Preserved Vasodilator Effect of Bradykinin in Dogs With Heart Failure

Jin Bo Su, PhD; Fabrice Barbe, PhD; Rémi Houel, MD; Thanh Tam Guyene, MD; Bertrand Crozatier, MD, PhD; Luc Hittinger, MD, PhD

Background—In heart failure (HF), vasoconstrictor systems are activated and endothelium-derived vasodilation is blunted. Bradykinin, a potent vasodilator, may play an important role in this setting. However, it is not known whether its vasodilator effect is modified in HF.

Methods and Results—Fourteen chronically instrumented dogs were studied in the control state and in pacing-induced HF (250 bpm for 3 weeks). The dose-dependent decrease in mean aortic pressure (MAP) induced by acetylcholine was significantly blunted in HF. In contrast, in both control and HF, bradykinin infusion caused similar dose-dependent decreases in MAP and increases in cardiac output (CO). This vasodilator effect of exogenous bradykinin was potentiated similarly in both states by enalaprilat, which blocks both angiotensin conversion and bradykinin degradation. For evaluating the role of endogenous bradykinin, the effects of enalaprilat were compared with those of ciprokiren, a pure renin inhibitor. In control, ciprokiren did not produce any effect. Enalaprilat, however, produced a significant decrease in MAP and a significant increase in CO, which were attributed to the inhibition of bradykinin degradation, because these effects were absent after pretreatment with Hoe 140 (a bradykinin B2 receptor antagonist). In contrast, in HF, vasodilator effects of ciprokiren were observed, but enalaprilat produced larger changes in MAP and CO, and after Hoe 140, the hemodynamic effects of enalaprilat were significantly decreased, showing the effects of endogenous bradykinin, which were similar to those measured in control.

Conclusions—In this model of HF with a blunted endothelium-derived vasodilation, the vasodilator effects of exogenous and endogenous bradykinin are preserved. These results suggest that bradykinin may play an important role in HF, in which vasoconstriction is present and endothelium-dependent vasodilation is blunted. (Circulation. 1998;98:2911-2918.)

Key Words: bradykinin ■ heart failure ■ renin ■ angiotensin ■ enzymes

Abnormalities in vasomotor tone, including enhanced vasoconstriction at rest and diminished vasodilation in response to various stimuli, occur during the development of heart failure (HF).1–6 Activations of neurohumoral systems, such as the sympathetic system and the renin-angiotensin system (RAS), contribute to the enhanced vasoconstriction. The diminished vasodilation in response to various stimuli in HF in patients and in animals is recognized as the consequence of a blunted vascular endothelial function, ie, decreased synthesis and release of endothelium-derived relaxing factors such as nitric oxide (NO) in response to various endothelium-dependent vasodilators.1–6

Bradykinin is a potent endogenous vasodilator that participates, in human coronary vessels, in the regulation of NO production7 and vasomotor control8 and is involved in the effects of ACE inhibitors, as demonstrated in isolated vessels and hearts from normal animals,9–11 in normal conscious dogs,12 in normotensive humans,13 and in animals with HF.14 Bradykinin may thus be an important vasodilator factor in HF, but there is no study that examines whether the vasodilator effects of bradykinin are altered in HF. Therefore, the present study was designed to answer this question in the pacing-induced HF model. First, the endothelial function was determined by dose-response curves of acetylcholine in both the control state (CS) and HF. Second, the hemodynamic effects of exogenous bradykinin and the influence of enalaprilat on hemodynamic effects of exogenous bradykinin were compared in both states. Finally, to assess the function of endogenous bradykinin, the effects of enalaprilat, which blocks angiotensin conversion and bradykinin degradation, were compared with and without Hoe 140 (a bradykinin B2 receptor antagonist) and with those of ciprokiren, a pure renin inhibitor.

Methods

Surgical Procedure and Instrumentation

Fourteen adult mongrel dogs were used in this study. After injection of thiopental sodium 18±2 mg/kg IV and incubation, the dog was
ventilated and anesthetized with 0.8% to 1.3% halothane mixed with air. As described previously, a thoracotomy was performed, under sterile conditions, through the fifth left intercostal space for implantation of Tygon catheters in the descending aorta and left and right atria, a micromanometer in the left ventricular (LV) cavity, an ultrasonic flowmeter around the ascending aorta, and 2 pacing leads on the right ventricular free wall. Buprenorphine hydrochloride 0.3 mg was injected subcutaneously to minimize pain after dogs had restored their autonomic respiration. Animals were given daily postoperative care. Ampicillin 1 g/d was given for 7 to 14 days. All experimental procedures were carried out in accordance with the official regulations of the French Ministry of Agriculture.

**Experimental Protocol**

All experiments were performed with the dogs in the conscious state.

In CS, experiments were performed when the dogs had fully recovered. To determine vascular endothelial function, in 5 dogs, acetylcholine was injected intravenously at doses of 0.3, 1, and 3 μg/kg. In a group of 8 dogs, after baseline data had been recorded, stepwise bradykinin infusions were performed (3, 10, and 30 ng/kg/min). After a rest period of ≥15 minutes, when the hemodynamic parameters had returned to their baseline levels, enalaprilat 1 mg/kg was injected intravenously. When a new steady state was reached, bradykinin infusions were repeated to determine the influence of enalaprilat on the hemodynamic effects of bradykinin. To examine the role of endogenous bradykinin, in 6 dogs, enalaprilat 1 mg/kg or ciprokiren 3 mg/kg was injected intravenously in random order on different days separated by 48 hours. Hemodynamic parameters were monitored for 20 minutes. The chosen dose of ciprokiren was based on a study in sodium-depleted dogs. In the same dogs, on a different day, 5 minutes after a pretreatment with Hoe 140 (10 μg/kg IV), the hemodynamic effects of enalaprilat 1 mg/kg IV were studied again.

After completion of the studies in CS, continuous right ventricular pacing was initiated (250 bpm) with a programmable miniature pacemaker placed in a pocket of a jacket on the back of the animal. Dogs were examined daily to confirm the continuous pacing and to evaluate cardiac function. After 3 weeks of right ventricular pacing, the same protocol as in CS was carried out. Experiments were performed after a 15-minute period of stabilization after the pacemaker interruption. Hemodynamic responses to acetylcholine were studied in 4 dogs. Bradykinin infusions were performed in 8 dogs in the absence and presence of enalaprilat. To analyze whether the effects of bradykinin were dependent on vascular tone, on a different day, bradykinin perfusions were performed in 5 dogs in which total peripheral resistance (TPR) was reduced by an injection of ciprokiren 1 mg/kg IV. Ciprokiren and enalaprilat were studied in 7 dogs. In these dogs, on a different day, the effects of enalaprilat were also examined in the presence of Hoe 140 10 μg/kg IV.

**Data Collection and Analysis**

Absolute values of LV pressure were obtained by calibrating the micromanometer in 37°C water against a Statham P23ID transducer (Gould Inc) before implantation. All signals were recorded on a microcomputer and analyzed with Hem v1.5 software (NOTOCORD Systems) and on a graphic recorder. TPR was calculated as (MAP–MRAP)/CO, where MAP is mean aortic pressure, MRAP is mean right atrial pressure, and CO is cardiac output. LV stroke volume was calculated as CO×heart rate.

**Plasma Renin Activity, Angiotensin I, and Angiotensin II Measurements**

To measure baseline plasma renin activity (PRA), angiotensin (Ang) I, and Ang II, blood samples were withdrawn from the aortic catheter before any drug injection in CS and in HF. In the subgroup in which hemodynamic effects of enalaprilat and ciprokiren were monitored for 20 minutes, blood samples were also collected 15 minutes after each drug injection. For plasma Ang I and Ang II measurements, 10 mL of blood was stored in iced EGTA-K tubes containing 0.5 mL of a mixture of inhibitors and centrifuged at 4000 rpm at 4°C for 10 minutes, and plasma samples were stored at −80°C until assay. PRA and plasma Ang I and Ang II were measured as described previously.

**Drugs**

Bradykinin was purchased from Sigma Chemical Co. Enalaprilat was a generous gift of Dr Sweet (Merck Sharp & Dohme Ltd, West Point, Pa), and ciprokiren (chemical formula: (S)-2-benzyloxy-N-((S)-1-(1S,2R,3S)-1-cyclohexylmethyl-3-cyclopropyl-2,3-dihydroxy-propylcarbamoyl)-2-(imidazol-4-yl)-ethyl)-3-[1-methyl-1-(morpholin-4-ylcarbonyl)-ethylsulfonyl methyl]-propionamide) was a generous gift of Dr Clozel (F. Hoffmann–La Roche Ltd, Basel, Switzerland).

**Statistical Analysis**

ANOVA was performed with SuperANOVA software (V1.11, Abacus Concepts Inc). Values are presented as mean±SEM. A 1-way ANOVA was used for intragroup interactions. When a significant trend was found by ANOVA, comparisons with baseline were performed using the contrasts. A 2-way ANOVA of repeated measurements for the same parameters over time was used to study intergroup interactions. When a significant trend was found by ANOVA, comparisons between means were performed by the Student-Newman-Keuls method. When only 2 means were compared, an appropriate t test was used. A value of P<0.05 was considered statistically significant.

**Results**

**Baseline Hemodynamics, PRA, and Ang I and Ang II Concentrations**

The HF state was characterized by exertional dyspnea, ascites, and significant hemodynamic changes (Figure 1). In HF, after a 15-minute interruption of the pacemaker, spontaneous heart rate was higher, mean right atrial pressure (from 0.7±0.4 mm Hg in CS to 5.9±1.0 mm Hg in HF, P<0.001) and LV filling pressure were increased, and MAP, LV dP/dt max, CO, and LV stroke volume were decreased compared with those in CS (all P<0.001). TPR was increased in HF (from 46±3 mm Hg·L−1·min−1 in CS to 60±5 mm Hg·L−1·min−1 in HF, P<0.01).

In HF, baseline PRA and Ang I and Ang II concentrations were increased from 0.7±0.1 ng·mL−1·h−1, 4.9±0.8 pg/mL, and 2.7±0.4 pg/mL in CS to 4.4±1.3 ng·mL−1·h−1, 40.7±10.3 pg/mL, and 17.7±3.2 pg/mL, respectively (all P<0.02).

**Hemodynamic Effects of Acetylcholine in CS and in HF**

In HF, the vasodilator effects of acetylcholine were significantly blunted with regard to the measured parameters (Figure 2), indicating an impaired vascular endothelial function.

**Hemodynamic Effects of Bradykinin in CS and in HF**

In both CS and HF, bradykinin infusion produced a dose-dependent decrease in MAP and a dose-dependent increase in CO (Table 1). The reduction in MAP was similar in both states (Figure 3). During bradykinin infusion, heart rate increased significantly in both states, but the magnitude was smaller in HF than in CS. Bradykinin did not produce significant changes in stroke volume in CS, whereas it increased stroke volume significantly in HF (Table 1). When changes in TPR induced by bradykinin (30 μg/min) were
plotted against corresponding baseline TPR, there was a linear correlation between these parameters. Changes in TPR induced by bradykinin in CS, HF, and HF with reduced TPR after ciprokiren fell on the same line. A significant linear correlation was also found between changes in MAP induced by bradykinin and baseline TPR ($y = -0.25x - 0.02$, $r = 0.54$, $P < 0.02$). This indicates that the effect of bradykinin is dependent on vasomotor tone and that the response to bradykinin is preserved in HF (Figure 4).

**Influences of Enalaprilat on Hemodynamic Effects of Bradykinin in CS and in HF**

After pretreatment with enalaprilat, the pressure-lowering effect of bradykinin was significantly enhanced in both CS and HF (Table 2, Figure 3). For example, 3 μg/min of bradykinin after pretreatment with enalaprilat produced a decrease in MAP equal to that induced by 30 μg/min of bradykinin in the absence of enalaprilat (Figure 3). The magnitude of the potentiation was similar in both CS and HF.

**Functional Role of Endogenous Bradykinin**

To evaluate the functional role of endogenous bradykinin, the effects of enalaprilat, which blocks both angiotensin conversion and bradykinin degradation, were compared with those of ciprokiren, a renin inhibitor.

In CS, ciprokiren did not produce any significant changes in hemodynamic parameters (Figure 5, left), despite significant inhibition of PRA and plasma Ang I and Ang II.
TABLE 1. Hemodynamics at Baseline and During Bradykinin Infusions in the Same Conscious Dogs (n=8) in CS and After Induction of HF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CS Baseline</th>
<th>B3</th>
<th>B10</th>
<th>B30</th>
<th>HF Baseline</th>
<th>B3</th>
<th>B10</th>
<th>B30</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>97.8±2.6</td>
<td>94.4±2.9</td>
<td>91.9±3.8</td>
<td>85.6±4.3</td>
<td>82.2±2.2</td>
<td>78.3±2.6</td>
<td>71.7±2.8</td>
<td>66.9±2.3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>102.7±5.3</td>
<td>120.7±5.1†</td>
<td>145.3±8.6</td>
<td>165.7±9.4</td>
<td>129.0±6.2</td>
<td>134.4±5.4</td>
<td>146.1±5.7</td>
<td>153.6±5.7†</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>11.6±1.2</td>
<td>10.9±1.6</td>
<td>10.9±2.7</td>
<td>11.0±3.1</td>
<td>32.2±2.1</td>
<td>29.9±1.8</td>
<td>28.3±2.6</td>
<td>28.5±2.5†</td>
</tr>
<tr>
<td>LV systolic pressure, mm Hg</td>
<td>123.5±3.1</td>
<td>119.4±3.6</td>
<td>117.8±4.4</td>
<td>115.4±4.2°</td>
<td>101.3±2.5°</td>
<td>97.2±2.4</td>
<td>91.3±2.7</td>
<td>87.7±3.0°</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>0.9±0.7</td>
<td>0.7±0.8</td>
<td>1.9±1.9</td>
<td>1.3±2.0</td>
<td>4.7±0.9°</td>
<td>4.9±0.9</td>
<td>5.6±1.0</td>
<td>6.5±1.3</td>
</tr>
<tr>
<td>LV dP/dt max, mm Hg/s</td>
<td>2981±150</td>
<td>3211±180°</td>
<td>3635±254†</td>
<td>4145±239†</td>
<td>1448±72‡</td>
<td>1442±65</td>
<td>1526±74</td>
<td>1627±62†</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>1.96±0.16</td>
<td>2.24±0.19</td>
<td>2.71±0.22†</td>
<td>3.17±0.28†</td>
<td>1.43±0.18‡</td>
<td>1.55±0.20</td>
<td>1.95±0.20</td>
<td>2.41±0.19‡</td>
</tr>
<tr>
<td>TPR, mm Hg·L⁻¹·min⁻¹</td>
<td>50±3</td>
<td>42±3</td>
<td>34±2†</td>
<td>27±1†</td>
<td>60±7</td>
<td>52±6</td>
<td>36±4†</td>
<td>26±1†</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>19.6±2.0</td>
<td>19.0±2.0</td>
<td>19.2±1.8</td>
<td>19.4±1.8</td>
<td>11.1±1.3†</td>
<td>11.5±1.3</td>
<td>13.4±1.3*</td>
<td>15.8±1.3†</td>
</tr>
</tbody>
</table>

B3, B10, and B30 indicate 3, 10, and 30 μg/min of bradykinin, respectively.

*P<0.05 and †P<0.01 vs corresponding baseline values. ‡P<0.01 vs baseline values in CS.

concentrations (Table 3), suggesting that the RAS plays a minimal role in the regulation of vascular tone in this state. In HF, ciprokiren significantly decreased MAP and significantly increased CO (Figure 5, left), showing the activation of the RAS. In both states, PRA was nearly completely inhibited by ciprokiren, and plasma Ang I and Ang II concentrations were reduced (Table 3), suggesting that the RAS plays a minimal role in the regulation of vascular tone in this state. In HF, ciprokiren significantly decreased MAP and significantly increased CO (Figure 5, left), showing the activation of the RAS. In both states, PRA was nearly completely inhibited by ciprokiren, and plasma Ang I and Ang II concentrations were reduced (Table 3).

In contrast with ciprokiren, in CS, enalaprilat produced a significant decrease in MAP and a significant increase in heart rate, CO, and LV dP/dt max, with an unchanged stroke volume (Figure 5, right). In HF, the pressure-lowering effect of enalaprilat was significantly larger than in CS (P<0.05) and larger than that induced by ciprokiren in the same state (P<0.05). In both states, enalaprilat increased PRA and plasma Ang I but decreased plasma Ang II to levels similar to those produced by ciprokiren (Table 3). The difference between the effects of enalaprilat and ciprokiren on MAP and on CO, which is probably related to endogenous bradykinin, was similar in CS and in HF (Figure 6).

**Hemodynamic Effects of Enalaprilat in the Presence of Hoe 140 in CS and in HF**

To verify that the difference between the effect of ciprokiren and enalaprilat was due to endogenous bradykinin, Hoe 140 was injected intravenously. In both CS and HF, injection of Hoe 140 10 μg/kg did not produce any significant hemodynamic change (Table 4), suggesting an unchanged baseline endogenous bradykinin.

In CS, in the presence of Hoe 140, enalaprilat did not produce any significant change in hemodynamics (Figure 7, left). In HF, after pretreatment with Hoe 140, the hemodynamic effects of enalaprilat were significantly smaller than those in the absence of Hoe 140, with a smaller reduction in
MAP and smaller increase in CO and stroke volume (Figure 7, right). The effects of endogenous bradykinin were apparent, as indicated by the difference between the effects of enalaprilat in the absence and presence of Hoe 140 (Figure 8). These effects were not only preserved but even increased in HF when MAP was considered (P<0.05; Figure 8, top) but were similar for CO in both CS and HF (Figure 8, bottom).

Discussion

The present study shows that in HF, despite an impaired vascular endothelial function, the vasodilator effects of exogenous bradykinin are preserved, as indicated by similar MAP changes and by a linear relationship between the changes in MAP and in TPR induced by bradykinin and baseline TPR in both CS and HF. Enalaprilat similarly potentiates the pressure-lowering effect of bradykinin in both CS and HF. In HF, the vasodilator effect of endogenous bradykinin (evaluated by the difference between the effects of enalaprilat and ciprokiren and that of enalaprilat in the absence and presence of Hoe 140) is similar to that in CS.

Characterization of the Model

Chronic ventricular tachycardia–induced HF is a well-established HF model that shares many of the characteristics of human dilated cardiomyopathy.16–20 In the present study, most of these characteristics were observed.

In our preparation, in CS, there was no apparent activation of the RAS, as shown by the absence of vasodilator effect of the renin inhibitor ciprokiren, which is in accordance with a previous study in normotensive subjects.11 After induction of HF, an increased contribution of the RAS in the control of arterial vascular tone was apparent, as suggested by increased levels of PRA, Ang I, and Ang II and by increased vasodilator effects of ciprokiren.

In agreement with previous studies in patients with HF,2,4,7 an impaired endothelium-mediated vasodilation with an im-
TABLE 3. Baseline PRA, Ang I and Ang II Concentrations, and Changes Induced by Enalaprilat or Ciprokiren Injections in Conscious Dogs in CS and HF

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline</th>
<th>Enalaprilat 1 mg/kg</th>
<th>Ciprokiren 3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA, ng · ml⁻¹ · h⁻¹</td>
<td>CS</td>
<td>6</td>
<td>0.6±0.1</td>
<td>159±92</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>7</td>
<td>5.5±2.4</td>
<td>224±53†</td>
</tr>
<tr>
<td>Ang I, pg/mL</td>
<td>CS</td>
<td>6</td>
<td>4.8±1.1</td>
<td>259±66†</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>7</td>
<td>49±20₉</td>
<td>327±70†</td>
</tr>
<tr>
<td>Ang II, pg/mL</td>
<td>CS</td>
<td>6</td>
<td>2.4±0.5</td>
<td>-83±8†</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>7</td>
<td>17±5†</td>
<td>-93±2†</td>
</tr>
</tbody>
</table>

* and †, Increase or decrease is statistically significant at P<0.02 and P<0.005 levels vs corresponding baseline values.

Role of Exogenous and Endogenous Bradykinin in HF

A major new finding of the present study is that, in contrast with acetylcholine, vasodilator effects of exogenous bradykinin were preserved in HF and that these effects were dependent on the vasomotor tone (Figure 3 and 4). It is worth noting that, in association with similar decreases in MAP, exogenous bradykinin increased CO similarly in both CS and HF. However, the increased CO induced by bradykinin in CS was due in large part to the increased heart rate, because calculated stroke volume was not modified. In contrast, stroke volume increased significantly during bradykinin infusion in HF, suggesting an improved cardiac function. The small increase in LV dP/dtmax after bradykinin infusion (Table 1) may have been due to the increased heart rate and/or to an increased sympathetic stimulation secondary to bradykinin-induced vasodilation. This increase in sympathetic tone may have modified CO and thus TPR. However, the fall in aortic pressure induced by bradykinin in the failing dogs demonstrates a preserved response to this agent.

The preserved response to bradykinin suggests that, in addition to the NO pathway, the vasodilator action of bradykinin may be also mediated by other substances, such as prostaglandins and a nonidentified endothelium-dependent hyperpolarizing factor,10,22 or substances that are not endothelium dependent, such as nonendothelial vasodilator prostanooids.23,24 Hyperpolarizing factor may not be an important primary mediator of endothelium-dependent relaxation in most normal blood vessels, but it appears to back up or enhance the relaxing action of NO. When NO synthesis is inhibited and in this case only, high potassium concentration can affect the cGMP-independent hyperpolarizing and relaxing effect of bradykinin.25 This suggests that hyperpolarizing factor may take over when the NO pathway is impaired. Another possibility is that NO could inhibit the formation or action of hyperpolarizing factor, and the blunted NO production in HF may suppress this inhibition.26 However, these hypotheses remain to be demonstrated.

Another important finding of the present study is that in HF and in CS, enalaprilat potentiated the vasodilator effect of bradykinin to a similar extent. Although the potentiation of the vasodilator effect of bradykinin has been observed in HF,14 the present study shows for the first time that the potentiation of the vasodilator effect of bradykinin induced by enalaprilat is unchanged after induction of HF (Figure 3). The vasodilator role of endogenous bradykinin was confirmed by comparing the effects of ciprokiren, which affects only the RAS, with those of enalaprilat, which affects both the RAS and bradykinin degradation.27,28 (Figure 6). The local accumulation of bradykinin contributes to the vasodilator effect of enalaprilat, because our data also show that a specific bradykinin B₂ receptor antagonist, Hoe 140, markedly reduced the effects of enalaprilat in both CS and HF (Figure 7). In addition, enalaprilat increased CO and stroke volume in HF, but the increased CO and stroke volume were prevented by Hoe 140, demonstrating the role of endogenous bradykinin in the improvement of cardiac function in this setting. The preserved effect of Hoe 140 on the effect of
enalaprilat in HF also suggests a preserved role of endogenous bradykinin.

The preserved hemodynamic effects of bradykinin in HF may be explained by a preserved response of bradykinin B₂ receptors to bradykinin in HF, and the similar potentiation of the vasodilator effect of bradykinin by enalaprilat in both CS and HF suggests a preserved function of ACE in the degradation of bradykinin in this model. However, our preparation did not allow us to examine the cellular mechanisms, but whatever the underlying mechanisms are, the present study shows a preserved vasodilator effect of exogenous bradykinin in HF, despite an impaired vascular endothelial function, and a beneficial role of endogenous bradykinin.

**TABLE 4. Baseline Hemodynamics Before and After Hoe 140 Injection (10 μg/kg IV) in CS and HF**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CS Control (n=6)</th>
<th>Hoe 140 (n=6)</th>
<th>HF Control (n=7)</th>
<th>Hoe 140 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>104.5±6.4</td>
<td>104.5±6.5</td>
<td>129.3±3.4*</td>
<td>132.8±2.9</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>103.8±3.0</td>
<td>105.2±3.8</td>
<td>86.9±1.8†</td>
<td>87.8±1.7</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>4.6±1.4</td>
<td>5.2±1.6</td>
<td>27.5±2.0†</td>
<td>26.4±2.3</td>
</tr>
<tr>
<td>LV systolic pressure, mm Hg</td>
<td>123.3±3.2</td>
<td>124.8±4.2</td>
<td>102.8±2.1†</td>
<td>102.6±1.9</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>−0.3±0.4</td>
<td>−0.1±0.4</td>
<td>10.1±1.0†</td>
<td>10.0±1.3</td>
</tr>
<tr>
<td>LV dP/dtₑₑₑₑₑₑ, mm Hg/s</td>
<td>2390±204</td>
<td>2994±238</td>
<td>1420±72‡</td>
<td>1400±78</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>2.75±0.30</td>
<td>2.74±0.31</td>
<td>1.41±0.18†</td>
<td>1.37±0.18</td>
</tr>
<tr>
<td>TPR, mm Hg · L⁻¹ · min⁻¹</td>
<td>42±4</td>
<td>41±4</td>
<td>61±7*</td>
<td>61±8</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>26.4±2.5</td>
<td>26.3±2.5</td>
<td>10.7±1.5†</td>
<td>10.3±1.5</td>
</tr>
</tbody>
</table>

*P<0.05 and †P<0.005 vs control values obtained in CS. In HF as well as CS, Hoe 140 injection did not produce significant hemodynamic changes.

**Figure 7.** Hemodynamic effects of enalaprilat 1 mg/kg in absence and presence of Hoe 140 in control state (left) and in HF (right). △ indicates change. Abbreviations as in Figure 1. *P<0.05 and †P<0.01 vs baseline values. P value in each graph is P value obtained by ANOVA for comparison between effects of enalaprilat in absence and presence of Hoe140.

**Figure 8.** Evaluation of effect of endogenous bradykinin by difference between effects of enalaprilat in absence and presence of Hoe 140 in control state and in HF. Difference (△) was obtained by subtracting changes induced by enalaprilat in presence of Hoe 140 from changes induced by enalaprilat in absence of Hoe 140. This difference was larger after induction of HF than in control state when MAP was considered (ANOVA, P<0.05) but was not significantly different for CO.
Clinical Implications
In HF, enhanced vasoconstriction due to the activation of vasoconstrictor systems increases the workload of the failing heart. The presence of a blunted production or release of NO, a major endothelium-derived relaxing factor, may worsen the vasoconstriction and thus HF. The preserved vasodilator effect of exogenous and endogenous bradykinin suggests that bradykinin remains a potent vasodilator agent in HF. However, because in the phase of HF that we studied, the response to endothelium-independent dilators, such as nitroprusside and nitroglycerin, is normal, as shown by previous studies, the results may be different in the late phase of HF, in which the response of smooth muscle cells to endothelium-independent dilators is also abnormal. Also, because the present study examined the effects of short-term exogenous bradykinin and the effects of endogenous bradykinin through short-term enalaprilat and Hoe 140, these results may not be directly extended to the situation of the chronic stimulation of the bradykinin system. In addition, in some cases, an excessive production of bradykinin may not be well tolerated and may induce an excessive hypotension in patients during therapy with ACE inhibitors. Conversely, improved cardiac function in response to exogenous bradykinin and to enalaprilat suggests that, in addition to the inhibition of the vasoconstrictor systems, adequate stimulation of an endogenous vasodilator, such as bradykinin, may be useful in the management of HF.

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