Evidence for a direct renal stimulating effect of prostaglandin E\textsubscript{2} on renin release in patients with congestive heart failure

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ABSTRACT The reduced responsiveness of the renin-angiotensin system to hemodynamic changes in patients with congestive heart failure (CHF) could be due to a defect of the juxtaglomerular apparatus. To test this hypothesis, the responses to viprostol, an analog of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) that is known to stimulate both the macula densa and the juxtaglomerular cells, and to nitroprusside were compared in patients with CHF. An average fall in mean arterial pressure (MAP) of 6 mm Hg with viprostol was associated with a fivefold increase in plasma renin activity (PRA) from 11.4 ± 6.4 to 47.9 ± 31.0 ng/ml/hr; in contrast PRA did not change with nitroprusside, despite a significant decrease in preload and an average decrease in MAP of 16 mm Hg. These data demonstrate that (1) the renin-angiotensin system could be activated by PGE\textsubscript{2} in patients with CHF, (2) this activation is not related to the global hemodynamic changes induced by PGE\textsubscript{2}, and (3) the previously reported unresponsiveness of the renin-angiotensin system in patients with CHF cannot be attributed to a defective response of the juxtaglomerular apparatus.

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THE RESPONSE of the renin-angiotensin system to a decrease in arterial pressure and/or intracardiac pressures in patients with congestive heart failure is abnormally attenuated.\textsuperscript{1} This abnormality has been attributed to a decrease in reflex response of the pressoreceptors to hemodynamic changes.\textsuperscript{2,3} However, to our knowledge no attempts have been made to assess whether in patients with congestive heart failure the response of the juxtaglomerular cells and the macula densa is intact and whether an elevated baseline plasma renin activity could inhibit further activation of the renin-angiotensin system. The present study was undertaken to evaluate in patients with congestive heart failure the effect on the renin-angiotensin system of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}), since prostaglandins have been shown to stimulate renin release through a direct effect on the juxtaglomerular cells\textsuperscript{4} and on the macula densa.\textsuperscript{5,6} The effects on the renin system of a synthetic analog of PGE\textsubscript{2}, viprostol [methyl ester of (±)-15-deoxy-16-hydroxy-16(α/β)-vinyl PGE\textsubscript{2}, American Cyanamid Company], in normal subjects and in patients with severe heart failure were compared. To evaluate the effect on renin release of concomitant hemodynamic changes the effects of viprostol and nitroprusside, a vasodilator with no known direct effect on the macula densa and juxtaglomerular cells,\textsuperscript{7} were compared in the same group of patients with congestive heart failure.

Methods

Study population. Nine subjects (four women and five men, mean age 50 years, range 22 to 64) with chronic heart failure were evaluated. The diagnosis was established clinically by a history of dyspnea and/or exercise intolerance, the presence of a third heart sound, pulmonary rales, jugular venous distention, or peripheral edema, and radiologic evidence of an increase in cardiac size and pulmonary vascular congestion. Heart failure was due to coronary artery disease (documented myocardial infarction or/and angiographically proven significant coronary artery disease) in four patients and to primary cardiomyopathy in five. The diagnosis of primary cardiomyopathy was made when no other cause of heart failure could be demonstrated. Patients with an acute myocardial infarction within the previous 3 months, angina pectoris, arterial hypertension, or primary valvular or pulmonary disease were excluded. By New York Heart Association classification four patients were in functional class III and five were considered to be in class IV. Vasodilator drugs were discontinued at least 72 hr before the study. Patients were maintained on daily digoxin and antiarrhythmic therapy and diuretic drugs were omitted only on the day of the study. Each patient was in stable condition on a sodium-restricted diet when the study began.

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A preliminary dose-finding study was carried out in six healthy normal volunteers (mean age 45 ± 11 years) recruited from the University Hospital staff through advertisements in the University newspaper. A medical history was obtained from each volunteer. Physical examination, 12-lead electrocardiography, and complete hematologic and blood chemistry tests were performed before enrollment. None of the patients or normal volunteers had received drugs that inhibit prostaglandin synthesis during the 2 weeks preceding the study.

The protocol was approved by the Committee on the Use of Human Subjects in Research of the University of Minnesota. Written informed consent was obtained from each subject before they entered the study.

**Procedures.** In each patient with congestive heart failure a No. 7F thermodilution Swan-Ganz flow-directed balloon-tipped catheter was inserted percutaneously under local anesthesia by way of an antecubital or internal jugular vein and advanced into the pulmonary artery for measurement of right atrial, pulmonary arterial, and capillary wedge pressures. Systemic arterial pressure was measured directly with a short Teflon needle inserted into the brachial artery. Pressures were measured with Statham P23Db pressure transducers connected to a Hewlett-Packard multichannel recorder. The midaxillary line was used as a zero reference level. Mean pressures were obtained by electronic damping. Cardiac output was measured in triplicate by the thermodilution technique. Heart rate was monitored continuously during the study from an electrocardiographic lead.

Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and pulmonary arteriolar resistance (PAR) (dyne·sec·cm⁻⁵) were calculated from the following formulas:

\[
SVR = \frac{(MAP - RAP)}{CO} \times 80
\]

\[
PVR = \frac{MPP}{CO} \times 80
\]

\[
PAR = \frac{(MPP - PWP)}{CO} \times 80
\]

where MAP = mean systemic arterial pressure; RAP = mean right atrial pressure; MPP = mean pulmonary pressure; PWP = pulmonary wedge pressure (in mm Hg); CO = cardiac output (in liters/min).

Central venous blood samples were obtained for the measurement of plasma renin activity (PRA) by radioimmunoassay and of plasma norepinephrine (PNE) by radioenzymatic assay.

In normal volunteers systemic arterial pressure was measured directly through a short Teflon needle inserted into the brachial artery; heart rate was monitored through an electrocardiographic lead. Cardiac output was determined by the carbon dioxide rebreathing method. Blood samples for the measurement of PNE and PRA were obtained through a peripheral venous cannula. The same cannula was used for the administration of PG E₂.

**Protocol.** The study was initiated in the morning after an overnight fast. Baseline supine measurements were obtained in duplicate at least 60 min after positioning of the catheters. After hemodynamic and hormonal control measurements were obtained, viprostol [methyl ester of (±) -15-deoxy-16-hydroxy-16α/β-vinyl PGE₂, American Cyanamid Company] was given intravenously over a 5-min period to normal volunteers beginning at a dose of 10 ng/kg and increasing to 30, 100, 300, and 1000 ng/kg every 30 min until a maximum dosage of 1000 ng/kg was administered and/or mean arterial pressure fell more than 15% or no further hemodynamic change was observed. If hemodynamic measurements did not return to the baseline levels within 30 min the next dose of viprostol was postponed until this occurred. The 10 ng/kg dose was hemodynamically ineffective in all normal subjects; therefore, dosing in patients with congestive heart failure was started at 30 ng/kg. After the last dose of viprostol both patients and normal volunteers were monitored for at least 2 additional hours. Six of the patients with congestive heart failure also received an infusion of sodium nitroprusside (Nipride, Hoffmann-La Roche, Inc.). This infusion was initiated at least 2 hr after the last dose of viprostol and after hemodynamic measurements had returned to control levels. Nitroprusside was infused into a peripheral vein by an IVAC infusion pump starting at a dose of 10 μg/min with increases of 10 μg/min every 10 min until mean arterial pressure decreased by 15%.

The electrocardiogram and pressures were monitored continuously throughout the study; cardiac output was measured 10 and 30 min after each dose of viprostol and during each dose of nitroprusside. Blood samples for determination of PRA and PNE were obtained 10 min after each dose of viprostol, 30, 60, and 120 min after the last dose, and at 10 min during the infusion of each dose of nitroprusside.

**Data analysis.** Data are expressed as the mean value ± SD. The responses to viprostol in the normal subjects and in patients with heart failure were analyzed with the paired Student t test. The responses to nitroprusside were compared with the responses to viprostol among the patients with heart failure with use of a paired t test of the differences between peak effect and baseline values for each drug.

**Results**

The hemodynamic response to viprostol was dose related in both normal volunteers and patients with congestive heart failure. Figure 1 illustrates, in a representative patient with heart failure, the progressive increase in cardiac output and fall in mean arterial pressure with increasing doses of intravenous viprostol. In contrast, heart rate plateaued after an initial increase with the lower doses. In normal volunteers the maximum dose administered was 300 ng/kg in two and 1000 ng/kg in four subjects. Six patients with congestive heart failure received a maximum dose of 1000 ng/kg, and two received 300 ng/kg, whereas one patient received only 30 ng/kg because he experienced abdominal pain after this dose. A peak hemodynamic effect was observed 10 min after each dose of vipros-
tol, with return of hemodynamics to the baseline level usually within 30 min. The hemodynamic responses noted in both groups with the maximal administered dose of viprostol are reported in table 1. Viprostol produced a significant decrease in mean arterial pressure and systemic vascular resistance and a significant increase in cardiac index that was exclusively due to an increase in heart rate in normal subjects. In contrast, both heart rate and stroke index increased in patients with heart failure. Left and right ventricular filling pressures were unchanged after viprostol in patients with congestive cardiac failure. Mean right atrial pressure was 11.8 ± 5.3 mm Hg at baseline and 13.0 ± 3.9 mm Hg after viprostol; mean pulmonary capillary wedge pressure was 28.0 ± 4.2 mm Hg before and 28.0 ± 7.8 mm Hg after viprostol.

PNE rose from 268 ± 110 to 622 ± 110 pg/ml (p < .01) in normal subjects and from 848 ± 733 to 1150 ± 863 pg/ml (NS) in patients with heart failure. PRA rose from 1.6 ± 0.6 to 15.2 ± 13.5 ng/ml/hr (p < .05) in the control group and from 9.6 ± 6.4 to 46.5 ± 37.9 ng/ml/hr (p < .01) in the heart failure group. PRA increased in each subject in the two groups (figure 2).

Six patients with congestive heart failure received both nitroprusside and viprostol (table 2). The hemodynamic response to nitroprusside differed from that to viprostol in that nitroprusside reduced the pulmonary capillary wedge pressure and the right atrial pressure whereas viprostol did not and in that viprostol produced tachycardia whereas nitroprusside did not. A fall in mean arterial pressure averaging 16 mm Hg in response to nitroprusside was accompanied by an unchanged PRA. A fall in mean arterial pressure averaging 6 mm Hg in response to viprostol was accompanied by a fivefold increase in PRA.

The administration of viprostol produced abdominal discomfort and nausea in each subject in this study. In only one patient with congestive heart failure were these symptoms severe enough to preclude the administration of a higher dose of the drug.

Discussion

Although the renin-angiotensin system is often activated in patients with severe congestive heart failure, the responsiveness of this system to hemodynamic changes may be impaired. Orthostatic tilt, which consistently stimulates renin and sympathetic activity in

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**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>SVR (dynes-sec-cm⁻¹)</th>
<th>PNE (pg/ml)</th>
<th>PRA (ng/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>66 ± 17</td>
<td>93 ± 8</td>
<td>2.8 ± 0.7</td>
<td>1540 ± 310</td>
<td>268 ± 110</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>V</td>
<td>99 ± 18     †</td>
<td>70 ± 9      †</td>
<td>4.6 ± 0.6     †</td>
<td>664 ± 71             †</td>
<td>622 ± 110     †</td>
<td>16.2 ± 13.5  †</td>
</tr>
<tr>
<td>CHF (n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87 ± 16</td>
<td>82 ± 6</td>
<td>1.8 ± 0.4</td>
<td>1797 ± 514</td>
<td>848 ± 733</td>
<td>9.6 ± 6.4</td>
</tr>
<tr>
<td>V</td>
<td>96 ± 17    ‡</td>
<td>74 ± 10     ‡</td>
<td>2.5 ± 0.6     ‡</td>
<td>1120 ± 360           ‡</td>
<td>1150 ± 863</td>
<td>46.5 ± 37.9   ‡</td>
</tr>
</tbody>
</table>

Mean values ± SD.

HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; SVR = systemic vascular resistance.

†p < .01; ‡p < .05.

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**FIGURE 2.** Individual responses of PRA in nine patients with congestive heart failure given viprostol. C = control values; V = values obtained during administration of viprostol. In each patient PRA increased after V. The closed circles connected by a dotted line indicate the mean values for the entire group.
normal subjects, does not increase PRA or consistently increase PNE in patients with heart failure. The apparent abolition of the neurohumoral response to orthostasis in heart failure suggests an abnormality of the low-pressure mechanoreceptors. Abnormal structure and function of these receptors have been demonstrated in experimental heart failure and appear to be normalized after reversal of heart failure. The reflex sympathetic response to tilt has been shown to improve in patients with congestive failure after converting enzyme inhibition, suggesting that the autonomic changes are not irreversible.

Hypotensive stimuli may activate the sympathetic nervous system through stimulation of the aortic and carotid baroreceptors. Response of the renin-angiotensin system in this situation could either relate to the renin-stimulating effect of adrenergic discharge to the kidney or to a direct effect on renal baroreceptors and/or macula densa. The hypotensive response to the infusion of nitroprusside is a potent stimulus to increase PRA and PNE in normal subjects, but in patients with heart failure PNE does not consistently increase and the rise in PRA is only modest. The slight increase in PRA without an increase in PNE in response to the administration of a vasodilator in patients with heart failure therefore has suggested the possibility that direct renal mechanisms are intact, whereas central reflex mechanisms are impaired. Since prostaglandins have been shown to stimulate renin release through a direct effect on both the macula densa and juxtaglomerular cells, we have used a synthetic analog of PGE, nitroprusside, in this study to test whether an abnormal responsiveness of the juxtaglomerular apparatus could be responsible for the subnormal response of the renin-angiotensin system to hemodynamic changes in patients with congestive heart failure. The effect of prostaglandin was compared with that of nitroprusside, which has no direct effect on the macula densa and juxtaglomerular cells. Nitroprusside did not stimulate PRA at all in these patients, despite a greater fall in arterial pressure and a marked decrease in preload. The decrease in arterial pressure with nitroprusside should have promoted a reflex increase in plasma renin by stimulating both central and intrarenal baroreceptors. In contrast, the increase in the afferent arteriolar radius resulting from PGE,-induced renal vasodilation would be expected, in the absence of significant hypotension, to increase wall tension and thus decrease the release of renin.

Our data suggest that a nonhemodynamic mechanism is operative in determining the response of the renin-angiotensin system to PGE and indicate that juxtaglomerular mechanisms suberving renin release are intact in patients with heart failure. Despite the elevated basal level of PRA in patients with congestive heart failure, PGE produced a striking further abrupt rise in PRA, suggesting that in these patients the decreased responsiveness of the renin-angiotensin system to orthostasis and vasodilation could not be attributed to its maximal stimulation at baseline. Although

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>NP</th>
<th>B2</th>
<th>V</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>93 ± 27</td>
<td>87 ± 17</td>
<td>89 ± 18</td>
<td>98 ± 18</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>83 ± 7.0</td>
<td>67 ± 2.6</td>
<td>82 ± 7.9</td>
<td>76 ± 8.9</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>mrap (mm Hg)</td>
<td>10.5 ± 4.0</td>
<td>5.0 ± 2.7</td>
<td>11.6 ± 6.7</td>
<td>11.5 ± 4.8</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>MPP (mm Hg)</td>
<td>44 ± 7.0</td>
<td>29.8 ± 6.9</td>
<td>43.1 ± 8.4</td>
<td>45.5 ± 7.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>29.5 ± 3.1</td>
<td>18.1 ± 6.0</td>
<td>27.1 ± 5.0</td>
<td>29.6 ± 8.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>CI (1/min/m²)</td>
<td>1.99 ± 0.38</td>
<td>3.03 ± 0.44</td>
<td>1.99 ± 0.36</td>
<td>2.62 ± 0.62</td>
<td>NS</td>
</tr>
<tr>
<td>SVR (dynes-sec-cm⁻²)</td>
<td>1724 ± 533</td>
<td>957 ± 239</td>
<td>1647 ± 504</td>
<td>1182 ± 407</td>
<td>NS</td>
</tr>
<tr>
<td>PVR (dynes-sec-cm⁻²)</td>
<td>1066 ± 442</td>
<td>460 ± 173</td>
<td>1038 ± 473</td>
<td>818 ± 337</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>PAR (dynes-sec-cm⁻²)</td>
<td>366 ± 232</td>
<td>180 ± 81</td>
<td>390 ± 245</td>
<td>279 ± 190</td>
<td>NS</td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>876 ± 720</td>
<td>732 ± 586</td>
<td>912 ± 911</td>
<td>1077 ± 1071</td>
<td>NS</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>15.5 ± 11.7</td>
<td>12.2 ± 5.0</td>
<td>11.4 ± 6.4</td>
<td>47.9 ± 31.0</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Mean values ± SD.

B1 indicates control values obtained before administration of nitroprusside.

B2 indicates control values obtained before administration of viprostol.

HR = heart rate; MAP = mean arterial pressure; mrap = mean right arterial pressure; MPP = mean pulmonary pressure; PCW = pulmonary capillary wedge; CI = cardiac index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; PAR = pulmonary arteriolar resistance.

*p values determined for the differences between (B1-NP) vs (B2-V).
the mechanism stimulating renin release in heart failure remains uncertain, the present data combined with previous studies allow for some speculation. The previously described poor correlation between PNE and PRA in heart failure and the unresponsiveness of the renin-angiotensin system to orthostasis and hypotension suggest that the sympathetic nervous system and the central and renal baroreceptors may not be involved in the renin stimulation. In contrast, the striking renin response to furosemide and PGE2 and the previous report of a correlation between prostaglandin metabolites and plasma renin in heart failure suggest that local renal stimulation at the level of the macula densa and/or juxtaglomerular cells, perhaps through prostaglandins, may be an important contributor to the release of renin in the presence of heart failure. This hypothesis, if proved correct, may reconcile the findings of high baseline renin levels and reduced responsiveness of the renin-angiotensin system to hemodynamic changes in patients with congestive failure. The increase in PRA after PGE2 was significant in both normal subjects and patients with heart failure. However, due to the limited number of observations and differences in baseline levels of renin our data did not allow us to assess whether the response of the renin-angiotensin system to PGE2 was quantitatively different in the two groups.

Another observation in this study was that the arterial dilating effect of prostaglandin was not accompanied by a fall in left and right ventricular filling pressures as is consistently noted in response to sodium nitroprusside. The most likely explanation for this finding is that PGE2 does not exert a venodilating effect, which is a prominent pharmacologic effect of nitroprusside. However, the possibility that the rise in PRA exerts a vasoconstrictor effect that counteracts the vasodilating effect of viprostatol must be considered. The absence of a fall in pulmonary arterial pressure and the modest fall in arterial pressure in response to these infusions of viprostatol could be consistent with an angiotensin-mediated inhibition of the vascular actions of prostaglandin. Consistent with this hypothesis is our recent observation that furosemide, a known stimulator of prostaglandin synthesis and PRA, produces an acute vasoconstrictor effect that may have a deleterious hemodynamic effect in patients with severe heart failure.

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