**α₂-Receptor–Mediated Vasoconstriction in Patients With Congestive Heart Failure**

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α₂-Adrenoceptors exist postsynaptically to subserve vasoconstriction and presynaptically to modulate norepinephrine release into the synaptic cleft. Because adrenoceptors may down-regulate in response to chronic stimulation, we investigated the activity of α₂-receptor–mediated vasoconstriction in patients with congestive heart failure, who had increased levels of plasma norepinephrine. We used the isolated forearm model and intra-arterial infusions of subsystemic doses of yohimbine, a specific α₂-blocker, in 11 patients with heart failure and in 15 normal subjects. Yohimbine produced a dose-related increase in forearm blood flow and decrease in forearm vascular resistance. These findings were consistent with a direct vasodilator effect mediated by blockade of the postsynaptic α₂-vascular receptor. Furthermore, the vasodilator responses in patients with heart failure were similar to the normal subjects in terms of the percent increase in forearm blood flow, the dose-response relation, and the fractional response to hyperemia and phentolamine; thus, α₂-receptor–mediated vasoconstriction is neither enhanced nor down-regulated in heart failure. In addition, in patients with heart failure and in normal subjects, yohimbine produced an increase in the forearm venous norepinephrine concentration, consistent with an inhibition of the presynaptic α₂-receptor resulting in an augmented release of norepinephrine into the synaptic cleft. Thus, these data suggest that the postsynaptic α₂-receptor is an important mediator of vasoconstriction in patients with heart failure. Despite chronic elevations in plasma norepinephrine in patients with heart failure, α₂-receptor mechanisms subserving vasoconstriction and inhibition of norepinephrine release into the synaptic cleft are still functional in heart failure. (*Circulation* 1989;80:1660–1667)

It is known that α₂-adrenoceptors exist postsynaptically to subserve vasoconstriction in response to norepinephrine and presynaptically to modulate norepinephrine release into the synaptic cleft. Because β-adrenergic receptors down-regulate in response to chronic stimulation, it is possible that sustained stimulation of the sympathetic nervous system might also result in attenuation of α₂-receptor–mediated vasoconstriction, as well as α₂-receptor–mediated inhibition of norepinephrine release into the synaptic cleft. Patients with congestive heart failure are characterized by excessive peripheral vasoconstriction and chronic sympathetic stimulation, which are manifested by high circulating levels of plasma norepinephrine and increased sympathetic nerve traffic. However, the activity of postsynaptic α₂-receptors in mediating vasoconstriction in heart failure has not been examined. Furthermore, maintenance of heightened synaptic cleft norepinephrine concentrations might reflect a defect in the negative feedback regulation of presynaptic release of norepinephrine and, therefore, may indicate down-regulation of postsynaptic α₂-receptors.

The present study was designed to determine whether α₂-receptor–mediated responses are intact in patients with congestive heart failure despite chronic elevations in norepinephrine. We used the isolated forearm model to measure the effects of yohimbine, a specific blocker of α₂-receptors, on two separate but interrelated responses. First, we examined the effects of yohimbine on forearm blood flow, as a measure of postsynaptic α₂-receptor activity, and second, we assessed norepinephrine release into the forearm venous circulation, as a measure of presynaptic α₂-receptor activity.
Subjects and Methods

Study Population

The study population consisted of 11 patients referred for evaluation of congestive heart failure and included seven men and four women with a mean age of 62±10 years (range, 42–74 years). Ejection fractions measured by gated blood pool scans ranged between 10% and 39%, with a mean of 24±8%. All patients were clinically stable without acute decompensations of heart failure and were admitted to the Clinical Research Center for monitoring 1 day before the study. All patients were taking diuretics, and eight patients were taking digoxin. Nine patients also had been receiving vasodilator therapy with either captopril, enalapril, or the combination of isosorbide dinitrate and hydralazine. Vasodilator drugs were withheld 2–3 days before the study; digoxin and diuretics were withheld the morning of the study only.

The control group included 15 normal men with a mean age of 33±10 years (range, 21–59 years). Medical history, physical examination, routine blood tests, and electrocardiogram established that each subject was free of medical illness, heart disease, and diabetes mellitus. No subjects were taking medications, and all refrained from caffeinated beverages on the day of the study. Informed consent was obtained from all participants, and this study was approved by the Human Rights in Research Committee.

Isolated Forearm Model

All studies were performed in the morning, after an overnight fast except for a light breakfast, in a room of constant temperature. The isolated forearm model has been previously described. The study arm was supported in a comfortable position, at a level slightly higher than the heart, in a position of approximately 30° of abduction. An 18-gauge arterial cannula was inserted percutaneously into the brachial artery of the nondominant arm and connected to a three-way stopcock for pressure recordings (model P23XL pressure transducer, Gould, Cleveland, Ohio) and for infusions of the study drug by means of an infusion pump (Harvard Apparatus, South Natick, Massachusetts). A 16-gauge cannula was inserted into the ipsilateral basilic vein to obtain venous effluent blood samples. A second peripheral venous cannula was placed in the contralateral arm to collect blood samples representing the systemic circulation. Heart rate was continuously recorded with a precordial electrocardiographic lead. Blood pressure was obtained as the phasic and electronically integrated mean and recorded as systolic, diastolic, and mean arterial pressures.

Forearm blood flow (FBF) was measured with a mercury-in-silastic strain gauge placed around the upper third of the forearm and connected to an electronically calibrated plethysmograph (model EC-5, Hokanson, Issaquah, Washington). A venous occlusion cuff placed around the upper arm was rapidly inflated to 40 mm Hg by means of a compressor (model E-10, Hokanson) for each flow curve. A pediatric blood pressure cuff was placed around the wrist and inflated to suprasystolic pressure to exclude the hand circulation from the FBF determinations. Five consecutive flow measurements were averaged and expressed as milliliters per minute per 100 ml of forearm volume (FAV) for each intervention. FAV was measured by the water displacement technique and was 1,284±158 ml and 1,229±339 ml for the normal subjects and for patients with heart failure, respectively. Forearm vascular resistance was calculated by dividing the electronically integrated mean arterial pressure by FBF and was expressed in resistance units.

α2-Receptor Antagonists

Yohimbine, a selective α2-receptor antagonist, was supplied in powder form by the Food and Drug Division of Sigma Chemical, St. Louis, Missouri, under a physician-sponsored IND (S.H.K., J.N.C.). The infusate was freshly prepared before each use by dissolving the yohimbine in bacteriostatic water for injection and filtering the solution through a 0.22-μm filter. Necessary dilutions were made with the vehicle, 5% dextrose in water.

Because the minimal and maximal doses of yohimbine needed to produce a localized effect on α2-receptors in patients with congestive heart failure were not known, yohimbine doses of 0.5, 1.0, 2.5, 5.0, and 10 μg/min/100 ml FAV were given. Previous studies using this same isolated forearm preparation in normal subjects have demonstrated that a yohimbine dose of 1 μg/kg/min would have specific blocking effects on the decreases in FBF induced by an α2-receptor agonist without any effects on the decreases in FBF induced by an α1-receptor agonist. The average yohimbine doses in the present study were comparable with the previous units at 0.08, 0.16, 0.39, 0.78, and 1.56 μg/kg/min.

Phentolamine, a nonselective α1- and α2-receptor antagonist, was commercially available as an intravenous formulation (Regitine, CIBA, Summit, New Jersey). Phentolamine was also prepared before each use and diluted in 5% dextrose in water. The same doses of 0.5, 1.0, 2.5, 5.0, and 10 μg/min/100 ml FAV were given.

Study Protocol

After catheter placement, the subjects rested quietly for at least 30 minutes before determinations of baseline FBF. A second measurement was repeated after 15 minutes to ensure a stable baseline. Blood samples were also taken for baseline plasma renin activity and plasma norepinephrine.

The first reference intervention was postocclusion hyperemic flow, a measure of metabolic vasodilating capacity not mediated by α2-receptor blockade, which has previously been shown to be reduced in
patients with heart failure.\textsuperscript{15} This was obtained by inflating the venous occlusion cuff around the upper arm to 30–40 mm Hg above systolic pressure for 5 minutes. The arterial catheter was flushed every minute during occlusion to prevent thrombosis. After release of the occluding pressure, measurements of FBF commenced immediately, and the average of the first two flow determinations was used as the measure of peak flow.

To assess the effects of the 5% dextrose vehicle, determinations of FBF were obtained during vehicle infusion. The 5% dextrose in water vehicle was infused at a rate of 2.5 ml/min, which was equal to the maximum volumetric rate used with the highest doses of drug administration. FBF was measured continuously during the infusion, but only the determinations during the fourth minute of infusion were reported as the vehicle effect.

After recontrol measurements, the first infusion of yohimbine was started at the 0.5 µg/min/100 ml FAV dose. FBF measurements were made continuously during the 4-minute infusion, but because there were no significant differences between the measurements during each minute, only the 4-minute FBF determinations were reported. After the fourth minute of infusion, blood pressure and heart rate were measured. After a 1–2-minute washout between doses, the next higher dose was given by increasing the amount of infusate. The largest volume of infusate for the 10 µg/min/100 ml FAV dose was 2.5 ml/min. The same procedure for measuring FBF and blood pressure during the 4-minute infusion of each dose was repeated.

After a 45–60-minute washout period after the last dose of yohimbine, recontrol measurements were obtained. Phentolamine administration was identical to yohimbine; 4-minute infusions of doses of 0.5, 1.0, 2.5, 5.0, and 10 µg/min/100 ml FAV were used. To simplify data presentation, only the data from the 10 µg/min/100 ml FAV dose are reported.

Forearm Venous Norepinephrine Response

Forearm venous plasma concentration of norepinephrine was measured as a guide to changes in forearm synaptic cleft concentration of norepinephrine. Because no systemic effects of local forearm infusion of yohimbine were observed, changes in norepinephrine concentration in the forearm venous effluent would be expected to reflect changes in release rate or reuptake rate in the synaptic cleft in response to the local drug infusion. Blood samples for plasma norepinephrine assay were obtained from the venous catheters of the ipsilateral and contralateral arms during the control period and during the last minute of infusion of vehicle and the 10 µg/min/100 ml FAV dose of yohimbine. The forearm venous norepinephrine response was calculated as the difference between the postinfusion and preinfusion norepinephrine in the experimental forearm. Plasma norepinephrine was measured in the contralateral forearm venous blood to detect any systemic neurohormonal effect.

Neurohormonal Measurements

Norepinephrine concentration was measured by Dr. Ada Simon in the Cardiovascular Biochemistry Core Laboratory, University of Minnesota, Minneapolis, by use of a radioenzymatic technique with an 8% intraassay variation.\textsuperscript{16} Plasma renin activity was measured with a radioimmunoassay.\textsuperscript{17}

Statistical Analyses

The FBF dose response curves for the patients with heart failure were compared with those from the normal control subjects by analysis of variance with repeated measures.\textsuperscript{18} In particular, the interaction between the two groups for the FBF and forearm vascular resistance responses was used to assess whether or not the dose-response curves were parallel between groups. Post hoc tests to compare the effect of each dose with vehicle were done by paired \textit{t} tests with a Bonferroni correction for multiple comparisons (i.e., \( p < 0.05/5-0.01 \) was considered significant). Group comparisons for other variables including the peak response to postocclusion hyperemia and phentolamine were done by a \textit{t} test for independent groups. Baseline plasma norepinephrine and renin activity data were compared by means of the Wilcoxon rank-sum test because these data were not normally distributed. To further assess the relative vasodilator capacity of yohimbine, the yohimbine responses to the 10 µg/min/100 ml FAV dose as a fraction of the peak response to hyperemia and the peak response to the 10 µg/min/100 ml FAV dose of phentolamine were compared between the patients with heart failure and the normal subjects by unpaired \textit{t} tests.

Results

Baseline differences between the patients with heart failure and the normal subjects are shown in Table 1. The patients with heart failure tended to have a lower baseline FBF and mean arterial pressure and higher forearm vascular resistance when compared with the normal subjects, but the group differences did not reach statistical significance. However, the patients with heart failure did demonstrate the expected activation of the neurohormonal vasoconstrictor systems, demonstrated by the significantly higher levels of plasma norepinephrine and plasma renin activity.

Forearm Blood Flow Responses

Figure 1 summarizes the responses of FBF to the dose range of yohimbine in normal subjects and in patients with heart failure. Both groups demonstrated dose-related increases in FBF in response to the \( \alpha_2 \)-receptor antagonist. Although the absolute increase in FBF with 10 µg/min/100 ml FAV yohimbine appeared to be greater in the normal subjects (from 3.13 to 5.17 ml/min/100 ml FAV) than in the
TABLE 1. Baseline Comparison of Patients With Heart Failure With Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects (n=15)</th>
<th>Patients with heart failure (n=11)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm blood flow (ml/min/100 ml FAV)</td>
<td>3.13±1.04</td>
<td>2.26±1.17</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>84±10.1</td>
<td>78±11.9</td>
<td>0.20</td>
</tr>
<tr>
<td>Forearm vascular resistance (units)</td>
<td>32±16</td>
<td>44±21</td>
<td>0.13</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65±8.5</td>
<td>74±17.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Plasma norepinephrine (pg/ml/hr)</td>
<td>229 (174–979)</td>
<td>438 (311–1,156)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>3.6 (2.4–5.0)</td>
<td>8.6 (2.5–22.7)</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

Values are mean±SD. For plasma norepinephrine and plasma renin activity, the median value is given with the range in parentheses. FAV, forearm volume.

*Determined by the Wilcoxon rank-sum test.

patients with heart failure (from 2.26 to 3.72 ml/min/100 ml FAV), both responses represent a similar 65% increase in flow. Furthermore, the dose-response curves for the normal subjects and patients with heart failure were not significantly different from parallel (p=0.32); thus, the similarities of the yohimbine responses between the two groups were again confirmed.

Since the dose-response curves were parallel, the effect of each dose was estimated by combining the data from both groups. Compared with the FBF during vehicle infusion of 3.10±0.27 ml/min/100 ml FAV, the mean changes were 0.10±0.09, 0.22±0.15, 0.64±0.12, 1.01±0.15, and 1.46±0.19 ml/min/100 ml FAV for the 0.5, 1, 2.5, 5.0, and 10 μg/min/100 ml FAV doses, respectively. The differences during the three highest doses of yohimbine were significant at the p<0.001 level.

Figure 2 summarizes the heart rate, blood pressure, and forearm vascular resistance responses to the dose range of yohimbine. Overall heart rate and

![Figure 1](http://circ.ahajournals.org/)

**FIGURE 1.** Plot of forearm blood flow responses to intra-arterial administration of yohimbine. Yohimbine produced dose-related increases in forearm blood flow in patients with heart failure (open symbols) and in normal subjects (closed symbols). There was no difference in the yohimbine responses between the two groups. Data are mean±SEM. FAV, forearm volume.

![Figure 2](http://circ.ahajournals.org/)

**FIGURE 2.** Plot of heart rate, mean arterial pressure, and calculated forearm vascular resistance during the intra-arterial administration of yohimbine in patients with heart failure and in normal subjects. Because there were no changes in mean arterial pressure or heart rate, the changes in forearm vascular resistance are the reciprocal of changes in forearm blood flow and are consistent with a direct vasodilator effect of yohimbine. Data are mean±SEM. FAV, forearm volume.
TABLE 2. **Comparison of Forearm Blood Flow Responses to Different Stimuli**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Normal subjects</th>
<th>Patients with heart failure</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postocclusion hyperemia (ml/min/100 ml FAV)</td>
<td>30.7±2.9</td>
<td>18.0±2.5</td>
<td>0.005</td>
</tr>
<tr>
<td>Phentolamine (10 μg/min/100 ml FAV)</td>
<td>7.1±1.1</td>
<td>4.4±0.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Yohimbine/postocclusion hyperemia</td>
<td>8±2%</td>
<td>9±2%</td>
<td>0.53</td>
</tr>
<tr>
<td>Yohimbine/phentolamine</td>
<td>32±3%</td>
<td>45±10%</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Responses are defined as the resultant forearm blood flow minus the respective control value for each intervention and expressed as ml/min/100 ml FAV. The yohimbine data are from the 10 μg/min/100 ml forearm volume (FAV) infusion.

Blood pressure did not change; thus, the lack of systemic responses with the very small doses of yohimbine used in this study was confirmed. Because mean arterial pressure was constant, the forearm vascular resistance responses were the mirror images of the changes in FBF; these findings are consistent with a direct vasodilator action of yohimbine.

A comparison of the responses to postocclusion hyperemia and phentolamine between the normal subjects and patients with heart failure is shown in Table 2. The normal subjects demonstrated a nearly 10-fold increase in FBF after postocclusion hyperemia, with an increase of 30.7±2.9 ml/min/100 ml FAV. The patients with heart failure demonstrated an attenuated hyperemic response of only 18.0±2.5 ml/min/100 ml FAV, which was significantly less than the responses in the normal subjects (p<0.005). The normal subjects responded to the 10 μg/min/100 ml FAV dose of phentolamine with an increase in FBF of 7.1±1.1 ml/min/100 ml FAV, which was greater than the 4.4±0.9 ml/min/100 ml FAV increase in the patients with heart failure, but this difference did not reach statistical significance (p=0.08). Because overall vasodilating responsiveness in the patients with heart failure was decreased, we compared the yohimbine responses as a fraction of the responses to hyperemia and phentolamine. However, there were no differences in the yohimbine responses as a fraction of either peak hyperemia or phentolamine between the normal subjects and patients with heart failure.

**Forearm Venous Norepinephrine Responses**

Changes in forearm venous norepinephrine concentration in response to the interventions are shown in Figure 3. In response to the administration of vehicle, there were no significant changes in the forearm venous norepinephrine concentration in either group. With the administration of yohimbine, there was a significant increase of 55±19 pg/ml (p<0.05) in the forearm venous norepinephrine concentration in the ipsilateral arm of the normal subjects; this finding is consistent with an augmented release of norepinephrine from sympathetic nerve terminals. In the patients with heart failure, yohimbine again produced a significant increase of 186±37 pg/ml (p<0.05), which was also significantly greater than the response in the normal subjects. In contrast, there were no significant differences in the forearm venous norepinephrine concentration in the contralateral arm after yohimbine administration in either the normal subjects or patients with heart failure.

The mechanisms by which yohimbine produced a greater rise in forearm venous norepinephrine response in patients with heart failure may be related to the higher baseline plasma norepinephrine. When both groups were combined, there was a significant correlation between baseline plasma

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Bar graphs showing forearm venous norepinephrine responses in normal subjects (NL; open bars) and in patients with congestive heart failure (CHF; striped bars) in response to vehicle and the 10 μg/min/100 ml forearm volume (FAV) dose of yohimbine. There were no significant changes with vehicle. With yohimbine, there was a significant increase in forearm venous norepinephrine response in the ipsilateral arm for NL and for CHF. There were no significant changes in the response after yohimbine was measured in the contralateral arm; this finding suggests that there were no centrally mediated effects.
norepinephrine and the forearm venous norepinephrine response \( (r=0.52; p=0.02) \). However, within the group with heart failure this relation did not exist \( (r=0.36; p=0.42) \).

Although the two groups were different in terms of age, neither the forearm venous norepinephrine response \( (r=0.26; p=0.40) \) nor the increase in FBF in response to yohimbine \( (r=0.10; p=0.72) \) was associated with age among the normal subjects. Finally, we spiked three blood samples from the same patient with 50 \( \mu g \) yohimbine and found that the addition of yohimbine did not change the blinded measurements of plasma norepinephrine; thus, the increase in plasma norepinephrine levels is not explained by assay cross-reactivity.

Discussion

These data demonstrate that yohimbine, a specific \( \alpha_2 \)-receptor antagonist, given in sub-systemic doses into the brachial artery, will cause dose-dependent forearm vasodilation. To our knowledge, these are the first data evaluating the yohimbine responses in patients with congestive heart failure and confirm that the postsynaptic \( \alpha_2 \)-receptor is another important mediator of vasoconstriction in heart failure. Although patients with heart failure had higher baseline levels of plasma norepinephrine, the yohimbine responses were similar to those seen in normal subjects in terms of the percent increase in FBF, the dose-response relation, and the fractional response to hyperemia and phenolamine. These findings suggest that \( \alpha_2 \)-Receptor-mediated vasoconstriction is neither enhanced nor down-regulated in congestive heart failure.

Vasoconstriction produced by activation of the sympathetic nervous system involves at least two subtypes of postjunctional \( \alpha \)-receptors. Stimulation of the postjunctional vascular \( \alpha_1 \)-receptor with agonists such as norepinephrine and methoxamine will lead to vasoconstriction, whereas \( \alpha_1 \)-receptor agonists such as doxazosin and prazosin produce vasodilation.19--21 Structurally and pharmacologically distinct \( \alpha \)-receptors are also present in a postjunctional vascular site, so that other studies, some using the same isolated forearm model, have shown that specific \( \alpha_2 \)-receptor agonists, including B-HT-933 (azepexole), will cause decreases in FBF and vasoconstriction, while specific \( \alpha_2 \)-antagonists, such as yohimbine, will cause vasodilation.1,3,19,22 The demonstration in the present study that yohimbine administration led to vasodilation in patients with congestive heart failure confirms that the \( \alpha_2 \)-receptor is active in maintaining vascular tone in congestive heart failure.

It has been postulated that \( \alpha \)-adrenoceptors may down-regulate in response to chronic stimulation, such as has been demonstrated with \( \beta \)-adrenoceptors.6,7 This possibility may be particularly pertinent for \( \alpha \)-receptors in patients with congestive heart failure, because the postjunctional \( \alpha_2 \)-receptor is preferentially activated by circulating, rather than neurally released, norepinephrine.5,23 However, despite the increased levels of plasma norepinephrine in the patients with heart failure, the postsynaptic \( \alpha_2 \)-receptor appeared to remain active in serving vasoconstriction.

The findings of \( \alpha_2 \)-receptor-mediated vasoconstriction in patients with congestive heart failure may have important implications regarding the clinical use of vasodilator treatment. It is possible that the lack of prolonged benefit after the use of specific \( \alpha_2 \)-receptor antagonists, like prazosin, may be related to maintained vasoconstriction mediated by \( \alpha_2 \)-receptor mechanisms.24,25 It is also possible that \( \alpha_2 \)-receptor blockade might increase activity of \( \alpha \)-vascular receptors, but studies in patients with congestive heart failure have not been performed. Finally, these data raise the possibility that an \( \alpha_2 \)-receptor antagonist may be useful vasodilating treatment for patients with heart failure, but such an agent should not cross the blood brain barrier, because it would likely increase overall sympathetic activity by means of centrally mediated \( \alpha_2 \)-receptor blockade.26,27

This study also demonstrated that blockade of the \( \alpha_2 \)-receptor with yohimbine resulted in an increase in the forearm venous norepinephrine concentration; this finding suggests that the presynaptic \( \alpha_2 \)-receptor may be active in inhibiting norepinephrine release into the synaptic cleft in normal subjects and in patients with heart failure. These data confirm the report of Jie et al.28 who also found this augmentation of norepinephrine release with yohimbine after pretreatment with tyramine in normal subjects. To our knowledge, these are the first data exploring the presynaptic \( \alpha_2 \)-receptor mechanism in patients with heart failure. An increase in forearm venous norepinephrine concentration can only serve as an imprecise estimate of norepinephrine release into the synaptic cleft due to presynaptic \( \alpha_2 \)-receptor activity. More sophisticated measurements of limb norepinephrine kinetics with radioactive tracers would provide additional insight into the site and mechanism of this blockade. Furthermore, measurement of true norepinephrine release would require calculation of norepinephrine flux, with the product of FBF and the arteriovenous norepinephrine difference. In this model, arterial norepinephrine concentrations cannot be measured during intra-arterial drug infusion. However, the assumption that arterial norepinephrine concentration does not change is supported by the fact that the norepinephrine concentration from the contralateral forearm, reflecting the systemic concentration, did not change. Finally, increases in forearm venous norepinephrine levels may also reflect defects in transport, reuptake, or clearance of norepinephrine from the intravascular space.

The significance of the finding that the presynaptic \( \alpha_2 \)-receptor may be active in inhibiting norepinephrine release into the synaptic cleft in heart failure is uncertain. In particular, it is not clear why
maintenance of presynaptic $\alpha_2$-receptor activity does not lead to decreases in plasma norepinephrine in heart failure. Furthermore, there may be important interrelations with postsynaptic $\alpha_1$- and $\alpha_2$-receptor mechanisms. It is possible that postsynaptic $\alpha_2$-receptor–mediated vasoconstriction after yohimbine administration is partially counteracted by postsynaptic $\alpha_1$-receptor vasoconstriction, stimulated by the increase in norepinephrine release caused by the presynaptic effect of yohimbine. Because the measurement of FBF reflects the sum of these competing influences, the present study cannot distinguish these processes.

It is noteworthy that the responses to phentolamine, a nonspecific $\alpha_1$- and $\alpha_2$-blocker, were also similar between the normal subjects and patients with heart failure; these responses suggest that both $\alpha_1$- and $\alpha_2$-receptor–mediated responses are intact in heart failure. In contrast, vasodilator capacity associated with the metabolic stimulus of postocclusion hyperemia was markedly decreased in heart failure. These findings would suggest that enhanced vasoconstriction in heart failure is not necessarily dependent on tonic increases in $\alpha$-receptor–mediated vasoconstriction.

Although the subjects with heart failure were significantly older than the normal subjects, age does not appear to be a primary factor regulating these responses. There was no correlation between age and the response to yohimbine within the age range of normal subjects. Furthermore, the changes in peripheral blood flow induced by phentolamine and epinephrine have not been different in studies evaluating older age groups.29–32

In conclusion, the present study has demonstrated that the intra-arterial administration of yohimbine, a specific $\alpha_2$-receptor antagonist, is associated with a direct forearm vasodilator effect. The yohimbine responses in patients with heart failure were similar to those in normal subjects; thus, the postsynaptic $\alpha_2$-receptor appeared to remain active in subserving vasoconstriction in patients with congestive heart failure. In addition, in normal subjects and in patients with heart failure, yohimbine administration produced an increase in the forearm venous norepinephrine concentration, consistent with inhibition of the presynaptic $\alpha_2$-receptor and an augmented release of norepinephrine into the synaptic cleft. Thus, this study has demonstrated that, despite chronic elevations in plasma norepinephrine in patients with congestive heart failure, the $\alpha_2$-receptor mechanisms subserving vasoconstriction and inhibition of norepinephrine release are still functional in heart failure.

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