Dynamic Mitral Regurgitation
An Important Determinant of the Hemodynamic Response to Load Alterations and Inotropic Therapy in Severe Heart Failure

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Cardiac performance and mitral regurgitation were measured by Doppler echocardiography and right heart catheterization in 12 patients with severe congestive heart failure who performed isometric exercise during control and intravenous administration of dobutamine and nitroglycerin. During control isometric exercise, mitral regurgitant volume increased from 18±13 to 31±17 ml (p<0.01), while forward stroke volume, by both thermodilution and Doppler echocardiography, substantially decreased. At rest, dobutamine decreased mitral regurgitant volume from 18±13 to 11±10 ml (p<0.05), while forward stroke volume increased from 46±13 to 55±15 ml (p<0.05). During isometric exercise, dobutamine tended to decrease mitral regurgitant volume (24±12 vs. 31±17 ml; NS) when compared with control exercise. At rest, nitroglycerin decreased mitral regurgitant volume from 18±13 to 11±11 ml (p<0.05), while forward stroke volume, by both thermodilution and Doppler echocardiography, substantially increased. Similarly, during isometric exercise, nitroglycerin decreased mitral regurgitant volume from 31±17 to 20±14 ml (p<0.05), while significantly increasing forward stroke volume. At control rest, the median mitral regurgitant fraction was 24% for the 12 patients. Neither dobutamine nor nitroglycerin changed significantly forward stroke and mitral regurgitant volumes at rest and during isometric exercise in the six patients with resting mitral regurgitant fraction below the median. In contrast, dobutamine and nitroglycerin significantly decreased mitral regurgitant volume and increased forward stroke volume both at rest and during isometric exercise in the six patients with mitral regurgitant fraction greater than the median. Thus, aggravation of mitral regurgitation contributes substantially to the fall in forward stroke volume noted during isometric exercise in patients with severe congestive heart failure. The presence and severity of functional mitral regurgitation appears to be an important determinant of the hemodynamic response to acute therapy with dobutamine and nitroglycerin in these patients. (Circulation 1989;80:306–313)

During isometric exercise in normal subjects, the rise in systemic arterial pressure is accompanied by an increase in cardiac output, but in patients with severe congestive heart failure, a fall in cardiac output may occur.1–8 This latter abnormal hemodynamic response to isometric exercise has been explained by a lack of myocardial contractile reserve or the descending limb of the Frank-Starling curve.6,7,9 More recently, worsening of functional mitral regurgitation, which is frequently observed in patients with dilated cardiomyopathy, has been shown to contribute to the fall in cardiac output during isometric exercise.10,11

Whether changes in the amount of mitral regurgitation contribute substantially to the hemodynamic response to increased afterload and vasodilator or inotropic therapy is unclear in patients with severe heart failure.12–14 Accordingly, the present study was undertaken to evaluate the hemodynamic response to isometric exercise in patients with severe congestive heart failure and to compare it with that of patients successively treated with dobutamine and intravenous nitroglycerin. The amount of functional mitral regurgitation during isometric exercise was determined from left ventricular volumes measured by two-dimensional echocardiography and forward stroke volume obtained by Doppler echocardiography and by thermodilution.
Methods

Patient Population

We studied nine men and three women with dilated cardiomyopathy and severe chronic congestive heart failure who were in New York Heart Association functional Class III or IV despite therapy with diuretics, digitalis, and nitrates. Their average age was 64 years (range, 52–78 years). All patients were in sinus rhythm except one, who was in atrial fibrillation. Left ventricular ejection fraction averaged 24% (range, 20–35%). In six patients, the etiology of dilated cardiomyopathy was coronary artery disease, which was documented by previous myocardial infarction(s), abnormal coronary angiograms, or both. Patients with coronary artery disease had no clinical or electrocardiographic evidence of myocardial ischemia during maximal stress test. No patient had sustained myocardial infarction within 6 months before the study. The dilated cardiomyopathy was of unknown etiology in the remaining six patients. All patients were evaluated carefully by Doppler echocardiography. None had primary valvular disease, flail mitral leaflet, or aortic regurgitation. Five patients had mild tricuspid regurgitation. Left ventricular end-diastolic volume, which was substantially increased in all patients, averaged 238 ml (range, 175–297 ml). The six patients with coronary artery disease did not have significant left ventricular asynergy.

Patients who had not been previously treated with captopril, hydralazine, or prazosin were admitted to the coronary care unit for monitoring the hemodynamic response to investigational inotropic or vasodilator agents. Long-acting nitrates were discontinued 72 hours before admission to the coronary care unit.

Hemodynamics

The patients underwent right heart catheterization with a flow-directed, balloon-tipped, thermilution catheter (Edwards Labs). Mean pulmonary arterial, pulmonary capillary wedge, and right atrial pressures were monitored and recorded (Electronics for Medicine). Cardiac output was determined by thermilution technique using iced 5% dextrose in water and obtained in triplicate with less than 10% variation. Cardiac output was calculated with a bedside computer (Model 9520A, Edwards Labs). In five patients with mild tricuspid regurgitation, cardiac output measured by thermilution was closely correlated with that derived from the Fick principle, with determination of oxygen uptake and systemic arteriovenous oxygen difference. Systemic arterial pressure was measured by either intra-arterial indwelling catheters or standard cuff techniques. Derived hemodynamic indices were calculated by standard formulae. An electrocardiographic lead was monitored continuously throughout the study.

Noninvasive Studies

A Hewlett-Packard ultrasound imaging system (77020AC) was used for both imaging and Doppler flow studies. The system has a phased-array sector scanner and a movable Doppler cursor that allows sampling directed by two-dimensional echocardiographic imaging in the pulsed Doppler mode.

The echocardiography-Doppler operator trained carefully with each patient so that while obtaining the noninvasive studies, he was well acquainted with the optimal windows and necessary adjustments. Of note, the operator was kept unaware of the hemodynamic parameters.

Total stroke volume by two-dimensional echocardiography. The apical four-chamber view was used for volume estimation, as previously described by Schnittger et al12 and Gordon et al16 and later used in our studies.12,17 The patient was positioned in the left lateral decubitus position. Every effort was made to obtain the maximal length and width of both right and left ventricles. Optimal and reproducible transducer angulation was ensured by angling the imaging plane dorsally and ventrally to visualize the mitral and tricuspid valve leaflets and left atrium. Internal and external landmarks were noted on the baseline study so that similar landmarks would be used for guidance during intervention. Because the intervention was short term and the delay between the end of baseline study at each stage and obtaining an intervention study was only a few minutes, it was easy to maintain similar position, transducer location, and steady gain setting for each patient for the whole study. Moreover, the transducer position was marked on the chest wall at the apical region and was steady during the intervention, except for small rotations performed from the four-chamber view to obtain cardiac volumes and from the apical long-axis view to obtain aortic flow velocity tracings.

Images were accepted for analysis according to the guidelines proposed by Gordon et al16 when at least 80% of the endocardium was seen. Echocardiographic studies were interpreted by the same investigator (G.K.), who did not have knowledge of the hemodynamic data. The endocardial echocardiograms were traced with an integrated Echo-Doppler Analyzer (Microsonics Datavue, Indianapolis, Indiana) programmed for single plane area, length, and volume computation by Simpson’s rule.12,17 Left ventricular volumes were measured at end diastole (i.e., largest dimension or onset of the QRS complex) and at end systole (i.e., smallest dimension or one frame before opening of the mitral valve). Total stroke volume was the difference between end-diastolic and end-systolic volumes. Three cardiac cycles were analyzed when patients were in sinus rhythm (<5% variation per cycle) and 10 cycles were analyzed in the patient with atrial fibrillation. Analysis of the baseline and peak isometric exercise echocardiographic studies was repeated in seven patients. The reproducibility of
the echocardiographic volume determination was excellent, with a correlation coefficient of 0.96 (p<0.001).

Forward stroke volume by pulsed Doppler cardiography. Left ventricular outflow was recorded from the apical position at the level of the aortic annulus. The sample volume was placed in the middle of the left ventricular outflow tract, immediately proximal to the leaflets of the aortic valve. Slight adjustments were required to optimize the orientation between the sample volume and flow.

Forward aortic flow volume was determined as the product of the time velocity integral of aortic outflow and the cross-sectional area of the aortic annulus. Curves exhibiting the highest peak velocities were selected. The average of the time velocity integral was obtained by tracing the contour of the darkest portion of the curve. The cross-sectional area of the aortic annulus was calculated as \( \pi r^2 \), where \( r \) is half of the maximal annular diameter measured in the parasternal long-axis view, immediately proximal to the points of insertion of the aortic leaflets during systole.

Mitrail flow study. Every effort was made to detect the presence of mitral insufficiency by scanning the atrium near the mitral valve for regurgitation flow. Mitrail regurgitation was detected by pulsed Doppler in all patients at the beginning of the study.

Left ventricular outflow velocities were recorded on videotape (Model AG6300, Panasonic) and on a black-and-white paper hardcopy recorder (Model 77500B, Hewlett-Packard) at a paper speed of 100 mm/sec. Three Doppler flow tracings were analyzed in the patients with sinus rhythm and seven tracings were analyzed in the patient in atrial fibrillation.

The regurgitant volume was derived as the difference between total stroke volume obtained by two-dimensional echocardiography and forward stroke volume by thermodilution or Doppler echocardiography. Regurgitant fraction was calculated as the regurgitant volume divided by the total stroke volume. This methodology has been previously reported and validated.12,17-21

The ratio of peak systolic pressure and end-systolic volume was calculated from peak systolic blood pressure and end-systolic volume by two-dimensional echocardiography, as previously reported.22-24

Study Protocol

Patients remained supine for at least 1 hour before the study. Hemodynamic measurements and echocardiographic determinations were obtained at rest and during handgrip exercise. Sixty minutes after return of the resting hemodynamic parameters to baseline values, the same protocol was repeated during administration of dobutamine and, thereafter, during intravenous administration of nitroglycerin.

Isometric exercise was performed using a commercially available calibrated hand dynamometer (Stoelting Company). Once the patients had been familiarized and had practiced the handgrip exercise, they were asked to compress the dynamometer once to the maximum extent possible with their dominant arm. They were then asked to maintain 30% of their previously determined maximal compression pressures while breathing normally and avoiding performance of the Valsalva maneuver. Patients were able to maintain this level of isometric exercise for a total of 5–7 minutes.

Drug Administration

Administration of dobutamine was begun at 3 \( \mu g/kg/min \), and the dose was titrated at 10-minute intervals in increments of 2 \( \mu g/kg/min \). Titration of dobutamine was continued to a maximum dose of 13 \( \mu g/kg/min \) until a plateau in cardiac output was reached or undesirable side effects were elicited. Adverse effects were defined as a 15% increase in heart rate, a 15% decrease in mean systemic arterial pressure, or the development of complex ventricular arrhythmias. After all hemodynamic parameters returned to baseline and steady hemodynamic state was established for at least 60 minutes, intravenous nitroglycerin was administered at a starting dose of 10 \( \mu g/min \). The dose of intravenous nitroglycerin was titrated by successive increments of 10, 15, 25, and 35 \( \mu g/min \), given at intervals of 15 minutes, to lower capillary wedge pressure to less than 12 mm Hg without aborting the increase in cardiac output, decreasing systemic arterial pressure, or increasing heart rate by more than 15%.

Statistical Analysis

Values are given as mean±SD. Hemodynamic and Doppler echocardiographic measurements were assessed with a two-factor within-subject analysis of variance model. Each patient was assessed at rest and during isometric exercise, both before and after administration of dobutamine and intravenous nitroglycerin, for a total of six observations. Hemodynamic and echocardiographic parameters were analyzed as a function of the effect of exercise (rest vs. isometric exercise), the effect of the drug (control vs. dobutamine or nitroglycerin administration), and the interaction of the two factors. In the presence of exercise drug interactions, \( F \) tests for the single effects of drugs during isometric exercise were performed with orthogonal contrasts.

Results

Left ventricular performance was reduced at rest in all 12 patients, as evidenced by a reduced cardiac index of 2.08±0.54 l/min/M² and an elevated pulmonary capillary wedge pressure of 18±9 mm Hg (Table 2). During isometric exercise, forward stroke volume decreased from 46±13 to 39±13 ml (p<0.05) when calculated from thermodilution and from 45±12 to 40±13 ml when calculated from Doppler, while pulmonary capillary wedge pressure increased from 18±9 to 31±10 mm Hg (p<0.01; Figure 1). During resting conditions (control), stroke volume by ther-
TABLE 1. Hemodynamic Effects of Isometric Exercise Performed During the Control Period and During Administration of Dobutamine and Intravenous Nitroglycerin

<table>
<thead>
<tr>
<th></th>
<th>Control period</th>
<th>Dobutamine</th>
<th>Intravenous nitroglycerin</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>IEx</td>
<td>Rest</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>80±12</td>
<td>90±16</td>
<td>88±8*</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>87±12</td>
<td>104±14</td>
<td>91±11*</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.08±0.54</td>
<td>1.92±0.53</td>
<td>2.97±0.83*</td>
</tr>
<tr>
<td>FSV (ml)</td>
<td>46±13</td>
<td>39±13</td>
<td>55±15*</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>7±7</td>
<td>13±7</td>
<td>3±4*</td>
</tr>
<tr>
<td>FCWP (mm Hg)</td>
<td>18±9</td>
<td>31±10</td>
<td>12±8*</td>
</tr>
<tr>
<td>SVR (dyn/sec/cm⁻²)</td>
<td>1,912±629</td>
<td>2,385±882</td>
<td>1,503±568*</td>
</tr>
<tr>
<td>LVSW (g/ml)</td>
<td>43±16</td>
<td>39±16</td>
<td>60±18*</td>
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IEx, isometric exercise; p, statistical significance of IEx vs. rest; HR, heart rate; SAP, mean systemic arterial pressure; CI, cardiac index; FSV, forward stroke volume (thermodilution); RAP, mean right atrial pressure; FCWP, mean pulmonary capillary wedge pressure; SVR, systemic vascular resistance; LVSW, left ventricular stroke work index.

*Statistical significance less than 0.05 vs. control at rest or IEx; †statistical significance less than 0.01 vs. control at rest or IEx.

Modulation correlated well to Doppler (r=0.8). Heart rate increased from 80±12 to 90±16 beats/min (p<0.01), and mean systemic arterial pressure and vascular resistance rose from 87±12 to 104±14 mm Hg (p<0.001) and 1,912±629 to 2,385±882 dyn·sec/cm⁻³ (p<0.01), respectively (Table 1). Although the increase in left ventricular end-diastolic volume (Table 3) from 238±39 to 241±34 ml and the decrease in end-systolic volume from 175±38 to 168±36 ml did not reach statistical significance, their difference (i.e., total stroke volume) increased significantly from 64±14 to 70±13 ml (p<0.05). The decrease in forward stroke volume during isometric exercise was due to a decrease in aortic flow velocity from 47±10 to 43±10 cm/sec and shortening of systolic ejection period from 267±40 to 248±50 msec and occurred concomitantly with a significant increase in mitral regur- gitant volume from 18±13 to 31±17 ml (p<0.01; Figure 2, Table 3). Thus, mitral regurgitant fraction increased from 28±14% to 43±18% (p<0.01). The results for mitral regurgitant volume, as calculated from Doppler (i.e., TSV-ASV; Table 3), were similar. The ratio of peak systolic pressure to ventricular end-systolic volume increased during isometric exercise from 0.71±0.27 to 0.84±0.32 mm Hg/ml (p<0.05).

At rest, dobutamine at an average dose of 7.4 μg/kg/min (range, 3–12 μg/kg/min) increased forward stroke volume from 46±13 to 55±15 ml (p<0.05) and reduced pulmonary capillary wedge pressure from 18±9 to 12±8 mm Hg (p<0.05; Figure 1, Tables 2 and 3). Heart rate increased from 80±12 to 88±8 beats/min, and mean systemic arterial pressure rose from 87±12 to 91±11 mm Hg.

**FIGURE 1.** Plot of forward stroke volume and pulmonary capillary wedge pressure at rest (R) and during isometric exercise (IEx) performed during the control period (C, —) and during administration of dobutamine (DOB, ——) and intravenous nitroglycerin (NTG, ———).**

**FIGURE 2.** Relation between stroke volume (forward and total) and mean systemic arterial pressure at rest (R) and during isometric exercise (IEx) performed during the control period (C) and during administration of dobutamine (D, dotted area) and intravenous nitroglycerin (N, striped area). During the control period, mitral regurgitant volume (MRV; total stroke volume minus forward stroke volume) increased while mean systemic arterial pressure rose. Dobutamine significantly decreased MRV at rest, while mean systemic arterial pressure was significantly increased. During isometric exercise, dobutamine tended to decrease MRV when compared with control exercise. Intravenous nitroglycerin significantly decreased MRV at rest and during isometric exercise, while mean systemic arterial pressure was significantly decreased at rest and during isometric exercise when compared to the control period. **p<0.05 versus mitral regurgitant volume at rest control; ***p<0.05 versus mitral regurgitant volume during control isometric exercise.**
(p<0.05; Figure 2, Table 2). Both left ventricular end-diastolic and end-systolic volumes decreased from 238±39 to 222±26 ml (p<0.01) and 175±38 to 156±24 ml (p<0.05; Table 3), respectively. Total stroke volume did not change (i.e., 67±11 vs. 64±14 ml; NS). Consequently, mitral regurgitant volume was substantially reduced from 18±13 to 11±10 ml (p<0.05; Figure 2). The increase in forward stroke volume and decrease in mitral regurgitation were documented when calculations were made by both thermodilution and Doppler (Tables 2 and 3). Dobutamine caused an increase in aortic flow velocity from 47±10 to 62±12 cm/sec and shortening of systolic ejection period from 267±40 to 245±19 msec. The ratio of peak systolic pressure to ventricular end-systolic volume was increased at rest by dobutamine from 0.71±0.27 to 0.82±0.21 mm Hg/ml (p<0.001).

During isometric exercise, intravenous dobutamine improved left ventricular performance relative to control. Forward stroke volume was higher (47±12 vs. 39±13 ml; p<0.05) and pulmonary capillary wedge pressure was lower (24±11 vs. 31±10 mm Hg; p<0.05; Table 2). Heart rate during isometric exercise was higher than during the control period of exercise (100±9 vs. 90±16 beats/min; p<0.01), while systemic arterial pressures were similar (105±11 vs. 104±14 mm Hg; Table 2). Although left ventricular end-diastolic volume increased during isometric exercise performed on dobutamine (from 222±26 to 233±23 ml; p<0.05), it remained less than that observed during the control period of exercise (233±33 vs. 241±34 ml; NS). Similarly, left ventricular end-systolic volume tended to be lower during isometric exercise performed on dobutamine than that noted during the control period of exercise (162±23 vs. 168±36 ml; NS), while total stroke volume during isometric exercise performed on dobutamine was similar to that noted during the control period of exercise (72±10 vs. 70±13 ml; NS). Mitral regurgitant volume tended to be lower during isometric exercise performed on dobutamine than during the control period of exercise (24±12 vs. 31±17 ml; NS). Similar results were obtained when calculations were performed from echocardiography-Doppler (Table 3). The drop in forward stroke volume was due to a decrease in aortic flow velocity (62±12 to 54±10 cm/sec) and shortening of systole (245±19 to 232±21 msec; Table 3). The ratio of peak systolic pressure to ventricular end-systolic volume increased significantly during isometric exercise performed on dobutamine (from 0.82±0.21 to 0.92±0.20 mm Hg/ml; p<0.01) and was more than the ratio (0.84±0.32 mm Hg/ml) noted during the control period of exercise (p<0.01).

At rest, intravenous nitroglycerin at a mean dose of 32 μg/min (range, 10–105 μg/min) decreased pulmonary capillary wedge pressure from 18±9 to 11±7 mm Hg; p<0.001), while forward stroke volume increased (from 46±13 to 51±13 ml; p<0.05; Figure 1, Table 2). Systemic arterial pressure decreased (from 87±12 to 81±11 mm Hg; p<0.01), while heart rate was not significantly altered. Resting left ventricular end-diastolic and end-systolic volumes were significantly decreased by intravenous nitroglycerin (from 238±39 to 225±28 ml; p<0.01, and from 175±38 to 164±28 ml; p<0.05, respectively) (Table 3). Resting total stroke volume decreased slightly (from 64±14 to 61±11 ml; NS). Consequently, resting mitral regurgitant volume was lowered substantially by nitroglycerin (from 18±13 to 11±11 ml; p<0.05; Figure 2, Table 2). Similar mean values were obtained when calculations were performed only from noninvasive data (ASV, MRV, Table 3), with a similar general trend of change. The ratio of peak systolic pressure to ventricular end-systolic volume was reduced significantly at rest by intravenous nitroglycerin (from 0.71±0.27 to 0.63±0.15 mm Hg/ml).

Intravenous nitroglycerin during isometric exercise improved left ventricular performance compared with that noted during control exercise. Forward stroke volume was higher (44±8 vs. 39±13 ml; p<0.05; Figure 1, Table 2), while pulmonary capillary wedge pressure was significantly lower

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TABLE 2. Ventricular Volumes and Doppler-Derived Parameters at Rest and During Isometric Exercise Performed During the Control Period and During Administration of Dobutamine and Intravenous Nitroglycerin

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control period</th>
<th>Dobutamine</th>
<th>Intravenous nitroglycerin</th>
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<tbody>
<tr>
<td>LVEDV (ml)</td>
<td>238±39</td>
<td>241±34</td>
<td>NS</td>
</tr>
<tr>
<td>LVESEV (ml)</td>
<td>175±38</td>
<td>168±36</td>
<td>NS</td>
</tr>
<tr>
<td>ASV (ml)</td>
<td>45±12</td>
<td>40±13</td>
<td>0.05</td>
</tr>
<tr>
<td>TSV (ml)</td>
<td>64±14</td>
<td>70±13</td>
<td>0.05</td>
</tr>
<tr>
<td>MRV_e (ml)</td>
<td>18±13</td>
<td>31±17</td>
<td>0.01</td>
</tr>
<tr>
<td>MRV_v (ml)</td>
<td>18±11</td>
<td>29±16</td>
<td>0.01</td>
</tr>
<tr>
<td>PSP/ESV (mm Hg/ml)</td>
<td>0.71±0.27</td>
<td>0.84±0.32</td>
<td>0.05</td>
</tr>
</tbody>
</table>

IEx, isometric exercise; p, statistical significance of IEx vs. rest; LVEDV, left ventricular end-diastolic volume; LVESEV, left ventricular end-systolic volume; ASV, aortic stroke volume by Doppler; TSV, total stroke volume; MRV_e, mitral regurgitant volume as the difference between TSV and FSV by thermodilution; MRV_v, mitral regurgitant volume as the difference between TSV and ASV by Doppler; PSP/ESV, peak systolic pressure/end-systolic volume.

*p<0.01 vs. control period; †statistical significance less than 0.05 vs. control period.
(17±7 vs. 31±10 mm Hg; p<0.01). Left ventricular performance during isometric exercise while on nitroglycerin was similar to that observed at rest in the control state (Figure 1). Systemic arterial pressure reached during isometric exercise performed on intravenous nitroglycerin was significantly lower than during control isometric exercise (92±11 vs. 104±14 mm Hg; p<0.01; Figure 2, Table 2), while heart rates were similar (90±13 vs. 90±16 beats/min). Left ventricular end-diastolic volume increased significantly during isometric exercise performed on nitroglycerin (from 225±28 to 233±31 ml; p<0.05; Table 3) but tended to be less than that reached during the control period of exercise (233±31 vs. 241±34 ml; NS). Left ventricular end-systolic volume did not change significantly during isometric exercise performed on nitroglycerin. Total stroke volume tended to be lower than that observed during the control period of exercise (64±13 vs. 70±13 ml; NS). Mitral regurgitant volume was significantly lower during isometric exercise performed on nitroglycerin than during the control period of exercise (20±14 vs. 31±17 ml; p<0.05). The changes, calculated from echocardiography-Doppler data, were similar. The decrease in forward stroke volume was mainly due to a decrease in aortic flow velocity (Figure 2, Table 3). The ratio of peak systolic pressure to ventricular end-systolic volume increased significantly during isometric exercise performed on intravenous nitroglycerin (from 0.63±0.15 to 0.71±0.18 mm Hg/ml; p<0.01) but was significantly lower than the ratio (0.84±0.32 mm Hg/ml) noted during the control period of exercise (p<0.05; Table 3).

The resting mitral regurgitant fraction ranged from 0% to 48% for the 12 patients, with a median value of 24%. Regurgitant fraction averaged 10% in the six patients with a fraction lower or equal to the median (i.e., group A) and averaged 42% in the patients with a fraction higher than the median (i.e., group B). Patients in groups A and B received similar doses of dobutamine (7.2±4 vs. 7.6±3 µg/kg/min, respectively) while the doses of intravenous nitroglycerin were slightly higher in patients in group B (43±17 vs. 35±14 µg/min; NS). In patients in group A, dobutamine tended to increase resting forward stroke volume (from 54±11 to 58±13 ml; NS; Figure 3), but nitroglycerin did not. During isometric exercise, both dobutamine and nitroglycerin did not change forward stroke volume. At rest, dobutamine slightly increased mitral regurgitant volume (from 8±4 to 12±10 ml; NS) but nitroglycerin did not (Figure 3). During isometric exercise, dobutamine did not change mitral regurgitant volume, while nitroglycerin tended to decrease it (from 19±12 to 15±10 ml; NS). In patients in group B, both dobutamine and nitroglycerin increased resting forward stroke volume (from 38±10 to 55±15 ml; p<0.05, and from 38±10 to 50±13 ml; p<0.05, respectively) (Figure 3). Resting mitral regurgitant volume decreased (from 29±7 to 11±9 ml; p<0.05) with dobutamine and (from 29±7 to 14±10 ml; p<0.05) with nitroglycerin. During isometric exercise, dobutamine and nitroglycerin increased forward stroke volume (from 32±15 to 44±15 ml; p<0.05, and from 32±13 to 44±12 ml; p<0.05, respectively). They both decreased mitral regurgitant volume (from 41±14 to 27±11 ml; p<0.05, and from 41±14 to 25±13 ml; p<0.05, respectively).

**Discussion**

The present study demonstrates that in patients with severe congestive heart failure, the rise in cardiac afterload associated with isometric exercise augments the amount of mitral regurgitation, which, in turn, results in a fall in forward stroke volume despite an increase in total stroke volume. Moreover, the reduction in mitral regurgitation produced by acute administration of dobutamine or nitroglycerin contributes substantially to the augmentation in forward cardiac output produced by these drugs.

Functional mitral regurgitation is frequently observed in patients with congestive heart failure, but the mechanisms that determine the presence and severity of the functional mitral regurgitation are incompletely understood. Left ventricular size, extent of emptying, mitral annular diameter, papillary muscle function, and left atrial size have been implicated. In general, the severity of mitral regurgitation appears to be related to the size of the mitral annulus and not the absolute left ventricular
end-diastolic volume, which led Boltwood et al.\textsuperscript{25} to suggest that left atrial size may be an important determinant of the size of the mitral annulus and regurgitant orifice. Studies in animal models of experimental mitral regurgitation\textsuperscript{13,14} have shown a dynamic change in mitral regurgitant orifice associated with both ventricular volume alterations, as well as changes in ventricle-atrial pressure gradients. During isometric exercise, mitral regurgitation worsens in patients with severe congestive heart failure. Because the square root of the pressure gradient between left ventricle and atrium and the duration of systole are minimally affected by isometric exercise, an increase in regurgitant area is likely to be responsible for the worsening of mitral regurgitation.

Of interest, while the forward stroke volume falls concomitantly with the increase in mitral regurgitant volume, the sum of the two volumes (i.e., total stroke volume) does not decrease but rises, as previously demonstrated by Wiggers et al.\textsuperscript{26} in studies of experimental mitral regurgitation. Total left ventricular stroke work is increased. The fall in left ventricular stroke work index, derived from forward stroke volume, which has been reported during isometric exercise in patients with severe congestive heart failure, is more apparent than real because mitral regurgitant volume was not included in the calculation of ventricular stroke work index. Tricuspid regurgitant volume may also have increased during isometric exercise, particularly in the five patients with mild tricuspid regurgitation observed at baseline. Such an increase could lead to overestimation of forward stroke volume by thermodilution. However, even if present, this would not vitiate our argument. The similar changes in forward stroke volume obtained by thermodilution and Doppler echocardiographic techniques argue that tricuspid regurgitation did not worsen significantly during isometric exercise in these patients.

Although, overall, administration of dobutamine to patients with severe congestive heart failure increases resting cardiac output and lowers pulmonary capillary wedge pressure, individual responses are extremely variable.\textsuperscript{27,28} Some of our patients, as previously reported,\textsuperscript{29,30} did not experience significant hemodynamic benefits from dobutamine. The lack of hemodynamic response to dobutamine has been attributed to a reduced positive inotropic action of the drug, which may be secondary to a desensitization of myocardial \(\beta\)-adrenergic receptors in patients with severe congestive heart failure.\textsuperscript{31} The degree of attenuation of the positive inotropic effect of dobutamine appears to be inversely related to both the degree of plasma norepinephrine elevation and the reduction in cardiac output.\textsuperscript{27} Similarly, we have found that the changes in myocardial contractility produced by dobutamine were variable in patients with congestive heart failure and could be somewhat predicted by baseline levels of myocardial contractility, as reflected by left ventricular \(dP/dt\).\textsuperscript{29} Nevertheless, despite eliciting a modest increase in myocardial contractility, dobutamine resulted in substantial improvement in ventricular performance, which was attributed to reduction in peripheral arterial resistance mediated by withdrawal of sympathetic tone, direct \(\beta\)-adrenergic stimulation, or both.

Our present data indicate that the presence and severity of functional mitral regurgitation is an important determinant of the hemodynamic response to dobutamine in patients with dilated cardiomyopathy. Although positive inotropic agents increase the pressure gradient between the left ventricle and atrium, in experimental models of mitral regurgitation, they decrease mitral regurgitant volume by reducing substantially the mitral regurgitant orifice.\textsuperscript{13,14} Similarly, in our patients, dobutamine decreased mitral regurgitant volume at rest and to a lesser extent during isometric exercise, despite moderately increasing the pressure gradient between the left ventricle and atrium. Thus, dobutamine probably reduced mitral regurgitation by decreasing the regurgitant orifice. Whether this results entirely from the positive inotropic effect of dobutamine or from its direct and indirect effects on the peripheral circulation is unknown.

The present data demonstrate that in patients with dilated cardiomyopathy and functional mitral regurgitation, intravenous nitroglycerin reduces mitral regurgitant volume at rest and during isometric exercise, and thereby increases forward cardiac output. Intravenous nitroglycerin invariably lowers pulmonary capillary wedge pressure, but cardiac output does not always increase in patients with severe congestive heart failure.\textsuperscript{32,33} The presence and severity of functional mitral regurgitation appears to account for the variability in cardiac output response to acute administration of nitroglycerin in patients with severe congestive heart failure.\textsuperscript{34} This is in agreement with the preliminary findings of Roth et al.,\textsuperscript{35} who found that during isometric exercise, transdermal nitroglycerin increases cardiac index while lowering pulmonary capillary wedge pressure in patients with chronic heart failure. Nitroglycerin does not alter significantly the systolic pressure gradient between left ventricle and atrium and thus most probably reduces the mitral regurgitant orifice.\textsuperscript{12,34} The relative contributions of a decrease in left ventricular and atrial volumes or an improvement in the anatomical position of the mitral valve apparatus in decreasing the regurgitant orifice cannot be determined by the present study.

In summary, the decrease in forward cardiac output observed during isometric exercise in patients with severe congestive heart failure is secondary to a worsening of the functional mitral regurgitation. In addition, a reduction of functional mitral regurgitation produced by acute administration of dobutamine or nitroglycerin to these patients contributes substantially to the increase in forward cardiac output. Thus, the presence and severity of func-
tional mitral regurgitation is an important determinant of the acute hemodynamic response to inotropic and vasodilator therapy in severe heart failure.

References

Keywords • mitral regurgitation • stroke volume • heart failure, congestive
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