Regional Left Ventricular Mechanics in Hypertrophic Cardiomyopathy

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Background. Nonuniformity is a determinant of diastolic function. In patients with hypertrophic cardiomyopathy, hypertrophy, abnormal calcium handling, and regional ischemia can also play a role. This study was designed to assess regional mechanics, asynchrony, and asynery in patients with hypertrophic cardiomyopathy.

Methods and Results. Nine control subjects and 22 patients with hypertrophic cardiomyopathy were studied by biplane left ventriculography and high-fidelity pressure tracings for the assessment of diastolic function by computing the time constant of isovolumic relaxation, peak filling rate, and the constant of passive chamber stiffness. Regional mechanics were evaluated by dividing the left ventricle into six sectors in the right and left anterior oblique projections. Systolic and diastolic asynchrony were assessed from the coefficient of variation of the regional time intervals from end diastole to end systole and to peak filling rate, respectively. Asynery was evaluated from the coefficient of variation of the regional area reduction. Regional passive elastic properties were estimated by computing the regional constant of chamber stiffness. In patients with hypertrophic cardiomyopathy, isovolumic relaxation was prolonged (time constant of isovolumic relaxation 101±41 versus 51±16 milliseconds in control subjects; P<.001) and the constant of chamber stiffness was increased (0.056±0.038 versus 0.025±0.010 mL⁻¹; P<.001). Both systolic and diastolic asynchrony as well as asynery were found. Regional mechanics showed hyperkinesia in the free wall, whereas the septum exhibited normal wall motion and increased constant of chamber stiffness.

Conclusions. Diastolic function is impaired in hypertrophic cardiomyopathy, and such an impairment is the consequence of nonuniformity and hypertrophy. The regions where the myopathic process is more pronounced show normal wall motion but increased stiffness. The inhomogeneity of regional wall motion with regional hyperkinesia and normokinesia of neighboring regions results in left ventricular asynery. (Circulation. 1993;88[part 1]:2206-2214.)

Key words • diastole • hypertrophy

Hypertrophic cardiomyopathy is a primary myocardial disease characterized anatomically by left ventricular asymmetric hypertrophy and pathophysiologically by normal or supernormal systolic ejection performance and impaired diastolic function.¹⁻⁹ Diastolic dysfunction has been extensively studied in hypertrophic cardiomyopathy. Isovolumic relaxation is prolonged,⁶⁻⁸,¹⁰,¹¹ whereas the rate of rapid filling is either normal,⁸ or reduced.⁷ Further evidence for abnormalities in the filling phase is supported by the observation that a smaller percentage of the filling volume is accommodated by the left ventricle during rapid filling (and, conversely, the atrial contribution to filling volume is increased).⁵,¹¹ Furthermore, left ventricular chamber stiffness is elevated in hypertrophic cardiomyopathy.⁹

Left ventricular nonuniformity is an important determinant of diastolic function,¹² since it can delay relaxation¹⁴⁻¹⁷ and impair diastolic filling¹⁸⁻²² in the experimental animal as well as in patients with coronary artery disease. In patients with hypertrophic cardiomyopathy, because of the broad heterogeneity in the distribution of left ventricular hypertrophy, it is reasonable to expect that spatial and temporal nonuniformity is present and might play a role in left ventricular diastolic dysfunction. Bonow and coworkers²³ have shown that patients with hypertrophic cardiomyopathy have a higher than normal degree of asynchronous as well as heterogeneity in regional distribution of the amount of early versus late filling. Furthermore, administration of verapamil improved left ventricular synchronicity and increased the rate of early filling,²³ thus suggesting a link between asynchrony and abnormal filling properties in hypertrophic cardiomyopathy. A recent study demonstrated a direct relation between spatial nonuniformity (ie, asynery rather than asynchrony) and isovolumic relaxation in patients with hypertrophic cardiomyopathy,²⁴ but the impact of temporal and spatial nonuniformity on early and late filling dynamics has yet to be elucidated.

The present study is aimed at assessing the relation between heterogeneity of left ventricular regional me-
chanics and diastolic function in patients with hypertrophic cardiomyopathy undergoing diagnostic cardiac catheterization. Throughout this paper, abnormal spatial nonuniformity will be referred to as asynery and abnormal temporal nonuniformity as asynchrony.

**Methods**

**Patient Selection**

We studied retrospectively 22 patients with hypertrophic cardiomyopathy (14 men and 8 women) with a mean age of 44 years (range, 24 to 62 years). The diagnosis of hypertrophic cardiomyopathy was based on echocardiographic evidence of disproportionate septal thickness in the absence of any identifiable secondary causes of hypertrophy.25 M-mode echocardiographic measurements included septal thickness, posterior wall thickness, and their ratio. No patient had any associated cardiac, coronary, or pulmonary diseases, including atrioventricular conduction abnormalities or left bundle branch block.

All patients were symptomatic, exhibiting one or more of the following symptoms: angina-like chest pain (12 patients), dizziness and/or syncope (10 patients), dyspnea (7 patients), and arrhythmias (7 patients).

Patients were admitted to undergo diagnostic left and right heart catheterization; the indication thereof was the evaluation of noninvasive signs of left ventricular outflow tract obstruction (at rest or provokable) in all except one. The remaining patient underwent cardiac catheterization for repeated episodes of dizziness.

Patients were treated with verapamil (10 patients), β-blockers (7 patients), verapamil and β-blockers (2 patients), or amiodarone (2 patients); one patient was not taking any drugs. Patients discontinued all cardiac medications 24 to 48 hours before the study.

We also analyzed data of a control group. They were nine subjects (four men and five women) with a mean age of 40 years (range, 28 to 52 years) who underwent cardiac catheterization for evaluation of atypical chest pain (six subjects) or diagnostic assessment of systolic heart or vascular murmurs (three subjects). They were selected as those having normal angiographic and hemodynamic findings (no shunts, no pressure gradients, normal coronary arteries). In particular, patients with systemic hypertension or mitral valve prolapse were not included in the control group.

**Cardiac Catheterization**

Patients were in the fasting state and premedicated with chlorzadepoxide 10 mg PO 1 hour before the study.

Right heart catheterization was performed via the right femoral vein. Cardiac output was measured by the Fick method and indexed to body surface area.

Left heart catheterization was performed transseptally, introducing an 11.5F Brockenbrough catheter into the left ventricle and advancing a 7F Millar micromanometer-angiographic catheter through it. Left atrial (mean and peak V wave) and left ventricular pressures were measured via the Millar catheter; aortic pressure was measured by a fluid-filled 8F pigtail catheter introduced retrogradely into the ascending aorta. This approach was used in 19 patients and in 4 subjects of the control group. In the remaining 3 patients and 5 control subjects, left-sided catheterization was performed by the retrograde aortic route using an 8F pigtail Millar catheter, and instead of left atrial pressure, pulmonary wedge pressure was recorded. Left atrial and pulmonary wedge pressures measured at the peak of the V wave were considered an estimate of mitral valve opening pressure.

The Millar catheter was calibrated electronically, and the calibration was checked by superimposing the micromanometer pressure tracing onto the pressure tracing obtained from the port of the fluid-filled lumen. Pressures, the first derivative of left ventricular pressure (dP/dt), and an ECG lead were recorded at a paper speed of 250 mm/s.

Simultaneous biplane left ventriculography was performed in the 30° right anterior oblique and in the 60° left anterior oblique projections and recorded on 35-mm film at a rate of 50 frames per second. This temporal resolution (ie, one frame every 20 milliseconds) has proved quite adequate for measurements of systolic and diastolic events.26 Each frame was identified by a number, which corresponded to a mark on the pressure recording strip. Simultaneous pressure-volume data were derived in each patient at 20-millisecond intervals for one cardiac cycle.

At the end of the study, coronary arteriography was performed for diagnostic purposes using the Judkins technique in patients >40 years of age.

**Data Analysis**

Left ventricular pressure and volume data were collected from the same beat, which was selected as the first beat providing adequate opacification of the left ventricle. Extrasystolic or postextrasystolic beats were excluded from the analysis.

Left ventricular volumes were calculated frame by frame from biplane left ventriculography using the area-length method.27 The long axis was determined in the right anterior oblique projection as the longest chord originating from the aortomitrall angle (Fig 1). The short axis was calculated as the geometric mean of the derived short axes in both left and right anterior oblique projections. Time-volume curves were normalized to the patients’ body surface area and filtered with a five-point temporal smoothing algorithm; on such curves, ejection fraction was calculated as usual, and peak filling rate was identified as the maximum of the first derivative occurring before diastasis and expressed in mL·s⁻¹·m⁻² or in stroke volumes per second (normalization to stroke volume). Diastasis was considered to begin at the frame (between end systole and the following end diastole) in which the second derivative of the time-volume curve changed sign. Diastasis could not be identified in 3 patients (all of them with a heart rate ≥100 beats per minute). Therefore, data for sector areas and asynery during diastasis refer to 19 patients.

In patients with hypertrophic cardiomyopathy, left ventricular outflow tract gradient was measured as peak-to-peak pressure difference from left ventricular inflow cavity and aorta; this measurement was obtained from the Brockenbrough catheter before the Millar catheter was inserted, so that pressures were recorded with similar techniques (fluid-filled catheters) in both left ventricle and aorta. Left ventricular outflow tract gradients were assessed under resting conditions and
after provocation with Valsalva maneuver or postextrasystolic potentiation. In the three patients in whom retrograde left heart catheterization was performed, gradients were measured during catheter pull-back from left ventricle to aorta.

Left ventricular high-fidelity pressure was digitized with an electronic graphic tablet (Numonics Corp) interfaced with a minicomputer (PDP 11/34, Digital Equipment Corp). Isovolumic relaxation was computed in the time interval spanning from minimum dP/dt to a pressure value 5 mm Hg above the following end-diastolic pressure, which can be considered a fair estimate of the mitral valve opening pressure (in the present series, this pressure value correlated with peak V wave left atrial pressure, yielding a correlation coefficient of \( r = 0.68, P < 0.001 \)). The variable asymptote method was used: briefly, the equation \( P = P_0 e^{-at} + P_b \) is derived to time \( t \), yielding \( dP/dt = -aP + P_b \), which represents a linear relation between negative dP/dt and pressure. The negative reciprocal of the slope of such correlation (ie, \(-1/a\)) was called the time constant of isovolumic relaxation, whereas the asymptote \( (P_0) \) was calculated as the extrapolated pressure value at which dP/dt reached 0.28

Pressure values measured every 20 milliseconds were matched to the corresponding volume data to obtain the pressure-volume relation. Passive elastic properties were calculated from minimal pressure to end diastole by computing the constant of left ventricular chamber stiffness \( (k) \) using a simple elastic model with shifting asymptote29: \( P = B + A e^{V} \), where \( P \) is pressure, \( V \) is volume, \( A \) is a fitting constant, \( B \) the pressure asymptote, and \( e \) the base of natural logarithm. Fitting was achieved by a computer program for nonlinear curve fitting.30

Analysis of Left Ventricular Regional Function

Fig 1 illustrates the method used in the analysis of regional function. The method has been previously described and validated31; briefly, the left ventricular silhouette was divided into six sectors starting from the midpoint of the long axis in both the right and left anterior oblique projection, excluding the area of the aortic root (Fig 1). The area of each sector was measured in arbitrary graphic tablet units and expressed in cm² by normalizing its relative area to global left ventricular area (calculated by the area-length method, as described above). From each sector, time-area curves were obtained after five-point temporal smoothing; the curves were normalized to body surface area to correct for interpatient differences in body size. Regional ejection fraction and peak filling rate were calculated in a fashion similar to that for global time-volume curves.

In 10 patients with hypertrophic cardiomyopathy, regional analysis could not be performed in the right anterior oblique projection because of the extreme ballerina foot shape of the left ventricle, which caused the center of the long axis to fall outside the left ventricular silhouette during systole. Therefore, regional function was assessed only in the left anterior oblique projection in these patients.

Systolic asynchrony was evaluated by adding the individual values of time measured from end diastole to minimum area in the six sectors of the left and right anterior oblique projections and by computing their coefficient of variation [ie, (standard deviation/mean value) × 100]. Likewise, diastolic asynchrony was determined by the coefficient of variation of the regional time intervals from end diastole to peak filling rate.

Regional wall motion was estimated from area-time curves as follows: the area, as a percentage of end-diastolic area, was determined and plotted at different time intervals during the cardiac cycle: (1) end diastole, identified as the beginning of the upstroke of dP/dt; (2) aortic valve opening, as the point of left ventricular and aortic pressure crossover; (3) end systole, as the time when left ventricular pressure equals aortic incisural pressure; (4) mitral valve opening, as the first occurrence of unopacified blood entering the left ventricle; (5) the time of occurrence of peak filling rate on the global volume curve; (6) the time of occurrence of diastasis on the global volume curve; and (7) end diastole, as above (Fig 1).

Asynchrony was computed as the coefficient of variation of the areas in both projections for each phase of the cardiac cycle.

Regional passive diastolic function was assessed by computing regional constant of chamber stiffness using regional area changes in an algorithm similar to that for the global volume.

Statistics

Data are given as mean ± SD. The unpaired \( t \) test was used to compare results in control subjects and in patients with hypertrophic cardiomyopathy. A two-way ANOVA for repeated measures36 was used to test differences in regional area-time curves. Comparison of parameters measured in different regions in control subjects and patients with hypertrophic cardiomyopathy was carried out with ANOVA; if the analysis was significant, Tukey's test was used as a post hoc test.30 Nonparametric assessment of incidence was carried out with the \( \chi^2 \) test with correction for continuity. Differ-
Hemodynamic Data in Control Subjects and in Patients With Hypertrophic Cardiomyopathy

<table>
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<tr>
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<tr>
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<tr>
<td>Rest</td>
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<td>Constant of chamber stiffness, mL⁻¹</td>
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<td>0.025±0.010</td>
<td>&lt;.001</td>
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bpm indicates beats per minute.

*Left atrial pressure measured in 19 patients and 5 control subjects; in the remaining 3 patients and 4 control subjects, pulmonary wedge pressure is supplied.

Results

Patient Characteristics

Basal septal thickness ranged from 13 to 33 mm, with a mean of 22±5 mm; mean posterior wall thickness was 12±3 mm; their mean ratio was 1.9±0.4. The patient with the lowest septal thickness had a mostly apical form of hypertrophy.

Fourteen patients had a significant (ie, ≥30 mm Hg) left ventricular outflow tract gradient at rest (range, 0 to 115 mm Hg; average for the 14 patients with significant resting gradients, 65±24 mm Hg), whereas all but 2 patients had provokable obstruction. Fourteen patients had mitral regurgitation (regurgitant fraction ranging between 5% and 40%). No patient had significant coronary artery narrowing.

Global Left Ventricular Function

The Table shows major hemodynamic findings in patients and in control subjects. Left atrial and left ventricular end-diastolic pressures were significantly elevated in patients with hypertrophic cardiomyopathy compared with control subjects. Ejection fraction was higher in patients with hypertrophic cardiomyopathy than in control subjects, whereas peak filling rate was similar in the two groups. The time constant of isovolumic relaxation was significantly increased in patients with hypertrophic cardiomyopathy, and it was abnormal in 18 of the 22 patients (82%) (Fig 2). Passive diastolic function, as assessed from the constant of left ventricular chamber stiffness, was abnormal in 55% of patients with hypertrophic cardiomyopathy and was significantly larger in the hypertrophic cardiomyopathy group as a whole than in control subjects.

Regional Left Ventricular Function

The coefficients of variation for the time interval from end diastole to end systole (systolic asynchrony) and for the time interval from end diastole to peak filling rate (diastolic asynchrony) were significantly higher than in control subjects (Fig 3). It is noteworthy that systolic and diastolic asynchrony were found in only 11 and 5 patients, respectively, with hypertrophic cardiomyopa-

Fig 2. Graph showing individual values for the time constant of isovolumic relaxation (τ) in control subjects (o) and in patients with hypertrophic cardiomyopathy (HCM) (c), patients with diastolic asynchrony; •, patients without diastolic asynchrony. Circles with vertical bars represent mean±SD. The normal range is indicated by the hatched area (ie, mean value±2 SD). τ indicates time constant of isovolumic relaxation.
thy (50% and 23%) (Fig 3). Patients with diastolic asynchrony were analyzed separately; in the 5 patients in whom diastolic asynchrony was present (ie, coefficient of variation for the time from end diastole to peak filling rate >13%), lower values of peak filling rates were found than in control subjects (3.4±0.9 versus 5.6±1.2 stroke volumes per second, \(P<.005\)) and than in patients without asynchrony (272±98 versus 375±97 mL·m⁻²·s⁻¹, \(P<.05\); and 3.4±0.9 versus 5.4±1.3 stroke volumes per second, \(P<.005\)). In addition, patients with diastolic asynchrony had lower values of left ventricular outflow tract gradients than those without asynchrony (12±16 versus 44±33 mm Hg, \(P<.05\) and a trend toward lower values of left ventricular systolic pressure (141±40 versus 156±34 mm Hg); furthermore, the incidence of significant (≥30 mm Hg) outflow obstruction was less among patients with than without diastolic asynchrony (1 of 5 as opposed to 11 of 17, \(P<.05\)). No relevant differences were found when patients were stratified to the presence of systolic asynchrony.

The evaluation of asynery revealed that the coefficient of variation for the different regions was significantly larger in hypertrophic cardiomyopathy than in control subjects at end systole, at the time of mitral valve opening, at the occurrence of peak filling rate, and at diastasis (Fig 4). This index of asynery was abnormal in 82% of the 22 patients at end systole, in 73% at the time of mitral valve opening, in 64% at peak filling rate, and at diastasis in 59% of the 19 patients in whom diastasis could be identified.

In patients with hypertrophic cardiomyopathy, wall motion was significantly enhanced throughout the cardiac cycle in the anterobasal, anterior, anteroapical, and inferoapical sectors of the right anterior oblique projection and in the lateral and posteroapical sectors of the left anterior oblique projection (Fig 5). In all other sectors, wall motion did not differ from control subjects.

Regional constant of chamber stiffness was significantly increased in patients with hypertrophic cardiomyopathy in the inferoapical region in the right anterior oblique projection and in the middle septum in the left anterior oblique projection (Fig 6). Regional constant of chamber stiffness was almost significantly different in patients with hypertrophic cardiomyopathy from that in control subjects in the upper septum (\(P=.06\)) in the left anterior oblique projection (Fig 6). To assess whether changes in regional stiffness were associated with abnormalities in regional wall motion and its timing, Fig 6 also depicts regional values of end-systolic area (ie, the...
phase of cardiac cycle when asynchrony was found in most patients and time to end systole (ie, the event when asynchrony was present in 50% of patients with hypertrophic cardiomyopathy). End-systolic area was significantly less in patients with hypertrophic cardiomyopathy (ie, wall motion was supranormal) in the inferoapical, anteroapical, and anterior regions in the right anterior oblique projection and in the posteroapical and postero-lateral regions in the left anterior oblique projection, with the lateral region almost reaching the significance level \((P=.08)\) (Fig 6). Time from end diastole to end systole was significantly shorter in patients with hypertrophic cardiomyopathy than in control subjects in the inferior region in the right anterior oblique projection.

**Influence of Left Ventricular Obstruction on Global and Regional Mechanics**

Patients were divided into two subgroups according to the presence or absence of a significant outflow tract gradient (ie, peak-to-peak pressure difference between left ventricular inflow tract and aorta \(\geq 30\) mm Hg at rest). Patients with outflow tract obstruction had higher mean left atrial and left ventricular end-diastolic pressures than patients with nonsignificant outflow tract gradients (14±4 versus 10±5 mm Hg, \(P<.05\), and 22±7 versus 14±7 mm Hg, \(P<.025\), respectively). Despite a significant difference in left ventricular systolic pressure (175±31 mm Hg in patients with as opposed to 130±14 mm Hg in patients without outflow obstruction, \(P<.001\)), the time constant of isovolumic relaxation was similar irrespective of obstruction (95±42 versus 109±40 milliseconds, respectively). In contrast, peak filling rate was higher in patients with than without obstruction (387±119 versus 302±51 mL \(\cdot m^{-2} \cdot s^{-1}\), \(P<.05\)). Left ventricular outflow tract gradient at rest was higher in patients with obstruction by definition; provokable gradients, however, were similar in both subgroups (92±37 mm Hg in patients with obstruction and 101±41 mm Hg in patients without obstruction). No further differences were observed in any parameters of global and regional left ventricular function.

**Discussion**

**Global Diastolic Function**

Left ventricular relaxation and passive elastic properties are altered in patients with hypertrophic cardiomyopathy. Isovolumic relaxation is abnormal in the vast majority of patients (82%) and significantly slowed compared with the control subjects (Fig 2). Prolonged isovolumic relaxation affects the early diastolic filling phase, since isovolumic relaxation lasts after mitral valve opening, thereby decreasing wall distensibility (ie, increasing operative stiffness) and reducing the rate of early filling.7,10,22 In our study group, the rate of early diastolic filling was not significantly different between patients with hypertrophic cardiomyopathy and control subjects (Table). This finding is consistent with previous studies4,8 and is not surprising because mitral valve opening pressure, an important determinant of early filling velocity,32 was increased in patients with hypertrophic cardiomyopathy (Table) and thus compensated for the slowed velocity of relaxation. An additional mechanism could stem from regional differences in wall motion: Hori and coworkers33 demonstrated that diastolic suction takes place if inotropic state increases and end-systolic volume decreases. If hyperdynamic left ventricular regions led to a regional diastolic suction in our patients, that could partly compensate for regions with slowed relaxation and account for normal velocities of global early filling.

The impairment of isovolumic relaxation can be caused by several factors, such as altered loading conditions, subendocardial ischemia, increased cytosolic calcium content,34 hypertrophy, and nonuniformity.35 In particular, loading conditions can be germane in patients with the obstructive form of hypertrophic cardiomyopathy; to address this issue, we analyzed separately patients with significant (≥30 mm Hg) resting left ventricular outflow tract gradients and found that, despite higher left ventricular peak systolic pressure than in nonobstructive patients, isovolumic relaxation was similar. This lack of effects of increased left ventricular pressure on isovolumic relaxation can be the outcome of increased nonuniformity in

![Graph showing regional constant of chamber stiffness](http://circ.ahajournals.org/)

Fig 6. Graphs showing regional constant of chamber stiffness (top panels), end-systolic area (middle panels), and time to end systole (bottom panels) in six sectors of the right (left panels) and left anterior oblique projections (right panels) in patients with hypertrophic cardiomyopathy. Vertical bars represent 1 SD. Hatched areas represent the normal range (ie, mean value ±2 SD).
nonobstructive patients; alternatively, because obstruction may take place late in systole, the resulting increase in left ventricular pressure can occur in the second half of systole and, hence, be considered as relaxation load, which increases the speed and shortens the duration of isovolumic relaxation.13,26 Peak filling rate was higher in patients with than without obstruction; this difference, however, is the consequence of an elevation in left atrial pressure. These findings suggest a minor impact of obstruction on diastolic function. It should also be pointed out that all but two patients had provable obstruction, with similar provocable gradients irrespective of the resting gradients; hence, we did not compare true nonobstructive and obstructive patients and cannot discount the role of altered loading conditions (ie, obstruction) on mechanics.

Besides alterations in active diastolic properties, cellular disarray and myocardial fibrosis, which are typically seen in patients with hypertrophy, contribute to the deterioration of passive diastolic function. Passive diastolic properties are also altered in hypertrophic cardiomyopathy (Table): the constant of chamber stiffness was significantly larger than in normal subjects, and it was abnormal in half of the patients. Thus, in patients with hypertrophic cardiomyopathy, functional and anatomic factors can affect both active (ie, relaxation) and passive diastolic properties. Because the shape and function of the left ventricle are markedly altered in hypertrophic cardiomyopathy, it is important to evaluate the impact of nonuniformity on diastolic function.

Asynchrony and Asynergy

Systolic and diastolic asynchrony (as evaluated by the coefficient of variation of regional time intervals from end diastole to end systole and to peak filling rate, respectively) were significantly different from control subjects in patients with hypertrophic cardiomyopathy (Fig 3). It is to be pointed out, however, that diastolic asynchrony was found in only 23% of patients with hypertrophic cardiomyopathy. In addition, although the time constant of isovolumic relaxation was abnormal in 10 of the 11 patients with systolic asynchrony and in all 5 patients with diastolic asynchrony (Fig 2, open squares), there were 8 patients and 13 patients, respectively, with impaired relaxation who had no systolic or diastolic asynchrony (Fig 2, closed symbols). It is to be pointed out, however, that patients without diastolic asynchrony had greater left ventricular outflow tract gradients and a higher incidence of significant obstruction than patients with diastolic asynchrony. This was associated with a trend toward higher left ventricular systolic pressure values, which could, at least in part, account for slowed isovolumic relaxation in patients without asynchrony. The observation that asynchrony is associated with less incidence and severity of obstruction is consistent with the finding that sequential atrioventricular pacing, which induces asynchrony,22 reduces the degree of left ventricular outflow tract obstruction.37

Bonow and coworkers23 have shown that both systolic and diastolic asynchrony are usually present in patients with hypertrophic cardiomyopathy and that diastolic asynchrony is inversely related to peak filling rate. Our results show that asynchrony, especially diastolic asynchrony, is not commonly seen in patients with hypertrophic cardiomyopathy. Such discrepancy can be explained by the extent of diastolic dysfunction: their patients had reduced peak filling rate (normalized to stroke volumes per second) compared with normal subjects, whereas our patients had normal values. When we considered only those patients with diastolic asynchrony, peak filling rate (normalized to stroke volumes per second as in the study by Bonow et al) was significantly lower than in normal subjects.

Thus, isovolumic relaxation is altered in the majority of patients with hypertrophic cardiomyopathy irrespective of the presence of diastolic asynchrony, and the velocity of early filling is not reduced, since it is compensated for by the increase in filling pressure; when asynchrony develops, it contributes to the impairment of early diastolic function with a reduction in peak filling rate. The origin of asynchrony is unclear, but it might be the consequence of ischemia,38 which can be observed in patients with hypertrophic cardiomyopathy with normal coronary arteries.39 Ischemia has been explained by abnormal small coronary arteries in the hypertrophied septum, increased wall stress, delayed relaxation, and increased coronary vascular resistance.39,40

In contrast to asynchrony, the vast majority of patients with hypertrophic cardiomyopathy have left ventricular asynergy. The coefficient of variation for the changes in regional area was significantly higher, throughout the cardiac cycle, in patients with hypertrophic cardiomyopathy than in control subjects (Fig 4).

Regional Mechanics

Left ventricular regional wall motion was supernormal in the anterobasal, anterior, anteroapical, and inferoapical regions in the right anterior oblique projection and in the lateral and posteroapical regions in the left anterior oblique projection (Fig 5). In the remaining regions, wall motion did not differ from that in normal subjects. This inhomogeneity accounts for the marked asynergy observed in patients with hypertrophic cardiomyopathy (Fig 4).

In the left anterior oblique projection, regional stiffness was higher than normal in the middle septum, in which wall motion was normal; in contrast, the lateral wall was hyperdynamic and exhibited normal stiffness (Fig 6). In the right anterior oblique projection, stiffness was increased in the inferobasal region, in which wall motion was normal, whereas wall motion was hyperdynamic in the inferoapical, anteroapical, and anterior regions, associated with normal stiffness. These findings indicate that the left ventricular regions in which the myopathic process is less pronounced are those in which stiffness is normal and wall motion is supernormal; in contrast, the septum is stiffer and exhibits reduced wall motion compared with the adjacent regions. Inferior regions reflect properties of the inferior wall as well as of the septum because of structure overlap.

Our results are compatible with the conclusions of Hayashida and coworkers,24 who found a prolongation of the time constant of regional stress decrease (which is thought to be an estimate of regional isovolumic relaxation) in the most hypertrophied regions in patients with hypertrophic cardiomyopathy; when regional stress declines more slowly in the hypertrophied regions of patients with hypertrophic cardiomyopathy, then isovolumic relaxation lasts into the filling phase, which may induce an increase in operative stiffness.22,41 Conversely,
Ohsato and coworkers have shown in hypertrophic cardiomyopathy that changes in myocardial structure with increased diameter of myocytes, regional fibrosis, and muscle fiber disarray are determinant of abnormalities in diastolic function. Because these changes are likely to occur in the regions where the myopathic process is more pronounced, they can encompass the anatomic substrate responsible for diastolic asynergy.

**Mechanisms of Asynchrony in Hypertrophic Cardiomyopathy**

Our study cannot explain the reason for spatial nonuniformity in patients with hypertrophic cardiomyopathy. Anatomic nonuniformity (i.e., asymmetric hypertrophy) may have an impact on functional asynergy: augmented wall thickness can lead to an increase in regional stiffness, whereas altered calcium handling can also affect relaxation and, thus, diastolic filling. Furthermore, severe myocardial hypertrophy can affect diastolic function by subendocardial ischemia. In addition, a recent observation provided evidence that altered regional glucose metabolism is associated with reduced wall motion of the same regions.

**Conclusions**

Isovolumic relaxation and chamber stiffness are abnormal in patients with hypertrophic cardiomyopathy. Diastolic asynchrony is not increased in the majority of our patients with hypertrophic cardiomyopathy, but in those in whom it is present, an impairment in peak filling rate can be observed. In contrast, asynergy is a very common finding in patients with hypertrophic cardiomyopathy and is likely to be caused by regional differences in load, metabolic condition, and wall stiffness.

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