Sustained improvement of cardiac function in
patients with congestive heart failure after short-
term infusion of dobutamine

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ABSTRACT  Fifteen patients with congestive cardiomyopathy (six idiopathic and nine alcoholic)
manifested by heart failure (New York Heart Association class III or IV) were randomly assigned to a
protocol in which dobutamine (n = 8) or 5% dextrose in water (n = 7) was infused continuously for 72
hr. The dose of dobutamine was titrated to increase cardiac output to twice the baseline values. The
patients were evaluated before infusion, shortly after infusion, and 1, 2, and 4 weeks thereafter.
Functional class improved in six of eight dobutamine-treated patients but in only two of seven control
patients during the 4 week observation period. Maximal exercise time and left ventricular ejection
fraction increased significantly above baseline only in the dobutamine group. However, neither dobuta-
mine nor placebo infusion produced significant changes shortly after infusion in heart rate, cardiac
index, or total peripheral vascular resistance at rest or during exercise at similar workloads. The group
receiving dobutamine did show a reduction in systemic systolic and pulmonary arterial mean and
diastolic pressure at rest (123 ± 5 to 108 ± 6, 32 ± 5, to 24 ± 3, and 26 ± 4 to 20 ± 2 mm Hg,
respectively). In addition, total body oxygen consumption during similar workloads was lower after
dobutamine infusion than before. These changes occurred without alteration in plasma catecholamine
or arterial blood lactate concentrations. The improvement in resting hemodynamics, exercise toler-
ance, and symptoms observed for at least several weeks after dobutamine infusion suggests that there is
a sustained effect on cardiac function after short-term inotropic stimulation. This may represent an
innovative form of long-term therapy for debilitating cardiac failure.


DOBUTAMINE, a synthetic sympathomimetic amine
with predominant β1-adrenergic activity, is a potent
inotropic agent that is less arrhythmogenic and chron-
otropic than naturally occurring catecholamines.1,2
Continuous short-term infusion of dobutamine in man
casted a sustained improvement in systolic function,
left ventricular ejection fraction, and cardiac index in
the failing heart 30 min after termination of the infu-
sion.3 These improved parameters of left ventricular
performance as well as functional class have also been
shown to be sustained over several months.4 The
mechanism for the sustained effects of dobutamine in
the failing heart are not known. Limited data have been
reported pertaining to parameters of metabolism or
function that may be altered by continuous dobutamine
infusion in patients with severe congestive heart
failure.

The purpose of this double-blind controlled study
was to determine whether 72 hr of continuous dobuta-
mine infusion in patients with symptomatic congestive
cardiomyopathy is associated with any hemodynamic
or metabolic alterations of cardiovascular function to
account for the sustained improvement in left ventricu-
lar performance.

Methods

Patient selection. Thirteen men and two women (table 1)
with either idiopathic or alcoholic cardiomyopathy manifested
by stable chronic congestive heart failure (New York Heart
Association class III or IV) were randomly assigned to a proto-
col in which dobutamine (n = 8) or 5% dextrose in water (n =
7) was infused continuously for 72 hr. Informed consent was
obtained from all patients. None of the patients had severe aortic
or mitral stenosis, atrial fibrillation, angina pectoris, acute myo-
TABLE 1

Demographic data of patients

<table>
<thead>
<tr>
<th></th>
<th>Dobutamine (n = 8)</th>
<th>Placebo (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51 ± 4</td>
<td>56 ± 4</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/0</td>
<td>5/2</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>152 ± 3</td>
<td>140 ± 5</td>
</tr>
<tr>
<td>Height (inches)</td>
<td>69 ± 1</td>
<td>65 ± 2</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Duration of symptoms (yr)</td>
<td>8.5 ± 2.5</td>
<td>8.1 ± 3.0</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Cardiac infarction within 1 year of study, uncontrolled hypertension (diastolic pressure greater than 100 mm Hg), or a recent history of alcohol abuse. All patients were maintained on digoxin and diuretics (furosemide, hydrochlorothiazide, or spironolactone) (table 2) and a 2 g/day sodium diet throughout the study. Six patients also received long-term vasodilator therapy. Three patients were treated for chronic ventricular arrhythmias with quinidine or disopyramide. All medications were started at least 1 month before the study and were unchanged throughout the study period.

Experimental design. The study design consisted of three phases (figure 1). Initially, all patients were hospitalized for a preinfusion baseline evaluation lasting 2 to 3 days, followed by a 72 hr infusion period. All patients were seen in the outpatient clinic 1, 2, and 4 weeks after hospital discharge (postinfusion period).

Preinfusion period. The preinfusion evaluation included the following.

Clinical evaluation: An assessment of the functional class of congestive heart failure according to the New York Heart Association criteria was made by a physician examiner who remained blinded to the treatment selection throughout the study. Body weight was also recorded. Blood samples were taken for measuring blood urea nitrogen and creatinine.

Echocardiography: M mode echocardiograms were obtained with patients in the left lateral decubitus position by means of an Irex Recorder. Measurements by techniques previously described included left ventricular end-diastolic and end-systolic dimensions and the velocity of circumferential fiber shortening at the widest point of the left ventricle below the tips of the mitral valve leaflets.

Resting equilibrium gated blood pool scintigraphy: 25 mCi of technetium-99m were injected into an antecubital vein by a technique for labeling red cells in vivo. Imaging was performed with a Technicare Sigma 410 camera (Technicare Corp.) with a high-resolution parallel-hole collimator in the 45 degree left anterior oblique projection. Calculation of the left ventricular ejection fraction was done with an interfaced GAMMA-11 program on a PDP-11/34 minicomputer system.

Right-side cardiac catheterization: A balloon-tipped flow-directed catheter was inserted percutaneously or via a cutdown in the antecubital space and advanced into the main pulmonary artery for measuring cardiac output with an Edwards thermodilution cardiac output computer (Edwards Laboratories) and for recording pulmonary arterial systolic, diastolic, and wedge pressures. In addition, a catheter was inserted into a radial artery for monitoring arterial blood pressure. All catheters were connected to Hewlett Packard 267AC pressure transducers positioned at the midchest level, and systemic and pulmonary arterial pressures were displayed on a Sanborn recorder.

Exercise treadmill testing: A unit mets protocol was used to determine exercise tolerance as limited by fatigue or dyspnea. The test was done on a Collins treadmill (Warren E. Collins, Inc.) connected to a Marquette exercise monitoring recorder. A practice run was performed 2 to 3 days before the preinfusion

![FIGURE 1](http://circ.ahajournals.org/)

**FIGURE 1.** Experimental design, showing the preinfusion, infusion, and postinfusion follow-up phases.
baseline exercise to familiarize the patients with the treadmill protocol. All exercise tests were done approximately 2 hr after a light lunch and at least 4 hr after the last dose of orally administered vasodilators, if any. Before commencing exercise, pulmonary and systemic arterial blood pressures and cardiac output were taken in triplicate and the average was recorded. Radial and pulmonary arterial oxygen contents were measured with a Lex-O2-Con analyzer. Total body oxygen consumption was calculated from the product of the difference between radial and pulmonary arterial oxygen content and the cardiac output. The exercise protocol included an initial 3 min stage of 1 mph at 0% grade and a second 3 min stage of 2 mph at 0% grade, followed by subsequent stages of exercise, each for 3 min, with a 3.5% grade increase with each stage. No patient developed chest pain or severe claudication during exercise. Heart rate and pressures were recorded continuously during exercise, while measurements of cardiac output and blood oxygen contents were repeated between the second and third minute of each stage of the treadmill test and at maximally tolerated exercise. Total exercise time was recorded.

Biochemical measurements: Arterial blood samples were obtained at rest and at maximal exercise for determination of lactate,10 pyruvate,11 and plasma norepinephrine levels.12 Personnel making these measurements were also blinded to the treatment selection.

Infusion period. Within a few hours after completion of the preinfusion exercise studies, the patients were randomly assigned, by means of a random number table, to receive either an infusion of 5% dextrose in water (control) or dobutamine dissolved in 5% dextrose in water. Persons who had knowledge of drug selections or who administered the infusions were excluded from participating in data analysis. In patients receiving dobutamine, the initial dose of 5 μg/kg/min was increased at 20 min intervals until cardiac output increased to twice the value obtained immediately before the infusion or until the heart rate increased by 25 beats/min or mean arterial blood pressure rose 15 mm Hg above baseline values. The dose of dobutamine was adjusted to maintain this end point throughout the infusion period. The average dose given to the patients at the end of infusion period was 25.3 μg/kg/min (range 15 to 35). Within 2 hr after termination of the infusion, the exercise treadmill test was repeated along with measurements of resting and maximal exercise systemic and pulmonary blood pressures, cardiac output, total body oxygen consumption, plasma norepinephrine, and blood lactate and pyruvate concentrations. Measurements were also taken at the time at which peak exercise was achieved during the preinfusion test so that similar workloads could be compared. The radial and pulmonary arterial catheters were then removed. Echocardiography and resting gated blood pool scintigraphy were then repeated at rest. Blood urea nitrogen was measured again, and the patients were discharged from the hospital 1 or 2 days later.

Postinfusion period. Patients were evaluated in the outpatient clinic 1, 2, and 4 weeks after the infusion. At each visit an assessment of functional class was made. At weeks 1 and 4, echocardiography, resting gated blood pool scintigraphy, and blood urea nitrogen determinations were repeated as well as an exercise test without catheterization to determine maximal exercise tolerance.

Analysis of data. Results are expressed as mean ± SE. Among treated and control groups, serial measurements of functional class, ejection fraction, left ventricular dimension and velocity of circumferential fiber shortening, exercise duration, and various responses to exercise were treated with two-way analysis of variance for independent groups with trend analysis,13 and the significance of the differences between preinfusion and postinfusion values was determined by Dunnett’s test.14 Student’s t test was used to determine the statistical significance of two means. Values are considered significant at p < .05.

Results

All 15 patients completed the 4 week study; eight received dobutamine and seven served as controls (table 1). There were no significant differences between the two groups in age, weight, height, functional class, and duration of symptoms at the preinfusion baseline evaluation. There were also no significant differences in baseline serum creatinine levels (1.3 ± 0.2 vs 1.7 ± 0.3 mg/dl) and blood urea nitrogen (26 ± 4 vs 37 ± 8 mg/dl) between the dobutamine and dextrose groups. Blood urea nitrogen decreased to 16 ± 3 mg/dl (t = 4.65, degrees of freedom = 7, p < .005) after 3 days of dobutamine infusion but returned to baseline values (24 ± 4 mg/dl) 4 weeks later. In contrast, dextrose infusion did not affect blood urea nitrogen either immediately after infusion (39 ± 8 mg/dl) or 4 weeks later (31 ± 3 mg/dl).

Body weight did not change significantly immediately after the 72 hr infusion or 4 weeks later in either group. Peripheral edema was present in five patients during the baseline period. Two of these patients received dobutamine, and the other three received dextrose. Leg edema diminished during the 4 week follow-up period in one patient after dobutamine infusion but increased in the other. Of patients who received dextrose, peripheral edema increased in one, decreased in one, and remained unchanged in the third. In addition, one patient who did not have peripheral edema before dextrose infusion developed slight edema of the leg during the study.

Although the functional classification of the two groups was initially similar, an improvement of at least one grade occurred in six of the eight dobutamine-treated patients by the first outpatient visit, 1 week after termination of the infusion (figure 2). One patient improved two grades. This improvement was sustained throughout the remainder of the study. Among the seven patients in the control group, the functional class remained unchanged in four, improved in two, and deteriorated in one over the 4 week period (figure 2).

Resting left ventricular function. Figure 3 shows that left ventricular ejection fraction improved significantly above baseline 4 weeks after 72 hr dobutamine infusion but did not improve in control subjects. The left ventricular end-diastolic dimension was similar in dobutamine-treated and control patients throughout the entire study period except at 4 weeks after dobutamine infusion, when the dimension was significantly increased from baseline (7.4 ± 0.1 vs 7.1 ± 0.1 cm
before infusion). There was no change in the end-diastolic dimension of controls from the start to the end of the study (7.0 ± 0.4 vs 7.1 ± 0.6 cm). The velocity of circumferential fiber shortening also increased significantly after dobutamine infusion at the 4 week evaluation (0.79 ± 0.07 circumferences/sec) compared with baseline (0.68 ± 0.07 circumferences/sec). This improvement in velocity of circumferential fiber shortening was not observed in controls. Neither heart rate nor arterial blood pressure differed between the two groups at any of the outpatient follow-up visits. Arterial blood pressure was 118 ± 8/84 ± 5 and 122 ± 9/81 ± 3 mm Hg in the dobutamine and placebo groups, respectively, 4 weeks after infusion.

Treadmill exercise tolerance. Mean exercise treadmill time was significantly improved above baseline in dobutamine-treated patients but did not change in control patients during any of the serial postinfusion exercise tests (figure 3). The baseline values of the exercise duration did not differ significantly between the two groups.

Hemodynamic, metabolic, and noradrenergic responses to exercise. Table 3 shows the hemodynamic measurements at rest and during exercise immediately before and after infusion. Because patients receiving dobutamine were able to exercise longer on the treadmill after infusion than before, results are presented for two levels of exercise after infusion in these patients. Exercise I represents the values obtained at the exercise level that the patients had achieved before infusion, and exercise II indicates the values at maximal exercise achieved by the patients after infusion. Since the total exercise time did not differ between preinfusion and postinfusion studies in patients receiving placebo, these values are reported at peak exercise for both conditions. Before infusion, treadmill exercise caused significant increases in heart rate, cardiac index, mean pulmonary arterial pressure, and pulmonary arterial diastolic pressure for both groups. Pulmonary arterial diastolic pressure agreed well with pulmonary arterial wedge pressure (coefficient of variation = 3.3%, n =
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### TABLE 3
Hemodynamic responses to exercise in patients before and after dobutamine and dextrose infusions

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Arterial pressure (mm Hg)</th>
<th>Cardiac index (l/min/m²)</th>
<th>Total peripheral vascular resistance (dyn·sec·cm⁻⁵ × 10⁻²)</th>
<th>Mean pulmonary arterial pressure (mm Hg)</th>
<th>Pulmonary arterial diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td></td>
<td></td>
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<tr>
<td>Dobutamine group (n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Preinfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>97 ± 6</td>
<td>123 ± 5</td>
<td>72 ± 4</td>
<td>1.7 ± 0.1</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>Ex I</td>
<td>116 ± 5*</td>
<td>139 ± 8*</td>
<td>72 ± 4</td>
<td>3.1 ± 0.4*</td>
<td>1.4 ± 0.2*</td>
</tr>
<tr>
<td>Postinfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>101 ± 7</td>
<td>108 ± 6*</td>
<td>60 ± 3</td>
<td>1.7 ± 0.1</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>Ex I</td>
<td>113 ± 7*</td>
<td>126 ± 9*</td>
<td>62 ± 4</td>
<td>2.6 ± 0.3*</td>
<td>1.4 ± 0.1*</td>
</tr>
<tr>
<td>Ex II</td>
<td>125 ± 9*</td>
<td>125 ± 9*</td>
<td>60 ± 4</td>
<td>2.8 ± 0.2*</td>
<td>1.3 ± 0.1*</td>
</tr>
<tr>
<td>Placebo group (n = 7)</td>
<td></td>
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<tr>
<td>Preinfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>85 ± 6</td>
<td>125 ± 6</td>
<td>71 ± 5</td>
<td>1.6 ± 0.1</td>
<td>2.6 ± 0.2</td>
</tr>
<tr>
<td>Ex</td>
<td>111 ± 6*</td>
<td>148 ± 12*</td>
<td>71 ± 4</td>
<td>3.6 ± 0.4*</td>
<td>1.3 ± 0.2*</td>
</tr>
<tr>
<td>Postinfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>89 ± 5</td>
<td>124 ± 7</td>
<td>71 ± 4</td>
<td>1.7 ± 0.1</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>Ex</td>
<td>110 ± 6*</td>
<td>149 ± 12*</td>
<td>69 ± 3</td>
<td>3.4 ± 0.3*</td>
<td>1.4 ± 0.1*</td>
</tr>
</tbody>
</table>

Values are mean ± SE.

Statistical comparisons: *Values that significantly differ from the values obtained before exercise at p < .05 (two-tailed); †postinfusion values that differ from their respective preinfusion values at p < .05 (two-tailed).

In the patients at rest. Systolic systemic arterial blood pressure increased during exercise but diastolic arterial pressure did not change significantly. Total peripheral vascular resistance decreased with exercise.

### TABLE 4
Biochemical responses to exercise

<table>
<thead>
<tr>
<th>Group</th>
<th>ΔAVo₂ (ml/100 ml)</th>
<th>Lactate (mM)</th>
<th>Lactate:p-pyruvate ratio</th>
<th>NE (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine (n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>10.2 ± 0.6</td>
<td>1.6 ± 0.2</td>
<td>8.3 ± 1.0</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Ex I</td>
<td>12.8 ± 0.7*</td>
<td>3.0 ± 0.5*</td>
<td>15.2 ± 2.5*</td>
<td>1.5 ± 0.4*</td>
</tr>
<tr>
<td>Postinfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>8.1 ± 0.7*</td>
<td>1.4 ± 0.1</td>
<td>8.4 ± 1.1</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Ex I</td>
<td>11.2 ± 0.4*</td>
<td>3.4 ± 0.8*</td>
<td>15.6 ± 2.7*</td>
<td>1.8 ± 0.4*</td>
</tr>
<tr>
<td>Ex II</td>
<td>13.1 ± 0.6*</td>
<td>4.5 ± 0.9*</td>
<td>19.3 ± 3.0*</td>
<td>2.5 ± 0.6*</td>
</tr>
<tr>
<td>Placebo (n = 7)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>8.6 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>9.2 ± 1.5</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Ex</td>
<td>12.0 ± 0.8*</td>
<td>3.8 ± 0.8*</td>
<td>19.0 ± 2.6*</td>
<td>2.2 ± 0.6*</td>
</tr>
<tr>
<td>Postinfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>8.3 ± 0.6</td>
<td>1.2 ± 0.1</td>
<td>7.3 ± 0.6</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Ex</td>
<td>11.9 ± 0.6*</td>
<td>3.9 ± 0.6*</td>
<td>19.9 ± 2.9*</td>
<td>2.1 ± 0.5*</td>
</tr>
</tbody>
</table>

ΔAVo₂ = arteriovenous oxygen difference; NE = norepinephrine. Values are mean ± SE.

Statistical comparisons: *Values that significantly differ from the values obtained before exercise at p < .05 (two-tailed); †postinfusion value that differs from its preinfusion value at p < .05 (two-tailed). Simultaneously, arteriovenous oxygen difference (table 4) and total body oxygen consumption (figure 4) increased. Maximum total body oxygen consumption did not differ between the dobutamine (722 ± 97 ml/min) and placebo (748 ± 112 ml/min) groups before the infusion. However, total body oxygen consumption in the dobutamine group at exercise I was significantly lower in the postinfusion period compared with that in the preinfusion period (figure 4). This improvement was not seen in the placebo group (from 748 ± 112 before to 680 ± 72 ml/min after the infusion).

In the immediate postinfusion exercise test, the resting hemodynamic values were similar to those before infusion, except that the systemic and pulmonary arterial blood pressures were significantly lower and the arteriovenous oxygen difference was significantly smaller than the respective preinfusion values in the dobutamine-treated patients. However, responses of these hemodynamic parameters to exercise were similar to those that occurred before infusion.

Changes in blood lactate levels, lactate-to-pyruvate ratio, and plasma norepinephrine levels are shown in table 4. At rest there was no significant change from the baseline evaluation in any of these parameters after the infusion period in either the dobutamine or the placebo group. Exercise increased blood lactate levels, the lactate-to-pyruvate ratio, and plasma norepinephrine...
FIGURE 4. Total body oxygen consumption at rest and during exercise before and after dobutamine infusion. Bars show SE. Total body oxygen consumption increased significantly (p < 0.05, two-tailed) under both conditions. Asterisk indicates value that differs significantly from the corresponding value obtained before dobutamine infusion at p < 0.05 (one-tailed).

riene levels in both groups. In addition, there was no difference between values before and after infusion in both groups at similar workloads.

Discussion

The results of this study support those of previous investigations demonstrating a long-term improvement in left ventricular performance and symptoms in patients with congestive cardiomyopathy after either a short-term or intermittent infusion with dobutamine. In this controlled study we found a sustained improvement in the functional status of treated patients as well as an improvement in left ventricular ejection fraction and the velocity of circumferential fiber shortening at rest. Total body oxygen consumption for a submaximal workload was decreased after dobutamine infusion. Systemic arterial pressure also decreased immediately after dobutamine but returned to preinfusion baseline values within 1 week. Thus the sustained changes in ejection phase indexes probably indicate an increase in myocardial contractility. Exercise tolerance was also significantly improved.

Previously we reported that infusion of dobutamine into dogs at regular intervals for 5 weeks produced cardiovascular and metabolic effects similar to those of exercise training. The responses included a blunted exercise response in heart rate, cardiac output, and concentrations of lactate and plasma catecholamines, with an increase in arteriovenous oxygen difference. Myocardial contractility increased while resting heart rate decreased. Mean aortic blood pressure was unchanged. In the present study, patients had significantly lower systemic systolic, mean pulmonary arterial, and pulmonary arterial diastolic pressures at rest after completion of the infusion with dobutamine, whereas heart rate, cardiac index, and total peripheral vascular resistance did not differ from preinfusion values. Left ventricular end-diastolic dimension increased slightly 4 weeks after infusion, but the physiologic significance of this small increase is equivocal. Furthermore, dobutamine did not affect exercise responses of heart rate, cardiac index, or lactate and norepinephrine levels, but it did decrease total body oxygen consumption at submaximal exercise.

Although our results indicate that a conditioning effect is not responsible for the observed changes, they are not incompatible with our canine data, since any conditioning effect by dobutamine, if it were to occur, is unlikely to be seen after a short infusion period. It is well known that physical training requires several weeks of regular exercise. Recently, weekly dobutamine infusions were administered over 24 weeks to patients with congestive cardiomyopathy. Cardiovascular responses similar to the immediate responses in our study were observed, including a reduction in mean systemic blood pressure and an increase in left ventricular circumferential fiber shortening without any change in resting heart rate. It cannot be concluded from these data, however, whether or not a conditioning effect was produced. Interpretation of the results are further hampered by our lack of information regarding conditioning effects in patients with congestive heart failure. These patients might not respond to physical training with changes that usually occur in healthy individuals.

The reason for the lowered arterial pressure after dobutamine infusion is unclear. Since plasma norepinephrine levels did not change after dobutamine infusion, the decrease in blood pressure probably was not caused by a reduction in sympathetic tone. Nevertheless, it might be caused by the α-receptor blocking property of the (+)-isomer of dobutamine or its metabolites, although this mechanism is entirely hypothetical at this time. The reduction in mean pulmonary arterial and pulmonary arterial diastolic pressure prob-
ably was related to the decrease in systemic arterial blood pressure, e.g., decreased afterload, as well as to an improvement in cardiac function.

Thus our present study shows that short-term dobutamine infusion in patients with congestive cardiomyopathies was effective in bringing about improvements in symptoms and exercise tolerance over several weeks. This therapy appears to be a promising modality for the long-term treatment for severe cardiac failure. However, many of these improvements were not observed until long after the infusion of dobutamine was completed. Further studies are warranted to determine how long these improvements will last and whether and to what degree repeated infusions allow persistence of this effect. Studies also are needed to study whether such infusions would alter mortality in patients with congestive heart failure. In addition, the mechanism of the improvement and the factors that account for its time course remain unclear but may be related to reparative processes that dobutamine may effect. Unverferth et al.\(^\text{18, 22}\) have shown that a 72 hr dobutamine infusion caused an improvement of myocardial mitochondrial structure and increased the ATP/creatinine ratios of the endocardial biopsy specimens in patients similar to ours. The time course for any additional changes remains unknown, but there appears to be an ultrastructural basis for the observations we have made. Additional studies are needed to investigate the mechanism by which these mitochondrial changes occur and their significance.

We thank Dr. Frank Richeson for his critical review of the manuscript. We also thank Andrew Wong, Samuel Rivers, Stephanie Arnold, Song Que Lee, Debra Ginsburg, and Mary Diauto for their excellent technical and nursing assistance.

References


Sustained improvement of cardiac function in patients with congestive heart failure after short-term infusion of dobutamine.
C S Liang, L G Sherman, J U Doherty, K Wellington, V W Lee and W B Hood, Jr

_Circulation_. 1984;69:113-119
doi: 10.1161/01.CIR.69.1.113

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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