**β-Adrenergic Stimulation With Isoproterenol Enhances Left Ventricular Diastolic Performance in Hypertrophic Cardiomyopathy Despite Potentiation of Myocardial Ischemia**

**Comparison to Rapid Atrial Pacing**

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Impaired left ventricular relaxation and filling is an important pathophysiologic mechanism in hypertrophic cardiomyopathy. To determine whether isoproterenol, known to improve relaxation in isolated cardiac muscle, could favorably modify this effect, we assessed simultaneous left ventricular volume and regional systolic asynchrony (by radionuclide angiography), left ventricular pressure (by micromanometer catheters), and lactate metabolism in 12 patients with hypertrophic cardiomyopathy. Pressure-volume relations were studied during atrial pacing stress to induce myocardial ischemia and during isoproterenol infusion to similar heart rates. Angina occurred in 10 patients with pacing and in 11 patients during isoproterenol infusion; lactate consumption was reduced in nine patients during isoproterenol compared with pacing, including five patients who produced lactate with isoproterenol. During isoproterenol compared with pacing, peak left ventricular pressure was higher (205±33 vs. 142±21 mm Hg, p < 0.001), ejection fraction was higher (77±10% vs. 71±12%, p < 0.02), and regional systolic nonuniformity was diminished. Despite ischemia, these changes in load and nonuniformity during isoproterenol were associated with enhanced diastolic function compared with pacing tachycardia: isoproterenol reduced T1/2, the halftime of pressure decline after peak negative dP/dt (from 46±10 to 33±6 msec, p < 0.001), shifted the diastolic pressure-volume curve downward and rightward in 10 of 12 patients, and increased end-diastolic volume (from 77±18% to 100±11% of control values, p < 0.001) with no change in end-diastolic pressure (19±7 to 19±5 mm Hg, p = NS). Thus, despite ischemia, isoproterenol improved left ventricular relaxation and filling compared with tachycardia in the absence of β-adrenergic stimulation. Although isoproterenol is detrimental in hypertrophic cardiomyopathy by provoking ischemia, these data suggest that the adverse effects of ischemia on ventricular relaxation and distensibility may be alleviated by β-adrenergic stimulation, possibly as a result of enhanced inactivation and restored load sensitivity. (*Circulation* 1989;79:371–382)

Myocardial ischemia has been shown in the intact heart to impair left ventricular relaxation.1–4 Proposed mechanisms for this effect include reduced calcium ion sequestration by the sarcoplasmic reticulum, leading to delayed inactivation and insensitivity to loading conditions, and increased regional nonuniformity,5 both of which are likely to occur concurrently in human heart disease. Importantly, abnormalities in both relaxation and filling may occur early in the ischemic process and can be identified before the onset of systolic dysfunction.1,6,7 These mechanisms may be operative not only in patients with coronary artery disease but also in those with hypertrophic cardiomyopathy (HCM), a disease in which myocardial ischemia6–10 and alterations in left ventricular relaxation and filling11–16 play prom-

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inent and interrelated pathophysiologic roles. Clinically, these factors contribute to increased left ventricular stiffness, elevated left ventricular and left atrial pressures, and the development of symptoms such as dyspnea.

In this study, we sought to determine whether the adverse effects of ischemia on left ventricular relaxation and filling in HCM may be favorably modified by the pharmacologic influence of β-adrenergic stimulation. In isolated cardiac muscle, the β-agonist isoproterenol enhances relaxation even in the absence of a positive effect on contractility; in the intact preparation, it reduces the time constant describing left ventricular pressure fall during isovolumic relaxation. We therefore hypothesized that isoproterenol, which has possible detrimental effects in HCM (by increasing contractility, augmenting myocardial oxygen demand and aggravating ischemia), might also have favorable effects by facilitating left ventricular relaxation and filling on the basis of altered loading conditions, changes in nonuniformity, or acceleration of the inactivation process.

Methods

Patient Selection

We studied 12 patients with the clinical and echocardiographic diagnosis of HCM, defined as a hypertrophy, nondilated left ventricle in the absence of an identifiable cardiac or systemic stimulus to hypertrophy. There were nine men and three women, ranging in age from 23 to 62 years (mean, 38 years). All patients were symptomatic with either dyspnea or angina and had been treated with either β-blocking or calcium channel blocking drugs (or both) without satisfactory improvement in symptoms. Catheterization studies were undertaken to determine the presence and magnitude of resting or provokable left ventricular outflow tract obstruction to determine the patient’s suitability for operation. All patients gave informed consent for participation in the study protocol. Medications were discontinued for at least 48 hours before catheterization.

Cardiac Catheterization and Hemodynamic Measurements

The methods in this study were similar to those previously reported in our laboratory. After sedation with 10 mg diazepam administered orally, patients were taken to the catheterization laboratory, usually at 8:00 AM, in the fasting state and without any other premedication. A thermoludation catheter (Elecath Corp) was introduced into the right atrium percutaneously via the right internal jugular vein. The great cardiac vein, which is the recipient of blood from the left anterior descending arterial system, was cannulated via the coronary sinus. The thermoludation technique for determining great cardiac vein flow has been described previously. This method of coronary flow measurement was chosen for two reasons. First, in our experience, the catheter advanced into the great cardiac vein is stable in position with minimal or no movement even during pacing, and reproducible flow measurements may be achieved at rest and during pacing. Second, measurements of anterior circulation venous flow might allow estimation of coronary flow and myocardial metabolism in that portion of the ventricle most diseased in the majority of patients with HCM (i.e., the anterior septum and free wall). Position of the thermoludation catheter in the great cardiac vein was verified initially by small injections of contrast material and kept constant throughout the study by frequent inspection of the relation of the pacing electrodes on the catheter to bony landmarks via fluoroscopy.

A 20-g catheter was placed in the left brachial artery for arterial pressure measurements. An 8F end-hole pigtail catheter equipped with two pressure transducers 10 cm apart (Millar Instruments, Houston, Texas) was advanced to the apex of the left ventricle, such that the transducers sampled pressure simultaneously in the left ventricular cavity and in the proximal ascending aorta. Frequent inspection of the position of the catheter by fluoroscopy and of simultaneous left ventricular pressure and aortic waveform before and during interventions confirmed stable position of the catheter tip in the body of the ventricle. There was no evidence of catheter entrapment in any patient under control conditions or during pacing and isoproterenol interventions. Cardiac output was measured with a balloon-tipped thermodilution catheter in the pulmonary artery. Arterial and left ventricular pressures and electrocardiographic monitor leads I, aV_{RF}, and V_{S} were recorded with each coronary flow measurement. Lactate samples were obtained from the great cardiac vein and collected in tubes containing sodium fluoride and potassium oxalate for inhibition of glycolysis. Samples were immediately centrifuged at 4°C at 5,000 rpm for 5 minutes. The decanted serum was then processed for lactate content on a Du Pont automatic clinical analyzer (Wilmington, Delaware) by a modification of the technique of Marbach and Weil. Lactate consumption was calculated as the great cardiac vein flow multiplied by the difference between the arterial and great cardiac vein lactate concentrations.

Pacing coronary flow study. Before the pacing study, all patients underwent diagnostic right and left heart catheterization. Contrast ventriculography and coronary angiography with multiple angulated views were then performed. All patients had normal coronary arteries (interpreted independently by two experienced observers), as was required for entry into the study.

The study protocol was initiated at least 20 minutes after use of angiographic contrast material so that any effects of the dye on coronary blood flow and metabolism would subside. Great cardiac vein flow, lactate, and oxygen content were determined...
at rest, as were measurements of cardiac output and left ventricular peak systolic and end-diastolic pressure. Pacing via the coronary sinus thermodilution catheter was initiated at a heart rate of 100 beats/min and maintained for 3 minutes, followed by pacing at 130 beats/min for 3 minutes (except for one patient who was paced at 120 beats/min). Hemodynamic measurements and measurements of coronary flow, lactate, and oxygen content were repeated for each intervention.

**Isoproterenol study.** After a 10-minute pause to allow baseline conditions to be reestablished, isoproterenol was infused beginning at a rate of 1 µg/min and increasing by increments of 1 µg/min at 1-minute intervals to achieve a heart rate of 100 beats/min and maintained for 3 minutes. The infusion was then increased to achieve a heart rate of 130 beats/min for 3 minutes (10 patients). The patient paced to 120 beats/min was stimulated to this heart rate during isoproterenol. One patient was not stimulated beyond 100 beats/min as an extreme outflow gradient (164 mm Hg) developed with isoproterenol infusion at this lower heart rate. In one of the 10 patients stimulated to a heart rate of 130 beats/min, technical problems precluded data acquisition at 130 beats/min. Hemodynamic data, coronary flow, and metabolic measurements were obtained at each level.

**Radionuclide Angiographic Studies**

During placement of the right heart catheter, red blood cells were labeled in vivo with 15–25 mCi technetium-99m. Ten minutes after the radionuclide administration, the patient underwent anticoagulation with heparin (5,000 units i.v.), and retrograde left heart catheterization was begun. After equilibration of the blood pool tracer and placement of catheters in the pulmonary artery and left ventricle, a portable gamma camera equipped with a high-sensitivity parallel hole collimator was positioned over the left thorax in a modified left anterior oblique position for optimal separation of the left from the right ventricle. Electrocardiographic (ECG)-gated equilibrium scintillation data were collected in LIST mode to a preset count limit of 10 million counts for the baseline study and to a preset time comprising the middle 2 minutes of each 3-minute intervention (atrial pacing or isoproterenol). High temporal resolution (20 msec/frame) left ventricular time-activity curves were generated from the cardiac image sequence after background correction and exclusion of extrasystolic and postextrasystolic cycles. The time activity curve represents a measure of relative left ventricular volume changes during the cardiac cycle. End-diastolic counts, endsystolic counts, stroke counts, and ejection fraction were computed for each study after correction for physical decay of the isotope. Changes in end-diastolic, end-systolic, and stroke counts for each intervention were expressed as a percentage of control counts to indicate relative changes in left ventricular volumes to compare directional changes in each patient relative to the control values. Regurgitant volume across the mitral valve was quantitated from the thermodilution stroke volume and the radionuclide stroke volume ratio of the left and right ventricles.

**Regional analysis.** In addition to these indexes describing global left ventricular function, we also analyzed relative regional left ventricular asynchrony by sector analysis. The left ventricular region of interest was divided into 20 sectors of equal arc (18°), each emanating from the end-diastolic left ventricular center of gravity. The inner one third of each sector was then excluded, yielding anular sectors constituting the outer two thirds of the left ventricle. From these fixed regions, sectorial time-activity curves were generated, representing the change in counts within each sector during the average cardiac cycle. From these data, we computed an index of regional systolic asynchrony. Each sector time-activity curve was fit to a two harmonic Fourier expansion. The nadir of this curve was used to approximate the time to minimal volume (measured from the R wave) of each sector. The regional variation in time to minimal volume among sectors was assessed quantitatively as the SD about the mean for the 20 sectors.

**Left Ventricular Pressure-Volume Analysis**

Analysis of the left ventricular pressure-volume relation throughout the entire cardiac cycle was performed in all patients. The left ventricular pressure data were obtained via the transducer-tipped catheter simultaneously with the radionuclide data acquisition. The left ventricular pressure data were collected with LIST mode electrocardiographic gating, with subsequent exclusion of extrasystolic and postextrasystolic cardiac cycles, such that the average left ventricular pressure-time curve was constructed from the same cardiac cycles used to create the radionuclide angiographic time-activity curve. The pressure data were obtained at an acquisition rate of 250/sec (4 msec/point) and were then condensed to 20 msec/point to correspond to the radionuclide data. The resulting pressure curve and the left ventricular time-activity curve were then combined automatically to create loops representing high temporal resolution (20 msec) instantaneous relations between left ventricular pressure and relative volume throughout an average cardiac cycle. Relative pressure-volume stroke work, represented by the area enclosed by the pressure-volume loop, was determined by planimetry as an estimate of relative myocardial demand. These areas were measured in triplicate and then averaged.

**Left ventricular pressure analysis.** For investigation of left ventricular isovolumic relaxation, the high temporal resolution left ventricular pressure data (4 msec/point) were analyzed. A time constant \( T_{1/2} \) was computed for each acquisition as the time required for the pressure at the time of peak nega-
were the residuals of the residuals distributed about the first ventricular curve. The time occurrence, minimum diastolic to time the chose not to yield a monoexponential function with nonzero asymptote. Panel C: Plot of residuals of the curve fit. Despite a high correlation coefficient, the residuals of the fit are not randomly distributed about the fitted curve.

tive dP/dt to decline to one half of its value at peak negative dP/dt. This method was used according to the recommendation of Mirsky for analysis of the time course of pressure fall in ventricles in which the decline of pressure may be nonexponential due to spatial and temporal heterogeneity of relaxation and filling, as is the case in HCM. Attempts to fit the pressure decline with a monoexponential function yielded residuals reflecting the differences between the observed data and the fitted curve that were consistently nonrandom (Figure 1). Thus, we chose not to use an exponential curve fitting model. Time to peak negative dP/dt was determined from the beginning of the R wave gating sequence. The minimum diastolic pressure and the time of its occurrence, as well as end-diastolic pressure, were also taken directly from the digitized pressure-time curve. The time of aortic valve closure was estimated as the time of occurrence of the incisura of the proximal aorta pressure waveform, which was also collected from the pressure transducer catheter as a physiologic input signal with LIST mode electrocardiographic gating and processed as described for the left ventricular pressure data. The peak left ventricular outflow tract gradient was determined from the left ventricular and proximal aortic pressure curves.

Statistical Analysis
Statistical significance of the mean values for the hemodynamic and radionuclide variables were analyzed by the paired t test or, where appropriate for comparison of two interventions with baseline values, by a repeated measures analysis of variance. Group means were considered significantly different at p < 0.05.

Results

Measurements in the Basal State
Hemodynamic, coronary flow, and metabolic data recorded in the basal state are shown in Tables 1, 2, and 3. Basal heart rates ranged from 51 to 94 beats/min (mean ± SD, 76 ± 12 beats/min). Because of the presence of resting left ventricular outflow tract gradients in 11 patients, left ventricular peak systolic pressures were elevated in many patients and ranged from 123 to 204 mm Hg. Ejection fractions (as determined by the radionuclide angiographic data) ranged from 55% to 93% (Table 1); in six patients, ejection fraction was above the upper limit of normal (72%) for our laboratory, as was the mean ejection fraction for the group (75%). Left ventricular minimum diastolic pressure ranged from 4 to 14 mm Hg (mean, 8 ± 3 mm Hg), with left ventricular end-diastolic pressure ranging from 12 to 20 mm Hg (mean, 17 ± 2 mm Hg); the left ventricular end-diastolic pressure was 15 mm Hg or greater in 11 of the 12 patients. Resting coronary sinus flow (measured by thermodilution) ranged from 43 to 107 ml/min, and the product of coronary sinus flow and the arterial-venous lactate difference yielded values for basal lactate consumption of 8–75 mM·ml/m.

Effects of Atrial Pacing
Studies chosen for analysis were those with the highest paced heart rate for which a corresponding isoproterenol study at matched heart rate was performed. The mean paced heart rate for the group was 123 ± 12 beats/min. Coronary sinus flow (measured in 11 patients) increased to 139 ± 47 ml/min (p < 0.001 vs. basal flow). Lactate consumption decreased in six patients (one patient produced lactate) and increased in five patients (Table 1). In the six patients with decreased lactate consumption during pacing, coronary flow increased by an average of 49%, whereas in the four patients with increased lactate consumption, flow increased by...
### Table 1. Effect of Interventions on Left Ventricular Systolic Performance

<table>
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<th>Patient</th>
<th>Heart rate (beats/min)</th>
<th>Peak systolic LV pressure (mm Hg)</th>
<th>LV ejection fraction (%)</th>
<th>End-systolic volume (% baseline)</th>
<th>Regional LV asynchrony* (msec)</th>
<th>Regurgitant volume (ml)</th>
<th>Pressure-volume stroke work (% baseline)</th>
<th>LV outflow tract gradient (mm Hg)</th>
<th>Cardiac output (l/min)</th>
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Mean 76 123 118 162 142 205 75 71 77 107 88 16 11 91 73 111 59 131 56 39 106 5.0 5.5 7.3 68 45 62

Mean SD 12 12 13 24 21 33 13 12 10 55 30 7 6 41 47 59 18 25 32 25 34 1.0 1.6 1.9 21 16 15

\( p < 0.001 \) NS \(< 0.05 \) \(< 0.001 \) NS \(< 0.02 \) NS \(< 0.02 \) NS \(< 0.001 \) NS \(< 0.001 \) NS \(< 0.001 \) NS \(< 0.001 \)

B, baseline; P, atrial pacing; I, isoproterenol infusion; LV, left ventricular.

*Regional asynchrony assessed as the regional variation in time to minimum volume among 20 sectors.

139%. Chest pain compatible with myocardial ischemia occurred in 10 of 12 patients during pacing.

**Effect of pacing on systolic performance.** Peak systolic left ventricular pressure decreased during atrial pacing from the mean basal value of 162±24 to 142±21 mm Hg (\( p<0.005 \)). Although ejection fraction decreased in eight patients, there was no significant change in the group ejection fraction compared to baseline values (Table 1). End-diastolic counts decreased in 11 of 12 patients (\( p<0.001 \)), reflecting reduced end-diastolic volume at reduced cycle length. Hence, stroke volume and stroke volume index decreased (\( p<0.001 \)), but cardiac output and index did not change significantly from baseline. End-systolic counts decreased in five patients and increased in seven patients compared with baseline, such that the mean change during pacing was not significantly different from baseline.

**Effect of pacing on diastolic performance.** During pacing, minimum left ventricular diastolic pressure increased in nine patients, resulting in an increase in the mean value to 14±7 mm Hg (\( p<0.01 \)). Although end-diastolic pressure increased in seven patients (despite lower end-diastolic volume), the group mean was not significantly different from baseline values. There was no relation between changes in lactate consumption from baseline to pacing and changes in minimum or end-diastolic pressure; the six patients with decreased lactate consumption during pacing had the same change in minimum and end-diastolic pressure as did the four patients with increased lactate consumption. The diastolic pressure-volume relation shifted upward in 10 patients during pacing (Figures 2 and 3), and a pattern of impaired relaxation (i.e., a continuing decline of pressure through late diastole\(^{37,38}\)) was observed in seven patients (Figures 3 and 4).

**Effects of Isoproterenol**

During isoproterenol infusion, the mean heart rate was 118±13 beats/min, similar to that of pacing. The changes in coronary sinus flow were quite variable; although the mean value was greater than that observed under basal conditions, it was not significantly different from that during pacing. Chest pain occurred in 11 of 12 patients. Changes in myocardial lactate consumption reached borderline statistical significance (\( p=0.05 \)). However, compared with the pacing study, lactate consumption decreased in nine of 11 patients during isoproterenol, with five patients producing lactate (Table 3). In two patients who did not produce lactate, the reduction in lactate consumption was accompanied by a decrease in coronary flow despite an increase in stroke work. Thus, at least seven patients appeared to have more intense ischemia during isoproterenol than during pacing.

**Effect of isoproterenol on systolic performance.** The left ventricular peak systolic pressure increased in all patients (Table 1), related to an increase in the left ventricular outflow tract gradient (from 56±32 to 106±34 mm Hg, \( p<0.001 \)), a dynamic process.
to 301 ± 46 msec from the onset of R wave gating, p < 0.005), and the minimum diastolic pressure
substantially affected by increased contractility.39–41

TABLE 2. Effect of Interventions on Left Ventricular Diastolic Performance

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<th>Peak negative dP/dt (mm Hg/sec)</th>
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p < 0.001 < 0.05 < 0.005 < 0.001 < 0.05 < 0.001 < 0.02 < 0.001
B, baseline; I, isoproterenol infusion; LV, left ventricular; MDP, minimum diastolic pressure; P, pacing; PSP, peak systolic pressure; T1/2, time required for pressure at peak negative dP/dt to decrease to one half its value.

TABLE 3. Effect of Interventions on Coronary Flow, Lactate Metabolism, and Symptoms

<table>
<thead>
<tr>
<th>Patient</th>
<th>Coronary flow (ml/min)</th>
<th>Lactate consumption (mm · ml/min)</th>
<th>Chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>P</td>
<td>I</td>
</tr>
<tr>
<td>1</td>
<td>61</td>
<td>66</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>121</td>
<td>158</td>
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<td>3</td>
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<td>5</td>
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<tr>
<td>12</td>
<td>86</td>
<td>135</td>
<td>247</td>
</tr>
</tbody>
</table>

Mean 80 130 151 32 33 10
SD 22 17 41 24 48 47
p < 0.001 NS NS 0.05

B, baseline; P, atrial pacing; I, isoproterenol infusion.

*Data obtained at pacing rate of 130.
decreased (from 14±7 to 9±7 mm Hg, \( p < 0.005 \)) to a value not significantly different from baseline. In addition, the average rate of pressure decline, measured either from peak systolic pressure or from peak negative dP/dt, was significantly enhanced by isoproterenol. Peak negative dP/dt during isoproterenol, but not other indexes of relaxation, correlated significantly with peak systolic pressure \( (r=0.77, \ p < 0.005) \) and the magnitude of the outflow gradient \( (r=0.60, \ p < 0.05) \).

A beneficial effect on diastolic pressure-volume relations was evident during isoproterenol, with an increase in end-diastolic volume in 11 of the 12 patients \( (p < 0.001) \), whereas end-diastolic pressure was not different between pacing and isoproterenol-induced tachycardia. Isoproterenol also produced a downward and rightward shift in the diastolic pressure-volume relation in 10 patients compared with the pacing data (Figures 2 and 3). In all 10 of these patients, chest pain consistent with ischemia was present during both interventions. In six of these patients, either lactate was produced during isoproterenol (four patients) or lactate consumption decreased concomitantly with increased oxygen demand (increased relative stroke work) and decreased coronary flow (two patients) indicating more severe myocardial ischemia during isoproterenol. Qualitatively, all seven of the abnormal diastolic pressure-time waveforms obtained during pacing were improved. Two examples of this effect are shown in Figure 4.

Data were analyzed separately for the seven patients with more intense ischemia during isoproterenol compared with pacing (either lactate production or a decrease in lactate consumption with increased oxygen demand and decreased coronary flow). In these patients, similar improvement was observed during isoproterenol compared to pacing in \( T_{1/2} \) (33±7 vs. 50±10 msec, \( p < 0.001 \)), time to peak negative dP/dt (286±42 vs. 315±57 msec, \( p < 0.04 \)), minimum diastolic pressure (11±3 vs. 16±7 mm Hg, \( p < 0.05 \)), and the average rate of pressure decline, measured either from peak systolic pressure to minimum pressure (820±380 vs. 437±110 mm Hg/sec, \( p < 0.03 \)) or from peak negative dP/dt to minimum pressure (590±89 vs. 477±103 mm Hg/sec, \( p < 0.04 \)). These patients also achieved higher end-diastolic volumes with isoproterenol than during pacing (97±11% vs. 71±19% of control, \( p < 0.006 \)) with unchanged end-diastolic pressure. The data presented in Figures 2 and 3 were obtained in four of these seven patients.
Discussion

In this study, we assessed the effect of the pure \( \beta \)-adrenergic agonist isoproterenol on indexes of diastolic performance in HCM, a disease in which abnormalities of relaxation and filling play prominent pathophysiologic roles, contributing to the genesis of symptoms such as dyspnea, angina, and fatigue. Previous studies involving both isolated cardiac muscle and the intact heart demonstrating that \( \beta \)-adrenergic stimulation with isoproterenol improves parameters describing cardiac muscle relaxation. Our results demonstrate that in patients with HCM, \( \beta \)-stimulation with isoproterenol favorably modifies several measures of diastolic performance when compared with the effects of atrial pacing at similar heart rates. Of note, this evidence of enhanced diastolic function often occurred in the presence of myocardial ischemia, which was in some patients even more severe than that developing during atrial pacing—severe enough to be accompanied by lactate production.

The hemodynamic responses to the two interventions were distinct. Atrial pacing did not alter cardiac output, as stroke volume decreased in response to reduced end-diastolic volume. There was also an increase in both minimum and end-diastolic left ventricular pressure, associated with

**Figure 3.** Plots of diastolic pressure-volume relations in the same four patients presented in Figure 1. During atrial pacing, the curves shift upward and leftward, and left ventricular (LV) pressure continues to decline through the filling period (evidence for impaired relaxation). During isoproterenol, the curves shift downward and rightward toward the baseline, despite more severe myocardial ischemia in all cases, and there is less evidence of impaired relaxation.

**Figure 4.** Plots of left ventricular (LV) pressure-time curves in two patients. With atrial pacing, a pattern of impaired relaxation (a continuing decline of pressure through diastole) is evident in both patients. During isoproterenol, pressure decline is complete early in diastole.
an upward shift in the diastolic pressure-volume relation. A pattern of abnormal pressure decay developed in seven patients, with continuing decay of pressure through late diastole. These hemodynamic changes were accompanied by symptoms compatible with myocardial ischemia in 10 of the patients.

During isoproterenol infusion, relative stroke work increased greatly without a significant change in coronary flow, and chest pain compatible with ischemia occurred in 11 patients. The severity of ischemia was often more severe in individual patients during isoproterenol, with actual production of lactate in five patients. In two other patients, stroke work increased in association with reduced coronary flow. Although lactate consumption decreased in these two patients, it remained positive, presumably reflecting a sampling of ischemic and nonischemic regions via the great cardiac vein. Potentiation of myocardial demand ischemia would be expected to further delay relaxation, elevate left ventricular diastolic pressures, and aggravate diastolic pressure-volume relations. However, isoproterenol produced the opposite effect and enhanced multiple indexes of left ventricular diastolic performance compared with pacing tachycardia; peak negative dP/dt increased, time to peak negative dP/dt decreased, the time constant of isovolumic pressure decline decreased (returning to baseline values), minimum ventricular diastolic pressure decreased, the diastolic pressure-volume relation shifted downward and rightward, and end-diastolic volume increased with no associated increase in end-diastolic pressure. Thus, compared with pacing, isoproterenol hastened the onset and enhanced the rate (and possibly the extent) of relaxation, associated with improved diastolic distensibility.

As isoproterenol simulates the hemodynamic effects of exercise, these data may explain the common clinical observation that patients with HCM tolerate exercise-induced tachycardia better than spontaneous supraventricular tachycardia at the same heart rate. Our results may also provide a basis for the lack of therapeutic success of β-blocking drugs in alleviating symptoms in some patients.

Complex and simultaneous changes in hemodynamic and loading conditions preclude definitive statements regarding the mechanism of isoproterenol's beneficial effects on diastolic performance in this study. However, previous studies in isolated cardiac muscle, as well as experimental studies in the intact dog heart and in the clinical setting, have demonstrated the ability of β-adrenergic stimulation to accelerate relaxation, even in the absence of a positive effect on contractility. Through the pathway mediated by cyclic AMP-dependent protein kinase, sarcolemmal β-receptor stimulation increases the rate of calcium transport from the myocellular cytosol into the sarcoplasmic reticulum, thereby speeding the detachment of cross-bridges. This more rapid disappearance of force-generating sites would be manifest as an accelerated decay of pressure, indicated in the present study by increased peak negative dP/dt, decreased time constant of relaxation, and reduced time from aortic valve closure to minimum diastolic pressure. Seven of our patients demonstrated a pattern of abnormal pressure decay during pacing ischemia, similar to that described by Lorell et al. An enhanced rate of relaxation in our patients during isoproterenol was associated with a more complete fall in pressure before the onset of filling (Figure 4).

For a given state of inactivation, loading conditions affect the timing, rate, and extent of relaxation. An enhanced state of inactivation during β-stimulation would be expected to heighten the influence of the prevailing loading conditions. From our data, several important effects of isoproterenol on ventricular loading are evident. First, left ventricular systolic pressure increased markedly during isoproterenol, due to an aggravation of the outflow tract obstruction. This pressure load in hypertrophic cardiomyopathy may act as a “contraction load,” tending to delay the onset and slow the rate of relaxation, although the experimental models supporting this concept may not apply to HCM. Second, it is very likely that systolic shortening was greater during isoproterenol than during pacing, as end-diastolic volume was greater during isoproterenol while end-systolic volume was similar for both interventions. Augmented systolic shortening has been shown to be an important loading parameter resulting in an increased rate of left ventricular relaxation. Third, isoproterenol resulted in a decrease in the extent of regional nonuniformity (as reflected by the measurements of regional times to minimum volume), another loading influence that would be expected to enhance left ventricular relaxation. Finally, the mitral regurgitant volume increased during isoproterenol (Table 1), related to an increase in the outflow tract gradient. This may have the loading effect to augment the extent of relaxation by increasing wall stress at the time of mitral valve opening, governed by the LaPlace relation at a time when the relaxing ventricle is unable to support such a load. Additionally, an increased left atrial-left ventricular pressure gradient would enhance the rate and extent of filling independent of the state of relaxation. Hence, the net effect of isoproterenol infusion represents the interaction of these many loading influences with the heightened state of inactivation, with the result being more rapid pressure decay and lower pressures for a given volume during diastole.

There are other external loading factors that influence relaxation, but we do not believe that these played a role in accounting for our results. Arterial impedance, or the reflected waves resulting from the compliance of the peripheral vascular tree, are unlikely to have played a major role, as the dynamic left ventricular outflow tract gradient caused...
very high left ventricular systolic pressures, far in excess of the arterial pressure. Rapid filling of the coronary bed during early diastole is another external load that may affect relaxation. Although coronary filling during early diastole was not measured directly in the present study, coronary sinus flow, reflecting the anterior left ventricular circulation, was not significantly different between the interventions. Because of the small ventricular volumes present in these patients, with no increase during either intervention compared with control measurements, it is also unlikely that pericardial or right ventricular interactions played an important role in these results. In addition, it is important to emphasize that these data represent an average of events occurring over 2 minutes during the respective interventions. It is not clear whether the beneficial effects of isoproterenol on relaxation and filling would have been maintained in the face of continued ischemia. Other experimental studies suggest that this would not be the case.

That these improved diastolic mechanics took place in the setting of myocardial ischemia is of particular interest. Numerous experimental studies, as well as clinical studies of patients with coronary artery disease and patients with primary or secondary left ventricular hypertrophy, have demonstrated the adverse effects of demand ischemia on ventricular relaxation and diastolic pressure-volume relations. The underlying process may involve dysfunction of the calcium sequestration function of the sarcoplasmic reticulum, resulting in prolonged or complete deactivation of force-generating sites. These effects are compounded in the setting of myocardial hypertrophy.

If improved ventricular relaxation and diastolic pressure-volume relations in our patients during isoproterenol resulted from enhanced inactivation despite an ischemic milieu, these results imply that β-adrenergic stimulation can overcome the detrimental effects of ischemia on relaxation. Thus, impaired relaxation stemming from myocardial ischemia may be reversible even while the ischemic insult persists. This concept may be analogous to that of “inotropic reserve” in which the reversibility of systolic dysfunction during regional ischemia may be unmasked by inotropic intervention.

One of the limitations of our data analysis involves the choice of T₂/₁ as a “time constant” of isovolumic relaxation. There is no general consensus regarding the best method for calculating a time constant of relaxation, and any method of analysis of pressure decline during isovolumic relaxation in a ventricle that is performing heterogeneously is limited. Chamber pressure in this situation merely reflects the summation of nonuniform rates of relaxation in different parts of the ventricle, and a time constant derived from a decrease in chamber pressure does not necessarily reflect actual changes in relaxation at a cellular level. This is true of most clinical studies of diastolic events in human heart disease and is apt to be particularly so in HCM, due to the marked spatial and temporal heterogeneity of relaxation, which may result in a nonexponential decay of pressure. In the present study, an attempt was made to fit the pressure data to an exponential model. However, even in several cases with good correlation coefficients, the residuals reflecting the differences between the observed data and the derived curve were consistently nonrandom. Therefore, we chose not to use an exponential curve-fitting model. In a previous study, T₂/₁ values were shown to correlate well with a “true” time constant derived from nonfilling beats in an intact dog heart model, in which pressure fall would more directly reflect the decline in wall tension. In addition, we believe that the concordant and significant changes in T₂/₁, peak negative dP/dt, time to peak negative dP/dt, and the average rate of pressure decline indicate that the rate of pressure decay was indeed more rapid during isoproterenol compared with pacing tachycardia.

The limitations of using changes in lactate metabolism to reflect the presence or severity of myocardial ischemia have been previously described. In this study, we have considered the presence of either lactate production or decreased lactate consumption in association with a decrease in coronary flow and an increase in oxygen demand as indicative of more severe ischemia during isoproterenol compared with pacing. Although intense β-adrenergic stimulation with isoproterenol (at very high concentrations) may cause lactate production in isolated myocytes and in the isolated heart by stimulating glycogenolysis, this may reflect relative cellular hypoxia resulting from the markedly increased demand. It also appears from studies in humans with coronary artery disease given doses of isoproterenol similar to those used in the present study that ischemia is indeed present when lactate is produced.

In summary, our data demonstrate that β-adrenergic stimulation with isoproterenol enhances left ventricular relaxation and improves diastolic pressure-volume relations in HCM compared with the effects of pacing tachycardia to the same heart rate. These effects are mediated by load-dependent mechanisms, such as elevated peak systolic pressures, increased systolic shortening, and reduced asynchrony, and possibly also by direct effects on myocardial inactivation. Although it is evident that isoproterenol should not be used in the therapy of ischemia in the presence of HCM, the finding of improved relaxation with isoproterenol despite myocardial ischemia is evidence that the adverse effect of ischemia on diastolic performance might be favorably modified in HCM, at least temporarily, by pharmacological intervention.

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Key Words • hypertrophic cardiomyopathy • β-adrenergic stimulation • isoproterenol • myocardial ischemia • left ventricular function
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