The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy

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ABSTRACT Symptoms of congestive heart failure frequently reflect abnormalities in both systolic and diastolic performance. While much work has been reported regarding the mechanisms by which positive inotropic and vasodilator therapy affect systolic performance, little is known about their effect on diastolic function. In 12 patients with diffuse congestive cardiomyopathy micromanometer left ventricular and aortic pressure measurements were recorded simultaneously with two-dimensionally targeted M mode echocardiograms and thermodilution-determined cardiac output. Each patient received dopamine (2, 4, and 6 μg/kg/min), and dobutamine (2, 6, and 10 μg/kg/min), and 10 received nitroprusside (0.125 to 2.0 μg/kg/min). Baseline hemodynamics were characterized by low cardiac index (2.1 ± 0.7 liter/min/m², mean ± SD), high left ventricular end-diastolic pressure (24 ± 10 mm Hg), and increased end-diastolic (6.8 ± 1.0 cm) and end-systolic dimensions (6.0 ± 1.0 cm). All patients had abnormal left ventricular pressure decay with a prolonged time constant (67 ± 20 msec) and reduced peak diastolic lengthening rates. Dopamine and dobutamine decreased the time constant of relaxation and increased the peak lengthening rate. Dobutamine also reduced the minimum diastolic pressure from 14 ± 7 to 10 ± 9 mm Hg (p < .01); neither drug reduced end-diastolic pressure. In fact, dopamine elevated end-diastolic pressures in seven patients, despite more rapid pressure decay. Diastolic pressure-dimension relations after dopamine and dobutamine showed a leftward shift with a reduced end-systolic chamber size, but no significant changes in passive chamber stiffness. Nitroprusside decreased left ventricular minimum diastolic pressure by 4 ± 2 mm Hg and end-diastolic pressure by 7 ± 4 mm Hg (p < .01). It did not consistently accelerate left ventricular pressure decay at the doses tested. The decreased end-diastolic pressure with nitroprusside was due to a reduced end-diastolic dimension in five patients. In the other patients, all of whom had elevated right atrial pressures, diastolic pressure-dimension relations showed a parallel downward shift after nitroprusside. Thus, positive inotropic therapy with β1-adrenoceptor agonists enhances early diastolic distensibility by accelerating relaxation, augmenting filling, and reducing end-systolic chamber size. Vasodilator therapy is much more effective in lowering diastolic pressures. In some patients this is due to a reduction in extrinsic restraint of the pericardium and/or right ventricular interaction, while in others it simply reflects a decrease in chamber size without alterations in ventricular passive chamber properties.


AS OUR UNDERSTANDING of the pathophysiology of the heart failure syndrome has improved, certain classes of drugs have assumed prominent roles in its treatment. The administration of vasodilating agents is a logical result of the discovery of abnormal peripheral vascular loading conditions, which elevate resistance to ventricular ejection and produce high filling pressures.positive inotropic therapy remains a reasonable approach since a reduction in the contractile state of the myocardium appears central to the disease process. Little attention has been focused on striking diastolic abnormalities found in the failing heart. In this study we used isovolumetric pressure decay, left ventricular lengthening rates, diastolic pressure–chamber size relations, and pressure measurements throughout diastole to characterize the diastolic properties found in diffusely dilated, cardiomyopathic ventricles.
We hypothesized that positive inotropic therapy should be accompanied by an acceleration in isovolumetric pressure decay and enhancement of early diastolic distensibility. To study this issue, the myocardial β₁-adrenoreceptor agonists dobutamine and dopamine were used. Although both of these drugs affect systemic vascular tone, only dopamine is capable of modulating vascular tone through peripheral dopaminergic receptors. In addition, α-receptor activation may further modify dopamine’s actions.

We further hypothesized that vasodilating agents may decrease diastolic pressures by several mechanisms. Diastolic pressures should decrease to a greater degree than chamber size if ventricular interaction and/or pericardial restraint are present. We chose to study the well-known agent nitroprusside, a drug with nonspecific venous and arterial vasodilator actions.

By studying all three agents in each patient, we hoped to gain a more complete understanding of the differential effects of positive inotropic and vasodilator therapy on diastolic function in patients with congestive cardiomyopathy. In so doing, additional insights into the pathophysiology and treatment of congestive heart failure could be revealed.

Methods

Patient population. Twelve patients with congestive cardiomyopathy were studied. There were eight men and four women who ranged in age from 26 to 62 years (mean = 48). The cause of the cardiomyopathy was idiopathic in eight patients and probably due to systemic hypertension in four patients. Although mild-to-moderate coronary artery disease (one to two vessels with at least 50% diameter narrowing) was present in five patients, no patient had a history of clinical infarction. Patients were included in the study only if their echocardiograms were of high quality and showed a diffusely hypokinetic, dilated left ventricle. Patients with significant regional wall motion abnormalities were excluded from the study. By Doppler examination seven had no significant mitral regurgitation and five had moderate regurgitation without intrinsic mitral valve abnormalities. The QRS complex was prolonged to 110 msec or greater on the resting electrocardiogram of four patients. All patients had symptomatic heart failure despite therapy with digoxin and diuretics; New York Heart Association functional class ranged from 2 to 4 (mean = 3.4) while on therapy. All patients gave written informed consent to a protocol approved by the Human Investigation Committee of the University of Chicago.

Cardiac catheterization. Patients were studied while in the fasting state and after premedication with diazepam (5 mg orally) and atropine (0.5 mg subcutaneously). Vasodilators were withheld for 48 hr in the two patients taking them.

Right and left heart catheterizations were performed from the femoral artery and vein in all patients. A Millar catheter with a high-fidelity pressure transducer at the distal end (Model SPC-484A) was used in two patients and a catheter with an additional pressure transducer 5 cm proximal to the end (Model SVP-684D) was used in the remaining patients. The catheter tip was soaked in warm saline for 45 to 60 min before calibration and subsequent insertion. The side port of the arterial sheath was used for pressure reference relative to micromanometer pressures. A triple-lumen, balloon-tipped thermodilution catheter was placed with its distal portion in the pulmonary artery and its proximal port in the right atrium. The side port of a venous sheath was used for administration of drugs. Thermodilution cardiac outputs were averaged from three to five measurements such that variability was less than 10%.

In all patients, pressure tracings and the surface electrocardiogram (lead II) were simultaneously recorded on a Hewlett-Packard recorder (4568C) and a Mennen-Greatbatch Series 939 computerized catheterization system. In the last seven patients studied, data were directly digitized on-line and stored on diskette with the use of an IBM-PC with an analog-digital interface board (Data Translation). Data were digitized at 400 Hz.

Ultrasound imaging (Hewlett-Packard) was performed with a 5 MHz transducer with the patient in the left lateral decubitus position. Two-dimensionally targeted M mode echocardiographic recordings of the left ventricular cavity were obtained with simultaneous left ventricular and central aortic pressure tracings (figure 1). The papillary muscles and mitral apparatus were used as internal landmarks to ensure a stable and reproducible position for left ventricular cavity measurements.

Drug infusions. Control measurements were obtained at 20 min after placement of all catheters. Subsequently either dopamine or dobutamine was infused. Even-numbered patients received dopamine first while odd-numbered patients received dobutamine first. Dopamine was infused at sequential rates of 2, 4, and 6 μg/kg/min; dobutamine was infused sequentially at rates of 2, 6, and 10 μg/kg/min. After each drug infusion was completed, a minimum of 15 min elapsed before the beginning of a new control period. Subsequent recordings of cardiac outputs and pressures were used to confirm a return to baseline hemodynamics. After completion of dopamine and dobutamine

![FIGURE 1. Data from a representative patient showing high-fidelity left ventricular and aortic pressures recorded simultaneously with a two-dimensional targeted M mode echocardiogram on the left ventricle. Note the dilated chamber with high diastolic pressures. ECG = electrocardiogram; IVS = interventricular septum; LV = left ventricular; PW = posterior wall.](http://circ.ahajournals.org/lookup/fig/0001026065.jpg)
infusions and return to baseline hemodynamics, nitroprusside was infused at sequential doses of 0.125, 0.25, 0.5, 1.0, and 2.0 
µg/kg/min until there was a significant reduction in mean arterial 
pressure (minimum of 5 mm Hg) or a reduction in systolic 
pressure to 90 mm Hg. Two patients did not receive nitroprusside 
because a mean pressure was less than 90 mm Hg during the 
control period. Data obtained at the maximal infusion rate of 
nitroprusside are presented.

On completion of the drug infusions, coronary arteriographic 
examinations by the Judkins technique were performed in all 
patients.

**Data analysis**

**Pressures.** Left ventricular systolic, end-diastolic, and mini-
mum diastolic pressures as well as maximum positive dP/dt, 
central aortic pressure, pulmonary arterial pressure, and right 
atrial pressure were computed by the Mennen-Greatbatch com-
puter and verified by recordings on photographic paper.

Recordings of left ventricular pressure at a paper speed of 200 
mm/sec were digitized and stored on a PDP 10/20 computer in 
the first five patients. In subsequent patients on-line digitized 
data from the IBM-PC were used. From these data three indexes 
of isovolumetric pressure decay were computed since uncertain-
ity exists as to the proper method to use in patients with different 
diseases. The ½ was the time for pressure to fall to one-half of 
its value at peak negative dP/dt. The time constant of isovolu-
metric pressure decay, Tp, was computed as the negative recipro-
cal of the linear regression of the natural logarithm of pressure 
vs time. Finally, a linear regression of pressure vs dP/dt was 
used to compute Tp (the negative reciprocal of the slope) and Pp 
(the pressure axis intercept of the computed linear regression). 
This method was included since there is no assumption of a zero 
baseline.

**Echocardiographic data.** Left ventricular internal dimen-
sions and pressures were digitized on a computer (Quantic 
1200, Bruce Franklin, Inc. Seattle) to yield diastolic pressure-
dimension relations and early diastolic peak lengthening rates. 
They were also expressed as normalized lengthening rates by 
dividing by end-systolic dimension. Pressure-dimension plots 
were constructed with coordinates from five time references. 
These included the time at which pressure had decayed to 50 
mm Hg, at diastolic pressure nadir, and at end-diastole. Two 
additional coordinates were at dimensions midway between the 
three. This allowed construction of representative diastolic 
pressure-dimension plots that could be averaged for all patients 
under control conditions and at the maximum drug dose. 

The left ventricular diastolic pressure-dimension relation may 
be influenced by the pericardium and right ventricle. Systemic 
venodilation with nitroprusside could reduce these influences.

Therefore, the 10 patients who received nitroprusside were di-
vided into two groups based on their mean right atrial pressures. 
There were five patients with elevated right atrial pressure 
(range 10 to 22 mm Hg) and five with no significant abnormality 
in right atrial pressure (range 3 to 7 mm Hg). We hypothesized 
that those with a grossly elevated right atrial pressure could have 
pericardial restraint and/or ventricular interaction and therefore 
could respond to nitroprusside with a parallel downward shift in 
the left ventricular diastolic pressure-dimension relation.

Pressure (P) and dimension (D) coordinates (n = 5) after the 
diastolic pressure nadir were fit to a power law function (P = 
AD^P) as suggested by Minsky. The resulting passive chamber 
stiffness measurement, α, was used to assess the effects of the 
medications on an intrinsic diastolic parameter.

**Statistical analysis.** The statistical significance of effects 
of each dose vs control was tested with use of a paired comparison 
and, for multiple comparisons, a Bonferroni correction factor. 
Statistically significant differences were accepted at p less than 
.05/k, where k = number of comparisons.

For comparison of effects of the maximum drug dose vs 
control a paired t test was used and a significant difference was 
indicated by a p value less than .05. Values are expressed as the 
mean ± SD unless otherwise stated.

### Results

In tables 1, 2, and 3 standard hemodynamic and 
echocardiographic data obtained during control peri-
ods, after each dose of dopamine and dobutamine, and 
at the highest dose of nitroprusside are presented.

#### TABLE 1

**Hemodynamic response to dobutamine**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dobutamine, 2 µg</th>
<th>Dobutamine, 6 µg</th>
<th>Dobutamine, 10 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>89 ± 15</td>
<td>88 ± 14</td>
<td>90 ± 16</td>
<td>94 ± 11</td>
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<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.1 ± 0.7</td>
<td>2.3 ± 0.7b</td>
<td>2.7 ± 0.6c</td>
<td>2.9 ± 0.5c</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>25 ± 9</td>
<td>27 ± 10a</td>
<td>31 ± 10c</td>
<td>32 ± 8a</td>
</tr>
<tr>
<td>Aortic mean pressure (mm Hg)</td>
<td>93 ± 18</td>
<td>95 ± 19</td>
<td>97 ± 22</td>
<td>96 ± 12b</td>
</tr>
<tr>
<td>Peak systolic LV pressure (mm Hg)</td>
<td>112 ± 26</td>
<td>117 ± 30a</td>
<td>122 ± 32a</td>
<td>117 ± 16c</td>
</tr>
<tr>
<td>End-diastolic (mm Hg)</td>
<td>24 ± 10</td>
<td>25 ± 11</td>
<td>23 ± 12</td>
<td>21 ± 11</td>
</tr>
<tr>
<td>Diastolic minimum (mm Hg)</td>
<td>14 ± 8</td>
<td>13 ± 8</td>
<td>12 ± 9</td>
<td>11 ± 9c</td>
</tr>
<tr>
<td>Max + dP/dt (mm Hg/sec)</td>
<td>855 ± 247</td>
<td>957 ± 299b</td>
<td>1136 ± 459b</td>
<td>1215 ± 250c</td>
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<tr>
<td>LV dimensions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic (cm)</td>
<td>6.8 ± 1.0</td>
<td>6.8 ± 1.0</td>
<td>6.7 ± 1.1</td>
<td>6.9 ± 1.0</td>
</tr>
<tr>
<td>End-systolic (cm)</td>
<td>6.1 ± 1.0</td>
<td>6.0 ± 1.1</td>
<td>5.8 ± 1.1b</td>
<td>6.1 ± 1.0b</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>11 ± 4</td>
<td>12 ± 5</td>
<td>14 ± 4b</td>
<td>13 ± 4c</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>29 ± 11</td>
<td>27 ± 10</td>
<td>30 ± 13</td>
<td>30 ± 16</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>11 ± 7</td>
<td>11 ± 6</td>
<td>9 ± 5</td>
<td>9 ± 5</td>
</tr>
</tbody>
</table>

LV = left ventricular.

*p < .05 vs control; b *p < .017 vs control; c *p < .001 vs control.
Baseline left ventricular function. All patients had significant cardiac dysfunction. Cardiac index (2.1 ± 0.7 liters/min/m²), left ventricular shortening fraction (11 ± 4%), and maximum +dP/dt (855 ± 247 mm Hg/sec) were reduced, while left ventricular end-diastolic pressure was elevated (24 ± 10 mm Hg). Minimum left ventricular diastolic pressure was 14 ± 8 mm Hg. Left ventricular chamber size was increased in all patients, with an average end-diastolic dimension of 6.8 ± 1.0 cm and an average end-systolic dimension of 6.0 ± 1.0 cm.

Baseline diastolic function was also abnormal, with prolonged isovolumetric pressure decay and reduced peak lengthening rates (table 4). The left ventricular $T_{1/2}$ was 65 ± 20 msec. The dP/dt vs pressure method of quantitating pressure decay revealed a T value of 106 ± 29 msec, with a P of −30 ± 20 mm Hg. In addition, the $t_{1/2}$ was prolonged at 53 ± 13 msec. The peak rate of diastolic lengthening was reduced at 6.4 ± 3.2 cm/sec compared with a normal range of 9 to 15 cm/sec.

Dobutamine. Data were collected in all patients at dobutamine doses of 2 and 6 μg/kg/min. In nine patients a 10 μg/kg/min infusion of dobutamine was also given. Failure to acquire data after 10 μg/kg/min dobutamine in three patients was due to hypertension in one, tachycardia in another, and ventricular ectopy in a third.

Dobutamine caused a dose-dependent increase in systolic performance, as evidenced by augmentation of maximum +dP/dt and cardiac index and a decrease in end-systolic chamber size. Dobutamine also accelerated left ventricular pressure decay, as evidenced by all indexes for this variable. $T_{1/2}$ fell from 65 ± 20 to 51 ± 19 msec after 10 μg/kg/min (p < .01). An example of the change in the left ventricular wave form is shown in figure 2. This accelerated pressure decay lowered diastolic pressures; minimum left ventricular pressure decreased from 14 ± 8 to 11 ± 9 mm Hg (p < .05) at the maximum dose (figure 3), but there was no significant (p < .08) reduction in end-diastolic pressure (figure 4). In figure 5 the left ventricular dia-

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**TABLE 2**

<table>
<thead>
<tr>
<th>Hemodynamic response to dopamine</th>
<th>Control</th>
<th>Dopamine, 2 μg</th>
<th>Dopamine, 4 μg</th>
<th>Dopamine, 6 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>86 ± 12</td>
<td>83 ± 11</td>
<td>83 ± 9</td>
<td>84 ± 11</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.2 ± 0.6</td>
<td>2.5 ± 0.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.8 ± 0.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.9 ± 0.5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>26 ± 8</td>
<td>30 ± 8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>34 ± 9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>35 ± 10&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>92 ± 16</td>
<td>93 ± 20</td>
<td>97 ± 18</td>
<td>99 ± 17</td>
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<tr>
<td>Peak systolic LV pressure (mm Hg)</td>
<td>111 ± 24</td>
<td>113 ± 26</td>
<td>123 ± 26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>128 ± 25&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>End-diastolic (mm Hg)</td>
<td>24 ± 7</td>
<td>25 ± 7</td>
<td>26 ± 9</td>
<td>23 ± 10</td>
</tr>
<tr>
<td>Diastolic minimum (mm Hg)</td>
<td>14 ± 7</td>
<td>13 ± 6</td>
<td>13 ± 8</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>Max +dP/dt (mm Hg/sec)</td>
<td>866 ± 233</td>
<td>937 ± 269&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1117 ± 297&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1344 ± 370&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>LV dimension</td>
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<td></td>
</tr>
<tr>
<td>End-diastolic (cm)</td>
<td>6.9 ± 1.0</td>
<td>6.8 ± 1.0</td>
<td>6.8 ± 1.0</td>
<td>6.8 ± 1.1</td>
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<tr>
<td>End-systolic (cm)</td>
<td>6.1 ± 1.0</td>
<td>6.0 ± 1.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.8 ± 1.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.7 ± 1.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>12 ± 4</td>
<td>13 ± 4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15 ± 5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17 ± 5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>28 ± 11</td>
<td>30 ± 10</td>
<td>33 ± 13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30 ± 13</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>11 ± 6</td>
<td>11 ± 6</td>
<td>12 ± 7</td>
<td>9 ± 5</td>
</tr>
</tbody>
</table>

LV = left ventricular.

<sup>a</sup>p < .05 vs control; <sup>b</sup>p < .017 vs control; <sup>c</sup>p < .001 vs control.

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**TABLE 3**

<table>
<thead>
<tr>
<th>Hemodynamic response to nitroprusside</th>
<th>Control</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>84 ± 14</td>
<td>87 ± 12</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.4 ± 0.6</td>
<td>2.4 ± 0.5</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>29 ± 9</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>96 ± 16</td>
<td>89 ± 15&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Peak systolic LV pressure (mm Hg)</td>
<td>121 ± 30</td>
<td>108 ± 27&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>End-diastolic (mm Hg)</td>
<td>24 ± 8</td>
<td>17 ± 9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic minimum (mm Hg)</td>
<td>13 ± 8</td>
<td>9 ± 7&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Max +dP/dt (mm Hg/sec)</td>
<td>935 ± 308</td>
<td>921 ± 290</td>
</tr>
<tr>
<td>LV dimension</td>
<td></td>
<td></td>
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<tr>
<td>End-diastolic (cm)</td>
<td>6.9 ± 1.0</td>
<td>6.7 ± 1.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>End-systolic (cm)</td>
<td>6.1 ± 1.1</td>
<td>5.9 ± 1.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>12 ± 4</td>
<td>13 ± 4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>32 ± 11</td>
<td>24 ± 12&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>11 ± 7</td>
<td>9 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

LV = left ventricular.

<sup>a</sup>p < .05 vs control; <sup>b</sup>p < .017 vs control; <sup>c</sup>p < .001 vs control.
THERAPY AND PREVENTION-CARDIOMYOPATHY

stolic pressure-dimension data are shown for the control period and the period after dobutamine at its maximum dose. In early diastole dobutamine caused a leftward shift due to the reduced end-systolic chamber size and reduced pressures relative to chamber diameter. After the diastolic pressure nadir the diastolic pressure-dimension relation for dobutamine was superimposable on the control state relation. The passive chamber stiffness constant, \( \alpha \), was not significantly altered (12.0 ± 9.4 vs 18.0 ± 25.6). Dobutamine also increased peak lengthening rate, as shown in figure 6 for normalized lengthening rates.

Dopamine. The 6 \( \mu \text{g/kg/min} \) infusion of dopamine was not given to two patients due to an excessive rise in left ventricular diastolic pressure and right atrial mean pressure. Dopamine augmented systolic performance to a degree comparable to that seen with dobutamine.

Dopamine accelerated pressure decay and increased peak lengthening rates (table 4). \( T_{\text{n}} \) fell from 66 ± 16 to 48 ± 11 msec after dopamine at 6 \( \mu \text{g/kg/min} \). However, unlike after dobutamine, minimum left ventricular pressure rose in five patients (figure 3) after dopamine, despite the accelerated pressure decay and reduced end-systolic chamber size (6.1 ± 1.0 to 5.7 ± 1.1 cm at 6 \( \mu \text{g/kg/min} \), \( p < .01 \)). In addition, left ventricular end-diastolic pressure rose in seven patients (figure 4). In figure 5 the left ventricular diastolic pressure-dimension relation for all patients is shown. After the maximum dose of dopamine there was a leftward shift in early diastole due to the smaller end-systolic chamber size and reduced pressures relative to chamber diameter in early diastole. In late diastole dopamine caused no definite shifts in pressure-dimension relations. The passive chamber stiffness constant was unaltered (10.6 ± 4.9 vs 12.8 ± 17.0).

Nitroprusside. Nitroprusside consistently lowered pressures. There was a significant reduction in mean aortic (96 ± 16 to 89 ± 15 mm Hg, \( p < .01 \)) and left ventricular end-diastolic pressure (24 ± 8 to 17 ± 9 mm Hg, \( p < .01 \)). Transients such as maximum +dP/dt and –dP/dt were unaltered (figure 2). There was no statistically significant change in the isovolumetric pressure decay time constant \( T_{\text{p}} \) (60 ± 17 to 57 ± 19 msec). The \( T_{\text{p}} \) was slightly but significantly reduced after nitroprusside. No consistent alteration in peak lengthening rate occurred (figure 6). There was a reduction in end-systolic dimension from 6.1 ± 1.1 to 5.9 ± 1.1 cm (\( p < .05 \)) and in end-diastolic dimension from 6.9 ± 1.0 to 6.7 ± 1.1 cm (\( p < .05 \)).

In figure 7 diastolic pressure-dimension relations are shown for the patients after separation into two groups according to right atrial pressures. Those pa-

patients (\( n = 5 \)) with normal or minimally elevated right atrial pressures demonstrated a leftward shift with a decrease in end-diastolic pressure simply due to a decrease in end-diastolic dimension. In contrast those patients with elevated right atrial pressures (\( n = 5 \)) showed a parallel downward shift due to a decreased end-diastolic pressure without a significant change in dimension. These patients also had more dilated left ventricles.

Discussion

This study demonstrates that isovolumetric pressure decay is very slow, lengthening rates are reduced, and the diastolic pressure-dimension relation is altered in patients with congestive cardiomyopathy. Resultant diastolic pressures are grossly elevated. These striking abnormalities in diastolic function and their modification by positive inotropic and vasodilator agents link the known pharmacologic actions of dopamine, dobutamine, and nitroprusside to distinctive hemodynamic effects that improve left ventricular diastolic performance.

The elevation of filling pressures in patients with congestive cardiomyopathy has been attributed predominantly to two causes. First is chamber dilation due to the disease process itself. This is further exacerbated by renal retention of sodium and water; chamber dilation causes a rightward shift in the diastolic pressure-volume relation in the ventricle. This normally produces higher end-diastolic pressures, but in those with longstanding congestive cardiomyopathy a new pressure-volume relation is achieved that blunts the rise in diastolic pressures.\(^9\,10\) The second cause of elevated filling pressures is increased chamber stiffness. Functional and pathologic studies of the myocardium have revealed increased muscle stiffness with increased amounts of interstitial fibrosis and myocardial hypertrophy.\(^9\,10\) These studies have emphasized the passive muscle properties and have assumed that intracavitary diastolic pressures simply reflect the interaction of passive muscle stiffness and chamber volume.

This study emphasizes the fact that left ventricular diastolic pressures are also influenced by other dynamic factors in patients with congestive cardiomyopathy. These include the rate of isovolumetric pressure decay, the restraining role of the pericardium, and/or the interaction of the two ventricles.

Patients with congestive cardiomyopathy have been reported to have a severe reduction in the rapidity of pressure fall during the left ventricle’s isovolumetric relaxation period.\(^11\) A fundamental abnormality of intracellular calcium fluxes has recently been suggest-

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TABLE 4

Left ventricular pressure decay and peak lengthening rate

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DB, 2 µg</th>
<th>DB, 6 µg</th>
<th>DB, 10 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>t½ (msec)</td>
<td>53 ± 13</td>
<td>52 ± 13</td>
<td>47 ± 14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42 ± 13&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>T&lt;sub&gt;n&lt;/sub&gt; (msec)</td>
<td>65 ± 20</td>
<td>62 ± 17</td>
<td>57 ± 22&lt;sup&gt;c&lt;/sup&gt;</td>
<td>51 ± 19&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>T&lt;sub&gt;dP/dt&lt;/sub&gt; (msec)</td>
<td>106 ± 29</td>
<td>94 ± 26</td>
<td>84 ± 22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65 ± 15&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>P&lt;sub&gt;0&lt;/sub&gt; (mm Hg)</td>
<td>-30 ± 20</td>
<td>-24 ± 21</td>
<td>-22 ± 15</td>
<td>-20 ± 9</td>
</tr>
<tr>
<td>max – dP/dt (mm Hg/sec)</td>
<td>-999 ± 414</td>
<td>-1117 ± 636</td>
<td>-1275 ± 682&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-1313 ± 425&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peak lengthening rate (cm/sec)</td>
<td>6.4 ± 3.2</td>
<td>6.8 ± 2.6</td>
<td>8.0 ± 3.2</td>
<td>9.4 ± 2.6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Normalized peak lengthening rate (length/sec)</td>
<td>1.1 ± 0.7</td>
<td>1.2 ± 0.5</td>
<td>1.4 ± 0.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5 ± 0.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

DB = dobutamine at dose per kilogram body weight per minute; DA = dopamine at dose per kilogram body weight per minute; T<sub>dP/dt</sub> = negative reciprocal of slope from dP/dt vs pressure; peak lengthening rate = peak rate of left ventricular endocardial dimension increase.

The prolongation of indexes of isovolumetric pressure decay and their variability may also be related to prolonged intraventricular times.

Three methods of quantitating isovolumetric pressure decay were used and, in general, gave similar results. This was important since there is uncertainty as to the best technique for calculating this value. The method using dP/dt vs pressure is attractive since no assumptions need be made about pressure decaying to a zero baseline. In patients with congestive cardiomyopathy and elevated right-sided pressures and possible pericardial effects assumption of a zero baseline would...

FIGURE 2. Left ventricular high-fidelity pressure tracings and their derivative (dP/dt) are shown for a typical patient during control conditions (solid lines), at the maximum dose of dobutamine (dotted lines, left), and at maximum dose of nitroprusside (dotted lines, right). Dobutamine increased peak systolic pressure, peak positive dP/dt, and peak negative dP/dt, while accelerating pressure decay and moving the early diastolic pressure nadir earlier. Similar changes were seen with dopamine (not shown here). After nitroprusside pressure transients were unchanged, but systolic and diastolic pressures were reduced in absolute terms.
TABLE 4
(Continued)

<table>
<thead>
<tr>
<th>Control</th>
<th>DA, 2 μg</th>
<th>DA, 4 μg</th>
<th>DA, 6 μg</th>
<th>Control</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 ± 10</td>
<td>51 ± 12</td>
<td>45 ± 10C</td>
<td>40 ± 8C</td>
<td>50 ± 11</td>
<td>46 ± 12A</td>
</tr>
<tr>
<td>66 ± 16</td>
<td>62 ± 18</td>
<td>56 ± 14C</td>
<td>48 ± 11C</td>
<td>60 ± 17</td>
<td>57 ± 19</td>
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<tr>
<td>99 ± 20</td>
<td>95 ± 23</td>
<td>88 ± 24</td>
<td>63 ± 14C</td>
<td>98 ± 24</td>
<td>85 ± 18</td>
</tr>
<tr>
<td>-29 ± 17</td>
<td>-26 ± 11</td>
<td>-28 ± 17</td>
<td>-13 ± 10C</td>
<td>-31 ± 18</td>
<td>-19 ± 12</td>
</tr>
<tr>
<td>-1012 ± 401</td>
<td>-1080 ± 435</td>
<td>-1198 ± 424B</td>
<td>-1399 ± 518B</td>
<td>-1083 ± 406</td>
<td>-1050 ± 353</td>
</tr>
<tr>
<td>6.2 ± 2.1</td>
<td>6.7 ± 2.2</td>
<td>8.3 ± 3.0C</td>
<td>9.0 ± 3.4B</td>
<td>6.8 ± 2.2</td>
<td>6.8 ± 1.8</td>
</tr>
<tr>
<td>1.0 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.5 ± 0.5C</td>
<td>1.5 ± 0.5A</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.3</td>
</tr>
</tbody>
</table>

**FIGURE 3.** Individual values for left ventricular minimum pressure are shown for all patients during control conditions and at the maximum drug dose. After dobutamine and nitroprusside there was a significant decrease. In contrast, dopamine had a variable effect.

**FIGURE 4.** Individual values for left ventricular end-diastolic pressure are shown as in figure 3. After dobutamine and dopamine no significant change was seen, although in many patients there was a fall in pressure with dobutamine and a rise with dopamine. Nitroprusside consistently lowered end-diastolic pressure.
be wrong. Yet the data variability and the additional noise introduced by differentiation make the dP/dt method less than ideal for use in patients with this disease. Both the t½ and logarithmic method have less variability, but it is important to remember that intracavitary pressures and pressures transients are influenced by factors extrinsic to the left ventricle.

The consequences of abnormal pressure decay include elevated diastolic pressures and reduced filling rates. These elevated diastolic pressures produce many of the typical signs and symptoms of heart failure, such as edema and dyspnea. In addition, elevated diastolic pressures increase wall stress and thus elevate myocardial oxygen consumption.

The response of our patients to β₁-adrenoceptor agonists is in agreement with isolated muscle studies showing positive inotropic and relaxation-promoting effects of other β₁-agonists. Despite the widespread use of dobutamine and dopamine in the treatment of congestive heart failure, there has been no previous documentation of their beneficial effects on pressure decay in man. The positive inotropic agents used in this study exert their effects through activation of the β₁-adrenoceptor. Activation of the β₁-adrenoceptor increases intracellular cyclic AMP, which accelerates the rate of calcium reuptake by the sarcoplasmic reticulum. Additional effects on reducing end-systolic chamber size and the inhomogeneity of contraction and relaxation could contribute to the observed acceleration of pressure decay. Monrad et al. have demonstrated that milrinone, a phosphodiesterase inhibitor, also accelerates the rate of left ventricular pressure decay in patients with heart failure. They suggested that milrinone's ability to increase intracellular cyclic AMP may mediate this beneficial effect.

The rate of pressure decay has been shown to be
sensitive not only to the myocardial deactivation process but also to the prevailing loading conditions. A reduction in end-systolic chamber size and/or wall stress will accelerate pressure decay. A reduction in end-systolic load may be produced by agents with positive inotropic, vasodilator, or combined activity. A reduction in end-systolic size occurred in our patients in response to nitroprusside, but no consistent effect on pressure decay was seen. It thus appears that the β,-adrenoceptor agonists we have studied have a more profound effect on ventricular pressure decay than does nitroprusside, at least in the doses of nitroprusside administered.

Reduced end-systolic diameter and accelerated pressure decay after dobutamine and dopamine account for the leftward shift in the diastolic pressure-diameter relation and slight downward shift in early diastole. The early diastolic pressure-diameter coordinates obtained during dopamine and dobutamine infusion show that for a given chamber dimension, pressure is less (figure 7). This presumably reflects more rapid and more complete decay from the preceding systole.

Figure 8 shows four possible mechanisms for alteration of the diastolic pressure-volume relation in patients with congestive cardiomyopathy. Many or all of these factors may be present and influence the response to therapy. In addition, viscous factors may further modify diastolic function.

An enhancement of the rate of left ventricular pressure decay is advantageous for the development of a left atrial–left ventricular pressure gradient in early diastole. This pressure gradient determines the inflow, i.e., filling pattern of the left ventricle. At a constant left atrial pressure, an acceleration of left ventricular pressure decay augments left ventricular early peak filling. Other positive inotropic agents have been shown to augment filling rates. In our patients, dopamine and dobutamine significantly increased peak lengthening rates; dobutamine did this despite a reduction in filling pressures. Data obtained during nitroprusside infusion showed no significant change in peak lengthening rates. This was probably due to a parallel reduction in absolute pressure in both the left atrium and ventricle and the lack of acceleration in left ventricular pressure decay. These data suggest that the low peak filling rate in patients with congestive cardiomyopathy is closely linked to abnormal left ventricular relaxation. In this study a measurement of left atrial pressure was not made. Accordingly, the effect of dobutamine and dopamine on the left atrial–left ventricular pressure gradient could not be assessed, as we have done in animal studies.

The pericardium usually does not exert a significant effect on the pressure-volume relations in the cardiac chambers. Since normal intrapericardial pressure fluc-
uates minimally around 0 mm Hg, the pressures measured within each cardiac chamber reflect, to an overwhelming degree, the chamber’s intrinsic properties. Yet there is a significant data base showing that with large, acute changes in loading conditions the pericardium plays a restraining role.\textsuperscript{19, 24-30} Vasodilation decreases heart size and thus total intrapericardial volume. This may produce a downward shift in the left ventricle’s diastolic pressure-volume relation, as shown in the clinical studies by Ludbrook et al.\textsuperscript{31} and confirmed by others.\textsuperscript{32} While intrapericardial pressures have not been measured in humans, the downward shift after vasodilation is strong indirect evidence that the pericardium does play a role in the predrug diastolic pressure-volume relationship.

Tyberg et al.\textsuperscript{33} have presented clinical data showing that after thoracotomy there is a close relationship between right atrial and pericardial pressures. It is presently unknown whether this close relationship is also present in patients with congestive cardiomyopathy. The presence of any tricuspid regurgitation would be expected to alter right atrial pressure independently of pericardial pressures.

Pericardial restraint and ventricular interaction may be intermittent and variable. This may produce significant difficulty in interpreting some hemodynamic data. Filling pressures are not true chamber distending pressures and therefore do not represent chamber preload.\textsuperscript{33} Even changes in filling pressure in the same patient may not represent a parallel change in preload. The response to nitroprusside in patients with elevated right atrial pressures shows that end-diastolic pressure may decrease significantly with no or minimal change in left ventricular chamber size. Most pharmacologic studies have used filling pressures (e.g., pulmonary capillary wedge or left ventricular end-diastolic) as indexes of chamber preload. These are typically plotted against a measurement of systolic performance, such as stroke volume or stroke work. The resultant curves represent the net interaction of numerous variables, making the interpretation of changes in curve position or individual data points difficult. In addition, in the calculation of constants of chamber stiffness or myocardial stiffness it is assumed that intracavitary pressures are true distending pressures. In the interpretation of drug action the potential influence of many factors needs to be considered, including varying pericardial pressure and ventricular interaction.

In the five patients in our study with grossly elevated right atrial pressures there was a parallel downward shift in the diastolic pressure-dimension relation after nitroprusside, with a reduction in diastolic pressure that was out of proportion to alterations in chamber size. In the five patients with normal right atrial mean pressure, nitroprusside did not produce a parallel downward shift in this relation. In these patients vasodilation reduced intracavitary pressures in proportion to the reduction in chamber size. These changes occurred without consistent alterations in ventricular pressure decay.

Our data also show that diastolic pressures often are lowered by dobutamine, but the response to dopamine is quite variable. Two patients had a significant elevation in left ventricular end-diastolic pressure requiring termination of the infusion of dopamine, and other investigators have reported similar findings.\textsuperscript{34-36} Indeed, the elevation of filling pressures by dopamine may limit its clinical use unless concomitant venodilator therapy is given. The mechanism involved in production of elevated filling pressures has not been defined. Our study shows that this is not due to a differential effect on myocardial relaxation. At the doses studied dopamine and dobutamine accelerate pressure decay to approximately the same degree.

The possibility that dopamine increased the degree of pericardial restraint and/or ventricular interaction is suggested by a tendency toward increased end-diastolic pressure without an increase in chamber size (figure 5). Indeed, dopamine increased right atrial pressure in seven of the 12 patients. In the venous system there are no dopamine, receptors but there are \( \alpha \)-adrenoceptors that are activated by dopamine.\textsuperscript{37} Our results are quite consistent with dopamine causing venoconstriction and increasing central blood volume.

In the normal heart dopamine and dobutamine accelerate pressure decay, increase peak lengthening rates, and leave the passive diastolic pressure-dimension relation unaltered.\textsuperscript{2, 21} Nitroprusside has been previously shown to accelerate pressure decay in normal animals.\textsuperscript{18} In our patients with severe cardiomyopathy this finding was not consistently demonstrated. The presence of low systolic pressures limited the dose of nitroprusside in several patients and may have contributed to the lack of acceleration in pressure decay. Yet even at these doses, shifts in the diastolic pressure-diameter relation were demonstrated. In the normal heart a parallel downward shift with nitroprusside is not expected, since baseline right atrial pressures would be normal. Thus, certain abnormalities in patients with congestive cardiomyopathy can modify the effects of medications compared with the response in those with a normal circulation.

Finally, several patients had mitral regurgitation of a moderate degree without mitral leaflet abnormalities.
Variation in the degree of mitral regurgitation during the administration of all three drugs could have altered diastolic pressures and lengthening rates. However, we did not observe any clear differences in the response to the three medications in those with and those without regurgitation. Further studies with a larger number of patients with significant regurgitation are needed to specifically address this question.

We conclude that positive inotropic therapy and vasodilator therapy produce significant but distinctively different effects on diastolic function in patients with congestive cardiomyopathy. The pharmacologic actions of each agent produce hemodynamic effects that are also dependent on the specific pathophysiologic abnormalities present in the individual patient.

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References
The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy.

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