A new echocardiographic approach for the detection of non-ischaemic fibrosis in hypertrophic myocardium

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Aims Regional myocardial fibrosis detected by magnetic resonance imaging (MRI) using late enhancement (LE) indicates an unfavorable prognosis. We investigated in a prospective study whether regional non-ischaemic fibrosis in hypertrophic myocardium can also be detected by ultrasonic strain-rate imaging based on specific visual features of the myocardial deformation traces.

Methods and results This diagnostic study aimed to define left ventricular fibrotic segments in 30 patients with hypertrophic cardiomyopathy (n = 10), severe aortic valve stenosis (n = 10), Fabry disease cardiomyopathy (n = 10), and 10 healthy controls. MRI and strain-rate imaging (=deformation imaging) was performed in all patients and controls to detect LE. In total, 42 segments showed LE according to MRI criteria. Using strain-rate imaging, all LE positive segments displayed a characteristic pattern consisting of a first peak in early systole followed by a rapid fall in strain rate close to zero and a second peak during isovolumetric relaxation. This ‘double peak sign’ was never seen in segments of healthy controls. However, it was detected in 10 segments without LE. These ‘false-positive’ segments belonged to Fabry patients who often develop a fast progressing fibrosis. In a follow-up MRI study after 2 years (available for 6/10 segments), all these segments had developed LE.

Conclusion The ‘double peak sign’ in strain-rate imaging tracings seems to be a reliable tool to diagnose regional fibrosis.

Introduction

In hypertrophic myocardium, regional fibrosis is a common finding.1–5 In particular, fibrosis is present in more advanced stages of the disease progress2–6 and is associated with a poor prognosis.2–6 Therefore, the early detection of regional fibrosis is of clinical relevance.6 Currently, the assessment of late enhancement (LE) by magnetic resonance imaging (MRI) is the non-invasive reference standard for the detection of regional fibrosis.2,4,5

The presence of non-contracting fibrotic tissue should also have an impact on myocardial function. Regional myocardial function can be easily assessed by ultrasonic strain-rate imaging.7,8 Peak systolic strain rate and strain values are reduced in a number of myocardial pathologies.6,9,10 However, in individual patients, the measurement of peak amplitudes (particularly strain rate) is technically demanding and therefore restricted to specialized centres. Most studies published to date reported time-averaged values and compared different groups to show significant differences. This has limited the clinical application and the evaluation of individual patients.

Besides changes in absolute values of the deformation, some specific changes in the temporal behaviour of the strain-rate traces have been reported. The most prominent finding is the presence of post-systolic deformation, mainly in ischaemic myocardium.11,12 Thus, it is conceivable that a specific feature in the pattern of the deformation curve could be used for the detection of regional fibrosis in an individual patient presenting with hypertrophic myocardium.

The aim of this prospective clinical study was to compare non-invasive functional measurements in patients with hypertrophic myocardium with the morphological finding of fibrosis assessed by LE imaging. We hypothesized that the presence of a typical pattern, rather than the measurement of peak values, would be a much easier and more reliable tool to detect regional fibrosis.
Methods

Study protocol

Consecutive patients with the diagnosis of either aortic valve stenosis (AS), hypertrophic cardiomyopathy (HCM), or Fabry cardiomyopathy were investigated for regional fibrosis by LE imaging using MRI. (The University Hospital Würzburg acts as a reference centre for patients with Fabry disease. Currently, a cohort of 104 males and females is followed prospectively with echocardiography and MRI.) Only patients showing LE in at least one left ventricular (LV) wall were included in the study. The final patient population comprised 10 patients with severe AS, 10 patients with HCM, and 10 patients with Fabry disease. In addition, standard echocardiography and strain-rate imaging was performed in all patients and also in 10 healthy controls. To match the assessment between MRI and echocardiography, the standardized myocardial segmentation for imaging of the heart was used.13 Coronary artery disease was ruled out in all patients with AS and in all other patients with angina pectoris by coronary angiography. None of the patients had more than mild aortic or mitral regurgitation.

It is known that regional fibrosis is progressing over time in hypertrophied myocardium. In six out of 10 Fabry patients follow-up data (echocardiography and MRI; mean follow-up time 2.0 ± 1.1 years) was available and, thus, used for analysis. All patients gave written consent for MRI and echocardiography studies including digital data storage and systematic analysis of the data. The investigation conformed to the principles outlined in the Declaration of Helsinki.

Magnetic resonance imaging

MRI was performed on Siemens Sonata-Avanto (Erlangen, Germany) or Philips Gyroscan ACS-NT (Best, The Netherlands) 1.5 T whole-body scanners with dedicated cardiac coils. Breath-hold cine images were acquired in multiple short-axis and three long-axis slices with steady-state free precession sequences. Ventricular coverage was achieved with contiguous 10 mm-thick slices or 7 mm slices (2-3 mm gap). Images for LE diagnostics were acquired 15 min after the injection of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany; 0.2 mmol per kilogram of body weight) with breath-hold segmented inversion-recovery sequence (inversion time 240-300 ms) acquired in the same views.

Standard echocardiographic measurements

LV end-diastolic (LVEDD) and end-systolic dimensions (LVESD) as well as end-diastolic thickness of the posterior wall (PWWT) and the septum were measured using standard M-mode echocardiographic methods from parasternal long-axis images (GE Vivid 7, Horten, Norway; 3.5 MHz). In addition, the end-diastolic wall thickness of each investigated segment was measured using the anatomic M-mode approach. LV ejection fraction (EF) was measured by manual segmentation of the endocardial borders of the end-diastolic and end-systolic frames using the biplane Simpson method in apical four- and two-chamber views. Blood pool pulsed Doppler traces of the mitral valve inflow (the sample volume was positioned between the tips of the mitral valve leaflets) were used to extract the ratio of early to late diastolic flow velocity (E/A) and deceleration time (DT).

Strain-rate imaging

Real-time two-dimensional colour Doppler myocardial imaging (CDMI) data were recorded from all LV walls using standard apical and parasternal views as described previously.6 CDMI data were analysed using dedicated software (Echopac dimension 06®, GE Ultrasound). The region of interest was continuously positioned within the wall during the cardiac cycle by manual tracking. Strain rates were derived by estimating the local spatial gradients in myocardial velocities. Strain-rate profiles were averaged over three consecutive cardiac cycles and integrated over time to derive natural strain profiles using end-diastole as the reference point. Mitral and aortic valve opening and closure were extracted from conventional blood flow traces and were used to define the isovolumetric contraction, the ejection, and the isovolumetric relaxation period.

From the resulting strain rate and strain curves the peak systolic (‘first’ peak) and peak post-systolic (‘second’ peak) strain rate, the end-systolic strain and the post-systolic strain (PSS) were measured (Figure 1). In apical views, strain-rate imaging was performed in the apical, mid-, and basal segments to assess longitudinal function and in the basal segment of the LV posterior wall for radial function. In addition, the duration from the beginning of the QRS complex to the peaks of the strain-rate curves were measured and normalized for heart rate. The analyses of each segment were carried out blinded for the MRI results. The intraobserver variability (expressed in percentage of the mean) for this method was previously published and averaged 10% for strain rate and 11% for strain.14

Statistics

Data are presented as mean ± 1 standard deviation. Differences between controls patient segments were compared using a Student t-test for unpaired data after testing for equality of variances by Levene’s test. Due to the pilot character of the present study no adjustment for multiple comparisons was implemented. All P-values are reported two-sided. Statistical analysis was performed using SPSS 13.0.1.

Results

The general data of the three patient groups and the healthy controls are given in Table 1. Patients with AS had an averaged aortic valve area of 0.7 ± 0.2 cm² (range: 0.5–1.1 cm²). In two patients with AS, biopsies were taken during surgery from the segments which were LE positive. Both biopsies showed subendocardial fibrosis (Figure 2). From the patients with HCM, four had septal, three had apical, two had inferior, and one had global hypertrophy. Three of them had an LV outflow tract gradient of more than 2 m/s. All Fabry patients had concentric hypertrophy and all were under enzyme replacement therapy. The diagnosis of Fabry disease was confirmed by genetic blood tests.
In all patients, a complete MRI data set including LE imaging could be acquired. In AS, the main distribution of LE was basal septal and basal lateral. These segments showed sub-endocardial LE. In patients with HCM, all segments with LE were within the thickened myocardium. In Fabry patients, LE was located mainly in the basal posterolateral segments. All these segments displayed mid-myocardial LE. Typical examples of LE in the three patient groups are given in Figure 3. A quantitative assessment of the amount of LE was not done.

Standard echocardiographic measurements

In all patients, a complete echocardiographic data set including strain-rate imaging could be acquired. The results for the standard systolic and diastolic echocardiographic measurements for each group are displayed in Table 2. Except for three patients with AS, all subjects had a normal EF above 50%. Three patients with AS and two patients with Fabry disease had an increased end-diastolic LV diameter of more than 56 mm. In patients with AS and in patients with Fabry disease the end-diastolic wall thickness in the LE positive segments was comparable with the remote region without LE. In contrast, in patients with HCM, the LE positive segments showed significant thicker end-diastolic wall thickness (16 ± 2 mm) compared with the LE negative remote region (11 ± 2 mm). (Table 2).

Strain-rate imaging: pattern of the curve

In all segments with LE (n = 42), a distinct pattern of the strain-rate curve was detected by visual inspection. This pattern consisted of a sharp early 'first' systolic peak (negative for longitudinal function and positive for radial function) followed by a rapid fall of strain rate close to the zero line and an additional 'second' strain-rate peak during the isovolumetric relaxation period (directed in the same direction as the first peak and at least 50% in magnitude compared with the first peak). Because all strain-rate curves extracted from the LE positive segments showed this typical sequence of two peaks, it was named 'double peak sign'. A typical longitudinal and radial strain-rate curve with the ‘double peak sign’ is shown in Figures 1 and 4. In contrast, the ‘double peak sign’ was never detected in any of the segments from the healthy control group. In addition, some LE negative segments (in AS n = 6; in HCM n = 7; in Fabry disease n = 5 and in controls n = 10) showed the known pattern of post-systolic deformation often seen in non-diseased myocardium characterized by a normal shaped strain-rate curve during the ejection period.

Table 1 General data

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AS</th>
<th>HCM</th>
<th>Fabry</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>56 ± 11</td>
<td>73 ± 5*</td>
<td>43 ± 17***</td>
<td>48 ± 8***</td>
</tr>
<tr>
<td>Male (%)</td>
<td>50</td>
<td>80</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1</td>
<td>3*</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Systolic RR (mmHg)</td>
<td>120 ± 10</td>
<td>131 ± 12</td>
<td>116 ± 14**</td>
<td>130 ± 20</td>
</tr>
<tr>
<td>Diastolic RR (mmHg)</td>
<td>80 ± 8</td>
<td>78 ± 8</td>
<td>73 ± 9*</td>
<td>80 ± 13</td>
</tr>
<tr>
<td>Heart rate (b.p.m)</td>
<td>60 ± 7</td>
<td>74 ± 13</td>
<td>60 ± 7***</td>
<td>64 ± 9**</td>
</tr>
<tr>
<td>Beta blockade (n)</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>ACE-inhibitor (n)</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ca channel blocker (n)</td>
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<td>0</td>
</tr>
<tr>
<td>Diuretics (n)</td>
<td>0</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

ACE, angiotension-converting enzyme inhibitor; AS, aortic valve stenosis; ca, calcium; HCM, hypertrophic cardiomyopathy; RR, blood pressure.

*P < 0.05 vs. controls.

**P < 0.05 vs. AS.

Figure 2   Histology of a patient with aortic valve stenosis (basal septal segment) showing the subendocardial fibrotic tissue assumed to be the histological correlate of both late enhancement and the ‘double peak sign’. See Supplementary material online for a colour version of this figure.

Figure 3   In a patient with Fabry cardiomyopathy, aortic valve stenosis, and hypertrophic cardiomyopathy, the magnetic resonance imaging short-axis views with late enhancement (arrows) are shown.
and ongoing deformation after aortic valve closure (these segments were not defined as 'double peak sign'). When analysing the strain-rate curves from disease related but LE negative hypertrophic segments, none of the AS or HCM patients showed the 'double peak sign' (Figure 5). However, in Fabry patients, 10 LE negative segments showed the 'double peak sign'. For six of these 10 segments, follow-up MRI data after 2.0 ± 1.1 years were available and all of them had developed LE in the follow-up study.

Even normal myocardium can show some amount of deformation after aortic valve closure (mainly in the basal segments). This also results in a (very small) second peak in the strain-rate trace. However, in all cases, one can delineate this physiological induced post-systolic deformation by defining the presence of the 'double peak sign' only when the second strain-rate peak was of at least 50% magnitude compared with the first peak. Additionally, it is easy to visually discriminate the physiological pattern from the 'double peak sign' (where the first peak is much more accentuated) since the reduction in the strain-rate curve after the first peak (i.e. back to the zero line) is much less pronounced in the presence of a physiological second peak.

**Table 2** Standard echocardiographic measurements

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AS</th>
<th>HCM</th>
<th>Fabry</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>50 ± 4</td>
<td>50 ± 10</td>
<td>47 ± 5</td>
<td>49 ± 7</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>31 ± 4</td>
<td>35 ± 9</td>
<td>31 ± 5</td>
<td>31 ± 5</td>
</tr>
<tr>
<td>PWWT (mm)</td>
<td>8 ± 2</td>
<td>13 ± 1</td>
<td>11 ± 2*</td>
<td>14 ± 3*</td>
</tr>
<tr>
<td>Septum (mm)</td>
<td>8 ± 1</td>
<td>13 ± 1</td>
<td>15 ± 7*</td>
<td>15 ± 3*</td>
</tr>
<tr>
<td>ROI wall thickness</td>
<td>9 ± 2</td>
<td>13 ± 1</td>
<td>16 ± 2</td>
<td>14 ± 3</td>
</tr>
<tr>
<td>thickness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote wall thickness</td>
<td>–</td>
<td>13 ± 2</td>
<td>11 ± 2</td>
<td>14 ± 3</td>
</tr>
</tbody>
</table>

EF (%) 64 ± 3   58 ± 17  63 ± 4   65 ± 9     
E/A 1.2 ± 0.3  0.8 ± 0.2* 1.4 ± 0.7** 1.1 ± 0.2**
DT (ms) 211 ± 32 317 ± 81* 198 ± 54** 289 ± 71*

AS, aortic valve stenosis; DT, deceleration time; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; PWWT, posterior wall thickness; ROI, region of interest; wall-thickness, end-diastolic wall thickness.

*P < 0.05 vs. controls.
**P < 0.05 vs. AS.

**Figure 4** Radial strain rate and strain curves from one heart cycle from a patient with Fabry cardiomyopathy extracted from a segment with late enhancement. AVC, aortic valve closure; LE, late enhancement.

**Figure 5** Longitudinal strain rate and strain curves from one heart cycle from a patient with aortic valve stenosis extracted from a segment without late enhancement. AVC, aortic valve closure; LE, late enhancement.

**Strain-rate imaging: peak values**

Table 3 lists the longitudinal and radial strain rate and strain measurements for each group. No statistical testing was performed within these groups due to low numbers per patient group. However, comparing summary statistics of controls vs. patients, the following differences were found: the longitudinal peak systolic strain rate was significantly higher in the control group segments compared with the patient segments without LE (−1.1 ± 0.2 s⁻¹ vs. −0.9 ± 0.2 s⁻¹; P < 0.05) and lowest in the segments of the patients with LE (−0.7 ± 0.3 s⁻¹; P < 0.05 vs. segments without LE). Regarding radial function, strain-rate values were only significantly different between the control segments and the LE positive segments (control = 2.1 ± 0.5 s⁻¹; LE negative = 1.9 ± 0.6 s⁻¹; LE positive = 1.4 ± 0.5 s⁻¹, P < 0.05 vs. control). With regard to the timing of the first strain-rate peak, the earliest appearance after the onset of the QRS complex was seen in segments with LE (131 ± 40 ms) followed by LE negative segments (175 ± 122 ms) and by controls (199 ± 47 ms). The second strain-rate peak in LE positive segments became apparent briefly after aortic valve closure (52 ± 18 ms). As shown in Table 4, the diagnostic characteristics of the 'double peak' sign were excellent and appeared superior to the diagnostic utility of peak strain rate, systolic strain, and post-systolic thickening.

**Discussion**

This study confirms that typical features of the tissue Doppler deformation curves can be used to detect regional fibrosis in hypertrophic myocardium. This approach appears more practicable and accurate compared with the quantitative analysis of peak deformation values to detect changes in myocardial deformation. In hypertrophic segments with fibrosis, a typical deformation pattern consisting of two clearly identifiable peaks was consistently and reliably identified and therefore named the 'double peak sign'.

**Deformation in segments with fibrosis**

The second strain-rate peak results from the well-documented typical finding of post-systolic deformation (post-systolic thickening for radial function and post-systolic...
Post-systolic strain has been observed in patients with acute ischaemic myocardium, chronic non-transmural infarctions and also hypertrophic cardiomyopathies. So far this phenomenon has only been described either visually or quantitatively based on the strain curves and only compared with the end-systolic strain. Our study demonstrates that using the strain rate curve and comparing the beginning of systole with the post-systolic phase (i.e. the ‘double peak sign’) allows for easy, reproducible, and accurate qualitative assessment (i.e. yes or no) of the presence of regional fibrosis.

Understanding the appearance of a double peak in the strain-rate curve requires knowledge on the relationship between contractile forces and deformation. Regional deformation in a myocardial segment is the result of several interacting factors. It is influenced by the intrinsic contractile force developed by the myocytes within the region of interest, the interaction with the surrounding (contracting) segments and the pressure/volume loading in the LV. Additionally, the local elasticity/stiffness of the tissue will influence the deformation. Changes in any of these factors will result in changes in both the magnitude and the time course (pattern) of the deformation.

The mechanism of post-systolic deformation was described in detail by Claus et al. In segments showing shortening for longitudinal function) in the strain curve. Post-systolic strain has been observed in patients with acute ischaemic myocardium, chronic non-transmural infarctions and also hypertrophic cardiomyopathies. So far this phenomenon has only been described either visually or quantitatively based on the strain curves and only compared with the end-systolic strain. Our study demonstrates that using the strain rate curve and comparing the beginning of systole with the post-systolic phase (i.e. the ‘double peak sign’) allows for easy, reproducible, and accurate qualitative assessment (i.e. yes or no) of the presence of regional fibrosis.

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when the LV pressure is low. On strain curves, this is represented by a further increase after aortic valve closure. Therefore, in segments with fibrosis, the regionally reduced contractile force combined with the interaction of surrounding segments and cavity pressure induces the typical 'double peak sign', as documented in the current study.

The individual values of the peaks in the deformation traces (the two strain-rate peaks, end-systolic strain, and post-systolic strain) were not very sensitive to detect an individual segment with fibrosis. However, on group level, peak values were significantly different between LE positive and LE negative segments and also between pathological segments without LE and control segments. This finding has been described earlier, especially with respect to longitudinal functional assessment.\textsuperscript{6,21,22}

In contrast, the double peak pattern of the strain-rate curve seems to be very sensitive to detect the individual segments with fibrosis. The comparison of the diagnostic test characteristics indicates an excellent diagnostic utility using the pattern of the curve (i.e. the 'double peak sign') compared with the quantitative peak values. Of note, the test characteristics for the 'double peak sign' were calculated including 10 'false-positive' segments. However, six out of 10 of these segments developed LE during the follow-up, whereas in four out of 10 no follow-up information was yet available. This suggests that some degree of fibrosis was already present at baseline which was detected by the 'double peak sign' but missed by the MRI scan. Thus, the diagnostic utility for the 'double peak sign' is likely to be a conservative estimate.

**Clinical prospective**

The assessment of regional myocardial fibrosis is of clinical relevance because it indicates a more advanced stage of the underlying cardiac disease.\textsuperscript{1–6} Thus, may be further clinical studies will prove that using the simple qualitative 'double peak sign' as described in this paper will help to detect disease progression at an early stage. This may be especially important in situations where disease aggravation impacts on therapeutic strategies.\textsuperscript{9} Importantly, none of the healthy controls but all hypertrophic segments with LE showed the 'double peak sign' (negative predictive value 0.99; Table 4). Hence, in a clinical situation, the absence of this marker might imply that regional fibrosis in an individual subject is highly unlikely. Further, the clinical application of the double peak sign may be facilitated by its angle-independency compared with the peak value analysis. However, although these imaging tools help to understand the mechanisms in cardiac fibrotic tissue, their impact on the clinical patient management is unknown. In order to reach the stage of clinical utility, innovative non-invasive technologies have to discriminate pathologies at group levels and improve the clinical management of the individual patient. This and the time consuming analysis of strain-rate studies might be the main reasons why strain-rate imaging is predominantly viewed as a research tool. However, the new qualitative visual approach proposed in this study may facilitate the diagnosis of LE by strain-rate imaging. Its possible impact on the management of patients with hypertrophic myocardium should be addressed in future studies.

**Limitations**

The current pilot study examined only three disease entities of hypertrophic myocardium with regional fibrosis. Whether the 'double peak sign' is also helpful in other patient groups with fibrosis is unknown. However, we examined a group with pressure induced fibrosis (AS), a group with a genetic cardiomyopathy (HCM), and a group with a storage disease (Fabry cardiomyopathy). We deliberately excluded ischaemic heart disease since it has a completely different pathophysiology.

In general, the 'double peak sign' was easier to define in Fabry patients and HCM, most probably because of the intramural location of the fibrotic tissue which was easy to track during post-processing. In contrast, in patients with AS, the sub-endocardial location of fibrosis made it more difficult and thus a very precise tracking of the computation area was necessary.

Because the 'double peak sign' is a qualitative fibrosis indicator, the quantitative assessment of the extent or the transmurality of fibrosis was not possible. Further studies are needed to evaluate the use of this sign for the quantitative assessment of the transmurality.

It should also be stated that the 'double peak sign' cannot be viewed as a specific marker for fibrosis in hypertrophic myocardium as the same pattern is known since years during ischaemia, myocardial dyssynchrony, and in non-transmural infarctions.\textsuperscript{11,16}

**Conclusions**

A distinct feature of the regional deformation trace, the 'double peak sign', appears to detect regional non-ischaemic fibrosis in hypertrophic myocardium.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Conflict of interest:** none declared.

**References**


