Drug-induced Conditioning in Congestive Heart Failure

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SUMMARY Continuous 72-hour infusions of dobutamine reportedly effect sustained clinical improvement in patients with congestive heart failure. This study was designed to determine if shorter, more frequent infusions, delivered in an outpatient setting, elicit a similar response. Twenty-six patients with moderately severe congestive heart failure were randomized, 11 into a control group and 15 into a dobutamine treatment group. Baseline data were collected for 4 weeks in each group. Thereafter, the dobutamine treatment group received 4-hour infusions of dobutamine weekly for 24 weeks. Systolic time intervals, echocardiography, cardiac index and treadmill exercise tolerance were used to follow the progress of the control and dobutamine treatment groups.

The ratio of ejection period to left ventricular ejection time and the cardiac index did not change significantly in either group. The velocity of circumferential fiber shortening and the percent change in the minor axis of the left ventricle during systole improved modestly (p < 0.05) above baseline in the dobutamine group after 14 weeks of treatment and above the corresponding control values (p < 0.05) after 22 weeks. Exercise tolerance (duration) improved 25-51% (all p < 0.05) above baseline in the dobutamine group compared with 10-17% (all p > 0.05 vs baseline) in the control group. Heart rate at maximal exercise did not change significantly from baseline for either group and did not differ significantly between the two groups. Functional classification improved in 12 of 15 dobutamine treatment patients and in only two of 11 control patients (p < 0.05).

In our patients with congestive heart failure, weekly 4-hour dobutamine infusions did not elicit a major change in resting left ventricular function; however, exercise performance and clinical status improved considerably.

A PREVIOUS REPORT from this laboratory indicated that up to 68% of patients with severe congestive heart failure experienced sustained clinical improvement after a 3-day i.v. infusion of dobutamine. A follow-up investigation showed that this improvement in clinical status persisted for as long as 10 weeks in more than 40% of these patients and was accompanied by documented improvement of noninvasive indexes of left ventricular function. Studies of the histologic and biochemical responses of the failing myocardium to the 3-day infusion of dobutamine showed that mitochondrial morphology and biochemical energetics (ATP, creatine phosphate, cyclic AMP) improved more with dobutamine than with bedrest and saline infusion.

We designed the present study to determine whether shorter, more frequent (4-5 hours/week for 24 weeks) i.v. infusions of dobutamine would improve the clinical status and the objective measurements of cardiovascular performance in patients with congestive heart failure. If dobutamine proved to be beneficial, shorter weekly infusions could be given to some of these patients as outpatient therapy.

Methods

Patients

Thirty patients with moderate-to-severe congestive heart failure gave written informed consent and entered the study. Three patients died during the study and one patient who deteriorated clinically was given vasodilator therapy. The data of these four subjects did not extend through the entire period and were withdrawn from analysis. A computer-generated, random-number format was used to randomize the patients into a control group of 11 and a dobutamine treatment group of 15 patients.

The clinical and laboratory features of the patients are presented in table 1. There were no significant differences in the age, sex, diagnoses, functional class, duration of symptoms, degree of cardiomegaly and electrocardiographic findings between the control and dobutamine groups. At entry, two control patients and four dobutamine patients had more than two-pillow orthopnea, five control patients and eight dobutamine patients had pitting pedal edema, and all patients in each group had dyspnea with mild exertion. All patients underwent cardiac catheterization within 3 months before the study; there was no significant difference between the control and dobutamine groups in mean cardiac index (2.06 ± 0.21 and 2.09 ± 0.26 l/min/m², respectively [± SD]) and left ventricular end-diastolic pressure (23 ± 4 and 24 ± 3 mm Hg, respectively). Four control and five dobutamine patients had mild mitral regurgitation, while two of the controls and three of the dobutamine patients had combined mild mitral and tricuspid regurgitation. To avoid angina-induced dose restriction and the poten-
TABLE 1. Clinical and Laboratory Features of the Patient Population

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 11)</th>
<th>Dobutamine (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)*</td>
<td>54 (32–68)</td>
<td>50 (32–68)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>7:4</td>
<td>10:5</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Remote history of ETOH</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Functional class (NYHA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III:IV</td>
<td>9:2</td>
<td>14:1</td>
</tr>
<tr>
<td>Mean duration (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of symptoms</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>Range</td>
<td>3–120</td>
<td>4–110</td>
</tr>
<tr>
<td>Mean frontal heart area*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>on chest x-ray</td>
<td>±33</td>
<td>±33</td>
</tr>
<tr>
<td>(±SD) (cm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Isolated left-axis deviation</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: NYHA = New York Heart Association; ETOH = alcohol.

Detrimental effects of administering a powerful inotropic agent to patients with myocardial ischemia in an outpatient setting (without direct hemodynamic monitoring), patients with > 50% narrowing of one or more major coronary vessels were excluded. Patients with moderate-to-severe valvular regurgitation were also excluded.

All control patients and 14 of 15 dobutamine patients continued to receive their usual doses of digoxin during the study. The mean digoxin plasma levels for the control group were 1.3 ± 0.3 ng/ml at baseline, 1.1 ± 0.4 ng/ml at 3 months and 1.2 ± 0.2 ng/ml at the end of the study. The corresponding mean digoxin plasma values for the dobutamine group were 1.0 ± 0.4, 1.1 ± 0.3 and 1.1 ± 0.4 ng/ml. Two control patients were receiving quinidine sulfate orally (400 mg and 200 mg every 6 hours); one patient of the dobutamine group was on oral quinidine sulfate (300 mg every 6 hours) and another was taking propranolol orally (250 mg every 4 hours). The antiarrhythmic drugs and dosages were not altered, and vasodilators and nitrates were not administered during this study. At entry into the study, nine of the 11 control patients were taking oral furosemide (average 80 ± 36 mg/day and two were taking oral hydrochlorothiazide (50 mg/day). Twelve of 15 dobutamine patients were taking oral furosemide (average 98 ± 60 mg/day), two were taking hydrochlorothiazide (50 and 100 mg/day) and one was taking chlorothiazide (1000 mg/day). Diuretic dosage was adjusted during the study period. There were no statistical differences between the medications (drugs and doses) taken by the control and the dobutamine groups at entry into the study.

Procedures and Measurements

The study was performed in the Congestive Heart Failure Research Laboratory in the outpatient clinic of the Ohio State University Hospitals.

Left ventricular function was evaluated by systolic time intervals and M-mode echocardiography performed on an Electronics for Medicine Echo IV unit using techniques and specifications described previously. The ratio of the prejection period to left ventricular ejection time (PEP/LVET) was used as one index of left ventricular function. The echocardiographic measures of left ventricular performance included percent change in the dimension of the minor axis of the left ventricle during systole (%ΔD), and the velocity of circumferential fiber shortening (Vcf). Cardiac index (cardiac output/body surface area) was measured by the 131I serum albumin (RISA) radioisotope-dilution technique. Exercise tolerance was determined by treadmill exercise testing using the Bruce protocol. Exercise testing was performed on an Avionics Del Mar 599 treadmill interfaced with a Sanborn 780-6A Hewlett Packard Visoscope and a Sanborn 500 Visocardette electrocardiograph recorder. The treadmill belt speed was standardized weekly. Inability of the patient to continue exercise because of severe dyspnea or fatigue was used as the end point of the exercise testing.

The dobutamine treatment group received dobutamine in 50 ml of normal saline. The solution was delivered intravenously over 4 hours with a calibrated syringe pump (Sage Instruments, model 341). The ECG was monitored throughout the infusion with a Roche 111 oscilloscope.

Protocol

The protocol is shown schematically in figure 1. The study of each patient was divided into baseline and treatment (dobutamine or control) phases. The baseline period was the same for the control and dobutamine groups. A clinical evaluation (history, physical examination and medication adjustment) by one of the investigators and an echocardiogram and systolic time intervals were performed weekly during the baseline period; a RISA cardiac output and treadmill exercise testing were obtained every 2 weeks during this period. Each patient performed a treadmill exercise test before the study to provide familiarization with the technique. The testing schedule of the two groups was the same during the treatment period. The technical staff performing the cardiovascular testing were
blinded during the treatment period. Clinical evaluation, echocardiography and systolic time intervals were performed every 2 weeks and treadmill exercise testing every 2 months on each subject during the treatment period. A RISA cardiac output was repeated at the end of the treatment period for each group. The patients in the dobutamine treatment group visited the heart failure clinic weekly for the dobutamine infusion; tests were performed before the dobutamine infusion.

The 4-hour dobutamine infusion consisted of dose-finding and maintenance infusions. Patients were given cumulative dose increments of 2.5 μg/kg/min over 30 minutes to a maximal dose of 10 μg/kg/min or to a dose that increased resting heart rate no more than 40% over the preinfusion heart rate. The infusion was then maintained at this level for 4 hours. The average maintenance dobutamine dose ranged from 7.41–8.69 μg/kg/min (fig. 1). Only one of 360 infusions was discontinued. The patient in whom an infusion was discontinued was receiving dobutamine at a rate of 10 μg/kg/min and developed ventricular tachycardia requiring cardioversion and hospitalization.

**Statistical Analysis**

The responses within a treatment group were analyzed by one-way analysis of variance, and intergroup comparisons by two-way analysis of variance. Autocorrelation corrections and Newman-Keuls tests were performed.

**Results**

Resting supine heart rate was not significantly altered by weekly dobutamine infusions (fig. 2). Although the mean resting supine systemic blood pressure was never significantly different between the two groups, the mean systemic pressure of the dobutamine treatment group dropped significantly below baseline after the eighth infusion week (fig. 2).

The PEP/LVET did not change from baseline for either group, and there were no differences between any of the corresponding values of the two groups (fig. 3). The %ΔD increased modestly above baseline at 18, 22 and 24 weeks in the dobutamine treatment group (fig. 3); there were no differences, however, between any corresponding %ΔD values of the two groups. The dobutamine treatment group experienced a significant increase in mean Vcf values above baseline at 14–24 weeks and above the corresponding values of the control group at 22 and 24 weeks (fig. 3). The RISA cardiac index, determined in nine of 11 control patients and in 12 of 15 dobutamine patients, did not change significantly from baseline for either group. The mean cardiac indexes for the dobutamine group were 2.4 ± 0.82 (± SD) and 2.61 ± 0.671/min/m² at baseline and 2.65 ± 1.02 1/min/m² after the 24-week treatment period; the corresponding values for the control group were 2.67 ± 1.24, 2.33 ± 0.70 and 2.54 ± 0.66 1/min/m². The differences between groups were not significant.

The mean exercise duration increased 25–51%
FIGURE 3. The ratio of preejection period to left ventricular ejection time (PEP/LVET), the percent change in the dimension of the minor axis of the left ventricle (%ΔD) and the mean velocity of circumferential shortening (Vcf) in the control and dobutamine treatment groups during the 7-month study.

Above baseline in the dobutamine group during the treatment period of the study; these changes were significantly higher than baseline and the corresponding values of the control group (fig. 4). Although the mean exercise duration of the control group increased 10–17% during the treatment period, these values were not significantly different from baseline. Mean heart rate at maximal exercise during treatment did not change from baseline for either group and the values of the two groups were not significantly different from each other (fig. 4).

Two of the 11 control group patients improved one functional class (New York Heart Association) and nine remained unchanged (fig. 5). Two of the fifteen dobutamine treatment patients improved two functional classes, 10 improved one functional class, and three remained unchanged. In the control group, seven patients required an increase in diuretic dosage during the study and four required no change. In the dobutamine group, three patients required an increase in diuretic dosage, nine no change and three a decrease. The mean body weight of the control group increased 2.7 kg (71.8 ± 17 to 74.5 ± 20 kg, p = 0.10) from baseline to the end of the treatment period; the mean body weight of the dobutamine group decreased 0.9 kg (72.3 ± 15 to 71.4 ± 15 kg, p < 0.10). The frontal heart area in the posteroanterior chest x-ray after treatment was not significantly different from baseline in either group (control 158 ± 33 cm² vs 158 ± 34 cm²; dobutamine 156 ± 33 cm² vs 155 ± 27 cm²).

Discussion

This study was designed to determine whether 4-hour weekly infusions of dobutamine elicited improvement in left ventricular function and clinical status similar to that noted with the 72-hour infusions of dobutamine.1, 2 The measurements of resting left ventricular function improved only slightly during the dobutamine treatment period; the PEP/LVET ratio and the RISA cardiac index did not change and %ΔD and Vcf by M-mode echocardiography improved modestly. The study was designed and initiated before the availability of exercise left ventricular function analysis by radionuclide ventriculography. Therefore, left ventricular performance during exercise might have been augmented for the dobutamine group during the treatment period.

Increased exercise tolerance and improved clinical status of the dobutamine treatment group were the major findings of this study. Exercise duration increased without an additional increase in heart rate at maximal exercise and without major improvement in
resting left ventricular function, which suggests that a conditioning effect was achieved by the weekly infusions of dobutamine. In retrospect, it is possible that some of the improvement in clinical status noted by heart failure patients after the 72-hour infusions of dobutamine was also related to a conditioning effect. The only objective evidence of such an effect in the resting measurements was the modest decrease from baseline in the mean arterial blood pressure; resting heart rate was not altered. The changes in functional classification (improvement in 12 of 15 dobutamine patients [80%] vs two of 11 control patients [18%]) are supported by the exercise tolerance studies and by the fact that mean body weight in the control group tended to increase despite increasing diuretic dosage (seven of 11 patients), whereas body weight and overall diuretic dosage were not altered for the dobutamine group.

Although the mechanism of the apparent conditioning effect by the dobutamine infusions is uncertain, the validity of our observations is supported by a study by Liang and colleagues. They infused dobutamine, 40 µg/kg/min, for 2 hours/day for 5 weeks into deconditioned dogs and compared the results with a control group that received a saline infusion and another group that exercised (4 mph, 10° grade) for 2 hours/day for 5 weeks. After 5 weeks, resting heart rate and exercise-provoked increases in heart rate, cardiac output, mean aortic blood pressure, arterial blood lactate, plasma renin activity and norepinephrine concentration decreased significantly for the dobutamine and exercise groups compared with the control group. Their study demonstrates a remarkable similarity between exercise conditioning and intermittent dobutamine infusions in their cardiovascular and metabolic responses. Our patient population was probably deconditioned because of the underlying cardiac disease (concomitant reduction in physical activity). The weekly 4-hour dobutamine infusion reversed some of the deconditioning while minimally altering the resting cardiac-ventricular function status.

It is unlikely that the improved exercise tolerance in the dobutamine group is secondary to a placebo effect. Exercise duration increased up to 51% in the dobutamine group and only 17% in the control group at the same maximal exercise heart rate. A placebo effect would probably have been accompanied by a higher heart rate response at the higher level of maximal exercise. Ideally, the control group should have received weekly 4-hour saline infusions. A pilot study on the first three patients indicated that a blinded patient could easily distinguish between infusions of saline and dobutamine; this finding in conjunction with our concern for patient compliance blunted our enthusiasm for administering saline for 4 hours every week for 6 months to the control patients.

Exercise conditioning elicits important physiologic and biochemical changes, including decreases in resting heart rate, mean arterial pressure and blood lactate and increases in exercise tolerance and maximal oxygen consumption. Certain mitochondrial enzymes of skeletal muscle also increase with regular exercise. Sympathetic stimulation during exercise may account for some of these changes. Dobutamine, a synthetic catecholamine, markedly increases ventricular contractility, cardiac output and limb musculoskeletal blood flow; at higher doses it elicits tachycardia as well. These cardiovascular effects are similar to those with exercise; with exercise, these effects are in large part secondary to activation of the sympathetic nervous system. An infusion of dobutamine probably simulates many of the physiologic responses to exercise (e.g., sympathetic nervous system activation, augmentation of blood flow to limb muscle) and as such represents a method of physical conditioning without exercise.

Compared with most other catecholamines, dobutamine has certain advantages in the patient with congestive heart failure. It does not change mean systemic blood pressure greatly, it tends to reduce left ventricular filling pressure during the infusion, and it appears to be less arrhythmogenic. When infused in—
termittently, other catecholamines may also effect a conditioning response. Norepinephrine is the catecholamine released during exercise. Presumably, its strong vascular α-receptor agonist (vasoconstriction) properties are reversed by the local vascular regulation during exercise, which would not be present during an infusion at rest.

We are not recommending weekly 4-hour catecholamine infusions as a major therapeutic tool for practicing physicians; this treatment may not be practical in many cases. Our intention is to report the phenomenon of drug-induced physical conditioning in deconditioned man with the hope that this concept can be applied to patients with heart failure and other chronic illnesses, immobilized patients and possibly some patients with skeletal myopathies. We suspect that other drugs may also act, in part, through this mechanism.

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References

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