Background—Left ventricular hypertrophy (LVH), the clinical hallmark of familial hypertrophic cardiomyopathy (FHCM), is absent in a significant number of subjects with causal mutations. In transgenic rabbits that fully recapitulate the FHCM phenotype, reduced myocardial tissue Doppler (TD) velocities accurately identified the mutant rabbits, even in the absence of LVH. We tested whether humans with FHCM also consistently showed reduced myocardial TD velocities, irrespective of LVH.

Methods and Results—We performed 2D and Doppler echocardiography and TD imaging in 30 subjects with FHCM, 13 subjects who were positive for various mutations but did not have LVH, and 30 age- and sex-matched controls (all adults; 77% women). LV wall thickness and mass were significantly greater in FHCM subjects (P < 0.01 versus those without LVH and controls). There were no significant differences in 2D echocardiographic, mitral, and pulmonary venous flow indices between mutation-positives without LVH and controls. In contrast, systolic and early diastolic TD velocities were significantly lower in both mutation-positives without LVH and in FHCM patients than in controls (P < 0.001). Reduced TD velocities had a sensitivity of 100% and a specificity of 93% for identifying mutation-positives without LVH.

Conclusions—Myocardial contraction and relaxation velocities, detected by TD imaging, are reduced in FHCM, including in those without LVH. Before and independently of LVH, TD imaging is an accurate and sensitive method for identifying subjects who are positive for FHCM mutations.

Key Words: cardiomyopathy • genetics • hypertrophy • systole • diastole

Familial hypertrophic cardiomyopathy (FHCM), the most common cause of sudden cardiac death in the young,1 is an autosomal-dominant disease caused by mutations in sarcomeric proteins.2 FHCM is diagnosed clinically by the presence of unexplained left ventricular hypertrophy (LVH), which is conventionally detected by echocardiography. LVH, however, is neither a sensitive nor an early marker for FHCM. Because of variable penetrance,2 LVH is absent in a significant number of mutation-positives until later in life, such as most patients with FHCM due to myosin-binding protein C mutations.2 Similarly, individuals with FHCM due to mutations in cardiac troponin T exhibit minimal LVH, despite having a high incidence of sudden death.2 An alternative approach to the early diagnosis of FHCM is genetic testing, which could identify mutation-positives independently of and before the development of LVH. However, genetic testing is compounded by extensive allelic and nonallelic heterogeneity,2 which restricts the availability of a rapid and convenient assay.
Individual data points for the lateral Sa and Ea velocities (A) and septal Sa and Ea velocities (B) of the study population.

3 age- and sex-matched adult groups from FHCM families: 30 normal subjects who were asymptomatic, did not carry the causal mutations, and had normal physical examinations, ECGs, and echocardiograms; 13 subjects who had a mutation but no evidence of LVH; and 30 FHCM patients with LVH and LV wall thickness ≥13 mm. Causal mutations were detected by direct sequencing. To exclude the possible interference of medications on echocardiographic and TDI variables, all drugs were discontinued for >3 days before TDI.

Echocardiographic Studies
Patients were imaged, and data were analyzed by a single observer who had no knowledge of genotype. Septal and posterior wall thicknesses, LV mass, and left atrial volumes were determined from 2D images, per published criteria. Peak early (E) and late (A) transmitral filling velocities, E/A ratio, deceleration time of E velocity, atrial filling fraction, and isovolumic relaxation time were measured from mitral filling velocities, E/A ratio, deceleration time of E velocity, atrial filling fraction, and isovolumic relaxation time were measured from mitral inflow velocities. The peak, duration, and time-velocity integral of pulmonary venous flow velocities were determined. Pulmonary venous flow systolic filling fraction was computed as the systolic/total forward time-velocity integral. The difference between the duration of atrial reversal and that of the transmitral A wave was calculated as atrial reversal minus mitral A duration.

TDI was applied in the pulse-Doppler mode to allow for a spectral display and recording of mitral annulus velocities at septal and lateral corners. Systolic (Sa), early diastolic (Ea), and late diastolic (Aa) TD velocities were measured, and the Ea/Aa ratio and the dimensionless parameter E/Ea were computed at both corners of the mitral annulus. The E/Ea index corrects for the influence of LV relaxation on mitral peak E velocity and provides a good estimate of LV filling pressures in FHCM patients.

Statistical Analysis
Variables were compared among the 3 groups by ANOVA, and the Bonferroni test was used for pairwise multiple comparisons. Statistical significance was defined by P≤0.05.

Results
The mean age and sex of the 3 groups were similar (Table 1). All patients had 2D and Doppler studies satisfactory for analysis.

The mutations in the 13 individuals without any evidence of a phenotype, including LVH, were V606M (4 subjects) and R719W (1 subject) for β-myosin heavy chain, R92Q for cardiac troponin T (1 subject), and InsG791 for myosin-binding protein C (7 subjects). None of the 13 mutation-positive individuals or 30 controls had LVH on ECG or echocardiography. In contrast, 26 of the 30 FHCM patients (87%) with LVH on echocardiograms also had LVH on ECG.

2D and Doppler Indices
Septal and posterior wall thicknesses, LV mass, and left atrial volume were increased in FHCM patients compared with mutation-positives without LVH and controls (Table 1). FHCM patients had a significantly lower E/A ratio, longer isovolumic relaxation time, longer deceleration time, and a larger atrial filling fraction than the other 2 groups (Table 1). Similarly, systolic filling fraction was increased and atrial reversal–A duration was prolonged in FHCM patients. In contrast, there were no significant differences in 2D and Doppler indices between the mutation-positives without LVH and controls.

TD Velocities
All FHCM patients and mutation-positives without LVH had reduced Sa and Ea velocities at both corners of the mitral annulus in comparison with normal controls (Figure and Table 2). TD velocities were lowest in the FHCM patients. Aa was also reduced in FHCM patients, but not in mutation positives without LVH, compared with controls. Accordingly, the Ea/Aa ratio was signifi-
TABLE 2. Tissue Doppler Velocities

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects (n=30)</th>
<th>Mutation-Positives Without LVH (n=13)</th>
<th>FHCM Patients (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral Sa, cm/s</td>
<td>15.6±2</td>
<td>8.7±1.7†</td>
<td>6±0.8*</td>
</tr>
<tr>
<td>Lateral Ea, cm/s</td>
<td>16±2.5</td>
<td>9.5±2.2†</td>
<td>5.9±1.6*</td>
</tr>
<tr>
<td>Lateral Aa, cm/s</td>
<td>9.4±1.1†</td>
<td>9.8±2.2†</td>
<td>6.8±1.5</td>
</tr>
<tr>
<td>Lateral Ea/Aa</td>
<td>1.8±0.3</td>
<td>0.92±0.3*</td>
<td>0.87±0.2*</td>
</tr>
<tr>
<td>Lateral E/Ea</td>
<td>5.4±1.45</td>
<td>7.99±1.4†</td>
<td>12.7±5.6*</td>
</tr>
<tr>
<td>Septal Sa, cm/s</td>
<td>14.5±1.4</td>
<td>7.96±1.6†</td>
<td>5.7±1*</td>
</tr>
<tr>
<td>Septal Ea, cm/s</td>
<td>15±2</td>
<td>8.5±2.27†</td>
<td>5.3±1.2†</td>
</tr>
<tr>
<td>Septal Aa, cm/s</td>
<td>9.2±1.6†</td>
<td>9.5±2.8†</td>
<td>6±1.6</td>
</tr>
<tr>
<td>Septal Ea/Aa</td>
<td>1.85±0.3</td>
<td>0.98±0.4*</td>
<td>0.92±0.3*</td>
</tr>
<tr>
<td>Septal E/Ea</td>
<td>5.8±0.92</td>
<td>8.65±1.5†</td>
<td>14±3.9*</td>
</tr>
</tbody>
</table>

*P<0.01 vs normal subjects; †P<0.03 vs FHCM patients.

Significantly lower in mutation-positive subjects and FHCM patients. The E/Ea ratio, an index of LV filling pressure, was higher at both corners of the mitral annulus in FHCM patients than in controls. However, the E/Ea ratio still predicted normal LV filling pressures in the mutation-positives without LVH. A lateral Sa <13 cm/s had a sensitivity of 100% and a specificity of 93% for differentiating the mutation positives without LVH from the controls. Similarly, a lateral Ea <14 cm/s had 100% sensitivity and 90% specificity. Concordantly, septal Sa <12 cm/s and Ea <13 cm/s both had 100% sensitivity and 90% specificity.

Discussion

We compared 13 individuals from FHCM families, each of whom carried a causal mutation but had not yet developed LVH, and 30 FHCM patients with LVH with 30 controls. TDI identified all 13 asymptomatic mutation-positives without LVH. Myocardial contraction and relaxation velocities by TDI were consistently reduced in the test subjects, irrespective of LVH, compared with the age- and sex-matched controls. These findings indicate that myocardial dysfunction is an early phenotype that occurs independently of LVH and that can be consistently detected by TDI. This novel approach could confer diagnostic and therapeutic opportunities for the screening and management of FHCM families.

Reduced TD velocities were present consistently for a variety of mutations in β-myosin heavy chain, cardiac troponin T, and myosin-binding protein C, the 3 most common proteins responsible for FHCM. These findings are in accord with our results in a transgenic rabbit model of human FHCM, in which 9 mutant transgenic rabbits without LVH exhibited reduced myocardial Doppler velocities. The reduced TD velocities in mutation-positives without LVH are also consistent with the hypothesis that myocardial dysfunction precedes and provides the stimulus for the development of LVH and with the results of functional studies of mutant sarcomeric proteins in cardiac myocytes and transgenic animals. Thus, reduced myocardial velocities by TDI suggest myocardial dysfunction in FHCM.

However, the reduced TD velocities, reflective of myocardial dysfunction, are in apparent contrast with the observation of preserved LVEF in FHCM patients. LVEF is a load-dependent index that does not necessarily reflect the contractile state of the myocardium. The preserved LVEF in FHCM may be the result of decreased afterload due to the small LV cavity.

Whether myocardial dysfunction by TDI reflects intrinsic myocyte abnormalities, disarray, or interstitial fibrosis remains to be explored. Elucidation of the molecular and histological bases of reduced myocardial TD velocities requires LV endomyocardial biopsy, which the current guidelines for diagnosis and management of FHCM patients do not justify. However, we suggest that because disarray and fibrosis are often late phenotypes and are unlikely to precede LVH, reduced myocardial velocities more likely reflect contraction and relaxation abnormalities of cardiac myocytes in FHCM.

This is the first study to establish the usefulness of TDI in the preclinical diagnosis of mutation-positives. In the proper clinical setting, detection of LVH by echocardiography is a highly specific marker. TDI does not have the limitations inherent in conventional echocardiography. To determine whether TDI, in comparison with genetic screening of FHCM families, will play an isolated or incremental diagnostic role requires a larger study of FHCM families. Abnormal TDI may determine whether LVH and other clinical and echocardiographic features of the disease develop later in life. Furthermore, because experimental data in transgenic animals show the reversibility of the histological phenotypes in FHCM through early drug therapy, preclinical diagnosis could afford the opportunity to prevent development of LVH with early drug therapy.

In summary, irrespective of LVH, TDI consistently detects myocardial dysfunction in patients with FHCM and in mutation-positive subjects without LVH. TDI can be used to identify mutation-positives before and independently of the development of LVH.

Acknowledgements

Supported by a grant from the National Heart, Lung, and Blood Institute, Specialized Centers of Research (P50-HL42267-01), and a Scientist Development grant (0030235N) from the American Heart Association National Center, Dallas, Texas.

References

Tissue Doppler Imaging Consistently Detects Myocardial Abnormalities in Patients With Hypertrophic Cardiomyopathy and Provides a Novel Means for an Early Diagnosis Before and Independently of Hypertrophy


_Circulation_. 2001;104:128-130
doi: 10.1161/01.CIR.104.2.128

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/2/128

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/