Stress and strain: double trouble or useful tool?

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Cardiac deformation imaging is being used more and more routinely in resting echocardiography. The technique can also be applied to stress studies, and may provide additional information to that obtained by standard analysis alone. This review explores its present role, limitations, and potential uses. Although currently not widely used in stress studies, deformation imaging has the capability to provide clinically useful information.

KEYWORDS
Stress echocardiography; Deformation imaging; Strain

Introduction

The assessment of left ventricular (LV) function with stress is important. Many cardiac conditions present with symptoms only on exertion, at least in the initial stages, and investigations at rest may be normal. To be able to detect subclinical LV dysfunction is the holy grail of echocardiography in many situations, and stress echocardiography, either with physical exercise or pharmacological stress, is well recognized as playing a role in the evaluation of ischaemic heart disease, valve disease, and hypertrophic cardiomyopathy among others.1

Standard stress echocardiography, using the visual assessment of wall motion to detect abnormalities, is qualitative and subjective, and despite efforts to standardize by using wall motion scores1 and enhance myocardial border detection with transpulmonary contrast,2,3 the learning curve is steep and there is still variable reproducibility between observers and institutions.4,5

Advanced echocardiographic techniques such as strain imaging, which is now widely used in resting echocardiograms, may also be applied to stress studies. This technique may be helpful in providing a more quantitative assessment of abnormalities and therefore reducing some of the current difficulties inherent in stress echo interpretation.

Strain imaging methods, feasibility, and normal patterns

Strain is a measure of myocardial deformation, and can be measured using either tissue Doppler imaging (TDI) or 2D speckle tracking echocardiography (STE). Each of these methods has its own advantages and disadvantages (see Table 1). Specific to the speckle tracking technique, however, is the ability to provide a measure of global strain, which is achieved by averaging the results from all segments of myocardium to produce a single overall value. This is useful when assessing conditions which affect the entire myocardium, such as valve disease. In stress echo though, the emphasis is often on detection of ischaemia or viability, which demands a more regional approach to analysis.

Regardless of the method chosen, measurements of strain and strain rate (SR; its derivative with respect to time, see Figure 1) have inherent limitations which must be considered when assessing the utility of the technique. First, there has to be a compromise between spatial resolution and background noise; SR measurement in particular is prone to noise interference which can make interpretation challenging. Reverberation artefacts (such as rib artefacts) and drop-out, which are not always immediately apparent on the 2D image, can give misleading results. Systole, particularly end-systole, needs to be clearly defined throughout stress (and as the heart rate increases), in order to differentiate systolic shortening from post-systolic shortening (see later on for further discussion on this). And finally, myocardial deformation is a three-dimensional process, and currently echocardiography is limited to assessing only one (i.e. TDI) or two (STE) dimensions at a time.

However, the feasibility of using both TDI and STE with stress has been examined,6,7 as has the feasibility of both techniques with either dobutamine stress echo (DSE) or exercise.8–12 Both echo techniques appear to be comparable, although reported feasibility with either one is variable on exercise; Davidavicius et al.8 and Pierre-Justin et al.9 reporting up to 40% of segments (particularly apical segments) proving impossible to analyse due to image degradation, but rather better feasibility being reported by Reuss...
Table 1  Comparison of TDI and STE techniques

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<tr>
<th>Advantage/Tissue Doppler imaging</th>
<th>Advantage/Speckle tracking imaging</th>
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<tr>
<td>High frame rates give good temporal resolution</td>
<td>Angle independent</td>
</tr>
<tr>
<td>Readily available on most modern echo machines</td>
<td>Deformation can be assessed in two dimensions</td>
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<tr>
<td>Analysis can be done online or offline</td>
<td>Can measure both regional and global strain</td>
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<tr>
<td>Less influenced by artefacts than TDI</td>
<td>More reproducible than TDI</td>
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<td>More reproducible than TDI</td>
<td>Semi-automated processing</td>
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<tr>
<th>Disadvantage/Tissue Doppler imaging</th>
<th>Disadvantage/Speckle tracking imaging</th>
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<tr>
<td>Highly angle dependent</td>
<td>Highly angle dependent</td>
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<tr>
<td>Can assess deformation in only one dimension</td>
<td>Can assess deformation in only one dimension</td>
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<tr>
<td>Size and placement of sample volumes done manually—variation significantly affects results</td>
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<tr>
<td>Strain data derived from tissue velocity data—prone to noise</td>
<td>Strain data derived from tissue velocity data—prone to noise</td>
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<tr>
<td>Apical segments particularly difficult to interpret</td>
<td>Apical segments particularly difficult to interpret</td>
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<tr>
<td>Can only measure regional strain; no equivalent to STE’s global strain</td>
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<tr>
<td>Lower spatial resolution than TDI as region of interest determined automatically</td>
<td>Tracking affected by out of plane cardiac motion</td>
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<td>Lateral resolution more limited than axial resolution</td>
<td>Lateral resolution more limited than axial resolution</td>
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<tr>
<td>Automatic tracking must be manually confirmed for each segment</td>
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<tr>
<td>Less readily available than TDI</td>
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TDI, tissue Doppler imaging; STE, speckle tracking echocardiography.

Figure 1  (A) Normal strain curve. (B) Normal strain-rate curve.
et al.\textsuperscript{10} and Goebel et al.\textsuperscript{11} in their studies, at around 80% for both tissue velocities and strain data.

In healthy adults, both peak tissue velocities and SR increase linearly with increasing heart rate.\textsuperscript{8–13} Strain, however, follows a biphasic pattern, initially increasing at low stress, but remaining constant or even decreasing slightly as heart rate increases. This could reflect a reduction in stroke volume at higher heart rates due to reduced LV filling time, and suggests that SR rather than strain itself may be a more sensitive marker of changes in myocardial function during stress.

Detection of ischaemia

Just as in daily clinical practice the main aim of most stress echocardiograms is the detection of myocardial ischaemia, so the majority of studies have focused on this area. Tissue velocities and displacement were investigated initially,\textsuperscript{14–17} but were limited by the fact that myocardial velocities and displacement are affected both by tethering from adjacent segments and by overall movement of the heart.\textsuperscript{18,19} Strain and strain-derived measures were found to be more reliable, and are subject to less influence from such events.\textsuperscript{16,20}

Post-systolic shortening (PSS) (Figure 2) then emerged as an attractive marker of ischaemia which could be easily identified, and was correlated with both ischaemia on myocardial scintigraphy (with confirmation of significant coronary lesions by angiography)\textsuperscript{13} and invasively measured end-systolic elastance (regarded as the gold standard measure of myocardial systolic function).\textsuperscript{21} These studies showed that PSS is highly sensitive to ischaemia, occurring in 100% of ischaemic segments, and the magnitude of post-systolic strain increases both with resting ischaemia or ischaemia induced with increasing heart rate.

However, it is recognized that PSS can occur in conditions other than ischaemia, such as LV hypertrophy,\textsuperscript{22} or left bundle branch block,\textsuperscript{23} and also in a proportion of normal hearts.\textsuperscript{24} Clearly in order to maximize the specificity of the stress test it is important to be able to distinguish between pathological and non-pathological PSS. Voigt et al.\textsuperscript{13} used the ratio of PSS to peak strain to improve specificity in their study, and Weidemann et al. suggested that SR during isovolumic relaxation (i.e. at the time of PSS) gives a clue—if SR is positive during this time then this points towards ischaemic PSS, whereas if SR is negative then another cause of PSS is likely. This rule of thumb was 100% sensitive and 87% specific in their small study. Another small study, this time using exercise testing, by Thambyrajah et al.\textsuperscript{25} also showed the value of post-systolic SR and its timing by demonstrating that changes in these parameters occurred in areas of myocardium supplied by stenosed coronary arteries after percutaneous revascularization but not in segments distant to the diseased artery.

Assessing the functional significance of moderate coronary disease causes particular difficulty in day-to-day practice. SR measures have been correlated with fractional flow reserve (FFR) by coronary angiography, in order to try and help with this situation. Dagelen et al.\textsuperscript{26} found that both strain and SR correlated with FFR within the left coronary system, and more recent work by Weidemann et al. showed that strain and SR in this situation changed in opposite directions—in ischaemic myocardium strain decreased with stress while SR stayed the same, while in non-ischaemic myocardium strain did not change with stress although SR increased. Analysis of receiver-operating characteristic curves showed the change in SR to be the best predictor of significance of intermediate coronary lesions, with a sensitivity and specificity of 89 and 86% respectively.\textsuperscript{27}

Assessment of viability

Deformation imaging can be helpful in differentiating different myocardial responses to stress after chronic ischaemia or infarction. Hoffman et al.\textsuperscript{28} validated strain imaging for myocardial viability at low-dose dobutamine against positron emission tomography in 37 patients with ischaemic

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure2}
\caption{Post-systolic strain.}
\end{figure}
cardiomyopathy. This study found that SR was better at predicting viability than tissue velocities, which was thought to be due to both regional SR being less susceptible to tethering effects from adjacent myocardium and also the lack of a basoapical gradient with strain measures. The following year, Weidemann et al. published a study carried out in pigs showing that strain and SR could differentiate transmural from non-transmural infarct (Table 2), and by including information on PSS, myocardial stunning could also be identified. The magnitude of the reduction in strain also appeared to be related to the size of the infarcted area, and therefore this information was semi-quantitative as well as qualitative.

Deformation with dipyridamole stress echo was investigated in an animal model by Marciniak et al. They compared deformation with dipyridamole (vasodilator stress) with the results following dobutamine stress in the same animals, known to have single vessel ischaemia. They found that normal and infarcted myocardium showed no change in deformation following dipyridamole, but both systolic strain and SR improved in viable but stunned myocardium.

In the clinical setting, Hanekom et al. looked at the use of SR in assessing viability by comparing values pre- and post-revascularization in 55 stable patients with LV dysfunction following previous myocardial infarction. They found similar results to other investigators, with lower strain and SR values at low doses of dobutamine (and lower increases in these measures from baseline) in myocardial segments which failed to show functional recovery after revascularization compared with those which recovered. These parameters, when used in combination with wall motion assessment, increased the sensitivity of predicting viability above wall motion assessment alone (82% compared with 73%, $P = 0.015$; area under the curve 0.88 compared with 0.73, $P < 0.001$), although specificities were similar.

In addition to systolic SR measures, SR in diastole has also been shown to differentiate viable from non-viable myocardium. Both early (E) and late (A) diastolic SR waves increased with dobutamine in viable segments compared with non-viable ones, and in an animal model radial SR E-wave was strongly correlated with the degree of interstitial fibrosis both at rest ($r = -0.75, P < 0.01$) and with dobutamine ($r = -0.86, P < 0.01$).

Other applications

Away from the assessment of ischaemia and viability, myocardial deformation with stress has also been shown to be helpful in a number of other conditions. Lancellotti et al. recently published data on longitudinal strain on exercise in chronic mitral regurgitation, using speckle tracking. They found that an increase in global longitudinal strain of $<1.9\%$ on exercise predicted post-operative LV dysfunction after mitral valve surgery with a sensitivity of 92% and specificity of 70%. Likewise, two studies have shown the utility of strain measures with stress in predicting response to cardiac resynchronization therapy (CRT). Ypenburg et al. used STE with low-dose dobutamine to assess regional contractile reserve in the area of likely LV lead placement prior to CRT implantation and showed that those patients who responded to CRT (as evidenced by a reduction in end-systolic volume at 6 months post-implant) had a significantly greater increase in strain with dobutamine than those who did not respond. Moonen et al.’s study assessed regional strain in a similar manner, but used exercise stress rather than dobutamine, and found comparable results.

In diabetics, a cardiomyopathy unassociated with coronary artery disease has been described, which is characterized by LV hypertrophy and abnormal LV wall mechanics. Galderisi et al. have examined the use of SR imaging in these patients during DSE and found a blunted response to dobutamine for both strain and SR (but not tissue velocities) in the diabetic patients compared with controls. This difference remained even once hypertensive patients or those with LVH had been excluded. Interestingly, however, they did not see the biphasic strain response to increasing heart rate described by the previous studies in either the control group or the diabetic group.

Several studies have examined its use in heart failure. In chronic heart failure, a small study looked at the effects of intra-coronary stem-cell transplantation on myocardial deformation with rest and stress in patients with severe LV dysfunction [mean ejection fraction (EF) 19%]. All patients had had a previous myocardial infarction with no evidence of reversible ischaemia on SPECT imaging, but despite the fact that there was no significant increase in EF after the stem-cell procedure, peak systolic strain and SR increased on exercise in viable segments. There was a trend towards symptomatic improvement in these patients, and these results may signify recruitment of hibernating myocardium after stem-cell treatment, and suggest that any such treatment should be targeted to viable areas of myocardium. In another study, looking at acute heart failure, the change in systolic SR with dobutamine (measured by speckle-tracking) was also found to be the best predictor of both a symptomatic improvement and improvement in brain-natriuretic peptide levels following levosimendan treatment ($P < 0.05$). Following cardiac transplantation, a study by Eroglu et al. published recently suggests that quantitative DSE with deformation imaging may be helpful in the...
diagnosis of coronary artery vasculopathy, which is important to detect and usually involves invasive coronary angiography. Peak systolic SR, however, during DSE appeared to be a sensitive measure to detect any degree of vasculopathy, with an increase in SR of < 0.5/s having a sensitivity of 88%, specificity of 85%, and a negative predictive value of 92%.

Stress deformation imaging has also been studied in congenital heart disease, after Kawasaki disease, and in athletes. With the exception of Stefani’s paper, which used isotonic exercise, strain and SR were found to be abnormal. With an increase in SR of 88%, specificity of 85%, and a negative predictive value of 92%, stress deformation imaging appears to be a sensitive measure to detect any degree of vasculopathy.

**Day-to-day use**

Despite data suggesting that deformation imaging with stress can help in the assessment of a variety of conditions, its acceptance into day-to-day clinical practice has still to occur. This is reflected in the fact that the European Association of Echocardiography (EAE), in their recent consensus statement, did not recommend its incorporation into routine stress echo studies. Feasibility of the techniques has been demonstrated, but the main barrier to their introduction is the time-consuming nature of the post-processing and analysis. In addition to this, each technique also has its own specific drawbacks; tissue Doppler is limited by the inherent angle-dependency of any Doppler-derived data, whereas for speckle-tracking excellent 2D image quality must be obtained. Both modalities are also difficult to use in conjunction with transpulmonary contrast, which was recommended for use by the EAE when necessary. Finally, in order for strain imaging to be incorporated into a routine study, incremental value over standard assessment of wall motion in terms of diagnostic capability or prognostic information needs to be demonstrated.

Hanekom et al. attempted to minimize these drawbacks in their study of 150 patients undergoing DSE and coronary angiography. They used a ‘sentinel segment’ approach; analysing one specific segment for each of the territories of the three main coronary arteries, by both TDI and STE. They found that at peak stress, STE was more difficult than TDI, although at rest STE was more reproducible. The accuracy of the two techniques for predicting significant coronary disease was similar to wall-motion assessment (WMA) in the left anterior descending (LAD) coronary circulation. STE was inferior to both WMA and TDI in the right coronary artery (RCA) territory, and in the circumflex territory both STE and TDI were less good at predicting disease than WMA. Overall, even with this limited segmental analysis, both TDI and STE strain imaging remained time-consuming (an average of 25 min of analysis per patient), and in this study at least, even with reasonable patient numbers, did not add incremental value to the diagnosis of coronary disease based on WMA alone.

More recently, however, an automated measurement algorithm has been reported and validated against coronary angiography. This customized algorithm uses a combination of STE to track the myocardium and TDI data, and may improve on post-processing times compared with manual analysis. Feasibility of strain and SR analysis during stress in this study of almost 200 patients was slightly lower than conventional WMA, but the sensitivity of the test increased with deformation imaging from 75% for WMA alone to 84–88% with the addition of the new techniques.

The same group, using the same analysis algorithm, has also demonstrated incremental prognostic value of deformation to that of assessment of WMA alone in a large study of 646 patients followed up over 7 years. In particular, systolic SR appeared to offer independent prognostic information. Another large study, albeit with a mean follow-up period of only 10.7 months, also demonstrated a lower cardiac event rate in those with normal deformation on stress compared with those in which strain was abnormal.

So, deformation stress echo appears feasible, able to identify pathology with as good if not better sensitivity than traditional wall motion analysis, and does appear to offer additional prognostic information to that gained by wall motion assessment alone. However, stress echo by any method has a steep learning curve and significant experience is needed in order to maximize its sensitivity. Unfortunately, these new tools at present may not significantly reduce this as the advanced echo techniques themselves demand a degree of expertise. There is also the time factor to overcome, but some of the newer more automated techniques may help in both these regards. In addition, appropriate cut-off values for normality vs. different types of abnormality (ischaemia, viability, etc.) need to be defined from a detailed meta-analysis of the literature, as currently there are no clear definitions and each study has used their own values according to varying endpoints.

Although it is perhaps too soon to unreservedly embrace deformation imaging into daily stress echo practice, there appears to be enough data to suggest that in time it may be used more routinely outside of the research environment. The answer though ultimately is likely to be a combination of the old and the new—balancing WMA with adjunctive information from deformation in order to obtain semi-quantification. In day-to-day clinical practice, where patient management is not just a science but also an art, adding some colour to black and white may eventually bring an additional dimension to decision-making.

Conflict of interest: none declared.

**References**

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