Impaired Acetylcholine-Mediated Vasodilation in Patients With Congestive Heart Failure

Role of Endothelium-Derived Vasodilating and Vasoconstricting Factors

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Background. The vasodilatory response to intra-arterial administration of acetylcholine is reduced in patients with congestive heart failure compared with that of normal subjects. The reduced response to acetylcholine may be related to decreased endothelial release of nitric oxide, interaction with peripheral α-adrenergic transmission, or production of cyclooxygenase-dependent vasoconstricting substances. The extent to which each of these mechanisms contributes to the reduced vasodilatory response to acetylcholine in patients with congestive heart failure is not known.

Methods and Results. Thirty-one patients with congestive heart failure (New York Heart Association functional class II–III) and five age-matched normal subjects were studied. Regional vascular responses in the forearm to infusions of acetylcholine, an endothelium-dependent vasodilator (10−4 to 10−5 mol/L) and nitroglycerin, an endothelium-independent vasodilator (10−4 mol/L) in the brachial artery were determined with venous occlusion plethysmography before and after regional α-adrenergic blockade with intra-arterial phentolamine (25 μg/min) and systemic cyclooxygenase inhibition with oral indomethacin (50 mg). Administration of phentolamine significantly increased resting baseline forearm blood flow in 11 patients with congestive heart failure (2.9±0.4 to 5.4±0.8 mL·min−1·100 mL−1) and normal subjects (4.6±0.3 to 11.3±2.1 mL·min−1·100 mL−1). Before administration of phentolamine, intra-arterial infusions of acetylcholine 10−7, 10−6, and 10−5 mol/L increased forearm blood flow to 4.0±1.0, 6.0±1.7, and 16.1±4.0 mL·min−1·100 mL−1, respectively, in patients with congestive heart failure and to 14.7±6.2, 20.2±4.7, and 38.7±7.9 mL·min−1·100 mL−1, respectively, in normal subjects. After administration of phentolamine, the vasodilatory responses to intra-arterial infusions of acetylcholine and nitroglycerin did not change in either patients or normal subjects. Administration of indomethacin did not alter resting forearm blood flow in 15 patients with congestive heart failure (2.7±0.4 to 2.7±0.4 mL·min−1·100 mL−1) or normal subjects (4.6±0.3 to 5.4±0.8 mL·min−1·100 mL−1). Administration of indomethacin significantly increased the vasodilatory responses to infusions of acetylcholine by an average of 39% in patients with congestive heart failure but did not change the vasodilatory response to acetylcholine in normal subjects. In patients with congestive heart failure, baseline forearm blood flow and the vasodilatory responses to intra-arterial infusions of acetylcholine and nitroglycerin were significantly less than those of normal subjects both before and after administration of phentolamine and indomethacin.

Conclusions. The reduced vasodilatory response to intra-arterial infusion of acetylcholine in patients with congestive heart failure probably results from several coexistent abnormalities in peripheral vascular function, including abnormal production of cyclooxygenase-dependent vasoconstricting factor, impaired endothelial release of nitric oxide, and decreased vascular smooth muscle responsiveness to cyclic GMP–mediated vasodilation. (Circulation 1993;88:55–61)

Key Words • acetylcholine • vasodilation • heart failure, congestive

The vasodilatory response to intra-arterial administration of acetylcholine has been shown to be reduced in patients with congestive heart failure compared with normal subjects of similar age.1,2 The reduced response to acetylcholine is compatible with an impairment of endothelium-dependent vasodilation in the peripheral circulation of patients with congestive heart failure. However, whereas in isolated vascular rings, the vasodilating action of acetylcholine can be entirely accounted for by the endothelial release of nitric oxide,3 intra-arterial administration of acetylcholine in the intact circulation may have several actions in addition to stimulating endothelial nitric oxide production. Acetylcholine released from cholinergic nerves directly inhibits norepinephrine release at a prejunctional site of the sympathetic nerve terminal and thereby mediates vasorelaxation.4–6 Previous reports have demonstrated that an inhibition of α-adrenergic
transmission does not modify the response to intraarterial acetylcholine administration in normal subjects and patients with essential hypertension. Whether this is also the case in patients with congestive heart failure, who frequently have high circulating levels of catecholamines, is unknown. Acetylcholine has also been shown to stimulate production of endothelium-derived vasoactive substances originating from the cyclooxygenase metabolic pathway. Whereas cyclooxygenase inhibition did not alter the regional vascular response to acetylcholine in the forearm circulation of normal subjects, an acetylcholine-mediated cyclooxygenase-dependent endothelium-derived vasoconstricting substance has been reported in an experimental canine model of heart failure.

Accordingly, the present study was undertaken to further characterize the mechanisms by which intraarterial administration of acetylcholine modulates vasoconstrictor tone in the peripheral vasculature of patients with heart failure. The regional vascular effects of intraarterial acetylcholine administration were determined in the forearm circulation in patients with heart failure and normal subjects before and after regional α-adrenergic receptor blockade with phentolamine and cyclooxygenase inhibition with indomethacin.

Methods

Study Population

Thirty-one patients with idiopathic dilated cardiomyopathy and five normal subjects were studied. Each study subject participated in one of three study protocols as described below. Eleven patients participated in a protocol to determine the regional vascular effects of α-adrenergic blockade on the vasodilatory response to intraarterial administration of acetylcholine in patients with congestive heart failure. This group of patients included nine men and two women (mean age, 58 ± 12 years) with a mean left ventricular ejection fraction determined by radionuclide angiography of 23 ± 8%. Seven of these patients were in New York Heart Association (NYHA) functional class III, and four were in functional class II. Fifteen patients participated in a protocol to determine the regional vascular effects of cyclooxygenase inhibition on the vasodilatory response to intraarterial administration of acetylcholine in patients with congestive heart failure. This group of patients included 12 men and three women (mean age, 56 ± 10 years) with a mean left ventricular ejection fraction determined by radionuclide angiography of 18 ± 6%. Thirteen of these patients were in NYHA functional class III, and two were in functional class II. Five additional patients were studied in a protocol to determine the reproducibility of the regional vascular response to administration of intraarterial acetycholine over time in the absence of indomethacin. This group of patients included four men and one woman (mean age, 58 ± 8 years) with a mean left ventricular ejection fraction determined by radionuclide angiography of 24 ± 9%. Four of these patients were in NYHA functional class III, and one was in functional class II.

All patients had clinically stable congestive heart failure of at least 3 months’ duration. Medical therapy for congestive heart failure consisted of furosemide in all patients, digoxin in 22 patients, angiotensin converting enzyme inhibition in 21 patients, and long-acting oral nitrate preparations in nine patients. Cardiovascular medications were withheld for at least 24 hours before the study. All patients were clinically well compensated at the time of the study, without evidence of peripheral edema. Serum sodium was >136 mEq/L in all patients. No patients had a clinical history of coronary artery disease, peripheral vascular disease, hypertension, diabetes mellitus, or serum cholesterol >240 mg/dL.

Three men and two women without clinical evidence of cardiovascular disease, as determined by medical history, physical examination, serum chemistry, and 12-lead ECG, served as normal controls. These subjects participated in a protocol to sequentially determine the regional vascular effects of α-adrenergic blockade and cyclooxygenase inhibition on the vasodilatory response to intraarterial administration of acetylcholine in normal subjects. The mean age of these normal subjects was similar to the mean age of the patient population (52.0 ± 7.0 versus 57.8 ± 10.7 years, NS). Normal subjects were free of diabetes mellitus, hypercholesterolemia, or hypertension and were not receiving medical therapy. The study was approved by the Ethical Review Board of the Albert Einstein College of Medicine. All patients and normal subjects gave written informed consent before the study.

Forearm Blood Flow Measurements

Forearm blood flow was measured in mL · min⁻¹ · 100 mL⁻¹ of forearm volume with strain-gauge venous occlusion plethysmography as previously described in detail. Briefly, with the arm resting comfortably 10 cm above the right atrium, a mercury-in-Silastic strain gauge was placed around the widest portion of the upper third of the forearm. The strain gauge was electrically coupled to a plethysmograph (Parks Electronics, Aloha, Ore) calibrated to measure percent change in volume. The plethysmographic tracings of forearm blood flow were recorded on photographic paper for analysis (model VR6, Electronics for Medicine). For each measurement, forearm venous blood flow was occluded just proximal to the elbow with the rapid inflation of a blood pressure cuff to 40 mm Hg (model E 20, Hokanson Instruments). A wrist cuff was inflated to suprasystolic pressures 1 minute before and during each measurement to exclude the hand circulation from the blood flow determination. The venous occluding cuff was rapidly inflated for 5 seconds at 15-second intervals; five plethysmographic recordings were averaged for each blood flow determination. During each blood flow measurement, mean arterial pressure was determined in the contralateral arm at 15-second intervals by the cuff method with an automated blood pressure measurement device (model 1846, Dinamap). Forearm vascular resistance, expressed in arbitrary resistance units, was determined as the ratio of mean arterial pressure and forearm blood flow.

Drug Administration

All drugs were prepared in 5% dextrose in water on the day of the study. Drug infusion rates were adjusted according to the resting basal forearm blood flow measured before each infusion to achieve final regional blood concentrations as stated. Acetylcholine, an endothelium-dependent vasodilator (10⁻³, 10⁻⁴, and 10⁻⁵
mol/L), and nitroglycerin, a direct-acting, endothelium-independent vasodilator (10⁻⁶ mol/L), were administered intra-arterially as a 2-minute continuous infusion in random sequence. Forearm blood flow was determined during the last minute of each infusion. After completion of each infusion, all catheters were cleared of vasoactive drugs and flushed with heparinized solution. Subsequent infusions were administered at 5-10-minute intervals when forearm blood flow had returned to basal values.

**Study Protocols**

All studies were conducted in a quiet, temperature-controlled room with the patients resting in a supine position. Under local anesthesia (1% lidocaine), a 20-gauge angiocatheter was placed into the right brachial artery for drug administration. Thirty minutes after catheter placement was completed, resting basal forearm blood flow was measured. Study subjects participated in one of the three protocols described below. Patients with congestive heart failure were assigned to either protocol 1 or 2 and normal subjects to protocol 3.

**Protocol 1: Regional vascular effects of α-adrenergic blockade in patients with congestive heart failure.** To evaluate whether presynaptic inhibition of α-adrenergic transmission contributes to the vasodilatory action of intra-arterial acetylcholine, a 10-minute infusion of phentolamine, a nonspecific α-adrenergic receptor blocker (25 μg/min), was administered into the brachial artery in 11 patients. The regional forearm vascular responses to administration of acetylcholine and nitroglycerin in the brachial artery were determined before and immediately after the phentolamine infusion. The extent of regional α-adrenergic blockade was assessed by determining the forearm vascular response to the cold pressor test before and after intra-arterial administration of phentolamine. The cold pressor test was performed by immersing the contralateral hand and wrist in ice water for 2 minutes before and after administration of phentolamine. Before phentolamine administration, 2 minutes of hand immersion in ice water significantly increased forearm vascular resistance from basal values of 35±5 to 50±7 resistance units (p<0.05). After phentolamine administration, basal forearm vascular resistance was significantly reduced compared with basal prephentolamine value and did not change after 2 minutes of hand immersion in ice water (21±7 versus 22±11 resistance units, NS). The reproducibility of the regional forearm vascular response to administration of acetylcholine over time was assessed in eight of the 11 patients (three patients were unable to complete this portion of the protocol). In the eight patients, administration of acetylcholine was repeated 90 minutes after the phentolamine infusion, when resting forearm blood flow had returned to resting values.

**Protocol 2: Regional vascular effects of cyclooxygenase inhibition in patients with congestive heart failure.** To determine the effects of cyclooxygenase inhibition on the vascular effects of intra-arterial administration of acetylcholine, 50 mg of oral indomethacin was administered orally to 15 patients with congestive heart failure. The regional forearm vascular responses to administration of acetylcholine and nitroglycerin in the brachial artery were determined before and 1 hour after indomethacin administration. The reproducibility of the regional vascular effects of intra-arterial administration of acetylcholine over time was determined in five additional patients with congestive heart failure. In these patients, the administration of acetylcholine was repeated at a 1-hour interval without other intervention.

**Protocol 3: Regional vascular effects of α-adrenergic blockade and cyclooxygenase inhibition in normal subjects.** Five normal subjects participated in a combined experimental protocol to sequentially determine the regional vascular effects of α-adrenergic blockade and cyclooxygenase inhibition on the vascular effects of intra-arterial administration of acetylcholine and nitroglycerin. In the five normal subjects, regional forearm vascular responses to administration of acetylcholine and nitroglycerin in the brachial artery were determined before and 10 minutes after infusion of phentolamine (25 μg/min). Ninety minutes after completion of the phentolamine infusion, when resting forearm blood flow had returned to basal values, regional forearm vascular responses to administration of acetylcholine and nitroglycerin in the brachial artery were determined before and 1 hour after oral administration of 50 mg of indomethacin.

**Data Analysis**

All values are expressed as mean±SEM. The regional vascular responses to acetylcholine and nitroglycerin infusions before and after phentolamine or indomethacin administration were compared within groups of patients or normal subjects with Student’s t test for paired observations. Comparisons between patients and normal subjects were made with ANOVA with the Sheffe test for post hoc determination of statistical significance. A two-tailed value of p<0.05 was considered statistically significant.

**Results**

**Regional Vascular Effects of α-Adrenergic Blockade**

**Patients with heart failure.** Administration of phentolamine in the brachial artery significantly increased resting forearm blood flow from a baseline value of 2.9±0.4 to 5.4±0.8 mL·min⁻¹·100 mL⁻¹ (p<0.002; Figure 1A). Before administration of phentolamine, intra-arterial infusions of acetylcholine 10⁻⁷, 10⁻⁶, and 10⁻⁵ mol/L increased forearm blood flow to 4.0±1.0, 6.0±1.7, and 16.1±4.0 mL·min⁻¹·100 mL⁻¹, respectively. After administration of phentolamine, intra-arterial infusions of acetylcholine 10⁻⁷, 10⁻⁶, and 10⁻⁵ mol/L increased forearm flow to 6.2±0.9, 11.0±2.5, and 20.5±5.1 mL·min⁻¹·100 mL⁻¹, respectively. The changes from baseline forearm blood flow in response to intra-arterial infusions of acetylcholine before and after phentolamine were similar (Figure 1B). The changes from baseline forearm blood flow in response to infusions of nitroglycerin 10⁻⁸ mol/L were similar before and after administration of phentolamine (Table 1).

Ninety minutes after completion of the administration of phentolamine, resting forearm blood flow had returned to resting basal values (3.2±0.5 versus 3.9±0.5 mL·min⁻¹·100 mL⁻¹, p=NS). The changes from baseline forearm blood flow in response to infusions of graded concentrations of acetylcholine in the brachial artery were similar before and 90 minutes after administration of phentolamine (Table 2).
Mean arterial pressure and heart rate did not change after the phentolamine infusion or during any infusion of acetylcholine or nitroglycerin.

Normal subjects. Administration of phentolamine in the brachial artery significantly increased resting forearm blood flow in patients with congestive heart failure and normal subjects (p<0.05, Figure 1A). Before administration of phentolamine, intra-arterial infusions of acetylcholine 10⁻⁷, 10⁻⁶, and 10⁻⁵ mol/L increased forearm blood flow to 14.7±6.2, 20.2±4.7, and 38.4±7.9 mL·min⁻¹·100 mL⁻¹, respectively. After administration of phentolamine, intra-arterial infusions of acetylcholine 10⁻⁷, 10⁻⁶, and 10⁻⁵ mol/L increased forearm blood flow to 21.2±6.4, 32.8±9.3, and 47.9±9.6 mL·min⁻¹·100 mL⁻¹, respectively. The changes from baseline forearm blood flow in response to intra-arterial infusions of acetylcholine before and after administration of phentolamine were similar (Figure 1B). The changes from baseline forearm blood flow in response to infusions of nitroglycerin were similar before and after administration of phentolamine (Table 1). Compared with patients with congestive heart failure, baseline forearm blood flow and the regional vascular responses to intra-arterial administration of acetylcholine and nitroglycerin were significantly greater in normal subjects both before and after phentolamine administration (all p<0.03).

![Figure 1. Bar charts. Panel A: Resting forearm blood flow (mL·min⁻¹·100 mL⁻¹) in patients with congestive heart failure (n=11) and normal subjects (n=5) before and after Regional alpha-adrenergic blockade with phentolamine. Panel B: Change in forearm blood flow from baseline value (mL·min⁻¹·100 mL⁻¹) induced by administration of increasing concentrations of acetylcholine in patients with congestive heart failure (n=11) and normal subjects (n=5) before and after administration of phentolamine. Phentolamine did not change the regional vascular response to acetylcholine in patients with congestive heart failure or normal subjects. All values are shown as mean±SEM. White and black bars represent mean values of patients with congestive heart failure before and after administration of phentolamine, respectively; light and dark striped bars represent mean values for normal subjects before and after administration of phentolamine, respectively. *p<0.05 vs. prephentolamine values.](http://circ.ahajournals.org/content/88/1/58)
Regional Vascular Effects of Cyclooxygenase Inhibition

Patients with heart failure. Administration of indomethacin did not change basal resting forearm blood flow (2.7±0.4 versus 2.7±0.4 mL·min⁻¹·100 mL⁻¹, p=NS; Figure 2A). Before administration of indomethacin, intra-arterial infusions of acetylcholine 10⁻⁷, 10⁻⁶, and 10⁻⁵ mol/L increased forearm blood flow to 3.7±0.9, 4.2±1.1, and 8.7±2.1 mL·min⁻¹·100 mL⁻¹, respectively. After administration of indomethacin, intra-arterial infusions of acetylcholine 10⁻⁷, 10⁻⁶, and 10⁻⁵ mol/L increased forearm blood flow to 4.7±1.0, 6.1±1.5, and 12.7±2.7 mL·min⁻¹·100 mL⁻¹, respectively. The changes from baseline forearm blood flow in response to infusions of intra-arterial acetylcholine were significantly greater after administration of indomethacin compared to those observed before indomethacin administration (all p<0.03; Figure 2B). The changes in forearm blood flow in response to intra-arterial infusions of nitroglycerin were similar before and after administration of indomethacin (Table 1). The vasodilatory responses to intra-arterial administration of acetylcholine repeated at 1-hour intervals were similar in five patients who did not receive indomethacin (Table 3).

Resting mean arterial pressures before and after administration of indomethacin were similar (84±11

| TABLE 2. Reproducibility of the Vasodilatory Response to Intra-arterial Administration of Acetylcholine in Patients With Congestive Heart Failure Before and 90 Minutes After Regional α-Adrenergic Blockade With Phentolamine | Forearm blood flow (mL·min⁻¹·100 mL⁻¹) |
|---|---|---|---|
| Baseline | ACh 10⁻⁷ mol/L | ACh 10⁻⁶ mol/L | ACh 10⁻⁵ mol/L |
| Before phentolamine (n=8) | 3.2±0.5 | 4.7±1.6 | 6.5±2.7 | 18.1±4.7 |
| After phentolamine (n=8) | 3.9±0.5 | 5.5±0.8 | 7.8±2.0 | 16.4±3.4 |

ACh, acetylcholine. All values are stated as mean±SEM.

**Figure 2.** Bar charts. Panel A: Resting forearm blood flow (mL·min⁻¹·100 mL⁻¹) in patients with congestive heart failure (n=15) and normal subjects (n=5) before and after cyclooxygenase inhibition with indomethacin. Panel B: Change in forearm blood flow from baseline values (mL·min⁻¹·100 mL⁻¹) induced by administration of increasing concentrations of acetylcholine in patients with congestive heart failure (n=15) and normal subjects (n=5) before and after administration of indomethacin. Indomethacin significantly increased the regional vasodilatory response to acetylcholine in patients with congestive heart failure but not in normal subjects. All values are shown as mean±SEM. White and black bars represent mean values of patients with congestive heart failure before and after administration of indomethacin, respectively; light and dark striped bars represent mean values for normal subjects before and after administration of indomethacin, respectively. *p<0.05 vs. preindomethacin values.
TABLE 3. Reproducibility of the Vaso dilatory Response to Intra-arterial Administration of Acetylcholine in Five Patients With Congestive Heart Failure

<table>
<thead>
<tr>
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<th>Forearm blood flow (mL · min⁻¹ · 100 mL⁻¹)</th>
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<tbody>
<tr>
<td></td>
<td>Resting</td>
<td>ACh 10⁻⁷ mol/L</td>
<td>ACh 10⁻⁵ mol/L</td>
<td>ACh 10⁻³ mol/L</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.5±0.5</td>
<td>5.4±0.5</td>
<td>9.5±1.4</td>
<td>22.4±4.0</td>
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<tr>
<td>1 Hour</td>
<td>4.5±0.6</td>
<td>5.7±0.6</td>
<td>9.6±1.5</td>
<td>22.7±3.7</td>
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ACh, acetylcholine. All values are stated as mean±SEM.

versus 86±8 mm Hg, respectively; p=NS). Mean arterial pressure and heart rate did not change during any intra-arterial drug infusions.

Normal subjects. Administration of indomethacin did not change resting forearm blood flow (4.6±0.3 versus 5.4±0.8 mL · min⁻¹ · 100 mL⁻¹, p=NS; Figure 2A). Similarly, administration of indomethacin did not change the regional vascular responses to intra-arterial infusions of acetylcholine (Figure 2B) or nitroglycerin (Table 1). Compared with patients with congestive heart failure, baseline forearm blood flow and the regional vascular responses to intra-arterial administration of acetylcholine and nitroglycerin were significantly greater in normal subjects both before and after administration of indomethacin.

Discussion

The present data confirm previous reports that patients with congestive heart failure caused by idiopathic dilated cardiomyopathy have a reduced vasodilatory response to acetylcholine in the forearm circulation compared with normal subjects of similar age.1,2 Our data also extend the previous findings reported in normal subjects and patients with essential hypertension to patients with congestive heart failure, i.e., that the vasodilatory response to acetylcholine is left unchanged by regional α-adrenergic blockade with phentolamine.7,8 Lastly, our data document for the first time that, in contrast to previous findings reported in normal subjects,8 cyclooxygenase inhibition with indomethacin enhances the vasodilatory response to acetylcholine in patients with congestive heart failure. These latter findings suggest that in patients with congestive heart failure, the reduced vasodilatory response to intra-arterial acetylcholine results from both impaired endothelial release of nitric oxide and abnormal production of cyclooxygenase-dependent vasoconstricting substance.

Regional α-adrenergic blockade with phentolamine increased resting blood flow in patients with congestive heart failure and normal subjects but did not alter the vasodilatory response to intra-arterial administration of acetylcholine. Since the vasodilatory action of acetylcholine was maintained in the presence of effective regional α-blockade (as evidenced by inhibition of the regional vasoconstrictor response to the cold pressor test), the regional vasodilatory effects of acetylcholine in the forearm circulation cannot be ascribed to prejunctional inhibition of norepinephrine release at the sympathetic nerve terminals. In addition, patients with congestive heart failure had a lower vasodilatory response to acetylcholine than normal subjects even after administration of phentolamine. This finding supports the view that increased adrenergic stimulation is not responsible for the impaired vasodilatory response to acetylcholine administration in patients with congestive heart failure.1

Systemic cyclooxygenase inhibition with indomethacin significantly increased the regional vasodilatory responses to intra-arterial administration of graded concentrations of acetylcholine, by an average of 39% (range, 27-46%), in patients with congestive heart failure. In contrast, administration of indomethacin did not alter either resting forearm blood flow or the regional vascular response to the direct-acting vasodilator nitroglycerin in patients with congestive heart failure or normal subjects. Together, these data suggest that intra-arterial administration of acetylcholine specifically stimulates production of a vasoconstricting substance that opposes the vasodilating effects of endothelium-derived relaxing factor (nitric oxide) in the forearm vasculature of patients with congestive heart failure. Acetylcholine-mediated, endothelium-dependent vasoconstrictor substances have been reported previously in a femoral artery preparation from a canine model of heart failure,11 in isolated vascular rings from canine femoral and basilar arteries,10,16 in isolated pulmonary artery rings from rabbits,17 and in isolated aorta and renal and carotid arteries from spontaneously hypertensive rats.18-20 Acetylcholine-stimulated release of a cyclooxygenase-dependent vasoconstrictor substance in patients with congestive heart failure may be related to activation of the sympathetic and renin–angiotensin systems in this patient population.9,21,22 Norepinephrine and angiotensin I and II have been reported to directly stimulate prostaglandin synthesis in vascular endothelial cells through inositol triphosphate–dependent activation of the phospholipase A₂.23-25 Of interest, angiotensin converting enzyme inhibitors have also been demonstrated to acutely stimulate synthesis of both prostacyclin and thromboxane A₂ in cultured endothelial cells, possibly by bradykinin-dependent mechanisms.26,27 Angiotensin converting enzyme inhibitors were withdrawn at least 24 hours before the present study; the effects of chronic angiotensin converting enzyme inhibition on endothelial prostaglandin release in patients with congestive heart failure have not been characterized.

Systemic cyclooxygenase inhibition with indomethacin did not exert any systemic or regional hemodynamic effects in our patients with clinically stable congestive heart failure and normal serum sodium concentration. In contrast, patients with decompensated congestive heart failure and associated hyponatremia have high serum levels of vasodilating prostaglandins and experience deleterious hemodynamic effects after acute cyclooxygenase inhibition.26,29 Increased neuroendocrine activation in the decompensated stage of congestive heart failure appears to play an important role in the production and release of prostaglandins by the endothelium.30

Characterization of the cyclooxygenase-dependent vasoconstricting substance released in response to acetylcholine in patients with congestive heart failure was not attempted in the present study. Cyclooxygenase-dependent vasoconstricting substances may be produced by vascular endothelium, platelets, or vascular smooth muscle cell. Muscarinic receptor–stimulated production of vasoconstricting prostaglandins has been reported previously only in vascular endothelial
cells. Prostaglandin $F_2\alpha$, thromboxane $A_2$, and related prostanoids synthesized by the vascular endothelium may directly mediate vasoconstriction in vascular smooth muscle. Superoxide anion has also been identified as a cyclooxygenase-dependent, endothelium-derived vasoconstricting factor that, in part, may mediate vasoconstriction by decreasing the half-life of nitric oxide.

In conclusion, the present study demonstrates that the impaired vasodilatory response to intra-arterial administration of acetylcholine results from several coexisting abnormalities in the peripheral circulation of patients with congestive heart failure. In addition to reducing endothelial release of nitric oxide, a cyclooxygenase-dependent vasoconstricting substance appears to limit the vasodilatory response to acetylcholine in patients with congestive heart failure. In addition, the present study confirms that the vasodilatory response to regional administration of nitroglycerin in patients with congestive heart failure was reduced compared with that of normal subjects. Consequently, impairment of the vasodilatory effector mechanism in vascular smooth muscle cells may also limit the vasodilatory response to acetylcholine in patients with congestive heart failure. Additional studies are needed to determine whether other endothelium-derived vasoactive substances, such as endothelin and endothelium-derived hyperpolarizing factor, also contribute to abnormal endothelial function in the peripheral circulation of patients with congestive heart failure.

References


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