Stress echocardiography is an established method for the diagnosis and prognostic stratification of coronary artery disease. In the last few years, the tremendous technological and conceptual versatility of this technique has been increasingly applied in challenging diagnostic fields. Today, in the echocardiography laboratory we can detect not only ischaemia from coronary artery stenosis, but can also recognize abnormalities of the coronary microvessels, myocardium, heart valves, pulmonary circulation, alveolar-capillary barrier, and right ventricle. Therefore, we evaluate coronary arteries as well as coronary microvascular disease (associated with diabetes and hypertension), suspected or overt dilated cardiomyopathy, systolic and diastolic heart failure, hypertrophic cardiomyopathy, athletes’ hearts, valvular heart disease, congenital heart disease, incipient or overt pulmonary hypertension, and heart transplant patients for early detection of chronic or acute rejection as well as potential donors for better selection of suitable donor hearts. From a stress echo era with a one-fits-all approach (wall motion by 2D-echo in the patient with known or suspected coronary artery disease) now we have moved on to an omnivorous, next-generation laboratory employing a variety of technologies (from M-Mode to 2D and pulsed, continuous and colour Doppler, to lung ultrasound and real-time 3D echo, 2D speckle tracking and myocardial contrast echo) on patients covering the entire spectrum of severity (from elite athletes to patients with end-stage heart failure) and ages (from children with congenital heart disease to the elderly with low-flow, low-gradient aortic stenosis). For each patient, we can tailor a dedicated stress protocol with a specific method to address a particular diagnostic question. Provided that the acoustic window is acceptable and the necessary expertise available, stress echocardiography is useful and convenient in many situations, from valvular to congenital heart disease, and whenever there is a mismatch between symptoms during stress and findings at rest. Increasing societal concern regarding cost, environment and radiation risks of medical imaging will lead to a preferential application of ultrasound over competing techniques, due to its unsurpassed versatility, portability, absence of radiation, and low cost.

Keywords
Cardiomyopathy • Echocardiography • Heart failure • Stress • Valvular heart disease

Introduction
Stress echocardiography (SE) provides a dynamic evaluation of myocardial structure and function under conditions of physiological or pharmacological stress. Guidelines recommend SE as a primary tool for evaluating patients with established or suspected coronary artery disease (CAD).1,2 However, the echocardiographic images obtained during conventional SE provide far more information. The baseline transthoracic echocardiogram (TTE) performed at the time of SE permits recognition of many causes of cardiac symptoms in addition to ischaemic heart disease, including dilated cardiomyopathy (DC) or hypertrophic cardiomyopathy (HCM), pulmonary hypertension (PH), and valvular heart disease (VHD). As with CAD, also in these diseases, the application of exercise or pharmacological 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.3

Nowadays, in the SE laboratory we can assess a variety of different parameters:4,5 coronary flow and ventricular function (Figure 1); valvular gradients and regurgitant flows (Figure 2); and left and right heart haemodynamics including pulmonary artery systolic pressure (PASP), ventricular volumes, and extravascular lung water (Figure 3). From a practical viewpoint, it is not feasible to do everything in all patients, since there is so little time during stress and there are so many things to see.6 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 1). Exercise is the test of choice for most applications—and bicycle

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semi-supine exercise is technically easier than upright bicycle or post-
treadmill. Vasodilation is the preferred modality for the evaluation of
coronary flow reserve (CFR) and dobutamine for contractile reserve.
A flexible use of exercise, vasodilator, and dobutamine stress maximizes
versatility, avoids specific contraindications of each, and makes it pos-
sible to tailor the appropriate stress to the individual patient.

Stress echocardiography is relatively simple and widely available,
but training recommendations should be followed. 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 sub-
jectivity of interpretation and operator experience.

**Stress echo in microvascular

disease**

The typical behaviour of microvascular disease during stress testing is
the frequent induction of chest pain, ST-segment depression, and
nuclear perfusion abnormalities without regional or global wall
motion changes (Figure 4), in striking contrast to the ‘classic’
ischaemic cascade found in CAD patients, where regional wall
motion abnormalities are an early and sensitive event. In the ‘alter-
native’ ischaemic cascade of microvascular disease, the reduction of
CFR identifies a group with worse long-term prognosis (‘wolves in
sheep’s clothing’) in different patient subsets including syndrome
X, hypertensives, diabetics, non-ischaemic DC, HCM, and
severe rejection of a transplanted heart. Vasodilator stress is per-
formed with flow velocity measurements in the mid-distal left anter-
ior descending artery interrogated with PW Doppler. Coronary
microvascular function can also be assessed with myocardial contrast
echocardiography (MCE). The evaluation of CFR is recommended in
European Association of Echocardiography (EAE) recommenda-
tions, since it ‘provides critical prognostic value when added to con-
tentional wall motion analysis’.

**Non-ischaemic dilated
cardiomyopathy**

In early stages of heart failure, when resting ejection fraction is still
normal or nearly normal, a blunted cardiac contractile reserve can
identify incipient, pre-clinical myocardial damage. Figure 5.
SE is also useful at a more advanced, overt stage of dilated cardiomyopathy, in patients with depressed ejection fraction in whom the presence of a significant contractile reserve is associated with better prognosis. Dobutamine SE may be used to recognize whether non-contracting myocardium is viable.17

From systolic blood pressure and end-systolic volume, left ventricle (LV) elastance can be calculated, and provides an index of LV contractility, theoretically independent of changes in loading conditions and prognostically useful.20 – 22

**Hypertrophic cardiomyopathy**

ACCF/AHA guidelines for the diagnosis and treatment of HCM assign exercise echocardiography a class IIa recommendation for the detection and quantification of exercise-induced dynamic LV outflow tract (LVOT) obstruction in patients who have a resting peak instantaneous gradient of 50 mmHg or less (level of evidence B). Marked gradients ≥ 50 mmHg, either at rest or with provocation, represent the conventional threshold for surgical or percutaneous intervention if symptoms cannot be controlled with medication,23 since they can be possibly responsible for symptoms24,25 and for development of stress-induced wall motion abnormalities in the absence of CAD.26 Additionally, SE may be used to identify transient regional wall motion abnormality due to functionally significant epicardial CAD,27 and reduction in CFR (in absence of regional wall motion abnormalities) due to microvascular disease.15,28

**Valvular heart disease**

Evidence accumulated over the last 5 years has led to the incorporation of SE in the guidelines of the ACCF/AHA2,29 and ESC.30 In the recent position paper of ESC on VHD and in the ACCF/ASE Appropriate Use Criteria for Echocardiography, SE has a definite role in the heart valve clinic, and is especially indicated when symptoms do not match the severity of the VHD at rest, or in the asymptomatic patient with evidence of severe valvular disease by echocardiography at rest23,31: Tab 1.

**Aortic stenosis**

According to the ESC 2012 guidelines, low dose dobutamine echocardiography may be helpful in patients with low flow, low gradient severe AS with reduced EF, to distinguish truly severe AS from pseudo-severe AS. Truly severe AS shows only small changes in valve area with increasing flow rate, but a significant increase in gradients, whereas pseudo-severe AS shows a marked increase in valve area but only minor changes in gradients. Aortic valve replacement should be considered in symptomatic patients with low flow, low gradient with reduced EF, and evidence of contractile (or flow)
Mitral stenosis

SE is especially valuable when symptoms and Doppler findings are discordant (class I, level of evidence C). SE is recommended in asymptomatic patients with resting echocardiography that demonstrate severe mitral stenosis and for symptomatic patients with resting evidence of moderate mitral stenosis. The usually adopted cut-off values during exercise, proposed by the ACCF/AHA guidelines, are a PASP ≥ 60 mmHg measured from the CW Doppler recordings of tricuspid regurgitation or mean transmitral pressure gradient > 15 mmHg at peak stress. Above these threshold values, valvuloplasty or valve replacement is recommended.30

Mitral insufficiency

The ACCF/AHA guidelines2,29 and ESC guidelines30 suggest that mitral valve intervention may be considered in asymptomatic patients with severe primary MR and normal LV function, high likelihood of durable repair, and low surgical risk, who have PASP ≥ 60 mmHg at exercise (class of IIb, evidence C).30 Exercise echocardiography is also useful in assessment of the symptomatic patient in whom resting echocardiography shows only moderate mitral insufficiency.2,32

Aortic insufficiency

With the sparse data supporting the incremental value of SE, it is not recommended for routine clinical use by either EAE5 or ACC/AHA guidelines29 although is still considered appropriate (score = 7) for ACCF/AHA 2011 appropriate use criteria for echocardiography.2

Pulmonary hypertension

By TTE, normal values are defined by PASP of less than 35 mmHg at rest.33 Pulmonary artery systolic pressure at peak semi-supine exercise can reach values ≥ 60 mmHg in many healthy individuals older than 60 and in young well-trained athletes.34 Of the group with exercise-induced PH, only a minority will develop resting PH within a 3-year period.33 The current European
Table 1  Applications of stress echo in clinical practice, beyond coronary artery disease

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>U</th>
<th>I</th>
<th>Source (ref)</th>
<th>Stress of choice</th>
<th>Cut-off values (ref)</th>
<th>Alternative technique</th>
<th>Class rec/lev evidence</th>
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<tr>
<td><strong>Microvascular disease</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Coronary flow reserve</td>
<td>✓</td>
<td></td>
<td></td>
<td>EAE 20095</td>
<td>Dipyridamole</td>
<td>CFR &lt; 2.05</td>
<td>Stress CMR</td>
<td>EC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(adenosine)</td>
<td></td>
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<tr>
<td><strong>Dilated cardiomyopathy</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractile reserve</td>
<td>✓</td>
<td></td>
<td></td>
<td>ESC 201227, EAE 20099</td>
<td>Dob (ex, dip)</td>
<td>WMSI &gt; 0.255</td>
<td>Stress CMR</td>
<td>EC</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Resting peak gradient &lt; 50 mmHg</td>
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<td></td>
<td></td>
<td>ACCF/AHA 201123</td>
<td>Exercise</td>
<td>&gt; 50 mmHg33</td>
<td>LH Cath</td>
<td>IIa, B</td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Severe</td>
<td>✓</td>
<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise (dob)</td>
<td>PASP &gt; 60 mmHg29</td>
<td>NA</td>
<td>II, C30</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise</td>
<td>MG &gt; 15 mmHg, PASP &gt; 60 mmHg29</td>
<td>NA</td>
<td>I, C29</td>
</tr>
<tr>
<td>Severe AR</td>
<td>✓</td>
<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise</td>
<td>LV reserve PASP increase5</td>
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<td>EC</td>
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<tr>
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<td>✓</td>
<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise</td>
<td>MG increase &gt; 20 mmHg20</td>
<td>NA</td>
<td>IIb, C20</td>
</tr>
<tr>
<td>Moderate AS, AR, MR, MS</td>
<td>✓</td>
<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise</td>
<td>Increase in degree of insufficiency/gradient Increase in PASP5</td>
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<td>EC</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise</td>
<td>Increase insufficiency/gradient Increase in PASP5</td>
<td>NA</td>
<td>EC</td>
</tr>
<tr>
<td><strong>Symptomatic VHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Moderate MS</td>
<td>✓</td>
<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise (dob)</td>
<td>MG &gt; 15 mmHg, PASP &gt; 60 mmHg29</td>
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<td>I, C29</td>
</tr>
<tr>
<td>Low flow, low gradient AS</td>
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<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Dobutamine</td>
<td>True stenosis: SV &gt; 20%, MG &gt; 40 mmHg, AVA &lt; 1.0 cm² and increase ≤ 0.3 cm²</td>
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<td>Ila, C20</td>
</tr>
<tr>
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<td>✓</td>
<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise</td>
<td>Increase in MR severity, increase in PASP5</td>
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<td>EC</td>
</tr>
<tr>
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<td>✓</td>
<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise</td>
<td>Increase insufficiency/gradient Increase in PASP5</td>
<td>NA</td>
<td>EC</td>
</tr>
<tr>
<td>Severe AS, MS, MR</td>
<td>✓</td>
<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>Exercise</td>
<td>Increase in PASP5</td>
<td>NA</td>
<td>EC</td>
</tr>
<tr>
<td><strong>Pulmonary hypertension</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected PAH in normal resting TTE</td>
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<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>S-Sex</td>
<td>No accepted cut-off34</td>
<td>RHC</td>
<td>EC</td>
</tr>
<tr>
<td>Re-evaluation of exercise-induced PH on therapy</td>
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<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>S-SEx</td>
<td></td>
<td>RHC</td>
<td>EC</td>
</tr>
<tr>
<td>Proven resting PH</td>
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<td></td>
<td></td>
<td>ACCF/AHA 20112</td>
<td>S-SEx</td>
<td></td>
<td>RHC</td>
<td>EC</td>
</tr>
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</table>

Continued
Respiratory Society/ESC guidelines for the diagnosis of pulmonary arterial hypertension (PAH) do not specify an indication for performing SE, because of limited information regarding standard values for PASP during exercise and the lack of prospective prognostic data, in spite of SE’s acknowledged great potential for detecting the preclinical stages of disease via the exercise-induced increase in PASP disproportionate to the increase in cardiac output.

Diastolic stress echocardiography

In presence of clinical symptoms and/or signs, mainly dyspnoea, and normal or only mildly reduced LV systolic function with normal LV volumes, the diagnosis of heart failure with preserved ejection fraction (HF-PEF) can be achieved in the presence of \( E'/e' \) ratio > 15 and excluded with \( E'/e' \) ratio < 8. However, it is not infrequent for the patient to fall within a ‘grey zone’ of indeterminate values. These patients are the main clinical target of diastolic SE. The recommended stress is exercise, with semi-supine bicycle. In patients with diastolic heart failure, the \( E'/e' \) ratio (a proxy of LV filling pressure) increases > 15 with exercise and PASP rises. With acute systolic or diastolic heart failure during stress, lung ultrasound may show B-lines or ultrasound lung comets, which is a simple, direct, semi-quantitative sign of extravascular lung water accumulation. According to 2012 ESC guidelines on heart failure, diastolic stress testing is an emerging procedure for identifying HF-PEF in patients with HF symptoms during physical activity, normal EF, and inconclusive diastolic function at rest.

Stress echocardiography in congenital heart disease

SE is increasingly used for the detection of coronary artery involvement in Kawasaki Disease and transplant CAD. Outside CAD, emerging SE applications focus mainly on the assessment of contractile reserve of the systemic morphological right ventricle, in aortic coarctation and isolated subaortic stenosis.

As recommended by a 2006 Statement of AHA, paediatric testing during stress should remain an integral part of paediatric cardiology training.

Stress echocardiography in heart transplant

Recent guidelines recognize that SE ‘may be useful for the detection of cardiac allograft vasculopathy in heart transplant recipients unable to undergo invasive evaluation’. SE appears promising in the selection of donor hearts for cardiac transplantation.

Stress echocardiography in athletes and extreme physiology

In athletes with a positive pre-participation cardiovascular screening result for sports practice according to the ESC guidelines (i.e. exercise-induced symptoms and/or ischaemia-like electrocardiographic changes), a significant LVOT gradient at rest (> 30 mmHg) or after
Exercise (>50 mmHg) may develop especially with patients in orthostatism in the absence of wall motion abnormalities, outlining a functional (and potentially treatable with beta-blockers) cause of angina and/or syncope.

The exaggerated PASP response in individuals susceptible to high-altitude pulmonary oedema is an increase in PASP >40 mmHg with 2h-hypoxia (with oxygen saturation of 80%, corresponding to an altitude of 4500 m) alone and >50 mmHg for hypoxia and supine

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**Figure 4** A concise view of the different pathophysiological situations of classic (coronary artery disease) and alternative (microvascular) ischaemic cascade. Stress-induced wall motion abnormalities are a very early sign in coronary artery disease, but are typically absent in microvascular disease, in spite of a comparable reduction in coronary flow reserve.

**Figure 5** The role of stress echocardiography in prognostic titration of cardiomyopathy. At an early stage, baseline function is normal but LV contractile reserve and coronary flow reserve are depressed. At an advanced stage, the baseline function is depressed but there is inotropic and coronary flow reserve. At a very advanced stage, myocardial fibrosis results in depression of resting function and abolition of inotropic and coronary flow reserve response.
exercise - with the caveats already described in the previous section on PH.  

**Pitfalls and limitations**

The evaluation of contractile reserve with WMSI is subjective and operator-dependent. The Doppler assessment of CFR is based upon a velocity ratio, which is a good surrogate of flow only when no significant change in epicardial artery diameter occurs during stress, and is limited by previous caffeine intake, which interferes with vasodilation induced by adenosine accumulation. Myocardial contrast echocardiography limitations include the need for an i.v. line and additional cost. Many indications are based on a level C weight of evidence and the proposed cut-off values remain consensus-driven rather than supported by outcome-based evidence.  

For the assessment of diastolic function, the E/e' ratio can be unreliable, even at rest, in the presence of annular calcification, mitral valve disease, regional LV dysfunction, or atrial fibrillation. In diastolic stress, E/e' has a limited correlation with invasively detected changes in LV filling pressures.  

The Doppler assessment of PASP has imperfect agreement with the gold standard of right heart catheterization, remains unfeasible in 15% of patients with inadequate TR jet and is unreliable in massive TR. During stress, we still lack accepted cut-off values between normal and abnormal responses. Pulmonary artery systolic pressure values are linearly dependent on cardiac output, and multiple-point pulmonary artery pressure-flow relationship should also be integrated with the evaluation of pulmonary vascular resistance. Post-exercise measurements are unreliable because of rapid return to baseline of pulmonary haemodynamics.  

**Future perspectives**

The clinical use of SE beyond CAD should harmonize with the standards of appropriateness of our imaging studies, therefore, clearly separating research-oriented, promising novel applications of the technique from established use of proven clinical value (Table 1).  

Evolving technologies will continue to advance the field, including 2D strain rate for objective assessment of regional and global, right and left, systolic and diastolic ventricular function; MCE; and 3D echocardiography for rapid acquisition of an unlimited number of planes, with reproducible volume measurements to assess ventricular arterial coupling. All have great potential but there is still insufficient evidence for general recommendations.  

Prospective large-scale and randomized (SE-guided vs. standard) outcome studies are needed to support more evidence-based treatment strategies. Increasing social concern regarding cost, environment and radiation risks of medical imaging will lead to a preferential application of ultrasound over competing techniques due to its wide availability, portability, relatively low cost, versatility, and absence of radiation.  

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