Chronic Oral Endothelin Type A Receptor Antagonism in Experimental Heart Failure

Daniel D. Borgeson, J. Aaron Grantham, Eric E. Williamson, Andreas Luchner, Margaret M. Redfield, Terry J. Opgenorth, John C. Burnett, Jr

Abstract—Endothelin-1 (ET-1) is a cardiovascular peptide that binds to two distinct receptors, ET\textsubscript{A} and ET\textsubscript{B}, resulting in systemic and regional vasoconstriction, alteration in sodium excretion, mitogenesis, and release of other vasoactive peptides such as atrial natriuretic peptide (ANP). A role for ET-1 has been proposed in congestive heart failure (CHF) based on the increase in circulating ET-1 in this cardiovascular disease state. The present study determined the cardiorenal and endocrine responses to chronic selective oral ET\textsubscript{A} antagonism in experimental CHF. Two groups of conscious dogs underwent 21 days of pacing-induced CHF. These groups included a control untreated group (n=6) and a group that received an orally active ET\textsubscript{A} receptor antagonist (A-127722, Abbott Pharmaceuticals, 5mg/kg PO bid, n=6). Each group was studied at baseline before the onset of CHF and after 14 and 21 days of CHF. Compared with the CHF control group, the ET\textsubscript{A} receptor antagonism group at 14 days of CHF showed lower mean arterial pressure and systemic vascular resistance. Similarly, ET\textsubscript{A} receptor antagonism markedly attenuated the increase in circulating ANP despite similar atrial pressures. At 21 days of CHF, ET\textsubscript{A} receptor antagonism lowered pulmonary artery pressure, pulmonary vascular resistance, and systemic vascular resistance in association with a higher cardiac output. Plasma ANP remained suppressed. Despite the lower mean arterial pressure and circulating ANP in the ET\textsubscript{A} receptor antagonist group, the absolute decrease in sodium excretion from baseline was less compared with the untreated CHF control group. The present investigation supports the conclusion that endogenous ET-1 participates in the systemic and pulmonary vasoconstriction, the elevation of ANP, and the sodium retention that characterize this model of experimental CHF, suggesting a potential therapeutic role for ET\textsubscript{A} receptor antagonism in CHF. (Hypertension. 1998;31:766-770.)

Key Words: natriuretic peptides ■ endothelium ■ vasoconstriction ■ neurohormones ■ kidney

Endothelin-1 is a potent cardiovascular peptide that binds to two distinct receptors, ET\textsubscript{A} and ET\textsubscript{B}, mediating vasoconstriction, sodium retention, and mitogenesis.\textsuperscript{1,2} In addition, the release of the cardiac hormone ANP has been reported to be linked to the ET\textsubscript{A} receptor in cultured atrial myocytes.\textsuperscript{3} While ET-1 may play a physiological role in cardiovascular regulation, studies have established the activation of tissue and circulating ET-1 in experimental and human CHF.\textsuperscript{4-6} The functional significance of the increase in plasma and tissue ET-1 in CHF has been suggested by the positive correlation between elevated plasma ET-1 and increased mortality in human CHF.\textsuperscript{7} In addition, exogenous infusion of synthetic ET-1 to mimic concentrations observed in CHF results in systemic and regional vasoconstriction.\textsuperscript{8,9} Direct evidence for the importance of ET-1 in CHF is supported by reports in experimental and human CHF that acute administration of selective ET\textsubscript{B} or dual ET\textsubscript{A} and ET\textsubscript{B} receptor antagonists results in systemic and regional vasodilation.\textsuperscript{10,11} More recently, in an infarct model of CHF, chronic selective ET\textsubscript{A} receptor antagonism was associated with a reduction in ventricular remodeling and mortality.\textsuperscript{12} In addition, recent studies using a rabbit model of pacing-induced cardiomyopathy reported that chronic subcutaneous ET\textsubscript{A} selective receptor antagonism improved left ventricular function and cardiac myocyte contractility.\textsuperscript{13} Although these more recent studies support an important role for endogenous ET-1 and the ET\textsubscript{A} receptor in myocardial function and structure in CHF, major questions remain with regard to the ability of an orally active ET\textsubscript{A} receptor antagonist to chronically attenuate the vasoconstrictor responses that characterize CHF, as well as the increases in the cardiac hormone ANP.

The present study was therefore designed to determine the effects of chronic ET\textsubscript{A} receptor antagonism in experimental CHF produced by rapid ventricular pacing in conscious dogs, with a focus on systemic and pulmonary vascular resistances, the activation of ANP, and the magnitude of sodium retention. The hypothesis of the present investigation was that during experimental CHF, chronic selective ET\textsubscript{A} receptor antagonism...
would attenuate systemic and regional vasoconstriction, impair the release of the cardiac peptide ANP, and reduce the magnitude of sodium retention.

Methods

Studies were conducted in two groups of conscious male mongrel dogs (18 to 23 kg) with pacing-induced experimental CHF in accordance with the Animal Welfare Act. Control animals consisted of normal male mongrel dogs (n=6) that were studied before and during 3 weeks of pacing-induced CHF and received no treatment. The treatment group (n=6) received the orally active ETA receptor antagonist (A-127722, Abbott Laboratories) at a dose of 5 mg/kg PO bid beginning 2 days before baseline measurements and continuing throughout the entire CHF protocol.

A-127722 is a potent orally active, nonpeptide ETA receptor selective antagonist that has been characterized by Opgenorth et al. The binding Kᵣ for the ETA receptor is over 1000-fold greater than for ETA receptors (specifically, ET₄=0.07 nmol/L and ET₅=140 nmol/L [human, Chinese hamster ovary cells] and is rapidly absorbed after oral administration, reaching peak plasma concentrations within 30 minutes with a bioavailability of 43.2% (canine). A-127722 inhibits ET-1-induced contraction of rat aorta, a known ETA-mediated response, in a dose-dependent manner. In vivo pseudoefficacy studies in conscious normotensive rats, A-127722 demonstrated maximum inhibition of ET-1 pressor effects at a dose of 10 mg/kg PO, with no greater effect seen at 30 mg/kg. The duration of inhibition of ET-1 pressor response remained at a maximum at 8 hours after dosing, with significant (>50%) inhibition of the ET-1 pressor effect at 24 hours. On the basis of these parameters, an oral dose of 5 mg/kg twice daily was chosen to provide efficacious chronic antagonism of the ETA receptor in a canine model of experimental CHF.

Surgical Preparation

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

A chronic femoral artery catheter (Model GPV Vascular-Accessory Port, Access Technologies) was placed for MAP monitoring and plasma sampling. The catheter was implanted into the left femoral artery with the self-scaling silicone rubber septum port tunneled subcutaneously to the left upper hindlimb. Dogs received preoperative and postoperative prophylactic antibiotic treatment with 225 mg clindamycin SC and 400 000 U procaine penicillin G plus 500 mg dicyclomycin IM (Cobictic, Pfizer Inc). Postoperative prophylactic antibiotic was continued through the first 2 postoperative days.

Pacing-Induced CHF

After a 14-day postoperative recovery period, baseline measurements were obtained (see below). After completion of the acute baseline measurements, right ventricular pacing was initiated at 245 bpm. Each dog was then continuously paced at 245 bpm through the 21-day protocol. Pacing capture was verified by surface electrocardiography twice each week.

Acute Protocol

The following acute protocol was undertaken in each of the animals at three separate times: (1) at baseline before the onset of CHF, (2) after 14 days of CHF, and (3) after 21 days of CHF. Renal function was characterized on two separate times, first before CHF and second after 21 days of CHF. On the day of the acute experiment, each dog was anesthetized with thiopental sodium (15 mg/kg IV) to allow sterile percutaneous placement of a flow-directed balloon-tip pulmonary artery catheter (model 93131-7F; American Edwards Laboratories) through an internal jugular vein. The chronic indwelling arterial catheter was connected to a pressure monitor for on-line measurement of aortic pressure and for blood sampling. A second balloon-tip catheter was inserted in the urinary bladder for urine collection.

After recovery from anesthesia, each dog was allowed to stand freely in a minimally restricting sling and was allowed to stabilize for a 60-minute equilibration period before measurement of any parameters. For characterization of renal function, a loading dose of PAH and inulin was followed by continuous infusion of a PAH and inulin solution at a rate of 1 mL/min to achieve plasma concentrations of approximately 25 and 50 mg/mL, respectively. The study period consisted of a 30-minute urine collection with hemodynamics and blood sampling occurring at the midpoint of the clearance.

During the experimental periods, the following hemodynamic data were collected: MAP, RAP, PAP, PCWP, and CO. CO was determined by thermodilution (American Edwards Cardiac Output Computer model 9510-A) and was measured four times, then averaged. SVR was calculated as [(MAP−RAP)/CO], PVR was calculated as [(PAP−PCWP)/CO]. RVR was calculated as [(MAP−RAP)/renal blood flow]. MAP was assessed by direct measurement from the chronic arterial port. Glomerular filtration rate was measured by inulin clearance. Renal blood flow was calculated from estimated renal plasma flow (PAH clearance) and hematocrit level. Urine was collected on ice during the entire clearance period for assessment of urine volume, electrolytes, inulin, and PAH. Plasma samples were 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.

ET-1 and ANP Analysis

Arterial blood was collected at the midpoint of the clearance for analysis of ET-1 and ANP. Plasma ET-1 was determined by [125I]ET-1,2 assay system from Amersham. Before the radioimmnoassay, plasma is acidified with 0.5% TFA. C8 Bond Elut cartridges were washed with 4 mL of methanol and 4 mL of water. After the plasma was applied, cartridges were washed with 2 mL of normal saline and 6 mL of water. ET-1 was eluted from the cartridges with 2 mL of 90% methanol in 1% TFA, then dried and reconstituted for the radioimmunoassay. The recovery of the extraction procedure is 81% as determined by the addition of synthetic ET-1 to plasma; interassay and intra-assay variations are 9% and 3%, respectively. The minimal level of detection is 0.5 pg per tube. The cross-reactivity of ET-2, ET-3, and big ET in this assay is 100%, <3%, and 37%, respectively. Plasma ANP was measured by a specific radioimmunoassay. Blood was collected in an EDTA tube and immediately placed on ice. After centrifugation at 2500 rpm at 4°C, plasma was separated and stored at −20°C until assay. ANP was extracted by use of C18 Bond Elut cartridges with recovery of 86%. ANP was measured by a radioimmunoassay using a specific antibody to huan ANP. Interassay variation was 9%, intra-assay variation was 6%, and cross-reactivity was 100% with canine ANP. Cross-reactivity to brain natriuretic peptide or C-type natriuretic peptide was <0.1%.

Selected Abbreviations and Acronyms

- ANP = atrial natriuretic peptide
- CHF = congestive heart failure
- CO = cardiac output
- ET = endothelin
- MAP = mean arterial pressure
- PAH = p-aminohippuric acid
- PAP = pulmonary artery pressure
- PCWP = pulmonary capillary wedge pressure
- PVR = pulmonary vascular resistance
- RAP = right atrial pressure
- RVR = renal vascular resistance
- SVR = systemic vascular resistance
Statistical Analysis

Results of the quantitative studies were expressed as mean±SEM. Data was assessed by Student’s unpaired t test and factorial ANOVA for comparisons between groups. Student’s paired t tests were used for single comparisons of absolute changes within each group and ANOVA for repeated measures, followed by Bonferroni’s post test. Statistical significance was accepted as P<.05.

Results

Cardiovascular Hemodynamics

Before CHF, there was no difference in CO, PCWP, or MAP between groups. In contrast, SVR was lower in the ETA receptor antagonist group compared with the untreated control group. There was no difference in PVR between treated and untreated groups (Table).

At 14 days of CHF, MAP and CO decreased and RAP, PCWP, PAP, SVR, and PVR increased in both groups. Compared with the untreated group, MAP was lower in the ETA receptor antagonist group, with no other difference between groups.

At 21 days of experimental CHF, RAP, PCWP, and PAP increased compared with at 14 days in the untreated group, while these values remained stable in the treated group. In comparing the two groups, CO was higher while PAP and PCWP were lower in the ETA receptor antagonist group. SVR and PVR also remained lower in the treated group.

Circulating ET-1 and ANP

Chronic oral ETA receptor antagonism resulted in a higher plasma ET-1 concentration at baseline before CHF compared with that in the untreated control group (Fig 1). Although a trend remained for plasma ET-1 to be higher in the antagonist group at 14 and 21 days of experimental CHF, this was not significant. Plasma ANP was not different between groups before CHF. In response to CHF, plasma ANP increased in both groups but was markedly lower in the treated group at 14 and 21 days of experimental CHF.

Renal Hemodynamics and Sodium Excretion

No differences were observed in renal hemodynamics or sodium excretion at baseline between the two groups (Table, Fig 2). At 21 days of CHF, renal blood flow and urinary sodium excretion decreased and RVR increased in the untreated group. In the ETA receptor antagonist group, although renal blood flow decreased, RVR and urinary sodium excretion were statistically unchanged from baseline. The absolute decrease in sodium excretion from baseline was less in the ETA receptor antagonist group compared with CHF controls.

Discussion

The present investigation was designed to investigate the modulating actions of chronic oral selective ETA receptor antagonism in experimental CHF, with a specific focus on systemic and regional vascular resistances, circulating ANP, and the magnitude of sodium retention. The major findings are that chronic oral ETA receptor antagonism results in sustained decreases in SVR and PVR, an impaired release of ANP, and an attenuation in the decrease in sodium excretion from baseline in a pacing-induced model of experimental CHF.

Before the induction of experimental CHF, the present study demonstrates a decrease in SVR, in response to the orally active selective ET_A receptor antagonist. This observation is in contrast to previous reports in which mixed ETA and ET_B receptor antagonists were used, but it is similar to a previous study using FR-139317, another highly selective ETA receptor antagonist. Additionally, recent human investigations demonstrated that acute intravenous administration of TAK-044, a nonselective ET receptor antagonist resulted in a decrease in peripheral vascular resistance and, to a lesser extent, arterial pressure. A possible explanation for such differences was offered by Shimoyama et al, who suggested that in the absence of CHF, the lack of decrease in arterial pressure or peripheral vasodilation with a mixed ETA and ET_B antagonist

Cardiorenal Function in Experimental CHF: Effects of ETA Receptor Antagonism

<table>
<thead>
<tr>
<th></th>
<th>Pre-CHF</th>
<th>CHF at Day 14</th>
<th>CHF at Day 21</th>
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<tbody>
<tr>
<td><strong>MAP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>123±2</td>
<td>112±2*</td>
<td>109±2*</td>
</tr>
<tr>
<td>Treated</td>
<td>112±4</td>
<td>94±5‡</td>
<td>97±6*</td>
</tr>
<tr>
<td><strong>CO, L/min</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Untreated</td>
<td>5.5±0.3</td>
<td>2.9±0.3*</td>
<td>2.2±0.1*</td>
</tr>
<tr>
<td>Treated</td>
<td>6.2±0.2</td>
<td>3.7±0.2*</td>
<td>3.4±0.2‡</td>
</tr>
<tr>
<td><strong>RAP, mm Hg</strong></td>
<td></td>
<td></td>
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<tr>
<td>Untreated</td>
<td>5.8±0.5</td>
<td>15.2±1.4*</td>
<td>19.6±0.8†</td>
</tr>
<tr>
<td>Treated</td>
<td>4.8±0.5</td>
<td>15.9±0.9*</td>
<td>16.5±1.5*</td>
</tr>
<tr>
<td><strong>PCWP, mm Hg</strong></td>
<td></td>
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<tr>
<td>Untreated</td>
<td>10.2±0.5</td>
<td>26.2±0.9*</td>
<td>33.2±1.7†</td>
</tr>
<tr>
<td>Treated</td>
<td>10.7±1.1</td>
<td>25.6±1.1*</td>
<td>28.3±1.5‡</td>
</tr>
<tr>
<td><strong>PAP, mm Hg</strong></td>
<td></td>
<td></td>
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<tr>
<td>Untreated</td>
<td>17.8±1.4</td>
<td>32.5±1.0*</td>
<td>38.0±1.5†</td>
</tr>
<tr>
<td>Treated</td>
<td>19.7±1.9</td>
<td>31.8±1.2*</td>
<td>32.0±1.2‡</td>
</tr>
<tr>
<td><strong>SVR, RU</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Untreated</td>
<td>21.7±1.5</td>
<td>35.7±3.6*</td>
<td>41.5±1.0*</td>
</tr>
<tr>
<td>Treated</td>
<td>17.3±0.9</td>
<td>21.2±1.5‡</td>
<td>25.1±3.5‡</td>
</tr>
<tr>
<td><strong>PVR, RU</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>1.47±.34</td>
<td>2.30±.21</td>
<td>3.14±.20*</td>
</tr>
<tr>
<td>Treated</td>
<td>1.44±.20</td>
<td>1.78±.31‡</td>
<td>1.77±.20†</td>
</tr>
<tr>
<td><strong>GFR, mL/min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>120±12</td>
<td>94±27</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>109±13</td>
<td>118±21</td>
<td></td>
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<tr>
<td><strong>RBF, mL/min</strong></td>
<td></td>
<td></td>
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<tr>
<td>Untreated</td>
<td>452±68</td>
<td>217±38*</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>359±29</td>
<td>244±35*</td>
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<tr>
<td><strong>RVR, RU</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>.28±.03</td>
<td>.47±.08*</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>.31±.04</td>
<td>.41±.14</td>
<td></td>
</tr>
<tr>
<td><strong>UNaV, µEq/min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>170±34</td>
<td>26±5*</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>113±18</td>
<td>55±24</td>
<td></td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate; RBF, renal blood flow; and UNaV, urinary sodium excretion.

*P<.05 vs baseline; †P<.05 vs CHF at 14 days; ‡P<.05 treated vs untreated.
Acute administration of a mixed ET\textsubscript{A} and ET\textsubscript{B} receptor antagonist in a canine model of CHF. Recently, Spinale et al\textsuperscript{13} demonstrated improvements in myocyte contractile function and left ventricular fractional shortening after chronic subcutaneous ET\textsubscript{A} receptor antagonism, thus also illustrating an overall improvement in ventricular function with ET\textsubscript{A} receptor antagonism in CHF.

In human CHF, circulating ET-1 correlates with PAP.\textsuperscript{23} Acute administration of a mixed ET\textsubscript{A} and ET\textsubscript{B} receptor antagonist in humans with symptomatic CHF reduces both PAP and PVR.\textsuperscript{11} Despite these observations, little is known about the effects of chronic ET\textsubscript{A} receptor antagonism during the progression of CHF. The present investigation confirms and extends previous reports supporting a role for ET-1 and the ET\textsubscript{A} receptor in the pulmonary vasoconstriction associated with CHF. Furthermore, the present study is the first to demonstrate that chronic ET\textsubscript{A} receptor antagonism in CHF chronically reduces PVR. These observations may have important clinical relevance because previous investigations have established that pulmonary hypertension in CHF has a negative impact on prognosis.\textsuperscript{7} Therefore, it is possible that this action of ET\textsubscript{A} receptor antagonism on PVR in the present study may be a mechanism that contributed to an improvement in mortality in the study recently reported by Sakai et al.\textsuperscript{12}

The present study provides the first in vivo evidence that ET-1 via the ET\textsubscript{A} receptor may regulate the release of ANP under pathophysiological conditions such as in experimental CHF in which atrial pressures are increased. In cultured atrial myocytes, ET-1 has been shown to be a potent secretagogue for ANP.\textsuperscript{3} ET receptor antagonists have been reported to suppress the ability of cultured atrial myocytes to secrete ANP.\textsuperscript{24} In isolated perfused atria, Skvorak et al\textsuperscript{25} demonstrated that BQ-123, an ET\textsubscript{A} selective antagonist, significantly attenuated stretch-induced release of ANP. Additionally, ET-1 antiseraum injected into anesthetized rats decreased basal and volume-stimulated increases in ANP.\textsuperscript{20} In the present investigation, we observed no change with ETA receptor antagonism on basal circulating ANP. In contrast, ET\textsubscript{A} receptor antagonism markedly attenuated the increase in circulating ANP during the progression of experimental CHF. Compared with findings in the CHF control group, ETA receptor antagonism after 14 days of experimental CHF attenuated the increase in circulating ANP without any significant differences in cardiac filling pressures. This study therefore provides evidence that the release of ANP by the heart in response to stretch during CHF involves ET-1 and the ET\textsubscript{A} receptor. At 21 days of experimental CHF, ANP remained lower than the untreated group in association with decreased cardiac filling pressures.

In the presence of ETA receptor antagonism, RVR did not increase in CHF, as was observed in the untreated control group. Furthermore, ETA receptor antagonism attenuated the magnitude of decrease in sodium retention from baseline during experimental CHF. Indeed, the preservation of glomerular filtration rate and sodium excretion occurred despite a greater trend for a greater reduction in MAP and lower
circulating ANP. This observation suggests a possible renoprotective action of ET₄ receptor antagonism, particularly in view of the important renal vasoconstricting role for the ET₄ receptor in the canine kidney. It should be noted that in the treated group, glomerular filtration rate relative to renal blood flow was preserved. This may be explained by an increase in the ultrafiltration coefficient Kᵣ.

The present study has clinical relevance in the treatment of heart failure. The need for additional therapeutic agents for CHF has emerged as a high priority based on the continuing high mortality even in the presence of angiotensin-converting enzyme inhibitors. If limiting systemic and pulmonary vasoconstriction is important in the therapeutics of CHF, ET₄ receptor antagonism may offer efficacy. Nonetheless, the suppression of ANP could be considered an adverse neurohumoral response that may limit efficacy of ET₄ antagonism as a sole treatment modality in CHF. Additionally, the most significant hemodynamic actions were noted at the end of the period of CHF investigated. Therefore, ET₄ receptor antagonism may be most useful in symptomatic or overt CHF, when the endothelin system appears to be activated to its greatest magnitude. In view of the report by Sakai et al of improved mortality with ET₄ receptor antagonism in experimental CHF, further studies focusing on this therapeutic strategy in heart failure are clearly warranted.

In summary, the present study reports that chronic oral ET₄ receptor antagonism results in improvements in systemic and pulmonary vasoconstriction, CO, and cardiac filling pressures in association with reductions in ANP. Despite the reduction in plasma ANP, there was an attenuation in the magnitude of sodium retention. These findings support the concept that endogenous ET-1 via the ET₄ receptor plays an important role in the systemic and pulmonary vasoconstriction, the increase in circulating ANP, and the sodium retention that characterize this model of experimental CHF. Lastly, this study provides evidence for a potential therapeutic role for ET₄ receptor antagonism in the treatment of CHF.

Acknowledgments
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References
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