Forearm Vascular Responsiveness to $\alpha_1$- and $\alpha_2$-Adrenoceptor Stimulation in Patients With Congestive Heart Failure

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Background The $\alpha$-adrenergic component of the sympathetic nervous system plays a major role in the pathophysiology, clinical manifestations, and natural history of human congestive heart failure (CHF). However, the functional integrity of vascular $\alpha_1$- and $\alpha_2$-adrenoceptors in CHF remains to be elucidated. The present study was designed to assess the vascular responsiveness of $\alpha_1$- and $\alpha_2$-adrenoceptors in patients with CHF.

Methods and Results To evaluate $\alpha_1$- and $\alpha_2$-adrenoceptor responsiveness, we studied the effects of the regional infusion into the brachial artery of increasing doses of phenylephrine (a selective $\alpha_1$-adrenoceptor agonist) and BHT 933 (a selective $\alpha_2$-adrenoceptor agonist) on vascular responses in 12 healthy subjects and in 24 patients with CHF secondary to primary dilated cardiomyopathy or ischemic heart disease. Left ventricular ejection fraction was measured by radionuclide angiography, and forearm blood flow was determined by venous occlusion plethysmography. Phenylephrine reduced forearm blood flow in normal subjects from 5.2±0.9 to 2.5±0.6 mL per 100 mL of tissue/min (P<.05) at the highest dose (−50.8±4.8% versus baseline). A similar vasoconstriction was obtained in patients with CHF (from 3.5±0.5 to 1.5±0.2 mL per 100 mL of tissue/min (P<.05) (−58.7±5.0% versus baseline). The dose-response curves produced by phenylephrine in the two groups were comparable. The highest dose of BHT 933 reduced forearm blood flow in normal subjects from 5.3±0.9 to 2.3±0.6 mL per 100 mL of tissue/min (P<.05) (−59.0±4.9% versus baseline). In patients with CHF, a similar vasocostriction was obtained (from 4.2±0.8 to 1.5±0.3 mL per 100 mL of tissue/min, P<.05, −62.1±6.5% versus baseline). The dose-response curves produced by BHT 933 also were comparable in the two groups. In patients with CHF, plasma concentrations of norepinephrine were significantly higher than in normal subjects.

Conclusions The results of the present study demonstrate that $\alpha_1$- and $\alpha_2$-adrenoceptor stimulations produced an equivalent vasoconstriction in patients with CHF and in normal subjects. This indicates that the vascular responsiveness to $\alpha$-adrenoceptor agonists may be preserved in the limb vessels of patients with CHF. (Circulation. 1994;90:17-22.)

Key Words • heart failure, congestive • adrenoceptors • norepinephrine

Central sympathetic stimulation results in direct vascular vasoconstriction through the action of $\alpha$-adrenergic receptors.¹ In humans, it is unknown whether this vasoconstriction is mediated by $\alpha_1$- or $\alpha_2$-adrenoceptor subtypes. In the coronary and femoral beds of normal dogs, it has been demonstrated that $\alpha_1$- or $\alpha_2$-adrenoceptor-mediated mechanisms may participate in the vasoconstrictive responses to both exogenous norepinephrine and sympathetic nerve stimulation.²⁻⁵

The $\alpha$-adrenergic component of the sympathetic nervous system plays a major role in the pathophysiology, clinical manifestations, and natural history of human congestive heart failure (CHF).⁶ In patients with CHF, both circulating and neurally released catecholamines produce vasoconstriction by $\alpha$-adrenergic stimulation.⁷ This vasoconstriction promotes detrimental hemodynamic effects in CHF patients because it increases right and left ventricular filling pressures and pulmonary and systemic vascular resistance.⁸ In fact, a higher mortality has been reported in patients with CHF and elevated plasma norepinephrine levels.⁸ The chronotropic and inotropic responses to $\beta$-adrenergic receptor agonists are reduced in experimental animals and in patients with CHF,⁹⁻¹² and the myocardial $\alpha_1$-adrenoceptors do not appear to be downregulated in heart failure¹³,¹⁴; however, the functional integrity of vascular $\alpha_1$- and $\alpha_2$-adrenoceptors in CHF remains to be elucidated. The understanding of this mechanism may contribute to further define the potential usefulness of $\alpha$-adrenergic antagonists in the treatment of CHF.

Accordingly, the present study was designed to assess the vascular responsiveness to $\alpha_1$- or $\alpha_2$-adrenoceptor stimulation in patients with CHF secondary to primary dilated cardiomyopathy or ischemic heart disease.

Methods

Study Population

Control Group

In this group we included 12 normal volunteers (8 men and 4 women). The medical history, physical examination, and routine laboratory tests showed no evidence of cardiovascular or any other disease. None of the subjects took any medication for at least 2 weeks before the study. Subjects were instructed to refrain from smoking cigarettes or drinking alcohol or caffeine-containing beverages for at least 12 hours before the study.
Patients With CHF

Twenty-four patients (23 men and 1 woman) were included in the study. The cause of CHF was primary dilated cardiomyopathy in 14 patients and ischemic heart disease in 10 patients. The etiology of CHF was assessed in all patients by accurate diagnostic evaluation including coronary angiography. All patients with ischemic cardiomyopathy had a documented history of previous myocardial infarction that occurred at least 6 months before the study. Only patients with chronic, stable CHF (in New York Heart Association functional classes II and III) were studied. Patients with diabetes mellitus, hypercholesterolemia, hypertension, or valvular heart disease were excluded from the study. Left ventricular ejection fraction, assessed by radionuclideangiography, ranged from 15% to 49% (average, 26.5±1.9). Left ventricular end-diastolic and end-systolic diameters were measured by two-dimensional echocardiography. Digoxin, diuretics, and all vasoactive medications were withheld for at least 72 hours before the study. In the week preceding the study, the subjects were maintained on a standard daily diet containing 130 mEq sodium and 60 mEq potassium. The protocol was approved by the Ethical Committee of our institution, and all subjects gave informed consent before participating in the study.

Radionuclide Angiography

ECG-gated blood pool cardiac imaging in frame data acquisition was used to assess global left ventricular function after in vivo red blood cell labeling with 25 mCi IV 99mTc pertechnetate. Each study was performed using a small field of view (25.9 cm in diameter) and an Anger camera (Siemens LEM ZLC) interfaced with a computer system (Digital PDP 11/34). The gamma camera was positioned in 45° left anterior oblique position with 15° cephalad tilt. A 2× digital zoom was used. After 10 minutes of tracer equilibration, blood pool images were acquired. The left ventricular ejection fraction was measured on the raw time-activity curve by standard technique, as previously reported.15

Measurements of Forearm Blood Flow

The studies were conducted in the afternoon (1 to 3 PM) at least 2 hours after the meal in a quiet room with a constant temperature of 20° to 24°C (=72°F) with the subjects in the supine position. Forearm volume was determined by water displacement before the study. The brachial artery was cannulated under local anesthesia with 2% (wt/vol) procaine with a 20-gauge polyethylene catheter (Vasculon 2); the antecubital vein of the opposite arm was also cannulated. Forearm blood flow (FBF) was measured 30 minutes after placement of the cannula with a mercury-in-Silastic rubber strain gauge applied around the dominant forearm supported above heart level.16,17 The gauge was connected to a calibrated plethysmograph (Vasculab, Meda Sonics, Mod. SPG 16); this was connected to a chart recorder to record flow measurements in the forearm. A wrist cuff was inflated to 200 mm Hg 1 minute before recording to occlude hand blood flow. A venous occlusion pressure of 40 mm Hg was used in the upper arm cuff, and FBF was measured as the slope of the change in the forearm volume.16,17 The mean of at least three measurements was obtained at each time point. Forearm vascular resistance was calculated by dividing mean blood pressure (mm Hg) by forearm blood flow and was expressed in units. Mean blood pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. Blood pressure was measured through the intravascular catheter connected to a pressure transducer (Baxter Healthcare Corp).

Study Protocol

Group 1: Effect of α2-Adrenoceptor Stimulation

To study α2-adrenoceptor responsiveness, we examined the effects of regional infusion of phenylephrine (a selective α2-adrenoceptor agonist) into the brachial artery on vascular re-
in either group. The FBF response to α₁-adrenoceptor stimulation in control subjects and in patients with CHF is reported in Table 2. Phenylephrine reduced FBF in normal subjects from 5.2±0.9 to 2.5±0.6 mL per 100 mL of tissue/min (P<.05) (−50.8±4.8% versus baseline) at the highest dose (1 μg/kg per minute). A similar vasorelaxation was obtained in patients with CHF (from 3.5±0.5 to 1.5±0.2 mL per 100 mL of tissue/min, P<.05, −58.7±5.0% versus baseline). Furthermore, the dose-response curves produced by phenylephrine in the two groups were not statistically different (Table 2 and Fig 1). Similarly, the phenylephrine-induced changes in vascular resistances were not different in the two groups (Table 2). After α₁-adrenoceptor blockade (prazosin), no changes in FBF were detected at any dose of phenylephrine.

Response to α₂-Adrenoceptor Stimulation in Control Subjects and in Patients With CHF

Incremental intra-arterial infusion of BHT 933 caused no changes in heart rate and systemic blood pressure in either group. The FBF response to α₂-adrenoceptor stimulation in control subjects and in patients with CHF is reported in Table 3. The highest dose of BHT 933 reduced FBF in normal subjects from 5.3±0.9 to 2.3±0.6 mL per 100 mL of tissue/min (P<.05) (−59.0±4.9% versus baseline). In patients with CHF, a comparable reduction of FBF was obtained (from 4.2±0.8 to 1.5±0.3 mL per 100 mL of tissue/min, P<.05, −62.1±6.5% versus baseline). The dose-response curves produced by BHT 933 were not different in the two groups (Fig 2). Similarly, the BHT 933-induced changes in vascular resistance were not different in the two groups (Table 3). After α₂-adrenoceptor blockade with yohimbine, no changes in FBF were detected at any dose of BHT 933.

Norepinephrine Plasma Levels

Plasma concentrations of norepinephrine were significantly higher in patients with CHF (n=18) than in normal subjects (n=12) (435±62 pg/mL and 177±21 pg/mL, respectively, P<.05). In group 1 (patients receiving phenylephrine), plasma norepinephrine concentra-
Effects of Regional Infusion of $\alpha_1$-Adrenoceptor Agonist in Normal Subjects and in Patients With Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Phenylephrine 1</th>
<th>Phenylephrine 2</th>
<th>Phenylephrine 3</th>
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<td>Forearm blood flow, mL per 100 mL of tissue/min</td>
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<td>Control</td>
<td>5.2±0.9</td>
<td>4.3±0.8</td>
<td>3.4±0.7*</td>
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<td>3.5±0.5</td>
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<td>2.1±0.4*</td>
<td>1.5±0.2††</td>
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<td>Resistance, U</td>
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<td>Control</td>
<td>19.8±4.2</td>
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<td>30.7±6.3*</td>
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<tr>
<td>CHF</td>
<td>32.8±5.9</td>
<td>49.4±12.9*</td>
<td>65.5±19.6††</td>
<td>95±29.6††</td>
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<td>Mean arterial pressure, mm Hg</td>
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<td>CHF</td>
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<td>Heart rate, beats per minute</td>
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<td></td>
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<tr>
<td>Control</td>
<td>63.7±6.4</td>
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<td>63.0±8.2</td>
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<tr>
<td>CHF</td>
<td>74.1±8.2</td>
<td>75.7±10.5</td>
<td>73.3±9.2</td>
<td>75.4±8.7</td>
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</table>

CHF indicates congestive heart failure.

*P<.05 vs baseline; †P<.05 vs Phenylephrine 1; ‡P<.05 vs Phenylephrine 2.

Discussion

The present study demonstrates that $\alpha_1$- and $\alpha_2$-adrenoceptor stimulations produce comparable vasoconstrictive responses of human forearm vasculature in patients with CHF and in normal subjects, thus indicating a preserved functional responsiveness of $\alpha_1$- and $\alpha_2$-adrenoceptors in patients with CHF.

Effect of Regional $\alpha_1$- and $\alpha_2$-Adrenoceptor Stimulation in Patients With CHF

Although it has been demonstrated that the $\alpha_1$-receptor population is not reduced in the failing human heart, the functional integrity of vascular $\alpha_1$- and $\alpha_2$-adrenoceptors in patients with CHF has not been yet investigated. A previous study performed in isolated coronary arterial rings from dogs with pacing-induced CHF demonstrated that in response to selective $\alpha_2$-adrenoceptor agonist stimulation, vascular contraction is diminished in the CHF preparation and that the stimulation of $\alpha_2$-adrenoceptors by BHT 920 produces relaxation in controls, which is enhanced at peak CHF. The different results obtained in our study might be due to the different experimental protocol used as well as to the differences in the vascular bed and/or in the species. Main and associates studied the effects of $\alpha_1$- and $\alpha_2$-adrenoceptor stimulation in isolated canine coronary arteries precontracted with KCl, which might be different from the effects obtained in vivo. In this regard, our group as well as other authors have demonstrated previously that $\alpha_2$-adrenoceptor stimulation induces coronary vasoconstriction in vivo and not relaxation, as shown by Main and associates. In addition, Jil and associates have shown that BHT 933 produced a 50% decrease in FBF in normal subjects (a degree of vasoconstriction consistent with that found in the control subjects of the present study).

Our current study is the first to examine the effect of $\alpha_1$- and $\alpha_2$-adrenoceptor stimulation in the limb vessels of humans with CHF. In fact, previous studies in CHF patients have been focused mainly on the role of $\beta$-adrenoceptors. In this regard, whereas ventricular myocardial $\beta_1$-receptors are downregulated in direct relation to the severity of ventricular dysfunction, the $\beta_2$-adrenergic receptor pathway is relatively well preserved in the failing human heart as well as in the peripheral vasculature of patients with CHF. Similarly, in our current study, no impairment in the phenylephrine- or BHT 933–induced limb vasoconstriction.

Fig 1. Line plot: Percent decrease of forearm blood flow (FBF) in response to graded intra-arterial infusion of phenylephrine (PHEN) in normal subjects and in patients with congestive heart failure (CHF). Dose-response curves produced by phenylephrine in the two groups were comparable. *P<.05 vs PHEN 1; †P<.05 vs PHEN 2.
TABLE 3. Effects of Regional Infusion of \( \alpha_{2} \)-Adrenoceptor Agonist (BHT 933) in Normal Subjects and in Patients With Congestive Heart Failure

<table>
<thead>
<tr>
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<th>Baseline</th>
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<th>BHT 2</th>
<th>BHT 3</th>
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<td>Forearm blood flow, mL per 100 mL of tissue/min</td>
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<tr>
<td>Control</td>
<td>5.3±0.9</td>
<td>4.5±0.9*</td>
<td>3.4±0.8†</td>
<td>2.3±0.6*</td>
</tr>
<tr>
<td>CHF</td>
<td>4.2±0.8</td>
<td>3.0±0.5*</td>
<td>2.1±0.3*</td>
<td>1.5±0.3†</td>
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<tr>
<td>Resistance, U</td>
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<td></td>
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</tr>
<tr>
<td>Control</td>
<td>22.2±4.4</td>
<td>27.3±4.9</td>
<td>40.1±10.1*</td>
<td>64.7±20.4*</td>
</tr>
<tr>
<td>CHF</td>
<td>24.1±5.3</td>
<td>33.3±7.4</td>
<td>47.4±7.9*</td>
<td>67.9±13.2**</td>
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<td>Mean arterial pressure, mm Hg</td>
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<td>Control</td>
<td>102.6±11.4</td>
<td>104.5±12.2</td>
<td>104.8±10.5</td>
<td>107.1±11.4</td>
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<tr>
<td>CHF</td>
<td>88.8±4.5</td>
<td>88.7±4.6</td>
<td>88.0±4.4</td>
<td>89.8±5.1</td>
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<tr>
<td>Heart rate, beats per minute</td>
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<tr>
<td>Control</td>
<td>63.0±6.1</td>
<td>63.3±5.3</td>
<td>68.0±9.0</td>
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<tr>
<td>CHF</td>
<td>70.1±8.0</td>
<td>71.3±7.9</td>
<td>72.0±9.2</td>
<td>72.1±8.5</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure.

*p<.05 vs baseline; †p<.05 vs BHT 1; ‡p<.05 vs BHT 2.

was found in a group of patients with mild to moderate CHF compared with a control group of normal subjects.

In patients with heart failure, increased peripheral sympathetic activity is often present.\(^{27}\) This enhanced sympathetic activity is frequently accompanied by an increase in circulating norepinephrine resulting from the spillover of this neurotransmitter from adrenergic nerve clefts.\(^{27,28}\) In CHF patients, the elevation of plasma norepinephrine concentrations is inversely correlated with survival and directly correlated with the hemodynamic severity of heart failure.\(^{29,30}\) This also might be related to the vasoconstriction mediated by \( \alpha_{1} \) and \( \alpha_{2} \)-adrenoceptors.

In this regard, the results of our study suggest that the preserved vasoconstrictive \( \alpha \)-adrenoceptor response in patients with chronic CHF and enhanced sympathetic activity may contribute to hemodynamic deterioration. In fact, the \( \alpha \)-adrenergic component of the sympathetic nervous system may play a major role in the pathophysiology, clinical manifestations, and natural history of CHF through the excessive increase in pulmonary and systemic vascular resistance\(^{6}\) and, consequently, an elevation of right and left ventricular filling pressures.

**Acknowledgments**

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