Additive effects of dobutamine and amrinone on myocardial contractility and ventricular performance in patients with severe heart failure

JOSEPH GAGE, M.D., HOWARD RUTMAN, M.D., DAVID LUCIDO, PH.D., AND THIERRY H. LEJEMTEL, M.D.

ABSTRACT The effects of amrinone, dobutamine, and a combination of the two drugs on peak positive left ventricular dp/dt and left ventricular performance were evaluated in 11 patients with chronic congestive heart failure. When administered alone, both dobutamine (10.9 μg/kg/min) and intravenous amrinone (1.9 mg/kg/min) significantly increased left ventricular dp/dt and performance. When compared with dobutamine alone, the addition of amrinone resulted in further increases in left ventricular dp/dt and cardiac index (to 1319 ± 419 from 1202 ± 376 mm Hg/sec, p < .002, and to 3.56 ± 0.78 from 3.04 ± 0.67 liters/min/m², p < .01, respectively). The combination also induced a further reduction in left ventricular end-diastolic pressure (to 15.3 ± 11.3 from 18.2 ± 10.3 mm Hg, p < .05) when compared with amrinone alone. The combination of dobutamine and amrinone increased heart rate slightly when compared with either drug alone, but did not further reduce systemic arterial pressure when compared with amrinone alone. The dose-response curve of left ventricular dp/dt and performance during titration of dobutamine with and without the addition of intravenous amrinone was evaluated in seven patients. The addition of amrinone to any dose of dobutamine produced higher cardiac index and lower systemic vascular resistance than dobutamine or amrinone alone. Thus, when compared with dobutamine alone in patients with chronic congestive heart failure, the addition of intravenous amrinone to dobutamine results in an additive improvement in left ventricular performance throughout the dose range.


DOBUTAMINE is a synthetic catecholamine that directly stimulates myocardial β₁-adrenergic receptors. It has been used extensively to improve myocardial contractility and ventricular performance in patients with acute left ventricular dysfunction or decompensated congestive heart failure.¹ ² Dobutamine is usually well tolerated. Through its effects on cardiac mechanics and hemodynamics, it has the potential to alter myocardial oxygen utilization (MVO₂) in several different ways. By increasing contractility and heart rate, it may increase MVO₂, but the simultaneous reduction in wall tension tends to lower oxygen use. In some situations the stimulation of contractility and heart rate may outweigh the reduction in wall tension to produce a net increase in myocardial oxygen demand. Thus, dobutamine use may potentially be detrimental in patients with limited coronary artery reserve in whom oxygen delivery cannot rise adequately to meet additional myocardial oxygen demand.³

Amrinone, a nonglycosidal, nonadrenergic, cardiotonic agent, selectively inhibits type III phosphodiesterase.⁴ ⁶ When administered intravenously to patients with congestive heart failure, amrinone produces increases in cardiac performance similar in magnitude to the effect seen with dobutamine.⁷–¹⁰ In addition to its positive inotropic action, amrinone causes substantial arterial and venous vasodilation, and thus reduces both cardiac afterload and preload. By decreasing loading as it increases contractility, amrinone tends to reduce rather than increase MVO₂.¹¹ This difference between amrinone and dobutamine in their potential effects on myocardial oxygen demand may have special importance when attempting to improve cardiac performance in patients with limited coronary reserve. Furthermore, it suggests that concomitant administration of dobutamine and amrinone may allow maximal inotropic stimulation and constitute a useful therapeutic intervention.

Accordingly, the effects of dobutamine, adminis-
tered alone and in addition to amrinone, on myocardial contractility and ventricular performance were evaluated in patients with severe congestive heart failure.

**Methods**

**Patient population.** The study population consisted of six women and five men (mean age 54 years, range 35 to 73) with severe chronic congestive heart failure who underwent left heart catheterization for diagnostic purposes. All patients had symptoms compatible with New York Heart Association functional class II to IV, despite therapy with digitalis and diuretics. The mean digoxin level immediately before the study was 1.0 ng/ml (range 0.5 to 2.1) and the mean daily dose of furosemide was 67 mg (range 40 to 120). No patients received vasodilators at the time of the study. Peak oxygen uptake, as measured during graded treadmill exercise in eight patients, was 12.2 ± 3.8 ml/kg/min. For the entire group left ventricular ejection fraction, by gated nuclear imaging, averaged 21% (range 14% to 37%).

The study was conducted in the cardiac catheterization laboratory. Coronary angiography was performed in all patients and showed triple-vessel coronary artery disease in three patients and the absence of significant coronary artery obstruction in the remaining eight patients. Five of these patients had idiopathic cardiomyopathy and the remaining three had longstanding hypertensive heart disease. Left ventricular cineangiography showed no mitral regurgitation in eight patients and 1+ mitral regurgitation in three patients.

The protocol was approved by the Committee on Clinical Investigations at the Albert Einstein College of Medicine. The nature and possible risks of the study were fully explained to patients and all gave informed consent.

**Hemodynamics.** Patients were evaluated while in the postabsorptive state. Right heart catheterization was performed with a triple-lumen, flow-directed, balloon-tipped thermodilution catheter that was inserted percutaneously via the internal jugular vein. Cardiac output was determined in triplicate (with less than 10% variation) by the thermodilution technique with the use of iced 5% dextrose in water. Left heart catheterization was performed from the femoral approach with a Millar micromanometer-tipped catheter. Peak positive left ventricular dP/dt was derived by on-line computer processing of the left ventricular pressure signal (Hewlett-Packard 5600M catheterization data analysis system). A low-pass Fournier filter with the cut-off frequency of the digital filter preset to 16 Hz was used to smooth noise fluctuations. Nine successive beats were analyzed. The three highest and lowest values for left ventricular dP/dt were discarded and the three remaining beats were averaged. This method permits the rejection of premature and postextrasystolic beats.

Forty minutes after completion of the diagnostic angiographic and ventriculographic studies, the initial baseline hemodynamic values were established by recording two similar sets of measurements separated by a 15 min interval. Titration of the dobutamine dose was then begun and the hemodynamic measurements were repeated at each dose. The dobutamine infusion was discontinued after measurements were made at the highest tolerated dose. After dobutamine was discontinued, hemodynamic variables were followed until they returned to their original baseline levels. This required a period ranging from 20 to 40 min. As demonstrated in table 1, hemodynamic values returned to the original baseline in all patients. Intravenous amrinone was then administered. When the amrinone effect was at its peak, titration of the dose of dobutamine and hemodynamic measurements were repeated.

**Drug administration.** All measurements were obtained at baseline and then again after 10 to 20 min to ensure that the patients were hemodynamically stable before infusion of drug. Administration of dobutamine was begun at 3 μg/kg/min and the dose was titrated upward at 5 min intervals in increments of 3 μg/kg/min. Titration of the dose of dobutamine was continued up to a maximum dose of 15 μg/kg/min, unless a maximal cardiac output plateau was reached at lower doses or an undesirable effect was 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, an intravenous bolus of 1.5 mg/kg of amrinone was administered. If the cardiac index failed to increase by at least 20% and the left ventricular end-diastolic pressure did not fall below 12 mm Hg, a second bolus of 0.75 mg/kg of amrinone was administered 5 to 10 min after the first dose. Immediately after determination of the hemodynamic response to intravenous amri-

<table>
<thead>
<tr>
<th><strong>TABLE 1</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control hemodynamic parameters</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CI</th>
<th>LVEDP</th>
<th>SAP</th>
<th>RAP</th>
<th>Peak LV dP/dt</th>
<th>HR</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>C2</td>
<td>C1</td>
<td>C2</td>
<td>C1</td>
<td>C2</td>
<td>C1</td>
<td>C2</td>
</tr>
<tr>
<td>1</td>
<td>2.36</td>
<td>2.62</td>
<td>29</td>
<td>27</td>
<td>80</td>
<td>78</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>1.40</td>
<td>1.41</td>
<td>31</td>
<td>33</td>
<td>94</td>
<td>94</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>1.46</td>
<td>1.88</td>
<td>25</td>
<td>24</td>
<td>121</td>
<td>120</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>2.40</td>
<td>2.38</td>
<td>22</td>
<td>23</td>
<td>85</td>
<td>78</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>2.34</td>
<td>2.17</td>
<td>31</td>
<td>36</td>
<td>99</td>
<td>94</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>2.35</td>
<td>2.24</td>
<td>20</td>
<td>19</td>
<td>117</td>
<td>115</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>1.41</td>
<td>1.52</td>
<td>36</td>
<td>35</td>
<td>108</td>
<td>105</td>
<td>19</td>
</tr>
<tr>
<td>8</td>
<td>2.51</td>
<td>2.48</td>
<td>29</td>
<td>20</td>
<td>124</td>
<td>123</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>2.73</td>
<td>2.72</td>
<td>32</td>
<td>30</td>
<td>95</td>
<td>94</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>1.98</td>
<td>1.88</td>
<td>19</td>
<td>18</td>
<td>84</td>
<td>83</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>1.65</td>
<td>1.56</td>
<td>25</td>
<td>30</td>
<td>96</td>
<td>95</td>
<td>20</td>
</tr>
<tr>
<td>Mean</td>
<td>2.05</td>
<td>2.07</td>
<td>27.2</td>
<td>26.8</td>
<td>100.3</td>
<td>98.0</td>
<td>13.8</td>
</tr>
<tr>
<td>SD</td>
<td>0.49</td>
<td>0.46</td>
<td>5.4</td>
<td>6.4</td>
<td>15.2</td>
<td>15.9</td>
<td>7.0</td>
</tr>
</tbody>
</table>

CI = cardiac index (liters/min/m²); LVEDP = left ventricular end-diastolic pressure (mm Hg); SAP = mean systemic arterial pressure (mm Hg); RAP = mean right atrial pressure (mm Hg); LV dP/dt = left ventricular dP/dt (mm Hg/sec); HR = heart rate (beats/min); SVR = systemic vascular resistance (dyne·sec·cm⁻²); C₁ = control before administration of dobutamine; C₂ = control after discontinuation of dobutamine.
none, administration of dobutamine was resumed. In the first four patients, administration of dobutamine was resumed at the highest dose previously given. In the remaining seven patients, full upward titration of the dose of dobutamine was repeated. Addition of the highest previously administered dose of dobutamine to the intravenous bolus of amrinone was well tolerated in all patients.

**Statistical analysis.** The results are expressed as mean ± SD and were considered significant at p < .05. Two different analysis of variance models were used to evaluate the peak dose effects and the dose-response data sets. The peak dose data set was analyzed with a two-within factor repeated-measures analysis of variance design. Each patient was evaluated at baseline and after administration of the peak dose of dobutamine with and without pretreatment with amrinone. Subsequent to the overall analysis of variance, tests of the single main effects were conducted to test the effects of dobutamine with each pretreatment (no amrinone vs amrinone). The dose-response data were evaluated with a one-within factor repeated-measures analysis of variance model. Each subject was evaluated at baseline (control 1) and after the administration of amrinone (control 2), as well as at three other dose levels of dobutamine with and without the addition of a constant amount of amrinone. Subsequent to the overall analysis of variance, a Scheffe test was conducted to evaluate pairwise differences between the dose levels.

**Results**

**Rate of rise in left ventricular pressure.** The effects of dobutamine and amrinone on peak positive left ventricular dP/dt are shown in figure 1. Dobutamine alone, at the highest administered dose (mean 10.9 µg/kg/min, range 3 to 15), raised left ventricular dP/dt from 867 ± 255 to 1202 ± 376 mm Hg/sec (p < .001). Amrinone alone, administered as a 1.9 mg/kg bolus (range 1.5 to 2.25), increased left ventricular dP/dt to 1048 ± 330 mm Hg/sec (p < .001). The addition of the highest dose of dobutamine to the bolus of amrinone further increased left ventricular dP/dt to 1319 ± 419 mm Hg/sec, which was significantly greater than that after dobutamine alone (p < .002).

Figure 2 shows left ventricular dP/dt for individual patients during each intervention. Dobutamine increased left ventricular dP/dt in all patients. When given alone, amrinone increased left ventricular dP/dt in all but one patient (No. 1), who also had only a modest response to dobutamine. In nine of the 11 patients, the effect of dobutamine with respect to increasing left ventricular dP/dt exceeded the effect of amrinone. For all patients, the combination of dobutamine and amrinone increased left ventricular dP/dt more than dobutamine alone.

The dose response of left ventricular dP/dt during titration of dobutamine, with and without the addition of amrinone, is shown in figure 3. While data from all 11 patients were available for the peak effect comparisons, the dose-response data are from only those seven patients that received all three doses of dobutamine. The smaller number of patients makes it difficult to demonstrate statistical significance. Nonetheless, the data suggest that at all doses of dobutamine, the com-
bination of dobutamine and amrinone resulted in a higher left ventricular dP/dt than dobutamine alone.

**Left ventricular performance.** At baseline, the 11 patients had a mean cardiac index of 2.05 ± 0.49 liters/min/m² and a mean left ventricular end-diastolic pressure of 27.1 ± 5.4 mm Hg. At the highest administered dose of dobutamine, cardiac index rose to 3.04 ± 0.67 liters/min/m² (p < .001), while left ventricular end-diastolic pressure fell to 21.4 ± 9.4 mm Hg (p < .05). Administration of intravenous amrinone alone increased cardiac index to 2.79 ± 0.77 liters/min/m² (p < .001) and reduced left ventricular end-diastolic pressure to 18.2 ± 10.3 mm Hg (p < .01). The addition of the highest dose of dobutamine to the bolus of amrinone further improved left ventricular performance: cardiac index rose beyond the level achieved with dobutamine alone to 3.56 ± 0.78 liters/min/m² (p < .01) and left ventricular filling pressure dropped even further than the level reached with amrinone alone to 15.3 ± 11.3 mm Hg (p < .05).

Mean systemic arterial pressure did not change significantly after administration of dobutamine alone, but it fell significantly from 100.3 ± 15.2 to 94.9 ± 19.4 mm Hg (p < 0.5) when amrinone was given alone. The combination of dobutamine and amrinone did not reduce systemic arterial pressure further. Systemic vascular resistance fell from 1991 ± 600 to 1416 ± 466 dyne·sec·cm⁻⁵ (p < .001) after administration of the highest dose of dobutamine, and to 1376 ± 479 dyne·sec·cm⁻⁵ (p < .001) after the bolus of amrinone. Addition of dobutamine at the peak of amrinone effect further lowered systemic vascular resistance to 1103 ± 392 dyne·sec·cm⁻⁵ (p < .001 compared with either drug alone). These increases in heart rate do not, however, entirely account for the improvement in cardiac index. As shown in figure 4, both amrinone and dobutamine significantly increased stroke volume index and reduced left ventricular end-diastolic pressure. The combination of dobutamine and amrinone significantly improved the stroke volume index–left ventricular end-diastolic pressure relationship beyond the improvement induced by either drug alone.

Dobutamine increased heart rate from 95.7 ± 11.5 to 104.3 ± 12.8 beats/min (p < .01), while amrinone raised it to 103.6 ± 13.7 beats/min (p < .001). When
the maximal dose of dobutamine was added at the time of peak effect of amrinone, heart rate rose significantly above the level reached with either drug alone (109.3 ± 11.9 beats/min, p < .05 compared with either drug alone).

Figure 3 shows the dose response of hemodynamic parameters during titration of dobutamine, with and without the addition of amrinone, for the seven patients who received all three dobutamine doses. These data show that for any dose of dobutamine, the combination of dobutamine and amrinone resulted in a higher cardiac index. They also suggest that the combination of both drugs reduced left ventricular end-diastolic pressure more than dobutamine alone. Systemic vascular resistance was also consistently lower during combined administration when compared with during amrinone alone.

Discussion

The present study demonstrates that the combined administration of dobutamine and amrinone to patients in severe congestive heart failure produces additive improvements in peak positive left ventricular dP/dt and ventricular performance. Moreover, the dose-response curve for the hemodynamic effects of dobutamine is shifted to the right by the addition of amrinone to dobutamine.

In the present study, dobutamine produced a maximal 34% increase in peak positive left ventricular dP/dt, similar to the 38% increase previously reported from our laboratory in patients with severe chronic heart failure.10-12 This study also confirms the previous finding that intravenous amrinone significantly increases peak positive left ventricular dP/dt.7,13 Other investigators have failed, however, to observe this increase in peak positive left ventricular dP/dt after the administration of intravenous amrinone to patients with chronic heart failure.14-16 To some extent, this discrepancy can be explained by the influence of cardiac loading conditions on peak positive left ventricular dP/dt.17 Amrinone, in large doses, produces potent direct arteriolar and venous dilatation that markedly reduces left ventricular filling pressure. This may, therefore, result in a fall in peak positive left ventricular dP/dt that tends to offset the rise produced by the positive inotropic action of the drug. In the present study, patients received moderate doses of intravenous amrinone and all but one exhibited a rise in peak positive left ventricular dP/dt. The lone patient who failed to experience an increase in left ventricular dP/dt after the administration of amrinone also had a modest inotropic response to dobutamine.

Beyond the effects of each individual agent, the present study demonstrates the therapeutic potential of the combination of amrinone and dobutamine. At the highest administered doses, the addition of amrinone to dobutamine produces a statistically significant improvement in peak positive left ventricular dP/dt that is greater than the effect of dobutamine alone. Similarly, during titration of the dose of dobutamine, amrinone appears to add to the effect of dobutamine throughout the dose-response curve, although statistical signifi-
cance could not be demonstrated because of the smaller number of patients (n = 7). These data suggest that a lower dose of dobutamine administered in combination with amrinone results in an increase in peak positive left ventricular dP/dt comparable to that with a larger dose of dobutamine administered alone.

The greater improvement in peak positive left ventricular dP/dt seen during combined administration suggests additive inotropic effects of dobutamine and amrinone. Since the combination of the two drugs further reduces preload and leaves mean arterial pressures unchanged, the augmentation in peak positive left ventricular dP/dt represents an inotropic effect. This could further be confirmed by examination of end-systolic pressure-volume relationships.

The combination of dobutamine and amrinone produces a 52% maximal increase in peak positive left ventricular dP/dt. While this does not reach the 100% increase produced by dobutamine alone in the normal canine myocardium, it represents a substantial improvement in patients with congestive failure. Given the limited inotropic reserve of patients with failing myocardium, the combined effects of dobutamine and amrinone produce a major increase in inotropic state. Nevertheless, the increase in left ventricular performance noted during combined administration of the drugs probably results from a significant improvement in loading conditions. The relative contributions of inotropic stimulation and afterload reduction to improvement in left ventricular performance could not be assessed in this study.

In addition to the ability of dobutamine and amrinone to increase left ventricular dP/dt, both drugs also exert significant impact on ventricular loading and myocardial oxygen demand, which influences the net overall effectiveness of these agents in clinical situations. Although intravenous amrinone does not increase left ventricular dP/dt as much as do butamine, its potent direct vasodilating properties contribute to an improvement in left ventricular performance similar in degree to that achieved by the highest dose of dobutamine alone. This substantial vasodilator effect of amrinone has a likely consequence. It explains why amrinone, in contrast to dobutamine, can improve left ventricular performance in the failing canine heart without increasing myocardial oxygen requirements, and without necessitating an increase in myocardial blood flow. Similarly, in patients with chronic congestive heart failure, amrinone improves ventricular performance, while it tends to reduce MVO₂.

The vasodilating properties of amrinone may also have important effects during combined administration with dobutamine. As shown in the present study, the combination of amrinone and dobutamine has additive effects and increases left ventricular performance beyond the increase induced by dobutamine alone. Furthermore, the combination significantly lowers left ventricular filling pressure and systemic vascular resistance, both of which tend to reduce myocardial tension. The dramatic reduction in ventricular loading with the only modest increase in heart rate should prevent a significant increase in myocardial oxygen demand during combined administration of dobutamine and amrinone. Thus, the addition of amrinone to intermediate doses of dobutamine produces greater positive inotropic effect and improvement in left ventricular performance than administration of dobutamine alone; this may also be accomplished at lower metabolic cost to the myocardium. In this regard, combined administration of dobutamine and amrinone may have particular importance for the treatment of left ventricular dysfunction in patients with critical coronary vessel obstructions.

We thank Drs. Alphonse Jordan and Joel Strom for their technical assistance in performing cardiac catheterization, and Dr. Edmund Sonnenblick for his review and insightful comments regarding this manuscript.

References
Additive effects of dobutamine and amrinone on myocardial contractility and ventricular performance in patients with severe heart failure.
J Gage, H Rutman, D Lucido and T H LeJemtel

Circulation. 1986;74:367-373
doi: 10.1161/01.CIR.74.2.367

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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/74/2/367

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/