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REVIEW

Non-ischaemic cardiac conditions: role of stress echocardiography

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Abstract

Stress echocardiography (SE) has a unique ability for simultaneous assessment of both functional class and exercise-related haemodynamic changes and as such is increasingly recognised for the evaluation of non-coronary artery disease pathologies. Some indications such as valvular heart disease or hypertrophic cardiomyopathy have been well established already, while others such as diastolic exercise testing are emerging of late. This paper addresses the main and best established indications for SE in non-ischaemic conditions, providing a practical perspective correlated with updated guidelines.

Introduction

Introduced in the 1970s (1), stress echocardiography (SE) is presently a main diagnostic functional test for individuals with known or suspected coronary artery disease (CAD) (2, 3). It is defined as the conjoint use of 2D echocardiography with either exercise or a pharmacological stress protocol and it relies on demonstration of new regional wall motion abnormalities as a marker of myocardial ischaemia. As such, SE is a widely used tool in the assessment of CAD, with the main benefit observed in patients who are not able to exercise or whose exercise ECG response is non-diagnostic (2). However, the echocardiographic information available during SE goes far beyond wall motion if flow and tissue Doppler protocols are also used during the test. When combined with exercise capacity and blood pressure and heart rate response, this additional information (Table 1) will provide a comprehensive, low-cost, non-invasive assessment of various pathologies (Table 2) beyond the assessment of myocardial ischaemia. The relative accuracies of SE in the assessment of CAD and some of the conditions listed in Table 2 cannot be compared in a head-to-head manner, but it is worth noting that while the acquisition of Doppler signals during exercise may be technically demanding, their interpretation is much less subjective than wall motion changes, therefore SE results in these conditions are likely to be reliable and reproducible. Moreover, the feasibility of Doppler signal acquisition can be improved with the use of bicycle rather than treadmill exercise (3) and is not an issue with pharmacological protocols. Available guidelines do recognise the value of SE in non-CAD conditions (2, 3, 4, 5, 6) and review papers emphasise its importance (7, 8), yet this application is still somewhat marginal in routine cardiology practice. No detailed statistics are available, but in our experience, representative for a typical general cardiology large hospital workload, only three out of 200 consecutive stress studies carried out over a period of 1 year were conducted for valvular heart disease (VHD) (A Chenzbraun, personal data). Similarly, out of 800 English language papers on stress echocardiography, published over the last 10 years, only 72 (9%) related to non-CAD uses of SE. A limiting factor in the more rapid acceptance of SE for non-ischaemic conditions is the lack of large-scale studies on its impact on these patients'

Table 1 Haemodynamic and functional information provided by stress echocardiography. Changes in measurements with either exercise or pharmacological stress are of diagnostic use in conditions listed in Table 2.

Echocardiographic technique			
Spectral Doppler	Tissue Doppler	Exercise protocols	DSE protocols
Transvalvular gradients LVOT gradients Pulmonary artery pressure Stroke volume Coronary flow	LV filling pressures	Functional capacity BP and HR response	Contractile reserve

BP, blood pressure; HR, heart rate; LV, left ventricle; LVOT, left ventricular outflow tract.

management. The purpose of this paper is to review the present status of the use of SE in conditions other than CAD (Table 2). To help with clinical decision making, reference is made in text to ESC or ACC/AHA guidelines and to the appropriateness criteria of the American Society of Echocardiography, whereby use of echocardiography in a given clinical scenario is graded as appropriate, uncertain or inappropriate using scoring of 7–9, 4–6 and 1–3 respectively (4).

SE beyond diagnosis of myocardial ischaemia

The use of SE for non-CAD conditions focuses on the following:

i) assessment of the true functional class when a discrepancy exists between the reported lack of symptoms and the objective assessment of patient's pathology as being severe.
ii) Establishing a correlation between exertional symptoms and the echocardiographically derived haemodynamic changes induced or unmasked by exercise if the patient's condition as assessed at rest is not considered severe enough to explain his symptomatic status.
iii) Assessment of left ventricular contractile reserve (CR) in patients who are considered poor surgical candidates due to a low left ventricular ejection fraction.

Discrepancy between symptoms and the reported severity of the patient's pathology is best assessed by a symptom-limited standard exercise test. Depending on the patient's ability, this can be performed as either a treadmill (usually the Bruce protocol) or a bicycle test using the usual diagnostic and safety end points. Higher workloads can be achieved with a treadmill protocol but Doppler signals are easier to continuously monitor and acquire with a bicycle protocol (3). In patients unable to exercise, pharmacological stress is of questionable value for symptoms and functional class assessment. CR in patients with low LVEF is best assessed with a low-dose (5–20 μg/kg per min) dobutamine protocol recording changes in stroke volume (SV), ejection fraction and gradients as appropriate. The dose dependency of the inotropic response is unpredictable and does not necessarily parallel the chronotropic response (9), but an increase in the heart rate of $\geq$10 b.p.m. can be taken as a marker of appropriate dobutamine stimulation (10).

SE in VHD

SE in VHD represents one of the most established indications for non-CAD conditions and is acknowledged by existing guidelines (3, 4, 5, 6). The combined use of 2D and Doppler techniques during symptom-limited exercise allows for accurate assessment of true exercise capacity and of changes in transvalvular gradients, regurgitant fractions and pulmonary artery pressure (PAP) and helps in deciding on surgical vs medical management in borderline cases. CR assessment with dobutamine helps in further assessment of operative risk and expected benefits from reparative surgery.

SE in aortic stenosis

1) Guidelines endorsement recommendation:
   i) not indicated with normal ejection fraction (EF) and symptomatic severe aortic stenosis (AS); IIa with reduced EF (5).
   ii) ASE appropriateness level: uncertain (5) with normal EF; appropriate (8) with reduced EF.

There are two scenarios when SE is potentially part of the assessment of patients with AS:

Table 2 Non-CAD indications for stress echocardiography.

Established or developing indications for SE in non-CAD conditions
Valvular heart disease
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Diastolic dysfunction
Pulmonary hypertension

Documented severe AS according to the accepted guidelines but no formal indication for aortic valve replacement due to normal LV contractility and apparent lack of symptoms According to available guidelines (5, 6), patients with severe AS (*V*max $\geq$4 m/s, mean gradient $\geq$40–50 mmHg and dimensionless velocity index $\leq$0.25) (5, 6) and normal LV contractility should undergo aortic valve replacement (AVR) once they become symptomatic. However, assessing the true symptomatic status may be challenging if the patient has inadvertently reduced the level of activity to avoid dyspnoea or fatigue, if symptoms are not mentioned due to the patient's perception of what is normal for age or if functional limitation is present due to coexisting non-cardiac conditions. Even targeted history taking may not be helpful and exercise testing is recognised as safe and advocated as a class IIa recommendation whenever a discrepancy is suspected between AS severity and the apparent lack of symptoms (5). The test should be symptom limited and performed under medical supervision by practitioners familiar with this particular indication. Patients with severe AS, who become symptomatic especially in the early stages of the exercise, should be reclassified as symptomatic AS even if the clinical history is not clear and considered for AVR as a class I indication (5, 6). Notably, available guidelines endorse standard exercise testing in these patients and not necessarily exercise echocardiography that is mentioned as useful but without any level of endorsement. Lack of increase in ejection fraction or an increase in the mean gradient of $\geq$20 mmHg with exercise (5) correlates with adverse events but the echo-derived data as such are not required in present evaluation guidelines.

Low-flow–low-gradient AS in patients with LV systolic dysfunction LV systolic dysfunction can be present in AS patients as a result of either concomitant pathology (CAD or cardiomyopathy) or long-standing severe AS. Low-flow–low-gradient (LF/LG) AS with low ejection fraction is defined as a combination of aortic valve area (AVA) $<$1 cm^2, mean gradient $<$40 mmHg and LVEF $<$50% (5) and is described in a minority of patients with AS (11). Although not very frequent, LF/LG AS faces the echocardiologist with the following two challenges:

i) to decide whether the AS is truly severe and the LG reflects low transvalvular flow or is mild to moderate only and the small valve area reflects the inability of a hypokinetic ventricle to fully open a mildly restricted valve (pseudo-severe AS) and

ii) to risk stratify the patient in terms of peri-operative risk and expected benefit of AVR.

Table 3 Response patterns to low-dose dobutamine SE in patients with LF–LG AS with low EF.

SV $\Delta\uparrow$	Gradient	AVA	Conclusion	AVR as a primary indication
$>$20%	$\leftrightarrow$	$\uparrow >$1 cm^2	CR, pseudo-severe AS	No
$>$20%	$\uparrow$	$\leftrightarrow$	CR, true severe AS	Yes
$<$20%	$\leftrightarrow$	$\leftrightarrow$	No CR, ?AS	No/?

SV, stroke volume; $\uparrow$, increase; $\leftrightarrow$, no change.

Establishing whether a given patient with reduced LV contractility and LF/LG AS has adequate LV CR is critical in answering both questions. Pharmacological SE using a low-dose DSE protocol is a class IIa recommendation (5) for these patients and is recognised as appropriate with a score of 8 by ASE criteria (4). CR is considered to be present if the dobutamine infusion results in $\geq$20% increase in the SV. The possible response patterns to dobutamine in patients with LF/LG AS are summarised in Table 3. Achieving a *V*max of $\geq$4 m/s with an AVA $\leq$1 cm^2 confirms the diagnosis of truly severe AS (5). Patients with truly significant AS and evidence of CR (Fig. 1) have a clear indication for AVR and the SE report has to be clear as to the significance of the haemodynamic response. Those without CR have a poor operative mortality and generally are not candidates for AVR, though their outcome with medical management is poor and in selected cases, they could be considered for either high-risk surgery or transcatheter aortic valve implantation (TAVI) (6).

An intriguing haemodynamic pattern of paradoxical LF/LG in the presence of normal LVEF has been recognised of late in a significant minority of AS patients, possibly related to relatively small LV cavities and subsequent low SV (12). These patients are increasingly managed as their counterparts with high gradients but the role of SE in this group is not yet defined.

SE in aortic regurgitation

i) Guidelines endorsement recommendation: no.
ii) ASE appropriateness level: appropriate (7).

Patients with chronic severe aortic regurgitation (AR) develop symptoms and LV dysfunction due to long-standing volume overload. As for AS, symptoms and/or evidence of otherwise unexplained LV dysfunction are

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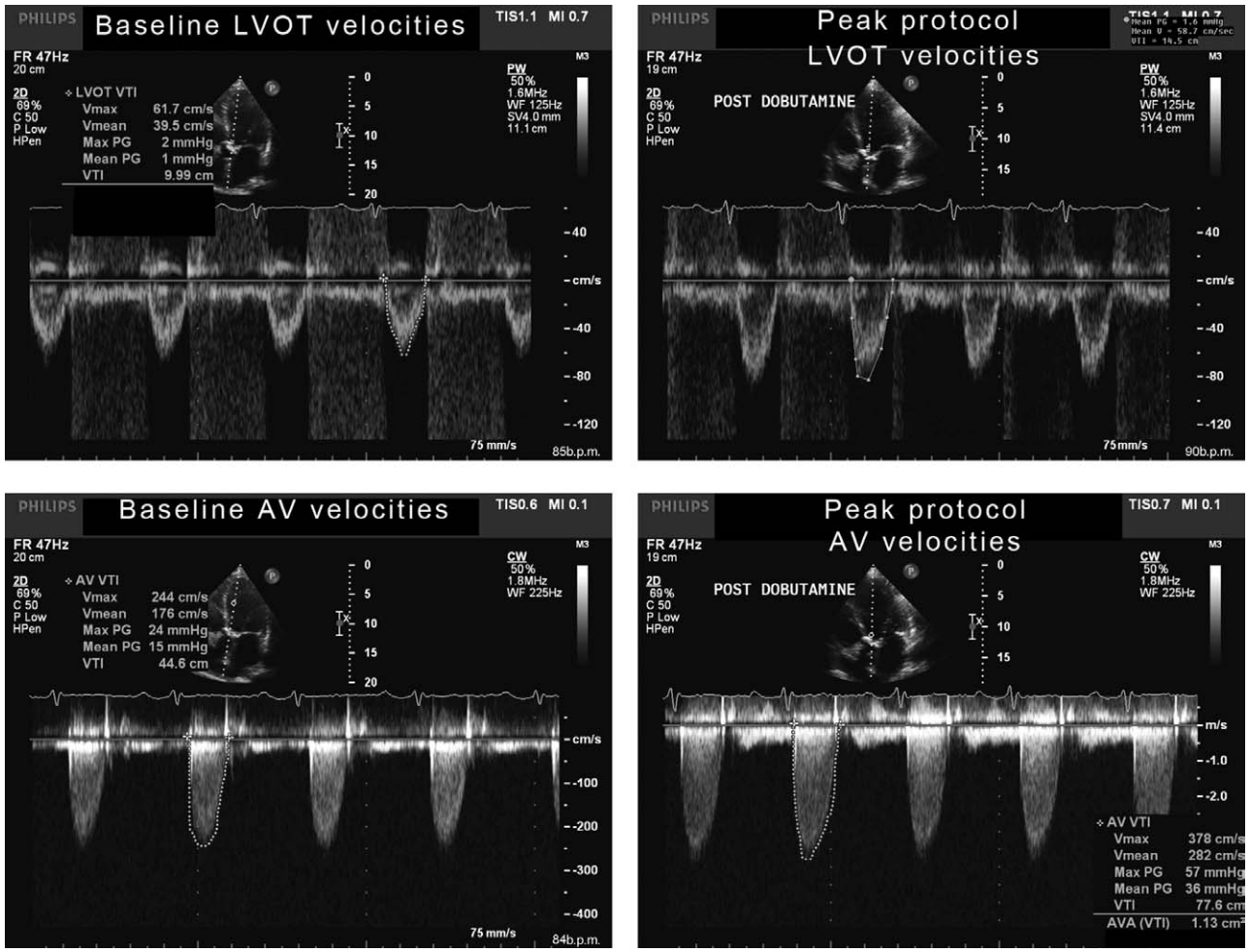

Figure 1
Low-dose dobutamine results consistent with contractile reserve and true significant AS in a patient evaluated for LF–LG AS with reduced LVEF. Left panel, baseline velocities; right panel, peak protocol velocities. Note the increase in LVOT velocity time integral (VTI) from 10 cm at baseline to 11.4 cm at peak protocol dose, consistent with an increase in the stroke volume. The aortic *V*max increased from 2.4 m/s at rest to 3.8 m/s at peak protocol dose, while the AVA remained at 1.1 cm^2.

indications for surgery. Exercise testing can be used if in doubt about the true symptomatic status, but the available evidence for its use is scarce and as such it is mentioned but not incorporated in available guidelines though SE in asymptomatic patients with severe AR and normal LV is considered appropriate by ASE criteria with a score of 7.

SE in mitral stenosis

i) Guidelines endorsement recommendation: I (5).
ii) ASE appropriateness level: appropriate (7).

Mitral stenosis (MS) patients with a mitral valve (MV) area of <1.5 cm^2 by pressure half-time or planimetry (13) are considered for surgery when they become symptomatic (5, 6). As opposed to other instances of VHD, significant LV dysfunction is not part of the haemodynamic spectrum of the disease; therefore, once the MS severity is established, symptom severity is the main if not the only information taken into account for class I surgical indications. Delaying intervention in severe MS because of the apparent lack of symptoms may lead to severe pulmonary hypertension (PHT) and deciding on intervention because of symptoms may be challenging in an individual with moderate–severe MS only. Exercise echocardiography is formally endorsed as a class I recommendation (5) and recognised as appropriate with a score of 7 by ASE criteria in the evaluation of MS patients with a

discrepancy between symptoms and MS severity by valve area and/or gradients. The end point of exercise echo in these patients is a comprehensive assessment of exercise capacity, changes in gradients and a significant rise in PAP. An exercise-induced raise of the mean transvalvular gradient to >15 mmHg or of the estimated PAP to >60 mmHg is considered significant (5). Notably, inappropriate rise in heart rate with exercise in AF patients may result in a marked increase in the transvalvular gradient and flag patients with moderate MS in whom optimised rate control may be more appropriate than surgical intervention for MS.

SE in mitral regurgitation

i) Guidelines endorsement recommendation: IIa (5).
ii) ASE appropriateness level: appropriate (7).

Patients with severe mitral regurgitation (MR) and evidence of LV systolic dysfunction have a class I surgical indication. As for other valvulopathies, the difficulty arises when there is a discrepancy between the symptomatic status as reported by the patient and the severity of MR as assessed at rest. Occasionally, a discrepancy may be noted between the degree of LV or LA enlargement and an apparently less than severe MR. In all these scenarios, a symptom-limited protocol can be used to assess the patient's true functional class, the degree of MR at the time of exercise-induced symptoms and any significant rise in PAP.

SE in cardiomyopathies

SE in hypertrophic cardiomyopathy

i) Guidelines endorsement recommendation: IIa (14).
ii) ASE appropriateness level: NA.

Exercise-related symptoms in hypertrophic cardiomyopathy (HCM) patients are due to a multitude of factors including excessive LVOT gradients, MR, diastolic dysfunction and myocardial ischaemia in the absence of epicardial CAD. Simple exercise testing in these patients will provide useful information on functional class, exercise-induced arrhythmia and blood pressure response. Exercise echocardiography can identify those without LVOT gradient at rest but who develop a peak LVOT of ≥30 mmHg with exercise and are therefore reclassified as having the obstructive form of HCM. HCM patients without significant LVOT obstruction at rest, whose gradient increases to ≥50 mmHg with exercise, may benefit from septal surgical myectomy or alcohol ablation and the use of exercise echocardiography to identify this subgroup is supported as a class IIa recommendation by present guidelines (14). Ancillary information provided by SE in these patients is worsening of MR, advanced diastolic dysfunction and evidence of ischaemia, but the impact of these end points in the risk stratification and clinical management of HCM patients is yet to be established and while potentially useful they are not incorporated in available guidelines. The preferred SE protocol in HCM patients is symptom-limited treadmill exercise, which is more physiological and avoids the confounding factor of increased venous return with supine bicycle protocols that can result in lower gradients; low-dose dobutamine is suitable for patients not able to exercise, but its usage is more limited (15), as it does not provide functional information and the occurrence of LVOT obstruction or MR is less specific, especially at high doses.

SE in dilated cardiomyopathy

i) Guidelines endorsement recommendation: NA.
ii) ASE appropriateness level: NA.

Cardiopulmonary exercise test is used in the assessment of pre-transplant congestive cardiac failure (CCF) patients, including those with dilated cardiomyopathy (DCMP), but SE as such is not incorporated in existing guidelines. Older studies (16) reported limited value of DSE in picking up underlying CAD in these patients. Better results are reported when DSE is used to assess CR for prognostic and risk stratification purposes (17, 18, 19).

SE for diastolic dysfunction assessment

i) Guidelines endorsement recommendation: NA.
ii) ASE appropriateness level: NA.

The importance of diastolic dysfunction for symptoms such as dyspnoea or exertional fatigue has been increasingly recognised over the last two decades and diastolic dysfunction is considered to be the main culprit in 30–50% of patients presenting with clinical heart failure. Underlying diastolic dysfunction could be the aetiology of otherwise not explained exertional symptoms such as breathlessness or poor exercise capacity. Doppler echocardiography is perfectly equipped to provide both a snapshot (at rest) and a dynamic (with exercise) assessment of diastolic dysfunction

and LV diastolic pressures (20). An increase in the E/E′ ratio with exercise has been shown to parallel increases in the left ventricular end-diastolic pressure (LVEDP) as recorded by invasive measurements (21). A 'diastolic assessment protocol' can be used as a stand-alone test or it can be added to the assessment of regional wall motion abnormalities during a SE protocol. E, A, E/A, E′ and E/E′ should be recorded at baseline and peak exercise according to the standard echocardiographic techniques. Diastolic SE protocols are not widely used as yet but they may prove to be of value in the assessment of exertional symptoms in patients with suspected heart failure with preserved ejection fraction and borderline diastolic abnormalities at rest (22).

SE in patients with PHT

i) Guidelines endorsement recommendation: III (23).
ii) ASE appropriateness level: uncertain (5).

Tricuspid incompetence, if present, allows for non-invasive measurement of systolic PAP calculated as $PAP = 4V^2_{TR\ max}$ + estimated right atrium (RA) pressure, in the absence of pulmonary stenosis. PHT can thus be detected much earlier than the advanced stages associated with indirect signs such as systolic septal flattening. Baseline and peak exercise PAP values can be obtained at rest and at peak exercise in patients with tricuspid regurgitation. Available data suggest that even normal individuals may exhibit high PAP values with exercise but only a minority of those exhibiting such a response will go on to develop PHT (23). This lack of specificity and the absence of well-defined normal values for exercise-induced raise in PAP are the reason for the lack of an established role for SE in the assessment of PHT, though it can be considered in selected patients.

Conclusion

SE is uniquely suited to assess haemodynamic changes during exercise and has already an established role in selected patients with VHD and HCM. Diastolic SE seems to be a promising tool in the assessment of patients with otherwise unexplained limiting exertional symptoms. Echocardiography services should become familiar with these expanded applications of SE and offer them routinely along with its standard use in patients with CAD. Prospective large-scale studies are required to firmly establish the value of SE in guiding treatment for non-CAD conditions.

Declaration of interest
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