Stress echocardiography in paediatric cardiology

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Stress echocardiography is a well-established technique in adult cardiology and is mainly used for assessing regional myocardial function in patients with known or suspected coronary artery disease (CAD). Apart from detecting ischaemia, stress echocardiography has found its place in the assessment of the haemodynamic significance of valve disease, particularly in selected patients with aortic stenosis and mitral regurgitation. Also in the paediatric population, stress imaging is most commonly used for the detection of ischaemia in patients with CADs such as post heart transplantation, Kawasaki Disease, and abnormal origin of coronary arteries. Other paediatric indications include the haemodynamic and myocardial response in patients with different types of congenital heart disease, the early detection of myocardial dysfunction in specific populations such as patients after anthracycline exposure, and the evaluation of pulmonary artery pressures and the right ventricular functional response. Techniques have evolved over time and in different paediatric echocardiographic laboratories, exercise stress echocardiography is replacing dobutamine stress echocardiography in older children. Moreover, integrating tissue Doppler and strain technology with stress imaging allows a more quantitative analysis of regional and global systolic and diastolic function. Current clinical applications mainly include patients after transplant, suspected CAD, and hypertrophic cardiomyopathy.

Keywords  Exercise echocardiography  •  Function  •  Children

Introduction

Stress echocardiography is a well-established technique in adult cardiology with guidelines published by the American Society of Echocardiography¹ as well as by the European Association for Echocardiography.² No specific guidelines or recommendations are available for the application of stress echocardiography in children. In adults, the main indications include proven or suspected coronary artery disease (CAD), valve disease [aortic stenosis (AS), mitral regurgitation, and prosthetic valves], detection of subclinical pulmonary hypertension, and assessment of diastolic dysfunction. In paediatric heart disease, diagnostic utilization of stress echocardiography is relatively limited due to challenges related to performing the test in children. Nevertheless, also in children stress echocardiography can add important diagnostic information. The aim of this review is to provide an overview of the current application of stress echocardiography in paediatric cardiology.

Techniques for stress echocardiography in paediatric heart disease

As in adults, pharmacological and exercise stress testing can be performed in children. Dobutamine is the most commonly used pharmacological agent in paediatric stress echocardiography. Dobutamine has a positive inotropic and chronotropic effect, which leads to increased myocardial oxygen demand. In contrast to exercise stress, it does not result in increased venous return and increased preload (Table 1). In the presence of significant CAD, increased oxygen demand can cause regional ischaemia reflected by regional wall motion abnormalities. Dobutamine stress echocardiography (DSE) protocols used in paediatric cardiology are very similar to the adult protocols. Generally, dobutamine infusion starts at 5 μg/kg/min and is increased at 3-min intervals to 10, 20, 30, 40, and 50 μg/kg/min. If the maximal target heart rate (HR) for age, is not reached, a low dose of atropine (0.01 mg/kg) is administered at a maximal dobutamine dose. Typical side effects include palpitations, nausea, headache, chills, urinary urgency, and anxiety. Cardiovascular side effects include angina, hypotension, hypertension, and cardiac arrhythmia. The side effects usually resolve quickly with termination of the infusion, given the short half-life of dobutamine. Life-threatening complications such as sustained ventricular arrhythmias are rare and occur mainly in patients with a history of myocardial infarction and/or ventricular dysfunction.³ However, no good data on complications are available in paediatric patients. In children 18 years of age, DSE requires general anaesthesia or deep sedation. In older children, conscious sedation may be required. During each stage, echocardiographic images are acquired...
and the myocardial response can be assessed qualitatively and quantitatively. Dobutamine can also be used at low or moderate doses (between 5 and 20 μg/kg/min) as a continuous infusion to assess cardiac contractile reserve. Exercise stress echocardiography (ESE) can be used in children >8 years of age who are cooperative and capable of performing an exercise test. Exercise is a more physiologic stressor: it increases HR, contractile function, blood pressure, as well as venous return to the heart. Image acquisition during exercise can, however, be more challenging related to motion and breathing artefacts. Different methods have been proposed. A treadmill exercise test with echocardiography\(^4\) during which images are acquired at rest and at peak exercise or within the first minute of the recovery phase. Owing to motion, it is generally impossible to acquire images during exercise on a treadmill. In addition, as the HR in children can drop very quickly during recovery, the interpretation of the results can be compromised. To obtain information during exercise, bicycle testing is a more suitable method. The test can be done either on an upright or a semi-supine bicycle. Both methods allow acquisition of echocardiographic images during incremental exercise as well as during recovery.\(^5\) As bicycle ergometers have been developed for adults, there is a minimal leg length, limiting the test to taller children (generally >8 years of age). On both ergometers, a modified Bruce protocol is used with the resistance being increased by 20–25 W every 3 min intervals until target maximal HR is reached or if the test is stopped because of symptoms or fatigue. After the first minute of each stage, 8–10 images can be acquired, and a typical image acquisition protocol tailored on the clinical question used in our laboratories is described in Tables 2 and 3. For specific indications, the protocols are adjusted to include, for example, Doppler images of the mitral and tricuspid valves to study aortic valve regurgitation or measuring gradients across outflow tracts.

Global and regional myocardial function during stress can be assessed qualitatively which is strongly operator-dependent. The introduction of tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) to stress imaging allows a more quantitative

<table>
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<tr>
<th>Table 1</th>
<th>Comparison between DSE and ESE in paediatrics</th>
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<tr>
<td>Age limit</td>
<td>None</td>
</tr>
<tr>
<td>Anaesthesia/sedation</td>
<td>&lt;8 years</td>
</tr>
<tr>
<td>HR response</td>
<td>+++</td>
</tr>
<tr>
<td>Blood pressure response</td>
<td>Variable</td>
</tr>
<tr>
<td>Inotropy</td>
<td>++++</td>
</tr>
<tr>
<td>Venous return (preload)</td>
<td>No increase/decrease</td>
</tr>
<tr>
<td>Complication rate</td>
<td>Low</td>
</tr>
<tr>
<td>Image acquisition</td>
<td>Easy</td>
</tr>
</tbody>
</table>

+++ , submaximal response.
++++ , maximal response.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Specific LV images/views</th>
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<tr>
<td>LV protocol</td>
<td>Image</td>
</tr>
<tr>
<td>Parasternal long axis</td>
<td>Grey scale</td>
</tr>
<tr>
<td>Parasternal short axis</td>
<td>Grey scale (60–120 fps) Papillary muscle level</td>
</tr>
<tr>
<td>Apical four-chamber view</td>
<td>Grey scale (60–120 fps)</td>
</tr>
<tr>
<td>Pulsed-wave Doppler mitral inflow</td>
<td>Optimize alignment At the tips of the mitral leaflet</td>
</tr>
<tr>
<td>Apical four-chamber view colour TDI</td>
<td>Optimize scale of colour TDI to avoid aliasing</td>
</tr>
<tr>
<td>Pulsed tissue Doppler base LV lateral wall</td>
<td>Optimize scale Alignment with longitudinal motion is key</td>
</tr>
<tr>
<td>Apical two-chamber view</td>
<td>Grey scale (60–120 fps)</td>
</tr>
<tr>
<td>Apical three-chamber view</td>
<td>Grey scale (60–120 fps)</td>
</tr>
<tr>
<td>LVOT CW</td>
<td>Alignment five-chamber or three-chamber view</td>
</tr>
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CW, continuous wave Doppler.

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evaluation of regional and global myocardial function. TDI images can be acquired at high frame rates, but myocardial TDI velocities are influenced by global cardiac motion (translation) and are angle-dependent. To assess systolic and diastolic function, peak systolic and diastolic velocities ($s'$ and $e'$) can be measured at rest and during exercise. Isovolumic acceleration (IVA) during myocardial acceleration, which has been demonstrated to be a relative load-independent index of contractility, can also be measured with colour TDI during exercise. STE allows to quantify regional myocardial deformation by calculating strain and strain rate and has been applied in paediatric heart disease. Owing to motion and breathing artefacts, STE analysis during exercise can be challenging. An important limitation of STE is that frame rates are fixed which implies that with increasing HR, less frames per cardiac cycle will be acquired. This could result in undersampling and inaccuracy in defining end-systolic and end-diastolic frames. The lower sampling rates also significantly affect strain rate calculations. In theory, three-dimensional stress echocardiography could be a useful tool for force–frequency relationship (FFR) during exercise.

**Table 3: Specific RV images/views**

<table>
<thead>
<tr>
<th>RV protocol</th>
<th>Image</th>
<th>Image analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical RV-centric view</td>
<td>Grey scale (60–120 fps)</td>
<td>Qualitative assessment</td>
</tr>
<tr>
<td>PW tricuspid inflow</td>
<td>Optimize alignment</td>
<td>FAC</td>
</tr>
<tr>
<td>CW tricuspid regurgitation</td>
<td>Optimize tracing</td>
<td>Measure peak E-velocity</td>
</tr>
<tr>
<td>Apical RV-centric view colour TDI</td>
<td>Optimize scale of colour TDI to avoid aliasing</td>
<td>If fused, we measure the peak of the fused wave</td>
</tr>
<tr>
<td>TAPSE</td>
<td>M-mode</td>
<td>Measure peak $s'$, $e'$-velocity, and IVA at the base of RV free wall and IVS</td>
</tr>
<tr>
<td>CW RVOT</td>
<td>Alignment</td>
<td>Measure TAPSE</td>
</tr>
</tbody>
</table>

TAPSE, tricuspid annular plane systolic excursion; CW, continuous wave Doppler; PW, Pulsed wave Doppler; RVSp, right ventricular systolic pressure.

**Figure 1** Colour TDI $e'$, $s'$, and IVA measurement at rest and during exercise in a normal control. A and B show the offline analysis at rest and peak of exercise at the level of the tricuspid valve annulus. C and D show the same analysis at the level of the mitral valve annulus.
A rare cause for ischaemic heart disease in children is an anomalous aortic origin and/or course of a coronary artery. This can be associated with an intramural ± interarterial course of the proximal coronary artery with risk for myocardial ischaemia and sudden death.\textsuperscript{32,33} The clinical management of these often asymptomatic patients remains controversial.\textsuperscript{14} Stress testing is generally considered a useful tool in the diagnostic work-up of these patients. Brothers\textit{ et al.} studied 24 children with anomalous origin of a coronary artery, using a multimodality approach including exercise stress technique to apply in children, but so far no group has published any experience with this technique in the paediatric population.

**Current experience with stress echocardiography in paediatric cardiology**

The application of stress echocardiography in paediatric heart disease is an evolving field with changing indications and certainly a change in practice of the techniques used over time. Despite the significant developments in stress imaging techniques that have occurred in the past several years, there are still relatively few studies published on ESE in children.\textsuperscript{11--13} The clinical utilization of ESE is increasing. Between 2011 and 2014, the Toronto group performed a total of 101 clinically indicated ESE studies in 64 heart transplant (HTx) patients, 15 hypertrophic cardiomyopathy (HCM) patients, and 22 other indications, mainly coronary anomalies, arterial switch patients (ASO), and coarctation patients. We also performed 381 ESE research studies in this period, which biases the results as clinicians were aware we were performing the studies in the context of clinical research. The number of DSE in the same era was 30.

**Paediatric ischaemic heart disease**

The most common indications for stress testing in the paediatric population are children at risk for ischaemic heart disease. These include children with Kawasaki disease (KD), after HTx, anomalous origin of the coronary arteries, or children after coronary reimplantation (ASO and Ross operation). The most common cause for acquired ischaemic heart disease in children is KD. Despite the improvements in therapeutic management, coronary aneurysms still occur and can cause myocardial ischaemia and infarction.\textsuperscript{14} Current guidelines recommend stress imaging for the clinical follow-up and risk stratification in patients with isolated small-to-medium coronary artery aneurysms in $\geq$ 1 coronary artery on echocardiography or angiography (class III), patients with $\geq$ 1 large coronary artery aneurysm including giant aneurysms, patients multiple or complex aneurysms without obstruction (class IV), and in patients with coronary artery obstruction confirmed by angiography (Class V).\textsuperscript{15} DSE is the most commonly used technique in children with KD. Noto \textit{et al.} studied 50 children with DSE and angiography. Twenty-one children had $>50\%$ occlusion on one of the major coronary artery documented on angiography and 19 of them also had a positive DSE. Of the remaining children with a negative angiogram, no one had positive DSE.\textsuperscript{16} The same group demonstrated the prognostic value of DSE for predicting cardiac events over a 15-year follow-up in KD patients.\textsuperscript{17} A positive DSE was shown to be a strong independent predictor of long-term major adverse cardiac events in this population. Pahl\textit{ et al.} used ESE to study stress response in 28 children with KD and CAD. Two children developed exercise-induced wall motion abnormalities and subsequently were demonstrated to have a critical stenosis on the left anterior descending coronary artery by angiography.\textsuperscript{18} Henein \textit{et al.} evaluated left ventricular (LV) longitudinal function by measuring M-mode mitral annulus excursion in children with KD. A reduction in global longitudinal function in children with KD was found compared with controls. Coronary artery vasculopathy (CAV) after HTx is the leading cause of re-transplantation, late morbidity, and late death in HTx recipients.\textsuperscript{20} Angiography is considered the gold standard for assessing the presence of CAV, but there is a role for DSE in screening for CAV.\textsuperscript{21,22} Dipchand \textit{et al.} compared DSE with coronary angiography for the diagnosis of CAV and reported that an abnormal DSE significantly increased the relative risk for angiographic abnormalities with high sensitivity and specificity. Chen \textit{et al.} evaluated paediatric HTx patients and demonstrated a 92% specificity and a 97% negative predictive value for the exclusion of significant CAV. ESE has been also used to study the functional response to exercise in paediatric HTx patients. Yeung \textit{et al.} used ESE to study myocardial function during exercise and found a reduced contractile response in paediatric HTx patients ($n = 7$) defined by a reduced velocity of fibre shortening vs. wall stress relationship at peak exercise. The reliability of the wall stress measurements at peak exercise is, however, uncertain. Our group recently described myocardial response to exercise in 43 paediatric HTx patients.\textsuperscript{24} Interestingly, we found a preserved global systolic and diastolic functional response to exercise in the transplant group when compared with a normal control group (Figure 2).

Coronary artery problems in children can also occur in patients after ASO for transposition of the great arteries (TGA). During the surgical procedure, the coronary arteries are translocated, and coronary artery stenosis and occlusion have been demonstrated by angiography and computed tomography in up to $\sim$ 5–7% of patients.\textsuperscript{27–29} As the functional significance of some of the coronary lesions is uncertain, stress echocardiography can be used in children after ASO to detect ischaemia. Hui \textit{et al.} used DSE to study LV function and wall motion abnormalities in 31 children after ASO. When compared with normal controls, ASO patients had reduced LV contractile parameters at rest [fractional shortening (FS), fractional shortening, and velocity of circumferential fibre shortening vs. wall stress] and reversible regional wall motion abnormalities could be detected with DSE in 74% of the patients. Twenty-two children underwent exercise myocardial perfusion scintigraphy and in 17 reversible myocardial perfusion defects were found in the myocardial segments with demonstrated wall motion abnormalities. As no angiography was performed in these patients, the functional significance of these findings remains uncertain. A recent study by Chen \textit{et al.} studied LV contractile reserve during ESE in children after ASO.\textsuperscript{31} They demonstrated reduced contractile response to exercise in children after ASO compared with controls, by constructing FFR curves based on LV myocardial IVA. They also noted a reduced diastolic response in tissue Doppler-derived $e'$ velocity. Further studies are needed, but there is an emerging role for ESE for detecting coronary abnormalities and evaluating functional reserve in patients after ASO (Figure 3A and B).
test, stress echocardiography, and stress myocardial perfusion scan. Despite being asymptomatic during the tests, nine of these children had positive findings suggesting ischaemic changes. The authors argued that a multimodality approach is warranted as the risk for false negative is high in these patients, given the often intermittent nature of the ischaemic episodes. Osaki et al. retrospectively evaluated 31 children diagnosed with anomalous coronary origin. Seventeen of these children underwent DSE as part of the preoperative assessment and with no patient having regional wall motion abnormalities. However, in seven children who underwent surgical repair, in four children abnormal coronary flow patterns were detected during DSE by Doppler echocardiography, and these findings contributed to the decision to intervene surgically.

Dynamic assessment of blood pressure response and gradients

A second clinical application of paediatric stress echocardiography is its use in assessing dynamic gradients. For valvular disease, this certainly is still investigational and has not been introduced in clinical practice. While in adult patients with asymptomatic AS ESE has been demonstrated to have a prognostic value, no data are available in children. Naik et al. showed the occurrence of regional wall motion abnormalities associated with ST-segment depression during ESE in children with AS, but the clinical significance of these findings is still uncertain as some of the patients with these findings only had mild AS at rest. No data are available in children with pulmonary valve stenosis, but a recent study in adults with mild-to-moderate pulmonary valve stenosis demonstrated a linear increase in gradient with increasing flow. Right ventricular (RV) function was preserved in this patient population, but a decreased overall exercise capacity was observed. Studying the effect of exercise on dynamic left ventricular outflow tract (LVOT) obstruction has mainly been used in paediatric patients with HCM. A significant number of HCM patients have no obstruction at rest, but can develop significant dynamic LVOT gradients during exercise. The clinical interpretation of data is still unclear how this affect the interpretation of exercise data of children with HCM. Our group also showed a reduced systolic and diastolic functional reserve in HCM patients, which was unrelated to the degree of outflow obstruction. Stress echocardiography has also been used to study residual gradients in patients with coarctation of the aorta. Recoarctation can be difficult to diagnose and the clinical significance of residual mild gradients across the aortic arch or transverse aorta remains controversial. ESE can be used to study the response of the residual arch obstruction during exercise. The clinical interpretation of data is
still uncertain, but the detection of a significant arch gradient during exercise together with arterial hypertension proximal to the stenosis is a relevant clinical finding that may require further investigation and treatment. In a recent study in patients who underwent stent implantation for coarctation or recoarctation, we found an abnormal blood pressure response in 80% of the patients. In adult patients with coarctation of the aorta, an abnormal contractile response has been demonstrated with a flattened increase in IVA and s’ with an increase in HR. Interestingly, the IVA slope correlated with the exercise-induced increase in systolic and diastolic blood pressure. This may suggest that there is an effect of the increase in afterload during exercise on contractile function or alternatively IVA could be afterload-dependent.

**Early detection of myocardial damage**

Stress echocardiography can be used to study early changes in myocardial function by evaluating the contractile and diastolic response to pharmacological stress or to exercise. Often early myocardial damage is difficult to detect at rest as the heart muscle uses different compensatory mechanisms to maintain pump function. When stressing the heart, revealing a decreased systolic or diastolic response, can be the first indication for early dysfunction. Patients with signs of early dysfunction may require a more regular follow-up compared with those with a preserved stress response. This approach could be used in patients who have been exposed to cardiotoxic agents like anthracyclines or patients with early forms of cardiomyopathy like phenotype-negative carriers of familial cardiomyopathies. There have been a few studies evaluating the stress response in childhood cancer survivors. De Wolf et al. used a low-dose dobutamine infusion (5 μg/kg/min) in 23 childhood cancer survivors who had been exposed to moderate doses of anthracyclines and had normal cardiac function at rest. In this patient group, a decreased systolic response was found in 85% of the patients mainly related to an abnormal wall stress response. Klewer et al. also described decreased LV posterior wall thickening and increased LV end-systolic wall stress in patients exposed to 10 μg/kg/min. In contrast, Lanzarini et al. found a normal response to 15 μg/kg/min in 71 long-term survivors, 7 years after being exposed to medium-dose anthracyclines. ESE has also been used in this patient population. A recent study by Ryerson includes 80 asymptomatic survivors at least 5 years post treatment. This study demonstrated

![Image](https://academic.oup.com/ehjcimaging/article-abstract/16/10/1051/2399773)
Figure 3 (Continued).

Figure 4 Exercise-induced LV outflow tract obstruction in a patient with hypertrophic cardiomyopathy.
some mild diastolic abnormalities at rest which disappeared during exercise. Sieswerda et al. 54 looked at the predictive value of peak exercise EF in 110 asymptomatic anthracycline-treated paediatric cancer survivors. This group found that peak exercise EF did not predict reduced EF 10 years later. As EF can be maintained in damaged myocardium due to compensatory mechanisms, research into early markers of myocardial dysfunction could potentially be more useful and further prospective research is required in this area.

**RV response**

Stress echocardiography can be used to study RV function and the pulmonary vascular response. ESE has been used to study the change in RV pressure during exercise as an indicator of increased pulmonary vascular resistance. Utilizing ESE, in patients with closed atrial and ventricular septal defects, Moller et al. 55 found an abnormal RV systolic pressure response in ~33% of the patients. Van de Bruaene et al. 56 found altered pulmonary haemodynamics during exercise in patients who underwent atrial septal defect closure later in life (>34 years). The dynamic response to exercise could be used to identify patients with abnormal pulmonary vascular resistance or subclinical pulmonary hypertension.

Stress echocardiography can also be used for studying the RV systolic and diastolic response to exercise. Children after tetralogy of Fallot (TOF) repair often have significant residual lesion, the most common being pulmonary regurgitation. This can cause progressive RV dilatation and dysfunction. Identification of early signs of RV dysfunction by stress echocardiography could be helpful at determining optimal timing for valve replacement. Ait-Alli et al. 57 studied 128 young adults after surgical repair for TOF with ESE. They obtained data on fractional area change (FAC), tricuspid annular plane systolic excursion, and RV systolic pressure. Results could be obtained in 96% of the patients. The authors defined two types of responses: one group of patients increased FAC with exercise (74 patients) whereas in the remaining 49 patients no increase in FAC or even a decrease was observed. The clinical characteristics of both groups were not significantly different, and it is the relevance of these findings. Roche et al. 58 studied asymptomatic TOF children with ESE and demonstrated a significant increase in markers of LV and RV dyssynchrony during exercise. Preliminary data from our group also suggest a reduced RV IVA vs. HR response in TOF patients compared with normal controls. 59,60 Hasan et al. utilized ESE to evaluate an RV functional response during exercise in 20 patients with an obstructed RV to pulmonary artery conduit. The authors assessed changes the exercise response before and after transcatheter pulmonary valve implantation. 61 Data from this study showed a substantial improvement in RV systolic function after intervention, as demonstrated by an increase in RV FAC, and RV global strain at rest and at peak exercise. Further data are required regarding the clinical utilization of exercise echocardiography in TOF patients, but the initial data seem promising.

**Conflict of interest:** None declared.

References


