Diminished Contractile Response to Increased Heart Rate in Intact Human Left Ventricular Hypertrophy
Systolic Versus Diastolic Determinants

Chun-Peng Liu, MD; Chih-Tai Ting, MD; William Lawrence, MD; W. Lowell Maughan, MD; Mau-Song Chang, MD; David A. Kass, MD

Background. Experimental studies indicate that in addition to diastolic dysfunction, hypertrophied myocardium can display depressed contractile responses, particularly at rapid heart rates, compounding reserve limitations. This study tests whether such abnormalities exist in intact human subjects at physiological paced rates and, if so, whether they are linked to simultaneous rate-dependent deterioration in diastolic function.

Methods and Results. Ten subjects with left ventricular hypertrophy (LVH) and 8 normal control subjects were studied. Most LVH patients presented with dyspnea and/or pulmonary edema and had concentric hypertrophy. Since rapid pacing simultaneously alters cardiac filling volumes and pressures, pressure-volume relation analysis was used to better define changes in contractile response. Patients were instrumented with a conductance catheter and micromanometer for pressure-volume data recording and a balloon occluder at the right atrial-inferior vena caval junction to vary filling and thus generate function relations. Data were obtained at baseline and at three atrial pacing rates (100, 120, 150 min⁻¹). In addition, single-beat force-interval data were used to indirectly examine calcium cycling kinetics. LVH subjects demonstrated baseline diastolic abnormalities, including prolonged relaxation, elevated end-diastolic pressure, and reduced chamber compliance. However, systolic function was similar to that in control subjects. With rapid pacing, normal subjects displayed a positive contractile response, whereas this was markedly diminished in LVH subjects. With abrupt termination of pacing and return to slower sinus rhythm, LVH subjects displayed greater initial potentiation followed by a more rapid decline than control subjects, suggesting abnormalities of calcium handling. Despite contractile abnormalities, diastolic function did not further deteriorate with rapid pacing and thus did not appear to be tightly linked to the systolic changes.

Conclusions. Pacing stress in intact human LVH can result in systolic impairment superimposed on preexisting but not worsened diastolic dysfunction. Abnormal calcium handling probably contributes prominently to this response. (Circulation. 1993;88[part 1]:1893-1906.)

Key Words • pressure-volume relation • pacing • hemodynamics

Clinical left ventricular hypertrophy (LVH) is principally considered a disorder of diastolic function. Resting isovolumic relaxation is prolonged, early rapid filling is slowed, and chamber and myocardial stiffness are increased.¹⁻⁴ These abnormalities in turn have been related to a variety of changes including altered calcium handling⁵⁻¹⁰ and collagen content.¹¹,¹² In contrast to diastole, resting systolic function often appears normal or even supernormal in humans with LVH, and a similar variability has been found in animal models.⁵,¹³⁻¹⁷

Both diastolic and systolic function of LVH hearts are reported to diminish at increased heart rate in intact animals,¹⁴,¹⁸,¹⁹ isolated muscle,⁸ and single cells.²⁰ Diastolic deterioration is commonly reported in the form of marked increases in end-diastolic pressure or tension and in systolic dysfunction by reduced force generation or shortening. Systolic changes have been more difficult to quantify in intact preparations, since varying cycle length simultaneously alters cardiac filling volume and pressures. This limits the interpretation of many frequently used systolic parameters such as maximal rate of pressure rise (dP/dtmax), peak systolic pressure, or fractional shortening.¹⁴,¹⁹,²¹,²² While isolated tissue results are more direct, the kinetics of calcium cycling itself appears to be slowed in these preparations compared with in situ²³ hearts, and this could influence the results. Finally, it remains unknown whether similar systolic changes exist in intact humans with LVH at physiological heart rates.

A more heart-specific analysis of systolic reserve during pacing is afforded by pressure-volume relations. Thus far, this approach has only been applied to the
normal canine left ventricle. However, recently developed catheter-based techniques enable repeated measurement of pressure-volume relations in the same human subject under a variety of acute conditions. Since this method uses mechanical rather than pharmacological changes in chamber load to generate the relations, it is ideally suited for studying pacing mechanics at multiple rates in the same subject.

In the present study, this method was used to test the hypothesis that heart rate–dependent inotropic reserve is limited in intact humans with significant LVH. Mechanisms for systolic depression were further explored by testing whether simultaneous deterioration of diastolic function was present and/or necessary and if altered calcium handling played a role. The latter was examined by measuring postextrasystolic potentiation, potentiation decay, and the contractile response to variations in individual-beat intracycle length.

**Methods**

**Subject Group**

Studies were conducted in 18 adult patients referred for diagnostic cardiac catheterization. Summary clinical data are provided in Table 1. Ten patients (mean age, 54 ± 11 years) had LVH documented by echocardiography, with a mean diastolic wall thickness of 1.9 ± 0.4 cm (mean ± SD). Most also had ECG evidence of LVH. LVH was concentric in 8 of the patients. The majority of LVH patients (n=7) presented with exertional or rest dyspnea (New York Heart Association [NYHA] class II to IV), with 5 of the subjects experiencing severe paroxysmal pulmonary edema. The remaining 3 patients presented with atypical chest pain and/or presyncope. Seven patients had a history of treated hypertension. No patient had documented hypertrophy and/or systolic murmurs from childhood or a family history of LVH. All subjects had normal coronary arteriography.

The control group comprised 8 patients aged 38±10 years, with normal ECGs, coronary arteriograms, contrast ventriculography, and echocardiograms. Four of these patients presented with atypical chest pain, and 4 had headache and/or dizziness and were admitted to evaluate possible early hypertension. These latter subjects had not received chronic treatment and were normotensive in the hospital. All patients in both LVH and control groups were in normal sinus rhythm. The research protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical
Institutions and the Clinical Investigation Committee of the Veterans General Hospital, Taipei, Taiwan. All patients provided informed consent, and there were no complications as a consequence of the study.

**Procedure**

Chronic medications were withheld for at least 24 to 48 hours before the study. Subjects were premedicated with benzodiazapam (10 mg) and diphenhydramine (50 mg) and then underwent routine coronary angiography, left ventriculography, and right heart catheterization via femoral access. This confirmed the absence of coronary artery, valvular, and pericardial disease. Subjects in whom concomitant disease was identified were excluded. Nonionic contrast was used to minimize hemodynamic sequelae.

After right and left heart catheterization, specialized catheters were placed for pressure-volume analysis. Details of this procedure have been reported elsewhere.27-29 Briefly, an 8F multielectrode conductance (volume) catheter (Webster Labs, Baldwin Park, Calif) was introduced via the femoral artery and advanced to the left ventricular apex. A micromanometer-tipped catheter (SPC-330A, or 320, Millar, Houston, Tex) was advanced through the full length of the conductance catheter to measure cavity pressure. The volume catheter was connected to a stimulator/microprocessor (Sigma V, CardioDynamics, Rijnsburg, The Netherlands, n=8, or VCU, Cardiac Pacemaker Inc, St. Paul, MN, n=10). These devices provide a low-amperage AC excitation current (20 kHz or 1 to 2 kHz, respectively) at base and apex electrodes. Measured voltages at intervening electrodes are converted to segmental conductances, which are then added in real time to yield a time-varying signal proportional to total chamber blood volume. Proper placement of the catheter within the ventricle is determined by fluoroscopic inspection and by examining each segmental pressure-volume loop. Moving up from the apex, the first electrode segment with a PV loop that is isovolumic or moves clockwise defines the position of the aortic valve. Only segments below this level are combined into a total volume signal.

In addition to volume and micromanometer catheters, a specially designed 7F balloon occlusion catheter (SP-9168, Cordis, Miami, Fla) was introduced through a femoral vein and placed within the right atrium. Inflation (15 to 25 mL of CO2) and gentle withdrawal of this balloon toward the inferior vena cava produced a transient reversible decline in venous return and thus, volume. This generated pressure-volume relations at each pacing rate. Atrial pacing was performed using a 2.5F bipolar flexible tip pacing wire (98-100H, Baxter, Irvine, Calif) advanced through the lumen of the balloon catheter.

**Protocol**

After placement of all catheters, cardiac output, simultaneous steady-state pressure-volume signals, and systolic and diastolic pressure-volume relations during transient inferior vena cava (IVC) occlusion were recorded. Right atrial pacing was then instituted at 90 to 100 min⁻¹ and increased by 20 to 30 min⁻¹ increments to a maximum of 150 to 170. Two minutes were provided at each steady-state heart rate before repeat data collection. Data also were recorded immediately after termination of pacing (ie, return to normal sinus rhythm). This provided evaluation of potentiation (first beat after pacing cessation) and decay of potentiation (termed recirculation fraction).30,31 Variation in baseline heart rate, Mobitz I second-degree heart block at rapid rates in two patients, and occasional difficulty in maintaining steady pacing during simultaneous preload reduction prevented all data from being obtained in every patient at each heart rate. However, generally, 80% or more of subjects were represented at each rate.

The mechanical response to varying pacing rate is known to be influenced by calcium cycling kinetics. Recent data in intact dogs suggest that these kinetics, as globally indexed by the mechanical restitution curve (MRC), appear much faster in intact preparations compared with isolated hearts32 or muscle.33,34 The MRC relates the contractile response of a test contraction to its prior cycle length and is thought to index the kinetics of calcium cycling.31-34 Thus, to better clarify the systolic pacing response, MRCs were obtained in a subset of patients (LVH, 7; controls, 4). Atrial pacing was set at 100 min⁻¹, and test stimuli then were introduced, varying the interval between the test beat and the last steady-state paced beat. This test stimulus interval (TSI) started short at 375 milliseconds and was gradually lengthened by 25 to 50 milliseconds until native sinus activity preempted the stimulus. Each TSI was separated by at least 10 steady-state beats. The MRC was generated by plotting the contractile response for each test beat versus TSI.

Throughout each study, ventricular pressure-volume loops were continuously displayed in real time using custom designed data acquisition and display software. Analog signals were digitized at 200 Hz and stored on removable hard drives for subsequent off-line analysis. This software also provided pacing triggers, which were transmitted to an isolated pacing spike generator (Bloom Associates, Reading, Pa).

**Data Analysis**

Our current approach to calibrating the volume catheter signal in humans has been reported recently.29 The volume signal is proportional to absolute left ventricular cavity volume with a nonzero offset and nonunity slope. The slope is determined from the ratio of thermodilution (or ventriculographic) stroke volume to the stroke volume measured by catheter. The latter is defined as the mean width of the pressure-volume loop. The calibration offset is determined by matching end-diastolic catheter volume or ejection fraction to ventriculography values. Calibration of the volume signal was performed at baseline only. Care was taken to assure that catheter position remained stable throughout the study, minimizing calibration error.

Ventricular pressures, volumes, and other steady-state parameters were derived from 5 to 10 successive cardiac cycles, synchronized to the R wave of the electrocardiogram, and signal averaged. End-diastolic pressure (P kep) was the pressure at the lower right corner of the pressure-volume loop, determined by automated algorithm.29 End-systolic pressure (P ees) was measured at the point of maximal elastance (maximal P/[V-V0]), where V0 is volume axis intercept of the end-systolic pressure-volume relation (ESPVVR). End-systolic and -diastolic volumes (V es and V ed) were determined by
averaging five volume points centered at mean left ventricular pressure during isovolumic contraction and relaxation, respectively. Stroke volume was the mean width of the pressure-volume loops, and stroke work was the area within the loop. The first derivative of pressure (dP/dt max) was digitally derived by a five-point weighted slope and normalized to V o to index contractile function. A second systolic parameter was maximal power (PWR max) divided by V o, where power was derived from the product of ventricular pressure and the derivative of volume. The time constant of isovolumic relaxation was determined from pressures extending from −dP/dt max to pressure at the onset of filling. Two methods were used, neither of which assumed a zero pressure asymptote at time = 0. One was the inverse slope of the linear regression of dP/dt versus P(t), \( \frac{dP}{dt} \) and the second used nonlinear regression to fit the model \( P(t) = P_o + P_i e^{-t/t_i} \). Arterial load was assessed by the effective arterial elastance \( E_a = P_a / SV \) and by total estimated resistance \( R_e = 0.9 \cdot E_a \cdot HR \).

**Pressure-Volume Relations**

In addition to steady-state parameters, systolic and diastolic chamber functions were assessed by pressure-volume relations derived from multiple cardiac cycles (13±5, mean±SD) at varying preload during transient IVC occlusion. Two systolic relations were obtained. The ESPVR was determined by linear regression as the set of points at maximal P/(V−V o) (average correlation coefficient, \( r = 0.98 ± 0.02 \)), with slope \( E_{sv} \) (end-systolic elastance) and volume intercept \( V_o \). The latter was obtained by an iterative method. The linear relation between stroke work and \( V_o \) was also derived from these same cardiac cycles, and the slope of this relation (\( M_{sw} \)) also indexed contractile function. This latter relation is measured over a broader range of values than the ESPVR and is independent of chamber size and volume signal gain, as the volume terms in both numerator and denominator cancel.

Diastolic chamber compliance was determined from the end-diastolic pressure-volume relation (EDPVR). This was generated by combining end-diastolic pressure-volume points from the latter third of cardiac filling from each beat during IVC occlusion. Data (mean of 31 points) were fit to a linear model to determine compliance, with a mean linear correlation of 0.88. A linear rather than monoeponential model was used since it fit the data virtually as well and was less sensitive to precise data point selection.

**Force-Interval Relations**

To better assess the role of altered calcium handling toward steady-state pacing results, responses to single-beat variations in intercycle length were measured and used to characterize (1) maximal systolic potentiation, (2) recirculation fraction, and (3) mechanical restitution. Although methods for measuring intracellular calcium exist for isolated tissues and hearts, these are not applicable to intact humans. Thus, at present, calcium handling can only be indirectly studied in humans by means of force-interval relations.

Postextrasystolic potentiation was assessed by examining the contractility of the first postpaced beat after cessation of atrial pacing. To minimize effects of simultaneous changes in both preload and afterload, contractile function was indexed by single-beat \( E_{sv} \) (using the \( V_o \) obtained during atrial pacing).

The rate of decay of potentiation after pacing cessation is thought to index the percent of calcium recycled through the sarcoplasmic reticulum, \( \frac{dP}{dt_{max}} \) and the recirculation fraction. After the initial postpacing potentiation, subsequent beats display a gradual geometric decline in contractility to baseline. Heart rate and \( V_o \) are nearly identical for these postpaced beats, allowing \( dP/dt_{max} \) to index contractile function. To obtain the recirculation fraction, the following parameter (\( R_a \)) was determined for the first 6 postpaced beats:

\[
R_a = \frac{[dP/dt_{max}(n)]/dP/dt_{max}(ss)]}{1}
\]

where the numerator and denominator are the values of \( dP/dt_{max} \) for beat n (n=1 to 6) and the fully decayed steady state (ss), respectively. \( R_a \) follows a geometric decay, that is, \( R_a = \kappa \cdot R_1 \), where \( \kappa \) is the recirculation fraction, (\( \kappa < 1.0 \)). It follows that \( R_{a+1} = R_a \cdot \kappa_a \) and applying linear regression to the \( R_a \) versus \( R_{a+1} \) points yields the value for \( \kappa \).

Mechanical restitution curves were obtained from single test cycle data described above. Contractile force for each test beat was estimated using single beat \( E_{sv} \) (assuming constant \( V_o \), obtained from the ESPVR at the steady-state cycle length, 600 milliseconds). The test stimulus interval (TSI) was directly measured between successive QRS complexes, varying slightly from the atrial stimulation interval due to AV delay. \( E_{sv} \) of each TSI was normalized to the value at the basic pacing cycle length (600 milliseconds). The resulting data were fit to a monoeponential in the form

\[
E_{sv}(TSI)/E_{sv}(600) = CR_{max} [1 - e^{-(TSL/Tc)}]
\]

where \( TSL \) is the longest stimulus duration at which no mechanical force develops, \( Tc \) is the time constant of mechanical restitution, and \( CR_{max} \) is the relation plateau giving contractile potentiation at long cycle lengths.

**Validation of Single-Beat Contractility Analysis**

Potentiation and mechanical restitution analysis required single-beat estimates of contractility that were little influenced by simultaneous loading change. As used by Freeman and Colson, single-beat \( E_{sv} \) served this purpose. The approach is supported by the following: \( E_{sv} \) derived from multiple cycles during IVC inflow occlusion (\( E_{sv}[ESPVR] \)) was compared with that measured from single beats at the same heart rate assuming the same \( V_o \) (\( E_{sv}[SB] \)). The two values were nearly identical: \( E_{sv}[ESPVR] = 1.0 \cdot E_{sv}[SB] + 0.186 \) (\( r = 0.943 \), SEE = 0.057, \( P < 0.0001 \)). Second, 6 studies were performed in isolated blood-perfused canine ventricles comparing MRCs derived under isovolumic conditions ("gold standard") with those determined under physiological ejection. As shown by example in Fig 1, the results were nearly identical. Under isovolumic conditions, developed pressure (DP) indexed contractility at each cycle length (Fig 1A), whereas \( E_{sv} \) was used when hearts "ejected" into the computer-simulated vascular system (Fig 1, B and C). The two MRCs derived from many test beats are shown in panel D and were virtually superimposable. Similar results were obtained in all 6 experiments.
**Statistical Analysis**

All data in the text and tables are provided as mean±SD. Figure data are displayed as mean±SEM to assist visual display of multiple mean trends and differences between subject groups. The influence of heart rate on a given parameter was determined by repeated-measures ANOVA, with post hoc testing using Dunnett’s multiple comparisons test. Between-group comparisons of heart rate influences were determined by covariance analysis, with individual differences analyzed with Dunnett’s test. Statistical significance was accepted at the *P*<.05 level.

**Results**

**Baseline Hemodynamic Data: Control Versus Hypertrophy**

Table 2 provides rest hemodynamic data for control and hypertrophy groups. Significant disparities were present only in diastolic parameters. End-diastolic pressure was nearly double in LVH patients (*P*<.01) at similar diastolic volumes, and the time constant of isovolumic relaxation was prolonged by 32% at similar mean end-diastolic pressure, volume, and heart rate. Pressure-volume analysis revealed a reduced chamber compliance (3.2±0.7 vs 5.1±2.3 mL/mm Hg, *P*<.05) in LVH. In contrast to diastole, virtually all systolic function parameters were similar at baseline. The LVH group had a somewhat higher *Eα*, but this achieved borderline significance (*P*=.093). Other contractility measures such as the slope of the stroke work to *Vo* relation (*Mα*) and maximal power and dP/dtmax normalized to *Vo* were similar at baseline.

**Systolic Response to Incremental Pacing**

Fig 2 summarizes mean systolic responses to pacing, and Table 3 provides the ANOVA testing for effects of heart rate and patient group (control vs LVH) on the pacing response. Stroke volume fell similarly in both groups with pacing, although cardiac output (not displayed) was unchanged. Rate-dependent reductions in end-systolic pressure and increases in (dP/dtmax)/*Vo* were similar in both groups. Increased pacing rate lowered *Vα* in control subjects but not LVH subjects, and ejection fraction was slightly lower in LVH (*P*<.05 vs control subjects at fastest rate). Maximal ventricular power normalized to *Vo* also demonstrated a marked blunted response in LVH subjects, rising by 86.1% in control subjects versus 40.9% in LVH (*P*<.01).

The *Vα*, EF, and maximal power data suggested an abnormal contractile response to increased heart rate in LVH subjects. This was better defined by pressure-volume relation analysis. Fig 3 shows ESPVRs for...
TABLE 2. Baseline Hemodynamic Values in Control and LVH Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>LVH</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Diastolic</strong></td>
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<tr>
<td>End-diastolic pressure, mm Hg</td>
<td>12.3±4.9</td>
<td>20.2±6.2</td>
<td>&lt;.01</td>
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<tr>
<td>End-diastolic volume, mL</td>
<td>108.1±27.9</td>
<td>114.0±40.4</td>
<td>NS</td>
</tr>
<tr>
<td>Relaxation (τ), milliseconds</td>
<td>40.8±10.6</td>
<td>52.6±13.9</td>
<td>.05</td>
</tr>
<tr>
<td>Peak filling rate/V∞, sec⁻¹</td>
<td>3.6±0.6</td>
<td>3.6±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic compliance, mL/mm Hg</td>
<td>5.1±2.3</td>
<td>3.2±0.7</td>
<td>&lt;.05</td>
</tr>
<tr>
<td><strong>Hemodynamic</strong></td>
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</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>71.1±9.4</td>
<td>79.6±14.1</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>64.9±19.2</td>
<td>58.2±17.8</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.6±1.3</td>
<td>4.6±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Total resistance, mm Hg · mL⁻¹ · s⁻¹</td>
<td>1.9±0.6</td>
<td>2.2±1.0</td>
<td>NS</td>
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<tr>
<td>Arterial elastance, mm Hg/mL</td>
<td>2.3±0.7</td>
<td>2.9±1.4</td>
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<tr>
<td><strong>Systolic</strong></td>
<td></td>
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<tr>
<td>Ejection fraction, %</td>
<td>60.1±8.7</td>
<td>54.5±17.4</td>
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</tr>
<tr>
<td>End-systolic pressure, mm Hg</td>
<td>137.4±16.2</td>
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</tr>
<tr>
<td>End-systolic volume, mL</td>
<td>43.9±14.9</td>
<td>55.4±37.4</td>
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</tr>
<tr>
<td>(dP/dt max)/V∞, mm Hg · s⁻¹ · mL⁻¹</td>
<td>18.7±6.1</td>
<td>19.0±7.3</td>
<td>NS</td>
</tr>
<tr>
<td>Powermax/V∞, W/mL·100</td>
<td>6.3±1.0</td>
<td>6.4±1.5</td>
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</tr>
<tr>
<td>End-systolic elastance, mm Hg/mL</td>
<td>2.1±0.9</td>
<td>4.2±3.8</td>
<td>.09</td>
</tr>
<tr>
<td>Slope of SW-V∞ relation, mm Hg</td>
<td>81.8±10.4</td>
<td>99.1±28.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy.

*Multiple pressure-volume loops in example control (panels a through d) and LVH (panels e through h) subjects. The baseline systolic relations are reproduced in each subsequent panel. In the control subject, rapid pacing resulted in an increase in the slope of the ESPVR (ie, positive inotropic response), consistent

FIG 2. Influence of heart rate on systolic function parameters. Data are as displayed. From left to right starting at the top, panels are SV, stroke volume; P∞, end-systolic pressure; EF, ejection fraction; dP/dt∞/V∞, first derivative of left ventricular pressure/V∞; V∞, end-systolic volume; and PWRmax/V∞, maximal ventricular power divided by V∞. *Significant differences within groups at a given rate compared with baseline; #significant between-group differences. ANOVA results comparing groups are provided in Table 2.
with the normal rate treppe. In contrast, the LVH subject displayed a flattening of the relation and a rightward shift, indicating worsened contractile function with increased heart rate.

Group data for slopes of ESPVR (Ea) and SW−Ved (Maw) relations are displayed in Fig 4. Data are shown normalized to baseline. In the control group, both contractility indexes significantly rose during rapid pacing, reaching a maximal percent increase of between 79.4% for Ea and 20.1% for Maw (both P<.05). In contrast, the inotropic response to pacing was severely blunted in LVH subjects, with no significant increase in either contractility index (P>.01 vs control).

The indication from all ejection phase measurements (EF, Ea, Maw, and PWRmax/Ved) that the inotropic response to pacing was abnormal in LVH stood in contrast to the result for (dP/dt max)/Ved, an isovolumetric index. To determine if differences in vascular loading explained this disparity, we compared total arterial resistance and effective arterial elastance for the two groups. Neither differed at baseline (Table 2). Pacing did not significantly alter resistance at any of the heart rates, and while Ea increased near linearly with rate, this response was similar in both groups. For example, at peak pacing rate, Ea was 82.1% above baseline in control subjects versus 75.3% in LVH subjects (P=NS).

Thus, there were no significant disparities in arterial load.

**Relation Between Systolic and Diastolic Pacing-Induced Abnormalities**

Several of the proposed mechanisms for a blunted systolic response to heart rate in LVH closely link it to simultaneous worsening of diastolic properties. In general, deterioration is evidenced by a marked increase in end-diastolic pressure or stress. To test for such interdependence in the present study, diastolic parameters were also examined (Fig 5 and Table 3).

Incremental pacing shortened diastolic filling period; thus, end-diastolic volume (Ved) fell with increased heart rate. Interestingly, and somewhat unexpectedly, this reduction was similar in both patient groups, suggesting that despite LVH, net chamber filling was not differentially compromised, at least up to heart rates near 150. End-diastolic pressure was elevated at baseline in the LVH group, and it remained so at all heart rates (P<.05). However, it did not disproportionately rise in the LVH subjects at faster rates. Similar results were found for chamber compliance, which remained significantly lower at each heart rate in the LVH group but demonstrated no change with pacing rate in either group. The time constant of isovolumetric relaxation

### Table 3. Statistical Tests of Heart Rate Influence on Cardiac and Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>LVH</th>
<th>LVH Effect</th>
<th>Interaction</th>
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<tr>
<td><strong>Diastolic</strong></td>
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<tr>
<td>End-diastolic pressure</td>
<td>.001</td>
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<td>&lt;.001</td>
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<tr>
<td>End-diastolic volume</td>
<td>&lt;.001</td>
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<tr>
<td>Relaxation (τ)</td>
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<td>Diastolic compliance</td>
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<td>&lt;.01</td>
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<tr>
<td><strong>Hemodynamic</strong></td>
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<tr>
<td>Stroke volume</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Cardiac output</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Arterial resistance</td>
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<td>NS</td>
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<td>NS</td>
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<tr>
<td>Arterial elastance</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<td>NS</td>
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<tr>
<td><strong>Systolic</strong></td>
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<tr>
<td>Ejection fraction</td>
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<td>End-systolic volume</td>
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<td>NS</td>
<td>.01</td>
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<tr>
<td>(dP/dt max)/Ved</td>
<td>&lt;.05</td>
<td>&lt;.02</td>
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<td>PWRmax/Ved</td>
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<td>&lt;.05</td>
</tr>
<tr>
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<td>NS</td>
<td>.01*</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>SW−Ved relation slope (Maw)</td>
<td>&lt;.01</td>
<td>.064</td>
<td>&lt;.05*</td>
<td>&lt;.01*</td>
</tr>
</tbody>
</table>

Four sets of P values are provided. The first two columns give repeated-measures ANOVA results within each subject group. The last two columns provide multiple regression analysis results testing for an independent effect of left ventricular hypertrophy (LVH, patient group) on heart rate dependence for each parameter. This effect is expressed as an offset (ie, LVH alters mean value of parameter but not dependence on rate) and interaction effect (LVH alters heart rate dependence). Raw data are provided in Figs 3 and 6.

*Analysis performed on data normalized to initial baseline to reduce effect of intersubject variability.
Fig 3. Pressure-volume loops and relations in an example control (a-d) and left ventricular hypertrophy (LVH) (e-h) subject at baseline (a and e, respectively) and with incremental atrial pacing. The baseline end-systolic pressure-volume relation (ESPVR) is shown by the solid line and is reproduced in each subsequent panel at increasing heart rate. Respective heart rates for each panel are a, 70; b, 100; c, 130; d, 160; e, 70; f, 100; g, 120; and h, 150 min⁻¹. For the control (non-LVH) patient, the slope of the ESPVR increased with each increment in heart rate. In contrast, this slope fell at faster rates in the LVH subject. Diastolic pressure-volume relations (lower boundary) were generated from these same data using the end-diastolic portion of each pressure-volume loop measured during transient preload reduction. See text for details.
was prolonged in LVH patients at baseline but actually got shorter and closer to control values at faster rates. Thus, in the present LVH patients, the observed systolic depression could not be directly related to further worsening of diastolic function at faster pacing rates.

Postpacing Potentiation, Recirculation Fraction, and Mechanical Restitution

An alternative mechanism for the attenuated inotropic response to increased heart rate in LVH subjects relates to altered Ca\textsuperscript{2+} cycling. This was explored by means of individual-beat force-interval relations. Upon stopping pacing, the intercycle duration of the first potentiated beat averaged 927±229 milliseconds in control subjects and 1031±208 milliseconds in LVH subjects (P=NS). Despite a similar pause, LVH subjects potentiated more than controls (Table 4). For example, after cessation of pacing at a heart rate of 120 min\textsuperscript{-1}, E\textsubscript{es} rose by 11±23\% on the first postpaced beat (return to sinus rhythm) in control subjects, whereas in LVH patients, the increase was 40±31.5\% (P<.05). Similarly, stroke work increased immediately after pacing and was greater at near identical preloads in LVH subjects (10±5\% for control vs 37.6±34.5\% LVH, P=.052). This result is consistent with enhanced calcium loading in LVH hearts.

Although the magnitude of potentiation was somewhat larger in LVH, it declined more rapidly over ensuing beats compared with controls. Fig 6 displays an
TABLE 4. Potentiation After Termination of Pacing

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>LVH Subjects</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-systolic elastance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-1</td>
<td>+14.1±15.4</td>
<td>+19.6±20.5</td>
</tr>
<tr>
<td>HR-2</td>
<td>+11.0±23.3</td>
<td>+39.8±31.5*</td>
</tr>
<tr>
<td>HR-3</td>
<td>+11.2±21.0</td>
<td>+20.3±34.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke work</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-1</td>
<td>+10.0±4.9</td>
<td>+37.5±34.5</td>
</tr>
<tr>
<td>HR-2</td>
<td>+41.8±22.2</td>
<td>+111.6±101.5*</td>
</tr>
<tr>
<td>HR-3</td>
<td>+135.2±57.0</td>
<td>+160.1±88.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>End-diastolic volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-1</td>
<td>+6.0±6.8</td>
<td>+11.9±6.2</td>
</tr>
<tr>
<td>HR-2</td>
<td>+26.9±15.0</td>
<td>+28.7±14.8</td>
</tr>
<tr>
<td>HR-3</td>
<td>+59.6±29.9</td>
<td>+53.3±25.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data (percent change compared with baseline during pacing) are provided for each steady-state pacing rate for end-systolic elastance, stroke work, and end-diastolic volume. LVH indicates left ventricular hypertrophy; HR, heart rate.

*Significant change (P<.05) by multiple comparisons test.

An example of the data used to determine this decay. Upon termination pacing, dP/dt\textsubscript{max} (top panel) increased and then declined over successive beats in a geometric (monoeponential) manner. Plotting data for beat n+1 versus n yielded a linear plot, whose slope is the decay constant, or recirculation fraction (0.51, or 51% in this example). For the overall group (combining data after termination of each rapid heart rate), the mean recirculation fraction was 46.3±2.5% for control subjects versus 30.1±3.7% for LVH subjects (P=.001).

These results suggested that the portion of calcium recycled via the sarcoplasmic reticulum was reduced by LVH. At faster heart rates, this could contribute to a fall in available calcium and thus reduced contractile force.

Analysis of mechanical restitution curves from both patient groups are provided in Table 4 and Fig 7. Relations for each patient comprised an average of 21±3 different test cycles, with the test stimulus spanning 400±54 to 930±170 milliseconds. Shorter cycle lengths were prevented by atrioventricular nodal blockade and longer lengths by spontaneous sinus activation. There was virtually no difference in the MRCs obtained from the control or LVH subjects. Furthermore, as previously reported in intact dogs,33 both sets of data demonstrated a rapid restitution time constant (T\textsubscript{2}) of 104.6±14.2 milliseconds in the control subjects and 116.2±16.4 milliseconds in LVH subjects (P=NS). This is more than twice as fast as observed in isolated whole canine hearts33 and as much as 6 to 10 times as fast as that of isolated muscle.33,34 This suggests that Ca\textsuperscript{2+} recycling is fast in both groups and is a less likely candidate to underlie the disparate contractile response to pacing.

**Discussion**

The primary goal of this study was to test whether the inotropic response to increased heart rate is blunted in...
intact human subjects with clinically significant LVH. The results from ejection phase indexes based on steady-state or multiple-beat pressure-volume relation analysis support this hypothesis. This finding is consistent with several prior experimental results. For example, in canine hypertrophy, systolic pressure and extent and velocity of shortening are reduced during pacing, suggesting a systolic decrement. In these canine LVH model studies, this decline is usually noted at very fast rates (>200 min⁻¹). This contrasts to the slower rate range (60 to 140 min⁻¹) over which the normal canine ventricle displays a positive inotropic response. In the present study, the LVH force-frequency response was diminished even at such slower heart rates, whereas in control subjects, a positive inotropic response was observed. This suggests that the phenomenon has clinical relevance, as these are heart rates typically achieved during exertion.

It is intriguing that all ejection phase contractile indexes demonstrated an abnormal response to pacing in the LVH patients, whereas this was not true of the isovolumetric index (dP/dt max)/V ed. As noted earlier, there were no significant differences in arterial loads between LVH and control subjects at each rate; thus, ejection load did not explain the disparity. It is also unlikely that this represents an artifact of simple versus more complex (pressure-volume relation-derived) hemodynamic analysis. There was consistency for all ejection phase measures despite their varying derivations. Furthermore, PWR max/V ed and ejection fraction were measured at steady state, like (dP/dt max)/V ed, yet they too demonstrated a blunted rate response. Additional support derives from a canine study of LVH in which velocity and extent of shortening were reduced at fast heart rates, whereas dP/dt max increased identical to controls.

An alternative explanation for this disparity is that it reflects fundamental differences in ejection-dependent aspects of contraction in LVH. This could be in the form of enhanced shortening deactivation or a greater internal ventricular resistance in LVH hearts. In some species, hypertrophied hearts undergo a myosin isoenzyme shift favoring slower actin-myosin interaction and sustained force development. While this exact biochemical alteration does not occur in humans, similar kinetic changes have been observed. Slowing of cross-bridge cycling kinetics could inhibit force generation when shortening must be achieved rapidly.

Additional mechanisms for a blunted systolic response to rapid pacing in human LVH include inadequate myocardial perfusion, a dependence upon worsened diastolic function, and alterations of calcium handling. Although the global nature of the present data precludes a precise examination of these mechanisms, the results do lend support to some over others.

Reduced myocardial flow caused by markedly elevated diastolic pressures and/or reduced coronary flow reserve could result in myocardial ischemia at fast rates. Arguing against this mechanism in the present data is the lack of simultaneous diastolic deterioration and the shortening of isovolumic relaxation. Diastolic abnormalities have been reported to precede systolic ones with pacing-induced ischemia. Furthermore, cardiodepression was not sustained after terminating pacing; rather, potentiation increased at the more rapid rates and then declined to the same steady state. These are admittedly indirect arguments, and they do not exclude a role for ischemia.

In many LVH pacing studies, systolic and diastolic deterioration occur simultaneously. For example, Fujii et al reported a near sixfold rise in end-diastolic wall stress at very rapid pacing rates (270 min⁻¹ in the dog) simultaneously with a significant decline in fractional shortening and systolic pressure. Recently, Gwathmey et al reported in isolated hypertrophied muscle strips that increasing the stimulation frequency resulted in a decline of developed pressure primarily caused by a rise in diastolic tension. The latter correlated with an increase in measured intracellular calcium, and the authors raised the possibility that calcium overload with LVH at rapid pacing rates simultaneously led to systolic and diastolic dysfunction. Similar simultaneous increases in systolic and diastolic calcium levels with pacing were not found in a recent study performed in isolated hypertrophied myocytes.

The present data question the notion that diastolic deterioration is required to observe diminished systolic function in hypertrophied hearts during pacing. Significant diastolic abnormalities existed at baseline; however, there was no significant further decline in diastolic function with pacing. In fact, relaxation time, which was prolonged at rest, shortened progressively more in the LVH subjects than in control subjects. In neither group did it ever achieve a duration at which incomplete relaxation would be anticipated. Interestingly, similar shortening of relaxation time has been reported in subjects with dilated cardiomyopathy during pacing and recently in isolated muscle strips from hypertrophied human hearts.

In a prior pacing study of human hypertrophic cardiomyopathy, Cannon et al reported a large rise in PE (>100% from a baseline of 13 mm Hg) at rates similar to the present investigation (maximum near 150 min⁻¹). These authors also demonstrated reduced coronary flow reserve at the maximal pacing rate and speculated that reduced chamber compliance from ischemia resulted in the elevated PE. Perhaps importantly, the
subjects of their study were younger, had asymmetric hypertrophy, and presented with chest pain as the dominant symptom. Typical pain was elicited in 90% of their subjects during rapid pacing. In contrast, subjects in the present study were older, had mostly eccentric hypertrophy, and primarily presented with dyspnea and pulmonary edema. None of the subjects developed chest pain or ECG changes during pacing. These differences suggest that the interdependence between systolic and diastolic dysfunction during pacing in LVH may vary, depending on the form and clinical presentation of the disease. There are clearly situations where the existence of both are strongly temporally correlated. However, as the present data demonstrate, this is not always the case.

Reduction of systolic force could stem from abnormalities of Ca\textsuperscript{2+} transients and cycling. In isolated hypertrophied myocytes, peak calcium transients are reduced at faster stimulation rates. Abnormalities of calcium handling are also suggested by enhanced extracellular calcium potentiation and a more rapid decay of potentiation in hypertrophied compared with normal muscle. The former behavior has been ascribed to a net increase in inward Ca\textsuperscript{2+} current and the latter to reduced sarcoplasmic reticular Ca\textsuperscript{2+} reuptake. Both could reduce systolic force generation at fast heart rates. The present data are consistent with several of these prior results, and, to our knowledge, represent the first demonstration of such phenomena in intact humans with LVH. Seed et al.\textsuperscript{30} reported recirculation fractions of 52% in normal subjects and 37% in subjects with dilated cardiomyopathy of various etiologies. This is strikingly similar to the results of the present investigation and may in part reflect the presence of congestive failure symptoms in many of the subjects.

Although these data are consistent with a role for altered Ca\textsuperscript{2+} handling toward systolic depression, they seem at odds with the finding that P\textsubscript{dp} did not significantly rise and that relaxation time constant significantly increased during rapid pacing in LVH subjects. However, P\textsubscript{dp} is critically influenced by passive as well as active chamber properties. These stem from collagen content, interstitial fibrosis, and fiber architecture.\textsuperscript{11,12} Changes in these factors with LVH may overwhelm changes caused by Ca\textsuperscript{2+} cycling abnormalities.\textsuperscript{52} Likewise, pressure decay is influenced by factors other than calcium reuptake such as passive elastic recoil and systolic loading. These factors might counter others related to active calcium cycling.

In addition to potentiation and potentiation decay, calcium handling is frequently assessed by the phenomenon of mechanical restitution. This monoeponential relation links the variation of contractile response of a single test beat to its preceding cycle length. Its time constant (T\textsubscript{c}) is thought to provide a measure of the time required for complete Ca\textsuperscript{2+} cycling, stemming mostly from the restitution time of the SR-Ca\textsuperscript{2+} release channel.\textsuperscript{53} It is near 250 milliseconds in blood-perfused isolated dog hearts\textsuperscript{52} and 700 milliseconds in isolated muscles.\textsuperscript{24} However, in intact dogs, Freeman andolson\textsuperscript{23} recently reported that T\textsubscript{c} was 64 milliseconds, close to the 100 milliseconds we found in both patient groups. This suggests that intactness of the preparation can have a profound influence on rates of Ca\textsuperscript{2+} cycling. The short time constant found in both patient groups suggests that only at heart rates faster than 400 milliseconds (150 min\textsuperscript{-1}) would one expect a decline in contractile force caused by inadequate diastolic time for full mechanical restitution. It is thus less likely to have explained the disparity between LVH and control responses.

### Study Limitations

Mechanics data are presented as chamber indexes (pressure-volume) rather than as estimated myocardial indexes (ie, stiffness or stress-strain). This was done because the echocardiographic data required to provide meaningful mass and wall geometry measurements were of inconsistent quality to provide precise numbers and were not obtained during preload reduction transients. However, since the study focused on relative changes within a given subject and wall mass and overall geometry were not acutely altered, the findings probably parallel those that would be obtained based on stress-strain calculations.

Left ventricular hypertrophy is recognized to be a heterogeneous disorder. The present study results are based on 10 patients, and while they all had substantial wall thickening, they no doubt represent a limited and mixed spectrum of disease. As noted above, there are some important differences between the present study subjects and those of prior human and animal model studies. For one, the present subjects were older and most presented with exertional or rest dyspnea and pulmonary congestion. Their pacing response may differ from younger subjects with genetic and asymmetric LVH. While several had a history of hypertension, there was no significant difference in arterial pressures between LVH and control subjects for the study. This is potentially an important difference when comparing these results with those from animal models using aortic banding, in which the baseline left ventricular pressures are often nearly twice those in the control group.\textsuperscript{14,19} Such marked pressure differences may contribute to worsened diastolic properties.\textsuperscript{54}

There are limitations to the volume catheter method for volume assessment that should be considered. Although prior studies have shown good linear correla-

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**TABLE 5. Mechanical Restitution Curves for Control and LVH Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Time Constant (T\textsubscript{c}), milliseconds</th>
<th>Plateau (C\textsubscript{m}),</th>
<th>Intercept (T\textsubscript{0}), milliseconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>116.2±16.4</td>
<td>1.04±0.016</td>
<td>266.1±19.6</td>
</tr>
<tr>
<td>LVH</td>
<td>104.5±14.2</td>
<td>1.06±0.013</td>
<td>266.6±16.8</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy. Data are fit to a three-parameter monoeponential (see "Methods"). There are no significant differences between the parameters estimated from control vs LVH relations.
tions between conductance catheter signals and other measures.55–57 There are concerns about potential non-linearity to the signal.56,57 However, this limitation was unlikely to have significantly influenced the results. First, identical methods were used over similar volume ranges in both subject groups; thus, calibration errors would not underlie consistent disparities. Second, multiple measures of chamber systolic and diastolic performance were used, some dependent and others independent of volume signal calibration. For example, neither $M_e$ or $PWR_{mm}/V_{cd}$ are dependent on either catheter calibration gain or offset (they have units of mm Hg and mm Hg/s, respectively), yet their results were analogous to $E_m$, which is volume dependent. Much of the pacing analysis compared each subject’s response with their respective baseline, further reducing the effects of calibration error.

**Conclusions**

The principal new findings of the present investigation are that in subjects with significant symptomatic LVH, systolic contractile response to physiological heart rate increase is markedly diminished. Furthermore, this systolic deterioration does not necessarily require simultaneous worsening of diastolic abnormalities, specifically elevations in diastolic pressure or further decline in relaxation or compliance. Analysis of force-interval relations suggests that abnormalities in calcium entry and reuptake probably contribute to the observed pacing-induced systolic dysfunction. In contrast, slowing of mechanical restitution (overall calcium cycling time) does not appear to play a major role.

Loss of a rate-dependent systolic reserve in human LVH suggests an additional mechanism beyond gradient reduction and improved filling whereby rate control by β-blocker therapy would be efficacious. Future studies with this and other therapies, such as calcium channel blockade and chronic AV sequential pacing, will be needed to determine if this abnormality can indeed be improved.

**Acknowledgments**

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