We sought to determine the mechanisms linking dynamic obstruction and exercise tolerance in patients with hypertrophic obstructive cardiomyopathy (HOCM).

Patients with HOCM have reduced exercise tolerance. However, the association between dynamic obstruction and peak oxygen consumption (VO2max) is weak.

We enrolled 25 patients with HOCM, 20 with hypertrophic cardiomyopathy (HCM), and 20 normal control patients. Two-dimensional, Doppler, strain, and left ventricular (LV) twist mechanics by speckle tracking echocardiography were obtained. The 25 HOCM patients had left heart catheterization, and 16 were re-examined after septal reduction.

Deformation measurements were the lowest in HOCM patients and increased (p < 0.05) after septal reduction. Twist and untwisting rate were not different between patients with HCM and control patients, but untwisting was significantly delayed in HCM patients and longest in HOCM patients. The delay related well with LV end-diastolic pressure (r = 0.76) and volume (r = -0.73), and VO2max (r = -0.75, all p < 0.01). After septal reduction, untwisting occurred earlier and accounted for the increase in end-diastolic volume (r = 0.65), and VO2max (r = 0.74, both p < 0.05).

Dynamic obstruction leads to delayed untwisting in HOCM, which accounts well for the increased LV filling pressures, the reduced LV volumes, and VO2max. After septal reduction, untwisting occurs earlier and leads to an improvement in LV filling and exercise tolerance. (J Am Coll Cardiol 2009;54:1326–34) © 2009 by the American College of Cardiology Foundation

Myocardial imaging has further refined the assessment of left ventricular (LV) systolic and diastolic function in this disease (9,10). We hypothesized that in patients with dynamic obstruction, delayed untwisting accounts for abnormal LV filling and diastolic dysfunction, which in turn leads to the reduced exercise tolerance. To examine this hypothesis, hypertrophic cardiomyopathy (HCM) patients with and without dynamic obstruction were compared with respect to cardiac mechanics and exercise tolerance before and after septal reduction therapy and in the absence of cardiac medications. The follow-up studies were performed at 4 months after septal reduction therapy and not acutely to exclude the effects of ischemia and stunning on myocardial function.

Methods

Study subjects. Forty-five consecutive patients with the clinical diagnosis (1) of HCM were enrolled in the study. All studies were performed after patients had discontinued their medications for 48 h. There were 25 patients...
who had dynamic obstruction due to systolic anterior motion of the mitral valve at rest with a gradient $\geq$30 mm Hg. From these 25 HCM patients with dynamic obstruction, 16 underwent repeat imaging and stress testing 4 months after septal reduction procedures (alcohol ablation in 14, and surgical myectomy in 2). The other 20 HCM patients had no obstruction at rest, or with Valsalva, or upright exercise. Three had diabetes mellitus. Twenty healthy normal subjects with a similar age were included as a control group. They had no evidence of cardiovascular disease and were referred to the echocardiography laboratory for the evaluation of a cardiac murmur or left ventricular ejection fraction (LVEF).

**Transthoracic echocardiography.** All patients were imaged by the use of a GE Vivid 7 ultrasound system (GE Healthcare Clinical System, Wauwatosa, Wisconsin). Two-dimensional grayscale images were acquired in the standard parasternal and apical (apical 4, apical 2, and apical long) views at a frame rate of 80 to 100 frames/s, and 3 cardiac cycles were recorded. Parasternal short-axis views were acquired at 3 levels: basal (circular cross section at mitral valve level), midpapillary, and apical (minimum cavity distal to papillary muscle level). In the apical 4-chamber view, mitral inflow and mitral annulus tissue Doppler velocities were recorded as previously described by pulse Doppler (11) at end expiration. The peak velocity of the tricuspid regurgitation jet was recorded from multiple windows by the use of continuous-wave Doppler and used to calculate pulmonary artery (PA) systolic pressure (11). All images were stored digitally for subsequent offline analysis.

**Echocardiographic analysis.** The analysis was performed offline by the use of EchoPac workstation without knowledge of any other data. Quantification of LV and LA volumes and LVEF were performed according to the recommendations of the American Society of Echocardiography (12). Maximum wall thickness and Maron-Spirito scores were determined from short axis views (13). Mitral inflow, tissue Doppler mitral annulus velocities, and ratio of mitral peak E velocity to annular early diastolic velocity ($E/e'$) were analyzed as previously described (11). After septal reduction therapy, LV peak systolic pressure was derived as the sum of systolic blood pressure and left ventricular outflow tract (LVOT) gradient by continuous-wave Doppler.

Myocardial deformation measurements were performed by the use of speckle tracking (14). In each of the apical views (4, 2, and long-axis), a global longitudinal strain curve was obtained, with all LV myocardial segments as the region of interest (15). The average value of peak systolic longitudinal strain from the 3 apical views was then calculated as global LV circumferential strain. Radial strain was measured in all 16 segments at the 3 short-axis views and averaged for use in statistical analysis.

Cardiac rotation was computed by speckle tracking (16). Counterclockwise rotation was marked as a positive value and clockwise rotation as a negative value when viewed from the apex. The basal and apical rotation data were exported into MATLAB program (Mathworks, Natick, Massachusetts). The difference between apical and basal rotations at each corresponding time point was calculated as LV twist, and the time derivatives of rotation were derived. Aortic valve closure was used to define the end of systole. Timing of untwisting was expressed as a percentage of systolic duration by the use of cardiac cycles with matched RR intervals. Interobserver reproducibility was assessed in 14 cases with previously acquired images, and a significant correlation was present ($r = 0.85, p < 0.01$), without a trend for over or underestimation.

**Exercise test.** All 45 patients with HCM performed symptom-limited treadmill exercise testing according to modified Bruce protocol, with simultaneous respiratory gas analysis. The 16 patients who underwent septal reduction therapy exercised before and 4 months after the procedure.

**Left heart catheterization.** Left heart catheterization was performed in the 25 HOCM patients with dynamic obstruction. A 7-F pigtail catheter was used for LV pressure measurements. Medex transducers were balanced before acquisition of hemodynamic data with zero pressure measurements. Medex transducers were balanced before acquisition of hemodynamic data with zero pressure measurements.

**Table 1 Clinical Status of Patients With HCM**

<table>
<thead>
<tr>
<th>Dyspnea</th>
<th>HCM (n = 20)</th>
<th>HOCM (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA—NYHA functional class II</td>
<td>16</td>
<td>2*</td>
</tr>
<tr>
<td>IB—NYHA functional class III/IV</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>Number with angina (%)</td>
<td>5 (25)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>IIA—CCS class II</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>IIIB—CCS class III</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Syncopete</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Number with AICD</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>$V_{O2max}$ (ml/kg/min)</td>
<td>$21 \pm 8$</td>
<td>$15 \pm 4^*$</td>
</tr>
<tr>
<td>Exercise duration (s)</td>
<td>$650 \pm 296$</td>
<td>$373 \pm 257^*$</td>
</tr>
<tr>
<td>METs achieved</td>
<td>$8.5 \pm 4$</td>
<td>$4.3 \pm 2.6^*$</td>
</tr>
</tbody>
</table>

$p < 0.01$ versus HCM.

**Abbreviations and Acronyms**

- **E/e’** = ratio of mitral peak E velocity to annular early diastolic velocity
- **HCM** = hypertrophic cardiomyopathy
- **HOCM** = hypertrophic obstructive cardiomyopathy
- **LA** = left atrial
- **LV** = left ventricular
- **LVEF** = left ventricular ejection fraction
- **LVOT** = left ventricular outflow tract
- **PA** = pulmonary artery
- **$V_{O2max}$** = peak oxygen consumption
- **AICD** = automatic implantable cardioverter-defibrillator
- **CCS** = Canadian Cardiovascular Society
- **HCM** = hypertrophic cardiomyopathy
- **HOCM** = hypertrophic obstructive cardiomyopathy
- **METs** = metabolic equivalents
- **NYHA** = New York Heart Association
- **$V_{O2max}$** = peak oxygen consumption
level at midaxillary line. Pressure measurements were performed before coronary angiography, and none of the patients had ventriculography. Left ventricular pre-A and LV end-diastolic pressure were recorded. The pre-A pressure was measured before the pressure increase due to atrial contraction, and LV end-diastolic pressure was determined before the increase in systolic pressure at end-expiration. The average of 3 cycles was used for analysis. Left ventricular peak and end systolic pressures were measured by the use of the simultaneously recorded LV and aortic pressures (by dual catheters).

### Statistical analysis.
Continuous data are presented as mean ± SD and dichotomous data as number and percentage. Comparisons were performed with 1-way analysis of variance if the data were normally distributed. Pairwise multiple comparison procedures were performed by use of the Holm-Sidak test. Differences in proportions were compared with chi-square tests. Paired t tests and McNemar tests were applied for the comparison of clinical status and LV function before and after septal reduction therapy. The Kolmogorov-Smirnov test was applied to evaluate normality of the variables that were correlated to one another in the regression analysis, and this test was passed. The relationship between continuous variables was analyzed by the use of regression analysis. Selection of independent predictors of exercise tolerance was performed with multiple linear regression analysis. The variables entered were deformation measurements, twist, delay in untwisting, and E/e’ ratio. A p value ≤0.05 was used to define a significant result.

### Results
Patients with HCM were all symptomatic with dyspnea, angina, or syncope. Patients with dynamic obstruction had a more advanced New York Heart Association functional dyspnea class and a greater incidence of angina (Table 1). Likewise, exercise tolerance was more limited in patients with dynamic obstruction. Three patients in the nonobstructive group had an automatic implantable cardioverter-defibrillator; 2 for primary prevention and the other after an episode of sudden cardiac death due to ventricular tachycardia. Five

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### Table 2 LV Structure in the Control Group and in Patients With HCM

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 20)</th>
<th>HCM (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>46 ± 13</td>
<td>49 ± 16</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>(10/10)</td>
<td>(13/12)</td>
</tr>
</tbody>
</table>

LV volumes:
- EDV (ml) 104 ± 25
- ESV (ml) 35 ± 12
- EF (%) 65 ± 6

LV mass:
- Mass (g) 65 ± 11
- Mass index to BSA (g/m²) 19
- Mass index to height (g/m².7) 22
- Maximum wall thickness (cm) 0.8
- Papillary muscle score (mm) 30
- LA volume (ml) 36 ± 16

### Table 3 LV Function in the Control Group and in Patients With HCM

<table>
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<tr>
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<th>Control (n = 20)</th>
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<td>Myocardial deformation (%)</td>
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<td>Global longitudinal strain</td>
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<td>-12.6 ± 3.4</td>
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<td>Global circumferential strain</td>
<td>-22 ± 2.5</td>
<td>-18.6 ± 5.9</td>
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<td>45 ± 4.4</td>
<td>33 ± 10.5</td>
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</table>

Twist mechanics:
- Twist (°) 13.6 ± 4.5
- Untwisting rate (°/s) -99 ± 26
- Time to untwisting/systolic duration (%) 111 ± 6

LV diastolic function:
- Lateral e’ (cm/s) 11 ± 2
- E/e’ 8.5 ± 3
- PA systolic pressure (mm Hg) 22 ± 2.5
- LVEDP invasively measured (mm Hg) -
- LV pre-A pressure invasively measured (mm Hg) -

LV systolic pressure and gradient:
- Systolic blood pressure (mm Hg) 125 ± 8
- LV peak systolic pressure (mm Hg) 128 ± 8
- LV end systolic pressure (mm Hg) 111 ± 11
- LVOT gradient (mm Hg) -

*p < 0.05 versus HOCM. †p < 0.01 versus HCM and HOCM. §Invasive measurements performed in 25 patients with HOCM.

LVEDP = left ventricular end-diastolic pressure; LVOT = left ventricular outflow tract; PA = pulmonary artery; pre-A = before the pressure increase due to atrial contraction; other abbreviations as in Tables 1 and 2.

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JACC Vol. 54, No. 14, 2009
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* *p < 0.05 versus HOCM. †p < 0.01 versus HCM and HOCM.

BSA = body surface area; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LA = left atrial; LV = left ventricular; MV = mitral valve; other abbreviations as in Table 1.

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patients in the group with dynamic obstruction had an automatic implantable cardioverter-defibrillator implanted for the primary prevention of sudden cardiac death.

Cardiac structure in HCM. All patients with HCM had asymmetric LV hypertrophy and a dilated LA. However, patients with dynamic obstruction had a significantly greater

Figure 1 Examples of Global Deformation and Twist From Control Subjects and HCM Patients With and Without Dynamic Obstruction

(Top) Global longitudinal (A to C), radial (D to F), and circumferential (G to I) strain are shown: a normal control in A, D, and G, hypertrophic obstructive cardiomyopathy (HOCM) in B, E, and H, and hypertrophic cardiomyopathy (HCM) in C, F, and I. Global longitudinal (A vs. B and C) and radial (D vs. E and F) strain were greater in normal control patients compared with those with either obstructive or nonobstructive HCM. There were smaller differences in circumferential strain (G vs. H and I). (Bottom) Twist from the 3 subjects was similar (J vs. K and L).
LV mass when quantitative and semiquantitative scores were applied, as well as a greater LA maximum volume (Table 2). Left ventricular volumes were significantly smaller in patients with HOCM when compared with HCM patients and the control groups (p < 0.01).

**Myocardial deformation in HCM.** In comparison with the control group, patients with HCM had significantly less deformation in the longitudinal, circumferential, and radial directions (Table 3). Notwithstanding, there were individual patients in whom 1 or more of the aforementioned deformation measurements were similar to the normal group. Myocardial strain was rather similar in HCM and HOCM patients (Fig. 1).

**Twist mechanics.** Twist and untwisting rate were similar between patients with HCM and normal control patients (Fig. 1). However, the onset of LV untwisting was significantly delayed in patients with HOCM compared with the normal group and patients with HCM (Table 3). A significant correlation was present in between the delay in untwisting velocity and flow propagation velocity (r = −0.43, p < 0.05), annular e’ velocity (r = −0.41, p < 0.05), and longitudinal strain (r = 0.58, r < 0.01).

**LV diastolic function.** Mitral annulus e’ velocity was significantly lower, whereas E/e’ ratio and estimated pulmonary artery systolic pressure were significantly greater in patients with HCM versus control patients. There were significant differences between HCM and HOCM patients, such that those with dynamic obstruction had evidence of more advanced diastolic dysfunction (Table 3). The delay in untwisting (as a percent of systolic duration) was significantly related to LVOT gradient, peak systolic pressure (r = 0.6, p = 0.01), and LV end-diastolic pressure as measured during left heart catheterization (Fig. 2A) in patients with dynamic obstruction. Likewise, it was significantly related to E/e’ ratio (Fig. 2B), LV end-diastolic volume (Fig. 3), and stroke volume (r = −0.58, p = 0.02) in all 45 patients. Similar results were noted when the delay in untwisting was expressed in relation to the diastolic filling period (r = 0.45 to 0.69, with p < 0.05).

**Determinants of exercise capacity in HCM.** In the patients with HOCM, significant relationships were observed between peak oxygen consumption (VO2max) and LVOT gradient (r = −0.52, p = 0.03). In all 45 patients, significant correlations were noted between VO2max and indices of LV systolic and diastolic function: global longitudinal strain (r = −0.46, p = 0.02), radial strain (r = 0.45, p = 0.03), LV twist (r = 0.44, p = 0.04), E/e’ ratio (r = −0.45, p = 0.026), and LV end-diastolic pressure by invasive measurements in the group with dynamic obstruction (r = −0.43, p = 0.04). Importantly, the delay in untwisting showed a good correlation with VO2max in patients with and without dynamic obstruction (Fig. 4). On multiple regression analysis (R2 = 0.62, p < 0.001), the independent predictors were timing of untwisting (β = −0.55, p < 0.001) and radial strain (β = 0.39, p < 0.001).

**Changes in clinical status and cardiac structure after septal reduction therapy.** In 16 patients, adequate pre- and post-septal reduction datasets were available for analysis. Clinical improvement occurred as well as an increase in exercise tolerance in this subset of patients (Table 4). Septal ablation led to a significant reduction in LV peak systolic pressure and LVOT gradient. Basal septal thickness was significantly decreased (2.1 ± 0.5 cm vs. 1.6 ± 0.4 cm, p < 0.01), but LV end-diastolic volume increased (88 ± 10 ml vs. 120 ± 12 ml, p < 0.05), whereas LVEF (71 ± 3% vs. 69 ± 5%, p = 0.1) was unchanged.

**Effect of septal ablation on myocardial deformation and LV twist.** Global deformation in the longitudinal, circumferential, and radial directions was significantly increased after therapy (Fig. 5A). However, LV twist and untwisting rate (Fig. 5B) were unchanged (Table 4). In contrast, LV untwisting occurred earlier (p < 0.01).

**Relation between untwisting, diastolic function, and exercise tolerance after septal reduction therapy.** Both the E/e’ ratio and PA systolic pressure decreased significantly. Overall the changes in LV diastolic function parameters paralleled the improvement in exercise tolerance. Importantly,
the earlier occurrence of untwisting was associated with the increase in LV end-diastolic volume (Fig. 6) and was the best predictor of VO$_{2\text{max}}$ (Fig. 7).

**Discussion**

Many patients with HOCM have limitations in their ability to exercise. We have shown in the current series that, in patients with dynamic obstruction, delayed untwisting plays a major role. This finding is supported by the earlier onset of untwisting after the decrease in LV systolic pressure with septal reduction therapy.

**LV twist mechanics.** LV rotation is determined by the helical arrangement of myocardial fibers. Hemodynamically, it is determined by LV contractility and loading conditions. LV untwisting begins in late systole in normal hearts and is completed during the isovolumetric relaxation period, preceding inflow across the mitral valve and is an important mechanism that aids LV filling at a normal LA pressure (17). A reduction or a delay in untwisting adversely affects LV filling as LV early diastolic pressures remain elevated and the transmitral pressure gradient is reduced unless LA pressure increases to maintain LV filling, end-diastolic volume, and hence, stroke volume.

In that regard, the determination of the hemodynamic variables that affect untwisting is important because their modulation can help patients with heart failure. To start with, intrinsic myocardial structure and contractility affect LV torsion, but loading conditions are also a factor. In particular, single-beat aortic constriction in canines (increased afterload) led to a significant delay in LV untwisting (18). However, the effect of afterload on untwisting in humans remains unclear. In that regard, patients with HOCM provide a unique opportunity to assess the clinical impact of afterload because increased afterload can be altered by septal reduction procedures that do not directly affect intrinsic myocardial function.

**LV untwisting in HOCM.** Patients with HCM have normal twist and untwisting rate as a group whether by echocardiography or magnetic resonance imaging (17,19–21), although individual variations occur. A previous study reported on delayed untwisting in 7 patients with HCM that adversely affected LV filling assessed by Doppler echocardiography (17). In our study, patients with HCM had a significant delay of...

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**Table 4** LV Function Before and After Septal Ablation

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>Before Ablation</th>
<th>After Ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class III to IV/I II</td>
<td>16/0*</td>
<td>0/16</td>
</tr>
<tr>
<td>VO$_{2\text{max}}$ (ml/kg/min)</td>
<td>14 ± 3*</td>
<td>19 ± 4</td>
</tr>
<tr>
<td>Exercise duration (s)</td>
<td>350 ± 215*</td>
<td>515 ± 153</td>
</tr>
<tr>
<td>LV systolic pressure/LVOT gradient (mm Hg)</td>
<td>75 ± 23*</td>
<td>15 ± 27</td>
</tr>
<tr>
<td>LVOT gradient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV peak systolic pressure</td>
<td>250 ± 35*</td>
<td>146 ± 25</td>
</tr>
<tr>
<td>Myocardial deformation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global longitudinal strain</td>
<td>−11.7 ± 3†</td>
<td>−14.3 ± 2</td>
</tr>
<tr>
<td>Global circumferential strain</td>
<td>−16.4 ± 4†</td>
<td>−22.6 ± 5</td>
</tr>
<tr>
<td>Global radial strain</td>
<td>32 ± 6.4†</td>
<td>38 ± 7</td>
</tr>
</tbody>
</table>

Twist mechanics

| Twist (°)                  | 15 ± 5         | 14.9 ± 5      |
| Untwisting rate (°/s)      | −108 ± 30      | −102 ± 34     |
| Time to untwisting/systolic duration (%) | 155 ± 18*  | 123 ± 8       |

LV diastolic function

| Lateral e’ (cm/s)         | 5.8 ± 1.3*     | 6.5 ± 1.3     |
| e’                         | 15 ± 6*        | 11 ± 5        |
| PA systolic pressure (mm Hg) | 39 ± 11*     | 30 ± 10       |

*p < 0.001 versus after ablation. †p < 0.05 versus after ablation. Abbreviations as in Tables 1 and 3.
untwisting (on average 11% vs. control patients), likely reflecting the well-known myocardial abnormalities in this disease.

More importantly, patients with dynamic obstruction exhibited a much longer delay (on average 38% vs. control patients and 24% vs. patients without obstruction) that was significantly coupled with smaller LV end-diastolic volume, as would be expected from its adverse effects on LV filling. Furthermore, the delayed untwisting was associated with a
more advanced degree of diastolic dysfunction as consistently observed by noninvasive measurements (LA volume, \(e'\) velocity, E/e' ratio, and PA systolic pressure) and invasively measured LV end-diastolic pressure. In conclusion, delayed untwisting led to greater filling pressures and reduced LV filling in HOCM, which in turn had a negative effect on exercise tolerance.

Changes in LV untwisting after septal reduction. Septal reduction led to a significant reduction in LV systolic pressures and an earlier onset of LV untwisting, which although still delayed was similar to patients with HCM. The earlier untwisting was accompanied by significantly larger LV end-diastolic volume and stroke volume because LVEF was unchanged. In addition, an improvement in LV diastolic function was observed as noted in previous studies (22,23), including those where invasive measurements were obtained (24). Finally, similar to baseline findings, the timing of untwisting remained tightly coupled with exercise tolerance (Fig. 7). There was also an improvement noted in global deformation measurements, which is similar to previous reports by cardiac magnetic resonance (19). Whether this change reflects an actual improvement in intrinsic contractility versus an increase in deformation related to decreased afterload remains to be determined, although the persistently reduced values of global longitudinal and radial strain favor the contribution of both intrinsic and extrinsic factors to the abnormal deformation measurements.

Study limitations. We included relatively few patients; however, the study was adequately powered (>80% power to detect an 8% difference between 3 groups with a SD of residuals of 5%, and alpha of 0.05) to address our hypothesis. Further, the results were consistent when several parameters of cardiac function were considered such that an alpha error is unlikely. Patients without dynamic obstruction did not undergo catheterization because there were no clinical indications for the procedure. Likewise, left heart catheterization was not performed at follow-up in the group who underwent septal reduction therapy because of the lack of clinical indications.

It would have been ideal to measure cardiac function during exercise. However, it is challenging to acquire adequate images during upright exercise, the ideal exercise modality in patients with HCM for provoking obstruction. Furthermore, the use of speckle tracking, which has greater feasibility and reproducibility than tissue Doppler, limits the frame rate during stress imaging such that it does not capture the rapid changes in mechanical events during exercise.

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Key Words: diastole • hypertrophic cardiomyopathy • mechanics • exercise.