Long-term Intermittent Dobutamine Infusion Combined With Oral Amiodarone Improves the Survival of Patients With Severe Congestive Heart Failure*

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Study objective: To evaluate the effects of long-term intermittent dobutamine infusion (IDI) with concomitant administration of low-dose amiodarone in patients with congestive heart failure (CHF) refractory to standard medical treatment.

Design: Prospective, interventional clinical trial.

Setting: Inpatient and outpatient heart failure clinic in a university teaching hospital.

Patients and interventions: Twenty-two patients with CHF refractory to standard treatment who could be weaned from dobutamine therapy after an initial 72-h infusion were included in this study. The first 11 patients (group 1) were treated with IDI, 10 μg/kg/min, as needed (mean, once every 16 days, lasting for 12 to 48 h); the next 11 patients (group 2) received oral amiodarone, 400 mg/d, and IDI, 10 μg/kg/min, for 8 h every 7 days.

Measurement and results: There were no differences in baseline clinical, hemodynamic, and five biochemical characteristics between the two groups. The left ventricular ejection fraction was 13.5 ± 4.5% in group 1 vs 15.5 ± 4.9% in group 2 (mean ± SD; p = 0.451); mean pulmonary capillary wedge pressure was 31.3 ± 4.4 mm Hg vs 29.4 ± 3.3 mm Hg (p = 0.316); serum creatinine was 1.9 ± 0.4 mg/dL vs 1.6 ± 0.5 mg/dL (p = 0.19); and serum Na was 139.6 ± 6.2 mEq/L vs 138.4 ± 3.1 mEq/L (p = 0.569). At 12 months of follow-up, 1 of 11 patients (9%) was alive in group 1 vs 6 of 11 patients (55%) in group 2 (p = 0.011). Furthermore, in group 2, the functional status improved significantly within the first 3 months of treatment, from New York Heart Association functional class IV to 2.63 ± 0.5 (p = 0.0001).

Conclusion: Long-term IDI in conjunction with amiodarone, added to conventional drugs, improved clinical status and survival of patients with severe CHF.

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Key words: amiodarone; congestive heart failure; dobutamine; survival

Abbreviations: CHF = congestive heart failure; IDI = intermittent dobutamine infusion; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

Congestive heart failure (CHF) is usually associated with progressive deterioration of left ventricular function and a poor long-term prognosis, despite the beneficial effects of angiotensin-converting enzyme inhibitors on survival. Patients with severe CHF have a high incidence of ventricular arrhythmias, and > 40% of them die suddenly.

Amiodarone is effective in controlling life-threatening arrhythmias, even when other antiarrhythmic drugs have been ineffective, has minimal negative inotropic effect, and prolongs the survival of patients with severe CHF. The long-term oral administration of positive inotropic agents is associated with increased mortality. Digoxin remains the only oral positive inotropic agent without adverse long-term effects on survival.

Dobutamine, a synthetic sympathomimetic amine with predominant β1-adrenergic activity, is a potent inotropic agent. When administered in continuous or intermittent infusions in patients with CHF refrac-
tory to a regimen of angiotensin-converting enzyme inhibitors, diuretics, and digitalis, dobutamine improves the clinical condition \textsuperscript{18–24} but not the survival of these patients.\textsuperscript{25} The higher mortality in patients treated with dobutamine infusions has been attributed to its pronounced proarrhythmic effects.\textsuperscript{26}

We hypothesized that the addition of amiodarone to long-term, intermittent dobutamine infusions (IDIs) might attenuate, or even suppress, its adverse effect on survival, and that the salutary effects of the two drugs might be synergistic in improving the clinical condition and the survival of these patients. The purpose of this study was to determine whether intermittent, long-term dobutamine infusions, administered in fixed doses at regular intervals in conjunction with oral amiodarone therapy, improves the 1-year survival of patients with CHF refractory to standard medical treatment.

**Materials and Methods**

**Patient Selection**

Twenty-two patients with CHF refractory to standard therapy (including digoxin, enalapril, and diuretics) who could be weaned from an initial 72-h infusion of dobutamine were included in this study. The first 11 patients (group 1) were treated with IV dobutamine infusions based on their clinical needs in order to maintain their New York Heart Association (NYHA) functional class of less than IV in the outpatient setting. The next 11 consecutive patients (group 2) were prospectively studied and received amiodarone, 400 mg/d, starting at least 4 weeks before the long-term, weekly, IV dobutamine infusions. Patients who could not be weaned from IV dobutamine were excluded from the study. All patients were men. In both groups, the underlying disease was idiopathic dilated cardiomyopathy in five patients and coronary artery disease in six patients. This study was approved by our institutional ethical review board, and all patients signed informed consent.

**Study Design**

All patients were hospitalized for initiation of standard treatment and continuous IV infusion of dobutamine, 10 µg/kg/min, for up to 72 h, with a goal of significant clinical improvement, particularly a decrease in NYHA functional class below IV. Group 1 patients were rehospitalized to receive an additional dobutamine infusion when their clinical condition deteriorated. Group 2 patients received the first dobutamine infusion, 10 µg/kg/min for 8 h, 7 days after their initial stabilization and weekly thereafter regardless of their clinical condition.

Once hemodynamically stabilized, all patients underwent a baseline laboratory evaluation, including echocardiography to evaluate the severity of mitral valve regurgitation, radionuclide ventriculography to measure left ventricular ejection fraction (LVEF), right heart catheterization, and biochemical tests. Thereafter, they were thoroughly reevaluated clinically every week and laboratory testing was repeated at 3 months of follow-up.

**Statistical Analysis**

Differences between variables measured in the two groups were tested by Student’s $t$ test for unpaired observations. In patients who had two repeat evaluations, Student’s paired $t$ test was used to compare changes in clinical status, LVEF, and hemodynamic variables. When the underlying assumptions of the $t$-test models were violated, the Mann-Whitney $U$ test or the Wilcoxon test were used. Survival curves were estimated by the Kaplan-Meier method. Differences between curves were evaluated by log-rank test. The prognostic value of several variables was assessed with the Cox regression model. Continuous variables were categorized by using the mean as the cutoff value. All $p$ values $<0.05$ were considered statistically significant.

**Results**

**Patient Populations**

Group 1 included 11 patients (mean age, 52.8 ± 10.8 years) who received dobutamine infusions when mandated by signs and symptoms of heart failure uncontrollable by the standard drug regimen (mean, once every 16 days, lasting for 12 to 48 h). Group 2 included 11 patients (mean age, 52 ± 11.5 years) who were treated with dobutamine infusion administered weekly for 8 h, starting after the first episode of cardiac decompensation refractory to standard treatment. These patients were also receiving long-term amiodarone therapy. All patients had a radionuclide LVEF of $<25\%$. There were no differences between the two groups with respect to clinical and hemodynamic status, doses of furosemide, and biochemical measurements (Table 1).

**Patient Survival**

No patient was unavailable for follow-up. At 12 months, 1 of 11 patients (9\%) was alive in group 1, vs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n = 11)</th>
<th>Group 2 (n = 11)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>53 ± 10.8</td>
<td>52 ± 11.5</td>
<td>0.966</td>
</tr>
<tr>
<td>Men/women, No.</td>
<td>11/0</td>
<td>11/0</td>
<td></td>
</tr>
<tr>
<td>Etiology (IDC/CAD), No.</td>
<td>5/6</td>
<td>5/6</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>4 ± 0</td>
<td>4 ± 0</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>95.5 ± 13.8</td>
<td>96.3 ± 6.36</td>
<td>0.554</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>13.5 ± 4.5</td>
<td>15.5 ± 4.9</td>
<td>0.451</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>88.6 ± 14.4</td>
<td>77.4 ± 10.3</td>
<td>0.055</td>
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<tr>
<td>RAP (mean), mm Hg</td>
<td>15.7 ± 4.03</td>
<td>13.7 ± 3.2</td>
<td>0.294</td>
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<tr>
<td>RVSP, mm Hg</td>
<td>66.6 ± 11.4</td>
<td>70.5 ± 12.3</td>
<td>0.535</td>
</tr>
<tr>
<td>PAP (mean), mm Hg</td>
<td>44.3 ± 6.6</td>
<td>44.9 ± 7.3</td>
<td>0.575</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>31.3 ± 4.4</td>
<td>29.4 ± 3.3</td>
<td>0.316</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.8 ± 0.41</td>
<td>3.3 ± 0.9</td>
<td>0.308</td>
</tr>
<tr>
<td>PVR (Wood)</td>
<td>2.8 ± 1.01</td>
<td>5.4 ± 3.2</td>
<td>0.114</td>
</tr>
<tr>
<td>Furosemide, mg/d</td>
<td>350 ± 142</td>
<td>238 ± 120</td>
<td>0.065</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.92 ± 0.4</td>
<td>1.61 ± 0.51</td>
<td>0.190</td>
</tr>
<tr>
<td>Na, mEq/L</td>
<td>139.6 ± 6.2</td>
<td>138.4 ± 3.1</td>
<td>0.569</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. IDC = idiopathic dilated cardiomyopathy; CAD = coronary artery disease; HR = heart rate; RAP = right atrial pressure; RVSP = right ventricular systolic pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; PVR = pulmonary vascular resistance.
6 of 11 patients (55%) in group 2 (p = 0.011; Fig 1). The combination of dobutamine and amiodarone was associated with a 51% (p = 0.011) reduction in risk of overall cardiac death (10 deaths in group 1 vs 5 deaths in group 2), 67% (p = 0.011) reduction in risk of sudden death (three in group 1 vs one in group 2), and 44% (p = 0.395) reduction in risk of death due to deterioration of the end-stage heart failure (seven in group 1 vs four in group 2).

Hemodynamic Measurements

In group 2, the acute response to dobutamine infusion (10 μg/kg/min for 10 min) was evaluated 2 weeks after the first episode of cardiac decompensation that was refractory to standard treatment. At that point, dobutamine had retained its positive inotropic effect, manifested by a significant reduction in right and left ventricular filling pressures, and a significant increase in cardiac index (Table 2).

At 3 months of follow-up, before the scheduled dobutamine infusion, a significant increase in LVEF from 15.5 ± 6.3% to 20.7 ± 2.2% (p = 0.032) and a decrease in pulmonary capillary wedge pressure from 28.8 ± 3.1 to 21.9 ± 7.9 mm Hg (p = 0.027) was measured in group 2 (Table 3).

Functional Evaluation at 3 Months

At 3 months of follow-up, a significant improvement in functional status from NYHA functional class IV to a mean of 2.63 ± 0.5 (n = 10; p < 0.0001) was measured in the surviving patients of group 2, accompanied by a maximum oxygen uptake of 16.5 ± 4.2 mL/kg/min (n = 7) on cardiopulmonary exercise testing (Table 3).

**Discussion**

Despite progress in the treatment of CHF, some patients continue to suffer from signs and symptoms that are uncontrollable by the most judicious use of diuretics, vasodilators, and digitalis. In these patients, the short-term administration of dobutamine is common practice in ICUs to treat episodes of acute cardiac decompensation.

Dobutamine was found to exert a sustained therapeutic effect, lasting up to 10 weeks after a single 72-h continuous infusion in patients with CHF. The tachyphylaxis to continuous dobutamine infusion administered in patients with severe CHF seems to begin at 2 h, and becomes significant after 72 h, with measurable β-receptor downregulation after 4-h infusion. Nevertheless, the management of CHF with long-term, weekly, 48-h dobutamine infusions has been shown to produce significant and sustained hemodynamic and clinical improvements. However, this treatment does not prolong survival. In a controlled, double-blind trial, 60 patients with CHF refractory to standard therapy were randomized to receive weekly dobutamine or placebo infusions for 48 h. The study was stopped prematurely because of the finding of a 17% mortality rate in patients treated with placebo, vs 40% in patients treated with dobutamine (p = 0.08).

The cause of increased death rate in patients treated with long-term, IDIs is uncertain, though dobutamine-induced proarrhythmia remains the most likely explanation. This hypothesis is supported by studies in which the infusion of dobutamine was found to (1) increase the dispersion of action-potential duration in adjacent areas of ischemic and non-ischemic human myocardium, (2) increase the incidence of spontaneous or inducible, sustained and nonsustained, ventricular tachycardia in experimen-

**Table 2—Hemodynamic Response to 10-min Dobutamine Infusion, 10 μg/kg/min**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline (n = 11)</th>
<th>Dobutamine (n = 11)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mean), mm Hg</td>
<td>13.3 ± 3.7</td>
<td>9 ± 3.6</td>
<td>0.000</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>75.1 ± 5.5</td>
<td>65.9 ± 10.1</td>
<td>0.011</td>
</tr>
<tr>
<td>PAP (mean), mm Hg</td>
<td>46.7 ± 7.5</td>
<td>41.2 ± 6.6</td>
<td>0.004</td>
</tr>
<tr>
<td>PCWP (mean), mm Hg</td>
<td>30.1 ± 3.3</td>
<td>24.4 ± 4.1</td>
<td>0.009</td>
</tr>
<tr>
<td>CI, L/m²/min</td>
<td>1.7 ± 0.46</td>
<td>2.5 ± 0.87</td>
<td>0.014</td>
</tr>
<tr>
<td>PVR (Wood)</td>
<td>6.2 ± 3.6</td>
<td>4.3 ± 2.9</td>
<td>0.125</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. CI = cardiac index; see Table 1 for other abbreviations.*
In patients with severe CHF, treatment with amiodarone was associated with an early (30 days) decrease in sudden death rate, and a late decrease in mortality due to progressive heart failure.12 Interestingly, this effect was not found in patients with less severe CHF.35 This decrease in mortality by amiodarone has been attributed to its antiarrhythmic 7–10 and antiadrenergic properties.11,12 These considerations led us to hypothesize that the addition of amiodarone might effectively mitigate the adverse effects of long-term, intermittent dobutamine treatment without suppressing its positive inotropic effect. In this study, an 8-h dobutamine infusion was used because it has been found to promote sustained improvements in left ventricular function with minimal tachyphylaxis29 and of sufficient duration to correct fluid retention, electrolyte abnormalities, and azotemia in patients with severe CHF. In this study, dobutamine retained its positive inotropic effect in the presence of amiodarone. In group 2, sustained hemodynamic and clinical improvements were observed, as well as, most importantly, a 51% decrease in the 12-month risk of cardiac death. The amiodarone-treated patients did not show arrhythmia acceleration during the 8 h of dobutamine infusion or late after the infusion. A single patient treated with the combination of dobutamine and amiodarone died suddenly. The sustained clinical and hemodynamic improvement, mostly attributable to dobutamine, is probably multifactorial, and has been suggested to be due to a conditioning effect,35–38 to an improvement in myocardial mitochondrial structure, to an increase in the myocardial adenosine triphosphate/creatinine ratio, to the correction of azotemia and increase in subendocardial blood flow,39 and to normalization of ventricular vascular coupling.40

The lower 12-month mortality rate in patients treated with the drug combination is probably attributable to both drugs. On one hand, amiodarone may have reduced the rate of sudden death, owing to its known efficacy in the suppression of life-threatening arrhythmias,7–10 which these patients might have had spontaneously or induced by dobutamine.14,22,26,27 On the other hand, dobutamine markedly improved the patients' hemodynamics and clinical status, and may have prevented deaths due to end-stage heart failure.

The results of this study are concordant with those of a 1998 study41 based on a similar hypothesis, and using a combination of enoximone and metoprolol in addition to standard medications. In that study, the survival of the patients treated with the drug combination was higher that in patients enrolled in the Cooperative North Scandinavian Enalapril Study trial.42

The 12-month survival of our group 2 patients was significantly higher than in group 1, as well as in the study by Krell et al.22 Survival in our group 1 patients, however, was comparable to that measured in the study by Krell et al22 (Fig 2).

Study Limitations

The most important limitation of our study was its nonrandomized design and the biases this may have introduced. The unscheduled dobutamine infusions

![Figure 2. Comparison of cumulative survival in group 1 vs group 2, vs that in patients described by Krell et al.22](http://journal.publications.chestnet.org/pdftools/ashx?url=data/journals/chest/21961/)
in group 1 was another weakness of the protocol. However, the similar survival of our group 1 patients, compared to that of the patients reported by Krell et al.\(^2\) (Fig 2) suggests that comparing our two groups was legitimate. The small number of patients is an additional limitation of our study, and the number of patients included in each subgroup was too small for valid comparisons. Nevertheless, these data must be verified in a larger randomized study.

In conclusion, our results suggest that long-term, IDIs combined with amiodarone in addition to standard therapy improve survival of patients with refractory CHF.

REFERENCES

34 Kirlin PC, Pitt B, Lucchesi BR. Comparative effects of prenalterol and dobutamine in a canine model of acute congestive heart failure. CHEST / 119/4/ APRIL, 2001 1177