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ORIGINAL ARTICLE
Myocardial Disease

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.[1–3] 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.[4–7]

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).[8] Moreover, layer-specific myocardial strain can now be measured at the innermost, midwall, and outermost LV layers using this technique.[9] Several studies using STE have reported that LS and RS are reduced in HCM patients, even though LVEF was preserved.[10–12] In contrast, studies of CS have alternately reported that this parameter is increased[10,11] or decreased.[12] 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.[9] 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.

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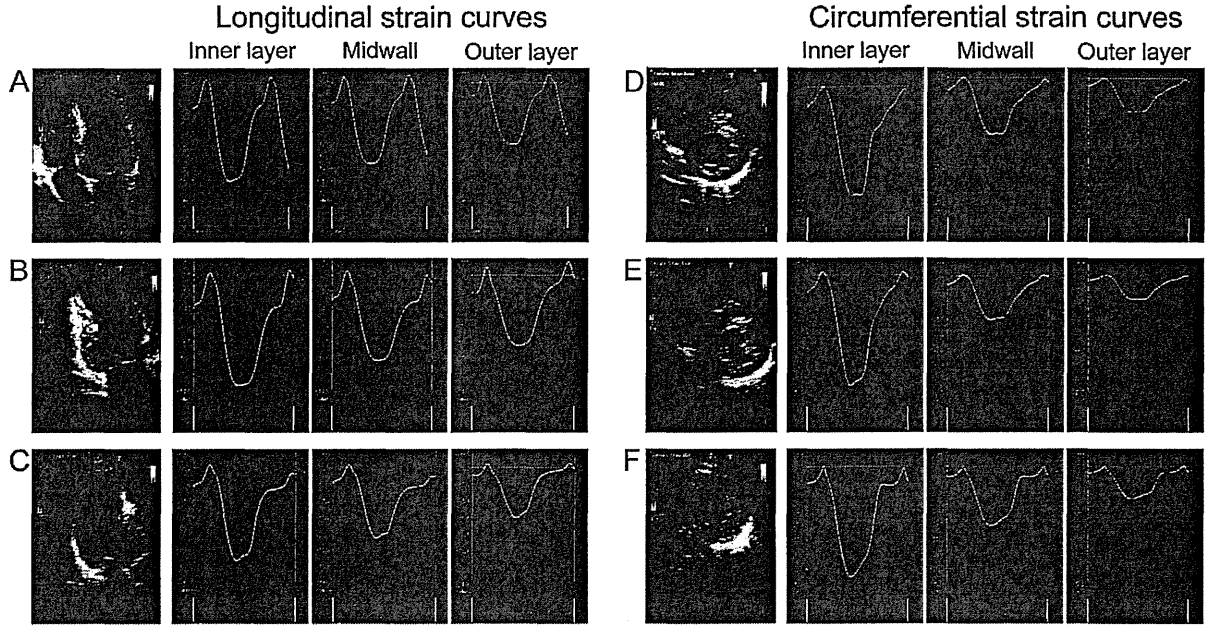

Figure 1. Measurement of layer-specific global longitudinal and circumferential strain. The layer-specific longitudinal strain curves were derived from the apical 4-chamber view (**A**), 2-chamber view (**B**), and long-axis view (**C**). The layer-specific circumferential strain curves were derived from the basal short-axis view (**D**), midventricular short-axis view (**E**), and apical short-axis view (**F**).

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 (FS_{mw}) 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 (LS_{inner}, LS_{mw}, and LS_{outer}). The layer-specific segmental peak CSs (CS_{inner}, CS_{mw}, and CS_{outer}) and peak RSs of the inner-half myocardium (RS_{inner}), outer-half myocardium (RS_{outer}) and full-thickness myocardium (RS_{total}) were measured in 3 short-axis views.

Table 1. Clinical Characteristics and Conventional Echocardiographic Parameters of Study Subjects

	Control (n=27)	HCM (n=41)	P value
Age (years)	53.2±9.7	59.0±18.8	0.10
M/F	15/12	24/17	0.81
Height (cm)	161.6±7.2	160.1±9.5	0.70
Body weight (kg)	61.2±9.2	58.5±7.0	0.17
Body surface area (m^2)	1.64±0.14	1.60±0.13	0.23
Systolic BP(mmHg)	119.4±12.2	126.4±19.9	0.08
Diastolic BP (mmHg)	70.7±9.6	67.3±12.1	0.23
Heart rate (beats/min)	67.4±11.1	59.7±9.7	<0.01
LVDd (mm)	46.2±3.8	45.2±4.1	0.35
LA dimension (mm)	35.9±3.8	41.8±6.5	<0.001
LA volume index (ml/m^2)	26.2±5.2	46.1±17.0	<0.001
IVST (mm)	8.7±1.0	19.8±5.1	<0.001
LV PWT (mm)	8.4±1.0	9.8±1.4	<0.001
LV ejection fraction (%)	65.0±4.2	70.1±6.7	<0.001
FS (%)	38.2±3.8	41.9±5.7	<0.01
FS_{mw} (%)	23.0±3.6	17.7±3.9	<0.001
Stroke volume (ml)	70.6±11.6	78.3±21.2	0.07

BP, blood pressure; FS, endocardial fractional shortening; FS_{mw}, midwall fractional shortening; HCM, hypertrophic cardiomyopathy; IVST, interventricular septal thickness; LA, left atrium; LV, left ventricle; LVDd, LV end-diastolic dimension; PWT, posterior wall thickness.

Layer-specific LS curves were constructed for 3 apical views (**Figures 1A–C**), and peak values were measured and averaged among the 3 views (GLS_{inner}, GLS_{mw}, and GLS_{outer}, respectively). In addition, layer-specific CS curves were also constructed for 3 short-axis views (**Figures 1D–F**), and the peak strain values were measured and averaged among the 3 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 (GRS_{inner}, GRS_{outer}, and GRS_{total}, 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 GLS_{inner}, 8% and 12% for GLS_{mw}, 13% and 22% for GLS_{outer}, 3% and 9% for GCS_{inner}, 6% and 6% for GCS_{mw}, 7% and 6% for GCS_{outer}, and 12% and 12% for GRS_{total}. In regard to the segmental parameters, they were 9% and 16% for LS_{inner}, 9% and 16% for LS_{mw}, 18% and 21% for LS_{outer}, 14% and 17% for CS_{inner}, 25% and 26% for CS_{mw}, 26% and 26% for CS_{outer}, and 20% and 22% for RS_{total}, 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 FS_{mw} 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 (GLS_{inner}, GLS_{mw}, and GLS_{outer}) were significantly lower in the HCM patients than in the controls (**Figure 2A**). Two of the global CS (GCS) values (GCS_{mw} and GCS_{outer}) were lower in the HCM patients than in the control subjects, but GCS_{inner} was comparable between groups (**Figure 2B**). Similarly, 2 of the global RS (GRS) values (GRS_{outer} and GRS_{total}) were significantly lower in HCM patients than in the controls, while GRS_{inner} 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 (LS_{inner}, LS_{mw}, and LS_{outer}) were significantly lower in the HCM patients than in the controls (**Figure 3A**). CS_{mw}, CS_{outer}, RS_{outer}, and RS_{total} were also lower in the HCM patients, whereas CS_{inner} and RS_{inner} 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**, LS_{inner}, CS_{outer}, and RS_{total} in the midventricular segments linearly and significantly correlated with segmental wall thickness in the patients with HCM (**Figures 4A,C,D**), but CS_{inner} did not (**Figure 4B**). As CS_{inner} was preserved, despite CS_{mw} and CS_{outer} being reduced, we

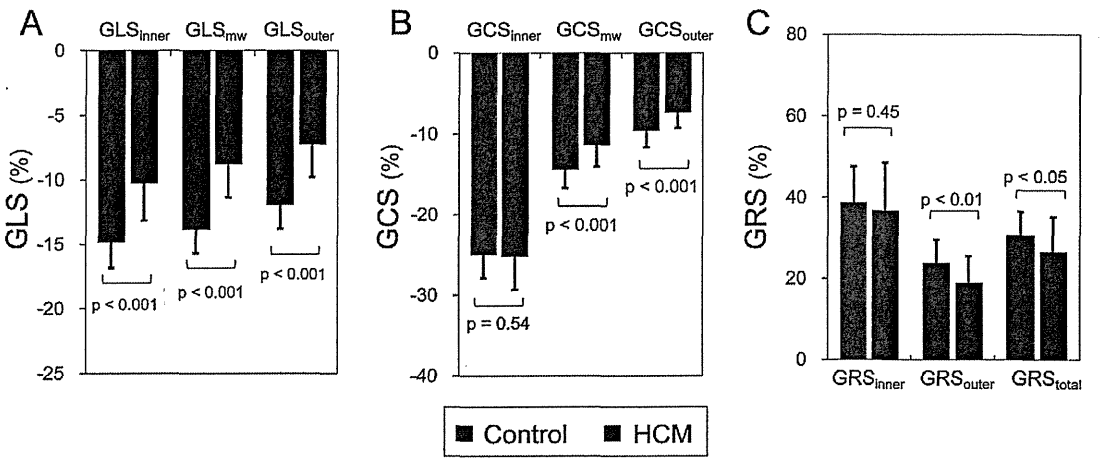

Figure 2. Comparison of layer-specific global strain in 3 orthogonal directions. Global longitudinal strain (GLS) in the inner layer, midwall, and outer layer (GLS_{inner}, GLS_{mw}, GLS_{outer}, respectively) (**A**), global circumferential strain (GCS) in the inner layer, midwall, and outer layer (GCS_{inner}, GCS_{mw}, GCS_{outer}, respectively) (**B**), and global radial strain (GRS) of the inner-half, outer-half, and full-thickness myocardium (GRS_{inner}, GRS_{outer}, GRS_{total}, respectively) (**C**) were compared between patients with hypertrophic cardiomyopathy (HCM) and control subjects.

Table 2. Comparisons of Segmental Wall Thicknesses in Study Subjects

	Control	HCM	P value
Wall thickness (mm)			
Septal	8.6±1.0	17.9±4.1	<0.001
Anteroseptal	8.5±1.0	21.4±5.5	<0.001
Anterior	8.5±0.9	18.9±4.8	<0.001
Lateral	8.4±1.2	14.3±3.1*	<0.001
Posterior	8.2±1.1	11.5±2.4*	<0.001
Inferior	8.2±1.2	12.8±3.1*	<0.001
ANOVA P value	0.60	<0.001	

*P values are for the comparison between control subjects and HCM patients. *P<0.01 vs. the septal, anteroseptal, and anterior wall in HCM by Scheffe's post hoc test. HCM, hypertrophic cardiomyopathy.*

considered that there may be some compensatory mechanism to maintain CS_{inner}. We thus investigated the relationships between (CS_{inner}–CS_{outer}) and several morphological parameters. The results showed that segmental relative wall thickness significantly correlated with (CS_{inner}–CS_{outer}) (**Figure 5**), whereas LVDd and LVDs did not.

The absolute value of GCS_{inner} positively correlated with LVEF, but that of GCS_{outer} did not (**Figures 6A,B**). In contrast, the absolute value of GLS_{inner} inversely correlated with LVEF (**Figure 6C**).

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.

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,[16,17] hypertensive heart disease,[16,18,19] aortic stenosis,[20] and diabetes mellitus.[21] 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

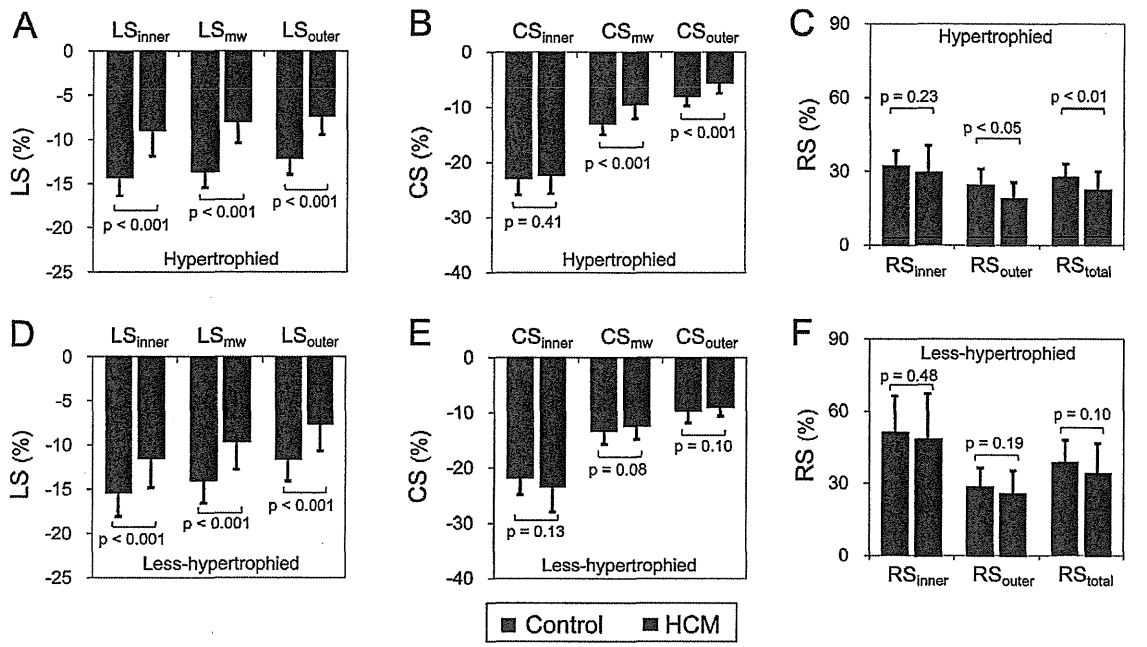

Figure 3. Comparison of layer-specific regional strain in hypertrophied and less-hypertrophied segments. Longitudinal strain (LS) in the inner layer, midwall, and outer layer (LS_{inner}, LS_{mw}, LS_{outer}, respectively) (**A**), circumferential strain (CS) in the inner layer, midwall, and outer layer (CS_{inner}, CS_{mw}, CS_{outer}, respectively) (**B**), and radial strain (RS) of the inner-half, outer-half, and full-thickness myocardium (RS_{inner}, RS_{outer}, RS_{total}, 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**).

patients was more severely depressed in the longitudinal direction than in the circumferential direction. At the same time, there was considerable transmural variation in the impairment of circumferential shortening in hypertrophied segments: normal endocardial shortening and a decrease in midwall and epicardial shortening; this finding is discussed in detail below.

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.

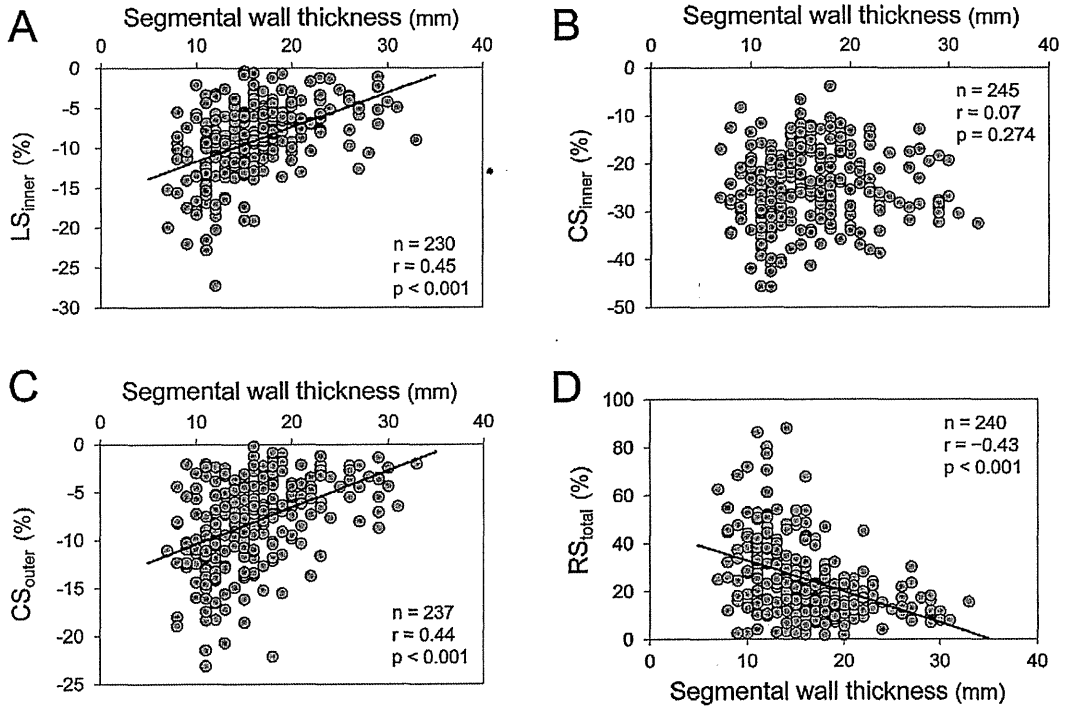

Figure 4. Relationship between segmental wall thickness and layer-specific strain in patients with hypertrophic cardiomyopathy. LS_{inner} (**A**), CS_{outer} (**C**), and RS_{total} (**D**) significantly correlated with segmental wall thickness, but CS_{inner} (**B**) did not. CS, circumferential strain; LS, longitudinal strain; RS, radial strain.

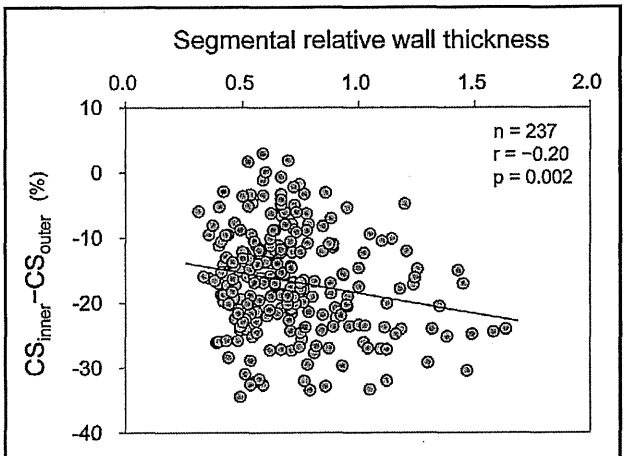

Figure 5. Relationship between segmental relative wall thickness and difference in circumferential strain (CS) between inner and outer layers in patients with hypertrophic cardiomyopathy.

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.

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.[23] 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.[24]

In the present study, we measured multidirectional and layer-specific STE-derived myocardial strain in patients with HCM, and found that there was considerable transmural variation in the reduction in CS. Endocardial CS and midwall or epicardial CS can be considered as indexes of LV chamber function and myocardial function, respectively, much as in studies dealing with hypertensive heart disease. It would then appear that the circumferential function of the LV chamber can be normal despite impaired myocardial circumferential shortening in the hypertrophied segments. It can also be considered that the development of concentric hypertrophy allows the maintenance of chamber function despite abnormal

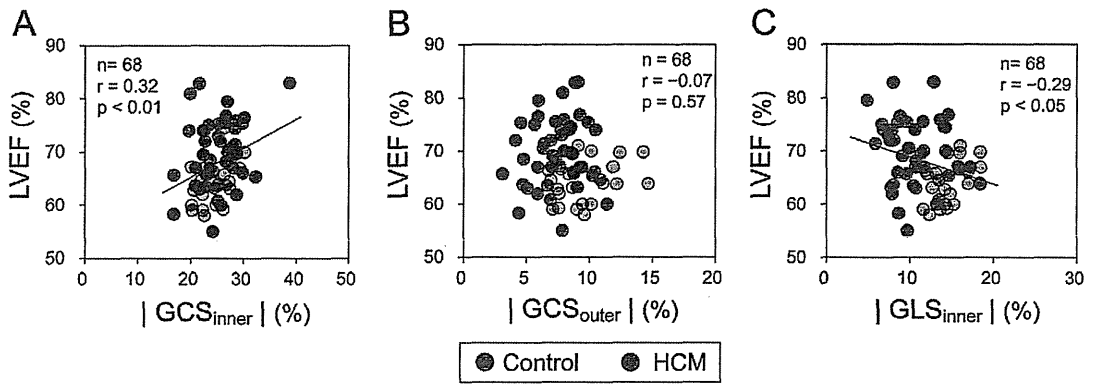

Figure 6. Relationships between layer-specific global strain and left ventricular ejection fraction (LVEF). The absolute value of GCS_{inner} positively correlated with LVEF (**A**), whereas that of GCS_{outer} was not associated with LVEF (**B**). The absolute value of GLS_{inner} inversely correlated with LVEF (**C**). GCS, global circumferential strain; GLS, global longitudinal strain.

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,[25] Doppler strain imaging,[26–28] or STE.[10–12,29–32] In contrast, circumferential myocardial shortening in HCM patients has variously been reported as increased[10,11,29] or decreased.[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.[10] In contrast, Serri et al reported a decrease in STE-derived CS using an ultrasound system from GE Medical Systems.[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.[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_{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_{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.[9] Above all, it is worth noting that, unlike FS_{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.[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.[34] 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. We therefore 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_{mw}, GLS_{outer}, GCS_{inner}, GCS_{mw}, GCS_{outer}, and GRS_{total} were not significantly different between patients taking and not taking a β-blocker. After adjustment for IVST, GLS_{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. In order to evaluate myocardial function in the circumferential direction, CS should be measured in the midwall or outer layer.

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Original Article

Sarcopenia evaluated by fat-free mass index is an important prognostic factor in patients with chronic heart failure

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ABSTRACT

Background and Aim: Chronic heart failure (CHF) is a major cause of morbidity and mortality, and cardiac cachexia and sarcopenia are serious complications associated with weight loss and increased catabolism. Fat-free mass index (FFMI) is an indicator of resting energy expenditure and is used for the clinical diagnosis of sarcopenia. In the present study, we investigated the impact of sarcopenia, as evaluated by FFMI, on cardiac prognosis in patients with CHF.

Methods and results: We calculated FFMI in 267 CHF patients who were prospectively followed until they died due to cardiac event, or until they were re-hospitalized. Fat-free mass (FFM) was estimated by the formula [FFM (kg) = 7.38 + 0.02908 × urinary creatinine (mg/day)] and normalized by the square of the patient's height in meters to calculate FFMI. During the follow-up periods, there were 83 cardiac events, including 19 cardiac deaths. FFMI was lower in patients with cardiac events than in those without (17.0 kg/m^2 vs. 17.6 kg/m^2, $P = 0.045$). Multivariate Cox hazard analysis revealed that decreased FFMI was associated with an unfavorable outcome (adjusted hazard ratio 0.68, 95% confidence interval 0.47–0.98). The patients were divided into two groups according to their median FFMI. The Kaplan–Meier analysis revealed that significantly higher cardiac event rate was observed in the low-FFMI group (log-rank test, $P = 0.017$).

Conclusions: Decreased FFMI was associated with an unfavorable prognosis in patients with CHF.

1. Introduction

Chronic heart failure (CHF) is an important health issue and still represents a poor prognosis despite advance in treatment [1]. In developed countries, CHF occurs in approximately 1–2% of the general population, but in 10% or more in those aged 70 years or older [2]. Over 60% of patients with CHF are reported to experience muscle weakness and fatigue caused by muscle atrophy, and these are two of the major symptoms in patients with CHF [3,4].

The pathophysiology of CHF is thought to involve detrimental levels of catabolism, since cardiac cachexia and sarcopenia, which both involve catabolic loss of muscle mass, emerge during the advanced stage of CHF [5]. Cardiac cachexia is defined by an overall loss of more than 7.5% of the previous normal weight during a period of more than 6 months, and that is caused by heart disease. Sarcopenia is defined as skeletal muscle loss and dysfunction during aging and affliction with a chronic disease [6,7]. Cardiac cachexia and sarcopenia are associated with metabolic, immune, and neurohormonal factors [8]. The imbalance of immune and neurohormonal systems contributes to the wasting process and leads to cardiac cachexia and sarcopenia.

Fat-free mass index (FFMI), which reflects the masses of skeletal muscle, organs, bone, and connective tissue and which is an indicator of resting energy expenditure, is used for the clinical diagnosis of sarcopenia. In contrast to body mass index (BMI), FFMI is not affected by fluid status in patients with CHF. Thus far, the association between FFMI and the severity of the CHF, as well as its prognosis, has not been fully determined. The purpose of this study was to clarify the relationship between FFMI and cardiac prognosis in patients with CHF.

2. Methods

2.1. Study population

Between September 2009 and October 2011, 469 patients were admitted to the Yamagata University Hospital, some for treatment of worsening CHF, others for diagnosis and pathophysiological investigations of CHF, and the reminder for therapeutic evaluation of CHF. The diagnosis of CHF was based on a history of dyspnea and symptoms of exercise intolerance followed by pulmonary congestion, pleural

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effusion, or left ventricular enlargement as determined by a chest X-ray or echocardiography [9]. Five patients undergoing chronic hemodialysis and 49 patients without data for serum albumin levels were excluded. In addition, 129 patients were excluded for whom data were unavailable to estimate FFMI.

The remaining 294 patients were enrolled in the present study. We also enrolled 30 age- and gender-matched control subjects without signs of significant heart disease to examine the FFMI in patients without CHF. All participants gave written informed consent prior to their participation. The procedures were approved by the institution's Human Investigation Committee and were performed in accordance with the Helsinki Declaration.

2.2. Anthropometry and measurement of blood biomarkers

The measurement of height and body weight was undertaken when the patients had recovered from acute decompensated heart failure. Venous blood samples were acquired on admission for measurement of blood biomarkers. The blood samples were centrifuged at 2,500 g for 15 min at 4 °C within 30 min of collection. Serum brain natriuretic peptide (BNP) concentrations were measured using a commercially available specific radioimmunoassay for human BNP (Shiono RIA BNP assay kit, Shionogi & Co., Ltd., Tokyo, Japan) [10].

2.3. Calculation of fat-free mass index

Fat-free mass (FFM) was calculated using the formula FFM (kg) = 7.38 + 0.02908 × urinary creatinine (mg/day), where urinary creatinine (mg/day) = 2.04 × age + 14.89 × body weight (kg) + 16.14 × height (cm) − 2244.45 [11,12]. FFM was then divided by the square of subject's height in meters to obtain FFMI, which normalizes FFM for the effect of height.

Table 1
Baseline characteristics of study participants.

	Control subjects ($n = 30$)	CHF patients ($n = 267$)	P value
Age, years	70 ± 3	71 ± 12	0.719
Male, n (%)	15 (50)	160 (60)	0.295
NYHA functional class, I/II/III, IV	–	59/99/109	–
Etiology, n (%)			–
Hypertensive heart disease	–	59 (22)	
Dilated cardiomyopathy	–	52 (20)	
Ischemic heart disease	–	50 (19)	
Valvular heart disease	–	41 (15)	
Other causes	–	65 (24)	
Presentation profile			
BMI, kg/m^2	23.0 ± 3.3	21.6 ± 3.6	0.059
FFMI, kg/m^2 (IQR)	18.3 (18.1–19.3)	17.3 (16.2–18.6)	<0.001
eGFR, ml/min/1.73 m^2	74.7 ± 15.4	62.4 ± 25.0	0.008
Blood biomarkers			
Albumin, g/dl	–	3.6 (3.1–4.0)	–
Fasting blood sugar, mg/dl	102 ± 35	113 ± 32	0.102
Total cholesterol, mg/dl	199 ± 25	168 ± 37	<0.001
Triglyceride, mg/dl	105 ± 51	91 ± 48	0.125
LDLc, mg/dl	122 ± 21	101 ± 34	<0.001
HDLc, mg/dl	58 ± 12	53 ± 20	0.154
Hemoglobin, g/dl	13.4 ± 1.3	12.2 ± 2.3	0.005
BNP, pg/ml (IQR)	26.3 (11.7–37.1)	390 (142–965)	<0.001
Echocardiographic data			
LV end-diastolic diameter, mm	–	55 ± 10	–
LV ejection fraction, %	–	50 ± 18	–
Medications, n (%)			
ACE inhibitors and/or ARBs	–	167 (63)	–
beta-Blockers	–	173 (65)	–

Data are presented as means ± SD or % unless otherwise indicated; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; FFMI, fat-free mass index; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; LV, left ventricular; NYHA, New York Heart Association.

Table 2
Comparison of patients with or without cardiac events.

	Event (−) ($n = 184$)	Event (+) ($n = 83$)	P value
Age, years	69 ± 12	74 ± 12	0.003
Male, n (%)	107 (58)	53 (64)	0.379
NYHA functional class, I/II/III, IV	50/71/63	9/28/46	<0.001
Etiology, n (%)			0.401
Hypertensive heart disease	45 (24)	14 (17)	–
Dilated cardiomyopathy	33 (18)	19 (23)	–
Ischemic heart disease	33 (18)	17 (20)	–
Valvular heart disease	29 (16)	12 (15)	–
Other causes	44 (24)	21 (25)	–
Presentation profile			
BMI, kg/m^2	21.9 ± 3.8	21.1 ± 3.5	0.104
FFMI, kg/m^2 (IQR)	17.6 (16.2–18.9)	17.0 (16.0–18.0)	0.045
eGFR, ml/min/1.73 m^2	66.9 ± 25.8	52.4 ± 20.2	<0.001
Blood biomarkers			
Albumin, g/dl	3.8 (3.1–4.0)	3.0 (2.4–3.3)	<0.001
Fasting blood sugar, mg/dl	112 ± 29	113 ± 37	0.808
Total cholesterol, mg/dl	173 ± 36	156 ± 38	<0.001
Triglyceride, mg/dl	98 ± 52	77 ± 32	<0.001
LDLc, mg/dl	104 ± 31	95 ± 37	0.036
HDLc, mg/dl	55 ± 21	50 ± 15	0.055
Hemoglobin, g/dl	12.5 ± 2.3	11.5 ± 2.2	0.001
BNP, pg/ml (IQR)	334 (128–890)	512 (221–1137)	0.507
Echocardiographic data			
LV end-diastolic diameter, mm	54 ± 9	56 ± 11	0.128
LV ejection fraction, %	52 ± 18	45 ± 17	0.003
Medications, n (%)			
ACE inhibitors and/or ARBs	116 (63)	51 (61)	0.947
beta-Blockers	109 (59)	64 (77)	0.081

Data are presented as means ± SD or % unless otherwise indicated; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; FFMI, fat-free mass index; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; LV, left ventricular; NYHA, New York Heart Association.

2.4. End points and follow-up

The enrolled patients were prospectively followed for a median duration of 10.7 months (interquartile range 3.0–20.3 months). For 83 patients, the studies ended upon cardiac death including death due to progressive CHF, myocardial infarction, and sudden cardiac death, as well as re-hospitalization for worsening CHF. The remaining 211 patients were ended upon the closure of the observation period. Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was confirmed by the attending physician. Two cardiologists, who were blinded to the blood biomarker data, reviewed the medical records and conducted telephone interviews to survey the incidence of cardiac events [10].

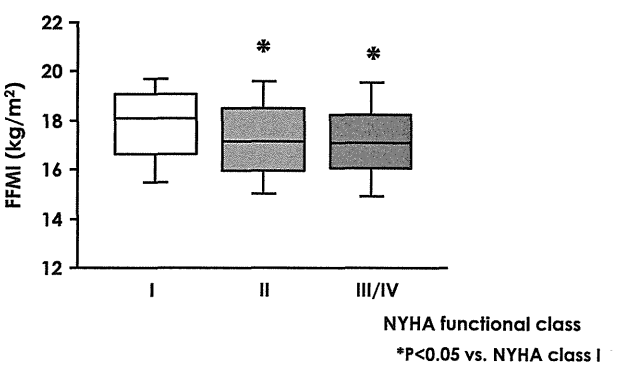

Fig. 1. The association between FFMI and NYHA functional class. Values of FFMI in NYHA functional class II and class III/IV patients were significantly lower than in class I patients (17.2 vs. 17.9, $P = 0.028$ and 17.3 vs. 17.9, $P = 0.010$, respectively). FFMI, fat-free mass index; NYHA, New York Heart Association.

Table 3
Relationships between FFMI and clinical parameters.

	FFMI	
	r	*P* value
Age	−0.27	<0.001
BMI	0.88	<0.001
eGFR	−0.01	0.872
hsCRP	−0.08	0.195
Fasting blood sugar	0.18	0.005
BNP	−0.11	0.083

BNP, brain natriuretic peptide; BMI, body mass index; eGFR, estimated glomerular filtration rate; FFMI, fat-free mass index; hsCRP, high-sensitivity C-reactive protein.

2.5. Statistical analysis

Data are presented as means ± standard deviation, except for those data not distributed normally, which are instead presented as medians and interquartile ranges. The unpaired Student's *t*-test and the chi-square test were used to compare two groups of continuous and categorical variables, respectively. The Mann–Whitney *U*-test was used when data were not distributed normally. Univariate- and multivariate analyses with Cox proportional hazards regression were used to determine significant predictors of cardiac events. Serum BNP levels were converted to logarithm values in the Cox analysis. The cardiac event-free curves were computed using the Kaplan–Meier method and were compared using the log-rank test. All statistical analyses were performed with a standard statistical program package (JMP version 10; SAS Institute, Cary, North Carolina).

3. Results

3.1. Subjects characteristics

Twelve of the 294 patients enrolled in the study underwent elective cardiac surgery during the follow-up period and another fifteen patients who were lost to follow-up. Only the remaining 267 patients were included in the final analysis. Baseline characteristics are listed in Table 1. These 267 patients include 160 (60%) males, and the mean age was 71 ± 12 years. One hundred and nine (41%) of the 267 patients were at the New York Heart Association (NYHA) functional class III stage or IV stage. CHF was caused by hypertensive heart disease in 59 (22 %) of the 267 patients, dilated cardiomyopathy in 52 (20 %) of the patients, ischemic heart disease in 50 (19 %) of the patients, valvular heart disease in 41 (15 %) of the patients, and others factors in the remaining 65 (24 %) of the patients. The median serum BNP level was 390 pg/ml (interquartile range 142–965), and the median FFMI was 17.3 kg/m^2 (interquartile range 16.2–18.6). There were 68 (25%) patients who presented sarcopenia [7]. Although there was no significant difference between the BMI of the CHF and control subjects, the FFMI was significantly lower in the CHF patients (17.3 kg/m^2 vs. 18.3 kg/m^2, $P < 0.001$, Table 1).

3.2. Comparison of CHF patients with and without cardiac events and association between FFMI and CHF severity

There were 83 cardiac events, including 19 cardiac deaths and 64 re-hospitalizations in patients with CHF during the follow-up period. The patients who experienced cardiac events were older, were in a more severe NYHA functional class, had a lower estimated glomerular filtration rate, had lower serum albumin levels, and had a lower left ventricular ejection fraction than those patients who did not experience cardiac events. Serum total cholesterol, triglyceride, low-density lipoprotein cholesterol, and hemoglobin levels were also lower in the patients with cardiac events than those without.

In addition, patients with cardiac events showed a lower FFMI than did those without (17.0 kg/m^2 vs. 17.6 kg/m^2, $P = 0.045$, Table 2).

Moreover, the median FFMIs of NYHA functional class II and III/IV patients were significantly lower than that of class I patients (17.2 kg/m^2 vs. 17.9 kg/m^2, $P = 0.028$ and 17.3 kg/m^2 vs. 17.9 kg/m^2, $P = 0.010$, respectively, Fig. 1).

3.3. Correlations between serum BNP levels, FFMI, and other variables

BMI ($r = -0.81$, $P < 0.001$) was strongly and significantly negatively correlated with FFMI. Moreover, age ($r = -0.27$, $P < 0.001$) and fasting blood sugar ($r = 0.18$, $P = 0.005$) were weakly but significantly correlated (negatively and positively, respectively) with FFMI. However, FFMI was not significantly correlated with serum BNP levels (-0.11, $P = 0.083$) (Table 3).

3.4. Association between FFMI and cardiac events

In the univariate Cox hazard analysis, the unadjusted hazard ratio for cardiac events was significantly decreased with increased FFMI (unadjusted hazard ratio 0.84, 95% CI 0.74–0.95) (Table 4). Multivariate analysis revealed that decreased FFMI was associated with an unfavorable cardiac prognosis (adjusted hazard ratio 0.68, 95% CI 0.47–0.98) after adjustments for age, gender, NYHA functional class, BMI, and logarithm of serum BNP levels (Table 4).

Moreover, decreased BMI was associated with cardiac events in patients with CHF after adjusting for age, gender, NYHA functional class, and logarithm of serum BNP levels (Model 1; adjusted hazard ratio 0.80, 95% CI 0.64–0.97). However, after addition of FFMI to Model 1 (Model 2), there was no association between BMI and cardiac events in patients with CHF (adjusted hazard ratio 1.50, 95% CI 0.80–2.82, Table 4).

When the patients were divided into two groups according to their median FFMI, serum BNP levels were significantly lower in the high-FFMI group than in the low-FFMI group (281.6 vs. 481.1, $P < 0.001$,

Table 4
Unadjusted and adjusted hazard ratio for cardiac events.

	Unadjusted HR	95% CI	*P* value	Adjusted HR*	95% CI	*P* value
Age (10 years increase)	1.12	1.23–1.91	<0.001	1.43	1.16–1.84	0.001
Gender (male)	1.16	0.74–1.81	0.515	2.20	1.12–4.35	0.023
NYHA functional class (III/IV)	1.93	1.25–2.99	0.003	1.64	1.02–2.64	0.040
BMI (1SD increase)	0.75	0.60–0.94	0.014	1.50	0.80–2.82	0.211
log BNP (1SD increase)	4.53	0.99–1.55	0.059	1.03	0.81–1.34	0.750
LV ejection fraction (10% increase)	0.94	0.99–1.25	0.085	–	–	–
FFMI (1 kg/m^2 increase)	0.84	0.74–0.95	0.006	0.68	0.47–0.98	0.038
BMI (1SD increase)						
Model 1 (age, gender, NYHA, log BNP)				0.80	0.64–0.97	0.042
Model 2 (Model 1 + FFMI)				1.50	0.80–2.82	0.211

BNP, brain natriuretic peptide; BMI, body mass index; CI, confidence interval; FFMI, fat-free mass index; HR, hazard ratio; log, logarithm; LV, left ventricular; NYHA, New York Heart Association.

* Adjusted HR, after adjustment of age, gender, NYHA functional class, BMI, and logarithm of serum BNP levels.

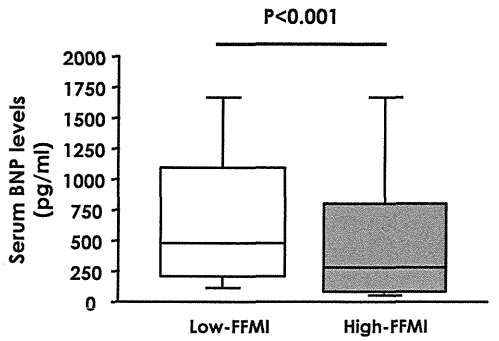

Fig. 2. Serum BNP levels and FFMI. Serum BNP levels in the high-FFMI group were significantly lower than in the low-FFMI group (281.6 vs. 481.1, $P < 0.001$). BNP, brain natriuretic peptide; FFMI, fat-free mass index.

Fig. 2). Furthermore, the Kaplan–Meier analysis revealed that a significantly higher cardiac event rate was observed in the low-FFMI group than in the high-FFMI group (log-rank test, $P = 0.0171$; Fig. 3).

4. Discussion

The present study clearly demonstrated an association between decreased FFMI and an unfavorable prognosis in patients with CHF.

BMI has been reported to be a simple and useful predictor of the prognosis of patients with various diseases [13,14]. For patients with malignancies and who have suffered from strokes, high BMI is associated with a favorable prognosis [15,16]. In contrast, being overweight or obese is a well-recognized independent risk factor for cardiovascular disease. However, a large number of cohort studies have shown that obesity is not necessarily associated with increased mortality but rather can be associated with a favorable prognosis in patients with CHF; "obesity paradox" [17]. It was reported that inflammatory cytokines such as interleukin 1 and 6, and tumor necrosis factor alpha—which are associated with cardiac cachexia, sarcopenia, and poor prognosis mediated by chronic adipose tissue inflammation and insulin resistance—are elevated in patients with CHF [18]. Anker et al. reported that the prevalence of cardiac cachexia and sarcopenia was 42% in outpatients with CHF, and patients who had cardiac cachexia showed an approximately 50% mortality rate during the 18-month period following the diagnosis of cardiac cachexia [19].

Note that we previously reported that insulin resistance, such as that associated with metabolic syndrome, negates any advantage that obese patients have with regards to CHF [20]. Wannamethee et al. [21] reported that CHF patients with normal body weights patients had low muscle mass, and it appears that BMI cannot definitively evaluate the effect of cachexia on mortality. In the present study, after adjusting for FFMI, BMI was not associated with cardiac events in patients with CHF. Since fluid retention is unrelated to cardiac cachexia and to sarcopenia in advanced CHF patients, BMI—which includes fluid retention in its measure of body mass—does not precisely reflect these diseases. In contrast, FFMI is scarcely affected by fluid status. In addition, BMI is inversely correlated with serum BNP levels [22]. In obese subjects, the expression of natriuretic peptide clearance receptor is increased in adipose tissue, which decreases serum BNP levels [23]. On the other hand, the present study showed no correlation between FFMI and BNP levels. Our results suggest that FFMI adds independent prognostic information to conventional prognostic factor including BMI and serum BNP levels.

Limitations of the present study include its relatively small sample size, and that we did not use bioelectrical impedance analysis or dual-energy X-ray absorptiometry to evaluate FFMI. Nevertheless, we were able to estimate FFMI according to the Forbes formula, which does not require specific equipment but instead simply uses urinary creatinine, and such a simple method to estimate FFMI is very useful in clinical practice [11]. All told, the techniques used in the present study revealed a significant relationship between decreased FFMI and cardiac events.

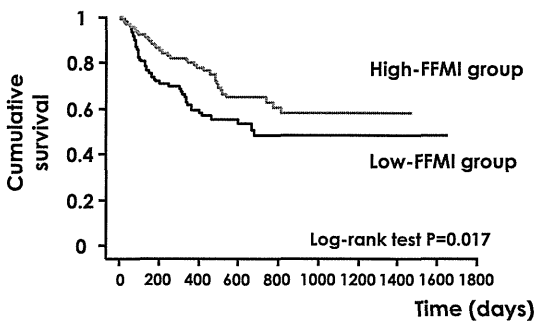

Fig. 3. The cardiac event-free curves. Kaplan–Meier analysis demonstrated that a significantly higher cardiac event rate was observed in the low-FFMI group (log-rank test, $P = 0.0171$). FFMI, fat-free mass index.

5. Conclusion

Decreased FFMI was associated with an unfavorable prognosis in patients with CHF. Future research is needed to assess whether therapeutic intervention to ameliorate sarcopenia such as cardiac rehabilitation can improve cardiac prognosis.

Learning points

- Decreased FFMI was associated with an unfavorable cardiac prognosis in patients with CHF. Not only body weight but also body composition is important to fully understand the pathophysiology of patients with CHF.
- A higher rate of cardiac events was observed in the low-FFMI group. Evaluation of FFMI provides additional independent prognostic information to conventional prognostic factors such as BMI and serum BNP levels in patients with CHF.

Contributors

TN, TW, and IK contributed to discussions regarding study design and data analyses. SK, TT, DK, MY, AF, and YH conceived and carried out the experiments. TN and TW participated in the interpretation of the results and the writing of the manuscript. SN, HT, TA, TS, and TM helped with data collection and analyses. All authors have read and approved the final manuscript.

Conflict of interest

None.

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ORIGINAL ARTICLE
Heart Failure

Temporal Trends in Clinical Characteristics, Management and Prognosis of Patients With Symptomatic Heart Failure in Japan

– Report From the CHART Studies –

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Background: Temporal trends in clinical characteristics, management and prognosis of patients with symptomatic heart failure (HF) remain to be elucidated in Japan.

Methods and Results: From the Chronic Heart Failure Analysis and Registry in the Tohoku District-1 (CHART-1; 2000–2005, n=1,278) and CHART-2 (2006-present, n=10,219) Studies, we enrolled 1,006 and 3,676 consecutive symptomatic stage C/D HF patients, respectively. As compared with the patients in the CHART-1 Study, those in the CHART-2 Study had similar age and sex prevalence, and were characterized by lower brain natriuretic peptide, higher prevalence of preserved left ventricular ejection fraction (LVEF) and higher prevalence of hypertension, diabetes mellitus and ischemic heart disease (IHD), particularly IHD with LVEF ≥50%. From CHART-1 to CHART-2, use of renin-angiotensin system inhibitors, β-blockers and aldosterone antagonists was significantly increased, while that of loop diuretics and digitalis was decreased. Three-year incidences of all-cause death (24 vs. 15%; adjusted hazard ratio [adjHR], 0.73; P<0.001), cardiovascular death (17 vs. 7%; adjHR, 0.38; P<0.001) and hospitalization for HF (30 vs. 17%; adjHR, 0.51; P<0.001) were all significantly decreased from CHART-1 to CHART-2. In the CHART-2 Study, use of β-blockers was associated with improved prognosis in patients with LVEF <50%, while that of statins was associated with improved prognosis in those with LVEF ≥50%.

Conclusions: Along with implementation of evidence-based medications, the prognosis of HF patients has been improved in Japan. (Trial registration: clinicaltrials.gov identifier: NCT00418041) (*Circ J* 2015; **79:** 2396–2407)

Key Words: Beta-blocker; Prognosis; Statin; Symptomatic heart failure

Heart failure (HF) is a major public health problem worldwide, and the number of HF patients has been increasing worldwide.[1–4] In the USA, there are approximately 5.7 million patients with HF, 0.87 million HF patients are newly diagnosed every year, and the number of HF patients is expected to rise to 8 million by 2030.[1] In Japan, although the precise number of HF patients is unclear, the number of outpatients with left ventricular (LV) dysfunction was estimated at 979,000 in 2005, which would be expected to rapidly increase by 90,000 every 5 years until 2020, then gradually by 24,000 every 5 years until 2035, reaching 1.32 million in 2035.[5] The Japanese Ministry of Health, Labour and Welfare reported that the number of HF deaths was 46,460 (370/million) in 2000, 56,327 (446/million) in 2006, and 71,881 (572/million) in 2013 in Japan.[6]

Editorial p2322

Between 2000 and 2005, we conducted a multicenter, prospective cohort of chronic HF (CHF) patients, named the

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Chronic Heart Failure Analysis and Registry in the Tohoku District-1 (CHART-1) Study (n=1,278).[7,8] The CHART-1 Study found that the prognosis of CHF patients in Japan was equally poor compared with those in Western countries.[7,8] In 2006, we then started the CHART-2 Study to further elucidate the characteristics and prognosis of CHF patients in stages B–D.[3,8] In the previous studies, we found a trend toward westernization of ischemic etiology for HF and better implementation of evidence-based medications from the CHART-1 to the CHART-2 Studies.[3,8] It is important to elucidate the temporal trend in symptomatic HF for better management of the disorder.

The aim of the present study was thus to elucidate the temporal trend in clinical characteristics, management and long-term prognosis of patients with symptomatic HF patients in Japan, by comparing the CHART-1 and the CHART-2 Studies.

Methods

CHART Studies

In the present study, a total of 4,682 symptomatic HF patients were enrolled from the database of the CHART-1 (n=1,278) and the CHART-2 (n=10,219) Studies.[3,6,7] The CHART-1 Study was conducted between February 2000 and December 2005 and a total of 1,278 patients with CHF from the 26 hospitals (Tohoku University Hospital and 25 affiliated hospitals) were enrolled.[7,8] The purpose of the CHART-1 Study was to elucidate the clinical characteristics, treatment and prognosis of Japanese CHF patients.[5,6] All patients had a structural disorder of the heart and were treated with standard therapies for CHF, including diuretics, digitalis, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and β-blockers. In 2006, we then started the CHART-2 Study, in which a total of 10,219 consecutive patients, including 5,483 cardiovascular patients at high risk for development of HF (stage A/B) and 4,736 patients with symptomatic CHF (stages C/D),[9] were registered by 2010 in the 24 hospitals (Tohoku University Hospital and 23 affiliated hospitals) and have been currently followed up. Tohoku University Hospital and 14 hospitals participated in both the CHART-1 and the CHART-2 Studies, enrolling patients accounting for 74.0% and 75.8% of the total subjects registered in the CHART-1 and the CHART-2 Studies, respectively. No patients were registered in the 2 Studies in a duplicate manner.

The CHART-1 Study was approved by the ethics committee of Tohoku University Hospital. The CHART-2 Study was approved by the human research committee of Tohoku University School of Medicine, conformed to the ethics guidelines of the 1975 Declaration of Helsinki and also by the local ethics committee in each participating hospital and registered in Clinical Trials.gov (Identifier: NCT00418041). Written informed consent was provided by each patient before enrollment. Information on medical history and baseline demographics, including medication and echocardiographic data, were obtained at the time of enrollment by clinical research coordinators.

Definition of Symptomatic HF and Etiology of HF

Diagnosis of HF was made based on the Framingham criteria,[10] while CHF stage was classified according to the ACCF/AHA HF Guidelines.[9] We defined symptomatic HF as HF in New York Heart Association (NYHA) II, III or IV. The cause of HF was diagnosed by an attending physician at each hospital and/or the investigators of the Tohoku Heart Failure Association. Ischemic heart disease (IHD) was defined as history of myocardial infarction or angina pectoris. Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) were diagnosed based on the definition of DCM and HCM in the Japanese Circulation Society guidelines.[11,12]

Subjects

In the CHART-1 Study (n=1,278), 24 patients with missing data were excluded. Of the remaining 1,254 patients, 1,006 patients (78.7%) were defined as having symptomatic HF in the CHART-1 Study. In the CHART-2 Study (n=10,219), 5 patients with missing data were initially excluded. Thereafter, in order to minimize selection bias, we selected 5,923 patients from the CHART-2 Study who met the following inclusion criteria of the CHART-1 Study: (1) LV ejection fraction (LVEF) <50%; (2) LV end-diastolic diameter (LVDd) ≥55 mm; or (3) at least 1 episode of congestive HF.[7,8] Among the 5,923 patients, 3,676 were defined as having symptomatic HF in the CHART-2 Study. Finally, in the present study, 1,006 and 3,676 symptomatic HF patients were enrolled from the CHART-1 and the CHART-2 Studies, respectively. In the present study, HF with LVEF ≥50% was defined as HF with preserved LVEF (HFpEF), while HF with LVEF <50% was defined as HF with reduced LVEF (HFrEF).[13]

Outcomes

The study endpoints were 3-year incidence of all-cause death, cardiovascular death and hospitalization for worsening HF. Mode of death was also examined. For all patients, only the main mode of death was used. A patient admitted for worsening HF had to show signs and symptoms of HF requiring treatment with i.v. diuretics.[14] Follow-up was made at least once a year by clinical research coordinators by means of review of medical records, survey and telephone interview.[3,8] All events were reviewed and assigned according to consensus of at least 2 independent physician members of the Tohoku Heart Failure Association, by reviewing case reports, death certificates, medical records and hospital course summaries provided by the investigators.

Statistical Analysis

The continuous results are expressed as mean±SE or median (IQR), as appropriate. The discrete results are expressed as count (percentage). Wilcoxon rank sum and Fisher's exact test were used to compare patient characteristics between the CHART-1 and the CHART-2 Studies. Kaplan-Meier curves were plotted to evaluate the association between symptomatic HF patients and all-cause death, cardiovascular death or hospitalization for worsening HF. Comparison of the survival time between the 2 Studies was done using log-rank test. To compare prognosis between the CHART-1 and the CHART-2 patients, we used the multivariate Cox proportional hazard model by adjusting for the following clinical backgrounds: age, sex and comorbidity (hypertension, diabetes mellitus [DM], dyslipidemia, atrial fibrillation and ventricular tachycardia). In addition, to evaluate the effect of medication, the covariates were selected as follows: first, univariate Cox models were fitted for all patients in both the CHART-1 and the CHART-2 Studies, with candidate variables of sex, age, body mass index (BMI), systolic blood pressure (SBP), heart rate, NYHA class, LVEF, LVDd, hypertension, DM, dyslipidemia, atrial fibrillation, ventricular tachycardia, brain natriuretic peptide (BNP) and estimated glomerular filtration rate (eGFR). Then, after the multivariate Cox models were fitted using all the covariates that had $P<0.2$ in the univariate model, the optimal subset of covariates was selected by backward stepwise elimination. Two-sided $P<0.05$ was considered to be

Table 1. Baseline Characteristics

	Total (n=4,682)		
	CHART-1 (n=1,006)	CHART-2 (n=3,676)	P-value
Age (years)	68.9±0.4	69.7±0.2	0.084
Male	642 (63.8)	2,412 (65.6)	0.287
BP (mmHg)			
Systolic	125.7±0.7	125.4±0.3	0.663
Diastolic	71.4±0.4	71.5±0.2	0.765
Heart rate (beats/min)	75.2±0.5	72.6±0.3	<0.001
BMI (kg/m²)	22.9±0.1	23.2±0.1	0.070
NYHA classification			<0.001
II	786 (78.1)	3,142 (85.5)	
III	210 (20.9)	495 (13.5)	
IV	10 (1.0)	39 (1.1)	
Laboratory data			
Hb (g/dl)	12.9±0.1	13.0±0.0	0.184
Anemia	395 (39.3)	1,375 (37.4)	0.287
BUN (mg/dl)	21.8±0.5	20.6±0.2	0.007
Cre (mg/dl)	1.09±0.03	1.08±0.01	0.790
eGFR (ml/min/1.73 m²)	60.0±0.8	59.4±0.4	0.485
BNP (pg/ml)	158.8 (69.0–334.0)	123.2 (50.3–267.0)	<0.001
Echocardiography			
LVEF (%)	49.8±0.5	55.7±0.3	<0.001
LVEF ≥50%	463 (46.0)	2,316 (63.0)	<0.001
LVDd (mm)	56.7±0.3	52.4±0.2	<0.001
LVDs (mm)	43.0±0.4	37.1±0.2	<0.001
Comorbidity			
Hypertension	468 (46.4)	3,203 (87.1)	<0.001
Dyslipidemia	163 (16.1)	2,879 (78.3)	<0.001
Diabetes mellitus	194 (19.4)	1,280 (34.8)	<0.001
Atrial fibrillation	423 (42.1)	1,529 (41.6)	0.829
Ventricular tachycardia	216 (21.5)	420 (11.4)	<0.001
Etiology			
Ischemic heart disease	269 (26.7)	1,749 (47.6)	<0.001
LVEF ≥50%	88 (8.7)	1,048 (28.5)	
LVEF <50%	181 (18.0)	701 (19.1)	
Cardiomyopathy	334 (33.2)	644 (17.5)	<0.001
DCM	267 (26.5)	505 (13.7)	
HCM	35 (3.5)	115 (3.1)	
Other cardiomyopathy	32 (3.2)	24 (0.7)	
Medication			
β-blockers	288 (28.6)	1,886 (51.3)	<0.001
RASI	689 (68.5)	2,677 (72.8)	0.006
ACEI	575 (57.2)	1,720 (46.8)	<0.001
ARB	125 (12.4)	1,105 (30.1)	<0.001
Aldosterone antagonists	182 (18.7)	984 (26.8)	<0.001
Loop diuretics	729 (76.7)	2,041 (55.5)	<0.001
Digitalis	478 (48.5)	921 (25.1)	<0.001
CCB	288 (29.2)	1,388 (37.8)	<0.001
Statins	NA	1,332 (36.2)	NA
ICD/CRTD	16 (1.6)	103 (2.8)	0.031

Data given as mean±SE, median (IQR) or n (%). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CCB, calcium channel blockers; CRTD, cardiac resynchronization therapy defibrillator; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RASI, renin angiotensin system inhibitors.

statistically significant. All calculations were performed using SPSS 22.0 for Windows and R version 3.0.2.

Results

Temporal Trend in Baseline Characteristics of Symptomatic HF

There were no significant differences in age, sex or blood pressure between the CHART-1 and the CHART-2 patients, whereas BNP was significantly lower in the CHART-2 patients (**Table 1**). In the echocardiography data, prevalence of preserved LVEF was higher and LV dimensions were smaller in the CHART-2 patients. The prevalences of HFpEF, hypertension, dyslipidemia and DM were all increased from CHART-1 to CHART-2. The prevalence of ischemic HF was significantly increased from CHART-1 to CHART-2 (26.7 vs. 47.6%, P<0.001), whereas the prevalence of HF due to CM was significantly decreased (33.2 vs. 17.5%, P<0.001). Interestingly, the prevalence of ischemic HF with preserved EF (≥50%) was dramatically increased from CHART-1 to CHART-2 (8.7 vs. 28.5%, P<0.001), but that of ischemic HF with reduced LVEF (<50%) remained unchanged. The use of β-blockers, renin-angiotensin system inhibitors (RASI) and aldosterone antagonists was increased, whereas that of loop diuretics and digitalis

Table 2. (A) Baseline Characteristics of Patients With Non-Ischemic HF and Those With Ischemic HF, (B) Baseline Characteristics of Patients With HFrEF and Those With HFpEF

A	Non-ischemic HF (n=2,664)			Ischemic HF (n=2,018)		
	CHART-1 (n=737)	CHART-2 (n=1,927)	P-value	CHART-1 (n=269)	CHART-2 (n=1,749)	P-value
Age (years)	68.2±0.5	68.4±0.3	0.685	71.0±0.7	71.1±0.3	0.866
Male	447 (60.7)	1,102 (57.2)	0.114	195 (72.5)	1,310 (74.9)	0.408
BP (mmHg)						
Systolic	125.6±0.8	124.1±0.5	0.104	125.9±1.3	126.8±0.5	0.537
Diastolic	71.6±0.5	71.5±0.3	0.852	70.8±0.7	71.5±0.3	0.342
Heart rate (beats/min)	75.0±0.7	73.8±0.4	0.130	75.7±0.9	71.2±0.3	<0.001
BMI (kg/m²)	22.9±0.2	23.0±0.1	0.864	22.8±0.2	23.5±0.1	0.034
NYHA classification			<0.001			<0.001
II	584 (79.2)	1,645 (85.4)		202 (75.1)	1,497 (85.6)	
III	146 (19.8)	262 (13.6)		64 (23.8)	233 (13.3)	
IV	7 (0.9)	20 (0.7)		3 (1.1)	19 (1.1)	
Laboratory data						
Hb (g/dl)	13.0±0.1	13.1±0.1	0.201	12.9±0.1	13.0±0.1	0.419
Anemia	279 (37.9)	690 (35.8)	0.345	116 (43.1)	685 (39.2)	0.228
BUN (mg/dl)	21.7±0.5	20.5±0.3	0.025	22.2±1.0	20.8±0.3	0.093
Cre (mg/dl)	1.07±0.04	1.00±0.02	0.053	1.15±0.05	1.17±0.02	0.782
eGFR (ml/min/1.73 m²)	61.5±0.9	61.6±0.5	0.880	55. 9±1.4	57.0±0.5	0.449
BNP (pg/ml)	150.0 (64.5–309.0)	134.0 (56.3–218.0)	0.020	181.4 (85.3–413.2)	107.0 (44.6–253.3)	<0.001
Echocardiography						
LVEF (%)	51.5±0.6	56.6±0.4	<0.001	45.2±0.9	54.6±0.4	<0.001
LVEF ≥50%	375 (50.9)	1,268 (65.8)	<0.001	88 (32.7)	1,048 (59.9)	<0.001
LVDd (mm)	56.5±0.4	52.0±0.2	<0.001	57.4±0.6	52.8±0.2	<0.001
LVDs (mm)	42.3±0.4	36.6±0.3	<0.001	45.1±0.6	37.7±0.3	<0.001
Comorbidity			<0.001			
Hypertension	339 (46.0)	1,623 (84.2)	<0.001	129 (48.0)	1,580 (90.4)	<0.001
Dyslipidemia	78 (10.6)	1,381 (71.7)	<0.001	85 (31.6)	1,498 (85.6)	<0.001
Diabetes mellitus	106 (14.4)	502 (26.1)	<0.001	88 (32.7)	778 (44.5)	<0.001
Atrial fibrillation	359 (48.7)	1,068 (55.5)	0.002	64 (23.8)	461 (26.4)	0.412
Ventricular tachycardia	155 (21.0)	249 (12.9)	<0.001	61 (22.7)	171 (9.8)	<0.001
Medication						
β-blockers	206 (28.0)	1,001 (51.9)	<0.001	82 (30.5)	887 (50.7)	<0.001
RASI	505 (68.5)	1,425 (73.9)	0.006	184 (68.4)	1,255 (71.8)	0.277
ACEI	417 (56.6)	932 (48.4)	<0.001	158 (58.7)	789 (45.1)	<0.001
ARB	96 (13.0)	576 (29.9)	<0.001	29 (10.8)	531 (30.4)	<0.001
Aldosterone antagonists	127 (17.8)	637 (33.1)	<0.001	55 (21.0)	347 (19.8)	0.679
Loop diuretics	543 (78.1)	1,226 (63.6)	<0.001	186 (72.9)	815 (46.6)	<0.001
Digitalis	402 (55.7)	679 (35.2)	<0.001	76 (28.9)	242 (13.8)	<0.001
CCB	187 (25.9)	622 (32.3)	0.002	101 (38.1)	766 (43.8)	0.084
Statins	NA	366 (19.0)	NA	NA	966 (55.2)	NA
ICD/CRTD	9 (1.2)	69 (3.6)	0.001	7 (2.6)	34 (1.9)	0.484

(**Table 2** continued the next page.)