Differential Actions of Vasopeptidase Inhibition Versus Angiotensin-Converting Enzyme Inhibition on Diuretic Therapy in Experimental Congestive Heart Failure

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Background—Omapatrilat (OMA), a vasopeptidase inhibitor, simultaneously inhibits angiotensin-converting enzyme (ACE) and neutral endopeptidase, which degrades vasodilatory factors (eg, ADM) and natriuretic peptides. Based on the beneficial cardiorenal and humoral properties of the natriuretic peptides, we hypothesized that an acute vasopeptidase inhibitor with or without diuretic would result in more favorable cardiorenal and hormonal actions than ACE inhibition plus diuretic (ACEI+D) in congestive heart failure.

Methods and Results—We compared the actions of OMA alone and with diuretic (OMA+D) to ACEI+D in a model of pacing-induced congestive heart failure. OMA+D decreased pulmonary arterial and pulmonary capillary wedge pressures to a greater level than OMA alone or ACEI+D. Glomerular filtration rate was lower with ACEI+D than with either OMA group. Plasma renin activity and aldosterone immediately increased with ACEI+D, whereas OMA+D resulted in higher plasma renin activity and a delayed increase in aldosterone. OMA alone did not increase plasma renin activity and aldosterone, but resulted in a sustained increase in plasma adrenomedullin, with higher urinary atrial natriuretic peptide, adrenomedullin, and cGMP excretions than with ACEI+D.

Conclusions—Acute administration of OMA with or without diuretic results in more favorable cardiorenal and humoral responses in experimental congestive heart failure than does ACEI+D. There is no acute activation of renin and aldosterone with OMA alone such as occurs with ACEI+D and OMA+D. Thus, OMA with or without a diuretic possesses beneficial cardiorenal and humoral actions comparable to those observed with ACEI+D that can be explained by potentiation of natriuretic peptides. (Circulation. 2002;105:639-644.)

Key Words: omapatrilat ■ natriuretic peptides ■ heart failure

Omapatrilat (OMA) is a potent vasopeptidase inhibitor (VPI) with selective and competitive inhibitory activity of angiotensin-converting enzyme (ACE) and neutral endopeptidase 24.11 (NEP). Both enzymes are key regulatory enzymes involved in the control of several neuroendocrine systems. NEP inactivates vasodilatory and natriuretic peptides (NPs), including bradykinin, adrenomedullin (ADM), atrial natriuretic peptide (ANP), brain NP, and C-type NP.1–3 Because all of these peptides are rapidly activated in the early stages of congestive heart failure (CHF), inhibition of NEP would protect them from enzymatic degradation. Consequently, VPI possesses unique diuretic effects based on potentiation of the endogenous NP system together with inhibition of ACE.

The combination of ACE inhibition with diuretic (ACEI+D) is currently the first-line therapy in the management of CHF with volume overload.4 Although ACE inhibition (ACEI) reduces mortality and morbidity in patients with CHF, there is no consistent evidence for a similar beneficial effect from diuretics alone. Acute NEP inhibition enhanced sodium excretion and glomerular filtration rate (GFR) in a canine model of CHF.5 In contrast, ACE catalyzes the conversion of angiotensin I to angiotensin II (Ang II), which has antinatriuretic, vasoconstricting, and growth-enhancing actions. Hence, co-inhibition of ACE and NEP prevents degradation of vasodilatory factors (eg, ADM) and NPs and inhibits production of the vasoconstricting peptide Ang II. Thus, simultaneous inhibition of NEP and ACE with a VPI emerges as a potential therapy for CHF.

In experimental CHF, VPI enhances cardiorenal function.6 In mild CHF, VPI was superior to ACEI alone in improving cardiorenal function, and NP-receptor blockade attenuated the actions of VPI.7 Additional studies in experimental and human CHF also document beneficial hemodynamic and renal actions with OMA.8,9 In a recent clinical trial, OMA improved New York Heart Association class and reduced...
morbidity and hospitalization in symptomatic CHF compared with ACEI alone. A major finding was that OMA compared with ACEI was associated with renoprotection, with lower serum creatinine, lower blood urea nitrogen, and fewer adverse renal events. A major question to be answered is whether dual inhibition of ACE and NEP with its favorable cardiorenal effects is equivalent or superior to ACEI + D. Although the NEP inhibitory component of VPI has important renal enhancing actions, the addition of a diuretic to an ACE inhibitor could have potentially deleterious actions, such as activation of the renin-angiotensin-aldosterone system (RAAS). The present study was therefore designed to test the hypothesis that acute VPI with or without diuretic would have more favorable cardiorenal and humoral properties than ACEI + D, suggesting a new therapeutic strategy for CHF.

**Methods**

The present study was performed in accordance with the Animal Welfare Act and with approval of the Mayo Clinic Animal Care and Use Committee.

**Pacing-Induced CHF**

CHF was induced in male dogs (weight 18 to 23 kg) by rapid right ventricular pacing at 180 bpm for 10 days, which resulted in a model of CHF with a cardiorenal and neurohumoral profile that mimics mild human CHF.11

**Acute Protocol**

Dogs were anesthetized with sodium pentobarbital (15 mg/kg IV), intubated, and mechanically ventilated with oxygen at 16 cycles/min. Heart rate was maintained at 180 bpm for the entire period of the study. Dogs were instrumented and monitored for hemodynamic measurements as described previously.7

After preparation, a 60-minute equilibration period was started with an intravenous inulin bolus, followed by a continuous inulin infusion to achieve a steady-state plasma inulin concentration between 40 and 60 mg/dL. Subsequently, a 30-minute baseline clearance was performed that consisted of hemodynamic measurements, arterial blood sampling, and urine collection. After the 30-minute baseline clearance, one group (n=9) received an intravenous bolus of OMA (Bristol-Myers Squibb; 1 μmol/kg) and furosemide 40 mg administered over 20 minutes. The second group (n=7) received an intravenous bolus of the ACEI fosinoprilat (Bristol Myers Squibb; 1 μmol/kg) and furosemide 40 mg administered over 20 minutes. The third group (n=8) received an intravenous bolus of OMA 1 μmol/kg administered over 20 minutes. Because OMA and fosinoprilat have similar ACE-inhibiting potency (K_i 7.3 and 7.2, respectively), equimolar doses were chosen that would result in maximal ACE and NEP inhibition. After a 15-minute lead-in period, three 30-minute clearances were performed followed by one 60-minute clearance.

Cardiovascular parameters measured during the experiment included mean arterial pressure (MAP), right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) determined by thermodilution. Blood was collected in heparin and EDTA tubes and placed on ice. After centrifugation, plasma was stored at −20°C until analysis. Urine was collected on ice. Samples for cGMP analysis were heated to >90°C before storage.

**Hormone and Electrolyte Analysis**

After plasma extraction, plasma and urine ANP, ADM, and cGMP and plasma renin activity (PRA) were measured by radioimmunoassay.12-15 Plasma aldosterone was measured by direct microassay.16 Urinary and plasma inulin were measured by the anthrone method and electrolytes by flame spectrophotometer. GFR was determined by inulin clearance.

**Statistical Analysis**

Results are expressed as mean±SEM. Data were assessed by 1-way ANOVA for comparisons within groups followed by post hoc Dunnett tests. Two-way ANOVA was used for comparisons among groups. The Student unpaired t test was performed for single comparison between groups (GraphPad Prism software). Data are reported as absolute values. When calculated as changes from baseline, results were essentially identical. Statistical significance was accepted at P<0.05.

**Results**

**Cardiovascular Function**

No significant differences in cardiovascular parameters were observed at baseline among groups. OMA + D and OMA resulted in a transient reduction of MAP during the first 30-minute clearance that returned to baseline by the third and second clearance, respectively. When compared among groups, a greater reduction in MAP was observed with OMA + D and OMA alone than with ACEI + D (P<0.0001 and P=0.0341, respectively; Table 1). OMA + D resulted in a greater reduction in MAP than OMA alone (P=0.005).
Figure 1 illustrates PAP, PCWP, CO, and systemic vascular resistance (SVR) at baseline and after OMA+D, ACEI+D, or OMA. OMA and ACEI+D reduced PAP and PCWP compared with baseline, with no difference between these groups. However, OMA+D reduced PAP and PCWP to a greater extent than either ACEI+D or OMA alone (all \( P<0.0001 \)). CO did not change with OMA and OMA+D but significantly decreased 90 minutes after ACEI+D. The differences in CO between ACEI+D and OMA or OMA+D were significant (\( P=0.001 \) and \( P=0.002 \), respectively); there was no significant difference between OMA groups. SVR decreased 30 minutes after OMA and OMA+D and subsequently returned to baseline; there was no significant difference between OMA groups. An increase in SVR was observed 150 minutes after ACEI+D. The differences in SVR between ACEI+D and OMA+D or OMA were significant (both \( P<0.001 \)).

### Renal Function

At baseline, no differences among groups were observed. GFR tended to increase after OMA+D and OMA and to decrease with ACEI+D. The differences in GFR between ACEI+D and OMA or OMA+D were significant (\( P<0.0001 \) for both; Figure 2). Renal blood flow (RBF) and renal vascular resistance (RVR) are reported in Table 1. RBF increased and RVR decreased immediately after OMA administration. ACEI+D and OMA+D had similar but more prolonged renal hemodynamic effects. However, no differences among groups were observed in RBF and RVR. OMA alone induced a gradual but sustained increase in urine flow and sodium excretion (Figure 2). In contrast, ACEI+D and OMA+D resulted in a more rapid but less sustained response. Sodium and water excretion were approximately 3 and 5 times greater in the ACEI+D group than in the OMA+D and OMA groups, respectively (both \( P<0.0001 \); Figure 2). Compared with baseline, urinary ANP, ADM, and cGMP increased after OMA administration, whereas there were no changes in the OMA+D and ACEI+D groups (Table 2). Importantly, OMA increased urinary ANP, ADM, and cGMP excretion compared with ACEI+D (\( P<0.0001 \) for all; Table 2). Although there were no significant changes in urinary ANP and cGMP excretion compared with baseline, OMA+D resulted in a higher excretion than with ACEI+D (\( P<0.0001 \) and \( P<0.0003 \), respectively).

### Humoral Function

No differences in plasma ANP, ADM, and cGMP were observed at baseline among groups (Table 3). Plasma ANP tended to increase only with OMA but not with OMA+D or ACEI+D. ADM immediately increased with OMA and after 150 minutes in the ACEI+D group, whereas it remained unchanged with OMA+D. Plasma cGMP increased in both OMA groups but did not increase with ACEI+D. The differences in cGMP between ACEI+D and OMA or OMA+D were significant (both \( P<0.0001 \)). PRA was not significantly different at baseline between the 3 groups (Table 3). PRA was markedly increased after OMA+D. ACEI+D also increased PRA but to a lesser extent than with OMA+D (\( P=0.0128 \)), whereas PRA was not activated with OMA.
alone. Aldosterone increased immediately with ACEI + D, whereas a significant increase with OMA + D was observed only after 150 minutes. No changes were observed with OMA alone (Table 3). No comparisons were done between OMA + D and the other 2 groups because of significant differences in aldosterone baseline levels. However, aldosterone was significantly elevated in the ACEI + D group compared with OMA alone (P < 0.0001; Table 3).

### Discussion

The present study defined the acute cardiorenal and humoral responses to simultaneous inhibition of ACE and NEP with VPI with and without diuretic compared with ACEI with diuretic in a model of CHF. We observed that OMA, with and without diuretic, resulted in more favorable cardiorenal and humoral responses than did ACEI + D, which may be explained by potentiation of endogenous vasodilatory factors and NPs.

We report that OMA and OMA + D induced a transient reduction of MAP that returned to baseline. Despite the nonsustained decrease of MAP, its reduction was greater than that observed with ACEI + D. Furthermore, OMA alone and ACEI + D reduced PAP and PCWP to similar levels, but OMA + D produced a greater reduction. OMA and OMA + D

### TABLE 2. Urinary Hormonal Responses

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>150 min</th>
</tr>
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<tbody>
<tr>
<td>ANP, pg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OMA – D†</td>
<td>36 ± 3</td>
<td>63 ± 8</td>
<td>48 ± 14</td>
<td>47 ± 7</td>
<td>31 ± 9</td>
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<tr>
<td>OMA‡</td>
<td>34 ± 7</td>
<td>167 ± 31*</td>
<td>106 ± 23*</td>
<td>118 ± 10*</td>
<td>127 ± 17*</td>
</tr>
<tr>
<td>ACEI + D</td>
<td>44 ± 5</td>
<td>29 ± 9</td>
<td>35 ± 12</td>
<td>19 ± 6</td>
<td>40 ± 25</td>
</tr>
<tr>
<td>ADM, pg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMA + D</td>
<td>131 ± 49</td>
<td>236 ± 94</td>
<td>210 ± 67</td>
<td>165 ± 62</td>
<td>164 ± 53</td>
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<tr>
<td>OMA‡</td>
<td>38 ± 10</td>
<td>946 ± 94*</td>
<td>202 ± 99*</td>
<td>210 ± 92*</td>
<td>394 ± 75*</td>
</tr>
<tr>
<td>ACEI + D</td>
<td>46 ± 17</td>
<td>46 ± 4</td>
<td>46 ± 8</td>
<td>39 ± 7</td>
<td>58 ± 1</td>
</tr>
<tr>
<td>cGMP, pmol/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OMA + D†</td>
<td>1876 ± 264</td>
<td>2748 ± 403</td>
<td>2931 ± 435</td>
<td>2539 ± 643</td>
<td>2373 ± 472</td>
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<tr>
<td>OMA‡</td>
<td>1291 ± 245</td>
<td>2341 ± 341*</td>
<td>2197 ± 357*</td>
<td>2194 ± 438*</td>
<td>1842 ± 272</td>
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<tr>
<td>ACEI + D</td>
<td>1763 ± 225</td>
<td>1770 ± 274</td>
<td>1656 ± 226</td>
<td>1363 ± 219</td>
<td>1277 ± 370</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM.

*P < 0.05 vs baseline; †P < 0.0003, OMA + D vs ACEI + D; ‡P < 0.0001, OMA vs ACEI + D.

### TABLE 3. Plasma Hormonal Responses

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>150 min</th>
</tr>
</thead>
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<tr>
<td>ANP, pg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OMA – D</td>
<td>294 ± 70</td>
<td>451 ± 245</td>
<td>190 ± 46</td>
<td>209 ± 44</td>
<td>164 ± 26</td>
</tr>
<tr>
<td>OMA</td>
<td>212 ± 80</td>
<td>306 ± 113</td>
<td>252 ± 47</td>
<td>345 ± 102</td>
<td>512 ± 196</td>
</tr>
<tr>
<td>ACEI + D</td>
<td>401 ± 50</td>
<td>410 ± 42</td>
<td>574 ± 193</td>
<td>417 ± 41</td>
<td>386 ± 74</td>
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<tr>
<td>ADM, pg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMA + D</td>
<td>61 ± 10</td>
<td>64 ± 45</td>
<td>119 ± 53</td>
<td>106 ± 28</td>
<td>80 ± 13</td>
</tr>
<tr>
<td>OMA</td>
<td>58 ± 11</td>
<td>102 ± 16</td>
<td>118 ± 17</td>
<td>118 ± 24</td>
<td>120 ± 16</td>
</tr>
<tr>
<td>ACEI + D</td>
<td>49 ± 14</td>
<td>89 ± 25</td>
<td>117 ± 33</td>
<td>112 ± 38</td>
<td>155 ± 82*</td>
</tr>
<tr>
<td>cGMP, pmol/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OMA – D‡</td>
<td>18.2 ± 1.6</td>
<td>26.1 ± 3.1</td>
<td>26.5 ± 2.1*</td>
<td>24.8 ± 1.9*</td>
<td>22.3 ± 1.9</td>
</tr>
<tr>
<td>OMA‡</td>
<td>18.7 ± 2.0</td>
<td>23.2 ± 1.9*</td>
<td>22.1 ± 1.9</td>
<td>24.2 ± 1.8*</td>
<td>19.9 ± 1.8</td>
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<tr>
<td>ACEI + D</td>
<td>16.6 ± 1.1</td>
<td>15.5 ± 1.6</td>
<td>16.9 ± 1.9</td>
<td>12.9 ± 0.8</td>
<td>13.7 ± 0.9</td>
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<tr>
<td>PRA, ng · mL⁻¹ · h⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OMA – D§</td>
<td>7.2 ± 2</td>
<td>16.6 ± 1*</td>
<td>16.1 ± 2*</td>
<td>16.8 ± 1*</td>
<td>14.2 ± 2*</td>
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<tr>
<td>OMA‡</td>
<td>8.3 ± 1</td>
<td>9.1 ± 1</td>
<td>9.3 ± 2</td>
<td>7.5 ± 2</td>
<td>7.8 ± 2</td>
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<tr>
<td>ACEI + D</td>
<td>8.9 ± 1</td>
<td>13.6 ± 2</td>
<td>13.3 ± 2</td>
<td>13.2 ± 2</td>
<td>11.3 ± 2</td>
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<td>Aldosterone, ng/dL</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>OMA + D</td>
<td>4.7 ± 1</td>
<td>6.9 ± 1</td>
<td>10.6 ± 2</td>
<td>12.1 ± 3</td>
<td>13.0 ± 3*</td>
</tr>
<tr>
<td>OMA‡</td>
<td>27.8 ± 6</td>
<td>29.9 ± 6</td>
<td>32.4 ± 7</td>
<td>33.2 ± 6</td>
<td>37.4 ± 8</td>
</tr>
<tr>
<td>ACEI + D</td>
<td>17.9 ± 3</td>
<td>33.2 ± 6*</td>
<td>38.2 ± 6*</td>
<td>39.5 ± 6*</td>
<td>43.0 ± 8*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM.

*P < 0.05 vs baseline; †P < 0.02, OMA + D vs ACEI + D; ‡P < 0.0001, OMA vs ACEI + D; §P < 0.007, OMA + D vs OMA.
maintained CO and reduced SVR, whereas the opposite was observed with ACEI+D; specifically, ACEI+D decreased CO after 90 minutes and increased SVR after 150 minutes. Although modest, a significant difference in CO was observed between ACEI+D and both OMA groups. Later in the protocol, there was a trend for CO to be reduced with OMA or with OMA+D but not to the degree observed with ACEI+D despite the fact that OMA+D caused a greater decrease in cardiac filling pressures. The mechanism of this differential hemodynamic response may be explained by a greater arterial and venous vasodilatation in both OMA groups than with ACEI+D as a result of inhibition of enzymatic degradation of vasodilatory peptides together with delayed activation of the RAAS. Specifically, cGMP, which is the second messenger of the endogenous NP, was increased with OMA+D and OMA compared with ACEI+D. This supports the concept that OMA, via its NEP inhibitions, possesses greater vasoactive properties than ACEI+D.

GFR tended to increase after OMA with and without diuretic while showing the opposite effect after ACEI+D. Moreover, this differential response was significant when GFR was compared between groups. RBF increased and RVR decreased immediately after OMA, whereas co-infusion of ACEI+D and OMA+D had a similar but more prolonged effect. OMA alone also induced a gradual but sustained increase in urine and sodium excretion that was less than that with OMA+D. Nonetheless, despite a greater natriuresis with ACEI+D, OMA+D resulted in the greatest magnitude of cardiac unloading. Therefore, in the OMA+D group, despite the decrease in MAP, a renovasodilatation was observed in association with maintenance of GFR and diuretic response.

Regarding the mechanism of the acute renal actions of OMA and OMA+D to preserve GFR, it is possible that this is related to the NP effects, because Chen et al. reported that the actions of OMA can be attenuated by NP-receptor blockade. Studies showed that ANP dilates the afferent and constricts the efferent arteriole, thus increasing glomerular hydrostatic pressure. Furthermore, ANP relaxes mesangial cells, thus increasing the ultrafiltration coefficient Kf. In addition, exogenous ANP inhibits tubuloglomerular feedback in experimental CHF, which would enhance GFR. Thus, the unique GFR action of OMA can be explained in part by enhancing the NP via its NEP-inhibiting properties, as indicated by the relatively increased excretion of urinary ANP and cGMP. The lack of increase in plasma ANP after OMA and OMA+D administration was probably due to hemodynamic improvement, specifically a reduction of PCWP, which is a stimulus for NP secretion via atrial stretch.

Investigations have established that mild CHF is characterized by normal circulating plasma renin and aldosterone, which is characteristic of our model of compensated CHF. However, diuretics are known to activate RAAS. The Studies of Left Ventricular Dysfunction (SOLVD) showed that PRA may be increased in asymptomatic CHF in patients receiving diuretics. Therefore, activation of the RAAS with ACEI+D and OMA+D was expected. In contrast, OMA alone was not associated with activation of the RAAS despite similar reductions in cardiac filling pressure and a greater reduction in MAP than with ACEI+D. This may be related to the renin- and aldosterone-suppressing actions of the NP.

Although the relatively high dose of furosemide may not be entirely relevant to the clinical situation of our model of CHF, we deliberately chose this dose to induce a marked diuretic effect with activation of RAAS to determine the action of NEP inhibition. Indeed, although the variabilities in baseline levels of aldosterone make the interpretation of its changes difficult, NEP inhibition with OMA delayed aldosterone activation even in the presence of a high dose of diuretic. Binding of ANP to its receptor occurs in a chloride concentration–dependent manner. By this mechanism, marked water and salt depletion can reduce the efficacy of endogenous NPs. In spite of the same dose of furosemide, water and salt excretion were 3 times higher with ACEI+D than with OMA+D, potentially leading to a relatively reduced chloride concentration. This could explain in part the more beneficial effect with OMA+D than with ACEI+D, which was associated with higher plasma and urinary cGMP despite similar plasma ANP concentrations.

Considering the local growth-promoting and fibrotic actions of aldosterone, its activation, if sustained, could be deleterious. The differential response between OMA and ACEI+D could be secondary not only to known inhibitory properties of the NP on renin and aldosterone secretion but also to the greater diuresis in the ACEI+D group; furthermore, the higher PRA with OMA+D than with ACEI+D may be due to sympathetic activation caused by lower MAP. A limitation of the present study is the absence of data regarding norepinephrine and endothelin. As more information emerges with regard to vasopeptidase inhibition, further neurohumoral characterization will be necessary.

ADM was immediately elevated only after OMA administration, both in plasma and urine, whereas it showed a delayed increase in plasma after ACEI+D and remained unchanged after OMA+D. This increase in plasma and urinary ADM with OMA has not been reported to date in CHF, although NEP inhibition alone has been reported to increase plasma ADM and potentiate renal actions of ADM in normal dogs. Thus, given the known natriuretic and vasodilatory properties of ADM, one can speculate that this peptide may contribute to the actions of OMA, as has been reported for NP. ADM secretion is increased in human CHF; therefore, lack of its increase with OMA in the presence of diuretic may be explained in part by the greater decrease in cardiac filling pressures and ADM secretion.

The present study has clinical relevance, particularly from the perspective of the use of diuretics in CHF. Despite greater natriuresis with the ACEI+D combination, the greatest unloading of the heart occurred with OMA+D. Furthermore, there was more immediate activation of aldosterone with ACEI+D than with either OMA or OMA+D. Thus, if the goal of therapy in CHF is to reduce congestive pulmonary symptoms with less activation of aldosterone in association with preserving GFR, the use of a diuretic with dual NEP and ACE inhibition may have advantages beyond those of the combination of ACEI+D. Further experimental and human studies are warranted.
In summary, OMA+D compared with ACEI+D was more effective in reducing PAP and PCWP despite a smaller diuretic effect. It decreased MAP and SVR and preserved CO. Additionally, it resulted in an increase in GFR, whereas activation of aldosterone was delayed. These findings demonstrate beneficial effects of additional NEP inhibition with OMA. Importantly, despite less diuresis, OMA without diuretic was as effective in reducing PAP and PCWP as ACEI+D. Furthermore, OMA alone increased GFR compared with ACEI+D and did not activate RAAS. We conclude that acute administration of OMA either with or without diuretic in experimental CHF results in more beneficial cardiorenal and humoral actions than does ACEI+D. Additional studies are warranted to determine whether these promising findings translate into improved long-term cardiorenal function in CHF.

Acknowledgments

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