Physiologic mechanisms governing hemodynamic responses to positive inotropic therapy in patients with dilated cardiomyopathy

KENNETH M. BOROW, M.D., ROBERTO M. LANG, M.D., ALEX NEUMANN, B.S., JOHN D. CARROLL, M.D., AND SOL I. RAIFER, M.D.

ABSTRACT  Clinical trials in patients with dilated cardiomyopathy (DCM) have shown a wide disparity in the hemodynamic responses to positive inotropic therapy. In addition, the response of the failing left ventricle to positive inotropic agents reflects the net interaction of multiple factors, including the magnitude of contractile abnormality and compensatory mechanisms. In the current study, left ventricular geometry, loading conditions, and contractile state were assessed in 13 patients with nonischemic DCM with the use of simultaneous high-fidelity pressure measurements and echocardiographic recordings. Comparisons were made with echocardiographic and calibrated carotid pulse data acquired in nine age-matched normal subjects. The patients with DCM were divided according to the left ventricular end-diastolic wall thickness-to-dimension ratio into groups with “appropriate” hypertrophy (i.e., ≤2 SDs from mean normal; n = 5; group 1) and “inadequate” hypertrophy (i.e., >2 SDs from mean normal; n = 8; group 2). Age, New York Heart Association functional class, left ventricular wall mass index, and left ventricular end-diastolic pressure and dimension were similar for the DCM groups. Baseline left ventricular afterload (defined as circumferential end-systolic wall stress, σws) was 168% and 203% greater than normal in groups 1 and 2, respectively. The administration of the β-adrenoceptor agonist dobutamine decreased left ventricular afterload by 12% in the normal subjects and by 10% in group 1 patients, while augmenting afterload by 5% in group 2 patients. The latter response occurred despite a 17% fall in systemic vascular resistance. Overall left ventricular performance, as assessed by the rate-corrected mean velocity of fiber shortening (Vcf), was related to left ventricular afterload (i.e., σws). The resultant σws – Vcf relationship, a sensitive measure of left ventricular contractility, was determined over a wide range of afterload conditions generated by methoxamine (normal subjects) or nitroprusside (DCM). Baseline left ventricular contractile state was 61% of normal for group 1 and 44% of normal for group 2. The contractile response to dobutamine infusion was 52% of normal for group 1 and only 22% of normal for group 2. Thus, positive inotropic therapy with dobutamine in patients with DCM is limited by (1) an attenuated contractile response and (2) elevated left ventricular afterload, which may be augmented further during its administration. The ability to separate and quantify abnormalities in left ventricular geometry, loading conditions, and contractile state allows a more thorough interpretation of the hemodynamic responses to a positive inotropic agent and may be useful in determining which patients with heart failure would benefit from treatment with specific cardiotonic agents.


POSITIVE INOTROPIC AGENTS are an integral part of the treatment of heart failure in patients with dilated cardiomyopathy (DCM).\textsuperscript{1,2} However, clinical trials have demonstrated a wide disparity in the hemodynamic responses to these agents even when administered in the same doses to patients with similar symptoms.\textsuperscript{3–5} This is due to numerous factors, including (1) interpatient differences in left ventricular contractile state, preload, afterload, heart rate, chamber geometry, and ventricular hypertrophy,\textsuperscript{6,7} (2) the variable activation of cardiac and peripheral vascular receptors by the same pharmacologic agent, and (3) the load dependency of traditional measures of overall left ventricular performance (e.g., cardiac output and ejection fraction) as well as their inability to distinguish...
between the cardiac and peripheral vascular effects of a drug.8, 9 These factors are further complicated by the use of systemic vascular resistance (SVR) as a measure of left ventricular afterload.10, 11 While SVR represents the resistance to steady flow to the periphery, left ventricular afterload, as measured by end-systolic wall stress (σes), incorporates both resistance and factors intrinsic to the heart. The importance of this difference is illustrated by the fact that a positive inotropic agent (such as norepinephrine) can decrease or only minimally change left ventricular afterload at a time that it markedly increases SVR.11

In an attempt to address these complex issues, several load-independent indexes of left ventricular performance have been developed.5, 12–14 One of the more clinically useful is the relationship between left ventricular σes and the rate-corrected velocity of fiber shortening (Vcf).15–18 This relationship is a sensitive measure of contractility that incorporates heart rate and afterload while being preload independent.19 In addition, it can quantify the contributions of altered loading conditions and changes in contractile state to the improvement in left ventricular performance induced by various cardioactive agents.11, 15, 20 The current study uses the σes – Vcf relationship in conjunction with measures of systemic vascular tone, left ventricular wall mass, and chamber geometry to elucidate the physiologic mechanisms governing hemodynamic responses to the positive inotropic agent dobutamine in patients with DCM.

Methods

Study population. Thirteen patients with DCM were studied. This diagnosis was made on echocardiographic evaluation and included patients with left ventricular end-diastolic minor- and long-axis dimensions (Dse and Lse) greater than 6.0 and 8.6 cm, respectively, in association with a left ventricular shortening fraction of 25% or less. Patients ranged in age from 25 to 62 years (mean ± SD, 46 ± 11) and included nine men and four women. Three patients were New York Heart Association (NYHA) functional class II, six were class III, and four were class IV. All patients were being treated with digoxin and diuretics. The cause of the DCM was idiopathic in 11 patients, postpartum in one patient, and doxorubicin cardiotoxicity in one patient. Five patients had a prior history of systemic hypertension. No patient had a history of myocardial infarction or angiography, but mild-to-moderate coronary artery disease (one to two vessels with 50% diameter narrowing) was present in five patients. In no case was a significant regional wall motion abnormality present by two-dimensional echocardiography nor was myocardial ischemia considered to be an important cause of the patient’s diffusely hypokinetik, dilated left ventricle. The presence of mitral regurgitation was assessed by left ventricular angiography or by pulsed Doppler echocardiography. Severity was graded as: 0 = none; 1 = trivial or mild; 2 = moderate; 3 = severe.

Data from the patients with DCM were compared with those from nine normal subjects matched for age (47 ± 15 years) and body surface area. These subjects were free of known cardiac disease and had normal two-dimensional echocardiographic studies.

In all cases, informed consent was obtained according to a protocol approved by the Clinical Investigation Committee of the University of Chicago.

Experimental design

Data acquisition. Patients with DCM were studied in the fasting state after premedication with diazepam (5 mg orally) and atropine (0.5 mg subcutaneously). Vasodilators were withheld for 48 hr before catheterization in the two patients taking them. Right and left heart catheterizations were performed from the femoral vessels. Left ventricular pressures and the peak rate of pressure change [dp/dt]max were recorded with a Millar catheter with a high-fidelity pressure transducer at the distal end.

In nine patients, a catheter with an additional pressure transducer 5 cm proximal to the distal end was used. The catheter was soaked in warm saline for 45 to 60 min before calibration and subsequent insertion. The side port of the arterial sheath was used as the pressure reference relative to micromanometer pressures. A triple-lumen, balloon-tipped thermodilution catheter was placed with its distal port in the pulmonary artery and proximal port in the right atrium. The side port of a venous sheath was used for drug administration. Thermodilution cardiac outputs were determined from three to five measurements such that variability was less than 10%. In all patients with DCM, pressure tracings and the surface electrocardiogram (lead II) were recorded on a Hewlett-Packard eight-channel recorder (4568C). Ultrasound imaging (Hewlett-Packard) was performed with either a 3.5 or 5 MHz transducer. Two-dimensionally targeted M mode echocardiographic recordings of the left ventricular cavity were performed with simultaneous pressure tracings. This allowed on-line assessment of regional wall motion abnormalities. All normal subjects underwent simultaneous recordings of the electrocardiogram, phonocardiogram, two-dimensional and M mode echocardiogram, carotid pulse tracing, and systemic blood pressure. The carotid pulse tracing was calibrated with pressures obtained from the Dinamap 1846P Vital Signs Monitor (Critikon, Tampa, FL). This method of calibration, which has been previously shown to be accurate over a wide range of systemic arterial pressures and cardiac outputs, involved assignment of systolic blood pressure to the peak of the tracing and diastolic pressure to the nadir.21 All other left ventricular ejection pressures were then determined from these values. Echocardiographic imaging was performed as described for the patients with DCM.

Drug interventions. Two drug interventions were performed in all study subjects. One involved establishment of baseline left ventricular contractile state over a wide range of pressures generated by methoxamine or nitroprusside infusions.11, 13, 15, 22 The other assessed the left ventricular contractile response to an infusin of dobutamine.

In patients with DCM, control measurements were obtained at least 20 min after placement of all catheters. These data, in conjunction with data obtained during infusion of sequential doses of nitroprusside (0.125, 0.25, 0.5, 1.0, 2.0 μg/kg/min), were used to assess baseline contractility over a wide range of left ventricular loading conditions. Dobutamine was administered at a rate of 6 μg/kg/min after establishment of a stable hemodynamic state, and data were recorded 8 min after initiation of drug infusion. Of note, recordings of cardiac output and pressures were used to confirm the presence of comparable baseline hemodynamics before nitroprusside and dobutamine infusions. On completion of drug administration, coronary arteriography was performed in all patients.
In normal subjects, atropine was administered to establish similar baseline heart rates between the groups. After acquisition of control data, an intravenous infusion of the α₁-adrenergic agonist methoxamine (infusion rate = 1 mg/min) was begun. The left ventricular response to the afterload challenge was assessed every 1 to 2 min until the peak arterial pressure had increased by 30 to 60 mm Hg above baseline. The methoxamine infusion was then stopped. The peak effect persisted for 2 to 4 min. In all cases, a minimum of four data points was recorded. After systolic arterial pressure returned to within 10% of baseline, a 5 μg/kg/min infusion of dobutamine was begun. Eight minutes later, data were recorded.

Data analysis. The timing of end-diastole was defined as the peak of the R wave on the electrocardiogram. End-systolic measurements were taken at the incisural pressure for the patients with DCM and at A2 on the phonocardiogram for the normal subjects. The left ventricular Dₐ and end-systolic minor-axis dimension (Dₐ) as well as wall thicknesses were measured from parasternal targeted M mode echocardiographic recordings acquired perpendicular to the left ventricular long axis and through the midline of short-axis images. Care was taken to record the largest left ventricular minor-axis dimensions present between the tips of the mitral valve leaflets and the superior aspect of the papillary muscles. This plane approximates the equator of the ventricle. In addition, the left ventricular Lₐ and end-systolic long-axis dimensions (Lₐ) were measured from the two-dimensional echocardiographic apical four-chamber view. The apical endocardium was defined as the point within the left ventricle in which the septum and lateral wall formed the most acute angle. This was accomplished by positioning the transducer as far lateral and/or inferior as necessary. The distance from the apex to the midpoint of the mitral valve anulus was maximized while simultaneously maximizing the width of the anulus. In this manner, tangential imaging of the left ventricle was avoided.

The ratio of left ventricular end-diastolic posterior wall plus septal thickness (2h) to Dₐ was determined and used as an estimate of adequacy of wall thickness to chamber size. This end-diastolic 2h/Dₐ ratio was used to separate the patients with DCM into groups with “appropriate” left ventricular hypertrophy (i.e., ≤2 SDs from mean normal; group 1) vs “inadequate” hypertrophy (i.e., >2 SDs from mean normal; group 2). Left ventricular wall mass index was calculated according to the method of Devereux et al. Overall left ventricular chamber shape was assessed using the long-axis dimension/minor-axis dimension (L/D) ratio obtained at end-diastole and end-systole. Values for L/D approximating 2:1 are characteristic of a prolate ellipsoid, while values approaching unity are consistent with a spherically shaped ventricle.

The left ventricular percent fractional shortening (ΔD/ΔD) was derived as (Dₐ - Dₐ)/Dₐ. The left ventricular end-systolic pressure was determined directly from the incisura of the aortic pressure tracing in the patients with DCM and from linear interpolation to the height of the incisura with use of a calibrated carotid pulse tracing in the normal subjects. The left ventricular ejection time (ET) was measured from the same tracings in the standard manner. The Vcf was calculated as:

\[ Vcf = \frac{\%\Delta D}{(LVET)/(RR)} = \frac{\%\Delta D}{(LVET)} \]

where RR = the interval between consecutive cardiac cycles (sec).

M mode echocardiographic recordings were digitized with a Franklin Quantic 1200 data analysis system (Bruce Franklin, Inc.). This device has a digitizing pad with a sampling rate of 400/sec. For the patients with DCM, left ventricular and aortic pressure tracings, dimensions, and wall thicknesses were digitized directly. For the normal subjects, the Quantic 1200 was programmed to correct for pulse transmission time by aligning the dicrotic notch of the carotid pulse tracing with the first high-frequency component of A₂. Left ventricular meridional wall stress (σₚ) was calculated as the product of pressure and a geometric factor that includes dimension and wall thickness.

The following angiographically validated formula was used:

\[ \sigma_m = \left( \frac{P}{4h} \right) \left( \frac{1}{1 + \frac{h}{D}} \right) \]

where σₚ is in g/cm², P is in mm Hg, D and h are in cm, and 1.35 converts pressure from mm Hg to g/cm². In a similar manner, left ventricular circumferential wall stress (σₑ) was calculated with the equation of Sandler and Dodge:

\[ \sigma_e = \left( \frac{P}{2h} \right) \left( \frac{1}{2L^3/(D + h)} \right) \]

where D is the minor-axis dimension (cm) and L is the long-axis dimension (cm). Control values for left ventricular end-systolic and end-diastolic meridional and circumferential wall stresses were determined by use of measured L and D values. For the normal subjects, baseline end-diastolic pressure was assumed to be 8 mm Hg.

It has been well-established for the normal as well as dilated ventricle that the relationship between left ventricular long-axis and short-axis dimensions reflects overall chamber shape. In addition, when determined at end-diastole, this L/D ratio is not altered by infusions of a peripheral vasodilator (e.g., nitroprusside), peripheral vasoconstrictor (e.g., methoxamine or phenoxyphrine), or a positive inotropic agent (e.g., dobutamine). In a similar manner, when a given subject is used as his own control, these pharmacologic interventions do not alter overall left ventricular shape at end-systole. It should be noted, however, that the actual value of L/D ratio differs depending on the phase of the cardiac cycle. With the use of the L/D ratio as a correlative shape factor in the calculation of wall stress, it was possible to determine values for end-diastolic, peak systolic, and end-systolic circumferential wall stress from appropriately timed meridional wall stress measurements obtained over a range of left ventricular loading conditions and under conditions of increased contractility. This reflects the fact that the relationship between σₑ and σₚ is predominantly a function of L/D ratio.
In the patients with DCM, mean aortic pressure and mean right atrial pressure were measured directly and cardiac output was calculated by the thermodilution technique. In the normal subjects, mean aortic pressure was determined by the vital signs monitor, mean right atrial pressure was assumed to be 4 mm Hg, and cardiac output was estimated with echocardiographically derived volumes determined by the method of Teichholz and colleagues. This assumes that the visualized portion of the ventricle is representative of global left ventricular performance, an assumption shown previously to be valid in normal subjects in the absence of left ventricular asynergy.

Statistical analysis. Each subject served as his own control. The paired t test was used to assess the hemodynamic changes induced by dobutamine relative to control values, with a p < .05 considered indicative of statistical significance. Intergroup comparisons were performed with an unpaired t test that was corrected by use of a Bonferroni factor for multiple comparisons whereby significance was accepted at a p value less than .05/k, where k = number of comparisons. Group data are expressed as the mean values ± SD.

Results

Left ventricular geometry and mass. The 13 patients with DCM were separated into two groups based on the left ventricular end-diastolic 2h/D ratio. As seen in table 1, five patients with DCM had normal ratios (group 1), while the remaining eight patients (group 2) had reduced ratios (p < .001 vs normal subjects and group 1). The ranges of values were 0.36 to 0.56 for the normal subjects, 0.34 to 0.58 for the group 1 patients, and 0.20 to 0.32 for the group 2 patients. Three patients in group 1 and two patients in group 2 had a prior history of systemic hypertension. One patient in group 1 was hypertensive at the time of study (systemic arterial blood pressure of 188/103 mm Hg). Left ventricular hypertrophy (i.e., increased wall mass index) was present in both DCM groups (p < .001 vs normal), but there was no difference in this variable between the groups. In addition, no significant differences existed between the DCM groups with respect to age, body surface area, NYHA functional class, severity of associated mitral regurgitation or, incidence of coronary artery narrowing (i.e., two of five in group 1; three of eight in group 2).

Data on the left ventricular long-axis/minor-axis ratio are presented in table 2. As expected, the left ventricles of the normal subjects approximated a prolate ellipsoid with L/D = 1.72 ± 0.05 at end-diastole and 2.10 ± 0.05 at end-systole. The ventricles in group 1 DCM patients were more spherical than normal at end-diastole (L/D = 1.49 ± 0.18). By end-systole, some restoration of normal shape had occurred (L/D = 1.63 ± 0.27). The patients in group 2 had left ventricular geometry that was nearly spherical at both end-diastole and end-systole (L/D = 1.22 ± 0.10 vs 1.26 ± 0.11). The left ventricles of these patients were distorted in shape as compared with either normal subjects (p < .001) or group 1 patients (p < .01).

Myocardial mechanics. In table 3, the baseline and dobutamine data for all study groups are presented. The following results were noted.

Heart rate. There were no differences in control heart rates between the normal subjects and group 1 and 2 patients. This reflects the use of atropine to increase baseline rate in the normal subjects from 68 ± 5 to 84 ± 6 beats/min. Dobutamine had a significant positive chronotropic effect only in the normal subjects.

Left ventricular preload. Left ventricular preload is the force or load acting to stretch ventricular fibers at end-diastole. When this was approximated with use of left ventricular DEd and LEd and end-diastolic pressure, increased values were obtained for both DCM groups. Meridional and circumferential end-diastolic wall stresses were significantly increased in the DCM groups; the group 2 patients had values more than 200% higher than group 1 patients. Dobutamine did not alter any of the measured end-diastolic indexes of preload in normal subjects or in patients with DCM.

Left ventricular systolic load

Systemic arterial pressures and resistance. Aortic peak systolic pressure was highest for the group 1 patients. No differences in pressures were present between group 2 patients and normal subjects. SVR was elevated only in group 2. Dobutamine increased aortic peak systolic pressure by 18 mm Hg in the

**TABLE 1**

Characteristics of study population

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>2h/D</td>
<td>0.45 ± 0.06</td>
<td>0.44 ± 0.10</td>
<td>0.26 ± 0.04a,b</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 ± 15</td>
<td>44 ± 10</td>
<td>47 ± 11</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.80 ± 0.08</td>
<td>1.93 ± 0.19</td>
<td>1.71 ± 0.08</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>104 ± 25</td>
<td>249 ± 57a</td>
<td>217 ± 61a</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0</td>
<td>2.6 ± 0.5a</td>
<td>3.3 ± 0.7a</td>
</tr>
<tr>
<td>MR</td>
<td>0</td>
<td>1.2 ± 0.4a</td>
<td>1.5 ± 0.8a</td>
</tr>
</tbody>
</table>

BSA = body surface area; LVMI = left ventricular wall mass index; MR = mitral regurgitation.

*p < .001 vs normal; †p < .001 group 1 vs group 2.

**TABLE 2**

Assessment of left ventricular shape (L/D ratio)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastole (ED)</td>
<td>1.72 ± 0.05</td>
<td>1.49 ± 0.18a</td>
<td>1.22 ± 0.10c</td>
</tr>
<tr>
<td>End-systole (ES)</td>
<td>2.10 ± 0.05</td>
<td>1.63 ± 0.27b</td>
<td>1.26 ± 0.11b,c</td>
</tr>
<tr>
<td>p value (ED vs ES)</td>
<td>&lt; .001</td>
<td>&lt; .01</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

*p < .01 vs normal; †p < .001 vs normal; ‡p < .01 vs group 1.
normal subjects (p < .01), by 11 mm Hg in group 1 patients, and by 8 mm Hg in the group 2 patients (p < .05). At the same time, dobutamine decreased SVR by 11% in the normal subjects (p < .05), by 14% in group 1 (p = .17), and by 17% in group 2 (p < .01).

**Left Ventricular Internal Load (Wall Stress).** Internal load is directly related to left ventricular dimension and pressure and inversely related to wall thickness.27,30,37 Figure 1 illustrates the dynamic nature of this relationship in all study groups. Throughout most of left ventricular ejection, changes in meridional and circumferential wall force closely paralleled each other. Under baseline conditions, peak systolic σm and σc were normal in group 1 but increased in group 2 (table 3). In contrast, end-systolic σm and σc were significantly elevated above normal in group 1 (202% and 164% respectively; p < .001) and group 2 (333% and 203% respectively; p < .001). In addition, end-systolic σm and σc were, respectively, 64% and 24% higher for group 2 than group 1 (p = .005 for σm; p = .068 for σc).

Infusion of dobutamine altered both the timing and magnitude of left ventricular systolic wall stress throughout ejection for the various study groups (figure 1). Dobutamine increased peak systolic meridional and circumferential wall stress values in normal subjects

### TABLE 3  
**Summary of hemodynamic data**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Control 1 (normal vs group 1)</th>
<th>Control 2 (normal vs group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Dob</td>
<td>Control</td>
<td>Dob</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV preload</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Dob</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pₑₑ</td>
<td>NA</td>
<td>NA</td>
<td>19 ± 9</td>
<td>17 ± 14</td>
<td></td>
</tr>
<tr>
<td>Dₑₑ</td>
<td>4.57 ± 0.28</td>
<td>4.35 ± 0.37</td>
<td>6.29 ± 0.88</td>
<td>6.07 ± 0.98</td>
<td></td>
</tr>
<tr>
<td>Lₑₑ</td>
<td>7.85 ± 0.37</td>
<td>7.82 ± 0.56</td>
<td>9.28 ± 0.70</td>
<td>8.97 ± 1.13</td>
<td></td>
</tr>
<tr>
<td>hₑₑ</td>
<td>1.02 ± 0.16</td>
<td>1.04 ± 0.18b</td>
<td>1.34 ± 0.14</td>
<td>1.37 ± 0.14</td>
<td></td>
</tr>
<tr>
<td>σₑₑ (m)</td>
<td>10 ± 2a</td>
<td>NA</td>
<td>25 ± 16</td>
<td>24 ± 23</td>
<td></td>
</tr>
<tr>
<td>σₑₑ (c)</td>
<td>21 ± 4b</td>
<td>NA</td>
<td>49 ± 29</td>
<td>47 ± 44</td>
<td></td>
</tr>
<tr>
<td>LV systolic load</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Dob</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pₑₑ</td>
<td>123 ± 10</td>
<td>141 ± 12c</td>
<td>140 ± 33</td>
<td>151 ± 43</td>
<td></td>
</tr>
<tr>
<td>Pₑₑ</td>
<td>74 ± 10</td>
<td>82 ± 8b</td>
<td>91 ± 14</td>
<td>83 ± 16</td>
<td></td>
</tr>
<tr>
<td>Pₑₑ</td>
<td>92 ± 11</td>
<td>102 ± 8</td>
<td>109 ± 21</td>
<td>112 ± 25</td>
<td></td>
</tr>
<tr>
<td>SVR</td>
<td>1381 ± 288</td>
<td>1223 ± 256b</td>
<td>1506 ± 446</td>
<td>1291 ± 383</td>
<td></td>
</tr>
<tr>
<td>Pₑₑ</td>
<td>96 ± 9</td>
<td>108 ± 12c</td>
<td>116 ± 28</td>
<td>119 ± 34</td>
<td></td>
</tr>
<tr>
<td>Dₑₑ</td>
<td>2.98 ± 0.29</td>
<td>2.63 ± 0.28c</td>
<td>5.30 ± 0.83</td>
<td>4.88 ± 0.84c</td>
<td></td>
</tr>
<tr>
<td>Lₑₑ</td>
<td>6.26 ± 0.50</td>
<td>5.52 ± 0.50d</td>
<td>8.49 ± 1.02</td>
<td>7.83 ± 1.25</td>
<td></td>
</tr>
<tr>
<td>hₑₑ</td>
<td>1.52 ± 0.17</td>
<td>1.73 ± 0.15c</td>
<td>1.79 ± 0.26</td>
<td>1.91 ± 0.24a</td>
<td></td>
</tr>
<tr>
<td>σₑₑ (m)</td>
<td>127 ± 13</td>
<td>164 ± 28c</td>
<td>146 ± 33</td>
<td>139 ± 29</td>
<td></td>
</tr>
<tr>
<td>σₑₑ (c)</td>
<td>272 ± 21</td>
<td>350 ± 52c</td>
<td>286 ± 44</td>
<td>278 ± 50</td>
<td></td>
</tr>
<tr>
<td>σₑₑ (m)</td>
<td>43 ± 8</td>
<td>34 ± 9b</td>
<td>87 ± 23</td>
<td>75 ± 25b</td>
<td></td>
</tr>
<tr>
<td>σₑₑ (c)</td>
<td>119 ± 16</td>
<td>105 ± 22c</td>
<td>195 ± 38</td>
<td>176 ± 51</td>
<td></td>
</tr>
<tr>
<td>Overall LV systolic performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>2.89 ± 0.33</td>
<td>3.71 ± 0.84c</td>
<td>2.82 ± 0.47</td>
<td>3.38 ± 0.51c</td>
<td></td>
</tr>
<tr>
<td>dp/dtmax</td>
<td>NA</td>
<td>NA</td>
<td>1035 ± 284</td>
<td>1574 ± 581b</td>
<td></td>
</tr>
<tr>
<td>σₑₑ (m)</td>
<td>325 ± 20</td>
<td>314 ± 23</td>
<td>280 ± 21</td>
<td>272 ± 20</td>
<td></td>
</tr>
<tr>
<td>σₑₑ (c)</td>
<td>34.8 ± 3.0</td>
<td>42.3 ± 3.7b</td>
<td>15.8 ± 3.3</td>
<td>19.7 ± 4.1c</td>
<td></td>
</tr>
<tr>
<td>Vcfₑₑ</td>
<td>1.07 ± 0.10</td>
<td>1.35 ± 0.11d</td>
<td>0.56 ± 0.08</td>
<td>0.72 ± 0.11b</td>
<td></td>
</tr>
</tbody>
</table>

**A**Assuming Pₑₑ = 8 mm Hg.
**b**p < .05 vs control; **p** < .01 vs control; **p** < .001 vs control.

Dob = dobutamine; NL = normal; LV = left ventricular; Pₑₑ = LV end-diastolic pressure (mm Hg); Dₑₑ = LV end-diastolic minor-axis dimension (cm); Lₑₑ = LV end-diastolic long-axis dimension (cm); hₑₑ = LV end-diastolic wall thickness (cm); σₑₑ (m) = LV end-systolic meridional wall stress (g/cm²); σₑₑ (c) = LV end-systolic circumferential wall stress (g/cm²); Pₑₑ = systemic peak systolic pressure (mm Hg); Pₑₑ = systemic diastolic pressure (mm Hg); Pₑₑ = systemic mean pressure (mm Hg); SVR = systemic vascular resistance (dyne·sec·cm⁻²); Cₑₑ = LV end-systolic (mm Hg); Dₑₑ = LV end-systolic minor-axis dimension (cm); Lₑₑ = LV end-systolic long-axis dimension (cm); hₑₑ = LV end-systolic wall thickness (cm); σₑₑ (m) = LV peak systolic meridional wall stress (g/cm²); σₑₑ (c) = LV peak systolic circumferential wall stress (g/cm²); σₑₑ (m) = LV end-systolic meridional wall stress (g/cm²); CI = cardiac index (l/min/m²); (dp/dt)max = maximal rate of LV pressure rise (mm Hg/sec); ETₑₑ = rate-corrected LV ejection time (msec); %Δ D = LV percent fractional shortening; Vcfₑₑ = LV rate corrected mean velocity of fiber shortening (circ/sec); NA = not available.
(p < .001) and in group 2 patients (p < .05), but did not alter values in group 1 patients. In contrast, end-systolic $\sigma_m$ and $\sigma_c$ fell in normal subjects (p < .01) and group 1 patients (p < .05 for $\sigma_m$; p = .13 for $\sigma_c$), while tending to rise in group 2 (p = .11 for $\sigma_m$, p = .09 for $\sigma_c$). The trends noted with dobutamine were similar whether meridional or circumferential wall stresses were evaluated. Since $\sigma_{cs}$ is the load that terminates left ventricular fiber shortening, it is clear that dobutamine had a similar afterload-reducing effect in the normal subjects and group 1 patients; changes in $\sigma_{cs}$ in normal subjects and group 2 differed (p = .002), as did changes in group 1 and group 2 patients (p = .017). To understand this differential effect of dobutamine, it is important to examine the physiologic factors affecting the calculation of $\sigma_{cs}$. Figure 2 shows grouped data for end-systolic $\sigma_{cs}$; similar conclusions resulted when end-systolic $\sigma_m$ was plotted. In the normal subjects, end-systolic pressure rose by 13%. This was more than counterbalanced by the 23% fall in the geometric factor and resulted in a 21% decrease in $\sigma_{cs}$ (p < .001). The group 1 patients also had a decreased geometric factor (−12%; p < .01), but this occurred without an alteration in end-systolic pressure and resulted in a 10% decline in $\sigma_{cs}$ (p = .13). The findings in the group 2 patients presented a distinct contrast to the results noted

FIGURE 1. Plot of control (C) and dobutamine (D) grouped mean data for left ventricular $\sigma_m$ and $\sigma_c$ over the course of ventricular systole. Closed squares (■) and closed circles (●) represent values at end-diastole and end-systole, respectively. Open circles (○) are peak systolic wall stress values. In general, dobutamine caused changes in $\sigma_m$ and $\sigma_c$ that closely paralleled each other. The arrows indicate the effects of dobutamine on the timing and direction of $\sigma_{cs}$.

FIGURE 2. Grouped data showing the effect of dobutamine on the major determinants of left ventricular circumferential $\sigma_{cs}$. $P_{cs}$ = left ventricular pressure at end-systole; $C_{es}$ = left ventricular geometric factor at end-systole.
in the other groups. End-systolic pressure rose by 8% while geometric factor fell by only 3%. The failure of the decrease in geometric factor to at least counterbalance the increase in end-systolic pressure resulted in the 5% rise in \( \sigma_0 \) in group 2 patients (\( p = .09 \)).

**Left ventricular systolic performance**

**Overall Function.** Control values for cardiac index were within the normal range for patients in group 1, but were significantly decreased in group 2 (\( p < .001 \) vs normal; \( p < .001 \) vs group 1). Left ventricular ejection time (ET\( \text{C} \)) was decreased in group 1 (\( p = .014 \) vs normal) and group 2 (\( p < .001 \) vs normal), without significant differences between the two groups. In addition, \( \% \Delta \text{D} \) and \( V_c \) were 45% and 52% of normal, respectively, for group 1 (\( p < .001 \)) and 27% and 34% of normal, respectively, for group 2 (\( p < .001 \) vs normal; \( p < .001 \) vs group 1). Control values for \((dP/dt)_{\text{max}}\) were higher for the group 1 than group 2 patients (\( p < .01 \)). At peak nitroprusside effect, no changes in \((dP/dt)_{\text{max}}\) were noted relative to control values (1035 \( \pm \) 284 vs 1050 \( \pm \) 395 mm Hg/sec for group 1; 778 \( \pm \) 176 vs 797 \( \pm \) 229 mm Hg/sec for group 2).

With dobutamine, cardiac index rose from control values by 0.80 liter/min/m\(^2\) in normal subjects (\( p < .001 \)), by 0.56 liter/min/m\(^2\) in group 1 (\( p < .05 \)), and by 0.50 liter/min/m\(^2\) in group 2 (\( p < .05 \)). No intergroup differences in the absolute change in cardiac index were present. In contrast, the increases in \( \% \Delta \text{D} \) and \( V_c \) were nearly twice as high in normal subjects as in group 1 patients (\( p < .001 \)) and more than four times higher in group 1 than in group 2 patients (\( p < .001 \)). The associated changes in \((dP/dt)_{\text{max}}\) were 3.5 times greater for the group 1 than for group 2 patients (538 \( \pm \) 321 vs 150 \( \pm \) 61 mm Hg/sec; \( p < .01 \)).

**Left Ventricular Contractility and Contractile Response.**

Figure 3 shows \( V_c \) plotted against left ventricular afterload (i.e., end-systolic \( \sigma_c \)) for individual normal subjects and patients with DCM. The resultant \( \sigma_c-V_c \) relationship is a preload- and heart rate-independent measure of left ventricular contractility. In this manner, comparisons can be made between study groups at comparable levels of left ventricular afterload. The downward displacement of data for the DCM groups relative to normal subjects is characteristic of a significant depression in left ventricular contractility. The magnitude of the decline in contractility was quantified as \( V_c \) at an end-systolic \( \sigma_c \) that was common to all groups (i.e., 200 g/cm\(^2\)) (figure 4). There were no overlapping data points between the groups with normal subjects having the highest \( V_c \) (0.89 \( \pm \) 0.09), group 1 patients having midrange values (0.55 \( \pm \) 0.10; \( p < .001 \) vs normal), and group 2 patients having the lowest values (0.40 \( \pm \) 0.04; \( p < .001 \) vs normal subjects and \( p < .001 \) vs group 1).

The three solid lines in figure 5 show the average end-systolic \( \sigma_c-V_c \) regression data obtained with either methoxamine or nitroprusside for the normal subjects (upper line), group 1 patients (middle line), and group 2 patients (lower line). The shaded circle (C) is the average end-systolic \( \sigma_c-V_c \) point obtained under control (i.e., predrug) conditions. The open square (D) represents the data obtained during dobutamine infusion. In the normal subjects, baseline \( V_c \) increased from 1.07 to 1.35 circ/sec (\( \Delta = 0.28 \)) during infusion of dobutamine (i.e., point C to point D). This improvement in overall left ventricular performance was associated with a fall in end-systolic \( \sigma_c \) from 119 to 105 g/cm\(^2\). If this reduction in \( \sigma_c \) had occurred as an isolated decrease in left ventricular afterload without an increase in contractile state, \( V_c \) would have increased from 1.07 to 1.12 circ/sec (point C'). By taking the difference between the \( V_c \) value due to afterload reduction alone (point C') and the value obtained with dobutamine (point D), it is now possible to quantify the positive inotropic effect of dobutamine with afterload eliminated as a confounding variable. In normal subjects 16% of the increase in \( V_c \) produced by dobutamine was due to afterload reduction, while 84% was due to an increase in contractility. Although the group 1 patients had only a 0.16 circ/sec increase in \( V_c \) with dobutamine (i.e., point C to point D), the relative contributions of afterload reduction (17%) and positive inotropic effect (83%) to improvement in overall left ventricular performance were similar to those found in normal subjects. In contrast to these findings, the group 2 patients had marginal improvement in overall left ventricular performance with dobutamine (point C to point D). This problem was further compounded by the associated increase in end-systolic \( \sigma_c \) (i.e., 242 to 255 g/cm\(^2\)). Since an isolated increase in left ventricular afterload results in a decrease in overall left ventricular performance (point C to point C' for group 2), the net increase in \( V_c \) (0.03 circ/sec) underestimated dobutamine’s actual positive inotropic effect (i.e., increase in \( V_c \) of 0.05 circ/sec, point C' to point D). When this analysis was performed with use of the end-systolic \( \sigma_m-V_c \) relationship, results similar to those obtained with the end-systolic \( \sigma_c-V_c \) relationship were noted.

Figure 6 is a plot of grouped data for the positive inotropic response to dobutamine determined with use of end-systolic \( \sigma_m-V_c \) and \( \sigma_c-V_c \) relationships. In the normal left ventricle, a large positive inotropic
response was observed. The contractile response to dobutamine was approximately 50% of normal in group 1 (p < .001 vs normal) and less than 25% of normal in group 2 patients (p < .001 vs normal and p < .001 vs group 1). There were no intragroup differences in contractile response when meridional and circumferential σes-Vcf analyses were compared.

**Discussion**

The current study examined myocardial mechanics in normal subjects and patients with DCM under baseline conditions and during infusion of the β1-adrenoceptor agonist dobutamine. The role of altered left ventricular geometry, wall mass, afterload, and contractility on the hemodynamic responses to this positive inotropic agent was assessed.

**Left ventricular geometry.** Regardless of the overall performance, the geometry of the symmetrically contracting left ventricle can be approximated by the long-axis/minor-axis ratio.\(^\text{26, 27}\) In our study, the normal ventricle at end-diastole resembled a prolate ellipsoid with an L/D ratio of 1.72. This closely approximated the normal values reported previously with the use of angiographic techniques.\(^\text{26, 27}\) As the ventricle dilated, it became more spherical in shape. This was evident from the end-diastolic L/D ratios of 1.49 and 1.22 for the group 1 and group 2 patients with DCM, respectively. At end-systole, the L/D ratio had increased by 22% in normal subjects, demonstrat-
Therapy and Prevention—Cardiomyopathy

![Graph showing circumferential end-systolic wall stress](image)

**FIGURE 5.** Average circumferential \( \sigma_{w} \cdot Vcf \) regression data obtained over a wide range of left ventricular afterload for our study groups. Dobutamine (D) had an afterload-reducing effect in the normal subjects and group 1 patients, while it failed to decrease afterload in the group 2 patients. C = control \( \sigma_{w} \cdot Vcf \) value before afterload manipulation. \( C' \) = predicted Vcf value obtained when dobutamine’s afterload-altering effect is isolated from its positive inotropic action. See text for detailed explanation.

In patients with DCM, an increase in left ventricular wall thickness and mass acts as an important compensatory mechanism. Under ideal conditions, the magnitude of the hypertrophic response is adequate to maintain maximal left ventricular systolic wall forces (i.e., peak systolic stress) within the normal range despite the large size of the ventricle. Indeed, several investigators have reported that the “appropriateness” of left ventricular hypertrophy can be used to predict clinical course in patients with DCM. For example, Feild et al. reported that 1 year survival for patients with DCM and ejection fractions less than 0.20 was 80% in the presence of appropriate left ventricular hypertrophy but only 34% if hypertrophy was inadequate. In our study, the end-diastolic 2h/D ratio and peak systolic wall stress values were normal in group 1 but markedly abnormal in group 2 patients. This was true despite intergroup similarities in left ventricular wall mass index, NYHA class, and severity of mitral regurgitation (table 1). Importantly, the maintenance of normal peak systolic wall stress and end-diastolic 2h/D ratio in the group 1 patients was associated with significantly better contractility and overall left ventricular performance as compared with values obtained in the group 2 patients. Thus, it is possible that our group 1 and group 2 patients with DCM may represent different stages of the same disease process. However, one cannot completely exclude the possibility that the relative differences in the prevalence of systemic hypertension were responsible for our observed intergroup differences in the “appropriateness” of left ventricular hypertrophy.

Left ventricular afterload. In many previous studies involving patients with heart failure, left ventricular afterload has been approximated with the use of SVR. However, SVR is a measure of peripheral vasomotor tone which, by definition, assumes that the left ventricle is a steady-state pump throughout the
cardiac cycle. This totally neglects the pulsatile nature of blood flow. The unreliability of SVR as an accurate measure of left ventricular afterload has recently been demonstrated in an animal preparation under various loading and inotropic conditions. In contrast, left ventricular systolic wall stress reflects the combined effects of instantaneous peripheral loading conditions and factors internal to the heart. According to LaPlace’s principle, left ventricular wall stress is directly related to chamber dimension and pressure and inversely related to wall thickness. As seen in figure 1, left ventricular instantaneous afterload (i.e., wall stress) in our normal subjects reached its peak value early in ventricular ejection. By end-systole, left ventricular meridional wall stress and circumferential wall stress had decreased by 66% and 56%, respectively, from their peak values. The ability of the ventricle to unload itself is crucial to the maintenance of normal myocardial mechanics since it is the wall stress at end-systole rather than the load throughout the course of ejection that determines the overall extent and mean velocity of fiber shortening. Thus, left ventricular $\sigma_{es}$ is a measure of the maximal load that can be sustained by the myocardial fibers at end-systole.

With this concept in mind, the importance of alterations in left ventricular afterload noted in our patients with DCM can be examined. In our group 2 patients, wall stress was higher than normal and the magnitude of the decline from peak to end-systole was attenuated (i.e., only 29% and 23% falls in $\sigma_m$ and $\sigma_c$, respectively). Ventricular afterload appeared to be “pressure driven” throughout all of ejection, reflecting failure of the left ventricular geometric factor to decrease significantly during systole. The net result is a ventricle that must undergo fiber shortening against a mechanically disadvantageous load. Augmenting myocardial contractility in these patients did not result in a decrease in left ventricular internal load. Indeed, dobutamine increased peak $\sigma_m$ and $\sigma_c$, while tending to augment $\sigma_{es}$. An increase in ventricular fiber load throughout all of ejection may be responsible for the elevation in myocardial oxygen consumption reported previously with dobutamine in severely dilated myopathic ventricles.

For any given patient, dobutamine resulted in parallel shifts in $\sigma_m$ and $\sigma_c$ as well as quantitatively similar changes in the $\sigma_{es}$-Vcf relationship. However, since Vcf approximates the summed effect of shortening in the circumferential direction, the more quantitatively correct measure of left ventricular afterload would be the wall stress acting in this plane (i.e., $\sigma_c$). Circumferential stress has the additional advantage of including the minor- and long-axis dimensions in its analysis. This is particularly important when one is performing comparisons between ventricles of different sizes and shapes.

Left ventricular contractility and contractile response. As seen in figures 3 and 4, the use of methoxamine and nitroprusside to generate the $\sigma_{es}$-Vcf relationship over a wide range of left ventricular afterload allowed intergroup comparisons to be made at common levels of left ventricular muscle load. Our data demonstrated a decrease in baseline left ventricular contractile state among the patients with DCM when compared with the normal subjects; the decline was greater for the group 2 than group 1 patients. In addition, the $\sigma_{es}$-Vcf relationship allowed us to separate dobutamine’s positive inotropic action from its afterload-altering properties (figures 5 and 6). Dobutamine significantly decreased left ventricular afterload in normal subjects and group 1, while augmenting afterload minimally in group 2. Since changes in overall left ventricular performance are inversely related to changes in afterload, all measures of left ventricular performance that are load dependent (such as ejection phase indexes) would be expected to give misleading results. In our study, the use of the $\sigma_{es}$-Vcf relationship allowed us to conclude that the contractile response to dobutamine was 52% of...
normal for group 1 and only 22% of normal for group 2. As shown in figure 5, if we had simply used an index of overall left ventricular shortening (e.g., Vcf,) rather than a load-independent approach, the result would have been an overestimation of the contractile response in normal subjects and group 1 patients and an underestimation in the group 2 patients. The trends noted with use of the $\sigma_{es}$-Vcf, relationship were supported by our (dP/dt)$_{max}$ data (table 3).

The heterogeneous contractile responses to dobutamine among our subjects may reflect differences in $\beta_1$-adrenoceptor density or coupling with adenylate cyclase, and may not be observed with agents that produce cardiotonic effects via other mechanisms. Although the response to dobutamine may underestimate the contractile reserve of the failing myocardium, the magnitude of the drug’s effect appears to decline as left ventricular function deteriorates; the latter is accompanied by a reduction in $\beta_1$-adrenoceptor density. Accordingly, the cardiotonic actions of dobutamine in groups 1 and 2 are consistent with our hypothesis that these two groups may represent different stages of a progressive disease process. Furthermore, for comparable cardiotonic activity, one would expect that other classes of positive inotropic agents would elicit comparable changes in left ventricular mechanics. The impact of these agents on cardiac output will also depend on other interactive phenomena, such as the degree of mitral regurgitation and chamber size. For example, since the left ventricular chamber size tended to be larger in group 2 than group 1 patients ($p = .10$), comparable increments in cardiac output could be elicited in both groups even though a relatively weaker positive inotropic stimulus was being applied in the group 2 patients.

**Left ventricular preload.** The forces acting to stretch myocardial fibers immediately before left ventricular systole reflect the interaction of end-diastolic transmural pressure, dimensions, and wall thickness. However, we have previously shown that intracavitary diastolic pressures may be significantly influenced by left ventricular–right ventricular interaction and pericardial restraint. This is particularly true in patients with DCM who have increased right atrial pressures. Thus, the true distending force for the sarcomere is difficult to quantify by use of any measure that incorporates intracavitary pressures. With this limitation in mind, end-diastolic wall stress was twofold higher in group 2 than in group 1, regardless of whether $\sigma_m$ or $\sigma_c$ was measured. The infusion of dobutamine did not alter any of the measures of left ventricular preload in either DCM group.

**Clinical implications.** The present study demonstrates that in patients with DCM, it is possible to quantify intergroup differences in left ventricular geometry, loading conditions, and contractility as well as overall left ventricular performance (figure 7). The importance of the approach used in this study is evident when one considers that identical doses of dobutamine had a moderately strong afterload-reducing effect and positive inotropic effect in our group 1 patients and an afterload-augmenting effect with only minimal positive

---

**LV SHAPE**

<table>
<thead>
<tr>
<th>(L/D)$_{ed}$</th>
<th>ADEQUACY OF LVH</th>
<th>BASAL AFTERLOAD</th>
<th>BASELINE CONTRACTILITY</th>
<th>CONTRACTILE RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2h)</td>
<td>$(\sigma_{es})$</td>
<td>Vcf$<em>C$ at $(\sigma</em>{es})$ of 200 g/cm$^2$</td>
<td>Vcf$_C$ Shift from NP or Methox Line</td>
</tr>
<tr>
<td>NORMAL</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>D = 1.0</td>
<td>L = 1.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP 1</td>
<td>98%</td>
<td>168%</td>
<td>61%</td>
<td>52%</td>
</tr>
<tr>
<td>D = 1.0</td>
<td>L = 1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP 2</td>
<td>58%</td>
<td>203%</td>
<td>44%</td>
<td>22%</td>
</tr>
<tr>
<td>D = 1.0</td>
<td>L = 1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 7.** Summary of the major derangements and compensatory mechanisms noted in our patients with DCM. L = left ventricular long-axis dimension; D = left ventricular minor-axis dimension; ed = end-diastolic; h = left ventricular wall thickness; NP = nitroprusside; Methox = methoxamine. All other abbreviations as in previous figures.
inotropic effect in our group 2 patients. Since most clinical trials of heart failure consist of a random mixture of group 1 and group 2 patients, it is not surprising that a wide disparity in clinical and hemodynamic responses to a single therapeutic agent is observed. Further studies using this approach are needed to determine whether similar results will be observed with positive inotropic agents of other classes.

We thank David James, Pat Pitre, and Dorothy Douglas for their expert assistance in the preparation of this manuscript and Kirk Spencer and Glenn Hallam for their many contributions to data analysis. We also thank the technical and nursing staffs of the echocardiography and cardiac catheterization laboratories, including Pat Wolinski, Dianne Altman, Paulette Niemyski, Carolyn Hughes, Fetima R. Davis, Martin Perez, Petri Alibali, and Steven Genger. Finally, we appreciate the helpful comments and suggestions of Drs. Morton F. Arnsdorf and Daniel David.

References
40. Firth BG, Dehmer GJ, Markham RV, Willerson JT, Hillis LD: Assessment of vasodilator therapy in patients with severe congestive heart failure: limitations of measurements of left ventricular ejection fraction and volumes. Am J Cardiol 50: 954, 1982
44. Weinstein JS, Baim DB: The effects of acute dobutamine administration on myocardial metabolism and energetics. Heart Failure 2: 110, 1986
Physiologic mechanisms governing hemodynamic responses to positive inotropic therapy in patients with dilated cardiomyopathy.
K M Borow, R M Lang, A Neumann, J D Carroll and S I Rajfer

Circulation. 1988;77:625-637
do: 10.1161/01.CIR.77.3.625

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/77/3/625

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/