Sustained Improvement in Flow-Mediated Vasodilation After Short-Term Administration of Dobutamine in Patients With Severe Congestive Heart Failure

Mrugesh B. Patel, MD; Ilya V. Kaplan, MD; Rajiv N. Patni, MD; Daniel Levy, MD; Joel A. Strom, MD; Jamshid Shirani, MD; Thierry H. LeJemtel, MD

Background—In patients with severe congestive heart failure (CHF), short-term administration of dobutamine exerts sustained clinical benefits that are partially mediated by a training-like effect on skeletal muscle. Recently, physical training has been shown to enhance endothelial function in the skeletal muscle vasculature by improving endothelial function. Whether the dobutamine-induced training effect is also associated with an improvement in endothelial function in the skeletal muscle vasculature is currently unknown.

Methods and Results—Flow-mediated vasodilation in response to peak reactive hyperemia was evaluated in the forearms of 9 patients with severe CHF who were treated with dobutamine for 72 hours. Resting and peak hyperemic brachial artery blood flow and diameter (BABF [mL/min] and BAD [mm], respectively) were measured by 2-dimensional and Doppler ultrasonography at baseline, at 3 and 72 hours during dobutamine infusion, and at 2 and 4 weeks after discontinuation of dobutamine therapy. In addition, the brachial artery response to sublingual (SL) administration of nitroglycerin (NTG) was evaluated at baseline and at 2 and 4 weeks after discontinuation of dobutamine therapy. Ten patients with severe CHF who did not receive dobutamine served as control subjects. Resting BABF was significantly increased at 3 and 72 hours (391.2±31.8 and 366.8±31.0 mL/min, respectively, compared with 289.8±18.6 mL/min at baseline; P<0.05). Peak hyperemic BABF was not altered by dobutamine infusion compared with baseline values. The increase in BAD during peak hyperemic response was greater after infusion of dobutamine for 72 hours (15.2±2.7% versus 9.1±1.8%, P<0.05) and remained significantly greater for ≥2 weeks after discontinuation of dobutamine (12.3±2.2% versus 9.1±1.8%, P<0.05). In contrast to the peak hyperemic response, the increase in BAD (%) induced by SL NTG was unchanged by administration of dobutamine for 72 hours. Two and 4 weeks after discontinuation of dobutamine, NTG-induced increases in BAD were similar to the BAD noted at baseline.

Conclusions—In patients with severe CHF, short-term administration of dobutamine for 72 hours selectively improves vascular endothelial function for ≥2 weeks. (Circulation. 1999;99:60-64.)

Key Words: heart failure ■ nitroglycerin ■ vasodilation

Treatment of compliant patients with severely symptomatic congestive heart failure (CHF) despite therapy with drugs such as ACE inhibitors, loop diuretics, long-acting nitrates, and cardiac glycosides remains a therapeutic challenge. Short-term administration of dobutamine has been shown to produce sustained clinical effects in these patients.1 The persistence of the clinical effects after discontinuation of dobutamine has been attributed to 2 mechanisms: a sustained improvement in myocardial contractility—left ventricular performance and a training-like effect on the skeletal muscles.2,3 Physical training has recently been shown to specifically enhance flow-mediated vasodilation in patients with CHF.4,5 Whether dobutamine-induced training also involves the vascular endothelium is currently unknown.

Accordingly, the present study was undertaken to serially assess endothelium-dependent vasodilation (brachial artery dilatation in response to 5 minutes of occlusion) and endothelium-independent vasodilation (regional response to sublingual [SL] administration of nitroglycerin [NTG]) in patients with severe CHF who were treated for 72 hours with dobutamine. Patients with severe CHF who were not treated with dobutamine served as control subjects.

Methods

Patient Population

Twelve men and 7 women with CHF and symptoms compatible with New York Heart Association functional class IV were studied. Extensive coronary artery disease was documented in all patients by coronary angiography. In addition, 8 patients had type II diabetes mellitus, and 5 had a history of hypertension. None of the patients were smokers. All patients were treated with furosemide (80 to 240 mg/d), digoxin (mean serum level, 0.9 ng/mL), captopril (25 to 75
mg/dl), or enalapril (10 to 30 mg/d). Long-acting nitrates were discontinued 48 hours before the study. Nine of 19 patients were treated with dobutamine at a mean infusion rate of 3.5 μg · kg⁻¹ · min⁻¹ (range, 2.5 to 5.0 μg · kg⁻¹ · min⁻¹) for 72 hours. The rate of infusion of dobutamine was adjusted according to clinical response during the first 2 hours of administration, as evidenced by an increase in urinary output, enhanced peripheral perfusion, and relief of symptoms. The remaining 10 patients were not treated with dobutamine and served as control subjects. The clinical characteristics of the 9 patients who received dobutamine and the 10 who did not receive dobutamine are summarized in Table 1. All patients who were treated with dobutamine remained ambulatory during the 4 weeks after discontinuation of dobutamine therapy. All patients gave written, informed consent. The study protocol was approved by the Albert Einstein College of Medicine Committee of Clinical Investigations.

Two-Dimensional and Doppler Ultrasonography

This method has been described previously.²,⁶ Ultrasound examination of the brachial artery in the dominant forearm was performed with the use of a high-resolution 5- to 10-MHz ultrasonic transducer connected to an ATL HDI 3000cv Ultrasound System that allows measurement of arterial diameter with a precision of 0.1 mm. With the patient supine, the transducer was positioned 5 to 10 cm above the antecubital fossa. The brachial artery was identified and carefully scanned to determine its origin, course, and the presence and extent of atheroma. Exclusion criteria included extensive arterial wall atheromatous changes, arterial narrowing, or a Doppler signal consistent with proximal arterial stenosis. The origin of the vessel was avoided because of changes in velocity profile at the branching point. Once the optimal portion of the artery was visualized, the position of the transducer was marked on the skin. The center of the vessel was identified when the clearest images of the anterior and posterior walls of the artery were obtained, and the transmit zone was set to the level of the anterior wall. Depth and gain settings were optimized to identify the lumen-to-vessel wall interface and were kept constant during each study. Before any Doppler measurements were attempted, great care was taken to visualize the vessel at its largest diameter with the vessel walls parallel in the 2-dimensional sector image. When the vessel walls are parallel, one can assume that the ultrasound beam is directed parallel to the longitudinal axis of the vessel.² Transducer position was then adjusted to minimize the incident angle of the ultrasound beam. An angle of fewer than 60° was obtained in all instances and was kept constant in each subject. Automatic internal correction for the Doppler angle was used with the aid of an on-screen cursor. A 2- to 3-mm sample volume was placed in the center of the vessel, and fine adjustments of its position were made until a narrow Doppler spectrum was obtained. Under these conditions, the maximal velocity, corresponding to the central position in a parabolic velocity profile, was recorded. Even though this variable tended to overestimate the actual velocity across the whole cross section of the vessel, this approach maximized reproducibility of the Doppler signal. Two-dimensional and Doppler studies were recorded on commercially available videocassettes for later analysis.

Flow-Mediated Vasodilation and Response to NTG

Flow-mediated vasodilation was measured in the response of the brachial artery after peak reactive hyperemia. Peak reactive hyperemia was induced by inflation of a blood pressure cuff around the forearm to a pressure of 200 mm Hg for 5 minutes, followed by release. The wrist was not occluded during the final minute of forearm occlusion. The brachial artery was scanned at rest and for 30 seconds before and 180 seconds after cuff deflation. The maximum increase in brachial artery diameter (BAD) occurred at 90 seconds after release of cuff occlusion. The scan was performed at 5 time points: baseline (before dobutamine), at 3 and 72 hours after administration of dobutamine was begun, and at 2 and 4 weeks after discontinuation of dobutamine therapy. In the control patients, the scan was performed at baseline (day 1), day 3, 2 weeks, and 4 weeks.

The brachial artery response to NTG was assessed before treatment with dobutamine and at 2 and 4 weeks after discontinuation of dobutamine therapy. After optimal visualization of the brachial artery, a dose of 0.4 mg of NTG was administered, and the brachial artery was scanned over the next 5 minutes. The brachial artery response to SL administration of NTG was not assessed in patients who did not receive dobutamine.

Data Analysis

Arterial diameters were measured by 2 observers using ultrasonic calipers (NovaMicrosonics) from the anterior-to-posterior interface between the media and adventitia, at a fixed distance from an anatomic marker such as a vein or fascial plane. The mean diameter was calculated from 8 cardiac cycles (4 from each observer) incident with the R wave on a continuously recorded ECG. We performed analysis of Doppler velocity by integrating the darkest portion of the spectral display throughout systole and diastole and dividing by the R-R interval. The results of 5 cardiac cycles were averaged. In case of arrhythmias, beats were excluded from analysis. Blood flow was calculated by multiplying the velocity-time integral by the heart rate and artery cross-sectional area. During the peak hyperemic response, BAD, blood flow velocity, and heart rate were obtained at 30, 60, 90, 120, and 180 seconds after release of arterial occlusion.

Statistical Analysis

All data are presented as mean±SD. Hemodynamic parameters were analyzed by 1-way ANOVA with repeated measures, followed by Scheffe’s post hoc test for statistical significance. Statistical significance was accepted at the 95% confidence interval (P<0.05).

Results

Resting Brachial Artery Blood Flow

During administration of dobutamine at an average infusion rate of 3.5 μg · kg⁻¹ · min⁻¹, resting brachial artery blood flow (BABF) increased from 289.8±18.6 mL/min at baseline to 391.2±31.8 mL/min at 3 hours and 366.8±31.0 mL/min at 72 hours (both P<0.05 versus baseline). At 2 and 4 weeks after discontinuation of dobutamine, resting BABF returned to 310.8±20.2 and 296±17.6 mL/min, respectively, values that were not statistically different from baseline (Figure 1).

Peak Hyperemic BABF and Diameter

Peak hyperemic BABF occurred 30 seconds after release of the 5-minute arterial occlusion and was similar at baseline and during and after administration of dobutamine (Figure 2A). Similarly, the increase in peak blood flow velocity was identical at baseline and during and after administration of dobutamine (Figure 2B). The increase in BAD (%) during

### Table 1. Clinical Characteristics of Study and Control Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study Patients</th>
<th>Control Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n M/F</td>
<td>9 (6/3)</td>
<td>10 (6/4)</td>
</tr>
<tr>
<td>Age, y</td>
<td>63±5</td>
<td>61±2</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>27±2</td>
<td>27±1</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>92±19</td>
<td>87±15</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>2.6±0.4</td>
<td>2.4±0.3</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>150±4</td>
<td>155±3</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>History of hypertension, n</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; BUN, blood urea nitrogen.
peak hyperemic response was maximal at 90 seconds after release of the 5-minute arterial occlusion. During administration of dobutamine, the increase in BAD was only significantly greater at 72 hours when compared with baseline (15.2±2.7% versus 9.1±1.8%, P<0.05; Figure 3). Two weeks after discontinuation of dobutamine, the increase in BAD remained significantly greater than BAD noted at baseline (12.3±2.2% versus 9.1±1.8%, P<0.05; Figure 3).

Brachial Artery Responses to SL NTG
Administration of SL NTG resulted in a significant increase in BABF. The increases in BABF were similar before and at 2 and 4 weeks after discontinuation of dobutamine (Figure 4). SL NTG–induced increases in BAD were also similar before and at 2 and 4 weeks after discontinuation of dobutamine (Figure 5).

Control Subjects
Resting and peak hyperemic BABF and increase in BAD during hyperemic response are detailed in Table 2 for the 10 patients with severe CHF who did not receive dobutamine. These parameters remained unchanged at baseline, at 3 and 72 hours of dobutamine therapy, and at 2 and 4 weeks after therapy was discontinued.

Discussion
The present data indicate that in patients with severe CHF, flow-mediated vasodilation remains improved for ≥2 weeks after short-term administration of dobutamine for 72 hours. During administration of dobutamine, resting BABF steadily increased at 3 and 72 hours, whereas flow-mediated vasodilation was only improved at 72 hours. The lag between the increase in blood flow and the improvement in flow-mediated vasodilation is similar to that reported with physical training.4

Flow-mediated dilatation in response to 5 minutes of arterial occlusion tended to be greater in our patients with severe CHF than in healthy subjects studied by Celermajer et al (9.2% versus 8.2%).9 However, the peak increase in BAD occurred at 90 seconds after the release of occlusion in our patients, whereas Celermajer et al reported the increase in BAD at 60 seconds. Our data are within the range reported by Hornig et al,4 who observed an increase in arterial diameter of 6.8% and 12% after arterial occlusion for 4 and 8 minutes, respectively. Peak hyperemic BABF only increased by a factor of 2 in our patients. This substantially depressed peak hyperemic response probably reflects the severe symptoms experienced by our patients, because peak reactive hyperemia and functional capacity are closely correlated in patients with CHF.10 The lack of improvement in peak hyperemic response after administration of dobutamine for 72 hours is in agreement with the data of Khan and colleagues.11 These investigators reported that peak reactive hyperemia is not immediately improved despite restoration of cardiac output to near normal values after insertion of a left ventricular assist device.11

The selective improvement in flow-mediated but not in NTG-induced vasodilation points to a specific effect of
dobutamine on the vascular endothelium. Flow-mediated vasodilation can be enhanced by either increased release of endothelium-derived relaxing substances or increased sensitivity of the vascular smooth muscle cells to relaxing substances. Because the response to NTG was left unchanged by short-term administration of dobutamine, an increased release of endothelium-derived relaxing substances rather than increased vascular smooth muscle cell sensitivity to relaxing substances probably accounts for the improvement in flow-mediated vasodilation. How short-term administration of dobutamine persistently increases the release of endothelium-derived relaxing substances is not fully understood.

Short-term administration of dobutamine may promote release of endothelium-derived relaxing substances by exposing the vasculature to increases in blood flow and thereby in shear stress.12,13 Physical training, which also transiently increases blood flow, has been reported to enhance constitutive NO synthase (cNOS) gene expression and NO production in experimental models of CHF.14 In contrast, cNOS gene expression was found to be unchanged in the skeletal muscle vasculature of patients with CHF who experienced a 20% increase in peak aerobic capacity after physical training.15

Elevated levels of cytokines in patients with severe CHF may activate the inducible form of NOS, which in turn increases NO production.16 However, the inducible pathway of NO production was most likely lessened by the short-term administration of dobutamine, which lowers cytokine levels in patients with CHF.17

Last, short-term administration of dobutamine may have altered vasomotor tone in patients with CHF by lowering neurohormonal activation. In turn, alterations in vasomotor may affect flow-mediated vasodilation. However, the steadiness of the NTG and peak hyperemic responses before and after short-term administration of dobutamine argues against alterations in vasomotor tone.

Limitations of Study
All of our patients were extremely symptomatic, and thus, medications such as ACE inhibitors and cardiac glycosides, which affect endothelial function, could not be discontinued. The etiology of vascular endothelial function was probably multifactorial in our patients because many were diabetics

<table>
<thead>
<tr>
<th>TABLE 2. BABF and Diameter in Control Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1  Day 3  2 Weeks  4 Weeks</td>
</tr>
<tr>
<td>Baseline BABF, mL/min</td>
</tr>
<tr>
<td>BABF at peak hyperemic response, mL/min</td>
</tr>
<tr>
<td>Increase in BAD at peak hyperemic response, %</td>
</tr>
</tbody>
</table>
and/or had a history of hypertension. Moreover, all had extensive coronary artery disease. Nevertheless, the improvement in flow-mediated vasodilation induced by short-term administration of dobutamine suggests that CHF was at least partially responsible for the impaired flow-mediated vasodilation.

References

Sustained Improvement in Flow-Mediated Vasodilation After Short-Term Administration of Dobutamine in Patients With Severe Congestive Heart Failure
Mrugesh B. Patel, Ilya V. Kaplan, Rajiv N. Patni, Daniel Levy, Joel A. Strom, Jamshid Shirani and Thierry H. LeJemtel

_Circulation_. 1999;99:60-64
doi: 10.1161/01.CIR.99.1.60

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 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/99/1/60

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/