

REVIEW ARTICLES

Stress Echocardiography: An Update

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Abstract:

Stress echocardiography (SE) is an established technique for the assessment of extent and severity of coronary artery disease. The combination of echocardiography with a physical, pharmacological or electrical stress allows to detect myocardial ischemia with an excellent accuracy. A transient worsening of regional function during stress is the hallmark of inducible ischemia. In recent years, SE has become an established method for the assessment of a wide spectrum of challenging clinical conditions, including systolic or diastolic heart failure, non-ischaemic cardiomyopathy, valvular heart disease, pulmonary hypertension (PH), athletes' hearts, congenital heart disease (CHD) and heart transplantation. Advantages of SE include the ubiquitous availability of echocardiography, lack of ionising radiation, choice of physiological or pharmacological stressors, good diagnostic accuracy and robust supporting evidence base. SE has evolved significantly as a technique over the past three decades and has benefitted considerably from improvements in overall image quality (superior resolution), machine technology (e.g. digital cine-loop acquisition and side-by-side image display) and development of second-generation ultrasound contrast agents that have improved reader confidence and diagnostic accuracy. SE provides similar diagnostic and prognostic accuracy as radionuclide stress perfusion imaging or magnetic resonance, but at a substantially lower cost, without environmental impact, and with no biohazards for the patient and the physician. A paradigm shift will occur when from a highly expertise qualitative reading SE will move to a quantitative approach that would make it easier also for less skilled readers. Technological premises are there at hand but they have not reached a full-blown status to be used on a routine clinical basis. Society recommendations and guidelines are mostly based on consensus and level of evidence C. The gap of knowledge should be filled with prospective large scale studies to support evidence-based treatment strategies. The purpose of this article is to review the breadth of SE in contemporary clinical cardiology.

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Introduction:

Stress echocardiography (SE) is the combination of 2D echocardiography with a physical, pharmacological, or electrical stress with atrial pacing. Stress-induced ischemia generates new or worsening regional wall motion abnormalities in the segment supplied by the stenosed coronary artery. SE plays an important role in identifying these wall motion abnormalities in the assessment of ischemic heart disease. In recent years, SE has become an established method for the assessment of a wide spectrum of challenging clinical conditions, including systolic or diastolic heart failure, non-ischaemic cardiomyopathy, valvular heart disease,

pulmonary hypertension (PH), athletes hearts, congenital heart disease (CHD) and heart transplantation.^{1,2}

Stress Echocardiography Methods:

SE provides a dynamic valuation of myocardial structure and function under conditions of physiological (exercise) or pharmacological (inotrope, vasodilator) stress. SE can unmask structural/functional abnormalities, which—although occult in the resting or static state—may occur under conditions of activity or stress, and lead to wall motion abnormalities, valvular dysfunction, or other haemodynamic abnormalities.³⁻⁶ Exercise is the test of choice as this preserves the integrity of the

electromechanical response. Semi-supine bicycle exercise is optimal for obtaining Doppler data during exercise. Dobutamine is the preferred alternative modality for the evaluation of contractile and flow reserve. Vasodilator SE is especially convenient for combined assessment of wall motion and coronary flow reserve.^{7,8}

Haemodynamic Effects of Myocardial Stressors:

All SE stressors result in a myocardial supply/demand mismatch and may induce ischaemia in the presence of a reduction in coronary flow reserve (CFR), due to epicardial stenosis, LV hypertrophy or microvascular disease.⁹

Exercise: During exercise, heart rate increases 2 to 3 fold, contractility 3 to 4 fold and systolic BP by $\geq 50\%$,¹⁰ while systemic vascular resistance decreases. Coronary blood flow increases 3 to 5 fold in normal subjects¹¹ but (< 2 fold) in one-third of patients with non-ischaemic dilated or HCM. In the presence of a reduction in CFR, the regional myocardial oxygen-supply mismatch determines subendocardial myocardial ischemia and regional dysfunction, which can be observed in 10–20% of patients with angiographically normal coronary arteries and either dilated or HCM.

Dobutamine: acts on β_1 receptors of the myocardium, producing an increase in heart rate 2-to-3-fold, end-diastolic volume 1.2 fold, systolic arterial pressure 1.5- to 2-fold & myocardial contractility over 4-fold in normal subjects and (< 2 fold) in patients with DCM.¹² The activation of β_2 receptors by dobutamine contributes to the mild decrease in BP common at higher dobutamine dose, through a vasodilatory effect.

Vasodilators : Vasodilator SE performed with dipyridamole or adenosine, act on vascular A2A adenosine receptors. In the presence of a critical epicardial stenosis or microcirculatory dysfunction, vasodilator administration results in heterogeneity of coronary blood flow between areas subtended by stenosed vs. normal coronary arteries, a supply–demand mismatch, and a decrease in subendocardial flow in areas of coronary artery stenosis via steal phenomena.

Stress echocardiography protocols^{19,20}:

- During Exercise SE following Parameters can be assessed at each stage (at rest, 20-25W, 100-120bpm, peak & at recovery)—LV function, RV function, Regional Wall Motion/RWM, Mitral Regurgitation/MR, Gradient (Valve, LVOT), Systolic Pulmonary Arterial Pressure/SPAP, Ratio of early transmitral diastolic velocity to early TDI velocity of the mitral annulus (E/P).
- Diagnostic End Point: Maximal dose/workload, Target heart rate, Obvious ECG positivity (ST segment shift > 2 mm), Obvious Echo positivity (new or worsening of WMA), Severe chest pain.
- Causes of test cessation—Intolerable symptoms, Muscular exhaustion, Hypertension (220/120 mmHg), Symptomatic hypotension (< 40 mmHg decrease), Arrhythmias (Sustained Ventricular Tachycardia/SVT, AF, frequent or complex ventricular ectopy).
- Abnormal test (≥ 1 criteria): (1) Symptoms-Angina, dyspnea, dizziness, syncope or near syncope, fatigue at low workload. (2) Ischemia- New or worsening

Test	Equipment	Protocol
Exercise	Treadmill (Bruce/Modified Bruce Protocol)	Each warm up stage lasting 3 min. First is at 1.7 mph & a 0% grade.
Exercise	Semi-supine bicycle ergometer	Workload (watts) (60 rotation/min); Start at 25W with 25W increments at 3 min interval.
Dobutamine	Infusion Pump	Starting with 5 mcg/Kg/min and increasing to 10, 20, 30 & 40 mcg/Kg/min every 3 min interval. If no endpoint is reached, atropine (0.25 x 4) up to 1 mg is added.
Dipyridamole	Syringe	0.84 mg/Kg over 6 min or 0.84 mg/Kg over 10 min. If no endpoint is reached, atropine (0.25 x 4) up to 1 mg is added.
Adenosine	Syringe	140 mcg/Kg/min over 6 min
Pacing	External Pacing	From 100 bpm with increments of 10 beats/min up to target heart rate

RWMA, ≥ 2 mm ST segment depression in comparison to baseline level. (3) Arrhythmias (SVT/NS). (4) Specific targeted features (>50 mmHg intraventricular obstruction).

- **Image Acquisition:** Several parameters can be assessed, including ventricular and valvular function, valvular and subvalvular gradients, regurgitant flows, left and right heart haemodynamics including systolic pulmonary artery pressure (SPAP), ventricular volumes, B-lines (also called ultrasound lung comets, a sign of extravascular lung water), and epicardial coronary flow reserve. Most protocols rely on post-exercise imaging, which is generally limited to apical, parasternal and/or subcostal views. It is imperative to complete post-exercise imaging within 1–2 min. However, when the LVOT gradient is assessed in athletes or HCM patients, it may be more relevant to obtain this measurement with the patient in the upright position. The most important advantage of semi-supine bicycle exercise is the chance to obtain images during the various levels of exercise.
- **Interpretation of the Test:** During stress, a *normal response* involves the augmentation of function in all segments and increases in LVEF and cardiac output. The presence of a new or worsening wall motion abnormality *identifies ischaemia* while the improvement of regional wall motion by ≥ 1 grade in dysfunctioning segments characterizes *recruitable viable myocardium*.¹³ *Global contractile reserve* in patients with no regional resting dysfunction is often defined as an increase by $\geq 5\%$ in LVEF while a *flow reserve* is defined as an increase in forward stroke volume by $\geq 20\%$. Any change in cardiac function (improvement or worsening in wall motion, EF, or global longitudinal function as assessed by strain rate imaging), haemodynamic parameters (stroke volume, SPAP, E/e, LVOT gradients), severity of valvular disease (improvement or worsening of mitral regurgitation (MR), aortic valve area and pressure gradients) must be reported according to the specific diagnostic question. Blood pressure and heart rate must also be reported to understand the relationship between contractile and haemodynamic responses. During vasodilator SE, the presence of viability and/or ischaemia and the degree of coronary flow reserve are described.

- **Diagnostic accuracy of SE:** In a meta-analysis of 55 studies with 3,714 patients, exercise, dobutamine, dipyridamole, and adenosine echocardiography showed a sensitivity, respectively, of 83, 81, 72, and 79%, and a specificity of 84, 84, 95, and 91%.¹⁴ However it depends on appropriate protocol selection. For instance, a patient with severe hypertension and/or a history of significant atrial or ventricular arrhythmias can more reasonably undergo to the dipyridamole stress test which, unlike dobutamine, has no arrhythmogenic or hypertensive effect.

In contrast, a patient with severe conduction disturbances or advanced asthmatic disease should undergo the dobutamine stress test, since adenosine has a negative chronotropic and dromotropic effect, as well as a documented bronchoconstrictor activity.

Patients either taking xanthine medication or under the effect of caffeine contained in drinks (tea, coffee, cola) should undergo the dobutamine test.

Antianginal medical therapy (in particular, beta-blocking agents) significantly affects the diagnostic accuracy of all forms of stress; therefore, it is recommended, whenever possible, to withhold medical therapy at the time of testing to avoid a false-negative result^{15,16}.

Indications to Stress Echocardiography¹⁹:

- Diagnosis of CAD in patients in whom exercise ECG is contraindicated, not feasible, uninterpretable, non-diagnostic or gives ambiguous results.
- Prognosis and Risk stratification in patients with established diagnosis (e.g. after myocardial infarction).
- Pre-operative risk assessment (high-risk non emergent, poor exercise tolerance).
- Evaluation after revascularization (not in the early post-procedure period, with change in symptoms).
- Search for viability in patients with ischemic cardiomyopathy eligible for revascularization.
- Coronary artery disease of unclear significance at angiography or computed tomography.
- Evaluation for cardiac aetiology of exertional dyspnoea.
- Ischaemia localization.

- The three main specific indications for pharmacologic stress echocardiography can be summarized as follows:
 - (i) Patients in whom the exercise stress test is contraindicated (e.g. patients with severe arterial hypertension).
 - (ii) Patients in whom the exercise stress test is not feasible (e.g. those with intermittent claudication)
 - (iii) Patients in whom the exercise stress test was nondiagnostic or yielded ambiguous results: inability to achieve the target heart rate response, presence of chest pain in the absence of significant electrocardiographic changes, and a concomitance of conditions lowering the reliability of the ECG marker of ischemia (female gender, arterial hypertension, repolarization abnormalities on ECG under resting conditions or after hyperventilation, and the need to continue drugs such as digitalis or anti-arrhythmic that potentially induce ST-segment and T wave changes)

Clinical use of SE in IHD:

Pathophysiology:

Myocardial ischaemia results in a typical 'cascade' of events in which the various markers are hierarchically ranked in a well-defined time sequence. Flow heterogeneity, especially between the subendocardial and subepicardial perfusion, is the forerunner of ischaemia, followed by metabolic changes, alteration in regional mechanical function, and only at a later stage by electrocardiographic changes, and pain.

The reduction of (CFR) is the common mechanism. Regardless of the stress used, ischaemia tends to propagate centrifugally with respect to the ventricular cavity: it involves primarily the subendocardial layer, whereas the subepicardial layer is affected only at a later stage if the ischaemia persists¹⁷.

In the absence of coronary artery disease (CAD), CFR can be reduced in microvascular disease (e.g. in syndrome X) or left ventricular (LV) hypertrophy (e.g. arterial hypertension). In this condition, angina with ST-segment depression can occur with regional perfusion changes, typically in the absence of any regional wall motion abnormalities during stress. Wall motion abnormalities are more specific than CFR and/or perfusion changes for the diagnosis of CAD¹⁸. Diagnostic criteria¹⁹:

Normal response: A segment is normokinetic at rest and normal or hyperkinetic during stress.

Ischemic response The function of a segment worsens during stress from normokinesia to hypokinesia (decrease of endocardial movement and systolic thickening), akinesia (absence of endocardial movement and systolic thickening), or dyskinesia (paradoxical outward movement and possible systolic thinning). However, a resting akinesia becoming dyskinesia during stress reflects purely passive phenomenon of increased intraventricular pressure developed by normally contracting walls and should not be considered a true active ischemia. **Necrotic response** :A segment with resting dysfunction remains fixed during stress.

Viability response :A segment with resting dysfunction may show either a sustained improvement during stress indicating a nonjeopardized myocardium (stunned) or improve during early stress with subsequent deterioration at peak (biphasic response). The biphasic response is suggestive of viability.

Stress echo in special subsets of patients:

Hypertensive patients: CFR may be significantly reduced independent of the presence of significant CAD. CFR impairment reduces the diagnostic value of ETT and nuclear techniques due to high rate of false positive responses. SE provides superior diagnostic specificity than ETT with no differences in sensitivity. Moreover, dipyridamole SE is most accurate than perfusion scintigraphy to assess coronary artery disease in patients with ETT positive for ischemia¹⁹.

Diabetic patients :Exercise electrocardiography is of limited value in diabetic patients because exercise capacity is often impaired by peripheral vascular disease, neuropathic disease, and obesity. The coexistence of epicardial coronary artery stenosis with microangiopathy can explain the low specificity of perfusion imaging compared to SE in the detection of CAD in asymptomatic and symptomatic diabetic patients. So, SE has shown a higher specificity than exercise electrocardiography and myocardial perfusion scintigraphy in diabetic patients¹⁹.

Women:The diagnostic specificity of exercise electrocardiography and myocardial perfusion scintigraphy is definitely lower in women than in men. Reduction of CFR in syndrome X (mostly affecting female patients), hormonal influences for exercise testing, and breast attenuation for nuclear technique are potential explanations. In contrast, echocardiography combined with exercise or pharmacologic agents

provides similar sensitivity but a better specificity as compared to exercise electrocardiography and perfusion scintigraphy.¹⁹

Left bundle branch block:

The presence of LBBB makes the electrocardiogram uninterruptable for ischemia and, therefore, a stress imaging is necessary. The abnormal sequence of LV activation determines increased diastolic extravascular resistance, with lower and slower diastolic coronary flow, accounting for the stress-induced defect often observed by perfusion imaging in patients with normal coronary arteries. SE is the best diagnostic option in patients with LBBB. It is more specific than perfusion imaging, and its sensitivity is good, albeit reduced in the left anterior descending territory in the presence of a dyskinetic septum in resting conditions¹⁹.

Noncardiac vascular surgery:

Perioperative ischemia is a frequent event in patients undergoing major noncardiac vascular or general surgery and coronary disease is known to be the leading cause of perioperative mortality and morbidity following vascular and general surgery. The updated ESC guidelines recommend an imaging stress testing before high-risk surgery in patients with more than two clinical risk factors and poor functional capacity (Class I, Evidence C)²¹. Pharmacological stress echocardiography has been proven to be an effective tool for risk stratification when compared to perfusion scintigraphy.

Clinical use of se in non-ischaemic heart disease²⁰:

1) **DIASTOLIC SE:** Exercise-induced changes in E/P allow recognition of impaired LV diastolic function reserve and the resulting increase in LV filling pressures in patients with dyspnoea and suspected heart failure with preserved LVEF. Exercise Doppler echocardiography is helpful in the assessment of the symptomatic patient with normal or equivocal diastolic function during resting images. Criteria used to diagnose heart failure with preserved LV EF are:

Exercise Average E/P >14 or Septal E/P >15 & Exer. Peak TR velocity >2.8 m/sec & Rest Septal P velocity <7 cm/sec or lateral P <10 cm/sec.

2) **hypertrophic cardiomyopathy:** Exercise SE is an important and useful tool for evaluation of symptoms and monitoring the response to therapy in patients with HCM. Dynamic LVOTO (>50 mmHg) can be easily assessed. Abnormal blood pressure response to exercise, blunted contractile (systolic) and diastolic reserve, and

worsened MR are associated with poor exercise capacity and outcome. SE is not indicated when a gradient >50 mmHg is present at rest or with Valsalva manoeuvre.

3) heart failure with depressed LV systolic function and non-ischaemic cardiomyopathy:

In patients with heart failure, SE is useful to identify the cause of dyspnoea and clinical deterioration and for individual risk stratification. SE also appears promising for guiding and monitoring response to treatment. The absence of contractile reserve is a strong determinant of outcome and a potential marker of response to cardiac resynchronization therapy.

4) native valve disease:

Mitral regurgitation- Exercise SE provides information about disease severity and individual outcome in MR. MR severity, SPAP, and left and right ventricular contractile reserve should be evaluated according to the clinical context. An increase by ≥ 1 grade in MR (from moderate to severe MR), an SPAP ≥ 60 mmHg, and a lack of contractile reserve (<5% increase in EF or <2% increment in global longitudinal strain) TAPSE <18 mm are markers of poor prognosis.

Aortic regurgitation- In AR, SE is used to assess symptoms, exercise tolerance, and the LV response to stress but not the valve disease severity. A lack of contractile reserve is associated with post-operative LV dysfunction.

Mitral stenosis- SE is indicated to reveal symptoms and assess haemodynamic consequences of MS—based on the gradient and SPAP increase during stress—in patients with discordance between symptoms and stenosis severity. Exercise SE is preferred for SPAP assessment. MS should be considered severe if exertion results in a mean gradient >15 mmHg and SPAP >60 mmHg.

Aortic stenosis- In patients with asymptomatic severe AS, exercise SE may uncover the development of symptoms, necessitating consideration for AVR. The main risk markers are a marked (>18–20 mmHg) increase in mean pressure gradient, a deterioration of LV systolic function, the lack of LV functional reserve, and the development of PH (SPAP >60 mmHg) during exercise. These markers can also be used to adjust the timing of follow-up in patients with moderate AS.

Low-flow low-gradient AS- In classical low-flow, low-gradient AS with reduced LVEF, a low-dose dobutamine SE is recommended to: (i) reserve, which is helpful for surgical risk stratification and (ii) differentiate true from

pseudo-severe AS, which is key for guiding the decision to perform AVR. In paradoxical low-flow, low-gradient AS with preserved LVEF, exercise or dobutamine SE may also be used to differentiate true- from pseudo-severe AS.

Post heart valve procedure-In patients with aortic or mitral prosthetic valves and mild-to-moderate elevation of the resting transprosthetic gradients, exercise SE is useful to confirm: (i) the presence of significant prosthetic valve stenosis or PPM, (ii) the symptomatic status. In patients with aortic or mitral prosthetic valves and LF state with small resting EOA or abnormal Doppler velocity index, low-dose dobutamine SE is used to differentiate true significant prosthesis dysfunction or PPM vs. pseudo-dysfunction. In symptomatic patients with mitral valve annuloplasty and mild increase in resting trans-mitral gradients, exercise or dobutamine SE is useful to confirm the presence of functional MS.

Pulmonary hypertension and pulmonary arterial pressure assessment-Doppler assessment of PAP with stress is feasible with exercise and is suggested as an adjunct in the assessment of patients with dyspnoea. In conjunction with PAP assessment, patients undergoing SE for suspected PH should have an assessment of RV function and oxygen saturation. Supine bike or hypoxic Doppler SE may be considered in the evaluation of patients at increased risk for PAH and to screen for HAPE and chronic mountain sickness. While the role of SE in patients with established PH is less proven, it may be useful in SE in the assessment of contractile reserve of the RV.

Congenital heart disease-

ASD-SE may be useful in patients with an atrial septal defect. Bicycle SE testing is feasible to evaluate the RV performance in open and closed atrial septal defect patients. RV performance indirectly relates to SPAP at maximal exercise. Bicycle SE testing might be useful to detect increased dynamic PVR, which is hypothesized to be related to minimal pulmonary vascular disease.

Tetralogy of Fallot-Exercise echocardiography can be used in tetralogy of Fallot patients to study the RV and LV contractile reserve. RV function can be studied measuring RVFAC, TAPSE, and tissue Doppler velocities.

Coarctation of aorta-In the context of coarctation of the aorta, exercise echocardiography can be used to assess blood pressure response and residual gradients across the aortic arch and distal aorta, as well as the myocardial response to exercise. An abnormal peak blood pressure

response seems associated with chronic hypertension and increased LV mass index. A decreased contractile response to exercise has been described in patients after coarctation repair.

Conclusion:

SE based on (RWMA) remains the cornerstone of diagnosis, but today we have the unprecedented possibility of supporting RWMA with newer indexes that provide extra information, with a minimal increase in imaging and analysis time, such as coronary flow velocity reserve on the left anterior descending coronary artery, extravascular lung water and left ventricular contractile reserve as the stress/rest ratio of systolic arterial pressure/end-systolic volume.

Effectiveness studies are already beginning for the next generation of SE, with the aim of recruiting >10,000 patients with >100 SE laboratories from >10 countries in 10 separate projects, in and beyond coronary artery disease, in the "SE 2020" study to fill the evidence gap in the field.²²

We see the analogy of SE as a smart-phone with myriad potentialities, being used as an old-fashioned landline telephone, based only on RWMA. A "smart SE" application is possible, and will continue to emphasize how the versatility of this technique is truly unique.

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