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**Title:** Aortic valve disease: novel imaging insights from diagnosis to therapy  
**Issue Date:** 2016-03-10
Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: speckle-tracking echocardiography analysis

Ewe SH, Haeck MLA, Ng ACT, Witkowski TG, Auger D, Leong DP, Abate E, Ajmone Marsan N, Holman ER, Schalij MJ, Bax JJ, Delgado V.

*Eur Heart J Cardiovasc Imag.* 2015 Sep;16(9):992-9.
Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: speckle tracking echocardiographic analysis

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Aims

The aim of this study was to characterize left ventricular (LV) mechanics in symptomatic and asymptomatic patients with moderate-to-severe or severe aortic regurgitation (AR) and preserved ejection fraction (left ventricular ejection fraction) using two-dimensional speckle tracking echocardiography (2D-STE). The association between baseline LV strain and development of indications for surgery in asymptomatic patients was also evaluated.

Methods and results

A total of 129 patients with moderate-to-severe or severe AR and LVEF > 50% (age 55 ± 17 years, 64% male, 53% asymptomatic at baseline) were included. Standard echocardiography and 2D-STE were performed at baseline. Compared with asymptomatic patients, symptomatic patients had significantly impaired LV longitudinal (214.9 ± 3.0 vs. 216.8 ± 2.5%, P = 0.001), circumferential (217.5 ± 2.9 vs. 219.3 ± 2.8%, P = 0.001), and radial (35.7 ± 12.2 vs. 43.1 ± 14.7%, P = 0.004) strains. Among 49 asymptomatic patients who were followed up, 26 developed indications for surgery (symptoms onset or LVEF ≤ 50%). These patients had comparable LV volumes, LVEF, and colour Doppler assessments of AR jet at baseline, but more impaired LV longitudinal (P = 0.009) and circumferential (P = 0.017) strains compared with patients who remained asymptomatic. Impaired baseline LV longitudinal (per 1% decrease, HR = 1.21, P = 0.04) or circumferential (per 1% decrease, HR = 1.22, P = 0.04) strain was independently associated with the need for surgery.

Conclusion

Multidirectional LV strain was more impaired in symptomatic than in asymptomatic patients with moderate-to-severe or severe AR, despite preserved LVEF. In asymptomatic AR patients, longitudinal and circumferential strains identified patients who would require surgery during follow-up.

Keywords

Aortic regurgitation • Echocardiography • Speckle tracking • Surgery • Ejection fraction

Introduction

Currently, the class I indications for aortic valve (AV) surgery in severe aortic regurgitation (AR) are when patients are symptomatic and/or when there is impairment of left ventricular ejection fraction (LVEF ≤ 50%). However, as the LV enlarges with time, and in the presence of inadequate preload reserve and/or excessive increase in afterload, impairment of LV function may occur even before the onset of symptoms. Previous studies have also reported that some indices of LV function (such as myocardial strain and mitral
annular plane systolic excursion) may be abnormal in asymptomatic patients with chronic severe AR, despite preserved LVEF. When symptoms of heart failure develop in these patients, irreversible damage to myocardial structure (fibrosis) and function may have already occurred, which may preclude the recovery of LV function following AV surgery. Thus, accurate detection of subclinical LV dysfunction before the onset of symptoms and a drop in LVEF may be clinically helpful to identify asymptomatic severe AR patients who are at risk, necessitating early referral for surgery.

Strain imaging is a more sensitive technique (when compared with LVEF) to evaluate the contractile properties of the myocardium in patients with chronic AR. Recently, myocardial deformation can be assessed using two-dimensional speckle tracking echocardiography (2D-STE), which allows angle-independent assessment of LV deformation by tracking the frame-to-frame natural acoustic markers (the so-called speckles) within the myocardium wall. Myocardial strain values may indirectly reflect structural changes in the myocardium including fibrosis. We hypothesized that impairment in LV strain can be demonstrated in patients with moderate-to-severe and severe chronic AR, despite being asymptomatic and having preserved LVEF, and that 2D-STE would be a helpful tool to identify those asymptomatic high-risk individuals who progress to require AV surgery. Therefore, the aims of this study were as follows:

1. To evaluate the presence of subtle LV systolic dysfunction, using 2D-STE, in asymptomatic and symptomatic patients with moderate-to-severe or severe chronic AR and preserved LVEF,

2. To evaluate the potential role of baseline LV strain, using 2D-STE, in identifying asymptomatic AR patients who later develop indications for AV surgery.

Methods

Patient population and data collection

The patient population comprised 129 patients with moderate-to-severe or severe AR who were identified in the echocardiographic database of the Cardiology Department at the Leiden University Medical Center (Leiden, the Netherlands). Patients with acute AR, concomitant valvular disease of more than mild severity, known ischaemic heart disease, previous cardiac or valve surgery, reduced LVEF (≤50%), and inadequate echocardiographic data for 2D-STE analysis were excluded.

All the data were retrospectively retrieved from the departmental electronic patient dossier information system (EPD-vision, Leiden, the Netherlands) and analysed. All patients were followed up by the treating physicians according to routine clinical practice. A detailed clinical history was retrospectively retrieved, focusing on patients’ symptoms that were deemed to be related to AR by the attending physicians. Subsequently, patients were divided into two groups based on the presence or absence of symptoms at the time of first echocardiographic examination. LV myocardial functions (radial, circumferential, and longitudinal strains) were evaluated using 2D-STE and compared between symptomatic and asymptomatic patients. In addition, in the group of patients who were asymptomatic at the initial echocardiographic examination, the clinical information was retrospectively analysed to identify those who later developed symptoms or deterioration in LV function (LVEF ≤50%), meeting the indications for AV surgery (according to the current guidelines).

The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patients’ written informed consent.

Echocardiography

Transthoracic echocardiographic images were acquired at rest with the patient in the left lateral decubitus position using a commercially available ultrasound system (Vivid-7 and E9, General Electric Vingmed, Horten, Norway) and were digitally stored for offline analysis (EchoPAC version 110.0.0, GE-Vingmed). Standard 2D, colour, pulsed, and continuous-wave Doppler echocardiographic acquisitions were performed. LV dimensions were obtained from the standard M-mode images at a parasternal long-axis view, and LV mass index was calculated according to Devereux et al. and corrected for body surface area (BSA). In addition, the relative wall thickness was calculated as a ratio of (2 × PWTd)/LVIDd, where PWTd is the posterior wall thickness and LVIDd is the LV internal diameter at end-diastole. Next, LV end-diastolic and end-systolic volumes were measured from the apical views (two- and four-chamber) using bplane Simpson’s method and corrected for BSA. LV ejection fraction was subsequently calculated and expressed as a percentage.

Detailed examination of the AV, aortic root, and proximal ascending aorta were performed according to the standard guidelines. To assess AR severity, comprehensive, colour, continuous, and pulsed-wave Doppler recordings were performed according to the recommendations that included the measurement of vena contracta width, regurgitation jet width, pressure half-time, and diastolic flow reversal in the descending aorta. The final grading of AR severity required integration of data from imaging of the aortic root, AV, and LV.

Two-dimensional speckle tracking echocardiography

Myocardial deformation can be assessed using 2D-STE, performed on greyscale images of the LV obtained in the apical two-, three-, and four-chamber views and parasternal mid-ventricular short-axis view. An LV longitudinal strain was evaluated in the three apical views, whereas LV circumferential and radial strains were evaluated in the mid-ventricular short-axis view. From the 2D images, the endocardial border was manually traced at end-systole, and the region-of-interest width was adjusted to include the entire myocardial wall thickness. After verification of myocardial tracking, the software package (EchoPAC version 110.0.0, GE-Vingmed) automatically tracked the myocardium. Manual adjustment was performed if necessary. In each echocardiographic view, the myocardium was automatically divided into six segments. Thus, global peak systolic longitudinal strain was calculated by averaging the peak systolic values of all the six segments from the mid-ventricular short-axis view. Accordingly, the global systolic LV performance was evaluated in all the three myocardial directions using advanced 2D-STE.

Follow-up and end points

Patients who were asymptomatic were divided into two groups: those who met and those who did not meet indications for AV surgery at follow-up. From the clinical and echocardiographic variables recorded at the time of first echocardiographic examination, independent determinants of AV surgery were identified.

Statistical analysis

Continuous variables were presented as mean and standard deviation. Categorical variables were presented as frequencies and percentages. Differences in baseline variables between the two groups were analysed using unpaired Student’s t-tests for continuous variables and χ² or Fisher’s exact test (for categorical variables). In the group of patients who were initially asymptomatic at the first echocardiographic examination and were...
followed up conservatively, uni- and multivariate Cox regression analyses (with an enter method) were performed to identify baseline clinical and echocardiographic determinants of AV surgery. The independent association between LV systolic strains and need of AV surgery, was assessed in a multivariate Cox regression analysis including known predictors of need for AV surgery (such as age, gender, LV end-systolic volume index, and AR vena contracta width) into the model. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value of baseline LV strain to predict AV surgery at follow-up. All statistical analyses were performed using SPSS for Windows, version 16 (SPSS, Inc., Chicago, IL, USA). A two-tailed P-value of < 0.05 was considered statistically significant.

### Results

#### Patient population

A total of 129 patients (age 55 ± 17 years, 64% male) with moderate-to-severe or severe chronic AR were evaluated. Of these, 61 (47%) patients reported to have symptoms at the time of the first echocardiographic examination. Table 1 summarizes the comparison of echocardiographic parameters in patients with and without symptoms recorded at baseline. There were no significant differences in age, gender, and cardiovascular risk factors between the two groups. In terms of the mechanism underlying AR, asymptomatic patients were more likely to have bicuspid AVs but less likely to have inflammatory/infective causes (Table 1).

#### Echocardiography in patients with and without symptoms

Table 2 summarizes the comparison of echocardiographic parameters in patients with and without symptoms at baseline. Patients with symptoms had a significantly larger LV end-diastolic volume index and a trend towards a larger LV end-systolic volume index when compared with those without symptoms. Accordingly, the LVEF was lower in patients with symptoms, although all patients had by definition a preserved LVEF (>50%). In terms of colour Doppler assessment of the AR, patients with symptoms had a significantly larger vena contracta width, a higher jet to LV outflow tract width ratio, and a shorter pressure half-time when compared with those without symptoms (Table 2).

Regarding the assessment of LV performance using 2D-STE, patients with symptoms demonstrated a significantly larger impairment in myocardial function in all three directions when compared with those without symptoms (Table 2). Patients with symptoms had a significant worse longitudinal strain compared with those without symptoms (−14.9 ± 3.0 vs. −16.8 ± 2.5%, P < 0.001). Similarly, circumferential (−17.5 ± 2.9 vs. −19.3 ± 2.8%, P = 0.001) and radial (35.7 ± 12.2 vs. 43.1 ± 14.7%, P = 0.004) strains were more impaired in patients with symptoms than in those without symptoms.

#### Asymptomatic patients

Of the 68 patients who were initially asymptomatic, 49 patients had clinical data at follow-up permitting retrospective analysis. Over a mean follow-up period of 4.2 ± 3.2 years (interquartile range 1.2–6.6 years), 26 (53%) patients progressed to meet indications for AV surgery (onset of symptoms in 21 patients and LVEF ≤50% in 5 patients). The remaining 23 patients were symptom-free with preservation of LVEF. Table 3 summarizes the baseline clinical and echocardiographic data of the 49 asymptomatic AR patients. Of note, no significant differences in clinical characteristics were

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline clinical characteristics of the study population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic (n = 61)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 16</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>42 (69)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.93 ± 0.21</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>74 ± 13</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 ± 22</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>70 ± 14</td>
</tr>
<tr>
<td>MDRD glomerular filtration rate (mL/min/1.73 m²)</td>
<td>81 ± 24</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>41 (67)</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>23 (38)</td>
</tr>
<tr>
<td>AR aetiology</td>
<td></td>
</tr>
<tr>
<td>Degenerative, n (%)</td>
<td>23 (38)</td>
</tr>
<tr>
<td>Bicuspid, n (%)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Rheumatic, n (%)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Inflammatory/infective, n (%)</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Annuloaortic ectasia, n (%)</td>
<td>10 (16)</td>
</tr>
</tbody>
</table>

AR, aortic regurgitation; MDRD, Modification of Diet in Renal Disease. 
*P-values for comparison between symptomatic and asymptomatic patients.
observed, except that those who required surgery were older. In particular, baseline LV volume indexes, LVEF, and colour Doppler assessment of the AR were not significantly different between the two groups (Table 3). However, 2D-STE demonstrated that baseline LV myocardial strain was significantly more impaired in the longitudinal direction (−15.7 ± 2.0 vs. −17.6 ± 2.7%, \( P = 0.009 \)) and circumferential (−18.3 ± 2.4 vs. −20.2 ± 2.9%, \( P = 0.017 \)) directions in patients who later required surgery than those who remained symptom-free without surgery (Table 3).

Next, Cox regression analyses were performed to identify baseline clinical and echocardiographic determinants of AV surgery. On univariate analysis, age and LV longitudinal and circumferential strains were significantly related to AV surgery (Table 4). Table 4 presents that besides a larger AR vena contracta width, both impaired LV longitudinal and circumferential strain provided a modest and significant incremental value over clinical and echocardiographic variables in predicting AV surgery (Figure 1). By ROC curve analysis, LV longitudinal strain > −17.4% provided the highest sensitivity (77%) and specificity (57%) to predict the future need of AV surgery [area under the curve (AUC) = 0.70, \( P = 0.008 \)]. Table 5 summarizes the predictive ability of LV longitudinal strain to identify patients who will require AV surgery, using several proposed cut-off values. Importantly, LV longitudinal strain ≥ −19.3% provided the highest sensitivity (100%) to predict AV surgery, with a negative predictive value of 100%.

**Discussion**

The present analysis demonstrated that, despite preserved LVEF, multidirectional LV strain was more impaired in patients with moderate-to-severe or severe AR with symptoms than those without symptoms. Furthermore, in asymptomatic patients with moderate-to-severe and severe AR, LV strain (in particular, longitudinal strain), as assessed using 2D-STE, appeared to be a valuable tool to identify patients who are at risk of requiring AV surgery.

**Multidirectional myocardial strain in chronic AR**

Chronic AR often progresses slowly over the years, and the LV adapts by replication of sarcomeres in series in the presence of chronic volume overload. This allows for elongation of myocytes, thereby increasing LV volume to generate a larger stroke volume to maintain forward output.21–23 The gradual LV enlargement is followed by LV wall thickening, resulting in the development of eccentric hypertrophy. This is an adaptive process in the early course of the disease, normalizing wall stress and permitting normal filling pressures despite a substantial increase in LV volume overload.22 In addition, LVEF is normally preserved during the compensated phase of chronic AR, and many patients may remain asymptomatic for years. With time, however, the combination of progressive LV enlargement and the increase in LV pressure will reach a point when it is no longer offset by an adequate increase in LV wall thickness and will result in an increase in systolic LV wall stress.21 This afterload mismatch, together with a limited preload reserve in dilated ventricles, marks

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**Table 2 Baseline echocardiographic parameters of the study population**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symptomatic (n = 61)</th>
<th>Asymptomatic (n = 68)</th>
<th>( P )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>57 ± 8</td>
<td>55 ± 8</td>
<td>0.11</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>36 ± 9</td>
<td>34 ± 7</td>
<td>0.25</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.39 ± 0.09</td>
<td>0.40 ± 0.06</td>
<td>0.30</td>
</tr>
<tr>
<td>LV end-diastolic volume index (mL/m²)</td>
<td>95 ± 33</td>
<td>83 ± 27</td>
<td>0.034</td>
</tr>
<tr>
<td>LV end-systolic volume index (mL/m²)</td>
<td>40 ± 16</td>
<td>34 ± 17</td>
<td>0.064</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59 ± 6</td>
<td>61 ± 5</td>
<td>0.012</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>134 ± 36</td>
<td>130 ± 37</td>
<td>0.50</td>
</tr>
<tr>
<td>LV outflow tract (mm)</td>
<td>24.1 ± 3.2</td>
<td>24.1 ± 3.4</td>
<td>0.97</td>
</tr>
<tr>
<td>Aortic sinus (mm)</td>
<td>38.1 ± 6.1</td>
<td>37.5 ± 6.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Sinotubular junction (mm)</td>
<td>32.9 ± 6.4</td>
<td>31.6 ± 6.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Ascending aorta (mm)</td>
<td>37.2 ± 9.5</td>
<td>34.6 ± 7.1</td>
<td>0.083</td>
</tr>
<tr>
<td>Vena contracta width (mm)</td>
<td>6.2 ± 1.1</td>
<td>5.5 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Jet to LV outflow tract width ratio (%)</td>
<td>58 ± 11</td>
<td>50 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pressure half-time (ms)</td>
<td>278 ± 95</td>
<td>367 ± 90</td>
<td>&lt;0.001</td>
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<tr>
<td>Two-dimensional speckle tracking echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV longitudinal strain (%)</td>
<td>−14.9 ± 3.0</td>
<td>−16.8 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV circumferential strain (%)</td>
<td>−17.5 ± 2.9</td>
<td>−19.3 ± 2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>LV radial strain (%)</td>
<td>35.7 ± 12.2</td>
<td>43.1 ± 14.7</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*\( P \)-values for comparison between symptomatic and asymptomatic patients.
the onset of impairment in LV performance in patients with chronic AR. When the LV adaptive mechanisms fail or are inadequate, symptoms generally occur and LVEF becomes reduced. However, when LV function was evaluated using 2D-STE, symptomatic patients had significantly more LV myocardial strain than asymptomatic patients. Symptomatic patients exhibited features of more severe AR when compared to asymptomatic patients with symptoms of heart failure (n = 26) when compared to those who remained asymptomatic during follow-up. 

### Symptomatic vs. asymptomatic patients and baseline predictors of AV surgery

In the present study, it is not surprising that the group of patients with symptoms exhibited features of more severe AR when compared with the group of asymptomatic patients. Symptomatic patients showed larger vena contracta width and LV dimensions, and lower LVEF. Despite significant differences in LVEF, both groups of patients with moderate-to-severe and severe AR when compared with asymptomatic patients, although all patients had a preserved LVEF by virtue of the inclusion criteria.

#### Table 3  Baseline characteristics of asymptomatic patients with clinical and echocardiographic data at follow-up

<table>
<thead>
<tr>
<th></th>
<th>Need AV surgery (n = 26)</th>
<th>No need AV surgery (n = 23)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 ± 16</td>
<td>42 ± 15</td>
<td>0.006</td>
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<tr>
<td>Male, n (%)</td>
<td>16 (62)</td>
<td>15 (65)</td>
<td>1.00</td>
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<tr>
<td>BSA (m²)</td>
<td>1.91 ± 0.17</td>
<td>1.89 ± 0.25</td>
<td>0.75</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>69 ± 15</td>
<td>70 ± 11</td>
<td>0.82</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129 ± 14</td>
<td>133 ± 18</td>
<td>0.47</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>68 ± 12</td>
<td>70 ± 9</td>
<td>0.60</td>
</tr>
<tr>
<td>MDRD glomerular filtration rate (mL/min/1.73 m²)</td>
<td>84 ± 19</td>
<td>86 ± 23</td>
<td>0.83</td>
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<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension, n (%)</td>
<td>15 (58)</td>
<td>11 (48)</td>
<td>0.57</td>
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<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>8 (31)</td>
<td>4 (17)</td>
<td>0.33</td>
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<tr>
<td>Diabetes, n (%)</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>0.61</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>8 (31)</td>
<td>4 (17)</td>
<td>0.33</td>
</tr>
<tr>
<td>Conventional echocardiography</td>
<td></td>
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<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>55 ± 7</td>
<td>55 ± 6</td>
<td>0.90</td>
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<tr>
<td>LV end-systolic diameter (mm)</td>
<td>35 ± 7</td>
<td>33 ± 6</td>
<td>0.28</td>
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<tr>
<td>LV end-diastolic volume index (mL/m²)</td>
<td>81 ± 30</td>
<td>83 ± 18</td>
<td>0.84</td>
</tr>
<tr>
<td>LV end-systolic volume index (mL/m²)</td>
<td>32 ± 15</td>
<td>35 ± 22</td>
<td>0.54</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>61 ± 5</td>
<td>62 ± 5</td>
<td>0.50</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>131 ± 33</td>
<td>130 ± 32</td>
<td>0.93</td>
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<tr>
<td>LV outflow tract (mm)</td>
<td>23.6 ± 2.7</td>
<td>24.8 ± 3.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Ascending aorta (mm)</td>
<td>35.4 ± 7.7</td>
<td>33.4 ± 5.6</td>
<td>0.30</td>
</tr>
<tr>
<td>Vena contracta width (mm)</td>
<td>5.5 ± 1.2</td>
<td>5.3 ± 1.0</td>
<td>0.37</td>
</tr>
<tr>
<td>Jet to LV outflow tract width ratio (%)</td>
<td>52 ± 10</td>
<td>48 ± 10</td>
<td>0.24</td>
</tr>
<tr>
<td>Pressure half-time (ms)</td>
<td>367 ± 118</td>
<td>374 ± 69</td>
<td>0.83</td>
</tr>
<tr>
<td>Two-dimensional speckle tracking echocardiography</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LV longitudinal strain (%)</td>
<td>−15.7 ± 2.0</td>
<td>−17.6 ± 2.7</td>
<td>0.009</td>
</tr>
<tr>
<td>LV circumferential strain (%)</td>
<td>−18.3 ± 2.4</td>
<td>−20.2 ± 2.9</td>
<td>0.017</td>
</tr>
<tr>
<td>LV radial strain (%)</td>
<td>38.6 ± 13.8</td>
<td>43.5 ± 13.2</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Abbreviations as listed in Table 1.

*P-values for comparison between patients who developed indications for surgery and those who remained asymptomatic during follow-up.

The present study showed that LV myocardial strain was more impaired in all the three directions in symptomatic patients with moderate-to-severe and severe AR when compared with asymptomatic patients, although all patients had a preserved LVEF by virtue of the inclusion criteria.
Myocardial strains in chronic AR

Our findings extend this observation to a larger cohort of chronic moderate and severe AR patients with preserved LVEF. More importantly, the present study showed that among asymptomatic patients with moderate-to-severe or severe AR and preserved LVEF, the group of patients who would later require AV surgery during follow-up had more impaired LV longitudinal and circumferential strains when compared with patients who remained asymptomatic. Very often in clinical practice, the distinction between the onset of mild symptoms and the total absence of symptoms is challenging.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Model included longitudinal strain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03 (1.00–1.05)</td>
<td>0.023</td>
<td>1.02 (1.00–1.05)</td>
<td>0.059</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.16 (0.51–2.64)</td>
<td>0.725</td>
<td></td>
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</tr>
<tr>
<td>LV end-systolic volume index (mL/m²)</td>
<td>0.97 (0.98–1.02)</td>
<td>0.706</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vena contracta width (mm)</td>
<td>1.31 (0.89–1.94)</td>
<td>0.173</td>
<td>1.61 (1.02–2.52)</td>
<td>0.041</td>
</tr>
<tr>
<td>Longitudinal strain (per 1% worsening)</td>
<td>1.21 (1.02–1.45)</td>
<td>0.030</td>
<td>1.20 (1.01–1.44)</td>
<td>0.044</td>
</tr>
<tr>
<td><strong>Model included circumferential strain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03 (1.00–1.05)</td>
<td>0.023</td>
<td>1.02 (1.00–1.05)</td>
<td>0.094</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.16 (0.51–2.64)</td>
<td>0.725</td>
<td></td>
<td></td>
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<tr>
<td>LV end-systolic volume index (mL/m²)</td>
<td>0.97 (0.98–1.02)</td>
<td>0.706</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vena contracta width (mm)</td>
<td>1.31 (0.89–1.94)</td>
<td>0.173</td>
<td>1.50 (0.95–2.37)</td>
<td>0.079</td>
</tr>
<tr>
<td>Circumferential strain (per 1% worsening)</td>
<td>1.18 (1.02–1.36)</td>
<td>0.025</td>
<td>1.22 (1.01–1.46)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

CI, confidence interval; LV, left ventricular; HR, hazard ratio.

Figure 1 Incremental value of LV peak systolic longitudinal (or circumferential) strain over clinical and echocardiographic variables in predicting AV surgery in asymptomatic patients with clinical and echocardiographic data at follow-up (n = 49). Model 1 included clinical variables (age and male gender). Model 2 included clinical and echocardiographic variables (LV end-systolic volume index and vena contracta width of the AR jet). Model 3 included clinical and echocardiographic variables and advanced speckle tracking strain imaging-derived LV peak systolic longitudinal strain. Corresponding values for peak systolic circumferential strain are given in parentheses.

with patients without symptoms (n = 38). Our findings extend this observation to a larger cohort of chronic moderate and severe AR patients with preserved LVEF.
and if the decision to proceed with corrective surgery is based exclusively on LVEF or symptoms onset alone, it is possible that significant LV dysfunction has already developed, thereby precluding full benefit of AV surgery. In a series of 52 patients with chronic severe AR undergoing surgery, Onishi et al. demonstrated that preoperative LV radial strain rate had the largest AUC among other parameters (including LVEF or LV dimensions) in predicting postoperative LV dysfunction at 12 months. A recent study by Kusunose et al. also showed that resting global LV strain, using velocity vector imaging, was independently associated with the need for early valve surgery in asymptomatic patients with moderately severe-to-severe AR. In line with this, the present study demonstrated that the presence of subtle myocardial changes occurring early in the disease process could be detected by 2D-STE, while other conventional parameters remain indistinguishable during the follow-up of asymptomatic patients with chronic AR. In fact, a more marked impairment in both the longitudinal and circumferential strains was already noted at the time of first echocardiography in patients who later required AV surgery compared with patients who did not need surgery on follow-up. This is also consistent with the findings of Olsen et al., who demonstrated that impaired LV longitudinal strain was associated with disease progression or impaired outcomes after surgery in 62 patients with moderate-to-severe AR, although no multivariate analysis was performed in that study. Importantly, the present study showed that either LV longitudinal or circumferential strain provided a significant incremental value over clinical and established echocardiographic predictors of poor outcome, including LV volume and parameters of AR severity (vena contracta width), in predicting those who would require AV surgery. Moreover, when applying the longitudinal strain cut-off value of $-19.3\%$ (which has a negative predictive value of 100%), it is capable of ruling out the risk of developing indications for AV surgery and thus, watchful waiting should be recommended. Accordingly, LV longitudinal strain may be viewed as a sensitive marker for detection of subtle myocardial changes and may serve as a potential screening tool in clinical risk stratification of asymptomatic patients with chronic moderate-to-severe AR and preserved LVEF. It has the ability to identify those at risk, when the longitudinal strain was more impaired, in whom more aggressive follow-up and early intervention should be considered.

We acknowledge that, due to the relatively small population, the present study should be considered as a hypothesis-generating study to examine the ability of LV strain in the prediction of AV surgery. Additional prospective studies including a larger patient population are warranted to further validate the usefulness of LV longitudinal strain for accurately predicting the need for AV surgery in asymptomatic AR patients with preserved LVEF.

### Conclusions

Multidirectional LV strain was more impaired in patients with moderate-to-severe or severe AR who had symptoms than those without symptoms, although LVEF was still preserved. Furthermore, subtle impairment in myocardial function, detectable with 2D-STE, can be used to identify asymptomatic patients who progress to require AV surgery during follow-up.

### Conflict of interest

The Department of Cardiology, Leiden University Medical Center, received research grants from GE Healthcare, Lantheus Medical Imaging, St Jude Medical, Medtronic, Boston Scientific, Biotronik, and Edwards Lifesciences. V.D. received consulting fees from St Jude Medical and Medtronic, and speaker fee from Abbott Vascular.

### Funding

S.H.E. was financially supported by the Ministry of Health Training Scholarship, Singapore. D.A. was financially supported by the ‘Programme de bourse de perfectionnement et de fellowship du Centre Hospitalier de l’Université de Montréal (CHUM)’ and de la Fondation du CHUM. T.G.W. was financially supported by the Research Fellowship Grant of the European Society of Cardiology. D.P.L. was supported by the National Heart Foundation of Australia, the National Health and Medical Research Council of Australia, and the Royal Australasian College of Physicians.

### References

4. Vinereanu D, Ionescu AA, Praser 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.

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Table 5  Predictive ability of baseline LV longitudinal strain in identifying asymptomatic patients who will require AV surgery

<table>
<thead>
<tr>
<th>Longitudinal strain cut-off value (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-19.3$</td>
<td>100</td>
<td>26</td>
<td>61</td>
<td>100</td>
</tr>
<tr>
<td>$-17.4$</td>
<td>77</td>
<td>57</td>
<td>67</td>
<td>68</td>
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<tr>
<td>$-15.1$</td>
<td>35</td>
<td>87</td>
<td>75</td>
<td>54</td>
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