Exercise-Induced Upward Shift of Diastolic Left Ventricular Pressure-Volume Relation in Patients With Dilated Cardiomyopathy

Effects of β-Adrenoceptor Blockade

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Background. The effectiveness of β-blocker therapy for dilated cardiomyopathy (DCM) may be attributed to the inhibition of detrimental effects on the failing heart of sympathetic stimulation during exertion. However, the harmful effects of activity as well as the protective effects of β-blockers have not been demonstrated. Diastolic ventricular function is known to be sensitive to transient myocardial metabolic insult. In this study, we investigated the effect of modest exercise with or without β-blockade on the diastolic left ventricular pressure-volume (P-V) relation in patients with DCM.

Methods and Results. The diastolic left ventricular P-V relation was obtained by high-fidelity pressure measurements and digital subtraction left ventriculography at rest and immediately after modest supine bicycle exercise in 12 patients with DCM. The effects of intravenous administration of 0.1 mg/kg propranolol on resting and exercise P-V relations were studied. The end-diastolic and lowest left ventricular pressures were significantly elevated by exercise (20±9 to 32±13 mm Hg, P<.01, and 12±6 to 21±11 mm Hg, P<.01, respectively) despite insignificant changes in left ventricular volumes. The administration of propranolol did not alter the resting diastolic P-V relation. However, propranolol significantly attenuated the exercise-induced upward shift of the diastolic P-V relation despite a significant increase in end-diastolic volume. The significant upward shift and attenuation by propranolol were observed even when the left ventricular pressure was corrected by the subtraction of right atrial pressure.

Conclusions. These results indicate that even modest exercise exerts detrimental effects on diastolic left ventricular function of the failing heart through β-adrenergic stimulation. The clinical effectiveness of β-blocker therapy in patients with DCM can be attributed in part to the inhibition of detrimental myocardial effects of sympathetic stimulation during daily activity. (Circulation. 1993;88[part 1]: 2215-2223.)

Key Words • heart failure • propranolol • diastole • β-adrenergic receptors • aorta • regurgitation

Previous studies have demonstrated that long-term β-blocker therapy improves cardiac function, exercise capacity, and survival in patients with dilated cardiomyopathy (DCM).1-7 However, the mechanisms responsible for the beneficial effects are still unclear. Heilbrunn et al7 demonstrated an increase in myocardial β-receptor density and consequent recovery of cardiac catecholamine sensitivity during long-term administration of metoprolol in patients with DCM. Their results may well explain the clinical efficacy of β-blocker therapy, particularly the improvement seen in exercise capacity. However, they did not demonstrate a significant correlation between the increase in β-recep-
be attributed to inhibition of detrimental cardiac effects of sympathetic stimulation during daily activities.

The purpose of this study was to investigate whether modest exercise similar to that experienced during daily activity exerts harmful effects on the failing cardiomyopathic heart and whether \( \beta \)-blockers attenuate these effects. As a clinical marker susceptible to transient metabolic insult, changes in diastolic left ventricular function were assessed. We also investigated patients with dilated but nonfailing hearts due to aortic regurgitation (AR) to examine whether changes in diastolic function during exercise are characteristic solely of failing hearts or are due to a nonspecific effect of cardiac enlargement.

**Methods**

**Subjects**

Twelve male patients with chronic heart failure due to DCM, ranging in age from 32 to 74 years (mean, 54 years), were studied as the DCM group. All patients were in sinus rhythm. Ten patients were classified as New York Heart Association (NYHA) functional class II, and two patients were classified as class I. The peak oxygen uptake measured during a preliminary ramp maximal upright bicycle exercise test ranged from 13.0 to 22.2 \( \text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \) (mean, 18.8 \( \text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \)). Routine diagnostic cardiac catheterization performed prior to the beginning of the study showed neither significant coronary artery lesions nor primary valvular diseases in any patient. Left ventricular ejection fraction assessed by contrast left ventriculograms ranged from 15% to 45% (mean, 32%), and end-diastolic volume ranged from 175 to 335 \( \text{mL} \) (mean, 222 \( \text{mL} \)). All had been treated with diuretics, digitalis, and/or vasodilators for at least 2 months. Neither \( \beta \)-adrenoceptor stimulants nor \( \beta \)-blockers were administered to any patient prior to the study. Digitalis, diuretics, and antiarrhythmic agents were continued, but vasodilators, including converting enzyme inhibitors and calcium antagonists, were withdrawn at least 24 hours before the study.

Five asymptomatic (NYHA class I) male patients with isolated AR and a dilated but normally ejecting left ventricle, ranging in age from 26 to 62 years (mean, 41 years), were also studied as the AR group. Their left ventricular ejection fraction ranged from 55% to 63% (mean, 59%), and end-diastolic volume ranged from 169 to 358 \( \text{mL} \) (mean, 259 \( \text{mL} \)). The peak oxygen uptake was normal in all patients, ranging from 25.0 to 41.2 \( \text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \) (mean, 32.1 \( \text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \)). Neither digitalis nor diuretics were given to any patient. In two patients, vasodilators were withdrawn 24 hours before the study.

The protocol was approved by the hospital ethics committee. A written informed consent was obtained from each patient before entering the study.

**Catheterization and Left Ventriculography**

Patients were premedicated with 5 mg diazepam before catheterization. Routine diagnostic cardiac catheterization, left ventriculography, and coronary arteriography were performed via the percutaneous femoral approach. Patients were allowed to rest for 30 minutes after completion of routine studies. An 8F pigtail angiographic micromanometer-tipped catheter (model 9815, Honeywell Co.) was advanced to the left ventricle via the femoral artery. The catheter was positioned carefully to avoid stimulation of ventricular ectopic beats. The micromanometer pressure was matched to the fluid-filled lumen pressure. A 7F catheter was advanced to the right atrium via the femoral vein to measure the right atrial pressure. The baseline left ventriculography was performed at 30 frames per second in the 30° right anterior oblique projection. Patients were instructed to maintain submaximal inspiration and to avoid the Valsalva maneuver. To minimize the amount of contrast medium for repetitive ventriculography, digital subtraction techniques using cineangiographic equipment (model Optimus M200, Philips, The Netherlands) interfaced directly to a digital radiographic computer (model DVI-CI, Philips) was used according to the method of Eichhorn et al\textsuperscript{a}; 20 mL of twice-diluted nonionic isotonic contrast medium, iopamidol, was injected into the left ventricle at a rate of 10 \( \text{mL/s} \) using a triggered injector. For digital subtraction, an R-wave–gated mask was derived from the cardiac cycle before the appearance of radiographic contrast and subtracted from the respective frames containing contrast. The digital ventriculograms were stored as a 512×512 matrix with an 8-bit gray scale. The left ventricular high-fidelity pressure, its first derivative (\( \text{dP/dt} \)), mean right atrial pressure, ECG, and timing signals of ventriculography were simultaneously recorded at a paper speed of 100 mm/s during left ventriculography.

**Protocol**

Fifteen minutes after the baseline digital ventriculography and pressure measurements, the control supine bicycle exercise test was conducted for 3 minutes. To prevent the formation of groin hematomas, the puncture site of the femoral artery was compressed by fingers of the angiographer during exercise. The exercise workload was set at a level of approximately 50% of the preliminarily determined peak oxygen uptake of individuals. Breath-by-breath respiratory gas analysis was performed during exercise using a respiro-monitor system (model RM-200, Minato Co, Tokyo, Japan), and the oxygen uptake was obtained as the mean value of every 30 seconds. Since the digital ventriculograms are influenced by body movements due to respiration and exercise, exercise left ventriculography and pressure recordings were performed within 15 seconds after cessation of exercise during held respiration. Since the exercise workload was modest, patients were able to hold respirations for several seconds during the postexercise ventriculography. To avoid effects of leg raising on hemodynamics, the postexercise ventriculography as well as the resting study was performed with legs on the level. Patients were allowed to rest for 30 minutes after completion of the control study to allow for the dissipation of effects of the first exercise and contrast medium. After confirming that heart rate and blood pressure had returned to the baseline values, 0.1 mg/kg propranolol diluted with saline was administered intravenously over 5 minutes. Ten minutes after the injection was completed, the left ventriculography and pressure measurements were repeated both at rest and after exercise at the same workloads and time intervals.

**Data Analysis**

Left ventricular volumes were obtained from digital ventriculograms. Well opacified and sinus beats were
selected and digitized frame by frame for an entire cardiac cycle by two investigators blinded to the sequence of ventriculograms. Left ventricular volumes were calculated with a standard angiographic area-length method.12 Angiographic end diastole and end systole were defined as the frame of the largest and smallest left ventricular volumes in each cardiac cycle, respectively. The variability of our volume measurements were tested by repeated analysis of 18 resting and 18 exercise digital left ventriculograms. The standard deviation (SD) for intraobserver measurements was 13.7 mL (n=36, r=.98, y=1.00x-.74, P<.0001), and the SD for interobserver measurements was 14.5 mL (n=36, r=.97, y=0.96x+8.22, P<.0001).

Pressure tracings in the beat selected for volume analysis were digitized every 3 milliseconds for an entire cardiac cycle by a blinded investigator using an electronic digitizer (model KD4300, Graphtec Co, Tokyo, Japan) interfaced with a personal computer (model PC-9801DR, NEC Co, Tokyo, Japan). The end-diastolic pressure was defined as that at the beginning of the rapid increase in left ventricular pressure immediately after the onset of the QRS complex. The time constant of left ventricular pressure decay was calculated as the negative reciprocal of the slope relating left ventricular pressure to dp/dt coordinates between peak negative dp/dt and the time at which pressure decreased to left ventricular end-diastolic pressure.13 Because of afterload dependency of the time constant, the index of the time constant divided by end-systolic left ventricular pressure was also calculated.14 To examine the completeness of relaxation, we used the technique of Weisfeldt et al,15 which assumes relaxation to be 97% complete at 3.5 time constants after peak negative dp/dt. The number of time constants elapsed was calculated at the time of the lowest diastolic pressure. As a simple estimate of left ventricular chamber stiffness, the index of ΔP (end-diastolic pressure minus the lowest pressure) divided by ΔV (end-diastolic volume minus the volume at the lowest pressure) was calculated.16 The pressure-volume relation of individuals was obtained by plotting left ventricular pressure with simultaneous left ventricular volume with the time interval of 33 milliseconds under four conditions, ie, at rest, immediately after exercise, and before and after propranolol administration. The average diastolic pressure-volume plots for each group were obtained with coordinates from five time references. These included the time at which pressure decayed to 60 mm Hg, at the lowest pressure, and at end diastole. Two additional coordinates were at volumes midway between the three. The relations were also obtained with the adjusted left ventricular pressure by subtraction of mean right atrial pressure from the measured left ventricular pressure.

Statistical Analysis

Data were expressed as mean±SD. Within-group comparisons were performed with two-way ANOVA with repeated measurements. Intergroup comparisons were performed with nonpaired t test. Correlation between two variables was tested by the linear regression analysis. P<.05 was regarded as statistically significant.

Results

Serious adverse effects related to exercise or propranolol administration were not observed in any patient. The oxygen uptake at the end of exercise was not affected by propranolol administration in the DCM group (10.6±3.2 to 10.6±2.6 mL•min⁻¹•kg⁻¹) and in the AR group (15.0±2.6 to 15.2±2.7 mL•min⁻¹•kg⁻¹), indicating that the exercise intensity was almost identical before and after propranolol administration. The Table shows resting and exercise hemodynamic data obtained before and after propranolol administration.

Baseline Hemodynamics

Resting heart rate, peak left ventricular pressure, and end-diastolic and end-systolic volumes were not significantly different between the DCM and AR groups. The lowest left ventricular pressure and mean right atrial pressure were significantly higher in the DCM group than in the AR group (P<.05 and P<.05, respectively), but end-diastolic pressure was not significantly different between the two groups. The maximal positive and negative dp/dt values were significantly lower in the DCM group than in the AR group (P<.05 and P<.05, respectively). Moreover, both the time constant and time constant corrected by end-systolic pressure were significantly greater in the DCM group than in the AR group (P<.05 and P<.05, respectively). The index of ΔP/ΔV was not significantly different between the two groups. The number of time constants elapsed at the lowest pressure was substantially but not significantly less in the DCM group than in the AR group.

Effect of Exercise

In the AR group, the modest exercise used in this study significantly increased heart rate and maximal positive and negative dp/dt by averages of 37%, 38%, and 30%, respectively. These variables also significantly increased with exercise in the DCM group; however, percent increases in maximal positive and negative dp/dt were only 24% and 13%, respectively, despite a comparable 41% increase in heart rate. In the AR group, the time constant and time constant corrected by end-systolic pressure substantially but not significantly decreased with exercise by averages of 16% and 27%, respectively, whereas both parameters remained unchanged in the DCM group. Mean right atrial pressure was not significantly elevated by exercise in both groups.

In the AR group, the diastolic pressure-volume relation was unaltered by exercise in individual patients (Fig 1A) or on the average plots (Fig 1B), although end-diastolic pressure was slightly elevated in proportion to the increase in end-diastolic volume. In the DCM group, the diastolic pressure-volume relation was clearly shifted upward by exercise in 10 of 12 patients (Fig 2). The upward shift was also demonstrated by the average plots (Fig 3A); the end-diastolic and lowest pressures were significantly elevated by exercise, despite insignificant changes in end-systolic and end-diastolic volumes. When left ventricular pressure was corrected for the transmural pressure by subtraction of simultaneous mean right atrial pressure from the measured left ventricular pressure, the lowest and end-diastolic pressures were also significantly elevated by exercise (6±5 to 14±10 mm Hg, P<.05, and 14±8 to 25±12 mm Hg, P<.05, respectively). Thus, the significant upward shift was also observed even when the left ventricular pressure was corrected for the transmural pressure (Fig 3B). In the DCM group, the exercise-induced rise in the lowest pressure was significantly correlated with resting...
### Hemodynamic Data for Patients With Aortic Regurgitation or Dilated Cardiomyopathy at Baseline and After Propranolol

<table>
<thead>
<tr>
<th>AR group</th>
<th>Baseline</th>
<th>Propranolol</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
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<tr>
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<td>Peak LVP, mm Hg</td>
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<td>Lowest LVP, mm Hg</td>
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<td>EDP, mm Hg</td>
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<td>RAP, mm Hg</td>
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<td>2072±529*</td>
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<td>EVD, mL</td>
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<td>ESV, mL</td>
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**DCM group**

<table>
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<tr>
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<th>Rest</th>
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<td>14±9</td>
<td>18±9§</td>
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<td>EDP, mm Hg</td>
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<td>32±13*</td>
<td>22±10</td>
<td>29±11</td>
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<td>935±250*</td>
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<td>Max(−)dP/dt, mm Hg/s</td>
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<td>1179±397*</td>
<td>971±308†</td>
<td>1020±350‡</td>
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<td>120±78</td>
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<td>ESV, mL</td>
<td>148±49</td>
<td>151±53</td>
<td>153±54</td>
<td>155±49</td>
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</table>

**AR** indicates aortic regurgitation; **DCM**, dilated cardiomyopathy; **HR**, heart rate; **LVP**, left ventricular pressure; **EDP**, end-diastolic LVP; **RAP**, right atrial pressure; **max(+)]dP/dt**, peak positive dP/dt; **max(−)dP/dt**, peak negative dP/dt; **T**, time constant of left ventricular pressure decay; **ESP**, end-systolic LVP; **Ts**, the number of time constants elapsed at the lowest LVP; **ΔP/ΔV**, (EDP minus the lowest LVP) divided by (end-diastolic-volume minus the volume at the lowest LVP); **EDV**, end-diastolic left ventricular volume; and **ESV**, end-systolic left ventricular volume. Values are mean±SD.

*P<.01, †P<.05 vs baseline rest.
‡P<.01, §P<.05 vs baseline exercise.

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left ventricular ejection fraction (Fig 4), suggesting that the degree of the upward shift depends on the severity of left ventricular dysfunction. The number of time constants elapsed at the lowest pressure significantly decreased during exercise in the DCM group, whereas it insignificantly increased in the AR group, suggesting incomplete relaxation in the DCM group and more complete relaxation in the AR group during exercise. Moreover, the index of ΔP/ΔV tended to increase during exercise in the DCM group (P<.1), whereas it was unaltered in the AR group.

**Effect of Propranolol on Resting Hemodynamics**

Propranolol significantly decreased resting heart rate as well as maximal positive and negative dP/dt in both groups, whereas changes in other resting hemodynamic variables were not significant except for the increase in end-diastolic volume in the AR group and increases in the time constant and corrected time constant in the DCM group. The resting diastolic pressure-volume relation was not altered with propranolol administration in both groups.

**Effect of Propranolol on Exercise Hemodynamics**

Propranolol significantly decreased heart rate as well as maximal positive and negative dP/dt and insignificantly increased the time constant and time constant corrected by end-systolic pressure during exercise in both groups. The mean right atrial pressure
Diastolic left ventricular pressure-volume relation at baseline rest (--) and during exercise with (-----) and without (----) propranolol administration of patients with aortic regurgitation. B, Average diastolic pressure-volume plots at rest (--) and during exercise with (-----) and without (----) propranolol administration obtained from five patients with aortic regurgitation. Data are expressed as mean±SD.

During exercise was slightly but significantly elevated with propranolol administration in both groups.

In the AR group, the exercise end-diastolic pressure was significantly increased in proportion to the increase in exercise end-diastolic volume by propranolol administration, and hence, the diastolic pressure-volume relation during exercise was essentially unaltered (Fig 1B). In the DCM group, the exercise-induced rise in the lowest pressure was significantly attenuated by propranolol administration. Moreover, despite a significant increase in end-diastolic volume, the exercise-induced rise in end-diastolic pressure also tended to
be attenuated by propranolol (P<.1). Thus, the exercise-induced upward shift of the diastolic pressure-volume relation was attenuated by propranolol administration (Fig 3A). This was more clearly demonstrated when left ventricular pressure was corrected for the transmural pressure by subtraction of mean right atrial pressure (Fig 3B); both the corrected lowest and end-diastolic pressures during exercise significantly decreased with propranolol administration (14±10 to 9±9 mm Hg, P<.05 and 25±12 to 20±12 mm Hg, P<.05, respectively). Moreover, the abnormal decrease in the number of time constants elapsed at the lowest pressure during exercise was significantly attenuated with propranolol administration in the DCM group.

When individual responses were examined, the beneficial effect of propranolol on the diastolic pressure-volume relation during exercise was observed in 7 of 10 DCM patients who showed the exercise-induced upward shift but it was not observed in the remaining 3 patients (Fig 2). In 2 of these 3 patients (patients 5 and 10), mean right atrial pressure during exercise was markedly elevated by propranolol administration (9 to 15 mm Hg and 1 to 13 mm Hg, respectively), suggesting an increase in external constraining pressure. In another patient (11), exercise heart rate decreased only slightly with propranolol administration (109 to 100 beats per minute), suggesting that the dose of propranolol was inadequate in this patient.
Discussion

In the present study, we have demonstrated that the left ventricular diastolic pressure-volume relation is transiently shifted upward by a modest level of dynamic exercise in patients with DCM, the shift is not observed in AR patients with comparably dilated but nonfailing left ventricles, and the exercise-induced upward shift in patients with DCM is attenuated by treatment with propranolol.

In patients with effort angina, exercise-induced myocardial ischemia causes a transient upward shift of the diastolic left ventricular pressure-volume relation. In this study, a similar upward shift was induced by exercise in patients with DCM even in the absence of significant coronary artery narrowings. This response is abnormal since in normal subjects the diastolic pressure-volume relation has been demonstrated to be shifted downward during symptom-limited supine bicycle exercise, probably due to an increased diastolic elastic recoil. In the present study, we further suggest that the upward shift in patients with DCM is not caused solely by cardiac enlargement, as the upward shift of the diastolic pressure-volume relation was not observed in patients with AR having a comparably dilated heart. Although the normal exercise-induced downward shift was also not observed in patients with AR, it is unclear whether the lack of the downward shift is due to an impaired diastolic elastic recoil in the dilated ventricle or to the light exercise level used in this study.

There are three possible mechanisms responsible for the exercise-induced upward shift of the diastolic left ventricular pressure-volume relation in patients with DCM. First, external constraints to left ventricular distension may increase during exercise. Second, abnormal pressure decay may cause incomplete relaxation during exercise. Finally, passive chamber stiffness may transiently increase during exercise. Changes in right ventricular filling pressure are known to influence the left ventricular diastolic pressure-volume relation via ventricular interaction within an intact pericardium. Tyberg et al demonstrated a correlation between right atrial pressure and left ventricular pericardial surface pressure, supporting the use of right atrial pressure as an index of the left ventricular constraining pressure. In our patients with DCM, right atrial pressure rose slightly with exercise (Table). However, adjustment of the diastolic pressure-volume relation to the left ventricular transmural pressure by subtraction of right atrial pressure from left ventricular pressure did not abolish the exercise-induced upward shift (Fig 3B). Moreover, other external constraints such as pulmonary-cardiac contact pressure were unlikely to play an important role since the upward shift was not observed in patients with comparably enlarged hearts due to AR.

Fig 3. A, Average diastolic pressure-volume plots at baseline rest (---) and during exercise with (-----) and without (----) propranolol administration obtained from 12 patients with dilated cardiomyopathy. B, Same diastolic pressure-volume relation replotted with the left ventricular transmural pressure obtained by subtraction of the right atrial pressure from the measured left ventricular pressure. Data are expressed as mean±SD.

Fig 4. Scatterplot demonstrating the relation between changes in the lowest left ventricular pressure with exercise and resting ejection fraction in 12 patients with dilated cardiomyopathy. There was a significant inverse correlation between the two variables (r = .58, P < .05).
Thus, it is plausible that mechanisms other than increases in the external constraint play a central role in the exercise-induced upward shift of the diastolic pressure-volume relation. It is of note that the number of time constants elapsed at the time of the lowest left ventricular pressure significantly decreased, and furthermore, the index of ΔP/ΔV tended to increase with exercise in patients with DCM (Table). These results strongly suggest that the exercise-induced upward shift of diastolic pressure-volume relation is attributed in part to incomplete relaxation and a transient increase in passive chamber stiffness during exercise.

It is unclear from our results why these abnormalities developed during exercise. However, several intrinsic abnormalities susceptible to exercise-induced sympathetic stimulation and consequent tachycardia are known in the failing heart. The decreased left ventricular relaxation rate in the failing heart has been suggested to be a reflection of abnormal calcium handling such as a reduced calcium sequestration by the sarcoplasmic reticulum.

Moreover, heart rate–dependent potentiation of relaxation has been demonstrated to be markedly impaired in failing hearts. In the presence of these abnormalities, sympathetic effects on increasing cytosolic calcium transient and shortening diastole may outweigh the sympathetic-mediated or frequency-dependent acceleration of the deactivation process, causing incomplete relaxation and increasing chamber stiffness through cytosolic calcium accumulation during diastole. Indeed, in our patients with DCM, maximal negative dP/dt increased only by 13%, and the time constant failed to decrease during exercise, despite a 41% increase in heart rate. In contrast, a comparable 37% increase in heart rate was accompanied by a 30% increase in maximal negative dP/dt and a 27% decrease in the time constant corrected by end-systolic pressure in patients with AR. Furthermore, exercise-induced diastolic dysfunction may also be associated with myocardial ischemia because evidence from human as well as animal model heart failure studies suggest that the failing heart has a reduced coronary vasodilator reserve and exists in an energy-depleted state. This speculation is supported by an experimental study of Hittinger et al. In dogs with chronic heart failure induced by aortic banding, they demonstrated that sympathetic stimulation by isoproterenol infusion led to a transient upward shift of the left ventricular diastolic pressure-volume relation by provoking subendocardial hypoperfusion. Thus, the exercise-induced upward shift of the diastolic pressure-volume relation in patients with DCM appears to be the combined result of several detrimental effects of sympathetic stimulation on failing myocardium, in concert with intrinsic abnormalities of myocardial metabolism. The inverse correlation between the rise in the lowest pressure with exercise and resting ejection fraction supports this hypothesis (Fig 4).

After administration of propranolol, the exercise-induced upward shift of diastolic pressure-volume relation was significantly attenuated in patients with DCM (Fig 3). This effect was likely to result from improvements in incomplete relaxation and chamber distensibility because the abnormal responses of the index of ΔP/ΔV and the number of time constants elapsed at the lowest pressure during exercise were concomitantly attenuated with propranolol administration (Table). Thus, the beneficial effects of propranolol on diastolic ventricular function during exercise are strong indirect evidence that exercise-induced sympathetic stimulation exerts deleterious metabolic effects on failing myocardium.

**Study Limitations**

A noncardioselective β-blocker, propranolol, was used in this study. It is, therefore, possible that the attenuation of the upward shift with propranolol is a result of systemic vasoconstriction via vascular β-receptor blockade or nonspecific myocardial effects such as a membrane stabilizing action rather than myocardial β-receptor blockade. However, these possibilities are unlikely as vasodilators have been reported to shift the diastolic pressure-volume relation downward through a decrease in pericardial constraint in patients with heart failure. Thus, β-blockade would actually enhance the upward shift through vasoconstriction. Nonspecific effects of propranolol are also negligible, as the drug did not shift the diastolic pressure-volume relation in patients with AR.

In the present study, reproducibility of hemodynamic measurements was not tested. Therefore, changes in resting and exercise hemodynamics observed after propranolol administration might be attributed to a placebo effect, an influence of the initial exercise test, or both. However, we confirmed with the use of right heart catheterization that the hemodynamic responses to the second symptom-limited exercise test performed 60 minutes after the first test are highly reproducible in patients with left ventricular dysfunction. In the present study, the summed interval between the two exercise tests was also 60 minutes; moreover, the exercise level used was modest. Thus, it is unlikely that the first exercise test influenced the results of the second exercise.

In this study, overall passive chamber stiffness was assessed using the average ratio of increase in left ventricular pressure to the increase in left ventricular volume from the lowest diastolic pressure to end-diastolic pressure. Although this technique may be too simple, the ratio has been demonstrated to be sensitive to changes in chamber stiffness. Moreover, this technique avoids many of the assumptions that are implicit in assuming a monoequilibrium diastolic pressure-volume relation. This advantage is particularly important during exercise because of possible errors of fitting a curve to a few points measured during exercise tachycardia.

**Implications**

The present study demonstrates that a modest exercise exerts deleterious effects on diastolic function of the cardiomyopathic failing heart, probably by provoking incomplete relaxation, calcium overload, and/or myocardial ischemia/energy deficiency. It is, therefore, plausible that daily exertions repeatedly evoke these metabolic abnormalities in the failing myocardium, gradually promoting progression of heart failure. This hypothesis explains well how heart failure is aggravated by stress such as exercise but improved by rest. The present study further suggests, on the basis of the beneficial effects of propranolol, that detrimental effects of exercise on failing hearts are mainly attributed to exercise-induced sympathetic stimulation. It is unclear from our results whether the acute beneficial effects of β-blockers we observed are associated with clinical effectiveness of long-term β-blocker therapy.
However, it is most likely that β-blockers protect the failing heart against detrimental effects of sympathetic stimulation during daily exertion, retarding progression of heart failure and hence restoring myocardial function after long-term administration. Thus, myocardial protection against exercise-induced sympathetic stimulation, as well as β-receptor upregulation, may be an important mechanism of the effectiveness of β-blocker therapy for patients with DCM, although further studies are necessary to test this hypothesis.

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**References**


H Sato, M Hori, H Ozaki, H Yokoyama, K Imai, M Morikawa, H Takeda, M Inoue and T Kamada

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