Myocardial Shortening in 3 Orthogonal Directions and Its Transmural Variation in Patients With Nonobstructive Hypertrophic Cardiomyopathy

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Background: Although longitudinal strain (LS) is known to be reduced in patients with hypertrophic cardiomyopathy (HCM), it has not been elucidated whether or not circumferential strain (CS) is reduced. We aimed to determine whether multidirectional and layer-specific myocardial strain is reduced in patients with nonobstructive HCM.

Methods and Results: Speckle-tracking echocardiography was performed in 41 HCM patients and 27 control subjects. Segmental and global LS and CS were measured in the inner, mid, and outer layers. Global LS was significantly lower in the HCM group than in controls in the inner (−10.3±2.9 vs. −14.8±2.0%, P<0.001), mid (−8.7±2.6 vs. −13.8±1.9%, P<0.001), and outer (−7.2±2.6 vs. −11.9±1.9%, P<0.001) layers. Global CS was preserved in the inner layer (−23.8±4.7 vs. −24.3±3.3%, P=0.69) but reduced in the mid (−10.3±3.1 vs. −13.3±2.5%, P<0.001) and outer layers (−6.7±2.3 vs. −8.6±2.3%, P=0.002). Differences in CS between the inner and outer layers correlated with segmental relative wall thickness (r=−0.20, P=0.002). Furthermore, only the absolute value of global CS in the inner layer positively correlated with left ventricular ejection fraction (r=0.32, P<0.01) among these multidirectional and layer-specific strains.

Conclusions: In patients with HCM, not only the LS in all layers but also CS in the mid and outer layers was reduced, presumably reflecting impaired myocardial function. In contrast, CS in the inner layer was preserved, being associated with maintenance of chamber function. (Circ J 2015; 79: 2471–2479)

Key Words: Ejection fraction; Hypertrophic cardiomyopathy; Myocardial function; Speckle-tracking echocardiography

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease characterized by asymmetric left ventricular (LV) hypertrophy without ventricular dilatation caused by inherited mutations in genes that encode the cardiac sarcomeric proteins. In patients with HCM, the LV ejection fraction (EF) is usually normal or increased, but the systolic mitral annular velocity, which is assessed by tissue Doppler imaging and reflects longitudinal myocardial shortening, is often depressed.

Recently, 2D speckle-tracking echocardiography (STE) has been developed and enables measurement of myocardial strain in 3 orthogonal directions; that is, longitudinal strain (LS), circumferential strain (CS), and radial strain (RS). Moreover, layer-specific myocardial strain can now be measured at the innermost, midwall, and outermost LV layers using this technique. Several studies using STE have reported that LS and RS are reduced in HCM patients, even though LVEF was preserved. In contrast, studies of CS have alternately reported that this parameter is increased or decreased. Even in normal subjects, circumferential myocardial shortening is known to have a transmural gradient; that is, CS is lower in the outer layers and greater in the inner layers. Accordingly, it is considered that CS should be assessed layer-specifically in all cases. We thus aimed to determine whether layer-specific myocardial strain in 3 orthogonal directions is reduced in patients with nonobstructive HCM.
Methods

Study Subjects
The study subjects consisted of 41 consecutive patients with HCM (24 men, 17 women; 59.0±18.8 years) and 27 control subjects (15 men, 12 women; 53.2±9.7 years) who were referred to Hokkaido University Hospital. HCM diagnosis was based on echocardiographic demonstration of a nondilated and hypertrophied LV with asymmetric septal hypertrophy in the absence of other cardiac or systemic diseases that might lead to the same degree of LV hypertrophy. LV hypertrophy was defined as a maximum wall thickness ≥13 mm, and asymmetric septal hypertrophy was defined as a ratio of interventricular septal thickness (IVST) to LV posterior wall thickness (PWT) >1.3. Exclusion criteria included the following: LV outflow tract obstruction, apical hypertrophy, reduced LVEF (<50%), regional wall motion abnormalities, moderate to severe valvular stenosis or regurgitation, and poor echocardiographic images. The control subjects were selected from patients who had normal electrocardiographic and echocardiographic findings without any history of cardiac or systemic disease such as hypertension, diabetes mellitus, or dyslipidemia. All the study subjects exhibited normal sinus rhythm. Among the HCM patients, β-blockers were prescribed to 20 (49%) patients, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker to 17 (41%), calcium antagonist to 14 (34%), diuretics to 6 (15%), and an antiarrhythmic drug to 8 (20%). This study was approved by the Research Ethics Committee of Hokkaido University Hospital, and all study subjects provided written informed consent.

Echocardiography
Using an Artida ultrasound system (Toshiba Medical Systems Co, Tochigi, Japan) equipped with a PST-30BT transducer (3 MHz), the LV end-diastolic dimension (LVDd), LV end-systolic dimension (LVDs), and left atrial (LA) dimension were measured and endocardial fractional shortening (FS) was calculated. IVST and LV PWT were measured at end diastole, and also at end systole to calculate midwall fractional shortening (FSmw) according to the formula reported by Shimizu et al.13 LV segmental end-diastolic wall thickness was measured in 6 segments on the parasternal short-axis view at the midventricular level, and segmental relative wall thickness was calculated in each segment as follows: 2×[segmental wall thickness]/LVDd.

LVEF and LA volume were measured using the biplane method of disks.14 LA volume was indexed for body surface area. Stroke volume was measured by pulsed Doppler method.15

Analysis of STE-Derived Strain
Myocardial strain was analyzed offline using the STE software (Toshiba Medical Systems). The LV endocardial and epicardial borders were manually traced on the apical 4-chamber, 2-chamber, and long-axis views, as well as on the basal, mid-, and apical short-axis views. The software algorithm discriminated the endocardial and epicardial borders, as well as the midpoint on the end-diastolic frame, and then tracked those speckle patterns in a frame-by-frame manner. Consequently, the layer-specific strain curves for each of 6 segments were automatically generated. The peak values of segmental LS in the inner layer, midwall, and outer layer were measured in 3 apical views (LSinner, LSmw, and LSouter). The layer-specific segmental peak CSts (CSinner, CSmw, and CSouter) and peak RSs of the inner-half myocardium (RSinther), outer-half myocardium (RSouter) and full-thickness myocardium (RStotal) were measured in 3 short-axis views.
Layer-specific LS curves were constructed for 3 apical views (Figures 1A–C), and peak values were measured and averaged among the 3 views (GLSinner, GLSmw, and GLSouter, respectively). In addition, layer-specific CS curves were also constructed for 3 short-axis views (GCS inner, GCS mw, and GCS outer, respectively). Similarly, the peak values of the RSs were also measured and averaged among the 3 short-axis views (GRSinner, GRSouter, and GRStotal, respectively).

Reproducibility

The reproducibility of the STE analysis was assessed in 15 study subjects. Two independent, blinded observers analyzed the same 2D cine-loops and one of them repeated the analysis on a separate day. The respectively intra- and interobserver variability values were 7% and 13% for GLSinner, 8% and 12% for GLSmw, 13% and 22% for GLSouter, 3% and 9% for GCSinner, 6% and 6% for GCSmw, 7% and 6% for GCSouter, and 12% and 12% for GRStotal. In regard to the segmental parameters, they were 9% and 16% for LSinner, 9% and 16% for LSouter, 18% and 21% for LSouter, 14% and 17% for CSinner, 25% and 26% for CSouter, 26% and 26% for CSouter, and 20% and 22% for RSStotal, respectively.

Statistical Analysis

Statistical analysis was performed using standard statistical software (IBM SPSS Statistics version 19; IBM SPSS Inc, Chicago, IL, USA). All numerical data are presented as the mean±standard deviation. Unpaired Student’s t-test and chi-square test were used for comparisons between groups. Linear regression analysis was carried out for the assessment of correlations between parameters. Comparisons of segmental wall thickness among 6 segments were tested by analysis of variance with Scheffe’s post hoc test. STE-derived parameters were compared between patients taking and not taking a β-blocker by Student’s t-test and analysis of covariance. P<0.05 was considered statistically significant.

Results

Clinical characteristics and conventional echocardiographic parameters are shown in Table 1. Heart rate was significantly lower, and the LA dimension, LA volume index, IVST, and LV PWT were significantly greater in the HCM patients than in the controls. LVEF and endocardial FS were significantly greater, but FSbw was significantly lower in the HCM patients. Comparisons between HCM patients and control subjects of the layer-specific global strains in 3 orthogonal directions are shown in Figure 2. The 3 global LS (GLS) values (GLSinner, GLSmw, and GLSouter) were significantly lower in the HCM patients than in the controls (Figure 2B). Two of the global CS (GCS) values (GCSmw and GCSouter) were lower in the HCM patients than in the control subjects, but GCSinner was comparable between groups (Figure 2B). Similarly, 2 of the global RS (GRS) values (GRSinner and GRSStotal) were significantly lower in HCM patients than in the controls, while GRSinner was comparable between groups (Figure 2C).

Although segmental wall thickness was significantly greater in the HCM patients than in the control subjects in all 6 segments, the septal, anteroseptal, and anterior segments were markedly hypertrophied (Table 2). Thus, the LV myocardial segments were divided into hypertrophied (septal, anteroseptal, and anterior) and less-hypertrophied (inferior, posterior, and lateral) segments. In the hypertrophied segments, all LS values (LSinner, LSouter, and LSStotal) were significantly lower in the HCM patients than in the controls (Figure 3A). CSinner, CSouter, RSinner, and RSStotal were also lower in the HCM patients, whereas CSinner and RSinner were comparable between groups (Figures 3B, C). In the less-hypertrophied segments, LS was lower in all myocardial layers in the HCM patients (Figure 3D), whereas CS and RS were preserved in all layers (Figures 3E, F).

As illustrated in Figure 4, LSinner, CSinner, and RSStotal in the midventricular segments linearly and significantly correlated with segmental wall thickness in the patients with HCM (Figures 4A, C, D), but CSinner did not (Figure 4B). As CSinner was preserved, despite CSouter and CSStotal being reduced, we
Depressed Longitudinal Shortening and Transmural Variation in Circumferential Shortening

LV myocardial shortening in the longitudinal direction has been reported to be more severely depressed than that in the circumferential direction in various diseases such as heart failure with preserved EF, hypertensive heart disease, aortic stenosis, and diabetes mellitus. This is generally attributed primarily to the fact that the longitudinally oriented, innermost myocardial fibers would be impaired first in these disease states. Also, in the present study in which patients with HCM were investigated, LV myocardial shortening in the longitudinal direction was reduced in all myocardial layers in both the hypertrophied and less-hypertrophied segments of HCM patients. In contrast, circumferential shortening in the less-hypertrophied segments was preserved in all layers. However, that in the hypertrophied segments was preserved in the inner layer but reduced in the midwall and outer layer. (b) According to the segment-based analysis, the degree of longitudinal shortening and that of radial thickening varied inversely with the segmental wall thickness. The degree of circumferential shortening in the outer layer also varied inversely with the thickness, whereas that in the inner layer was not associated with wall thickness. (c) Differences in circumferential shortening between the inner and outer layers correlated with segmental relative wall thickness. (d) Maintenance of circumferential shortening in the inner layer was associated with preserved LVEF.

Discussion

The principal findings of the present study were as follows. (a) Longitudinal shortening was reduced in all myocardial layers in both the hypertrophied and less-hypertrophied segments of HCM patients. In contrast, circumferential shortening in the less-hypertrophied segments was preserved in all layers. However, that in the hypertrophied segments was preserved in the inner layer but reduced in the midwall and outer layer. (b) According to the segment-based analysis, the degree of longitudinal shortening and that of radial thickening varied inversely with the segmental wall thickness. The degree of circumferential shortening in the outer layer also varied inversely with the thickness, whereas that in the inner layer was not associated with wall thickness. (c) Differences in circumferential shortening between the inner and outer layers correlated with segmental relative wall thickness. (d) Maintenance of circumferential shortening in the inner layer was associated with preserved LVEF.
Multidirectional and Layer-Specific Strain in HCM

In the present study, layer-specific myocardial strain was investigated and transmural variation in the impairment of circumferential shortening was demonstrated in patients with HCM. Although the mechanism underlying the transmural variation could not be precisely determined from the available data, one interpretation of our results is that the development of concentric LV geometry allows the maintenance of endocardial CS despite the decrease in active shortening of myocardial fibers, which was represented as a reduction in the midwall and epicardial CS values. Because the radius of the circumferential curvature of the LV wall is smaller than that of the longitudinal curvature, there may be substantial interactions between the layers involved in circumferential myocardial shortening. If so, then the circumferential shortening observed in a certain myocardial layer must reflect not only active shortening of the myocardial fibers in situ but also passive shortening caused by layer-to-layer interactions. For example, when the outermost myocardium shortens circumferentially, its radius simultaneously shortens with an increase in its thickness. As a result, the myocardium in the layer just inside it passively shortens in a circumferential direction. Accordingly, it is conceivable that the more inner the layer, the more passive shortening, because the action of the outer layers will contribute to its circumferential shortening. Consequently, an increase in relative wall thickness should result in an increased booster effect from the outer toward the inner layers in order to maintain endocardial circumferential shortening and therefore LVEF.

According to this theory, the reduction in midwall and epicardial CS values observed in the present study would reflect impaired myocardial function, and the preserved endocardial CS would reflect the effect of compensation for the impaired myocardial function through an increase in relative wall thickness. In fact, the degree of midwall and epicardial circumferential shortening varied inversely with segmental wall thickness, suggesting that they reflected the impairment of myocardial function. Furthermore, the higher the segmental relative wall thickness, the greater the difference in circumferential shortening observed between the endocardium and epicardium, suggesting that compensation through the transmural interactions had an even larger effect. However, our results also suggested that the contribution of the compensation through an increase in relative wall thickness was not great. Thus, there must be other compensatory mechanisms to maintain circumferential shortening in the inner myocardial layer.

Ozawa et al most recently reported that GLS was lower in all myocardial layers in patients with HCM compared with control subjects, and that GCS in HCM patients was lower in the outer layer but preserved in the inner layer compared with control subjects,22 similar to our results. However, they did not evaluate the relationship between the degree of hypertrophy and reduction in myocardial strain. Furthermore, they did not focus on the association between relative wall thickness and compensatory mechanisms to preserve LVEF in HCM patients.

Figure 3. Comparison of layer-specific regional strain in hypertrophied and less-hypertrophied segments. Longitudinal strain (LS) in the inner layer, midwall, and outer layer (LSinner, LSMw, LSouter, respectively) (A), circumferential strain (CS) in the inner layer, midwall, and outer layer (CSinner, CSmw, CSouter, respectively) (B), and radial strain (RS) of the inner-half, outer-half, and full-thickness myocardium (RSinner, RSouter, RStotal, respectively) (C) were compared between the hypertrophied segments of hypertrophic cardiomyopathy (HCM) patients and corresponding segments of control subjects. The same comparisons were made in the less-hypertrophied segments (D–F).
Impaired Myocardial Function and Compensatory Mechanism for the Maintenance of LV Chamber Function

Aurigemma et al reported that LV endocardial FS was preserved, despite a decrease in both FS_{mw} and LV long-axis shortening represented by mitral annular plane systolic excursion in hypertensive patients with LV hypertrophy and a normal LVEF, and concluded that there was a generalized myocardial shortening abnormality in each of 2 orthogonal directions in their patients. In addition, they demonstrated that differences in FS between the endocardium and midwall were directly related to relative wall thickness, and presumed that increased relative wall thickness contributes to normal LV chamber function despite abnormal myocardial function. It is thus generally considered that, through concentric LV geometric change, a given magnitude of systolic wall thickening and of the resultant endocardial shift toward the cavity’s center can be obtained with less myocardial fiber shortening in patients with hypertensive LV hypertrophy.

In contrast, the present study successfully demonstrated the contribution of concentric hypertrophy and transmural interactions in circumferential shortening to the compensatory mechanism for impaired myocardial function in order to maintain endocardial circumferential shortening and finally LVEF.
myocardial function. Our results and these considerations suggest that concentric geometry is an adaptive process to compensate for impaired myocardial function in patients with HCM, and that an analysis of midwall or outer CS is especially important in evaluating myocardial function in this disease. It should be noted that the use of endocardial indexes such as LVEF would overestimate myocardial function. Furthermore, the analysis of midwall and outer layer shortening may be helpful in predicting cardiovascular events and may be related to patient prognosis, although these possibilities remain to be proven in further studies.

Comparison With the Literature
Many previous studies have shown a decrease in the longitudinal shortening of the LV wall in patients with HCM by using tagged magnetic resonance imaging.\(^\text{26–28}\) Doppler strain imaging,\(^\text{26–28}\) or STE.\(^\text{10–12,29–33}\) In contrast, circumferential myocardial shortening in HCM patients has variously been reported as increased\(^\text{10,11,29}\) or decreased.\(^\text{12,30,31}\) Carasso et al investigated LV myocardial CS derived from STE using a Siemens ultrasound machine, and demonstrated that the CS was increased in HCM patients.\(^\text{30}\) In contrast, Serri et al reported a decrease in STE-derived CS using an ultrasound system from GE Medical Systems.\(^\text{12}\) We thus investigated the layer-specific LS and CS, and found that global LS was reduced in all 3 layers, and that both global CS and the averaged CS among hypertrophied segments were preserved in the inner layer but reduced in the midwall and outer layer. Our results regarding LS are in good accordance with those reported in the literature. On the other hand, our results regarding CS may provide a major clue to the cause of the discrepancy between the findings of Carasso et al and Serri et al. That is, these 2 groups may have observed the CS in different myocardial layers: more specifically, Carasso et al may have measured subendocardial CS, while Serri et al appear to have measured the averaged CS among layers over the full thickness. Thus, the former results conceivably represent the preserved LV chamber function, and the latter predominantly reflect impaired myocardial function. The measurement of layer-specific CS enables evaluation of LV chamber function and myocardial function independently. Recently, the prognostic effect of LV global strain has been established as greater than that of LVEF in patients with heart failure.\(^\text{16,33}\)

Myocardial function is considered to be more strongly associated with a patient’s prognosis than LV chamber function. Therefore, it is important to accurately estimate LV myocardial function rather than chamber function. It can be also considered that the differences in STE algorithms among ultrasound systems or among analysis software packages heavily influence the value of CS. In general, therefore, CS should not be averaged among myocardial layers but always measured layer-specifically.

Technical Advantages and Future Prospects
In the present study, depressed LV myocardial function in the patients with a normal EF was detected by STE-derived LS (in any myocardial layer) and CS in the midwall or outer layer. Longitudinal myocardial function can be assessed even by M-mode echocardiography and tissue Doppler imaging. Also, circumferential myocardial function can be assessed by FS\(^\text{mw}\). However, the newly developed STE possesses several advantages over such conventional methods. Measurement of mitral annular motion depends on the angle between the ultrasound beam and the direction of mitral annular motion, whereas STE-derived strain allows angle-independent measurement of myocardial shortening. FS\(^\text{mw}\) is mathematically derived from a 2-shell cylindrical model that does not take into account longitudinal shortening of the LV wall. In contrast, STE enables the direct calculation of myocardial strain and thus yields more accurate results than the conventional methods. Moreover, the measurement of layer-specific myocardial strain by 2D STE has been validated in an animal experiment.\(^\text{9}\) Above all, it is worth noting that, unlike FS\(^\text{mw}\), which is a global LV parameter, STE-derived strain is applicable to segmental LV wall motion analysis. In fact, in the present study, different results regarding circumferential myocardial shortening between hypertrophied and less-hypertrophied segments of the HCM patients could be achieved by using layer-specific strains, and this would never be possible using FS.

Such segmental LV analysis could be especially important for early detection of the dilated phase of HCM and helpful for identifying arrhythmia substrate in patients with HCM. Furthermore, the relationship between the amount of myocardial fibrosis and strain parameters has been reported.\(^\text{29,31}\) Layer-by-layer analysis of myocardial shortening by STE might provide...
additional information regarding the extent and distribution of LV fibrosis. In the present study, myocardial shortening was reduced in both the longitudinal and circumferential direction in patients with HCM. On the other hand, pronounced diastolic dysfunction is a well-known characteristic finding in HCM patients. Further studies to assess the relationship between regional myocardial shortening and relaxation using layer-specific and multidirectional STE analyses may provide more insights into the pathophysiology of HCM.

Study Limitations
Several limitations should be acknowledged. First, as is well known, longitudinally oriented myocardial fibers predominate in the subendocardial and subepicardial layers of the LV wall, and circumferentially oriented fibers in the midwall. Longitudinal and circumferential shortening should thus be appropriately measured in the layer in which the fibers are oriented in the same direction as the shortening to be measured. However, myocardial shortening in a given direction occurs not only by active shortening of the myocardial fibers oriented in the same direction, but also as a result of complex interactions between layers, as mentioned before. Furthermore, the myocardium of HCM patients is characterized by myofibrillar disarray. For these reasons, it is difficult to simply assume that myocardial shortening in a particular direction represents only shortening of the myocardial fibers oriented in the same direction. Therefore, we had to treat the LV myocardium as a homogeneous mass and examine multidirectional wall kinetics with a layer-specific method. Second, wall stress was not taken into account in the present study because the general formulae used to estimate wall stress could not be used here due to the asymmetric LV hypertrophy in patients with HCM. Myocardial function cannot be evaluated only by myocardial strain. However, patients with HCM are usually characterized by increased wall thickness, decreased cavity size, and normal blood pressure. Furthermore, we excluded patients with LV outflow tract obstruction, in whom LV wall stress might have been increased. LV wall stress may thus have been decreased in almost all the HCM patients. Therefore, the reduced myocardial strain observed in the present study (eg, LS in any layer and CS in the midwall or outer layer) can be assumed to reflect impaired myocardial function in this disease. However, it should be noted that whether or not preserved strain (eg, CS in any layer in the less-hypertrophied segments) indicates truly normal myocardial function remains unclear. Third, 20 of the 41 patients with HCM were taking a β-blocker, which might have affected myocardial contractility. However, GLS\textsubscript{outer}, GLS\textsubscript{inner}, GCS\textsubscript{outer}, GCS\textsubscript{inner}, and GRS\textsubscript{total} were not significantly different between patients taking and not taking a β-blocker. After adjustment for IVST, GLS\textsubscript{inner} was not significantly different between the 2 groups. Thus, the use of β-blockers might have had little influence on the results. Finally, the above-mentioned theory regarding the transmural variation in the impairment of circumferential shortening is purely speculative. It is difficult to demonstrate transmural interactions because the force operating between myocardial layers cannot be measured noninvasively at this time. We believe this is one of the most crucial issues to be addressed in the future.

Conclusions
LV myocardial shortening was more severely depressed in the longitudinal direction than in the circumferential direction in patients with nonobstructive HCM. At the same time, there was considerable transmural variation in the impairment of circumferential shortening. It is considered that the decrease in the midwall and epicardial shortening reflected impaired myocardial function, and that concentric LV geometry allowed the maintenance of chamber function, as represented by normal endocardial shortening. Measurement of layer-specific CS might enable evaluation of LV chamber function and myocardial function independently of each other.

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