Left ventricular longitudinal systolic function after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a long-term follow-up study focused on speckle tracking echocardiography

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Aims
To examine left ventricular (LV) longitudinal systolic myocardial function in patients with hypertrophic obstructive cardiomyopathy (HOCM) before and after transcoronary ablation of septal hypertrophy (TASH).

Methods and results
Twenty-three of 39 consecutive patients with HOCM had serial two-dimensional (2D) echocardiograms available for speckle tracking analyses before and up to 36 months after TASH. Before TASH, overall LV myocardial longitudinal 2D strain was decreased despite normal LV ejection fraction (EF). A significant reduction of LV mass and left ventricular outflow tract (LVOT) gradients occurred during long-term follow-up after TASH, but this was not accompanied by improvement of average LV longitudinal systolic strain. However, in the basal LV segments remote to the site of alcohol injection longitudinal systolic strain increased [baseline: \(-13.1 \pm 5.4\%\); 1 month: \(-16.0 \pm 5.5\%\) (NS); 12 months: \(-16.5 \pm 4.9\%\) (P < 0.05 vs. baseline); 36 months: \(-17.4 \pm 4.2\%\) (P < 0.01 vs. baseline)]. In contrast, the alcohol-treated basal segments of the septum and adjacent myocardium showed unchanged strain over time.

Conclusion
Average LV longitudinal myocardial systolic function is depressed in HOCM despite normal LV EF. TASH-induced reduction of the LVOT obstruction does not improve average LV longitudinal systolic 2D strain. This is in contrast to global improvement of longitudinal systolic function after valve replacement in aortic valve stenosis. The discrepancy may be caused by the fact that HOCM is a primary myocardial disease.

Keywords
Hypertrophic cardiomyopathy • Alcohol ablation • Speckle tracking • Strain

Introduction
Transcoronary ablation of septal hypertrophy (TASH) is an effective treatment for elimination or reduction of the subvalvular stenosis in patients with hypertrophic obstructive cardiomyopathy (HOCM).\(^1\)\(^−\)\(^3\) Apart from relief of the left ventricular outflow tract (LVOT) obstruction and improvement of symptoms, the procedure results in reduction of left ventricular (LV) mass, and improvement of LV diastolic function.\(^2\)\(^−\)\(^3\) However, the long-term impact of pressure overload reduction on LV longitudinal systolic myocardial function in HOCM patients is not well established.\(^7\) In this study, we analysed the effect of afterload reduction on regional and global LV myocardial longitudinal systolic function by means of serial speckle tracking echocardiography in HOCM patients before and during long-term follow-up after TASH.

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Methods

Patients

Between September 1998 and June 2004, 39 consecutive patients with a phenotype of HOCM underwent TASH and completed 3 years of follow-up. Indications for the procedure were drug refractory symptoms of dyspnea [New York Heart Association (NYHA) functional class III–IV], angina pectoris [Canadian Cardiovascular Society (CCS) class III–IV], or syncope. All patients had a LVOT pressure gradient >50 mmHg at rest or after provocation (after bicycle stress or following ventricular premature beats provoked during cardiac catheterization). Sixteen patients were excluded because two-dimensional (2D) echocardiograms were inadequate for speckle tracking analysis. Thus, the studied cohort included 23 patients in whom complete speckle tracking 2D strain analysis was available at baseline, 1 month, 12 months, and 36 months after the procedure.

All patients gave informed consent before the procedure. The study was approved by the Danish Data Protection Agency and the relevant institutional review boards.

Transcatheter Ablation of Septal Hypertrophy

The procedure was performed as previously described. An over-the-wire balloon catheter was placed into the septal perforator artery. After balloon inflation, echocardiographic contrast was injected through the balloon catheter to identify the perfusion bed of the septal branch. If the relevant septal myocardium was delineated, 1–5 mL of 96% ethanol was slowly injected through the balloon catheter. In some patients alcohol was injected in more than one branch. Before the intervention, a temporary right ventricular pacemaker (PM) lead was placed in patients with no permanent PM. If persistent advanced atrioventricular block occurred after the procedure a permanent dual chamber PM was implanted.

Echocardiography

Two-dimensional, M-mode, and continuous wave (CW) Doppler echocardiography were performed by the same operator (H.E.) using Vivid Five equipment (GE Medical Systems, Horten, Norway). Endocardial border detection was enhanced using second harmonic imaging. Echocardiograms were stored digitally, and analyses were performed subsequently without knowledge of the clinical status or timing of the recordings in relation to the procedure. Measurements of LV dimensions and wall thicknesses were made according to the guidelines of the American Society of echocardiography. LV volumes and ejection fraction (EF) were estimated using Simpson’s modified biplane method. LV mass was calculated by a validated anatomic formula. Peak LVOT pressure gradient was estimated by means of the simplified Bernoulli equation.

Left Ventricular Longitudinal Speckle Tracking Derived Strain Measurements

Two-dimensional echocardiographic images (frame rate: 65–80 s⁻¹) were obtained at rest during end expiration. A single observer (A.S.) performed the longitudinal systolic strain measurements offline from the digitally stored 2D image loops. By means of speckle tracking echocardiography longitudinal systolic 2D strain was analysed in the three standard apical views. A dedicated software package (EchoPAC Dimension, GE Healthcare, Horten, Norway) was used for tracing the LV endocardial contour in end-systolic frames. Subsequently the software automatically defined the myocardium and processed all frames of the loop. Adequate tracking was ensured by visual control and if necessary optimized by manual adjustment.

In accordance with the three apical views, an 18-segment model including the basal, middle, and apical segments of the LV was used to analyse peak systolic longitudinal 2D strain for each segment. Average LV longitudinal systolic 2D strain was calculated for the 18 segments. Average longitudinal systolic 2D strain was also calculated for the six basal, the six mid, and the six apical LV segments. In addition, analyses were performed for the basal LV septum, the target area of the TASH procedure (basal segments of the septum presented in the 4-chamber and apical long-axis view), for the basal segments of the adjacent myocardium (anterior and inferior basal segments seen in the 2-chamber view), and for the basal segments of the remote myocardium (lateral and posterior basal segments seen in the 4-chamber and in the apical long-axis view).

Statistics

Continuous variables were presented as mean ± SD. In the presence of normal distributions differences between groups were tested using students t-test; otherwise a non-parametric test (Mann–Whitney) was used. Comparison between more than two groups and repeated measurements was performed by analyses of variance with Tukey’s post test. Categorical variables were analysed using Fisher’s exact test. Correlations between variables were performed by Spearman’s rank correlation test. Intra- and inter-observer variability of average systolic longitudinal 2D strain were analysed using the Bland–Altman method and expressed as the average of the absolute difference ± SD between the measurements. Graphpad Prism version 5.02 for Windows, Graphpad Software, San Diego, CA, USA was used for the statistical analyses and P < 0.05 was considered significant.

Results

Baseline Characteristics and Transcatheter Ablation of Septal Hypertrophy

The 23 HOCM patients were 15 female and 8 male patients with a mean age of 61 ± 13 years. Coronary artery disease with no prior infarction was present in two patients (9%) and medically treated systemic arterial hypertension in 11 patients (48%). A definite family history of HOCM was evident in two patients (9%). None of the 23 patients suffered from diabetes mellitus. Before TASH, 12 patients (52%) were treated with beta-blockers, 7 (30%) with calcium channel blockers, and 4 (18%) with a combination of beta-blockers and calcium channel blockers. Diuretics were administered in 16 patients (70%) and 6 (26%) received angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists. The medical treatment was continued during follow-up. None of the patients were previously treated with surgical myectomy, but five patients (22%) had a dual chamber PM inserted earlier in an unsuccessful attempt to relieve LVOT obstruction. Baseline haemodynamic and echocardiographic measurements are listed in Table 1.

During the septal ablation procedure, alcohol was injected in 1.1 ± 0.3 septal branches. Mean volume of alcohol injected was 3.1 ± 0.9 mL. Mean peak CK-MB after TASH was 280 ± 164 IU/L. Of the 18 patients with no PM before the procedure, 10 patients...
required a permanent PM after the procedure because of procedural development of advanced atrioventricular block. One patient received an implantable cardioverter-defibrillator (ICD) due to a documented episode of ventricular tachycardia before TASH.

**Baseline myocardial function**

Baseline values of segmental and average LV longitudinal systolic 2D myocardial strain are presented in Table 2. Before TASH, significantly increasing LV longitudinal strain was noted from basal to apical LV segments (Table 2). Before the procedure, systolic longitudinal strain in the basal septum (−7.0 ± 4.5%) was significantly smaller than in the basal segments of the adjacent myocardium (−13.2 ± 7.4%; \( P < 0.01 \)) and remote myocardium (−13.1 ± 5.4%; \( P < 0.01 \)) (Figure 1).

There was no significant correlation between average LV longitudinal systolic strain and LVOT pressure gradient at rest (\( r = 0.20, \) NS) or after provocation (\( r = −0.05, \) NS). Furthermore, there was no correlation between average LV strain and LV mass (\( r = 0.14, \) NS).

**Clinical and conventional echocardiographic changes during follow-up**

The mean NYHA functional class improved significantly after TASH (baseline: 3.0 ± 0.4; 1 month: 1.9 ± 0.7; 12 months: 1.8 ± 0.7; 36 months: 1.8 ± 0.7; \( P < 0.001 \)) for all follow-up values vs. baseline).

Serial haemodynamic and echocardiographic measurements are shown in Table 1. Septal and posterior wall thicknesses, LV mass, and LVOT pressure gradients all decreased significantly following TASH. In all patients, LVOT pressure gradients were reduced to <50 mmHg at rest and after provocation.

**Left ventricular longitudinal systolic strain during follow-up**

During follow-up, no significant change was observed in average longitudinal systolic 2D strain for the entire LV or for the mid and apical segments. However, systolic longitudinal 2D strain improved significantly in the basal segments of the LV (Table 2).

The improvement of longitudinal systolic strain in the basal segments occurred in the remote myocardium only [baseline: −13.1 ± 5.4%; 1 month: −16.0 ± 5.5% (NS); 12 months: −16.5 ± 4.9% (\( P < 0.05 \) vs. baseline); 36 months: −17.4 ± 4.2% (\( P < 0.01 \) vs. baseline)] (Figure 1). In contrast, there was no significant change of longitudinal systolic strain in the basal segments of the LV (Table 2).

No correlation was present between changes of average LV longitudinal systolic 2D strain and changes of resting or provoked LVOT pressure gradients (\( r = 0.32 \) and \( r = 0.01 \), respectively, NS).

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**Table 1** Serial haemodynamic and echocardiographic changes during follow-up after TASH

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 month</th>
<th>12 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>134 ± 29</td>
<td>144 ± 16</td>
<td>149 ± 22</td>
<td>145 ± 23</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79 ± 12</td>
<td>82 ± 11</td>
<td>88 ± 11</td>
<td>84 ± 14</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>74 ± 16</td>
<td>75 ± 15</td>
<td>70 ± 14</td>
<td>75 ± 20</td>
</tr>
<tr>
<td>Septum thickness, mm</td>
<td>19 ± 5</td>
<td>17 ± 7</td>
<td>14 ± 4**</td>
<td>12 ± 3**</td>
</tr>
<tr>
<td>PW thickness, mm</td>
<td>13 ± 3</td>
<td>12 ± 3</td>
<td>11 ± 2**</td>
<td>11 ± 2**</td>
</tr>
<tr>
<td>LVOT-PG (rest), mmHg</td>
<td>59 ± 52</td>
<td>14 ± 12**</td>
<td>7 ± 7**</td>
<td>5 ± 4**</td>
</tr>
<tr>
<td>LVOT-PG (provoked), mmHg</td>
<td>115 ± 67</td>
<td>20 ± 20**</td>
<td>16 ± 12**</td>
<td>15 ± 10**</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>72 ± 9</td>
<td>74 ± 9</td>
<td>71 ± 10</td>
<td>72 ± 10</td>
</tr>
<tr>
<td>LV EDV, mL</td>
<td>82 ± 25</td>
<td>87 ± 25</td>
<td>78 ± 21</td>
<td>79 ± 27</td>
</tr>
<tr>
<td>LV ESV, mL</td>
<td>23 ± 9</td>
<td>24 ± 13</td>
<td>23 ± 10</td>
<td>23 ± 13</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>284 ± 117</td>
<td>245 ± 99</td>
<td>210 ± 77*</td>
<td>185 ± 67**</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PW, posterior wall; LVOT-PG, left ventricular outflow tract pressure gradient; LV EF, left ventricular ejection fraction; LV EDV, left ventricular end-diastolic volume; LV ESV, left ventricular end-systolic volume.

* \( P < 0.05 \); ** \( P < 0.01 \) vs. baseline.

**Table 2** Segmental and average left ventricular longitudinal systolic two-dimensional strain values during follow-up after TASH

<table>
<thead>
<tr>
<th>Longitudinal strain, %</th>
<th>Baseline</th>
<th>1 month</th>
<th>12 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal segments</td>
<td>−10.3 ± 4.3</td>
<td>−11.4 ± 2.9</td>
<td>−12.9 ± 4.3*</td>
<td>−13.2 ± 3.4**</td>
</tr>
<tr>
<td>Mid-LV segments</td>
<td>−14.6 ± 3.4†</td>
<td>−14.0 ± 2.7</td>
<td>−15.8 ± 3.7</td>
<td>−15.6 ± 3.5</td>
</tr>
<tr>
<td>Apical segments</td>
<td>−19.0 ± 4.1§</td>
<td>−17.8 ± 6.6</td>
<td>−21.6 ± 5.1</td>
<td>−20.9 ± 5.1</td>
</tr>
<tr>
<td>LV average</td>
<td>−15.7 ± 3.6</td>
<td>−14.4 ± 3.4</td>
<td>−16.8 ± 3.7</td>
<td>−16.4 ± 3.1</td>
</tr>
</tbody>
</table>

† \( P < 0.01 \) vs. basal segments at baseline.

‡ \( P < 0.01 \) vs. mid-LV segments at baseline.

§ \( P < 0.05 \); ** \( P < 0.01 \) vs. basal segments at baseline.

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for both). Furthermore, we found no correlation between changes of average LV strain and reduction of LV mass ($r = -0.03$, NS).

**Impact of permanent pacemaker inserted after alcohol septal ablation**

During follow-up, no differences in baseline values or changes of LVOT pressure gradients, LV mass, and average LV longitudinal systolic 2D strain were observed between patients with and without a permanent PM after TASH (Table 3). Baseline values and changes during follow-up of regional longitudinal systolic strain in the basal septum, adjacent, and remote myocardium were also similar for the three groups listed in Table 3.

**Intra- and inter-observer variability**

Intra- and inter-observer variability of average systolic longitudinal 2D strain were analysed in 10 randomly selected recordings from 10 different patients. Intra- and inter-observer variability was 0.02 ± 1.7 and 0.4 ± 1.9%, respectively.

**Discussion**

Earlier speckle tracking echocardiographic studies have demonstrated that average LV myocardial longitudinal systolic 2D strain in healthy individuals is about −18 to −20%. 21,22 In our patients, we found an average value of −15.7 ± 3.6% at baseline. Thus, one finding of our study is that LV longitudinal myocardial systolic 2D strain seems to be reduced in symptomatic HOCM patients despite preserved LV function assessed by EF. Secondly, a substantial reduction of the LVOT pressure gradients and a significant decrease of LV mass after TASH was not accompanied by or related to any significant improvement of average LV longitudinal systolic deformation. However, during the 3 years of follow-up longitudinal systolic strain increased regionally in the basal segments of the myocardium remote to the target area of the alcohol ablation.

Patients with HOCM often present with symptoms of heart failure despite a normal LV EF. These symptoms have been related to LV hypertrophy and diastolic dysfunction. 23,24 However, the functional importance of longitudinal systolic myocardial strain may have been underestimated as reduction of LV longitudinal systolic function might contribute to heart failure symptoms experienced by HOCM patients. 21,25 This mechanism may also play a similar role in other conditions such hypertensive heart disease and valvular aortic stenosis. 26–29

In accordance with previous studies of patients with valvular aortic stenosis and non-obstructive hypertrophic cardiomyopathy, we found that LV longitudinal strain increased from base to apex in our HOCM patients. 21,26 Although the hypertrophy may be most pronounced at the basis of the LV, at least in HOCM, the nature and significance of a gradient of systolic strain from basis to apex

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**Table 3** Baseline values and absolute changes three years after transcoronary ablation of septal hypertrophy classified in relation to permanent pacemaker status

<table>
<thead>
<tr>
<th></th>
<th>No PM (n = 8)</th>
<th>PM after TASH (n = 10)</th>
<th>PM before and after TASH (n = 5)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LVOT-PG (rest), mmHg</td>
<td>61 ± 36</td>
<td>73 ± 69</td>
<td>28 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>LVOT-PG reduction (rest), mmHg</td>
<td>57 ± 34</td>
<td>67 ± 68</td>
<td>23 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline LVOT-PG (provoked), mmHg</td>
<td>119 ± 33</td>
<td>134 ± 88</td>
<td>71 ± 47</td>
<td>NS</td>
</tr>
<tr>
<td>LVOT-PG reduction (provoked), mmHg</td>
<td>102 ± 29</td>
<td>103 ± 90</td>
<td>61 ± 46</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline LV mass, g</td>
<td>264 ± 62</td>
<td>323 ± 150</td>
<td>241 ± 108</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass reduction, g</td>
<td>73 ± 78</td>
<td>106 ± 146</td>
<td>75 ± 33</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline average strain, %</td>
<td>−18.0 ± 3.0</td>
<td>−14.8 ± 3.8</td>
<td>−13.7 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Change of LV average strain, %</td>
<td>1.5 ± 3.4</td>
<td>−1.3 ± 4.6</td>
<td>−0.3 ± 3.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
in these conditions is unclear. In healthy individuals, uniform longitudinal systolic strain from basis to apex seems to be present.\textsuperscript{18,22}

Left ventricular hypertrophy in HOCM is primarily considered to be a result of the genetic disorder and ensuing myofibillar abnormalities. However, in accordance with other echocardiographic and cardiac magnetic resonance (CMR) imaging studies, we demonstrated a reduction of LV mass during long-term follow-up after alcohol septal ablation.\textsuperscript{6–8} The findings indicate that myocardial hypertrophy is partly reversible after reduction of the subvalvular aortic stenosis.

In symptomatic valvar aortic stenosis, we recently documented a significant correlation between LV mass and LV longitudinal systolic function.\textsuperscript{29} In the same study, regression of myocardial hypertrophy and global improvement of LV longitudinal systolic strain occurred after relieving LV pressure overload by aortic valve replacement. Furthermore, reduction of LV mass was significantly related to improvement of average LV longitudinal systolic strain in patients with valvar aortic stenosis.\textsuperscript{29} In contrast, our study of HOCM patients showed that marked reduction of the subvalvular aortic stenosis did not result in any significant long-term improvement of average LV longitudinal strain. Moreover, we found no correlation between average LV longitudinal strain and LV mass before TASH or during follow-up. In addition, no correlation was found between average LV longitudinal strain and LVOT pressure gradients at baseline or between changes of these parameters during follow-up. Apparently, the degree of global LV hypertrophy and the pressure overload itself did not seem to be the most important determinants of global LV longitudinal systolic function in HOCM.

The difference between improved global longitudinal systolic strain after relief of valvar aortic stenosis vs. unchanged average longitudinal strain after reduction of subvalvular aortic stenosis may be explained by differences in myocardial pathophysiology. In valvar aortic stenosis LV hypertrophy and increased interstitial fibrosis is secondary to progressively increasing afterload.\textsuperscript{30} Global improvement of LV longitudinal systolic function after valve replacement in valvar aortic stenosis may be a result of regression of LV hypertrophy and myocardial fibrous content.\textsuperscript{30,31} In contrast, HOCM is primarily a structural disease of the myocardium with abnormal sarcomeric proteins, myocardial disarray, and a concomitant hypertrophic response.\textsuperscript{23} Quantitative analysis of the distribution of myocardial disarray has demonstrated significantly more cellular disorganization in the interventricular septum and anterior wall compared with the postero-lateral free wall.\textsuperscript{32} This conforms well to the observed difference between longitudinal systolic strain in the basal part of the septum and the remote postero-lateral wall. Similarly, myocardial areas with prominent disarray were associated with regional systolic dysfunction in transgenic mice with hypertrophic cardiomyopathy.\textsuperscript{23} Thus, TASH may well reduce LV pressure overload and result in some regression of LV hypertrophy while the fundamental structural abnormality of the myocardium is expected to remain unchanged with impaired LV longitudinal systolic dysfunction where the myocardial abnormalities are most prominent (Figure 1). In agreement with a recent CMR study, we observed a significant improvement of longitudinal systolic deformation in the basal myocardium remote to alcohol ablation with no impairment of myocardial function of the LV septum after TASH.\textsuperscript{7} The improvement of longitudinal systolic strain in regions remote to alcohol ablation is well in accordance with pressure unloading and a long-term regression of LV hypertrophy in these regions with less prevailing myocardial disarray. Furthermore, the myocardium remote to the target area of TASH may obviously be less affected by alcohol-induced necrosis than the basal septum and adjacent myocardium.

**Limitations**

The study included a relatively small number of patients, particularly regarding the subgroup analysis comparing the groups of patients with and without a permanent PM after the procedure.

We excluded 16 patients with 2D echocardiographic images of a quality inadequate for speckle tracking analysis. However, these patients were similar to the study group with respect to baseline characteristics and clinical and haemodynamic effects of the procedure.

HOCM was not genetically diagnosed in our study and medically treated arterial hypertension was present in nearly half of our patients. A phenotype of muscular subvalvular aortic stenosis mimicking HOCM may in some of these patients have expressed a particular manifestation of hypertensive heart disease.\textsuperscript{24} However, baseline values and changes during follow-up of LVOT pressure gradients, LV mass, and LV regional and average longitudinal systolic strain were similar for patients with and without arterial hypertension.

**Conclusions**

Patients with symptomatic HOCM have depressed LV longitudinal systolic myocardial function despite normal LV EF. The significant reduction in LVOT obstruction and LV mass after TASH appears solely to improve regional systolic longitudinal function in LV basal segments remote to the severely hypertrophied myocardium involved in the subvalvular aortic stenosis. This improvement might result not only from absence of direct action of alcohol but also from decreased LV pressure overload with subsequent regression of LV hypertrophy in these regions with less prevailing myocardial disarray. In contrast, valve replacement in valvar aortic stenosis results in global improvement of LV longitudinal systolic strain. Thus, the discrepancy between myocardial remodelling after abolishment of valvar aortic stenosis and subvalvular muscular stenosis may reflect that HOCM primarily is a structural myocardial disease with decreased potential for recovery of myocardial longitudinal systolic function.

**Conflict of interest:** none declared.

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