Clinical significance of global two-dimensional strain as a surrogate parameter of myocardial fibrosis and cardiac events in patients with hypertrophic cardiomyopathy

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Aims

Late gadolinium enhancement (LGE) on contrast-enhanced magnetic resonance imaging (MRI) in hypertrophic cardiomyopathy (HCM) has been reported to be associated with myocardial fibrosis and cardiac events. In patients with HCM, two-dimensional (2D) strain can identify subclinical global systolic dysfunction despite normal left ventricular (LV) chamber function. Therefore, this study tested the hypothesis that global 2D strain could detect subtle myocardial fibrosis and serve as a novel prognostic parameter in HCM patients.

Methods and results

Echocardiography and MRI were performed in 48 consecutive patients with HCM and normal chamber function. We measured global longitudinal strain (GLS) in apical two-chamber, four-chamber, and long-axis views using speckle-tracking analysis. The extent of LGE (%LGE = LGE volume/total LV volume) and LV mass index were calculated by MRI using Simpson’s rule and custom software. All patients were followed up for major cardiac events. Global longitudinal strain in patients with LGE was significantly lower than that without LGE (11.8 ± 2.8 vs. 15.0 ± 1.7%, P < 0.001). Multivariate analysis showed that GLS was an independent predictor of %LGE (standard coefficient 0.627, P = 0.001). During a mean follow-up period of 42 ± 12 months, five patients had cardiac events. When the patients were stratified based on the median level of GLS (12.9%), all events were observed in the worse GLS group (P = 0.018).

Conclusion

These results suggest that global 2D strain might provide useful information on myocardial fibrosis and cardiac events in HCM patients with normal chamber function.

Keywords

Hypertrophic cardiomyopathy • Global strain • Myocardial fibrosis • Cardiac events

Introduction

Myocardial fibrosis is a pathological entity associated with extra-cellular matrix remodelling that may lead to increased myocardial stiffness and left ventricular (LV) systolic and diastolic dysfunction. Late gadolinium enhancement (LGE) by cardiovascular contrast-enhanced magnetic resonance imaging (MRI) is frequently observed in patients with hypertrophic cardiomyopathy (HCM), and allows in vivo quantification of myocardial fibrosis. Previous studies demonstrated that the extent of LGE was correlated with LV systolic and diastolic dysfunction as well as adverse cardiac events such as sudden cardiac death, fatal arrhythmia, or worsening heart failure in patients with HCM.
Myocardial strain is a sensitive parameter of ventricular systolic function. Recently, two-dimensional (2D) speckle-tracking echocardiography was shown to provide an angle-independent, rapid, and accurate method for strain measurement. This technique identified global as well as regional subclinical abnormalities in patients with HCM that had apparently normal LV systolic function. Some previous studies reported that regional myocardial strain and wall thickening were affected by regional myocardial fibrosis in patients with HCM. However, the association between global 2D strain and the amount of myocardial fibrosis is unknown, and the clinical significance of global 2D strain remains unclear in HCM patients. Therefore, the aim of this study was to investigate whether global 2D strain could detect the extent of myocardial fibrosis and serve as a novel prognostic parameter in HCM patients.

Methods

Study subjects
We evaluated 51 consecutive patients with HCM. The diagnosis of HCM was made by echocardiography based on the criteria of the World Health Organization/International Society and Federation of Cardiology. The final analysis was based on data from only 48 patients, since three (6%) were excluded because of poor echocardiographic images. All patients were in sinus rhythm. An LV outflow tract obstruction was defined as a peak instantaneous gradient of 30 mmHg at rest. Exclusion criteria included the following: the LV ejection fraction <50% as assessed by echocardiography, a dilated stage of HCM, apical hypertrophy, cardiac muscle disease secondary to any known systemic condition, atrial fibrillation, implantation of a pacemaker or defibrillator, significant valvular heart disease, or known coronary artery disease. After echocardiography, plasma levels of brain natriuretic peptide (BNP) were also measured in all subjects, as previously reported. Of the study subjects, 26 (54%) were taking beta-blockers (14 metoprolol, 8 bisoprolol, 2 propranolol, 1 betaxolol, and 1 atenolol), 16 (33%) were taking calcium antagonists (9 diltiazem, 7 verapamil), and 13 (27%) were taking antiarrhythmics (12 cibenzoline, 1 amiodarone). All drugs were discontinued at least 24 h before echocardiographic and MRI evaluation. A past history of syncope (transient and complete loss of consciousness) and family history of sudden cardiac death in a first-degree relative were recorded. The study was approved by the Ethics Committee of Ehime University Graduate School of Medicine, and all patients and subjects gave informed consent prior to participation.

Echocardiographic examination
Echocardiographic examinations were performed using a Vivid 7 Dimension ultrasound machine (GE Healthcare, Milwaukee, WI) with an M4S probe. The end-diastolic LV diameter, end-systolic LV diameter, and diastolic thickness of the ventricular septum, and end-diastolic thickness of the LV posterior wall were measured by M-mode echocardiography. Left ventricular end-diastolic and end-systolic volumes and the ejection fraction were estimated by a modified Simpson’s rule from apical imaging planes and normalized to body surface area. Left atrial volume was measured using the biplane modified Simpson’s method at the ventricular end-systolic frame just before mitral valve opening from apical four- and two-chamber views, and the volume was indexed for body surface area. The LV pressure gradient was measured from continuous-wave Doppler recordings of the LV outflow tract. Early diastolic mitral annular velocity at the septal side (e') and the propagation velocity of LV early filling flow (Vp) were obtained using tissue Doppler imaging and colour M-mode Doppler echocardiography. The combined assessment of peak early diastolic transmitral flow velocity (E) and e’ was used to calculate E/e’. The measurements of e’ and Vp were averaged for at least five consecutive heart beats.

Data analysis for global and regional 2D strain
We measured global longitudinal strain (GLS) as global 2D strain. Regional peak systolic longitudinal strain was also assessed from apical two-chamber, four-chamber, and long-axis views using speckle-tracking analysis. Off-line speckle-tracking analysis was performed on all digitally stored greyscale images using custom software (EchoPAC PC BT08: GE Healthcare). All images were recorded with a high frame rate (≥50 frames/s). The cardiac cycle with the best image quality and without any artefacts was selected for all strain measurements. The endocardial border was manually traced at an end-systolic frame. The region of interest (ROI) width was adjusted to the thinner side of the myocardial wall in each plane. The software then automatically detected the frame-to-frame movement of the natural ultrasound reflecting markers (speckles) on standard ultrasonic images in two dimensions. The LV was divided into 17 segments, and each segment was analysed individually. Using dedicated software, regional peak systolic longitudinal strain was determined in all 17 segments from the three apical views. Global longitudinal strain for the LV was automatically provided as the average value of the regional peak systolic longitudinal strain of the three apical views by the software.

MRI examination and image analysis
Magnetic resonance imaging examination was performed within 2 weeks of the echocardiographic examination. Magnetic resonance imaging was performed using a Philips Intera Achieva (Best, The Netherlands) 1.5 T whole body scanner with dedicated cardiac coils. Breath-hold cine images were acquired in multiple short-axis views and apical three-chamber views with steady-state free precession sequences. Ventricular coverage was achieved with contiguous 8-mm thick slices (no gap). Images for LGE diagnostics were acquired 10 min after the injection of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany: 0.2 mmol/kg) with breath-hold segmented inversion-recovery sequences acquired in the same views. Inversion time was individually acquired using a Look-Locker inversion-recovery sequence. The left ventricular mass at end-diastole and the extent of LGE (%LGE = LGE volume/total LV volume) were semi-automatically calculated on the basis of Simpson’s rule using a workstation (Virtual Place Advance Plus, Aze, Japan) and manual revision by visual assessment. In addition, the presence and myocardial wall distribution of LGE was visually analysed in a 17-segment model according to previous reports. After the myocardial wall was visually divided into three layers (endocardial, mid, and epicardial), we evaluated the main layer for the presence of regional LGE. The visual revision and assessment were performed by two experienced observers who were blinded to patient identification and the clinical profile. The Left ventricular mass was normalized to body surface area. Myocardial tissue with LGE was defined as an area with a signal intensity of greater than two standard deviations from the mean of remote myocardium.
Clinical follow-up
All patients were followed up through regular outpatient visits every 2 or 3 months. The primary endpoint of the study was the composite incidence of sudden cardiac death defined as unexpected death (within 1 h of symptoms), fatal arrhythmia (ventricular fibrillation or sustained ventricular tachycardia), and hospitalization for worsening heart failure (NYHA functional class IV).

Statistics
Data were expressed as the mean ± standard deviation. Brain natriuretic peptide, left ventricular mass index (LVMI), and the echocardiographic parameters were compared with an unpaired t-test. Among echocardiographic parameters, the value of regional peak systolic longitudinal strain based on the main location (endocardial, mid, and epicardial) of LGE in the myocardial wall was compared with a one-way analysis of variance. Univariate regression analysis was performed on age, BNP, LVMI, and the echocardiographic parameters to determine the significant predictors of %LGE. Stepwise multivariate regression analysis was performed to determine the independent predictors of %LGE. The Kaplan–Meier method was used to determine cumulative event-free rates in HCM patients after they were stratified into two groups according to the median level of GLS. The difference in event-free rates between the two groups was tested with a log-rank test. The inter-observer and intra-observer variabilities were assessed for measurements of GLS in 10 randomly selected patients. The inter-observer variability was expressed as the coefficient of variation (SD/mean) of the differences between the measurements of two independent observers, who were unaware of the other patient data. The intra-observer variability was expressed as the coefficient of variation of the differences between the first and second determination (2-week interval) for a single observer. All statistical analyses were performed using SPSS 15.0j software for Windows (SPSS, Inc., Chicago, IL, USA). Values of \( P < 0.05 \) were considered statistically significant.

Results
The clinical characteristics of the HCM patients are displayed in Table 1. Late gadolinium enhancement was observed in 36 patients (75%) (mean %LGE = 6.8 ± 3.0%). The study parameters compared between patients with and without LGE are summarized in Table 2. The patients with LGE had significantly lower GLS, higher LVMI, lower \( e' \), and lower \( V_p \) than those without LGE. In contrast, the ejection fraction was not different between the two groups. Representative examples are shown in Figure 1.

In the regional analysis, LGE was observed in 192 of 816 segments. Regional peak systolic longitudinal strain at the LGE-positive segment was significantly lower than that at the non-LGE segment (\( -7.3 \pm 3.8 \text{ vs. } -14.1 \pm 5.4\% \), \( P < 0.001 \)). In addition, among the LGE-positive segments, LGE was mainly located at the endocardial layer in 43 segments, mid-layer in 100 segments, and epicardial layer in 49 segments. Regional peak systolic longitudinal strain based on the main location of LGE was not significantly different among the three groups (endocardial layer, \(-7.4 \pm 4.3\%\); mid-layer, \(-7.2 \pm 3.5\%\); epicardial layer, \(-7.5 \pm 3.9\%\); \( P = 0.925 \)).

In univariate regression analysis, %LGE was significantly correlated with GLS, LVMI, \( e' \), and \( V_p \) (Table 3). Multivariate regression analysis was performed to determine the independent predictors of %LGE among LVMI, \( e' \), Vp, and GLS. Among these variables, GLS was the strongest independent predictor of %LGE (standard

Table 1 Clinical characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 14</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>34/14</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>161 ± 9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>62 ± 12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.8 ± 3.1</td>
</tr>
<tr>
<td>Heart rate (l/min)</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136 ± 24</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75 ± 13</td>
</tr>
<tr>
<td>Family history of sudden cardiac death, n (%)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Unexplained syncope, n (%)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Left ventricular outflow tract obstruction &gt; 30 mmHg, n (%)</td>
<td>17 (35)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD.

Table 2 Study parameters in patients with and without LGE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LGE</th>
<th>No LGE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>44 ± 5</td>
<td>44 ± 5</td>
<td>0.900</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>26 ± 4</td>
<td>25 ± 5</td>
<td>0.457</td>
</tr>
<tr>
<td>Inter-ventricular septal thickness (mm)</td>
<td>18 ± 4</td>
<td>17 ± 4</td>
<td>0.633</td>
</tr>
<tr>
<td>Left ventricular posterior wall thickness (mm)</td>
<td>12 ± 3</td>
<td>12 ± 2</td>
<td>0.336</td>
</tr>
<tr>
<td>LV end-diastolic volume index (mL/m²)</td>
<td>42 ± 12</td>
<td>43 ± 11</td>
<td>0.674</td>
</tr>
<tr>
<td>LV end-systolic volume index (mL/m²)</td>
<td>12 ± 6</td>
<td>11 ± 4</td>
<td>0.494</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>71 ± 6</td>
<td>74 ± 6</td>
<td>0.154</td>
</tr>
<tr>
<td>Left atrial volume index (mL/m³)</td>
<td>56 ± 17</td>
<td>47 ± 22</td>
<td>0.190</td>
</tr>
<tr>
<td>E velocity (cm/s)</td>
<td>61 ± 16</td>
<td>71 ± 15</td>
<td>0.060</td>
</tr>
<tr>
<td>A velocity (cm/s)</td>
<td>71 ± 21</td>
<td>79 ± 24</td>
<td>0.264</td>
</tr>
<tr>
<td>E/A</td>
<td>0.98 ± 0.59</td>
<td>1.07 ± 0.68</td>
<td>0.666</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>254 ± 90</td>
<td>242 ± 67</td>
<td>0.645</td>
</tr>
<tr>
<td>( e' ) (cm/s)</td>
<td>3.2 ± 1.3</td>
<td>4.1 ± 1.2</td>
<td>0.040</td>
</tr>
<tr>
<td>( V_p ) (cm/s)</td>
<td>23 ± 8</td>
<td>37 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV pressure gradient (mmHg)</td>
<td>40 ± 44</td>
<td>36 ± 36</td>
<td>0.786</td>
</tr>
<tr>
<td>E/e'</td>
<td>18.7 ± 5.8</td>
<td>18.8 ± 6.5</td>
<td>0.969</td>
</tr>
<tr>
<td>LV mass index (g/m³)</td>
<td>114 ± 32</td>
<td>94 ± 18</td>
<td>0.031</td>
</tr>
<tr>
<td>BNP pg/ml</td>
<td>241 ± 208</td>
<td>210 ± 256</td>
<td>0.730</td>
</tr>
<tr>
<td>GLS (%)</td>
<td>-11.8 ± 2.8</td>
<td>-15.0 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD.
LGE, late gadolinium enhancement; LV, left ventricular; \( e' \), early diastolic mitral annular velocity; \( V_p \), propagation velocity; BNP, brain natriuretic peptide; GLS, global longitudinal strain.
In addition, clinical follow-up was performed in all patients. The mean follow-up period was 42 ± 12 months. During the follow-up period, five patients had major cardiac events. One patient died from sudden cardiac death, three patients showed sustained ventricular tachycardia (two were referred for implantable cardioverter defibrillator therapy), and one patient was hospitalized for worsening heart failure. All patients with cardiac events had LGE (mean %LGE = 10.6 ± 3.3 (range: 7.1–15.6 %)). Figure 2 shows the Kaplan–Meier cumulative cardiac event-free curves of the two groups that were stratified based on the median level of GLS (~12.9%). All events were observed in the lower GLS group. The difference in the cardiac event-free rate between the two groups was significant (P = 0.018).

The inter-observer and intra-observer variabilities for the measurement of GLS were 4.1 and 4.8%, respectively.

**Discussion**

The major findings of this study were that GLS was a useful surrogate marker of myocardial fibrosis, and a lower GLS might be
associated with major cardiac events in HCM patients with normal chamber function.

**The correlation between GLS and the extent of LGE in HCM**

Myocardial strain provides a quantitative evaluation of ventricular regional and global function and is considered to be a more sensitive and specific indicator of subclinical myocardial dysfunction. In general, patients with HCM have preserved LV chamber function as assessed by conventional methods. However, Serri et al. have reported that global 2D strain including GLS was significantly reduced in HCM patients compared with control subjects, despite a similar ejection fraction between the two groups. They concluded that 2D strain identified early abnormalities in HCM patients who have apparently normal LV systolic function. Thus far, segmental analysis by Popović et al. have shown that both the presence of segmental myocardial fibrosis represented by LGE and wall thickness were significant independent predictors of lower segmental longitudinal strain in HCM patients. In addition, some reports showed that the amount of segmental LGE was highly correlated with segmental wall thickening measured by MRI. Similarly, the present study showed that regional peak systolic longitudinal strain at the LGE-positive segment was significantly lower than that at the non-LGE segment. These observations suggest the possibility that the sum of longitudinal strain, like GLS, as well as segmental longitudinal strain is also affected by the extent of myocardial fibrosis, which supports our results.

On the other hand, some reports have shown that the extent of LGE was strongly correlated with the degree of LV hypertrophy in patients with HCM. The present study also showed that LVMI was correlated with %LGE, but it was not an independent predictor or with multivariate analysis. Several reports suggested that LV hypertrophy in itself decreased regional contractile function in patients with HCM. In addition, LV hypertrophy can result in LV microvascular abnormalities. Because the endocardium consists of longitudinal fibres and is most vulnerable to ischaemia, impaired LV function can be detected at an earlier stage by measuring longitudinal strain.

**The relationship between regional peak systolic longitudinal strain and LGE location in the myocardial wall**

Some papers reported that LGE was located predominantly at the mid- or epicardial-layer of the myocardial wall in patients with HCM. Therefore, the correlation between LGE and longitudinal strain, which largely reflects deformation of fibres in the subendocardium as mentioned above, seems counter intuitive. In the present study, of all segments with LGE, ~75% had LGE at the mid- or epicardial-layer. However, regional peak systolic longitudinal strain did not depend on LGE location in the myocardial wall. We are not sure of the precise mechanism responsible for this. Although the anatomy of layer structure at the segment with LGE is still unknown, LGE as a surrogate marker of myocardial fibrosis might affect the layer structure or lead to subendocardial ischaemia regardless of the exact LGE location in the myocardial wall.

**The correlation between GLS and prognosis in HCM**

Recently, GLS was reported to be more useful than conventional parameters in the prediction of major cardiac events in patients with chronic heart failure or acute myocardial infarction. This may be because the GLS is a sensitive marker of early subclinical myocardial dysfunction in the longitudinal direction of the LV. However, there was no previous information on the prognostic significance of GLS in HCM patients. There is evidence that the extent of LGE, which reflects the severity of fibrosis, is associated with a greater risk of major adverse cardiac events including sudden cardiac death and worsening heart failure in HCM patients. Although there was partial disagreement on the relationship between the extent of LGE and arrhythmic events, several reports showed a relationship between the presence or extent of LGE and arrhythmic events or surrogates of arrhythmic events. In addition, arrhythmic events seem to be the principal mechanism of sudden cardiac death in HCM patients. This relationship between LGE and major cardiac events is mainly because the extent of myocardial fibrosis promotes re-entrant ventricular arrhythmias and contributes to increased ventricular stiffness. In the present study, GLS was an independent predictor of %LGE, and all of the cardiac events occurred in the group with lower GLS. Since GLS was a sensitive marker of fibrosis as well as LGE, it seems reasonable that reduced GLS would also be associated with cardiac events.

**Clinical implications**

The present study suggested that GLS was linked to the extent of LGE after adjustment for several traditional echocardiographic parameters and could have prognostic value in patients with HCM. Therefore, GLS might be a promising parameter to stratify the risk of cardiovascular events in HCM patients.

**Limitations**

The present study has several limitations. First, the number of patients and clinical events in the study was small. The statistical power was relatively weak. Thus, more clinical studies in larger patient populations must be performed to confirm the validity of GLS as a marker for myocardial fibrosis and as a predictor of major cardiac events, using multivariate analysis including the conventional prognostic parameters. Secondly, GLS measured by 2D speckle tracking was not real global strain because GLS was measured from only three apical views. Since the distribution of LGE and wall thickness were significant independent predictors of lower segmental longitudinal strain in HCM patients, the correlation between GLS and the extent of LGE, which reflects the severity of fibrosis, is associated with a greater risk of major adverse cardiac events including sudden cardiac death and worsening heart failure in HCM patients. Finally, the acquisition of orbicular LV short-axis images from base to apex is often technically difficult. This issue will be settled by the development of 3D speckle tracking. Fourthly, histological data were not acquired invasively in this study.
We diagnosed HCM using echocardiographic and clinical data. Therefore, it might be difficult to strictly diagnose HCM. Finally, the ROI width at the hypertrophic segment might not cover the entire wall, because we adjusted the ROI to the thinner side of the myocardial wall. However, in the present study, regional peak systolic longitudinal strain did not depend on the LGE location in the myocardial wall. The development of software that can precisely trace the epicardial border might resolve this issue.

Conclusion

In conclusion, we suggest that global 2D strain has the possibility of providing useful information on myocardial fibrosis and prognosis in patients with HCM. This clinically promising parameter might be useful for risk stratification in patients with HCM.

Conflict of interest: none declared.

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Right ventricular enlargement in a patient with hereditary haemorrhagic telangiectasia: a rare case of pulmonary arteriovenous malformations with concomitant atrial septal defect

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We describe a rare case (32-year-old woman) with hereditary haemorrhagic telangiectasia and concomitant atrial septal defect (ASD). Transthoracic saline contrast echocardiography (TTCE) revealed several microbubbles appearing early (third cardiac cycle) and significant microbubbles appearing later (seventh cardiac cycle) in the left atrium and ventricle (LA/LV) after opacification of the right atrium in the four-chamber view (panel A). Total left to right shunt was calculated at 3.9 L/min (Qp:Qs = 1.8:1). Despite right ventricular (RV) enlargement, search for intracardiac shunting was not undertaken because chest CT confirmed significant pulmonary arteriovenous malformations (PAVMs) in the right lower lobe (arrows in panel B). Following successful transcatheter coil embolization, TTCE demonstrated significant microbubbles within two cardiac cycles (panel C), consistent with intracardiac shunting. Owing to findings of RV dilatation and early positive microbubbles, a transoesophageal echocardiogram (TOE) was performed, identifying a secundum ASD in the bicaval view (panel D) and three-dimensional (3D) TOE en-face view of the interatrial septum from the LA aspect (arrow in panel E). Using a 3D cross-sectional area of 0.48 cm², the shunt across the ASD was estimated at 2.9 L/min (Qp:Qs = 1.6:1), implying intrapulmonary PAVMs flow of 1.0 L/min prior to closure. Coexistence of intracardiac and extracardiac shunts should be considered when early appearance of microbubbles is seen with TTCE even if maximal microbubbles appear later.

Conflict of interest: none declared.

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

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