Attenuated Forearm Vasodilative Response to Intra-Arterial Atrial Natriuretic Peptide in Patients With Heart Failure

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It has been shown that renal responses to atrial natriuretic peptide (ANP) are markedly attenuated in patients with heart failure. This study aimed to determine if vasodilative response to ANP is altered in patients with heart failure. In patients with heart failure (n=7) and age-matched normal subjects (n=7), forearm blood flow was measured using a strain-gauge plethysmograph during intra-arterial infusion of α-human ANP (50, 100, 200, and 400 ng/min) or nitroglycerin (100, 200, 400, and 600 ng/min). Forearm vasodilatation evoked with intra-arterial α-human ANP in patients with heart failure was considerably less (p<0.01) than that in normal subjects. In contrast, nitroglycerin produced comparable forearm vasodilatation in the two groups. Plasma ANP and cyclic guanosine monophosphate (GMP) levels at rest were higher in patients with heart failure than in normal subjects (p<0.05 for both), but the increases in plasma ANP and cyclic GMP in the venous effluents during intra-arterial ANP infusion did not differ between the two groups. These results indicate that the direct vasodilative effect of ANP on forearm vessels was attenuated in patients with heart failure as compared with that in normal subjects. The mechanisms responsible for this alteration are not clear but might involve mechanisms other than down-regulation of the ANP receptors because the increases in venous plasma cyclic GMP caused by intra-arterial ANP were comparable between patients with heart failure and normal subjects. (Circulation 1990;82:147-153)

It has been suggested that atrial natriuretic peptide (ANP) may contribute importantly to the control of circulation and water and electrolyte balance.1–3 Previous investigators have shown that plasma ANP is markedly elevated in patients and animals with heart failure,4–8 which suggests that ANP may play a compensatory role in the control of circulation and fluid balance in heart failure. However, it also has been suggested that ANP binding sites may be down-regulated in patients with heart failure.9 Furthermore, a recent study has suggested that there may be an intracellular defect that prevents the mediation of the hormonal signal of ANP into biological action in animals with heart failure.10 The latter results raise the possibility that the attenuated biological effects of ANP may contribute to the pathophysiology of heart failure. Thus, the exact role of ANP in the control of circulation and fluid balance in heart failure is still not known.

Previous investigators have examined the renal and hemodynamic effects of intravenous ANP in large doses in patients with heart failure and in normal subjects.8,11–15 These studies have demonstrated that the renal responses to ANP were markedly attenuated in heart failure. Intravenous ANP had no or little effect on diuresis and natriuresis in patients with heart failure,9,11–13 whereas in normal subjects it caused rapid urine and electrolyte excretion.9,16–22 On the other hand, it has been reported that intravenous ANP in high doses improved left ventricular function in patients with heart failure but not in normal subjects.8,13 This beneficial effect of ANP on cardiac function in heart failure was attributed to the vasodilative action of ANP8,13,15; however, few studies have investigated whether the vasodilative response to intra-arterial ANP is augmented or attenuated in patients with heart failure.23 This study aimed to determine if the direct vasodilative effect of ANP is altered in patients with heart failure.24

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failure. We examined forearm vascular responses evoked with intra-arterial infusion of α-human ANP or nitroglycerin at graded doses in patients with heart failure and age-matched normal subjects. We also examined the increases in plasma cyclic guanosine monophosphate (cyclic GMP) in the venous effluents caused by ANP in the two groups.

Methods

Subjects

Seven patients with heart failure (six men and one woman) and seven normal men were studied. The clinical features of patients with heart failure are summarized in Table 1. Mean ages of the two groups were not different; ages of patients with heart failure ranged from 32 to 72 years (mean, 55±6 years) and those of normal subjects from 47 to 59 years (mean, 55±2 years). Five of seven control subjects were determined to be free of any cardiovascular disease by history, physical examination, and an electrocardiogram. Two subjects had no history of cardiovascular disease but showed mild systolic hypertension at the time of study. The other findings by physical examination and electrocardiogram were normal in these two subjects. Basic disorders of patients with heart failure included dilated cardiomyopathy in three, ischemic heart disease (old myocardial infarction) in two, rheumatic valvular disease (mitral stenosis and aortic regurgitation) in one, and cardiac amyloidosis in one patient. The patients with heart failure were hospitalized with acute pulmonary congestion with rale in lungs and chest radiograph findings consistent with pulmonary congestion. Congestive heart failure was precipitated by upper respiratory infection and atrial fibrillation with rapid ventricular response in three patients, atrial fibrillation with rapid ventricular response in two, and upper respiratory infection in one. In one patient, a precipitating factor was not apparent. These patients responded well to therapy with rapid digitalization and furosemide. Two patients received intravenous nitroglycerin for less than 2 days, but no other vasodilator drugs or antiarrhythmic drugs had been administered. The study was done on the 2nd to 8th day in hospital, by which time symptoms had improved so that patients could remain in a supine position for the study. At the time of the study, however, patients were still in heart failure, which was evidenced by physical examinations, chest radiograph findings, and elevated plasma levels of ANP. All patients had cardiomegaly with a cardiothoracic ratio greater than or equal to 51%, and four patients had a cardiothoracic ratio greater than or equal to 60%. Left ventricular ejection fraction assessed by radionuclide ventriculography, echocardiography, or both was less than or equal to 52% in all patients and less than 40% in five patients. Pulmonary artery wedge pressure was measured in two patients and was elevated to a level higher than or equal to 24 mm Hg.

Informed written consent was obtained from each subject.

Measurement of Forearm Blood Flow

The study was done with subjects in a supine position and in a postabsorptive state. Forearm blood flow was measured with a mercury-in-Silastic strain-gauge plethysmograph using a venous occlusion technique as previously described.4 The strain gauge was placed approximately 5 cm below the antecubital crease. Forearm blood flow (ml/min/100 ml of forearm) was calculated from the rate of increase in forearm volume while venous return from the forearm was prevented by inflating the cuff at the upper arm. The pressure in the venous occlusion or congesting cuff at the upper arm was 40 mm Hg. Circulation to the hand was arrested by inflating a cuff around the wrist. The wrist cuff was inflated before determining forearm blood flow and continuously throughout the measurements. Blood pressure was measured with a sphygmomanometer in the other arm. Forearm vascular resistance was calculated by dividing the mean blood pressure (mm Hg) by the forearm blood flow. These values are expressed as units throughout this report. Mean blood pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure. An average of five to eight flow measurements made at 15-second inter-

### Table 1. Summary of Patients With Congestive Heart Failure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>History of heart failure</th>
<th>Diagnosis</th>
<th>Precipitating factors</th>
<th>CTR (%)</th>
<th>LVEF (%)</th>
<th>LVDd (cm)</th>
<th>S3</th>
<th>Rale</th>
<th>Neck vein engorgement</th>
<th>Hepatomegaly</th>
<th>Peripheral edema</th>
<th>PAW (mm Hg)</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>72</td>
<td>+</td>
<td>DCM, MR</td>
<td>URI</td>
<td>29(R1)</td>
<td>6.6</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>50</td>
<td>-</td>
<td>DCM</td>
<td>URI, af</td>
<td>27(Echo)</td>
<td>5.0</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<tr>
<td>3</td>
<td>F</td>
<td>59</td>
<td>+</td>
<td>MS+ AR</td>
<td>URI, af</td>
<td>52(Echo)</td>
<td>5.0</td>
<td>(-)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>71</td>
<td>+</td>
<td>Old MI</td>
<td>URI, af</td>
<td>45(Echo)</td>
<td>5.5</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
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</tr>
<tr>
<td>5</td>
<td>M</td>
<td>32</td>
<td>+</td>
<td>Old MI</td>
<td>URI, af</td>
<td>26(R1)</td>
<td>5.2</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>59</td>
<td>-</td>
<td>DCM</td>
<td>URI, af</td>
<td>60(R1)</td>
<td>5.2</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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</tr>
<tr>
<td>7</td>
<td>M</td>
<td>41</td>
<td>+</td>
<td>amyloidosis</td>
<td>af</td>
<td>39(R1)</td>
<td>4.2</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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</tr>
</tbody>
</table>

CTR, cardiothoracic ratio; LVEF, left ventricular ejection fraction; LVDd, left ventricular dimension at end diastole; PAW, pulmonary artery wedge pressure; DCM, dilated cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; AR, aortic regurgitation; MI, myocardial infarction; URI, upper respiratory infection; af, atrial fibrillation; RI, radionuclide ventriculography; Echo, echocardiography.
vals was used for later analysis. Heart rate was determined by counting radial pulse for one minute.

**Forearm Vascular Responses to α-Human Atrial Natriuretic Peptide and Nitroglycerin**

A brachial artery was cannulated with a 20-gauge intravascular over-the-needle PTFE catheter (Quick-Cath, Travenol Laboratories, Inc., Baxter Healthcare Corporation, Dearfield, Illinois) for drug infusion, and a vein in the antecubital region of the same arm was cannulated to obtain blood samples for measuring plasma α-human ANP and cyclic GMP. After cannulae and a strain-gauge plethysmograph were placed, at least 15 minutes were allowed for subjects to become accustomed to the study conditions before beginning the experiments.

Forearm blood flow was measured during intra-arterial infusion of α-human ANP at a rate of 50, 100, 200, and 400 ng/min or nitroglycerin at a rate of 100, 200, 400, and 600 ng/min. Each dose of α-human ANP or nitroglycerin was infused for 5 minutes. Forearm blood flow during the last 1.5 minute of infusion of each dose was used for later analysis. The order of α-human ANP and nitroglycerin was alternated. After the study with the first drug, we waited for 20 minutes before beginning the study with the second drug, by which time forearm blood flow had returned to the baseline value.

**Measurements of Plasma Atrial Natriuretic Peptide and Cyclic Guanosine Monophosphate**

We sampled the ipsilateral venous blood for the measurements of plasma α-human ANP and cyclic GMP during saline infusion and during the last minute of intra-arterial drug infusion at the maximal dose.

Plasma α-human ANP levels in the venous effluents were determined by radioimmunoassay (RIA) using the method described previously. Briefly, the RIA assay buffer was 0.1 M Tris acetate, pH 7.4, containing 0.1% bovine serum albumin and 1 mM Na2 EDTA. The RIA incubation mixture consisted of 100 μl of standard α-human ANP, 100 μl of antiserum diluted in the assay buffer, 100 μl of [125I]-α-human ANP (10,000 cpm), and 200 μl of the assay buffer. The mixture was incubated for 24 hours at 4°C. The antibody-bound and free tracer peptide were separated by adding 100 μl each of anti-rabbit IgG antiserum (1:20), normal rabbit serum (1:200), and 15% polyethylene glycol in assay buffer.

Blood samples collected in chilled tubes containing Na2 EDTA (4 mM) and aprotinin (500 kallikrein inactivator units/ml) were separated by centrifugation at 4°C, and plasma was stored at −70°C until assay. One milliliter of each plasma was acidified by adding 1 ml of 4% acetic acid and was applied on a Sep-Pak C18 cartridge (Millipore Corporation, Milford, Massachusetts) was pretreated successively with 10 ml each of 1) a mixture of acetonitrile and 0.5% ammonium acetate (pH 4.0) (3:2), 2) distilled water, 3) 100% methanol, and 4) distilled water. The cartridge was washed with 10 ml of 4% acetic acid, and the absorbed peptide was eluted with 2 ml of a mixture of acetonitrile and 0.5% ammonium acetate (pH 4.0) (3:2). The eluates were evaporated, lyophilized, dissolved in the assay buffer, and subjected to RIA.

Plasma cyclic GMP levels in the venous effluents were determined at control and during intra-arterial infusion of the maximal dose of nitroglycerin or α-human ANP. Venous blood was sampled into the tube containing Na2 EDTA (1 mg/ml). Plasma cyclic GMP was measured in duplicate by RIA using RIA kits obtained from Yamasa Shoyu Co. (Tokyo, Japan) after succinylation as previously described. Briefly, for succinylation of cyclic GMP, 100 μl of a dioxygen and triethylamine mixture containing succinic anhydride was added to 100 μl of a sample (a standard or test solution). After 10 minutes at room temperature, the reaction mixture was added with 0.5–1.0 ml of 0.5 M imidazole buffer that contained 0.5% bovine serum albumin, 8 mM theophylline, and 0.01% streptomycin. To 100 μl of the above mixture was added 100 μl of [125I]succinyl cyclic GMP (15,000–20,000 cpm in an amount less than 10−14 mol) and 100 μl of the diluted antisera; the mixture was kept at 4°C overnight. To separate bound from unbound nucleotide, a cold solution of dextran-coated charcoal (0.5 ml) was added to the above mixture cooled in an ice-cold water bath. Charcoal was then spun down, and 0.5 ml of the supernatant was counted for radioactivity using a gamma spectrometer.

**Statistical Analysis**

Unpaired Student's t test was used for comparing the results between normal subjects and patients with congestive heart failure. Responses to the graded doses of the drugs in each group were examined by analysis of variance for repeated measurements. Comparisons of forearm vasodilator responses to drugs between the two groups were done by two-way analysis of variance. Values were considered significant at p<0.05. All data are expressed as mean±SEM.

**Results**

**Blood Pressure, Heart Rate, and Forearm Circulation**

At a control state, mean blood pressure was lower (p<0.01), heart rate was faster (p<0.01), forearm blood flow was lower (p<0.01), and forearm vascular resistance was higher (p<0.05) in patients with heart failure than in normal subjects (Table 2).

Intra-arterial infusion of nitroglycerin or α-human ANP did not alter mean blood pressure or heart rate in normal subjects and in patients with heart failure. In normal subjects and in patients with heart failure, intra-arterial infusion of nitroglycerin and α-human ANP at graded doses caused progressive increases in forearm blood flow (p<0.05 or p<0.01) and progressive decreases in forearm vascular resistance (p<0.01). Progressive percent increases in forearm blood flow
and progressive percent decreases in forearm vascular resistance caused by nitroglycerin were similar between the two groups. However, progressive percent increases in forearm blood flow and progressive percent decreases in forearm vascular resistance caused by α-human ANP were markedly attenuated in patients with heart failure as compared with those in normal subjects (p<0.01). Progressive percent changes in forearm vascular resistance caused by nitroglycerin and α-human ANP in the two groups are shown in Figure 1.

**Plasma Atrial Natriuretic Peptide and Cyclic Guanosine Monophosphate in the Venous Effluents**

Plasma ANP at a control state was higher in patients with heart failure (344±87 pg/ml, n=7) than in normal subjects (49±7 pg/ml, n=5; p<0.05). Intra-arterial infusion of α-human ANP at the maximal dose (400 ng/min) increased plasma ANP in the venous effluents to 2,890±840 pg/ml in patients with heart failure (p<0.05) and to 1,867±266 pg/ml in normal subjects (p<0.01). The magnitudes of the increases in plasma ANP in the venous effluents were not significantly different between the two groups.

Intra-arterial infusion of α-human ANP at the maximal dose (400 ng/min) increased plasma cyclic GMP in the venous effluents from 15.3±2.7 pmol/ml to 25.8±12.3 pmol/ml in patients with heart failure (p<0.05) and from 6.3 pmol/ml to 14.4±3.1 pmol/ml in normal subjects (p<0.01) (Figure 2). Plasma cyclic GMP at a control state was higher in patients with heart failure than in normal subjects (p<0.05), but the magnitudes of the increases caused by intra-arterial infusion of α-human ANP did not significantly differ between the two groups. Intra-arterial infusion of nitroglycerin at the maximal dose (600 ng/ml) did not increase plasma cyclic GMP in the venous effluents either in patients with heart failure (18.6±3.8 pmol/ml at control versus 18.2±2.9 pmol/ml during infusion) or in normal subjects (7.4±1.8 pmol/ml at control versus 6.9±1.4 pmol/ml during infusion) (Figure 2).

**Discussion**

The major finding of this study was that forearm vasodilatation evoked with intra-arterial ANP in patients with heart failure was considerably less than that in normal subjects. Forearm vasodilatation...
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caused by intra-arterial nitroglycerin and production of cyclic GMP during ANP infusion did not significantly differ between the two groups. These results suggest that forearm vasodilative response to ANP is markedly attenuated in patients with heart failure and that attenuated vascular response to ANP may not be accounted for by down-regulation of binding sites for ANP.

Previous investigators have examined the systemic hemodynamic effects of intravenous ANP in patients with heart failure. Many of these studies have reported that intravenous administration of ANP in large doses decreased pulmonary wedge pressure and systemic vascular resistance and increased cardiac output in patients with heart failure. The increase in cardiac output with intravenous ANP in patients with heart failure has been attributed to systemic vasodilation resulting from the vasodilative action of ANP. The responses in patients with heart failure differed from those in normal subjects in whom intravenous ANP often caused no changes in systemic vascular resistance and cardiac output. We examined whether the direct forearm vasodilative effect of intravenous ANP differed between patients with heart failure and normal subjects, and our results indicate that this effect was markedly attenuated in patients with heart failure as compared with that in normal subjects. These results are consistent with the results of a preliminary report in patients and in animals with heart failure that suggested that vascular responses to ANP were blunted in heart failure.

We need to consider the possibility that attenuated forearm vasodilative response to ANP in patients with heart failure might have resulted from nonspecific mechanisms. It has been shown that vasodilative response of limb vessels to exercise or reactive hyperemia is reduced in patients with heart failure. The reduced vasodilative capacity in heart failure has been attributed to increased neurohumoral vasostrictive stimuli and/or vascular changes characterized by the increased sodium and water content in the vessel wall. This possibility is unlikely, however, because intra-arterial nitroglycerin produced comparable forearm vasodilatation in patients with heart failure and in normal subjects. It is also unlikely that the difference in plasma ANP during infusion resulted in the difference in response between the two groups. Although the measurements were done at one point, plasma ANP in the venous effluents during intra-arterial infusion of ANP at the maximal dose was higher in patients with heart failure than in normal subjects. It also has been suggested that diuretics except for furosemide may attenuate the diuretic effects of ANP; however, it is not known whether diuretics alter the vasodilator effect of ANP. Furthermore, only furosemide had been given to our patients with heart failure.

As previously discussed, several studies have shown that intravenous ANP caused a greater fall in systemic vascular resistance in patients with heart failure than in normal subjects. The reasons for the difference in the results with intravenous and intra-arterial administration of ANP are not clear; however, several possibilities can be considered. First, it has been shown that in normal subjects, intra-arterial infusion of ANP into a brachial artery caused marked forearm vasodilatation, whereas intravenous ANP did not alter forearm systemic vascular resistance. The latter results suggest that during intravenous administration of ANP, secondary neurohumoral mechanisms compensated the direct vasodilative effect of ANP. Secondary neurohumoral adjustments might be less in patients with heart failure than in normal subjects because baroreflex mechanisms are blunted in heart failure. Second, it also is possible that vasodilator action of ANP may differ among various vascular beds and that response to ANP in some vascular beds might not be attenuated in heart failure. Third, the discordant results in this and previous studies might have resulted from the difference in doses of ANP because the plasma ANP level in the venous effluents of our patients during intra-arterial infusion was considerably less than the venous ANP levels during intravenous infusion reported in previous studies.
It has been shown that binding sites for ANP in platelets are down-regulated in patients with heart failure. Thus, it is possible that decreased receptor number in vascular smooth muscles resulted in attenuated forearm vasodilative response to ANP in heart failure. We examined this possibility by measuring production of cyclic GMP during ANP infusion. It has been shown that cyclic GMP is a second messenger mediating ANP-induced relaxation of vascular smooth muscle and that plasma cyclic GMP increases in proportion to the increase in plasma ANP. Fujita et al have shown in normal subjects that the magnitudes of forearm vasodilatation caused by intra-arterial ANP were related proportionally to the increases in plasma cyclic GMP in the venous effluents. The increases in plasma cyclic GMP in the venous effluents during intra-arterial infusion of ANP at the maximal dose did not differ between patients with heart failure and normal subjects. Thus, we consider that reduced binding sites for ANP were unlikely to account for attenuated forearm vasodilative response to intra-arterial ANP in patients with heart failure. Our results are consistent with those of Riegger et al in dogs with heart failure, which demonstrated that vascular response to ANP was blunted, but the production of cyclic GMP was not affected. As suggested by Riegger et al, it is possible that in heart failure there may be a defect in the intracellular mechanisms, beyond the production of cyclic GMP, that prevents the mediation of the hormonal signal into biological effect. However, it should be noted that we cannot be certain about this interpretation because the measurement of plasma cyclic GMP in the venous effluents might not be a sensitive way to assess alterations at the receptor or intracellular mechanisms. It is possible that the effects of ANP on veins might not be altered in heart failure and that increases in venous plasma cyclic GMP might have resulted from the venous effects.

Recent studies have demonstrated that there are two subpopulations of ANP receptors and that the majority of ANP receptors are not coupled to guanylate cyclase and are biologically ineffective. It is of particular interest to note that, in cultured rat vascular smooth muscle cells pre-treated with ANP, ANP binding sites were markedly reduced, but intracellular formation of cyclic GMP as stimulated by additional ANP was not altered as compared with the results in control cells. The latter results might suggest that the receptors coupled to guanylate cyclase are affected little by receptor down-regulation after exposure with ANP, whereas those not coupled to guanylate cyclase may be reduced. We speculate that the density of the receptors coupled to guanylate cyclase may not be reduced in heart failure.

In contrast to ANP, intra-arterial nitroglycerin produced comparable forearm vasodilatation in patients with heart failure and in normal subjects. Although the vasodilative effects of both ANP and nitroglycerin are mediated by the cyclic GMP–related intracellular mechanisms, ANP stimulates particulate guanylate cyclase, whereas nitroglycerin activates soluble guanylate cyclase. Thus, it is possible that a defect in heart failure may involve the intracellular process related to particulate guanylate cyclase but not the process related to soluble guanylate cyclase. The difference in the effects on venous plasma GMP between the two drugs also might have resulted from the difference in subpopulations of guanylate cyclase activated by the two drugs. In other studies, we have observed that intra-arterial infusion of sodium nitroprusside, which stimulates soluble guanylate cyclase, did not increase venous plasma cyclic GMP. Thus, it appears that venous plasma cyclic GMP may increase when the formation of cyclic GMP is catalyzed by particulate guanylate cyclase but not by soluble guanylate cyclase.

Most of our patients with heart failure showed no or mild left ventricular dilatation by echocardiogram. This finding is unusual for patients with chronic heart failure but resulted from the fact that we selected patients for study who had not been on vasodilator drugs. In many patients examined in this study, heart failure was precipitated by atrial fibrillation with rapid ventricular response with or without upper respiratory infection. Further studies are needed to examine the relevance of our results to patients with chronic heart failure and dilated left ventricle.

In summary, the results of this study indicate that direct forearm vasodilative response evoked with intra-arterial ANP was markedly attenuated in patients with heart failure as compared with that in normal subjects. The mechanisms responsible for this alteration are not clear. It is possible that attenuated vasodilative response to intra-arterial ANP might be caused by mechanisms other than down-regulation of the ANP receptors because the increases in venous plasma cyclic GMP were comparable between patients with heart failure and normal subjects.

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