Effects of β-Adrenergic Stimulation With Dobutamine on Isovolumic Relaxation in the Normal and Failing Human Left Ventricle

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Background. We tested the hypothesis that β-adrenergic receptor–stimulated acceleration of left ventricular (LV) isovolumic relaxation (i.e., positive lusitropic response) is attenuated in patients with severe congestive heart failure (CHF) compared with patients without LV dysfunction or CHF.

Methods and Results. The β-adrenergic agonist dobutamine was infused by the intracoronary route in 14 subjects (normal group, six; CHF patients, eight) and by the intravenous route in a second group of 14 subjects (normal group, four; CHF patients, 10). The positive inotropic response to intracoronary or intravenous dobutamine was substantially and significantly reduced in the patients with CHF. LV isovolumic relaxation rate was determined by the methods of Weiss (T1/2), Mirsky (T1/2), and by a nonlinear regression technique (TNL). LV isovolumic relaxation assessed by all three methods was significantly prolonged in CHF patients compared with normal subjects. Intracoronary and intravenous infusions of dobutamine caused significant acceleration of LV isovolumic relaxation in both normal subjects and patients with CHF. The magnitude of the dobutamine-stimulated acceleration of isovolumic relaxation in patients with CHF was comparable with that in normal subjects.

Conclusions. These data demonstrate that β-adrenergic receptor stimulation causes significant acceleration of LV isovolumic relaxation in both normal subjects and patients with severe CHF. Contrary to our hypothesis, the lusitropic response to β-adrenergic stimulation is well preserved in patients with severe CHF despite substantial attenuation of the β-adrenergic positive inotropic response. These findings have potentially important implications regarding the physiology and pharmacology of adrenergically mediated LV relaxation in humans. (Circulation 1991;84:1040–1048)

In myocardium from patients with congestive heart failure (CHF), there is an impairment of β-adrenergic receptor–stimulated force development resulting in a reduction in the effect of β-adrenergic receptor stimulation on left ventricular (LV) contractility and systolic pump performance. These abnormalities in systolic pump function are associated with reductions in β-adrenergic receptor density and abnormal G-protein function, so β-adrenergic receptor stimulation results in an attenuated production of cAMP. cAMP also plays an important role in the regulation of myocardial relaxation. The basal rate of LV isovolumic relaxation is prolonged in patients with CHF, and in vitro myocardium from patients with end-stage CHF exhibits prolongation of relaxation associated with a delayed fall in intracellular Ca2+ concentration.

Based on the preceding considerations, we hypothesized that the effect of β-adrenergic receptor stimulation on the rate of LV isovolumic relaxation would be attenuated in patients with severe CHF. This hypothesis is supported by observations in dogs with LV failure after aortic banding but has not been tested in humans. To test this hypothesis, we evaluated the effects of intracoronary and intravenous infusions of the β-adrenergic agonist dobutamine on the rate of LV isovolumic relaxation in patients with severe CHF and in normal subjects without LV dysfunction or CHF.
TABLE 1. Baseline Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>CHF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48±3</td>
<td>54±3</td>
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</tr>
<tr>
<td>LVEF (%)</td>
<td>64±5</td>
<td>22±2</td>
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</tr>
<tr>
<td>HR (beats/min)</td>
<td>70±4</td>
<td>84±3</td>
<td>0.007</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>92±5</td>
<td>85±2</td>
<td>0.10</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>125±7</td>
<td>103±3</td>
<td>0.0007</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>15±2</td>
<td>25±2</td>
<td>0.0006</td>
</tr>
<tr>
<td>LVmin (mm Hg)</td>
<td>6±3</td>
<td>16±1</td>
<td>0.0001</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>12±2</td>
<td>28±2</td>
<td>0.0001</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>3.6±0.5</td>
<td>2.3±0.2</td>
<td>0.006</td>
</tr>
<tr>
<td>+dP/dt max (mm Hg/sec)</td>
<td>1.271±129</td>
<td>877±66</td>
<td>0.006</td>
</tr>
<tr>
<td>−dP/dt max (mm Hg/sec)</td>
<td>−1.473±124</td>
<td>−948±88</td>
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</tr>
<tr>
<td>T₁ (msec)</td>
<td>50±5</td>
<td>71±4</td>
<td>0.001</td>
</tr>
<tr>
<td>T₁/2 (msec)</td>
<td>33±4</td>
<td>50±3</td>
<td>0.002</td>
</tr>
<tr>
<td>TₙL (msec)</td>
<td>50±5</td>
<td>71±3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; HR, heart rate; MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVmin, left ventricular minimum pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; +dP/dt max, peak positive left ventricular dP/dt; −dP/dt max, peak negative left ventricular dP/dt; T₁, τ, logarithmic method; T₁/2, τ, direct pressure half-time method; TₙL, τ, nonlinear method.

Methods

Patients

The study population consisted of 28 subjects divided into two groups. Group 1 (“normals,” n=10) had no evidence of LV dysfunction or symptomatic CHF. These patients (six men and four women; mean age, 48±3 years) had normal baseline hemodynamic function (Table 1). Of this group, seven had normal coronary arteries and three had minimal coronary artery disease. None had a history of CHF symptoms or had been treated for CHF, and none had evidence of cardiomegaly on chest x-ray. This group of patients underwent diagnostic catheterization for investigation of a chest pain syndrome. All had been taking nitrates or calcium channel antagonists, and these were discontinued the evening before catheterization. β-Blockers (two patients) were held for 24 hours before catheterization. None had evidence of mitral insufficiency.

Group 2 (those with CHF, n=18) consisted of patients with idiopathic (n=9), ischemic (n=7), and adriamycin-related (n=1) dilated cardiomyopathy (Table 1). In addition, one patient had muscular dystrophy with a dilated cardiomyopathy characterized by severe systolic dysfunction. All patients had severe New York Heart Association functional class III or IV CHF despite treatment with digitalis, diuretics, and vasodilators. One patient was also taking the phosphodiesterase inhibitor milrinone. Cardiac medications in this group were discontinued the evening before catheterization. There were 11 men and seven women (mean age, 54±3 years). All had evidence of severe LV systolic dysfunction by two-dimensional echocardiography or radionuclide ventriculography (mean LV ejection fraction, 22±2%). One patient had significant mitral insufficiency. Of the patients with ischemic cardiomyopathy, none had symptoms of angina at the time of investigation, and none had documented myocardial infarction within the previous 3 months.

The study protocol was approved by the Committee for the Protection of Human Subjects from Research Risks at the Brigham and Women’s Hospital, and written informed consent was obtained in all cases.

Hemodynamic Measurements

All patients initially underwent routine diagnostic left and right heart catheterization using the femoral approach. After the diagnostic procedure, at least 20 minutes elapsed before the beginning of this investigation. An 8F micromanometer-tipped catheter (Millar Industries, Houston, Tex.) was then placed in the LV. Femoral artery pressure was monitored via a 9F side-arm sheath (Cordis Laboratories, Miami, Fla.). In patients undergoing intracoronary dobutamine administration, a 7F L-4 Judkins catheter (Cordis Laboratories) was placed from the opposite femoral artery and advanced to the ostium of the left main coronary artery as would be done for routine contrast injection. In patients receiving systemic dobutamine administration, a 5F pacing catheter (Cordis Laboratories) was advanced to the right atrium (12 patients) or right ventricle (two patients). Pacing was initiated at a rate 10–15 beats/min above the resting control rate and was maintained constant throughout the study.

The electrocardiogram, femoral arterial pressure, LV pressure, and the first derivative of LV pressure (continuous electronic differentiation, model 2203A amplifier, Electronics for Medicine, Honeywell, Inc., Pleasantville, N.Y.) were recorded on a strip chart recorder. Measurements for heart rate, mean arterial pressure, LV systolic pressure, LV minimum diastolic pressure, LV end-diastolic pressure (LVEDP), LV peak +dP/dt (+dP/dt), and peak −dP/dt (−dP/dt) were made by averaging at least 15 consecutive beats under each experimental condition.

The time constant of LV isovolumic relaxation, τ, was calculated in three different ways. The first method is a modification of that described by Weiss et al: τ (T₁) = −1/slope of the regression line for the natural logarithm of LV pressure versus time for the period from peak −dP/dt to 5 mm Hg above the LVEDP. The second method used is the direct measurement of the pressure half-time (T₁/2) described by Mirsky. With this method, τ is directly measured from the pressure tracing as the time required for LV pressure to fall to one half of its value at −dP/dt max. The third method uses a nonlinear regression analysis of the relation between LV pressure and time, as recently used by Frais et al. LV pressure recordings were digitized at 3–5 msec intervals using a digitizing tablet (SUMMAGRAPHICS, Summagraphics Corporation, Fairfield, Conn.) interfaced with an IBM-XT.
personal computer. Values for τ represent the mean calculated from four consecutive cardiac cycles during each experimental condition.

**Dobutamine Administration Protocols**

Two protocols were used for dobutamine infusion. One group of 14 subjects (six normals, eight CHF) received dobutamine by continuous infusion into the left main coronary artery. Because it is theoretically possible that the intracoronary infusion of a positive inotropic agent could induce regional changes in LV systolic and/or diastolic function, a second group of 14 subjects (four normals, 10 CHF) received dobutamine by systemic intravenous infusion.

**Intracoronary Dobutamine Infusion**

After placement of catheters, control hemodynamic data were acquired during the fifth minute of intracoronary infusion of 5% dextrose in water (D₅W), the vehicle for intracoronary drug infusion, at a rate of 4 ml/min. Dobutamine diluted in D₅W was then infused at a rate of 25 μg/min, and hemodynamic measurements were made during the fifth minute of the infusion period. The infusion rate of 25 μg/min was chosen because our previous experience indicated that this infusion rate is associated with a moderate positive inotropic effect in patients with heart failure and is generally well tolerated in patients without heart failure. Assuming a left main coronary artery blood flow of 125 ml/min, the estimated dobutamine concentration in the coronary artery is approximately 200 μg/l, a level similar to or greater than that achieved during intravenous drug infusion at the systemic rate of 14 μg/kg/min. The 5-minute infusion interval was chosen on the basis of our previous experience, which demonstrated that the positive inotropic response to dobutamine reaches a plateau by the end of the fourth minute of intracoronary infusion.

**Intravenous Dobutamine**

Intravenous dobutamine was infused with upward titration of the infusion rate at 5-minute intervals according to the following schedule: 2.5, 5.0, 7.5, and 10 μg/kg/min. Hemodynamic measurements were made during the fifth minute of each infusion period. Upward titration continued until the 10 μg/kg/min dose was achieved or heart rate increased to above the paced rate. The +dP/dt response to each infusion rate of dobutamine reached plateau by the end of the fourth minute of infusion.

**Statistical Methods**

All data are presented as mean±SEM. Differences between two observations for one variable within the same group were determined by a two-tailed, paired t test. Differences between two groups were determined by a two-tailed, nonpaired t test. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

**Table 2. Hemodynamic Responses to Intracoronary Dobutamine**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dobutamine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal left ventricular function (n=6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>66±4</td>
<td>78±10</td>
<td>0.30</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>91±6</td>
<td>95±6</td>
<td>0.20</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>118±9</td>
<td>125±9</td>
<td>0.30</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>16±2</td>
<td>12±3</td>
<td>0.009</td>
</tr>
<tr>
<td>LVmin (mm Hg)</td>
<td>7±1</td>
<td>5±1</td>
<td>0.04</td>
</tr>
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<td>+dP/dtmax (mm Hg/sec)</td>
<td>1,154±124</td>
<td>2,053±342</td>
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</tr>
<tr>
<td>-dP/dtmax (mm Hg/sec)</td>
<td>-1,367±218</td>
<td>-1,602±306</td>
<td>0.10</td>
</tr>
<tr>
<td>TL (msec)</td>
<td>53±8</td>
<td>43±5</td>
<td>0.003</td>
</tr>
<tr>
<td>T₁/2 (msec)</td>
<td>38±5</td>
<td>30±4</td>
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</tr>
<tr>
<td>T₅₅ (msec)</td>
<td>54±7</td>
<td>45±8</td>
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</table>

**Congestive heart failure (n=8)**

<p>| | | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>81±5</td>
<td>87±8</td>
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<td>84±1</td>
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<td>LVSP (mm Hg)</td>
<td>102±3</td>
<td>107±2</td>
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</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>24±3</td>
<td>21±3</td>
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</tr>
<tr>
<td>LVmin (mm Hg)</td>
<td>15±2</td>
<td>12±2</td>
<td>0.006</td>
</tr>
<tr>
<td>+dP/dtmax (mm Hg/sec)</td>
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<td>1,149±160</td>
<td>0.01</td>
</tr>
<tr>
<td>-dP/dtmax (mm Hg/sec)</td>
<td>-962±71</td>
<td>-1,168±109</td>
<td>0.004</td>
</tr>
<tr>
<td>TL (msec)</td>
<td>74±7</td>
<td>57±4</td>
<td>0.002</td>
</tr>
<tr>
<td>T₁/2 (msec)</td>
<td>48±3</td>
<td>42±3</td>
<td>0.005</td>
</tr>
<tr>
<td>T₅₅ (msec)</td>
<td>76±5</td>
<td>56±5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

HR, heart rate; MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVmin, left ventricular minimum pressure; +dP/dtmax, peak positive left ventricular dP/dt; -dP/dtmax, peak negative left ventricular dP/dt; T₁, τ, logarithmic method; T₁/2, τ, direct pressure half-time method; T₅₅, τ, nonlinear method.

**Results**

**Baseline Hemodynamics**

See Table 1. Patients in the normal group had normal baseline hemodynamics. As expected, the patients in the CHF group had markedly elevated LV filling pressures, reduced cardiac index, higher resting heart rates, and lower LV systolic pressures. LV +dP/dt was significantly reduced in the CHF patients. T₁, τ by the method of Weiss et al,16 T₁/2, τ by the method of Mirsky,17 and T₅₅, τ by nonlinear regression,18 were each significantly increased in the CHF group. The correlation coefficients for the linear regression of time versus the logarithm of LV pressure during isovolumic relaxation were high in both the CHF and normal groups, averaging 0.992±0.003 for the combined groups.

**Hemodynamic Effects of Intracoronary Dobutamine**

See Table 2. In both the normal and CHF groups, the administration of intracoronary dobutamine at 25 μg/min was associated with no significant change in heart rate or mean arterial pressure. In the CHF group, there was a small increase in LV systolic pressure (p=0.04 versus control), which also tended to increase in the normal group. In both groups, the 25 μg/min infusion rate caused reductions in LVEDP (p=0.009 versus control for both groups) and LV
Hemodynamic Effects of Intravenous Dobutamine

See Table 3. All patients in both the normal and CHF groups achieved at least the 5 µg/kg/min infusion rate of intravenous dobutamine. At this infusion rate, there was a small increase in LV systolic pressure in the normal group (p=0.04 versus control) but no significant change in the CHF group. In both groups, there were no changes in heart rate or mean arterial pressure with dobutamine. LVEDP was reduced by dobutamine in the CHF group (p=0.02 versus control) but was unchanged in the normal group (p=0.4 versus control). LV minimum pressure was reduced by dobutamine in both groups (p<0.004 versus control for both groups). Intravenous dobutamine infusion at 5 µg/kg/min caused a significant increase in +dP/dt in both the normal and CHF groups. As with intracoronary dobutamine infusion, the +dP/dt response to intravenous dobutamine was significantly reduced in the CHF group (p<0.001; normals versus CHF).

In both groups, intravenous dobutamine was associated with an increase in the rate of LV isovolumic pressure decline. T1 was significantly reduced by intravenous dobutamine in both the CHF and normal groups (p<0.009 versus control for both groups), as were T1/2 (p<0.04 versus control for both groups) and TNL (p<0.02 versus control for both groups). Individual responses for T1 in both groups are shown in Figure 1B. As with intracoronary dobutamine, despite the significantly reduced positive inotropic response in the CHF group, the lusitropic responses were similar in the two groups (Figure 3, Table 3).

**FIGURE 1.** Plots show effects of intracoronary and intravenous dobutamine infusion on T1 (T), the time constant of left ventricular isovolumic relaxation, in individual patients. Panel A: Intracoronary dobutamine. Panel B: Intravenous dobutamine. NLS, normal subjects; CHF, patients with congestive heart failure.

**FIGURE 2.** Bar graphs show comparison of inotropic and lusitropic responses to intracoronary dobutamine infusion (25 µg/min) in normal subjects (NLS) and patients with congestive heart failure (CHF). Panel A: Absolute changes in +dP/dt and T1. Panel B: Percent changes in +dP/dt and T1.
TABLE 3. Hemodynamic Responses to Intravenous Dobutamine (5 μg/kg/min)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dobutamine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal left ventricular function (n=4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HR (beats/min)</td>
<td>74±8</td>
<td>74±8</td>
<td>0.40</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>95±10</td>
<td>102±8</td>
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<tr>
<td>LVSP (mm Hg)</td>
<td>127±11</td>
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</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>14±2</td>
<td>13±4</td>
<td>0.40</td>
</tr>
<tr>
<td>LVmin (mm Hg)</td>
<td>6±1</td>
<td>3±1</td>
<td>0.003</td>
</tr>
<tr>
<td>+dP/dtmax (mm Hg/sec)</td>
<td>1,446±264</td>
<td>2,817±613</td>
<td>0.03</td>
</tr>
<tr>
<td>−dP/dtmax (mm Hg/sec)</td>
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<td>−2,669±477</td>
<td>0.05</td>
</tr>
<tr>
<td>T1/2 (msec)</td>
<td>45±3</td>
<td>37±4</td>
<td>0.008</td>
</tr>
<tr>
<td>TNL (msec)</td>
<td>33±4</td>
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<td>0.03</td>
</tr>
<tr>
<td>HR (beats/min)</td>
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<td>0.70</td>
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<tr>
<td>MAP (mm Hg)</td>
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<td>0.60</td>
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<td>LVSP (mm Hg)</td>
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<tr>
<td>LVEDP (mm Hg)</td>
<td>25±2</td>
<td>22±2</td>
<td>0.02</td>
</tr>
<tr>
<td>LVmin (mm Hg)</td>
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</tr>
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<td>+dP/dtmax (mm Hg/sec)</td>
<td>830±96</td>
<td>980±114</td>
<td>0.005</td>
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<tr>
<td>−dP/dtmax (mm Hg/sec)</td>
<td>−952±137</td>
<td>−1,135±172</td>
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</tr>
<tr>
<td>T1/2 (msec)</td>
<td>70±4</td>
<td>60±4</td>
<td>0.0001</td>
</tr>
<tr>
<td>TNL (msec)</td>
<td>48±3</td>
<td>42±3</td>
<td>0.003</td>
</tr>
<tr>
<td>HR, heart rate; MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVmin left ventricular minimum pressure; +dP/dtmax, peak positive left ventricular dP/dt; −dP/dtmax, peak negative left ventricular dP/dt; T1/2, τ, logarithmic method; TL, τ, direct pressure half-time method; TNL, τ, nonlinear method.</td>
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</tr>
</tbody>
</table>

The absolute decreases in T1/2, TNL, and TNL were similar for the two groups (p>0.2; normals versus CHF for each method; Table 3, Figure 3A). Likewise, the percent changes in T1 (Figure 3B), T1/2, and TNL were not different between the groups (p>0.1; normals versus CHF for each method).

Baseline values for T1 were similar for patients with ischemic cardiomyopathy versus those with global LV failure: 72±8 msec versus 71±3 msec, respectively. Likewise, the lusitropic response to β-adrenergic receptor stimulation was similar in the two groups. For intracoronary dobutamine (25 μg/min), the absolute change in T1 in patients with ischemic cardiomyopathy (-18±4 msec) was not different from that in patients with global LV failure (-15±3 msec; p=NS). Likewise, with intravenous dobutamine (5 μg/kg/min) the absolute change in patients with ischemic cardiomyopathy (-7±1 msec) was not different from that in patients with global LV failure (-11±2 msec; p=NS).

The relation between the absolute changes in +dP/dt and T1 in response to various infusion rates of dobutamine is compared in the normal and CHF groups in Figure 4. At infusion rates of 2.5 and 5.0 μg/kg/min, the absolute changes in +dP/dt are greater in the normal group than in the CHF group.

By contrast, the absolute change in T1 at the 2.5 and 5.0 μg/kg/min infusion rates is similar in the two groups. At the higher infusion rates of 7.5 and 10.0 μg/kg/min, which were received only by the CHF patients, there is little further change in +dP/dt or T1.

Discussion

In patients with severe CHF, both the inotropic and chronotropic responses to intravenous dobutamine infusion (5 μg/kg/min) in normal subjects (NLS) and patients with congestive heart failure (CHF). Panel A: Absolute changes in +dP/dt and T1. Panel B: Percent changes in +dP/dt and T1.

Studies in muscle strips, isolated hearts, and intact animals have demonstrated that β-adrenergic receptor stimulation accelerates myocardial relaxation. However, relatively little data are available for normal humans. Starling et al reported decreases in T1 ranging from 9 to 23 msec with intravenous dobutamine infusion in three normal subjects. How-
ever, since heart rate also increased substantially in
two of these subjects, a direct myocardial effect of
\( \beta \)-adrenergic stimulation could not be distinguished
from a secondary effect because of the increase in
heart rate. Pouleur et al\textsuperscript{25} observed a significant
reduction in the time constant of LV isovolumic
relaxation with intravenous bolus infusion of isopro-
teranol in patients with coronary artery disease and
normal LV ejection fractions. Again, however, be-
cause heart rate increased substantially (by an aver-
age of 25 beats/min), conclusions regarding direct
myocardial stimulation versus the indirect effects of
increased heart rate were not possible. Recently,
Udelson et al\textsuperscript{26} demonstrated a direct effect of \( \beta \)-ad-
renergic receptor stimulation on LV isovolumic
relaxation, in addition to its effect on heart rate, by
showing that the acceleration of LV isovolumic
relaxation during intravenous infusion of isoproteranol
exceeds that caused by right atrial pacing at a similar
heart rate.

Because an increase in heart rate per se can cause
an increase in the rate of LV isovolumic relax-
ation\textsuperscript{16,23,26} we felt it was important that heart rate be
controlled by pacing during intravenous dobutamine
infusion. Our data indicate that in normal subjects, a
moderate (5 \( \mu \)g/kg/min) infusion rate of dobutamine
that increases \( +dP/dt \) by 95\% is associated with an
approximately 18\% decrease in \( \tau \) at a constant paced
heart rate. A similar acceleration of relaxation is also
observed with the intracoronary infusion of dobu-
tamine in normal subjects.

Two prior studies have provided observations on
the lusitropic effect of \( \beta \)-adrenergic stimulation in
patients with CHF. Carroll et al\textsuperscript{27} studied the effect
of dobutamine on several diastolic indexes including
\( \tau \) in 12 patients with dilated cardiomyopathy. At an
infusion rate of 6 \( \mu \)g/kg/min, they observed that \( T_L \)
decreased an average of 12\%. However, that study
did not include patients without CHF for compari-
son. Pouleur et al\textsuperscript{25} compared the effect of an intra-
venous bolus of isoproterenol in patients with ejection
fractions of less than 35\% or greater than 55\%.
Although the lusitropic responses of the two groups
were comparable, the interpretation of that study is
confounded by several factors: 1) All of the patients
in both groups had significant symptomatic coronary
artery disease; 2) some of the patients in the group
with normal ejection fraction had symptoms of CHF;
and 3) isoproterenol administration was associated
with substantial increases in heart rate, so the possi-
bile effects of myocardial ischemia to alter isovolumic
relaxation could not be excluded.\textsuperscript{28} The marked
chronotropic response in that study also made it
difficult to conclude that the observed changes in
isovolumic relaxation reflected a direct myocardial
effect of \( \beta \)-adrenergic receptor stimulation as op-
posed to the secondary effect of increased heart rate.

There are several possible explanations for the
relative preservation of the lusitropic response to
\( \beta \)-adrenergic receptor stimulation in patients with
CHF. First, although both the positive inotropic and
lusitropic responses to \( \beta \)-adrenergic stimulation are
mediated by cAMP, the pathways for these responses
diverge distal to cAMP generation.\textsuperscript{20} \( \beta \)-Adrenergic
receptor stimulation causes a positive inotropic re-
response caused by the action of cAMP to increase
inward conductance of calcium via L-type calcium
channels, therefore presenting more free calcium to
the contractile apparatus.20 By contrast, β-adrenergic receptor stimulation accelerates relaxation through the actions of cAMP to 1) accelerate reuptake of calcium by the sarcoplasmic reticulum, 2) reduce calcium sensitivity of the contractile apparatus, and 3) accelerate the rate of myofilament cross-bridge detachment.8–10,13,20 Our findings raise the possibility that the lusitropic pathway distal to cAMP is more sensitive to cAMP than is the inotropic pathway. If this were the case, reduced cAMP generation in response to β-adrenergic receptor stimulation might have little or no effect on LV relaxation despite causing a marked reduction in the inotropic response. These data further suggest that the pathways responsible for mediating an increase in myocardial relaxation are preserved in the failing heart and are consistent with the observation that basal29 and phospholamban-mediated stimulation30 of calcium uptake in sarcoplasmic reticulum of failing human myocardium are comparable with that in normal myocardium.

Another possible explanation for our findings may involve the potential effect of changes in myocardial end-systolic dimension on LV isovolumic relaxation. There is evidence that the positive lusitropic effect of β-adrenergic stimulation is, in part, due to a reduction in end-systolic chamber dimension,31,32 which may result in increased elastic recoil or restoring forces of the LV. However, recent studies in humans have suggested that τ is relatively insensitive to changes in LV loading conditions.24,27,33 For example, Carroll et al.27 found that although systemic administration of dobutamine and nitroprusside to patients with CHF caused comparable reductions in LV end-systolic dimension, only dobutamine caused a consistent acceleration of LV isovolumic relaxation assessed by τ. Although the effect of β-adrenergic receptor stimulation to decrease end-systolic LV volume is likely reduced in patients with severe heart failure and systolic dysfunction, we cannot exclude the possibility that the failing ventricle might have a heightened sensitivity to and/or a greater development of restoring forces for any given decrease in volume.

It is possible that the results of this study reflect, to some degree, the effects of β-adrenergic receptor stimulation to improve the synchrony of LV relaxation.34 For instance, in patients with hypertrophic cardiomyopathy, isoproterenol improves the synchrony of early LV filling.35 Potentially, an effect of β-adrenergic stimulation to improve the synchrony of LV relaxation might have affected our results. To approach this possibility, we compared the relaxation rates in the CHF subjects with ischemic cardiomyopathy, and therefore presumably substantial asynchrony, with the relaxation rates in the patients with global LV dysfunction. LV isovolumic relaxation rates at baseline were similar in these two groups, as were their lusitropic responses to β-adrenergic stimulation. Thus, it is unlikely that an alteration in synchrony associated with β-adrenergic receptor stimulation significantly affected our results. Conversely, it has been suggested that the regional application of a potent positive inotropic agent may cause asynchrony in the timing of ventricular events and thus might prolong the rate of LV pressure decline.36 Theoretically, such heterogeneity caused by intracoronary drug infusion might be more marked in the normal group because of their greater inotropic responsiveness and thereby might result in apparent blunting of the lusitropic response. It was this possibility that led us to confirm the results of the intracoronary protocol using intravenous drug infusion. Since the lusitropic effects of intravenous infusion were similar to those with intracoronary infusion, this theoretical effect does not appear to play an important role in the results of this investigation.

There is no consensus as to which mathematical model provides the most accurate and physiological description of LV isovolumic pressure decline. The logarithmic method of Weiss et al.,16 T1, has been criticized because it makes the nonphysiological assumption that LV pressure falls monoeXponentially toward zero pressure. It has been demonstrated that this assumption may not be true,37 and further, that values for the rate of LV pressure decay obtained by this method may be sensitive to changes in intrapericardial and intrathoracic pressure.38 Nevertheless, the monoeXponential model of Weiss et al. very closely approximates the directly measured half-time of LV pressure decline37 and is not affected by moderately large changes in afterload or preload.24,33 Thus, despite theoretical limitations, T1 is advocated by several authors24,33,39 as a reasonable index of LV isovolumic relaxation rate, particularly when the correlation between time and the logarithm of LV pressure is high, as it was in this study. We have also evaluated the rate of LV pressure decay by two additional methods, the direct pressure half-time technique proposed by Mirsky17 and a nonlinear regression analysis.18 These analyses make no assumptions concerning the LV pressure asymptote and have recently been used in several investigations of LV diastolic performance.18,26,35,40

Potentially, our failure to detect an attenuation of the β-adrenergic receptor–stimulated acceleration of LV isovolumic relaxation might reflect the selection of patients with relatively mild CHF. This possibility seems unlikely because the CHF patients in this study all had clinically and hemodynamically severe CHF associated with substantial prolongation of the resting isovolumic relaxation rate as well as substantial attenuation of the positive inotropic response to β-adrenergic receptor stimulation. There is also the possibility that the sample size in this investigation allowed a β-type error. However, there is actually a trend for the CHF group to have a greater lusitropic response than the normal group, thus making the possibility of a β-type error unlikely.

This investigation demonstrates that β-adrenergic receptor stimulation accelerates LV isovolumic relaxation in both normal and failing human hearts. Contrary to our hypothesis, the lusitropic response to
β-adrenergic stimulation is preserved in patients with severe CHF despite the presence of markedly attenuated inotropic and chronotropic responses. In this context, it is interesting that the arterial dilator response to β-adrenergic stimulation, like the lusitropic response, is also preserved in patients with severe heart failure.\(^{41}\)

The clinical implications of our findings are uncertain. Although β-adrenergic receptor stimulation accelerates the isovolumic phase of LV diastolic performance in patients with CHF, we did not examine the effects of β-adrenergic receptor stimulation on LV filling or the diastolic pressure–volume relation in this investigation. It should be noted that although β-adrenergic receptor stimulation causes a normal acceleration of LV isovolumic relaxation in patients with CHF, this effect is superimposed on a substantially prolonged basal relaxation rate. Even with the intense β-adrenergic stimulation of dobutamine, LV isovolumic relaxation in our patients with CHF is somewhat slower than the resting rate in normal subjects (see Tables 2 and 3). As a consequence, LV relaxation during sympathetic stimulation (e.g., during exercise) may still be sufficiently impaired to contribute to hemodynamic compromise.

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**References**


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