Discrimination of Nonobstructive Hypertrophic Cardiomyopathy From Hypertensive Left Ventricular Hypertrophy on the Basis of Strain Rate Imaging by Tissue Doppler Ultrasonography

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Background—The differentiation of hypertrophic cardiomyopathy (HCM) from hypertensive left ventricular hypertrophy (H-LVH) on the basis of morphological information obtained by conventional echocardiography is occasionally problematic. We investigated whether strain rate (SR) imaging derived from tissue Doppler imaging (TDI) is able to discriminate HCM from H-LVH.

Methods and Results—Conventional echocardiography and TDI were performed with 34 patients with LVH and 16 reference subjects. Mean values of systolic strain ($\varepsilon_{sys}$), peak systolic SR, and early diastolic SR obtained from 8 left ventricular (LV) segments were calculated. LV pressures were recorded simultaneously in the patients. Patients were diagnosed with HCM ($n=20$) or H-LVH ($n=14$) on the basis of conventional echocardiography and endomyocardial biopsy findings. Multivariate analysis revealed that septum/posterior wall thickness ratio ($P<0.00013$) and $\varepsilon_{sys}$ ($P<0.0001$) were each able to discriminate HCM from H-LVH. A $\varepsilon_{sys}$ cutoff value of $10.6\%$ discriminated between HCM and H-LVH with a sensitivity of 85.0%, specificity of 100.0%, and predictive accuracy of 91.2%. The $\varepsilon_{sys}$ parameter was significantly correlated with pulmonary arterial wedge pressure, LV end-diastolic pressure, the peak positive first derivative of LV pressure, and the time constant of LV pressure decay.

Conclusions—SR imaging is able to discriminate HCM from H-LVH, with $\varepsilon_{sys}$ reflecting myocardial contractile and lusitropic properties. (Circulation. 2004;110:3808-3814.)

Key Words: cardiomyopathy ■ echocardiography ■ diagnosis ■ hypertrophy ■ hypertension

Conventional echocardiography provides useful morphological information for the diagnosis of hypertrophic cardiomyopathy (HCM), with asymmetrical septal hypertrophy of the left ventricle (LV) being the most characteristic finding.1 In contrast, hypertensive left ventricular hypertrophy (H-LVH) is characterized by symmetrical (concentric) hypertrophy of the LV; however, 13% to 31% of patients with HCM show symmetrical hypertrophy,2,3 whereas 4% to 47% of patients with H-LVH manifest asymmetrical septal hypertrophy of the LV.3,4 It is therefore difficult to differentiate nonobstructive HCM from H-LVH in some individuals.

Strain rate (SR) imaging based on tissue Doppler imaging (TDI) is a newly developed echocardiographic modality that allows quantitative assessment of regional myocardial wall motion.5 Recent studies have suggested that strain and SR reflect both systolic and diastolic LV function5,6; however, the relevance of these parameters as indicators of LV function remains to be validated.

We hypothesized that SR imaging might be more sensitive than conventional echocardiographic parameters for the diagnosis of HCM and that it might be able to discriminate HCM from H-LVH. The aim of the present study was thus to determine whether SR imaging is able to provide detailed information on regional LV function and whether it is indeed able to discriminate between HCM and H-LVH.

Methods

Study Group

Thirty-four consecutive patients (29 men, 5 women) with an initial diagnosis of nonfamilial LV hypertrophy (LVH; maximum LV wall thickness of $>13\, \text{mm}$ and a suspected diagnosis of HCM or H-LVH) who were referred to Nagoya University Hospital between April 2002 and October 2003 underwent simultaneous cardiac catheteriza-
tion and echocardiography. All drugs were discontinued at least 4 days before subject evaluation. Patients were assigned to either the HCM or H-LVH group. The diagnosis of HCM was based on conventional echocardiographic demonstration of a nondilated, hypertrophic LV in the absence of other cardiac or systemic diseases.

The diagnosis of H-LVH was based on conventional angiography, and endomyocardial biopsy findings of myocyte disarray. The prevalence of which is reported to be higher in patients with H-LVH. Several patients with a suspected diagnosis of HCM were excluded from the study. We also excluded patients with apical hypertrophy or left ventriculography or with subaortic obstruction at rest revealed by left ventriculography. Sixteen healthy volunteers (14 men, 2 women) with normal ECGs and conventional echocardiograms underwent echocardiographic analysis as reference subjects.

Individuals with localized asynery revealed by 2D echocardiography or left ventriculography or with subaortic obstruction at rest were excluded from the study. We also excluded patients with apical hypertrophy, the prevalence of which is reported to be higher in Japan than in Western countries.

Endomyocardial biopsy procedures are accepted and financially covered by the National Health Insurance System of Japan for the discrimination of cardiomyopathies and to obtain information on the clinical condition of patients. The present study, including the biopsy procedures and, in particular, the analysis of mRNA in biopsy specimens, was approved by the appropriate Institutional Review Board and Institutional Ethical Committee for Human Research. All study subjects provided written informed consent with regard to the study procedures, including the analysis of mRNA in biopsy specimens for both clinical and research purposes.

### Cardiac Catheterization

A 6F pigtail angiographic, high-fidelity, micromonometer-tipped catheter (SPC-4646D; Millar) was advanced into the LV for measurement of LV pressure. The micromanometer pressure was matched to the pressure of the fluid-filled lumen. To measure pulmonary arterial wedge pressure (PAWP) and cardiac output, we positioned a 7F triple-lumen thermistor Swan-Ganz catheter (Baxter) in the pulmonary artery. All patients underwent selective coronary angiography, left ventriculography, and endomyocardial biopsy. Several (≥3) biopsy specimens of which were used for mRNA analysis, were obtained from the right side of the interventricular septum or the LV free wall (or both) at each examination.

### Pathological Evaluation

Myocardial disarray was detected and quantified as described previously, with some modifications. Myocyte disarray was defined as bundles of myocytes that were oriented perpendicularly or obliquely to each other or were interspersed in different directions. Each biopsy specimen was cross-sectioned in several different directions, each section was divided into 30 fields of equal size with the use of image-analysis software (Win ROOF; Mitani), and the presence or absence of disarray in each field was scored. The number of fields per section that showed disarray was computed as a percentage for each of the 10 sections per patient. In the present study, patients with >33% myocyte disarray in at least 1 of the cross sections examined were diagnosed with HCM. Patients stratified into the H-LVH group showed no or <5% myocyte disarray in all of the cross sections examined. The abundance of mRNAs for Ca2+-handling proteins was determined by quantitative reverse transcription and real-time polymerase chain reaction analysis.

### Echocardiography

Echocardiographic images were obtained in the parasternal long- and short-axis views and apical 2- and 4-chamber views using standard transducer positions with a Vivid Seven digital ultrasound system (GE VingMed Ultrasound). In patients with a suspected diagnosis of HCM or H-LVH, the extent and distribution of LVH were assessed from the 2D echocardiogram as described previously. Anterior ventricular septal thickness was evaluated by an integrated analysis of the 2D and M-mode recordings, and LV ejection fraction was calculated by the Teichholz method. Continuous-wave Doppler echocardiography was used to diagnose resting obstruction, and all studied subjects were confirmed to have no LV outflow obstruction. Peak early and late transmitral filling velocities and their ratio (E/A), the deceleration time of E, and isovolumic relaxation time were measured from mitral inflow velocities.

### TDI and Strain and SR Analyses

On completion of the standard echocardiographic measurements, color TDI was performed. Digital data were transferred for offline analysis with the software incorporated in the Vivid Seven system. Scanning was performed longitudinally from the apex to acquire apical 4- and 2-chamber views with a 5.0-MHz phased-array transducer and a frame rate of 100±20 frames per second, depending on the heart rate, to minimize the noise level. Early diastolic annular velocity (E0) was obtained by placing a tissue Doppler sample volume at the septal mitral annulus in the apical 4-chamber view, and the E/E0 ratio was calculated. Longitudinal strain and SR in the basal and apical segments of each (anterior, inferior, septal, and lateral) wall were estimated by measuring the spatial velocity gradient over a computation area of 8 by 10 mm2. The region of interest was continuously positioned within the interrogated segment with the use of a semiautomatic tracking algorithm and was analyzed as described previously. Systolic strain (εsyst), peak systolic SR (SRsyst), and peak early diastolic SR (SRE0) were calculated from the averaged SR profiles.

Two examiners who were unaware of the clinical status of the subject performed echocardiographic analysis independently of each other. Reproducibility of εsyst, SRsyst, and SRsyst was assessed in 9 subjects randomly allocated from the comparative study groups. Intraobserver reproducibility was assessed with a single observer (A.N.) on 2 separate occasions. Interobserver reproducibility was assessed with 2 independent observers (A.N. and T.K.).

### Data Analysis

LV pressure signals were digitized and analyzed with software developed in-house and a 32-bit microcomputer system (PC-9821-ST20; NEC). We calculated the peak positive dP/dt (first derivative of LV pressure with respect to time) as an index of contractility. To evaluate LV isovolumic relaxation, we calculated τ on the basis of direct measurement of the pressure half-time (T1/2) as described by Miresky.

### Statistical Analysis

Data are presented as mean±SD. Normality was evaluated for each variable from normal distribution plots and histograms and by the Kolmogorov-Smirnov test. ANOVA, with Scheffe’s F adjustment for multiple comparisons, was used to assess differences among groups. Hemodynamic variables were compared between HCM and H-LVH patients with Student’s unpaired 2-tailed t test. A probability value of <0.05 was considered statistically significant. Individual regression analysis was used to select potential independent predictors from echocardiographic indices for discriminating HCM from H-LVH. Covariables examined included LV end-diastolic internal dimension, LV ejection fraction, the ratio of interventricular septal and posterior wall thicknesses (IVST/PWT), E, the E/A ratio, isovolumic relaxation time, deceleration time of E, Eε, SResyst, SRe0, Eε0, and the E/E0 ratio. Individual predictors of HCM selected on the basis of a probability value of <0.05 were entered into a multivariate discriminant analysis. The discriminant score and discriminant probability were calculated by a discriminant function test. Optimal cutoff values of individual parameters for differentiation between HCM and H-LVH were determined with a receiver-operator characteristic curve. Sensitivity, specificity, and predictive accuracy were determined and expressed as percentages. Relations between hemodynamic variables and indices identified to discriminate independently patients with HCM from those with H-LVH by multivariate
among the 34 patients with LVH included in the present study, 20 individuals (17 men, 3 women) were diagnosed with HCM, and 14 individuals (12 men, 2 women) were diagnosed with H-LVH. Patients stratified into the HCM group had moderate to severe myocyte disarray (>33%) in at least 1 of the cross sections examined; those stratified into the H-LVH group showed no or minor myocyte disarray (Figure 1). The overall percentage area of myocyte disorganization for HCM patients determined from all 10 sections examined per patient was 7.6% to 34.7% (22.3±18.7%). Both HCM and H-LVH patients exhibited myocyte hypertrophy and some extent of intercellular fibrosis.

No amplification of genomic DNA was detected in any of the patients. Reverse transcription–polymerase chain reaction analysis of mRNAs for Ca2+–handling proteins revealed a tendency for the amount of sarco(endo)plasmic reticulum Ca2+–ATPase (SERCA2) mRNA in the ventricular myocardium to be reduced in the HCM patients compared with that in the H-LVH patients (data not shown), consistent with our previous observations.11

 Fifteen percent (3/20) of HCM patients had a history of or coexisting hypertension. With the exception of BP, clinical characteristics did not differ significantly among HCM patients, H-LVH patients, and reference subjects (Table 1).

### Conventional Echocardiographic Data

IVST was greater in patients with HCM and in those with H-LVH than in reference subjects, whereas the E/A ratio was smaller in both patient groups than in reference subjects (Table 1). The IVST/PWT ratio was greater and E was smaller in HCM patients than in reference subjects, whereas these parameters did not differ significantly between H-LVH patients and reference subjects. IVST and the IVST/PWT ratio were significantly greater in patients with HCM than in those with H-LVH (Figure 2a; Table 1).

### Strain and SR Data From TDI

Both εsys and SRdia differed significantly among the 3 groups of subjects (Figure 2b; Table 1). Absolute values of εsys and SRsys were significantly smaller in HCM patients than in H-LVH patients. The absolute value of SRsys was significantly smaller in patients with HCM and in those with H-LVH than in reference subjects, but it did not differ between the 2 groups of patients. The εsys also differed significantly among the 3 groups, being smaller in HCM patients than in H-LVH patients. The E/Em ratio was significantly greater in HCM patients than in reference subjects but did not differ between the 2 patient groups.

Intraobserver reproducibility was excellent, with the interclass correlation coefficient being 0.93, 0.96, and 0.94 for εsys, SRsys, and SRdia, respectively. Similar results were obtained for interobserver reproducibility, with interclass correlation coefficient values of 0.92, 0.94, and 0.93 for εsys, SRsys, and SRdia, respectively.

### Discrimination of Patients With HCM From Those With H-LVH

Individual analysis revealed that the IVST/PWT ratio, εsys, SRsys, and E/Em were significantly associated with HCM but not with H-LVH. These parameters were therefore used as dependent variables for multivariate analysis of discrimination between HCM and H-LVH. Only the IVST/PWT ratio and εsys were found to be independent predictors for discrimination of HCM patients from H-LVH patients (Table 2).

Receiver-operator characteristic curve analysis identified the optimal cutoff value of εsys for discrimination between HCM and H-LVH as 10.6%; this value was associated with a sensitivity, specificity, and predictive accuracy of 85.0, 100, and 91.2%, respectively (Figure 3). Similarly, an IVST/PWT ratio of 1.3 was associated with a sensitivity of 65.0%, specificity of 100%, and predictive accuracy of 79.4%. A discriminant function test revealed that a discriminant score (Z) defined by the following equation yielded the highest discriminant probability of 96.1%:

\[
Z = -1.7044 + (12.318 \times \text{IVST/PWT}) + (1.52687 \times \epsilon_{\text{sys}}),
\]

where \(Z>0\) indicates a diagnosis of HCM and \(Z<0\) indicates a diagnosis of H-LVH.

Given the time needed to obtain a sufficient number of study subjects with a diagnosis based on pathological find-
ings, we performed a supplementary examination with 9 external subjects with nonfamilial LVH. In this small validation sample, the predictive accuracy of our discriminant score based on $\epsilon_{sys}$ and the IVST/PWT ratio for the diagnosis of HCM versus H-LVH was 100%.

**Hemodynamic Variables**

Cardiac index, LV peak positive dP/dt, and LV peak negative dP/dt did not differ significantly between patients with HCM and those with H-LVH (Table 1). PAWP, LV end-diastolic pressure (LVEDP), and $T_{1/2}$ were significantly greater in HCM patients than in H-LVH patients.

Calculation of Pearson’s correlation coefficient revealed that $\epsilon_{sys}$ was correlated with PAWP ($r=0.39$, $P<0.05$) and LVEDP ($r=0.40$, $P<0.05$). Whereas $SR_{sys}$ was correlated with PAWP ($r=-0.55$, $P<0.001$), LVEDP ($r=-0.71$, $P<0.0001$), and $T_{1/2}$ ($r=-0.41$, $P<0.01$), $SR_{sys}$ was not correlated with any of the hemodynamic variables.

**Discussion**

We have demonstrated the ability of SR imaging derived from TDI to discriminate HCM from H-LVH. An $\epsilon_{sys}$ cutoff value of $-10.6\%$ was associated with a sensitivity of 85.0%, specificity of 100%, and predictive accuracy of 91.2% for discrimination between these 2 conditions. The $\epsilon_{sys}$ was associated with HCM rather than with H-LVH. The combi-
nation of the IVST/PWT ratio and $\varepsilon_{\text{sys}}$ was able to discriminate HCM from H-LVH with a predictive accuracy of 96.1%.

In most cases, the diagnosis of HCM is based on conventional echocardiographic findings; however, there is substantial overlap in the extents of LVH and asymmetrical septal hypertrophy between patients with HCM and those with H-LVH, as was apparent in the present results (Figure 2a) and in those of previous studies. Moreover, LVH results from multiple factors, and $\approx 20\%$ of HCM patients have hypertension, although the diagnosis of HCM with concomitant hypertension is inherently difficult. Previous studies have shown that TDI is able to quantify LV myocardial abnormalities. SR imaging based on TDI is a newly developed echocardiographic modality and an emerging technique for assessment of myocardial systolic and diastolic function. The superiority of SR imaging for evaluation of regional myocardial properties has been demonstrated. With the use of multivariate analysis, we have now shown that $\varepsilon_{\text{sys}}$ and the IVST/PWT ratio are powerful predictors for the diagnosis of HCM, with $\varepsilon_{\text{sys}}$ being the most specific predictor of this condition. The $\varepsilon_{\text{sys}}$ was related to the severity of HCM, which reflects the impairment of myocardial contractile and lusitropic properties; it was positively correlated with PAWP, LVEDP, and $T_{1/2}$ and was negatively correlated with peak positive dP/dt. The ability of $\varepsilon_{\text{sys}}$ to discriminate HCM from H-LVH is likely attributable to its relations both to LV relaxation abnormalities and to LV stiffness, the latter of which leads to an increased LVEDP or PAWP.

Although $\varepsilon_{\text{sys}}$ is nominally a systolic parameter, elastic recoil, which is determined by LV end-systolic volume, is an important determinant of relaxation rate. Furthermore, prolongation of LV relaxation can influence LV stiffness. LV systolic performance is thus dependent on LV diastolic performance. We therefore speculate that $\varepsilon_{\text{sys}}$ might also reflect LV relaxation and stiffness. The present data are consistent with those of our previous study demonstrating that Ca$^{2+}$ handling by the sarcoplasmic reticulum was impaired in patients with HCM, resulting in abnormal LV relaxation and diastolic distensibility and stiffness. We also recently showed that downregulation of SERCA2 mRNA and consequent changes in Ca$^{2+}$ handling may contribute to the impairment of LV contractile reserve in HCM patients. The superiority of $\varepsilon_{\text{sys}}$ as a tool for discriminating HCM from H-LVH also likely results in part from the fact that this parameter reflects regional nonuniformity in myocardial properties, which is an important feature of HCM and affects LV relaxation and filling. The large decrease in the absolute value of $\varepsilon_{\text{sys}}$ associated with HCM may provide new insight into the pathophysiology of this disease.

Comparison With Previous Studies

Previous studies have applied TDI and SR imaging techniques to evaluate LVH. Derumeaux et al proposed that systolic and diastolic myocardial velocity gradients are sensitive indices for differentiating between physiological

### TABLE 2. Multivariate Discriminant Analysis for Differentiation of Patients With HCM From Those With H-LVH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discriminant Coefficient</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVST/PWT</td>
<td>16.9</td>
<td>9.04 to 24.7</td>
<td>0.00013</td>
</tr>
<tr>
<td>$\varepsilon_{\text{sys}}$</td>
<td>1.69</td>
<td>1.00 to 2.39</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

Figure 3. Relation between IVST/PWT ratio and $\varepsilon_{\text{sys}}$ in patients with HCM (●) and those with H-LVH (○). Optimal cutoff values for discrimination between the 2 groups of patients are indicated.

Figure 4. Correlation between $\varepsilon_{\text{sys}}$ and either LVEDP (a) or $\tau$ ($T_{1/2}$; b) in HCM patients (●) and H-LVH patients (○).
and pathological LVH caused by pressure overload in rats. We also previously showed that the myocardial velocity gradient reflects myocardial diastolic abnormalities.22 Similar to these previous observations, SRdia differed significantly between HCM and H-LVH patients and was significantly correlated with PAWP, LVEDP, and T1/2 in the present study; however, SRdia was not able to distinguish HCM from H-LVH by multivariate analysis in the present study, probably because SRdia data are noisier than are strain data with the present version of the SR program, which appears to be an important limitation of SR imaging,20 and because the absolute values of SRdia are smaller than those of strain.

Although previous studies have focused mainly on differentiation between physiological (compensatory) and pathological (noncompensatory) LVH caused by pressure overload, HCM is caused by abnormalities of sarcomeric contractile proteins30 and is diagnosed clinically from LVH in the absence of increased external load. LVH has been found not to be sensitive or specific for HCM diagnosis, however.31,32 In addition, ≈20% of HCM patients have hypertension. As far as we are aware, the present study is the first to apply SR imaging to discriminate between HCM and H-LVH.

Ho et al20 showed that the combination of Ea and ejection fraction was highly predictive of affected genotype in HCM, but they failed to demonstrate that Ea alone was sufficiently sensitive as a sole diagnostic criterion. We also failed to demonstrate specificity for these parameters in discriminating HCM from H-LVH. We did, however, demonstrate a high sensitivity, specificity, and predictive accuracy for εsys alone in discriminating HCM from H-LVH, even though amplification of genomic DNA was not detected in any of the patients in the present study.

Study Limitations
We used the mean values of SR imaging indices obtained from 8 LV segments for our analysis, which potentially exaggerated our results because of the heterogeneity of myocardial abnormalities in patients with HCM. Conversely, our results may indicate that SR imaging is able to detect asynchrony or heterogeneity of myocardial properties much earlier than is visual assessment.

Although TDI has been found to be relatively insensitive to changes in preload,33 εsys is thought to be load dependent, as are myocardial Doppler velocities.21 Filling pressures would thus be expected to affect εsys.34 This load dependency should be taken into account when deformation parameters are used to identify potential changes in contractility and in lusitropic properties. In the present study, LV end-diastolic internal dimension did not differ significantly between HCM and H-LVH patients, although LVEDP was significantly greater in HCM patients than in H-LVH patients. This discordance may reflect a difference in LV myocardial stiffness between HCM and H-LVH patients, which may be responsible for the difference in εsys between these 2 groups in the present study. A limitation of the present study is the lack of pressure-volume curves to provide insight into the pathophysiology of HCM and H-LVH in the study patients.

Another limitation of the present study is the lack of a large validation population. Further prospective studies are thus needed to confirm the discriminant values of εsys and the IVST/PWT ratio.

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References


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