Renal Response to Acute Neutral Endopeptidase Inhibition in Mild and Severe Experimental Heart Failure

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**Background**—Neutral endopeptidase 24.11 (NEP) is a metalloprotease that is localized in the greatest abundance in the kidney and degrades natriuretic peptides, such as atrial natriuretic peptide (ANP). Mild congestive heart failure (CHF) is characterized by increases in circulating ANP without activation of the renin-angiotensin-aldosterone system (RAAS) or sodium retention. In contrast, severe CHF is characterized by sodium retention and coactivation of both ANP and the RAAS.

**Methods and Results**—We defined the acute cardiorenal actions of the NEP inhibitor candoxatrilat (8 μg·kg⁻¹·min⁻¹) in 4 groups of anesthetized dogs (normal, n=8; mild CHF, n=6; severe CHF, n=5; and severe CHF with chronic AT₁ receptor antagonism, n=5). Mild CHF was produced by rapid ventricular pacing at 180 bpm for 10 days and severe CHF at 245 bpm for 10 days. In mild CHF, urinary sodium excretion and glomerular filtration rate were greatest in response to acute NEP inhibition compared with the response in either control animals or those with severe CHF. Furthermore, an increase in glomerular filtration rate was observed only in mild CHF in association with increases in renal blood flow and decreases in renal vascular resistance and distal tubular sodium reabsorption. Urinary ANP and cGMP excretion, markers for renal biological actions of ANP, were greatest in mild CHF. The renal actions observed in mild CHF were attenuated in severe CHF and not restored by chronic AT₁ receptor antagonism.

**Conclusions**—The results of the present study demonstrate that acute NEP inhibition in mild CHF results in marked increases in renal hemodynamics and sodium excretion that exceed that observed in control animals and severe CHF. These studies underscore the potential therapeutic role for NEP inhibition to enhance renal function in mild CHF, an important phase of CHF that is marked by selective activation of endogenous ANP in the absence of an activated RAAS.

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Key Words: natriuretic peptides ▪ kidney ▪ neurohormones ▪ ventricles ▪ metalloprotease

Chronic congestive heart failure (CHF) is recognized as a progressive disease that evolves from mild to severe. Specifically, mild CHF represents a unique compensated phase of left ventricular dysfunction characterized by sodium balance with increases in endogenous atrial natriuretic peptide (ANP) without activation of the renin-angiotensin-aldosterone system (RAAS).¹⁻² Indeed, investigations have reported that ANP receptor antagonism in a canine model of mild CHF results in premature activation of the RAAS with sodium retention, consistent with a compensatory role for ANP in mild CHF to maintain sodium balance and suppress the RAAS despite ventricular dysfunction.⁴ In contrast to mild CHF, the hallmark of severe CHF is characterized by avid sodium retention with increased cardiac volume and pressure overload, peripheral edema, and an activated RAAS despite elevation of endogenous ANP. Indeed, severe CHF is known to be a state of renal hyporesponsiveness to ANP, in part due to the opposing renal actions of the RAAS.⁵⁻⁶

Neutral endopeptidase 24.11 (NEP) is a metalloprotease that is localized in the greatest abundance in the kidney and degrades natriuretic peptides such as ANP. NEP inhibition has emerged as a therapeutic strategy in the management of CHF through potentiation of the renal natriuretic and renin-inhibiting actions of ANP.⁷ To date, studies have reported that NEP inhibition results in natriuresis in cardiorenal disease states such as CHF and chronic renal failure, which are characterized by intravascular volume overload and elevation of circulating ANP.⁸⁻⁹ However, the results of studies are less clear regarding the renal responsiveness to NEP inhibition, particularly between mild and severe CHF.¹⁰⁻¹² Furthermore, the modulating actions of NEP inhibition—specifically on renal hemodynamics and tubular sodium...
reabsorption, both sites of action of ANP, in mild and severe CHF—are also poorly defined. Underscoring the priority of this question is the need to better identify therapeutic strategies in mild CHF, which was a major conclusion of the SOLVD prevention trial. Specifically, the concluding paragraph of the SOLVD prevention trial states, “Enalapril was well tolerated by patients with asymptomatic left ventricular dysfunction (ALVD) and it reduced the incidence of heart failure and related hospitalizations. However, the lack of a significant effect on overall mortality emphasizes the need to explore more effective means or additional means of treating ALVD.”

Based on the current understanding of NEP inhibition, the opposing properties of ANP and the RAAS, and the differential activation of these 2 humoral systems in mild and severe CHF, the present study was designed to define the renal actions of acute NEP inhibition in these 2 phases of CHF. We further defined the renal response to acute NEP inhibition in severe CHF in the presence of chronic angiotensin type 1 (AT1) receptor blockade to explore the potential limiting role of angiotensin II to NEP inhibition in severe CHF. The hypothesis of the present study was that acute NEP inhibition would result in an unique enhanced renal response in models of experimental mild CHF compared with control animals in association with an attenuated renal response in severe CHF. To address this hypothesis, cardiorenal and neurohumoral functions in response to acute NEP inhibition were assessed in normal anesthetized dogs and in those with experimental mild and severe CHF produced by rapid ventricular pacing for 10 days at a rate of 180 and 245 bpm, respectively.

Methods

The present study was conducted in 4 groups of anesthetized male mongrel dogs (weight 18 to 23 kg) in accordance with the Animal Welfare Act and with approval of the Mayo Clinic Animal Care and Use Committee. All 4 groups received acute NEP inhibition and consisted of normal dogs (n = 8), dogs with pacing-induced mild CHF (n = 6), dogs with pacing-induced severe CHF (n = 5), and dogs with pacing-induced severe CHF that also received 10 days of chronic AT1 receptor blockade before acute NEP inhibition (n = 5).

Pacing-Induced Mild and Severe CHF

Adult male mongrel dogs were anesthetized with 30 mg/kg pentobarbital sodium IV and ventilated with supplemental oxygen (5 L/min) via an endotracheal tube with the use of a Harvard Apparatus respirator. An epicardial lead (Medtronic) was implanted on the right ventricle via a left thoracotomy with a 1- to 2-cm pericardiotomy. The pacemaker lead was connected to a pulse generator (model 8329; Medtronic), which was then implanted subcutaneously in the chest wall. Pacing capture was verified intraoperatively before closure of the chest cavity. The pericardium was closed with suture, with great care taken to not distort the anatomy of the pericardium. The chest cavity and deep and superficial incisions were then closed in layers.

Dogs received preoperative and postoperative prophylactic antibiotic treatment with 225 mg clindamycin SC and 400,000 U procaine penicillin G plus 500 mg dihydrostreptomycin IM (Combicort; Pfizer, Inc). The administration of postoperative prophylactic antibiotic was continued through the first 2 postoperative days.

After a 14-day postoperative recovery period, mild CHF was produced through rapid ventricular pacing at 180 bpm for 10 days. In previous work by Redfield et al,14 this resulted in a model of mild CHF with a neurohumoral profile that mimics mild human CHF. Severe CHF was produced with rapid ventricular pacing at 245 bpm for 10 days, which in previous work by Margulies et al15 resulted in a model that mimics the neurohumoral characteristics of severe human CHF. Pacemaker capture was verified with a surface ECG every other day.

Acute NEP Inhibition

On the night before the acute protocol, the animals were fasted, administered 300 mg lithium carbonate for assessment of renal tubular function, and allowed access to water on an ad libitum basis. On the day of the acute experiment, dogs were anesthetized with 15 mg/kg sodium pentobarbital IV, intubated, and mechanically ventilated with supplemental with oxygen (Harvard Apparatus) at a rate of 16 cycles/min. A flow-directed balloon-tipped thermocatheter (Ohmeda; Criticath) was advanced to the pulmonary artery via the external jugular vein for cardiac hemodynamic measurement. The femoral artery was cannulated for blood pressure monitoring and blood sampling. The femoral vein was also cannulated for inulin and normal saline infusion. The left kidney was exposed via a flank incision, and the ureter was cannulated for urine collection. A calibrated electromagnetic flow probe was placed around the renal artery to measure renal blood flow (RBF). Supplemental nonhypotensive doses of pentobarbital sodium were administered as needed during the experiment.

A 30-minute baseline clearance was performed after a 60-minute equilibration period. Midway through the clearance, cardiac hemodynamics were measured, and arterial blood was drawn for hormonal and electrolyte analyses. After the 30-minute baseline clearance, the NEP inhibitor (Candoxatrilat) was administered as a intravenous bolus of 240 µg/kg followed by a continuous infusion at a rate of 8 µg · kg⁻¹ · min⁻¹. After a 15-minute lead-in period, a 60-minute NEP inhibition clearance was performed. In addition, in dogs with severe CHF who also received 10 days of oral administration of the selective AT1 receptor antagonist valsartan (320 mg PO BID), an additional clearance with a higher dosage of candoxatrilat (80 µg · kg⁻¹ · min⁻¹) was performed. After a 15-minute lead-in period at the dosage of 80 µg · kg⁻¹ · min⁻¹, a second 60-minute NEP inhibition clearance was performed. The dosage of 80 µg · kg⁻¹ · min represents the peak dose-response curve for candoxatrilat (unpublished observation, Pfizer UK). To validate that the AT1 blockade was effective, an intravenous bolus of angiotensin II (0.4 µg/kg) was administered to all 5 dogs at the end of this acute protocol. In a previous report from our laboratory, an intravenous bolus of angiotensin II (0.4 µg/kg) resulted in systemic and renal vasoconstriction.16 In this fourth group that received long-term treatment with valsartan, no systemic or renal vasoconstriction to angiotensin II was observed.

Cardiovascular parameters measured during the acute experiment included mean arterial pressure (MAP), right atrial pressure (RAP), pulmonary artery pressure (PAP), cardiac output (CO), and pulmonary capillary wedge pressure (PCWP). CO was determined through thermodilution in triplicate and averaged (Cardiac Output model 9510-A computer, American Edwards Laboratories). MAP was assessed via direct measurement from the femoral arterial catheter. Systemic vascular resistance (SVR) was calculated as [SVR=MAP−RAP)/CO]. Inulin was administered intravenously at the start of the equilibration period as a calculated bolus, followed by a 1 ml/min continuous infusion to achieve a steady-state plasma inulin concentration between 40 and 60 mg/dL. Glomerular filtration rate (GFR) was measured by inulin clearance. Renal vascular resistance (RVR) was calculated as [RVR=MAP−RAP/RBF]. Urine was collected on ice for assessment of urine volume, electrolytes, and inulin. Urine collected for cGMP analysis was heated to >90°C before storage. Arterial blood was collected in heparin and EDTA tubes and immediately placed on ice. After centrifugation at 2500 rpm at 4°C, plasma was decanted and stored at −20°C until analysis.

Hormone and Electrolyte Analysis

After plasma extraction, ANP was measured by radioimmunoassay (RIA) to α-human ANP as previously described.17 Plasma and
**Table 1. Cardiorenal and Humoral Function at Baseline Before Acute NEP Inhibition**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mild CHF</th>
<th>Severe CHF</th>
</tr>
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<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>132±7</td>
<td>116±7</td>
<td>115±6</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.7±0.2</td>
<td>2.5±0.2*</td>
<td>1.9±0.2*</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>0.4±0.6</td>
<td>2.5±0.7*</td>
<td>10.4±1.6†</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>4.6±0.7</td>
<td>10.7±0.9*</td>
<td>25.6±3.1†</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>13.8±1.2</td>
<td>14.5±1.1</td>
<td>29.4±2.6†</td>
</tr>
<tr>
<td>SVR, RU</td>
<td>36.7±2.3</td>
<td>47.5±5.1</td>
<td>55.0±4.8*</td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>38.9±6.7</td>
<td>30.0±4.6</td>
<td>23.3±9.9</td>
</tr>
<tr>
<td>RBF, mL/min</td>
<td>158±19</td>
<td>106±11</td>
<td>119±28</td>
</tr>
<tr>
<td>RVR, RU</td>
<td>0.93±0.12</td>
<td>1.16±0.17</td>
<td>1.04±0.22</td>
</tr>
<tr>
<td>UNaV, μEq/min</td>
<td>25.4±7.9</td>
<td>19.9±9.6</td>
<td>2.7±1.3*</td>
</tr>
<tr>
<td>DFRNa, %</td>
<td>98.0±0.5</td>
<td>98.5±0.4</td>
<td>98.9±0.5</td>
</tr>
<tr>
<td>UcGMPV, pmol/min</td>
<td>840±162</td>
<td>2251±625*</td>
<td>159±5.4†</td>
</tr>
<tr>
<td>ANP, pg/mL</td>
<td>31±7</td>
<td>227±91*</td>
<td>288±49*</td>
</tr>
<tr>
<td>cGMP, pmol/mL</td>
<td>7.3±1.0</td>
<td>17.7±2.6*</td>
<td>17.8±3.3*</td>
</tr>
<tr>
<td>PRA, ng·mL⁻¹·h⁻¹</td>
<td>1.3±0.3</td>
<td>2.2±1.0</td>
<td>8.2±1.8†</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
<td>9.0±1.8</td>
<td>9.2±1.9</td>
<td>37.1±9.4†</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM.

*p<0.05 vs normal.
†p<0.05 vs mild CHF.

Statistical Analysis

Results of the quantitative studies are expressed as mean±SEM. Data were assessed with factorial ANOVA for comparisons among groups, Student’s unpaired t test for single comparisons between any 2 groups, and Student’s paired t tests for single comparisons of absolute changes within each group (Prism; GraphPAD Software). Statistical significance was accepted as P<0.05.

Results

Cardiorenal and Neurohumoral Function at Baseline

Baseline cardiorenal and neurohumoral function in control animals and in animals with mild or severe CHF is summarized in Table 1. Mild CHF was characterized by decreased CO and increased RAP and PCWP, with the maintenance of urinary sodium excretion (UNaV) compared with control animals. Mild CHF was also characterized by increased plasma ANP, plasma cGMP, and urinary cGMP excretion (UcGMPV) in the absence of an activated RAAS. In contrast, severe CHF was characterized by decreased CO and increased RAP, PAP, PCWP, and SVR, together with avid sodium retention, compared with control animals. Severe CHF was also characterized by increased plasma ANP and cGMP with activation of the RAAS, but unlike mild CHF, no increase in urinary cGMP excretion was observed. Specifically, urinary cGMP excretion was significantly lower compared with both control animals and those with mild CHF.

Cardiorenal and Neurohumoral Function During Acute NEP Inhibition

Figure 1 illustrates GFR, UNaV, DFRNa, and UANPV in all 3 groups at baseline (open columns) and during acute NEP inhibition (filled columns). Normal indicates normal dogs (n=8); Mild CHF, dogs with mild CHF (n=6); Severe CHF, dogs with severe CHF (n=5). *p<0.05 vs baseline. †p<0.05 vs normal with acute NEP inhibition. ‡p<0.05 vs severe CHF with acute NEP inhibition.
the absence of changes in GFR, RBF, RVR, and DFRNa with acute NEP inhibition (Figure 1 and Table 2).

Plasma ANP, cGMP, renin, and aldosterone remained unchanged from baseline in all 3 groups with acute NEP inhibition. Baseline cardiovascular hemodynamics were also unchanged in all 3 groups during acute NEP inhibition, with the exception of a decrease in RAP observed in animals with severe CHF (10.4 ± 1.6 to 6.3 ± 0.9 mm Hg, P < 0.05).

Figure 2 illustrates the renal response in severe CHF without and with chronic AT₁ antagonism to acute NEP inhibition. Chronic AT₁ antagonism resulted in increased UNaV and UcGMPV associated with decreased DFRNa compared with untreated severe CHF at baseline before acute NEP inhibition (Figure 2). In response to acute low-dose NEP inhibition, UcGMPV was greater with chronic AT₁ antagonism with a trend for an increase in UNaV and UANPV and a trend for a decrease in DFRNa compared with untreated severe CHF (Figure 2). No further changes were noted in UNaV, DFRNa, or UcGMPV despite a trend for increased UANPV with high-dose NEP inhibition in the severe CHF with chronic AT₁ antagonism.

Discussion

The objective of the present study was to test the hypothesis that acute NEP inhibition in mild CHF would result in a unique enhanced renal natriuretic response compared with control animals, in association with an attenuated renal response to acute NEP inhibition in severe CHF. Our findings confirm this hypothesis and demonstrate that NEP inhibition in an experimental model of mild CHF results in an enhanced natriuresis compared with control animals and that this exaggerated renal response is secondary to increases in GFR and RBF and decreases in tubular sodium reabsorption. We observed a significant but reduced natriuretic response to NEP inhibition in severe CHF. Furthermore, chronic AT₁ blockade, which increased overall sodium excretion in severe CHF, did not significantly enhance the natriuretic response to NEP inhibition compared with untreated severe CHF despite

Table 2. Renal Function at Baseline and With Acute NEP Inhibition

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Acute NEP Inhibition</th>
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<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBF, mL/min</td>
<td>158±19</td>
<td>170±21</td>
</tr>
<tr>
<td>RVR, RU</td>
<td>0.93±0.12</td>
<td>0.88±0.11</td>
</tr>
<tr>
<td>UcGMPV, pmol/min</td>
<td>840±162</td>
<td>804±201</td>
</tr>
<tr>
<td>Mild CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBF, mL/min</td>
<td>106±11</td>
<td>145±20*</td>
</tr>
<tr>
<td>RVR, RU</td>
<td>1.16±0.17</td>
<td>0.90±0.13*</td>
</tr>
<tr>
<td>UcGMPV, pmol/min</td>
<td>2251±625</td>
<td>3106±564*†‡</td>
</tr>
<tr>
<td>Severe CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBF, mL/min</td>
<td>120±28</td>
<td>128±26</td>
</tr>
<tr>
<td>RVR, RU</td>
<td>1.04±0.22</td>
<td>0.91±0.13</td>
</tr>
<tr>
<td>UcGMPV, pmol/min</td>
<td>159±54</td>
<td>863±501*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM.
*P < 0.05 vs baseline.
†P < 0.05 vs normal with acute NEP inhibition.
‡P < 0.05 vs severe CHF with acute NEP inhibition.
maximal NEP inhibition. These results underscore the therapeutic efficacy of NEP inhibition as a natriuretic agent, which also enhances renal hemodynamics, with a unique efficacy in mild compared with severe CHF.

Previous investigations have established that NEP inhibition in experimental and human CHF results in an increase in sodium excretion, although the magnitude of natriuresis to NEP inhibition varies among reports. Indeed, the increases in urinary ANP and cGMP to acute NEP inhibition in mild CHF was associated with a decrease in sodium reabsorption at nephron sites known to be responsive to ANP. Such a mechanism is supported in the present study inasmuch as the enhanced natriuretic response was attributed to the potentiation of elevated circulating ANP secondary to inhibition of renal ANP degradation, leading to a decrease in sodium reabsorption at nephron sites known to respond to ANP. Such a mechanism is supported in the present study inasmuch as the enhanced natriuretic response to acute NEP inhibition in mild CHF was associated with a greater urinary excretion of ANP as well as urinary cGMP, the second messenger for the ANP and a marker for its renal actions. Indeed, the increases in urinary ANP and cGMP excretion were independent of any increases in plasma ANP or cGMP, again supporting the selective renal action of systemic NEP inhibition in states of elevated endogenous ANP. Because NEP also degrades other peptides, we cannot exclude that peptides such as kinins may have contributed to the natriuretic response.

The results of the present study extend previous investigations and provide insight into the mechanisms that explain the enhanced natriuretic response in mild CHF to acute NEP inhibition. We observed that the enhanced natriuresis was accompanied by an increase in GFR with an exaggerated reduction in distal tubular fractional reabsorption of sodium in mild CHF. Previous reports have shown that NEP inhibition in control animals and in severe CHF is not associated with an increase in GFR despite significant natriuretic actions. Thus, the enhanced GFR response to acute NEP inhibition in mild CHF was unexpected. One may conclude that the increase in GFR associated with an increase in RBF suggests that acute NEP inhibition resulted in afferent arteriolar dilatation with an increase in glomerular hydrostatic pressure. Based on the report that ANP may inhibit tubuloglomerular feedback control of GFR, it is tempting to speculate that an increased delivery of ANP to the macula densa during acute NEP inhibition resulted in afferent arteriolar dilatation. Because NEP has also been reported to be present in vascular smooth muscle of afferent arterioles, NEP inhibition alternatively may have potentiated ANP actions at the level of the afferent arteriole. This may have also resulted in a reduction in afferent arteriolar resistance consistent with the observed decrease in total renal vascular resistance reported in the present study. The exaggerated decrease in distal fractional reabsorption was predicted based on the known presence of ANP receptors at the level of the terminal nephron. Furthermore, the increased increase in urinary ANP and cGMP excretion in response to NEP inhibition in CHF also supports the concept that increased delivery of intact ANP during NEP inhibition results in the activation of luminal ANP receptors present in the medullary collecting duct.

An additional major finding of the present study is that the enhanced renal response to NEP inhibition observed in mild CHF was markedly attenuated in severe CHF. This places into perspective the spectrum of findings in previous studies in both humans and animal models of CHF in which NEP inhibition was investigated. Indeed, the present results demonstrate that NEP inhibition is markedly natriuretic in mild CHF but that this natriuretic action is reduced in severe CHF. This establishes the concept that the severity of CHF determines the magnitude of natriuresis in response to acute NEP inhibition.

The present study also provides insights into the mechanism of reduced renal responsiveness to NEP inhibition in severe CHF. First, we observed that despite the elevation of plasma ANP and cGMP, urinary cGMP excretion before acute NEP inhibition in severe CHF was reduced compared with that in animals with mild CHF and control animals, supporting the conclusion that a renal resistance to endogenous ANP was present. In the present study, chronic AT1 receptor antagonism resulted in increased urinary sodium excretion and urinary cGMP excretion before NEP inhibition in severe CHF, suggesting that angiotensin II via the AT1 receptor may in part contribute to the renal resistance to endogenous ANP. Such a conclusion is supported by studies that have reported that angiotensin II may directly oppose the renal actions of ANP. Indeed, a previous study reported that angiotensin II activates cGMP phosphodiesterases that may inhibit or reduce ANP-mediated intracellular cGMP accumulation. However, the present results show that chronic AT1 blockade did not restore the natriuretic response to NEP inhibition in severe CHF to the level achieved in mild CHF despite a trend to increase natriuresis. This implies that other neurohumoral systems, such as the endothelin, the adrenergic system, or aldosterone, may also play a role in the renal resistance to ANP in severe CHF and specifically to acute NEP inhibition. The present results also importantly extend a previous report that chronic inhibition of angiotensin II generation by ACE inhibition in severe CHF results in a potentiation of the renal hemodynamic and tubular actions of acute NEP inhibition. Based on the results that chronic AT1 blockade in severe CHF potentiated the actions of acute NEP inhibition to a much lesser degree compared with chronic ACE inhibition as reported in previous studies, it suggests that the potentiation of the kinins by chronic ACE inhibition may play an important role in accentuation of the renal actions of acute NEP inhibition. Further studies will be required to address this issue.

The present study has important therapeutic implications. First, emphasis has been placed on the initiation of therapy early during the progression of CHF with the use of ACE inhibitors in mild CHF. Indeed, studies support the conclusion that early drug intervention may delay the onset of CHF symptoms. Recently, in the SHEP study, the use of diuretic agents reduced the development of CHF in elderly patients with hypertension. The present study supports the use of NEP inhibition in mild CHF based on enhanced renal
hemodynamic and tubular actions. Indeed, these beneficial renal actions were unassociated with RAAS activation, which commonly occurs with the use of conventional diuretics. Further studies will be required to explore the potential efficacy of long-term NEP inhibition in mild CHF. An additional therapeutic implication relates to the use of NEP inhibition in severe CHF; because we observed an attenuated renal response to acute NEP inhibition in severe CHF in association with an activated RAAS, the dual inhibition of ACE and NEP in CHF may be a viable strategy that will require additional investigation.

In conclusion, the present study is the first to demonstrate that acute NEP inhibition in experimental mild CHF results in an enhanced natriuretic response compared with control animals that is linked to glomerular and tubular mechanisms. We also report that this natriuretic response is attenuated in severe CHF and is not restored with chronic AT1 blockade. We conclude that the efficacy of NEP inhibition to potentiate the renal actions of ANP in heart failure is determined by the severity of the disease and may have an important therapeutic role, particularly in mild CHF.

Acknowledgments

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References

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