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 vasoconstriction 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 $\alpha$-adrenoceptor 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.

Received March 22, 1994; revision accepted April 20, 1994. From the Division of Cardiology, Department of Medicine, University Federico II, Naples, Italy. Correspondence to Ciro Indolfi, MD, FACC, Division of Cardiology, University Federico II, Via Pansini, 5, 80131 Napoli, Italy. © 1994 American Heart Association, Inc.
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 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 radionuclide angiography, 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 research 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° caudal tilt. A 2x 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 (Vascularab, 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 and brachial artery. 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 α₁-Adrenoceptor Stimulation

To study α₁-adrenoceptor responsiveness, we examined the effects of regional infusion of phenylephrine (a selective α₁-adrenoceptor agonist) into the brachial artery on vascular response in 6 healthy subjects (4 men and 2 women; mean age, 45±11 years; range, 37 to 60) and in 13 patients with CHF (mean age, 55±3 years; range, 38 to 67). The clinical features of patients with CHF are summarized in Table I. Infusions were carried out with a Harvard pump to keep the flow rate below 0.8 mL/min. FBF was measured during control condition after a 3-minute infusion of 5% dextrose solution and after increasing intra-arterial concentrations of phenylephrine at the dosages of 0.1, 0.5, and 1 µg/kg per minute, each dose for 5 minutes. To assess the selectivity of α₁-adrenoceptor stimulation, in 3 additional subjects we performed three intra-arterial infusions of phenylephrine (at the doses described above) after an intra-arterial infusion of prazosin (a selective α₁-adrenoceptor antagonist) at the dose of 0.5 µg/kg per minute.

Group 2: Effect of α₂-Adrenoceptor Stimulation

To evaluate the functional integrity of α₂-adrenoceptor in 6 control subjects (4 men and 2 women; mean age, 46±5 years; range, 42 to 53) and in 11 patients with CHF (mean age, 52±3 years; range, 39 to 67), BHT 933 (a selective α₂-adrenoceptor agonist) was infused into the brachial artery. The clinical features of patients with CHF are summarized in Table I. FBF was measured during infusion of increasing concentrations of BHT 933 at dosages of 0.1, 1, and 10 µg/kg per minute, each for 5 minutes. Baseline measurements were obtained after a 3-minute infusion of 5% dextrose solution at the same infusion rate (0.8 mL/min). To assess the selectivity of α₂-adrenoceptor stimulation, in 4 additional subjects we infused three intra-arterial infusions of BHT 933 (at the dose described above) after an intra-arterial infusion of yohimbine (a selective α₂-adrenoceptor antagonist agent) at the dose of 5 µg/kg per minute.

Plasma Catecholamine Measurements

Venous blood samples for plasma norepinephrine assay were obtained at least 30 minutes after catheter placement. Samples were placed immediately on ice and centrifuged at 2°C. Plasma samples were stored at ~70°C. Plasma norepinephrine was measured using cation-exchange high-performance liquid chromatography with electrochemical detection after purification and concentration by extraction with alumina according to Anton and Sayre.18 Further details of this technique have been extensively described in a previous report from our laboratory.19

The accuracy and reproducibility of this technique for plasma catecholamine measurements have been determined previously in our laboratory.19 Repeated measures of norepinephrine levels within the same subject showed a coefficient of variation of 8.3%.19

Drugs

BHT 933 was obtained from Boehringer Ingelheim. Phenylephrine hydrochloride (Neo-Synephrine 1 mL, 10 mg) was purchased from Winthrop Laboratories. Prazosin was obtained from Sigma. Yohimbine HCl was obtained from Apotheek Academisch Ziekenhuis.

Statistical Analysis

FBF and forearm resistance data are presented as mean±SEM. All other data are expressed as mean±SD. Statistical analysis was performed by ANOVA for repeated measures using a SYSTAT program,20 and when a significant overall effect was detected, Tukey's test was applied to compare single values.21 Comparisons of data between the two groups were done by two-way ANOVA. Significant differences were assumed to be present at P<.05.

Results

Response to α₁-Adrenoceptor Stimulation in Control Subjects and in Patients With CHF

Incremental intra-arterial infusion of phenylephrine caused no changes in heart rate or systemic blood pressure.
in either group. The FBF response to \( \alpha_1 \)-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 \( (1 \mu g/kg \) per minute). 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). 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 \( \alpha_1 \)-adrenoceptor blockade (prazosin), no changes in FBF were detected at any dose of phenylephrine.

**Response to \( \alpha_2 \)-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 \( \alpha_2 \)-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 \( \alpha_1 \)-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-

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**Table 1. Individual Characteristics of Patients With Congestive Heart Failure Treated With Phenylephrine and BHT 933**

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<th>Patient</th>
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<th>Sex</th>
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<th>Diagnosis</th>
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<th>LVdd, mm</th>
<th>LVSd, mm</th>
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</table>

Mean 53.9 26.5 69.9 56.8

SE 1.9 1.9 1.7 1.6

LVEF indicates left ventricular ejection fraction; LVdd, left ventricular end-diastolic diameter; LVSd, left ventricular end-systolic diameter; NYHA, New York Heart Association; DCM, dilated cardiomyopathy; and ICM, ischemic cardiomyopathy.
tions were 420±82 pg/mL (n=10) (P<.05 versus control subjects); in group 2 (patients treated with BHT 933), plasma norepinephrine levels were 454±98 pg/mL (n=8) (P<.05 versus control subjects).

**Discussion**

The present study demonstrates that α₁- and α₂-adrenoceptor stimulations produce comparable vasocostrictive responses of human forearm vasculature in patients with CHF and in normal subjects, thus indicating a preserved functional responsiveness of α₁- and α₂-adrenoceptors in patients with CHF.

**TABLE 2. Effects of Regional Infusion of α₁-Adrenoceptor Agonist in Normal Subjects and in Patients With Congestive Heart Failure**

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>Phenylephrine 1</th>
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<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>5.2±0.9</td>
<td>4.3±0.8</td>
<td>3.4±0.7*</td>
<td>2.5±0.6†</td>
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<tr>
<td>CHF</td>
<td>3.5±0.5</td>
<td>2.7±0.5*</td>
<td>2.1±0.4*</td>
<td>1.5±0.2††</td>
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<td>Resistance, U</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>19.8±4.2</td>
<td>23.7±5.4</td>
<td>30.7±6.3*</td>
<td>46.1±8.5</td>
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<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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<tr>
<td>Mean arterial pressure, mm Hg</td>
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<tr>
<td>Control</td>
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<td>CHF</td>
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<td>96.1±6.2</td>
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</tr>
<tr>
<td>Control</td>
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<td>66.6±4.7</td>
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<td>CHF</td>
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<td>75.7±10.5</td>
<td>73.3±9.2</td>
<td>75.4±8.7</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure.

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

**Effect of Regional α₁- and α₂-Adrenoceptor Stimulation in Patients With CHF**

Although it has been demonstrated that the α₁-receptor population is not reduced in the failing human heart, the functional integrity of vascular α₁- and α₂-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 α₁-adrenoceptor agonist stimulation, vascular contraction is diminished in the CHF preparation and that the stimulation of α₂-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 α₁- and α₂-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 α₂-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 vasocostriction consistent with that found in the control subjects of the present study).

Our current study is the first to examine the effect of α₁- and α₂-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 β-adrenoceptors. In this regard, whereas ventricular myocardial β-receptors are downregulated in direct relation to the severity of ventricular dysfunction, the β-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...
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. This enhanced sympathetic activity is frequently accompanied by an increase in circulating norepinephrine resulting from the spillover of this neurotransmitter from adrenergic nerve clefts. In CHF patients, the elevation of plasma norepinephrine concentrations is inversely correlated with survival and directly correlated with the hemodynamic severity of heart failure. 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 and, consequently, an elevation of right and left ventricular filling pressures.

**Acknowledgments**

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**References**


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C Indolfi, A Maione, M Volpe, A Rapacciuolo, G Esposito, R Ceravolo, V Rendina, M Condorelli and M Chiariello

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