicycle exercise echocardiography is done with the patient either upright or recumbent (Fig. 17.3).

Treadmill exercise is usually performed following a standardized Bruce protocol (Table 17.3).

Table 17.2 Exercise methods

Parameter	Treadmill	Upright bicycle	Supine bicycle
Ease of study for patients	Moderate	High	High
Difficulty for sonographer	High	Moderate	Low
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 spasm	Higher	Lower	Lower
EDV normal response	Increase	Increase	Increase
ESV normal response	Decrease	Decrease	Decrease
PCWP	Increase	Increase	Larger increase
Preferred modality in	USA	Europe	SE lab

EDV end-diastolic volume, *ESV* end-systolic volume, *PCWP* pulmonary capillary wedge pressure

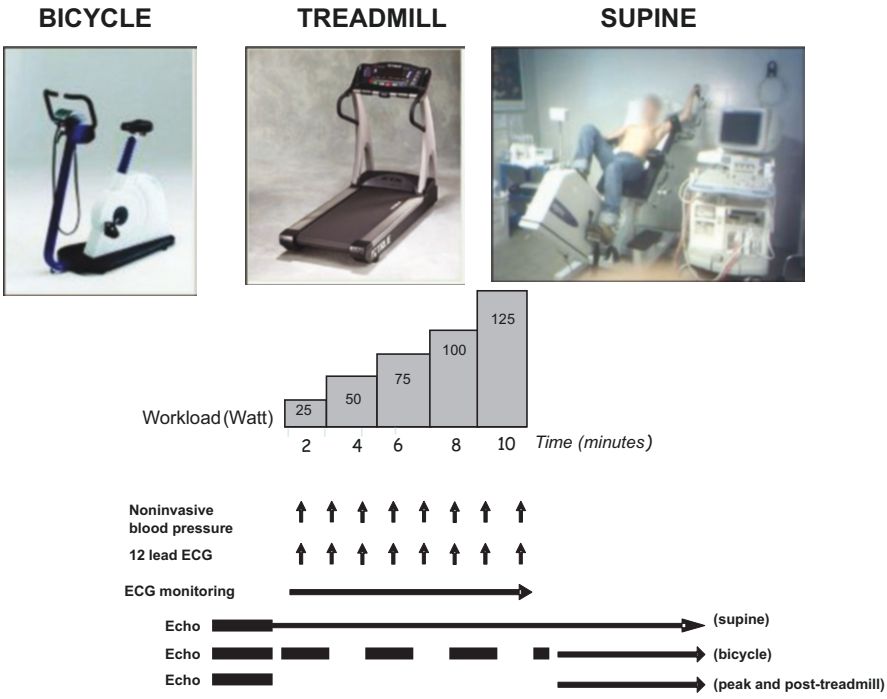

Fig. 17.3 Protocols of exercise SE: upright bicycle (*left*); treadmill (*middle*); semi-supine bicycle (*right*). Postexercise imaging is usually performed with a treadmill only, but peak treadmill imaging is also possible; at peak and postexercise upright; and during, at peak, and after exercise with semi-supine

Table 17.3 Bruce protocol for treadmill exercise

Stage	Grade (%)	Speed (%)	Time (min)	METS[a]
1	10	1.7	3	5
2	12	2.5	6	7
3	14	3.4	9	10
4	16	4.2	12	13
5	18	5.0	15	15
6	20	5.5	18	18
7	22	6.0	21	20

[a] *METS* metabolic equivalents, One MET = 3.5 mL O_2/kg/min

Table 17.4 Commonly used supine bicycle exercise protocol

Stage	Watts	Time (min)	METS
1	25	2	2.4
2	50	4	3.7
3	75	6	4.9
4	100	8	6.1
5	125	10	7.3
6	150	12	8.6
7	175	14	9.8
8	200	16	11.0
9	225	18	12.2
10	250	20	13.5

When treadmill exercise is performed, scanning during exercise is difficult, and therefore most protocols rely on postexercise imaging. 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, become part of the final interpretation.

With bike exercise, 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 (Table 17.4). 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 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 most 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 [16, 17], 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 [18]. Semi-recumbent exercise increases pulmonary capillary wedge pressure more than upright exercise [19]. These differences contribute to higher wall stress and an associated increase in myocardial oxygen demand compared with an upright bicycle. Coronary spasms are provoked more frequently during treadmill tests than during bicycle exercise [20].

The typical abnormal response pattern for regional wall motion abnormality is shown in Fig. 17.4.

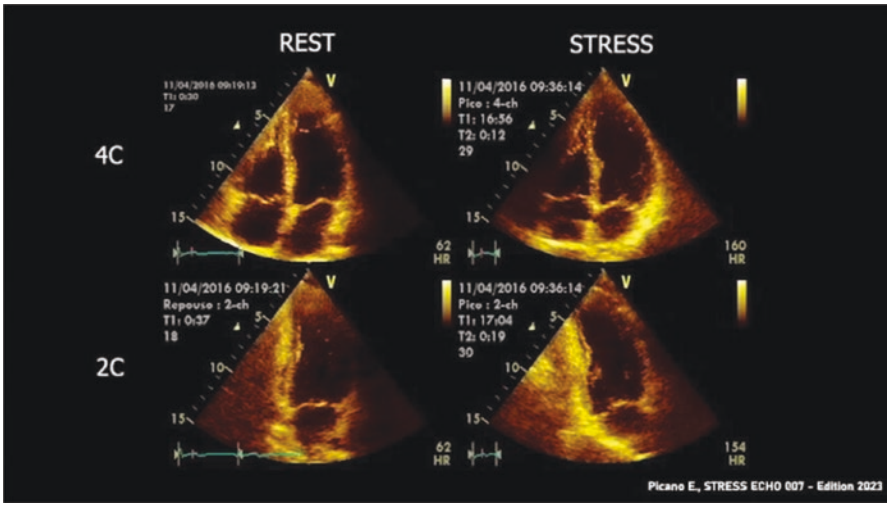

Fig. 17.4 End-systolic frames from apical four-chamber view (A4C, upper panels) and apical two-chamber view (A2C, lower panels) showing normal wall thickening at rest (left panels) and akinesia involving the lateral and apical walls, and mid-inferior and inferior apical segments, at peak treadmill test (right panel). See accompanying Video 17.1. (Video images courtesy of Jesus Peteiro, MD, Valencia, Spain. The video is available under the chapter's "Supplementary Material" on Springer Link)

17.4 Safety and Feasibility

The safety of exercise stress is witnessed by decades of experience with electrocardiography testing and stress imaging. In exercise echocardiography registries collecting over 85,000 studies, exercise echocardiography was the safest SE test [21–23]. Death occurs on average in 1 in 10,000 tests. Major life-threatening effects (including myocardial infarction, ventricular fibrillation, sustained ventricular tachycardia, and stroke) were reported in about 1 in 1000 patients with exercise in the international SE registry—twofold less than with dipyridamole echocardiography, and threefold less than with dobutamine echocardiography (Fig. 17.5).

Nevertheless, complications occur also during exercise, and it is important to be ready, with all the necessary drugs and equipment at hand in the laboratory. An example of a complication is shown in Fig. 17.6, with a cardiac tamponade for cardiac rupture, treated with echo-guided pericardiocentesis and cardiac surgery [24].

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 semi-supine testing which should be the test of choice for exercise SE. From the perspective of the SE laboratory, there is evidence that semi-supine exercise is easier, more feasible, and more informative than the other forms of exercise stress. It is also undisputed that semi-supine exercise is more technically demanding than dobutamine and much more technically demanding than vasodilator stress.

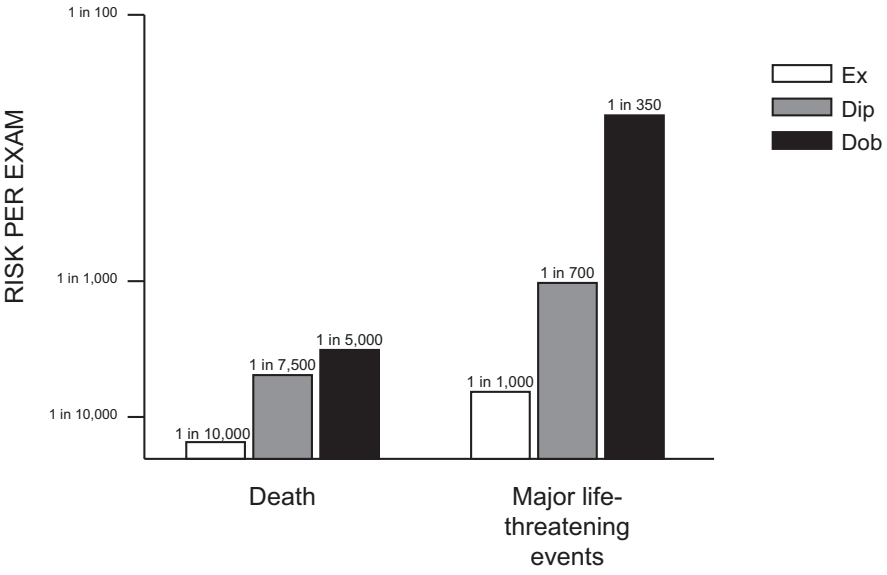

Fig. 17.5 Safety of SE: highest for exercise, intermediate for dipyridamole, lowest for dobutamine stress. (Original data from [21–23], summarized in [11])

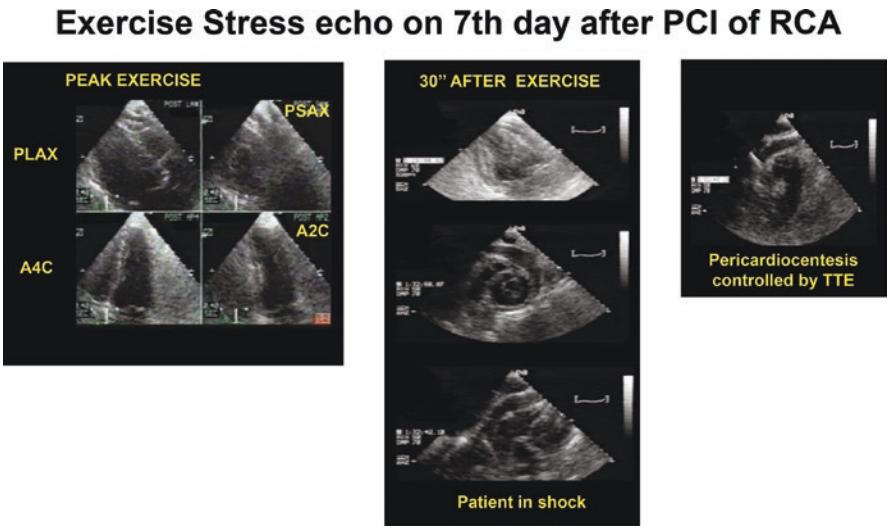

Fig. 17.6 Exercise SE in a patient with recent inferior myocardial infarction. The patient shows a pericardial effusion and syncope 30 s after the cessation of exercise. Echo-guided pericardiocentesis was performed. The patient was submitted to surgery at another Hospital with success. The patient died 12 years later of cancer. The availability of resuscitation know-how and facilities made all the difference [24], see accompanying Video 17.2. (Video images courtesy of Dr. Carlos Cotrim, from Lisbon, Portugal)

17.5 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 [25–29], 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 [29]. The diagnostic sensitivity is lowered in populations studied on beta-blockers, masking the ischemic effect of exercise, and these drugs should be discontinued to optimize the sensitivity of exercise echocardiography.

The specificity of exercise echocardiography is like dobutamine echocardiography, lower than dipyridamole echocardiography, and higher for all forms of SE compared to stress single-photon emission computed tomography [29]. The diagnostic accuracy is like other forms of stress imaging (dobutamine or dipyridamole SE or stress scintigraphy). 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 [30]. A maximum exercise test can also identify a biphasic response suggesting the presence of viable myocardium in jeopardy [31].

17.6 Prognostic Value

The presence, location, extent, and severity of exercise-induced wall motion abnormalities have a proven prognostic impact, as shown by over 20 studies on 5000 patients—ranging from patients with normal or abnormal baseline function [32–34] to women [35, 36] to patients evaluated early after an acute myocardial infarction [37, 38], after a coronary angioplasty [39], or in hypertensive subjects [40]. The prognostic value of exercise SE is high, comparable to other forms of pharmacological (dobutamine or dipyridamole) SE and stress scintigraphy [41].

Among patients who have a normal exercise echocardiogram, the prognosis is favorable, and the coronary event rate is quite low. An abnormal SE, 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 on the individual patient. The prognostic value is incremental over clinical and electrocardiographic variables [41].

Other 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 or severe mitral regurgitation. Their greatest clinical value is outside coronary artery disease, in patients with heart failure [42] or valvular heart disease [43, 44]. Patients with negative SE by regional wall motion criteria can still have an abnormal response if global indices of the cardiac reserve are used, beyond the load-dependent ejection fraction. These indices can be a force (systolic blood pressure/end-systolic volume), stroke index, or cardiac power (a measure of cardiac performance that incorporates both pressure and flow components) reserve [45–48]. With each of these indices, patients with negative exercise SE can show a heterogeneous risk, higher when the global left ventricular cardiac or contractile reserve is reduced. This is plausible since regional wall motion abnormalities mostly sense subendocardial ischemia. A more limited sub-endocardial impairment, or scar, necrosis, and subepicardial involvement may affect intramyocardial and intracavitary pressure development and volume reduction without affecting regional wall motion [49, 50]. The sub-endocardial layer mainly generates systolic thickening and intracavitary pressure, and the subepicardial layer mainly generates lower volumes for any given pressure with an acute antiremodeling effect during stress. Indices of global reserve such as ejection fraction, global longitudinal strain, force, cardiac power, or stroke index can be more sensitive than regional wall motion abnormalities in detecting a global disease of the left ventricle, and therefore their information is prognostically independent, and incremental over regional wall motion abnormalities both in and beyond coronary artery disease.

17.7 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 coronary artery disease, 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; left and right heart hemodynamics including pulmonary artery systolic pressure, ventricular volumes, and extravascular lung water. From a practical viewpoint, it is not feasible to do everything for all patients since there is little time during stress and there are so many things to see. 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. Exercise is the test of choice for most applications [51].

17.8 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 are 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 is capable to exercise sub-maximally, and one has an interpretable but challenging echocardiogram, which makes pharmacological SE a more practical option. Difficult echocardiograms can often be salvaged by ultrasound-enhancing agents for border enhancement of unreadable left ventricular segments at baseline and during stress. For risk stratification purposes, the negative predictive value of a negative exercise echo is lowered in presence of a submaximal exercise [52]. Even with maximal exercise, the negative predictive value is suboptimal in contemporary patient populations often studied under antiischemic therapy [53], and it can be enhanced by adding the evaluation of several other prognostic vulnerabilities of the patient beyond ischemia. The exercise test is suitable for the comprehensive ABCDE SE protocol, allowing the assessment of inducible ischemia (step A), pulmonary congestion (step B), contractile reserve (step C), Doppler-based coronary flow velocity reserve (step D), and heart rate reserve (step E) in one test, each step showing independent and incremental prognostic value [54]. The feasibility of step D is good with semi-supine exercise, but lower than with

pharmacological stress, and some centers prefer to adopt the standard exercise approach (with ABC and E steps) and to add the assessment of coronary flow velocity reserve with an intravenous adenosine test at the end of the recovery phase of exercise with a two-stress approach [55].

Outside coronary artery disease, the versatility of exercise SE is limited in assessing *E*/*e′* as a proxy of left ventricular end-diastolic pressure and tricuspid regurgitant jet velocity to estimate pulmonary artery systolic pressure. *E*/*e′* signal is often lost for wave fusion during tachycardia and should be measured before (at intermediate stages) or after (in the recovery phase) the fusion of E and A waves. The success rate of adequate imaging of tricuspid regurgitant jet velocity is reduced at a high workload. However, B-lines are related to pulmonary capillary wedge pressure and systolic pulmonary artery pressure variations during stress [56]. B-lines can be detected by lung ultrasound and their technical success rate is high at baseline and peak stress in patients with chronic coronary syndromes [57, 58], but also heart failure with preserved ejection fraction [59], valvular heart disease [59–61], hypertrophic cardiomyopathy [62], secondary ischemic mitral regurgitation [63]. Stress B-lines show a marked prognostic value, independent and incremental over conventional parameters such as regional wall motion abnormality or peak ejection fraction and therefore they can usefully complement standard transthoracic echocardiography for the assessment of pulmonary congestion during exercise SE.

17.9 Clinical Guidelines

Exercise is the only physiologic stressor. In patients with chest pain or dyspnea as the presenting symptom, exercise-echo is appropriate as a first-line test, since it combines the advantages of nonimaging exercise testing (exercise tolerance, symptoms, arrhythmias, blood pressure, and heart rate response) with the benefits of cardiac functional testing (ischemia, viability, integration with cardiac function and valvular function) [64]. If a patient can exercise, this is the preferred stress modality [64–66] (Table 17.5). The warranty period after a normal, maximal test is 1 year [66].

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, pulmonary hemodynamics, diastolic and systolic function, right ventricle, and intraventricular gradients (Table 17.6). In all these patients, the physiologic nature of exercise stress and the versatility of the echocardiographic technique allow one to tailor the most appropriate test to the individual patient in the SE laboratory [67].

Left ventricular contractile reserve and pulmonary pressure are important in almost all conditions, while some parameters are more specific for certain conditions, such as *E*/*e′* in heart failure with preserved ejection fraction or intraventricular gradients in hypertrophic cardiomyopathy. For applications outside coronary artery disease, the key point is that "*a variety of parameters may be assessed: ventricular function, valvular gradients, regurgitant flows, left and right heart hemodynamics including pulmonary artery systolic pressure, and ventricular volumes. As it is not*

Table 17.5 Applications of exercise SE in known or suspected coronary artery disease

Indication	CoR	LoE	Source
Assessment of symptoms, arrhythmias, blood pressure, heart rate	1	C	ESC 2019
Symptomatic patients to exclude coronary artery disease	1	B	ESC 2019
CTA has shown CAD of uncertain functional significance	1	B	ESC 2019
If a pt can exercise, this is the preferred stress modality	1	A	ASE 2020
Intermediate-to-high pretest probability (preserved or reduced EF)	1	A	ASE 2020
Resting ECG abnormality, LBBB, women	1	B	ASE 2020
Dyspnea as the presenting symptom	1	B	ASE 2020
New symptoms after CABG or PCI	2a	B	ASE 2020
Asymptomatic with diabetes, PVD, coronary calcium score >400	2b	B	ASE 2020
Intermediate-risk pts with acute chest pain and no known CAD	1	B	ACC 2021
Intermediate-risk pts with known CAD and new/worsening symptoms	2a	B	ACC 2021

ACC American College of Cardiology/American Heart Association [66], *ASE* American Society of Echocardiography [65], *CAD* coronary artery disease, *CABG* coronary artery bypass grafting, *COR* class of recommendation, *CTA* computed tomography angiography, *ESC* European Society of Cardiology [64], *LBBB* left bundle branch block, *LOE* level of evidence, *PCI* percutaneous coronary intervention, *PVD* peripheral vascular disease, *pt* patient

Table 17.6 Applications of exercise SE beyond coronary artery disease

Heart failure with a depressed ejection fraction	LV function, MR, TRV, TAPSE, B-lines
Heart failure with a preserved ejection fraction	*E*/*e′*, MR, LVOTG, TRV, GLS, B-lines
Valvular heart disease	LV function, MR, Valve gradients, B-lines
Congenital heart disease	TRV, TAPSE, LV function, B-lines
Hypertrophic cardiomyopathy	LV function, LVOTG, MR, B-lines
Athletes and extreme physiology	LVOTG, MR, TRV, TAPSE, B-lines
Pulmonary hypertension	TRV, TAPSE, B-lines

From Lancellotti et al. [67]
GLS global longitudinal strain, *LV* left ventricle, *LVOTG* left ventricular outflow tract gradient, *MR* mitral regurgitation, *TAPSE* tricuspid annulus systolic anterior excursion, *TRV* tricuspid regurgitant velocity jet

feasible to assess all possible parameters during stress, the variables of potential diagnostic interest should be prioritized for the individual patient based on the perceived importance of each. Physiology determines the choice of stress and the key echocardiographic variables of interest. Exercise is the test of choice for most applications. Bicycle ergometer stress testing is optimal for obtaining Doppler data during exercise, but patient endurance is generally less than with treadmill exercise unless the patient has trained cycling muscles." [67]. The prospective, large-scale, international validation of the protocol ABCDE as the new standard for exercise SE in chronic coronary syndromes and beyond coronary artery disease is currently in progress in the SE 2030 study, which aims to recruit in 5 years (2021–2025) ≥10,000 patients, allowing to build the platform of evidence required for changing the standard of practice [68].

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