Endocardial Fibrotic Lesions Have a Greater Effect on Peak Longitudinal Strain than Epicardial Fibrotic Lesions in Hypertrophic Cardiomyopathy Patients

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Summary

Peak longitudinal strain (PLS) of the left ventricular (LV) myocardium by transthoracic echocardiogram (TTE) is useful to detect LV myocardial damage. We hypothesized that myocardial fibrosis (MF) in the LV myocardium may influence PLS. Eighteen hypertrophic cardiomyopathy (HCM) patients (14 males; 58 ± 17 years old) underwent 1.5 Tesla cardiac magnetic resonance (CMR) and TTE. Patients with previous myocardial infarction were excluded. We used TTE to assess whole-layer PLS in an American Heart Association-defined 17-segment LV model. Whole-layer PLS was calculated using Echo PAC, version 113 (GE Healthcare). MF was assessed by T1-weighted CMR of the LV endocardial layer, the LV epicardial layer, or both the LV endocardial and epicardial layers for each lesion. Of the 306 segments, MF was detected in the LV endocardial layer only (13 segments), in the LV epicardial layer only (9 segments), or in both LV endocardial and epicardial layers (59 segments). PLS values were significantly lower in segments with MF affecting only the LV endocardial layer (7% ± 4%) (P < 0.05) and where MF was observed in both the LV endocardial and epicardial layers (9% ± 5%) (P = 0.001) compared with segments without MF (13% ± 7%). No significant difference in PLS values was detected between the MF segments for the LV epicardial layer only (10% ± 6%) and those without MF (13% ± 7%) (P > 0.05). In HCM patients, fibrotic lesions in the LV endocardium have a greater adverse effect on PLS than those in the LV epicardium. Our results are significant for HCM patients with fibrotic lesions within the LV endocardium.

Key words: Myocardium, Transthoracic echocardiogram, Magnetic resonance imaging

Myocardial fibrosis (MF) in the left ventricular (LV) myocardium is observed frequently on cardiac magnetic resonance (CMR) imaging in patients with hypertrophic cardiomyopathy (HCM).1-3 Previously, we reported that regional whole-layer peak longitudinal strain (PLS) of the LV myocardium on two-dimensional (2D) speckle tracking transthoracic echocardiogram (TTE) is useful for the early detection of LV myocardial damage, such as focal MF, at the corresponding sites on CMR in HCM patients.4 Recent advancements in CMR allow layer-specific differentiation of the location of focal MF such as in the LV endocardial layer (LVendo), in the LV epicardial layer (LVepi), or in both LVendo and LVepi.5

We speculated that layer-specific localization of focal MF on CMR may correlate with the values of regional whole-layer PLS on TTE.

Methods

This is a retrospective analysis acquired from a total of 18 HCM patients (14 males (78%); mean age, 58 ± 17 years) who underwent both 1.5 Tesla CMR (Achieva; Philips) and TTE (Vivid E9; GE Healthcare) within 13 months (mean interval between TTE and CMR was 4 ± 5 months).

Ischemic myocardial change occurs predominantly in LVendo, even in HCM patients, and may lead to a de-
crease in the regional whole-layer PLS. Thus, we have to rule out ischemic myocardial damage. All 18 HCM patients were evaluated for coronary artery disease. Eleven patients showed no significant stenosis in coronary arteries by cardiac CT (10 patients) or by invasive coronary angiogram (one patient). Among the remaining seven patients, one underwent a Treadmill test with negative finding and the other six revealed abnormal Q waves in 12-lead electrocardiogram (ECG), all of which were consistent with HCM rather than myocardial infarction. Therefore, none of the patients showed obvious previous myocardial infarction.

Whole-layer PLS measurement on TTE: Conventional 2D TTE assessment was performed using a Vivid E9 system with a 3.5-MHz transducer. The assessment included measurement of cardiac dimensions, volumes, and LV ejection fraction, as described previously.

Strain analysis was performed off-line by an investigator who was blind to the CMR results and clinical data. The LV myocardium was classified into an American Heart Association (AHA)-defined 17-segment model in each patient. The LV myocardium was classified into an American Heart Association (AHA)-defined 17-segment model in each patient (Figure 1).

Regional whole-layer PLS and peak circumferential strain (PCS) in each segment among 17 lesions for PLS and 12 lesions (only mid and basal portions) for PCS, as defined by the AHA, were calculated offline using 3 digitally stored 2D images (apical long-axis, 2-chamber, and 4-chamber) and analyzed by Echo PAC, version 113 (GE Healthcare) in each patient (Figure 1).

First, the endocardial border was traced manually at the end systolic frame by the point-and-click approach. A region of interest was then generated by the software to cover the entire thickness along the LV myocardium. Tracking was performed automatically, and the region of interest was adjusted manually to provide optimal tracking. The LV was divided into 6 segments in each apical view, and the tracking quality was validated for each segment. The myocardial motion was then analyzed by speckle-tracking within the region of interest. The semi-automated algorithm, using the AHA 17-segment model, provides regional whole-layer PLS for each LV segment.

In general, regional longitudinal strain (LS) values are presented as negative values, with a greater value (a smaller absolute value) indicating higher impaired regional function. The present study was based on the absolute values of LS.

Layer-specific MF measurement on CMR: CMR was performed in breath-hold mode with the use of a 1.5 Tesla CMR. Late gadolinium enhancement short-axis images were acquired every 3 mm (slice thickness, 6 mm) from base to apex. An inversion-recovery-prepared, T1-weighted, three-dimensional gradient-echo sequence was used to obtain late gadolinium enhancement to assess the presence of MF. Late gadolinium enhancement images were acquired at an average of 10 to 15 min after contrast administration. The contrast dose (gadopentetate dimeglumine [Magnevist; Schering AG]) was 0.15-0.20 mmol/kg.

We defined detection of MF qualitatively on CMR, and we regarded the borderline region as positive in this analysis.

The presence of MF was assessed by CMR as (1) neither in LVendo nor LVepi, (2) only in LVendo, (3) only in LVepi, or (4) both in LVendo and LVepi for each lesion (Figures 2, 3) based on the AHA 17-segment model. The differentiation of the LV endocardial layer and the epicardial layer used the midline (dotted line) of the LV myocardium qualitatively.

Figure 2. Schema of layer specific measurement of myocardial fibrosis (MF) on cardiac magnetic resonance (CMR). The presence of MF was assessed by T1-weighted CMR as located (1) only in the left ventricular (LV) epicardial layer, (2) only in the LV epicardial layer, and (3) both in LV endocardial and epicardial layers, based on the American Heart Association 17-segment model. The differentiation of the LV endocardial layer and the epicardial layer used the midline (dotted line) of the LV myocardium qualitatively.
Patient backgrounds and conventional TTE are shown in Table I, II.

Ten patients showed only asymmetric septal hypertrophy, four patients showed only apical hypertrophy, and four patients showed both asymmetric septal hypertrophy and apical hypertrophy. Four patients showed hypertrophic obstructive cardiomyopathy and none of these patients underwent percutaneous transluminal septal myocardial ablation. No patient underwent pacemaker or implantable cardioverter defibrillator implantation before CMR examination. Ten patients used a beta blocker, eight patients used an angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, and five patients used a calcium channel blocker. None of the patients showed dilated phase HCM, and the mean LV ejection fraction was relatively preserved (mean, 64.4% ± 6.5%) in this patient population.

Among the 18 patients, two revealed LV wall motion...
asynergy on TTE (one for the basal anterior wall and the other for the anterior septal wall). Both of these patients revealed MF in LVendo and LVepi on CMR, but showed no ECG findings that suggested myocardial infarction. Furthermore, both patients underwent cardiac CT in which no significant coronary arterial stenosis was observed.

Of the total 306 segments acquired from all 18 patients, 225 LV segments showed no MF and 81 LV segments had MF on CMR.

Regional whole-layer PLS between LV segments with and without MF indicated that PLS is significantly lower in LV segments with MF (8% ± 2%) than in those without MF (12% ± 2%; \( P < 0.001 \)).

On the other hand, there were no significant differences of whole-layer PCS between LV segments with and without MF (17.7% ± 6.4% versus 19.3% ± 7.8%; \( P = 0.203 \)).

Among the 81 LV segments with MF on CMR, 13 (16%), nine (11%), and 59 (73%) segments had MF only in LVendo, only in LVepi, and in both LVendo and LVepi, respectively.

Regional whole-layer PLS among LV segments of (1) neither in LVendo nor LVepi, (2) only in LVendo, (3) only in LVepi, and (4) in both LVendo and LVepi showed that PLS values are significantly lower in MF segments affecting only the LV endocardial layer (7% ± 4%; \( P < 0.05 \)) or both the LV endocardial and epicardial layers (9% ± 5%; \( P = 0.001 \)) compared with segments without MF (13% ± 7%). However, no significant difference in PLS values was detected between MF segments for the LV epicardial layer only (10% ± 6%) and those without MF (13% ± 7%; \( P = 0.562 \)).

In each patient, the numbers of segments (=semi quantitatively) with MF on CMR were significantly and negatively correlated with the absolute values of global LS (average of 17 segments) on TTE (correlation coefficient, -0.61; \( P < 0.05 \); Figure 5).

**Discussion**

In this study, in HCM patients, regional whole-layer PLS (absolute values) was significantly lower in LV segments with MF than in those without MF on CMR. These findings are consistent with those of previous studies.46

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**Table II.** Conventional Transthoracic Echocardiographic Findings in This Population

| Parameter                              | \( n = 18 \) |
|----------------------------------------|-------------|
| Left atrial dimension (mm)             | 44.1 ± 7.6  |
| Left atrial volume index (mL/m²)       | 29.8 ± 11.0 |
| Inter-ventricular septum thickness diameter on end diastole (mm) | 16.9 ± 5.0  |
| LV posterior wall thickness on end diastole (mm) | 10.1 ± 1.9  |
| LV end-diastolic dimension (mm)        | 48.1 ± 5.9  |
| LV end-systolic dimension (mm)         | 29.8 ± 4.2  |
| LV ejection fraction (%)               | 64.4 ± 6.5  |

Left ventricular (LV) size were within normal limits, and LV ejection was relative preserved (mean 64.4% ± 6.5%) in this population.
Furthermore, this is a first imaging study showing that focal MF on CMR is layer-specific as (1) only in LVendo, (2) only in LVepi, or (3) both in LVendo and LVepi. In addition, our results determined the influence of the presence of such MF on regional whole-layer PLS values on TTE at the corresponding sites.

Regional whole-layer PLS values were significantly lower in segments with MF only in LVendo and in both LVendo and LVepi than those in segments without MF. However, no significant differences in whole-layer PLS were observed between segments with MF only in LVepi and those without MF.

Accuracy of layer-specific detection of MF on CMR in HCM patients: Concerning the accuracy of detection of MF on CMR in HCM patients, a previous CMR study showed that MF is predominantly located in the mesocardial layer in HCM patients. In this study, we divided the location of MF into two (endocardial and epicardial layers) rather than three layers (endocardial, mesocardial, and epicardial layers). Therefore, MF located in the mesocardial layer may indicate MF located in both LVendo and LVepi in this study. Actually, in this study, of the 81 segments with MF on CMR, 73% of the segments had MF in both LVendo and LVepi, and only 16% and 11% of the segments had MF only in LVendo and only in LVepi, respectively.

Hypothesis of decrement of global LS in HCM patients compared with controls: Recently, multilayer strain TTE analysis in which endocardial, epicardial, and whole-layer-specific strain can be measured separately, has become available. Using this technique, we previously reported that in HCM patients with preserved LV ejection fraction, 2D LV global LS was lower than that in controls. However, those results showed that endocardial global circumferential strain (GCS) was maintained in compensation for the reduction in endocardial global LS. Thus, the percentage of endocardial GCS per epicardial GCS may increase, and increased LV size results in a smaller compensatory effect. However, from the results of the present study, we suggest that the decrement of 2D LV global LS in HCM patients compared with controls in the previous study may be due to the presence of focal MF, especially in LVendo or both in LVendo and LVepi.

Characteristics of hypertrophied LV myocardium: In patients with hypertrophied LV myocardium such as HCM, aortic stenosis, or hypertensive heart disease, there is a decrement of blood flow predominantly in LVendo compared with LVepi. However, in this study, we did not evaluate the decrement of blood flow, but we did detect MF in the LV myocardium on CMR. The MF is a permanent organic change, and, therefore, the decrement of regional whole-layer PLS in this study indicated MF and not a decrement of blood flow occurring typically in hypertrophied LV myocardium.

Intra- and inter-observer variabilities for PLS measurements and the areas of identified late gadolinium enhancement on CMR: In this study, all physicians who conducted analysis had more than 8 years of experience as cardiologists with specialty in non-invasive cardiac imaging (H. T. for CMR and K. O. for strain measurement). Previously, we assessed the capability of our laboratory in terms of intra- and inter-observer variabilities for LS measurements and the inter-observer variabilities for areas of identified late gadolinium enhancement. We reported inter- and intra-observer consistency in LV myocardial strain measurement on TTE in patients with severe aortic stenosis and preserved LV ejection fraction. Inter- and intra-observer correlation coefficients in whole-layer global LS estimates were 0.81 and 0.97, respectively. In addition, we reported that inter-observer agreement for detection of late gadolinium enhancement on CMR was 0.82 on segment-based analysis (P < 0.05) in patients suspected to have various myocardial diseases.

Clinical significance of the results in this study: In this study, we clarified that the fibrotic lesions in LVendo have a greater adverse effect on PLS than those in the LVepi. From the result, a previous paper reported that PLS on TTE is the prognostic indicator for HCM patients. Late gadolinium enhancement on CMR is also a prognostic indicator for HCM patients. However, there were some discrepancies between the decrement of PLS on TTE and the presence of late gadolinium enhancement on CMR in HCM patients. The location of late gadolinium enhancement, whether in LVepi, LVendo, or both on CMR, may influence PLS on TTE in HCM patients. In the future, we should evaluate the localization of late gadolinium enhancement on CMR, which may contribute to a more accurate prediction of prognosis in HCM patients. This is the most clinically significant result from this study.

Limitations: There are some limitations to this study. First, on TTE, there are three types of myocardial strain: longitudinal, circumferential, and radial strains. The current study examined only the longitudinal and circumferential strains. In this study, the presence of MF was assessed by CMR as located (1) neither in LVendo nor...
LVepi, (2) only in LVendo, (3) only in LVepi, or (4) both in LVendo and LVepi for each lesion based on the AHA 17-segment model. Therefore, from the method of analysis of CMR, which is perpendicular to the short axis of the left ventricle (Figure 2), the radial strain may be more preferable than LS. However, at present, measurement of radial strain is not available on the Vivid E9 in our institute.

Second, there was a significant difference between without MF and MF only in LVendo, but there was no significant difference between without MF and MF only in LVepi. On the other hand, there was no significant differences between MF only in LVendo and MF only in LVepi. We speculate that this discrepancy occurred due to the small numbers of patients and segments, especially MF only in LVepi and MF only in LVendo. We should re-evaluate the same design in a larger patient population.

Third, along with the presence of MF, the presence of hypertrophy in LV myocardium may influence the regional whole-layer PLS values and the influence of the degree of wall thickness determined by cine CMR should be considered (in this study, one patient could not undergo cine CMR because of the occurrence of headache).

Fourth, the differentiation of LVendo and LVepi on CMR used the midline of the LV myocardium qualitatively, as indicated in Figure 2. However, this definition does not indicate that LVendo is equal to the LV endocardium because the ratio of LV endocardium to the whole LV myocardial layer may differ due to the degree of LV hypertrophy.

Fifth, the interval (within [up to] 13 months) between TTE and CME seemed to be too long. This is a retrospective analysis, and to increase the numbers of the subjects to improve the reliability of the conclusion in this study, the interval reached 13 months. However, no patient was admitted into the hospital due to cardiac events such as worsened cardiac failure.

Sixth, we demonstrated a significant difference in regional PLS between with and without MF on CMR. However, the normal range of PLS is different for each segment. For instance, the PLS of the apical region is known to be higher than that of the basal region. However, it is difficult to find appropriate parameters to differentiate and classify strain in the apical region from that in the basal region because of fundamental differences of PLS in each segment. Therefore, we analyzed the PLS data without considering these fundamental differences in each segment.

Seventh, we showed that only LV lesions with CMR changes affected whole layer PLS. Therefore, we may not be able to conclude that the decrement of whole-layer PLS in LV indicates the presence of focal MF.

Eighth, the quantitative volume of MF on CMR may influence the regional whole-layer PLS on TTE, and a quantitative measurement of MF on CMR was not performed. Furthermore, the T1 mapping method on CMR is the gold standard for quantitative measurement of interstitial volume. In this study, we underwent semi-quantitative analysis in which absolute values of global LS (average of 17-segment regional peak LS) on TTE in each patient significantly and negatively correlated with the numbers of segments with MF on CMR (correlation coefficient, -0.61; \( P < 0.05 \)), and we speculated that there would be a significant relationship between global LS and quantitative volume of MF in HCM patients. Therefore, we hope to evaluate the relationship of global and regional LS and circumferential strain against interstitial volume measured by T1 mapping method.

Finally, using multilayer strain TTE technique, further studies in which endocardial and epicardial layer-specific LS, circumferential, and radial strain on TTE are compared with presence of MF in LVendo and LVepi on CMR, respectively, should be performed.

**Conclusion**

In HCM patients, MF lesions in LVendo (only LVendo or in both LVendo and LVepi) have a greater effect on whole-layer PLS than that of MF in only LVepi. Therefore, in HCM patients, if there is decrement of focal whole-layer PLS in LV myocardium on TTE, the physician should evaluate the presence of focal MF, especially in LVendo or in both LVendo and LVepi on CMR.

**Disclosures**

**Conflicts of interest:** There is no conflict of interest to declare.

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