Aims Early left ventricular (LV) dysfunction in asymptomatic patients with severe aortic regurgitation (AR) may go undetected due to the lack of a sufficiently sensitive diagnostic tool. Ultrasonic strain/strain rate (S/SR) imaging should now provide such sensitivity in detecting early dysfunction in regional LV systolic deformation. The aim of this study was to understand and define the changes in LV regional systolic deformation based on S/SR imaging in patients with asymptomatic or minimally symptomatic AR.

Methods and results Eighty-one individuals were studied: 59 asymptomatic patients with isolated non-ischaemic AR who were divided into three sub-groups such as mild, moderate, and severe AR and 22 age-matched healthy subjects. All patients underwent standard echocardiographic examinations including a tissue Doppler imaging study. For LV radial deformation, the posterior wall (LVPW) was examined. To assess LV longitudinal deformation, S and SR data were acquired from the LV lateral wall and septum. Radial as well as longitudinal peak systolic SRs were significantly decreased in patients with both moderate AR (LVPW, \( P = 0.0009 \); septum, \( P = 0.03 \); LV lateral wall, \( P = 0.0009 \)) compared with healthy subjects. Changes in regional LV deformation correlated inversely both with LV end-diastolic volume and with end-systolic volume.

Conclusions Strain rate imaging is a sensitive tool in detecting the spectrum of changes in radial and longitudinal deformation in asymptomatic or minimally symptomatic patients with AR. The index where volume was corrected by deformation should form the basis for predicting subclinical LV dysfunction in patients with increasing LV dilatation.

**Introduction**

Preoperative left ventricular (LV) systolic function is an important prognostic factor in patients with chronic aortic regurgitation (AR).\(^1\)\(^-\)\(^7\) Standard grey scale echocardiography has been used as a gold standard to quantify systolic LV function. It has been recommended that surgery in asymptomatic patients with AR should be performed before the ejection fraction (EF) falls below 50% and end-systolic dimension (ESD) exceeds 50 mm.\(^1\) However, the use of volume-based parameters, such as EF, to assess myocardial function, may have important limitations when loading conditions are altered. Changes in regurgitant volume or increases in LV systolic or diastolic pressure can mask underlying abnormal changes in myocardial force development due to myocardial damage.\(^8\) In addition, current conventional echocardiographic parameters assess only LV global function. In the context of AR, when there is regional variation in wall stress, it may be important to measure regional ventricular function. Furthermore, if surgery is postponed until the patient becomes symptomatic, there may be already irreversible LV dysfunction.\(^7\)\(^,\)\(^9\)\(^-\)\(^11\)

Although there have been several clinical studies which have identified abnormalities in LV function in patients with AR,\(^12\)\(^-\)\(^14\) none of them have been able to identify subclinical LV dysfunction.

Regional strain (S) and strain rate (SR) imaging is a new cardiac ultrasound modality (based on myocardial velocity imaging—MVI) which allows the detection of abnormalities in regional deformation which are closely related to changes in regional contractile function. It has been shown to be an accurate method for the non-invasive quantification of systolic deformation, and can in certain disease states detect changes in regional systolic function at a sub-clinical stage than either conventional echocardiography or MVI.\(^15\)\(^,\)\(^16\)
The aims of this study were to determine if SR/S imaging might add to the understanding of changes in regional LV systolic function in patients with different degrees of volume loading due to AR and to assess the potential of SR/S imaging in detecting sub-clinical LV dysfunction in patients with AR.

Methods

Study population

The study population consisted of 81 individuals: 59 patients (age 52 ± 11) with isolated, non-ischaemic AR and 22 healthy subjects (control group, age 50 ± 11). The patients with AR were a series of consecutive patients referred to the Department of Echocardiography, St. George’s Hospital, London, with a diagnosis of isolated AR. The aetiologies of the isolated long-standing AR were as follows: bicuspid aortic valve (AV) (30 patients), leaflet non-coaptation (23 patients), previously treated AV endocarditis (5 patients), and quadricuspid AV (1 patient).

All patients were in NYHA class ≤II, and isolated AR was confirmed by cardiac ultrasound in all 59 patients. They were subsequently subdivided into three groups according to regurgitant volume. Mild AR was associated with a regurgitant volume of <30 mL (n = 10), moderate AR: between 30 and 60 mL (n = 13), and severe AR >60 mL (n = 36). Aortic regurgitant volumes were quantified according to previously published guidelines. Aortic/mitral stroke volumes were obtained by multiplying the area of the mitral annulus/outflow tract with the velocity time integral of the puls Doppler trace of the flow through the respective valve.

Furthermore, moderate and severe AR were confirmed by the degree of holodiastolic flow reversal in the descending aorta.

Patients were excluded if they had acute AR, coronary artery disease, or co-existing disease of any other valve which was more than trivial. Patients with significant cardiac arrhythmia or conduction defects were also excluded. No patient had had previous cardiac surgery.

During the same period, healthy controls were recruited from the local population via advertisements using posters and announcements in the local media. From the 35 controls initially assessed in this way, all subjects (n = 22) comprised within ±1.5 standard deviations of the mean patient age were included for further data analysis. An informed written consent was obtained from all patients and controls.

Neither the control group nor the patients with mild, moderate, or severe AR had a history of ischaemic heart disease, or had significant risk factors. The resting 12-lead ECG showed no evidence of ischaemia.

A total of 26 patients with severe AR and 3 with moderate AR had coronary angiograms within 3 months of their echocardiogram. None had coronary artery disease.

Standard echocardiography

Standard echocardiographic data, including the acquisition of MVi data sets (for the calculation of SR and S), were obtained from all patients. All echocardiographic studies were performed using a Vivid 7 ultrasound scanner (General Electric–GE Vingmed). The images were acquired from standard parasternal and apical views. Standard LV M-mode measurements included the estimation of LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), intraventricular septum, and LV posterior wall thickness (LVPW). EF, end-diastolic volume (EDV), end-systolic volume (ESV), and stroke volume (SV) were measured using the biplane Simpson’s method.

Strain rate imaging study

For the evaluation of longitudinal function, mid-ventricular segment shortening was analysed for the septum and LV lateral walls. For LV radial function, mid-ventricular segment thickening of the LVPW was analysed.

Strain (S) defines the amount of local deformation expressed as a percentage and is derived by integrating the SR curve over time. SR measures the rate of segmental deformation and corresponds to the local spatial velocity gradient, expressed in s⁻¹. By convention, SR values are positive when a myocardial segment thickens/lengthens and negative when a segment thins/shortens. Computational areas with a length in the direction of the scan line of 10 mm (longitudinal) and 5 mm (radial) and with a width of 1 mm (to avoid averaging different ultrasound beams) were used. Frame-by-frame manual tracking performed during post-processing to maintain the computational area within the myocardial region of interest throughout the cardiac cycle. SR and S values were averaged over three consecutive cycles. AV opening and closure were defined using pulsed wave blood pool Doppler tracings acquired during the same examination and with a similar R–R interval in order to determine the duration of ejection. Peak systolic SR and end-systolic S during the ejection period were assessed for each segment analysed. In addition, a deformation index, normalizing the deformation parameters by the end-diastolic volume (SR/EDV and S/EDV), was determined in order to correct for the volume dependency of deformation.

All data were analysed off-line using a dedicated workstation (GE Echopac). A frame rate of 200–300 frames per second was used to acquire data. An image sector angle of 15° and an optimal depth of imaging were used to increase temporal resolution. Special attention was paid to the colour Doppler velocity range setting in order to avoid any aliasing within the image. For this purpose and to simultaneously optimize velocity resolution, pulsed repetition frequency (PRF) values were set as low as possible, just avoiding aliasing.

Statistical analysis

Results are expressed as means ± SD. Given the exploratory nature of this study, no formal sample size calculated and data were collected over a 1 year period. Statistical analysis was performed with Statistica (version 7.1, StatSoft Inc., Tulsa, OK). For correlations between variables, the Pearson correlation was calculated. A two-tailed P-value of <0.05 was considered statistically significant.

Results

The clinical and echocardiographic data of all patients are shown in Table 1. Patients with moderate AR had significantly increased EDD (P = 0.0009), and volumes (EDV, P = 0.003; ESV, P = 0.02; SV, P = 0.014) compared with the control group. Patients with severe AR had LV diameters (EDD, ESD) and volumes (EDV, ESV, and SV) which were significantly higher (P < 0.0001) while their EF was significantly lower (P < 0.0001) compared with control subjects. There were no differences between the mild AR and control group.

Left ventricular mass was significantly higher in the moderate and severe AR groups compared with controls (P = 0.0007 and P < 0.0001, respectively).

Strain and strain rate imaging data

Strain rate data sets could be obtained and analysed from all patients and controls. Eighty-one segments were used to quantify regional radial systolic function of the LVPW from the parasternal short axis. The apical four-chamber view was used to quantify longitudinal systolic deformation of the mid-segments of septum and LV lateral walls (162 segments were analysed).

Radial and longitudinal peak systolic SR values (Table 2) were significantly lower in the severe AR group compared with controls (P < 0.0001). Radial and longitudinal SR were significantly decreased in moderate AR (LVPW, P = 0.0009;
Table 1 Clinical and standard echocardiographic parameters

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 22)</th>
<th>Mild AR (n = 10)</th>
<th>Moderate AR (n = 13)</th>
<th>Severe AR (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50 ± 11</td>
<td>54 ± 9</td>
<td>56 ± 13</td>
<td>48 ± 13</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>60 ± 10</td>
<td>59 ± 10</td>
<td>68 ± 11</td>
<td>68 ± 12</td>
</tr>
<tr>
<td>LV EDD (cm)</td>
<td>4.5 ± 0.3</td>
<td>4.7 ± 0.5</td>
<td>5.3 ± 0.8*</td>
<td>6.6 ± 0.9*</td>
</tr>
<tr>
<td>LV ESD (cm)</td>
<td>2.9 ± 0.4</td>
<td>3.0 ± 0.3</td>
<td>3.4 ± 0.7</td>
<td>4.6 ± 1.0*</td>
</tr>
<tr>
<td>IVS (cm)</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>1.0 ± 0.2*</td>
</tr>
<tr>
<td>PWT (cm)</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.2*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>67 ± 6</td>
<td>63 ± 6</td>
<td>64 ± 6</td>
<td>55 ± 9*</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>107 ± 23</td>
<td>108 ± 27</td>
<td>148 ± 51‡</td>
<td>231 ± 70*</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>35 ± 11</td>
<td>37 ± 12</td>
<td>50 ± 24</td>
<td>103 ± 49*</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>72 ± 15</td>
<td>68 ± 20</td>
<td>93 ± 31</td>
<td>117 ± 37*</td>
</tr>
<tr>
<td>LV mass</td>
<td>139 ± 50</td>
<td>157 ± 51</td>
<td>226 ± 78**</td>
<td>413 ± 167*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
AR, aortic regurgitation; HR, heart rate; LV, left ventricle; EDD, end-diastolic diameter; ESD, end-systolic diameter; IVS, interventricular septum; PWT, posterior wall thickness; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume.
*P < 0.0001, **P = 0.0007, †P = 0.0009, ‡P < 0.05 vs. control group.

Table 2 Radial and longitudinal systolic function of the LV estimated by peak systolic strain rate

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 22)</th>
<th>Mild AR (n = 10)</th>
<th>Moderate AR (n = 13)</th>
<th>Severe AR (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasternal SAX</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LVPW (s⁻¹)</td>
<td>3.0 ± 0.5</td>
<td>3.0 ± 0.4</td>
<td>2.6 ± 0.5**</td>
<td>2.1 ± 0.6*</td>
</tr>
<tr>
<td>Apical four-chamber</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septum (s⁻¹)</td>
<td>1.54 ± 0.32</td>
<td>1.67 ± 0.32</td>
<td>1.32 ± 0.28**</td>
<td>1.11 ± 0.42*</td>
</tr>
<tr>
<td>LV lateral wall (s⁻¹)</td>
<td>1.63 ± 0.24</td>
<td>1.64 ± 0.37</td>
<td>1.22 ± 0.33‡</td>
<td>1.08 ± 0.28*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
AR, aortic regurgitation; LV, left ventricle; SAX, short axis; LVPW, left ventricular posterior wall.
*P < 0.0001, **P = 0.0009, †P = 0.03 vs. control group.

Table 3 Radial and longitudinal systolic function of the LV estimated by peak systolic strain

<table>
<thead>
<tr>
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<th>Control (n = 22)</th>
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<th>Moderate AR (n = 13)</th>
<th>Severe AR (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasternal SAX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVPW (%)</td>
<td>51 ± 9</td>
<td>45 ± 9</td>
<td>45 ± 16</td>
<td>32 ± 10*</td>
</tr>
<tr>
<td>Apical four-chamber</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septum (%)</td>
<td>21 ± 6</td>
<td>21 ± 4</td>
<td>18 ± 3</td>
<td>14 ± 6*</td>
</tr>
<tr>
<td>LV lateral wall (%)</td>
<td>21 ± 5</td>
<td>22 ± 4</td>
<td>19 ± 4</td>
<td>15 ± 5*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
AR, aortic regurgitation; LV, left ventricle; SAX, short axis; LVPW, left ventricular posterior wall.
*P < 0.0001 vs. control group.

Discussion

Patients with chronic AR develop LV dilatation in order to cope with the volume overload. In addition, LV hypertrophy occurs to cope with the required increase in contractility.

septum, \( P = 0.03 \); LV lateral wall, \( P = 0.0009 \) vs. control group). Radial and longitudinal end-systolic \( S \) values (Table 3) were also lower in the severe AR group compared with controls (\( P < 0.0001 \)) while no difference was found in deformation between moderate AR and controls. There were no significant differences in peak systolic SR and end-systolic \( S \) values between patients with mild AR and controls. Scatter plots of the peak systolic SR and end-systolic S values for radial and longitudinal deformation for all patients and controls are shown in Figure 1.

Strain rate values for moderate AR show significant overlap with controls, but in a few individuals it is seen that the speed of longitudinal deformation (SR) is already decreased while deformation itself (\( S \)) remains normal (Figure 1). For severe AR, SR and \( S \) values present to be significantly lower compared to the other groups but there is still an important overlap between part of deformation indices and these groups (Figure 1).

Radial and longitudinal peak systolic SR and \( S \) were inversely correlated with EDD as well as with ESD for both controls and patients with AR (Figures 2 and 3).

The index was calculated by dividing deformation by diameter: SR/EDV and S/EDV show a significant reduction in patients particularly with severe AR (Figure 4). Values of SR/EDV and S/EDV indices were included in Table 4 and showed significantly lower values in severe and moderate AR group compared with controls.

Example of longitudinal SR curves of a patient with severe AR and control subject is presented in Figure 5.
This ensures the preservation of a normal forward SV and maintains wall stress within normal limits. Despite having a dilated and hypertrophied heart, patients are usually clinically asymptomatic. However, when all compensatory mechanisms used to displace an increasing volume are exhausted, irreversible myocardial dysfunction occurs. Therefore, in order to prevent severe deterioration of LV systolic function and heart failure, the early detection of sub-clinical LV dysfunction is important in the clinical management of patients with valve regurgitation. Furthermore, it has already been demonstrated that patients with poor LV function due to AR have both increased postoperative morbidity and mortality.

Bruch et al. have shown that peak systolic and early diastolic annular velocities increase with increased SV in the presence of volume overload. This means that in patients with impaired systolic/diastolic performance and concomitant AR, the presence of an increased SV can result in normal or increased velocities despite impaired contractile function. However, if reduced longitudinal systolic velocities are detected in patients with AR during peak exercise, they clearly show signs of decreased myocardial function.

Attempts to assess regional function based on MVI have shown that this can provide complementary information for the assessment of EF and filling parameters in patients with AR. However, the values obtained are markedly influenced by the increased volumes and the exaggerated overall motion of the hyperdynamic hearts that are observed in these pathologies.

Previous studies have shown that the speed of deformation represented by $S$ increases with increasing SV and that deformation represented by SR parallels change in contractility. The LV response to increased SV is to increase both contractility and LV diameter, which is what we observe in the group of patients with severe AR where SR and $S$ values are within normal limits.
A chronic increase in SV, with a resulting dilatation, causes permanently increased wall stress which can lead to myocardial damage resulting in a decrease in peak systolic deformation indices when contractile function is no longer preserved. Such changes in deformation indices were detected in patients with severe AR. Patients with moderate AR showed changes in SR that reflects the speed of deformation closely linked to the intrinsic force generation. These results would suggest that while total deformation is preserved, the speed of deformation is already starting to decrease in moderate degree of regurgitation. However, on the basis of our results, deformation is not directly related to the degree of AR itself. Deformation is determined by the interaction of ventricular volume, the SV, and the contractility of the muscle.

We have already shown that, in patients with volume overload due to mitral regurgitation (confirmed by mathematical modelling), the size of the ventricle correlates with the deformation and that deformation indices decrease with increasing LV size. As in this study, the deformation index, which corrects for changes in geometry, was introduced for the assessment of the systolic LV function in AR. This could be of importance as the geometry of the ventricle changes.

According to the recently introduced AHA/ACC guidelines, asymptomatic patients with severe AR should be referred for surgery when their ESD reaches 5.0 cm. These guidelines have actually lowered the previously used surgical threshold of ESD of 5.5 cm suggested in 1998. This also indicates that it is very difficult to identify the optimum threshold for this group of asymptomatic patients using standard echocardiographic measurements that assess only global LV function.

We have shown that with increasing volume overload, while ESD increases, SR and S values decrease in patients with moderate and severe AR. When the deformation of the ventricle is corrected for geometry, an even more pronounced reduction in regional deformation parameters in patients with moderate and severe degree of AR occurs, even before we could measure pronounced changes in global deformation parameters. It has clearly been shown that in the groups with moderate and severe AR, there was a significant reduction in the index corrected for deformation (as compared with controls), despite a normal EF. Therefore, this confirms that changes in deformation could be identified before they are detected in standard echocardiographic parameters like EF.

**Figure 2** Correlation between radial strain rate (left), strain (right), and left ventricular diameters in all patients. EDD, end-diastolic diameter; ESD, end-systolic diameter. Grouping: cf. Figure 1.
The findings of our study, using an index corrected for geometry in patients with different degrees of AR, provide an initial impression that SR and S imaging might be a tool to detect sub-clinical changes in deformation. However, further outcome studies, evaluating the recovery of function as measured by both standard volume- and pressure-based indices and regional deformation, are required to confirm whether a fall in deformation indices in patients with isolated AR is a better index on which to base the timing of valve surgery. The initial impression gained during this study is suggestive that this may be a valuable new clinical approach.

Limitations
We might have over or underestimated the severity of AR by using the calculation of regurgitant volume. However, from our findings, regional end systolic strain would seem to be not mainly determined by the degree of AR itself, as we did not find a direct relationship between deformation and the grade of AR over a very wide range. For this reason, potential over or underestimation of the regurgitant volume would not change the conclusions of this paper.

We presumed that none of these patients had segmental dysfunction due to coronary artery disease. The majority of patients with severe AR had a coronary angiogram which excluded co-existing coronary artery disease but this procedure was not performed in all patients. However, none of these patients had clinical features of coronary artery disease and their physical examination and ECG did not show any evidence of this. The standard echocardiographic images also showed no signs of regional dysfunction due to ischaemia.

Conclusions
Our results show that in patients with a wide range of severity of AR, deformation derived from SR/S remains unchanged due to a balance of increased dimensions and increased stroke volume. Only when contractility is expected to change, deformation will significantly decrease.
Figure 4 Scatter plots of peak systolic SR/EDV and end-systolic S/EDV index for radial and longitudinal deformation. SR, strain rate; S, strain; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricle; Grouping: cfr. Figure 1.

Table 4 SR/EDV and S/EDV index values in each particular study group

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 22)</th>
<th>Mild AR (n = 10)</th>
<th>Moderate AR (n = 13)</th>
<th>Severe AR (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasternal SAX–LVPW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR/EDV</td>
<td>0.028 ± 0.009</td>
<td>0.024 ± 0.011</td>
<td>0.017 ± 0.009*</td>
<td>0.008 ± 0.005*</td>
</tr>
<tr>
<td>S/EDV</td>
<td>0.50 ± 0.17</td>
<td>0.46 ± 0.21</td>
<td>0.35 ± 0.20**</td>
<td>0.163 ± 0.099*</td>
</tr>
<tr>
<td>Apical four-chamber septum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR/EDV</td>
<td>0.014 ± 0.003</td>
<td>0.016 ± 0.006</td>
<td>0.010 ± 0.004†</td>
<td>0.005 ± 0.003*</td>
</tr>
<tr>
<td>S/EDV</td>
<td>0.20 ± 0.04</td>
<td>0.21 ± 0.07</td>
<td>0.14 ± 0.05†</td>
<td>0.07 ± 0.05*</td>
</tr>
<tr>
<td>Apical four-chamber–LV lateral wall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR/EDV</td>
<td>0.015 ± 0.004</td>
<td>0.015 ± 0.002</td>
<td>0.009 ± 0.004†</td>
<td>0.005 ± 0.003*</td>
</tr>
<tr>
<td>S/EDV</td>
<td>0.20 ± 0.06</td>
<td>0.22 ± 0.06</td>
<td>0.14 ± 0.06**</td>
<td>0.07 ± 0.04*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

AR, aortic regurgitation; LV, left ventricle; SAX, short axis; LVPW, left ventricular posterior wall.

*P < 0.0001, †P < 0.001, **P < 0.05 vs. control.
Strain rate imaging indices may potentially be useful in detecting sub-clinical deterioration in LV function in asymptomatic or minimally symptomatic patients with AR.

Acknowledgement

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Conflict of interest: none declared.

References


22. Vinereanu D, Ionescu AA, Fraser AG. Assessment of left ventricular long axis contraction can detect early myocardial dysfunction in asymptomatic patients with severe aortic regurgitation. Heart 2001;85:30–6.