Failure of Atrial Natriuretic Factor to Increase With Volume Expansion in Acute and Chronic Congestive Heart Failure in the Dog

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It remains unclear whether the levels of atrial natriuretic factor (ANF) observed in chronic CHF are appropriate for the magnitude of elevations in atrial pressures. Specifically, it is not known whether acute increases in atrial pressure in CHF can result in further significant increases in circulating ANF. The present study was designed to test the hypothesis that in chronic CHF there is an attenuated relation between circulating ANF and atrial pressure such that the heart is unable to respond to further increases in atrial pressure with appropriate increases in ANF. Cardiovascular hemodynamics and plasma levels of ANF were measured at baseline and after rapid right ventricular pacing (RRVP) to produce acute (n=10, 25 minutes RRVP) and chronic (n=7, 14–16 days RRVP) CHF. Acute saline volume expansion was then performed in each group to determine the response of circulating ANF to acute increases in atrial pressure in both acute and chronic CHF. In chronic CHF, right atrial pressure was much higher than in acute CHF (8.5±0.9 vs. 3.4±1.3 mm Hg, p<0.05); however, circulating ANF was not greater in chronic as compared with acute CHF (385±73 vs. 500±89 pg/ml), which is consistent with an attenuated release of ANF in chronic CHF. In response to volume expansion, right atrial pressure increased in both acute (3.4±1.3 to 12.1±7 mm Hg) and chronic (8.5±.9 to 13.3±1.0 mm Hg) CHF. Despite these marked further increases in atrial pressure, there was no increase in circulating ANF in acute (500±89 to 453±79 pg/ml) or chronic (385±73 to 379±95 pg/ml) CHF. These studies demonstrate maximal release of ANF in acute and chronic CHF that cannot be increased despite further, acute elevations in atrial pressure and is not overcome despite the chronically elevated atrial pressures observed in chronic CHF. (Circulation 1989;80:651–657)

Increases in atrial pressure with resultant atrial stretch are demonstrated to stimulate release of atrial natriuretic factor (ANF) from the cardiac atria.1 In both acute and chronic congestive heart failure (CHF), atrial pressures are elevated in association with elevation of plasma ANF.2 However, it remains unclear whether the level of ANF observed in chronic CHF is appropriate for the magnitude of elevations in atrial pressures. Specifically, it is not known whether in chronic CHF acute increases in atrial pressure can result in further significant increases in circulating ANF.

The present study was designed to address this question in the anesthetized dog with chronic CHF produced by rapid right ventricular pacing (RRVP). We also examined the response of circulating ANF levels to acute elevations in atrial pressure in the normal dog produced by two maneuvers. First, acute RRVP was performed to produce acute CHF with moderate elevations in atrial pressures. Then rapid acute saline volume expansion was performed during acute CHF to produce the marked elevations in atrial pressures observed in chronic CHF. This acute CHF group represents a control group allowing comparison of the effect of similar marked elevations in atrial pressures on plasma ANF levels in chronic CHF to the effect observed when atrial pressures are elevated acutely in the absence of chronic CHF. We used acute RRVP and rapid volume expansion as the maneuvers to increase...
atrial pressures acutely as previous studies have demonstrated that even with marked volume expansion, atrial pressures do not achieve the levels observed in chronic CHF.3-7

RRVP accurately and consistently reproduces the hemodynamic, neurohumoral, and renal derangements characteristic of the syndrome of CHF in the human and allows one to study both acute and chronic CHF. Acute RRVP causes immediate decreases in cardiac output (CO) and mean arterial pressure (MAP) with increases in filling pressures, thus reproducing the hemodynamic derangements characteristic of acute CHF.8,9 Chronic tachycardia-induced left ventricular dysfunction has been reported in two series of patients with chronic tachycardia and significant left ventricular dysfunction with no other cause for heart failure evident. Nearly all patients demonstrated a marked improvement in left ventricular function with surgical or medical control of the tachycardia as the sole therapeutic intervention.10,11 Coleman et al12 examined RRVP in the dog and demonstrated depressed myocardial contractility, elevated filling pressures, and reductions in blood pressure with RRVP for 2–3 weeks. Rieger et al13 and Reigger and Liebau14 demonstrated progressive depression of CO and blood pressure, progressive elevation of atrial filling pressures, and progressive activation of renin, angiotensin II, aldosterone, and catecholamines with RRVP for 2 weeks in the dog. These findings were confirmed in this same model by Armstrong et al.15 Rieger et al16 also demonstrated an attenuation of these hemodynamic and neurohumoral derangements with chronic captopril therapy in the dog with RRVP similar to the improvement seen in these parameters in response to angiotensin-converting enzyme (ACE) inhibition in the human with CHF.16 The cardiomyopathy induced by chronic RRVP in the dog has been demonstrated to be at least partially reversible as suggested by the observations made in human patients with incessant tachycardias.14,17 The mechanism of the tachycardia-induced cardiomyopathy remains unclear. Studies have not demonstrated hypertrophy of the myocytes as determined by cardiac weights.12,17 Chronic ischemia is not believed to play a role as studies have not demonstrated increases in myocardial lactate extraction, arterial venous oxygen difference, or histologic changes consistent with infarction. Coleman et al12 demonstrated modest but significant decreases in myocardial concentrations of high energy phosphates and suggested that an imbalance between energy supply and demand with chronic tachycardia may lead to myocardial dysfunction.

Preliminary studies have demonstrated that the plasma levels of ANF present in chronic CHF produced by RRVP are not significantly different from those observed with acute CHF produced by acute RRVP despite markedly higher atrial pressures in the chronic CHF group.8 Interpretation of studies in the RRVP model by Rieger et al13 suggested that the ability to further increase plasma ANF levels is lost in the later stages of CHF. In other models of chronic CHF, including the cardiomyopathic hamster and the rat with aortocaval fistula, those animals with the most severe CHF (and higher atrial pressures) do not demonstrate higher ANF levels than those with less severe heart failure.18,19 Based on these studies and others, we hypothesized that chronic CHF is characterized by an attenuated ability to increase circulating ANF in response to increases in atrial pressures. Cardiovascular hemodynamics and circulating ANF were measured at baseline and after production of acute and chronic CHF. Acute saline volume expansion was then performed in each group to assess the ability of the heart to increase plasma concentrations of ANF in response to acute increases in atrial pressures.

Methods

Seventeen anesthetized dogs (17–23 kg) underwent acute saline volume expansion in the presence of either acute (10 dogs) or chronic (seven dogs) CHF produced by RRVP.

In the acute heart failure group, animals were anesthetized with pentobarbital (30 mg/kg) and ventilated with supplemental oxygen at 4 l/min. The right external jugular vein was exposed, and a Swan-Ganz pulmonary artery catheter was placed. The femoral artery was cannulated for monitoring arterial pressure and blood drawing. The femoral vein was cannulated for infusions. A small incision was made in the left thorax to expose the cardiac apex; an epicardial pacing lead was attached to the right ventricular apex. Dogs were suspended in the prone position throughout the experiment. After a 60-minute equilibration period, two baseline measurements of hemodynamics and ANF were made over a 30-minute period. To ensure both optimal intravascular volume and cardiac filling pressures after surgical preparation, dogs received 1.8 ml/kg/min normal saline over 30 minutes followed by a 30-minute equilibration period. Acute CHF was then produced by RRVP at 250 beats/min for 15 minutes. Hemodynamics and ANF were measured after 10 minutes of pacing. The animals were then volume expanded during RRVP to increase atrial pressures to the levels observed in chronic CHF. To achieve the markedly elevated atrial pressures acutely, dogs were rapidly volume expanded with 6 ml/kg/min normal saline for 10 minutes. Cardiovascular hemodynamics and plasma ANF were measured during the last minute of volume expansion.

Plasma ANF levels were measured after at least 10–15 minutes of increased atrial pressure produced by acute pacing, after 10 minutes of acute volume expansion during acute CHF, and after 20–25 minutes of increased atrial pressure produced by volume expansion in the chronic CHF dogs. Previous studies have demonstrated that increases in atrial pressure sustained for 10 minutes produce marked
increases in ANF. Further, Metzler et al demonstrated in the dog with pulmonary artery and aortic constriction that the increase in ANF is present at 10 minutes and is maintained and stable over 60 minutes of elevated atrial pressure. The timing of ANF sampling is designed to allow for adequate periods of peak atrial pressures to produce increases in ANF.

In the chronic CHF group, programmable pacemakers (Model 8420, Medtronic) were implanted 3 weeks before the acute experiment. Baseline hemodynamics and plasma ANF levels were obtained at pacemaker implantation. Under pentobarbital anesthesia (30 mg/kg), a small incision was made in the right groin and a temporary femoral artery catheter was placed for measurement of arterial pressure and for sampling of arterial blood for baseline measurement of ANF and then withdrawn. The right external jugular vein was exposed, and a 7F Swan-Ganz pulmonary artery catheter was advanced under pressure monitoring and positioned in the pulmonary artery. Baseline measurements of right atrial (RAP) and pulmonary capillary wedge pressure (PCWP) as well as CO were obtained, and the catheter was withdrawn and replaced with the pacemaker lead. The lead was advanced under electrocardiographic monitoring until ventricular pacing was confirmed. The lead was tunneled subcutaneously and connected to the pacemaker in the dorsal neck. Two days after implantation, the pacemaker was programmed to 250 beats/min. The dogs were paced from 14 to 16 days at which time all dogs had elevated atrial pressures and reduced CO and most had gross ascites.

The day of the acute experiment, the dogs were anesthetized with fentanyl (0.005–0.01 mg/kg i.v.) and pentobarbital (5–10 mg/kg i.v.) and slowly titrated with supplemental doses given as needed throughout the experiment. The dogs were intubated, ventilated with a Harvard pump with supplemental oxygen at 4 l/min, and suspended in the prone position throughout the experiment. The left external jugular vein was exposed, and a Swan-Ganz pulmonary artery catheter was placed. The femoral artery was cannulated for monitoring of arterial blood pressure and for blood drawing. The femoral vein was cannulated for infusions. After surgical preparation, the dog was allowed to equilibrate for 60 minutes after which two measurements of hemodynamics and ANF were made over a 30-minute period. The dogs were then volume expanded with normal saline at 1.83 ml/kg/min for 30 minutes. Measurements of hemodynamics and ANF were made during the last 10 minutes of volume expansion. This level of volume expansion resulted in levels of atrial pressure comparable to the levels observed during volume expansion in acute CHF.

Cardiovascular hemodynamics measured or calculated included MAP, RAP, PCWP, CO, and SVR. CO was measured by thermodilution in triplicate

| Table 1. Atrial Pressures and Plasma ANF Levels in Acute Versus Chronic CHF |
|-----------------------------------------------|-----------------|
| RAP (mm Hg) | 3.4±1.3 | 8.5±0.9 |
| PCWP (mm Hg) | 15.8±1.8 | 17.6±1.8 |
| ANF (pg/ml) | 500±89 | 385±73 |

ANF, atrial natriuretic factor; CHF, congestive heart failure; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure.

*p<0.05 acute vs. chronic CHF.

and averaged (Cardiac Output Computer Model 9502-A, American Edwards). SVR was calculated as (MAP – RAP/CO) × 80 (dynes · cm · sec⁻¹).

Arterial blood drawn for ANF analysis was placed in an ethylenediaminetetraacetic acid tube and placed on ice. After centrifugation at 2,500 rpm at 5°C for 10 minutes, plasma was separated and stored at −20°C until assay. ANF was measured after extraction by radioimmunoassay as previously described.

All data were averaged and expressed as mean±SEM. Data were analyzed using Dunnett’s paired t test for multiple comparisons and Student’s t test for group comparisons. Significance was achieved at the p<0.05 level.

Results

Table 1 compares atrial pressures and plasma ANF levels in acute and chronic CHF before volume expansion. Though RAP was higher with chronic RRVP than with acute RRVP (8.5±0.9 vs. 3.4±1.3 mm Hg, p<0.005) and though PCWP tended to be higher with chronic RRVP, the level of circulating ANF in the chronic group (385±73 pg/ml) was not increased compared with the acute group (500±89 pg/ml, p=0.4, NS). Indeed, it tended to be lower in the chronic group. Figure 1 illustrates the change in RAP from baseline in acute and chronic CHF as well as the change in plasma ANF levels. The increase in RAP from baseline was greater with chronic CHF (Δ RAP=7.2±1.0 mm Hg) than with acute CHF (Δ RAP=3.5±1.2 mm Hg, p<0.04). However, the change in ANF seen in chronic CHF (Δ ANF=349±71 pg/ml) was not significantly different from that observed in acute CHF (Δ ANF=465±90 pg/ml). Again, both the absolute value and the change in ANF with CHF tended to be lower with chronic CHF despite the greater increase in RAP observed in chronic CHF.

The effects of acute RRVP and subsequent volume expansion in acute CHF on cardiovascular hemodynamics and circulating ANF levels are reported in Table 2 and Figure 2. With acute RRVP, MAP decreased from 106±4 to 97±3 mm Hg.
With subsequent volume expansion during acute RRVP, MAP decreased further to 88±5 mm Hg (p<0.05). CO decreased from 3.51±0.23 l/min at baseline to 2.72±0.19 l/min with acute RRVP (p<0.04) and did not change with subsequent volume expansion. RAP increased from −0.1±0.4 mm Hg at baseline to 3.4±1.3 mm Hg with acute RRVP (p<0.005). With volume expansion during acute RRVP, RAP increased further to 12.1±0.7 mm Hg (p<0.005). Similarly, PCWP increased from 2.4±0.8 mm Hg at baseline to 15.8±1.8 mm Hg with acute RRVP (p<0.005) and 25.9±1.6 mm Hg with volume expansion (p<0.005). Circulating ANF levels increased from 35±5 pg/ml at baseline to 500±89 pg/ml (p<0.005) after 10 minutes of acute RRVP but did not increase further (453±79 pg/ml) after volume expansion for 10 minutes, despite the large increases in atrial pressure.

The effects of chronic RRVP and subsequent volume expansion on cardiovascular hemodynamics and circulating ANF levels are reported in Table 3 and Figure 2. With chronic RRVP, MAP decreased from 118±4 to 89±5 mm Hg (p<0.005). With volume expansion, MAP decreased further to 83±5 mm Hg (p<0.04). CO decreased from 3.63±0.41 to 2.12±0.13 l/min with chronic RRVP (p<0.002) and did not change significantly with volume expansion. It should be noted that in both acute and chronic CHF, volume expansion was associated with a decrease in MAP in the presence of a stable CO, indicating a decrease in SVR. The systemic circulation retains the potential to respond to the increase in intravascular volume with a decrease in resistance. This decrease in resistance is likely mediated by stimulation of cardiopulmonary and aortosinus baroreceptors as well as ventricular mechanoreceptors. However, with RRVP, the ability to respond to the decrease in afterload with an increase in CO is lost in the face of decreased cardiac reserve due to the rapid rate and myocardial dysfunction. Thus, MAP decreased with volume expansion in both acute and chronic CHF. RAP increased from 1.3±0.4 mm Hg at baseline to 8.5±0.9 mm Hg with chronic volume expansion.

**Table 2. Systemic Hemodynamics and Plasma ANF Levels at Baseline, With Acute CHF, and With Volume Expansion in Acute CHF**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Acute CHF</th>
<th>VE in acute CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>106±4</td>
<td>97±3*</td>
<td>88±5‡</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.51±0.23</td>
<td>2.72±0.19*</td>
<td>2.67±0.25‡</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>−0.1±0.4</td>
<td>3.4±1.3*</td>
<td>12.1±0.7‡</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>2.4±0.8</td>
<td>15.8±1.8*</td>
<td>25.9±1.6‡</td>
</tr>
<tr>
<td>SVR (dynes · sec · cm⁻³)</td>
<td>2,644±245</td>
<td>2,880±22</td>
<td>2,443±242‡</td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td>35±5</td>
<td>500±89*</td>
<td>453±79</td>
</tr>
</tbody>
</table>

n=10.
ANF, atrial natriuretic factor; CHF, congestive heart failure; VE, volume expansion; MAP, mean arterial pressure; CO, cardiac output; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

*p<0.05 acute CHF vs. baseline, ‡p<0.05 VE in CHF vs. CHF.

**Table 3. Systemic Hemodynamics and Plasma ANF Levels at Baseline, With Chronic CHF, and With Volume Expansion in Chronic CHF**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Chronic CHF</th>
<th>VE in chronic CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>118±4</td>
<td>89±5*</td>
<td>83±5‡</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.63±0.41</td>
<td>2.12±0.13*</td>
<td>2.42±0.30</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>1.3±0.4</td>
<td>8.5±0.9*</td>
<td>13.3±1.0‡</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>3.9±0.7</td>
<td>17.6±1.8*</td>
<td>22.2±1.3‡</td>
</tr>
<tr>
<td>SVR (dynes · sec · cm⁻³)</td>
<td>2748±316</td>
<td>3,077±233</td>
<td>2,324±226‡</td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td>37±8</td>
<td>385±73*</td>
<td>379±95</td>
</tr>
</tbody>
</table>

n=7.
ANF, atrial natriuretic factor; CHF, congestive heart failure; VE, volume expansion; MAP, mean arterial pressure; CO, cardiac output; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

*p<0.05 chronic CHF vs. baseline, ‡p<0.05 VE in chronic CHF vs. chronic CHF.
RRVP (p<0.005) and to 13.3±1.0 mm Hg with volume expansion (p<0.005). PCWP increased from 3.9±0.7 mm Hg at baseline to 17.6±1.8 mm Hg with chronic RRVP (p<0.005). With volume expansion, PCWP increased further to 22.2±1.3 mm Hg (p<0.02). SVR tended to increase (2,748±316 to 3,077±233 dynes · sec · cm⁻²) with chronic RRVP but the increase was not statistically significant. With volume expansion, SVR decreased from 3,077±233 to 2,324±226 dynes · sec · cm⁻² (p<0.02). Cirulating ANF increased from 37±8 to 385 pg/ml (p<0.005) with chronic RRVP but remained unchanged (379±95 pg/ml) with volume expansion despite the large increases in atrial pressures. Figure 2 illustrates atrial pressures and ANF levels in acute versus chronic CHF at baseline, with CHF, and with volume expansion in CHF. While RAP and PCWP increased with volume expansion in acute and chronic CHF, ANF levels did not change with volume expansion.

Discussion

In the present study, acute and chronic CHF resulted in increases in atrial pressure and plasma ANF. When comparing acute with chronic CHF, this study demonstrates that despite markedly higher RAP in chronic CHF, plasma ANF was not different between acute and chronic CHF. This observation is consistent with an attenuated release of atrial peptide in chronic CHF. The absence of a further increase in circulating ANF in response to acute volume expansion in both acute and chronic CHF supports the conclusion that a maximal release of ANF may exist in states of acute and chronic volume and/or pressure overload.

The present study is consistent with preliminary studies by Edwards et al⑧ in which no increase in plasma ANF levels was noted in chronic CHF as compared with acute CHF in the dog despite higher levels of atrial pressures in the chronic CHF group.⑧ Similarly, though not specifically addressed in the study, Rieger et al⑨ measured atrial pressures and circulating ANF sequentially in dogs undergoing chronic RRVP. Plasma ANF increased in parallel with atrial pressures during the first 6 days of pacing but plateaued despite further increases in atrial pressures on days 6 through 9. In the hamster with familial cardiomyopathy, Ding et al10 observed lower plasma ANF levels in hamsters with severe CHF as compared with those with moderate CHF. Thus, the present study confirms these previous studies and supports the concept of an altered stimulus-release relation between atrial pressure and plasma ANF in chronic CHF such that further increases in atrial pressures fail to result in further increases in circulating ANF.

The present study importantly extends results of these previous studies by determining whether acute increases in atrial pressure in the presence of atrial pressure elevation can result in acute increases in plasma ANF. Our finding of the lack of increase in plasma ANF in the setting of chronic CHF supports the conclusion that maximal release of ANF is achieved in chronic CHF. Furthermore, the lack of increase in ANF to volume loading in acute CHF further supports the concept of a maximal release of ANF in vivo.

The present study supports the concept of a maximal release or a limited reserve of ANF in acute and chronic CHF. There may be a limit to the ability of the atrial and ventricular myocytes to increase the synthetic and secretory capabilities despite further stimulus. Alternatively, the relation between atrial pressure and atrial stretch, the final stimulus for ANF release,1 may be altered due to changes in atrial compliance. Changes in atrial compliance would likely play a larger role in chronic CHF than acute CHF. With chronic CHF, fibrosis and chronic edema may affect the compliance of the atrial myocyte. In both acute and chronic CHF, the relation between stretch and pressure may change at higher pressures, producing a flattening of the stretch-pressure curve and a decrease in the stimulus for ANF secretion (atrial stretch) at very high atrial pressures.

The present findings are supported by results from the study by Raine et al,21 which examined ANF levels and atrial pressures during exercise in humans with and without chronic CHF. These investigators observed that the increase in ANF in the chronic CHF group was less than the increase observed in the group without CHF despite much greater increases in atrial pressure in the CHF group.21 In contrast, Chien et al22 reported that the ability to respond to increases in atrial pressure with increases in plasma ANF was preserved in rats with myocardial infarction. However, the severity of heart failure present in these rats appeared to be mild as evidenced by modest elevations in atrial pressure, the lack of an exaggerated increase in atrial pressure with volume expansion, and a relatively small percentage of the rats with infarction of more than 40% of the left ventricle. The ability to increase ANF levels was preserved in these rats; this would confirm the progressive elevation in ANF observed in our study and by Holmer et al23 in early or mild heart failure. In a preliminary report of studies in humans with chronic CHF, Moe et al24 reported no significant increase in plasma ANF with posturally induced changes in atrial pressures although there was a trend toward increased ANF. Although the increases in atrial pressure were relatively modest and the patients' baseline atrial pressures were relatively low, this preliminary study would suggest that the present observation of a maximal ANF release is also present in the human with chronic CHF.

The limited ability to respond to further increases in atrial pressure in CHF with further increases in ANF may contribute to the escape of the renin-angiotensin-aldosterone system (RAAS) as well as the deteriorating renal excretory capacity observed.
in severe heart failure. In a model of chronic CHF produced by aortocaval fistula in the rat, Winaver et al. observed no differences in plasma ANF levels in those rats with severe heart failure and presumably higher atrial pressures as compared with those that were well compensated. Moe et al. observed suppression of renin, aldosterone, and norepinephrine during the early stages of RVP-induced CHF (days 1–4) associated with the increase in plasma ANF. This is in contrast to the activator of the RAAS, which occurs during the plateau of ANF observed in the later stages of CHF. Similarly, Villarreal et al. observed a suppression of the RAAS and a return to sodium balance associated with the increase in atrial pressures and ANF in the dog with CHF due to aortocaval fistula. Again, these dogs appeared to be in rather mild CHF with peak increases in atrial pressure of approximately 3 mm Hg. In these studies, when moderate elevations in atrial pressures were associated with appropriate elevations in ANF, renal excretory function was maintained and suppression of the RAAS was observed. However, when the increases in atrial pressure were not associated with increases in ANF levels, renal excretory function deteriorated and the RAAS was activated. The exact role that ANF plays in the syndrome of CHF is as yet not fully defined. However, these studies would suggest that the limited ANF reserve observed in this model of CHF may contribute to the decomposition observed in the late stages of CHF. There may be a relative deficiency of this hormone that is capable of potent suppression of the RAAS and preservation of renal function, thus allowing the vasoconstrictive, sodium-retaining systems to act unopposed. Such a speculation would be supported from the studies in humans with chronic CHF and activation of the RAAS in which exogenous administration of ANF may decrease plasma renin activity and/or aldosterone.

In conclusion, the present study importantly demonstrates that there is a limited ANF reserve in acute and chronic heart failure that prevents appropriate increases in plasma ANF in response to acute or chronic elevations in atrial pressure. This phenomenon may contribute to the limited ability to maintain renal function and suppress the RAAS in the later stages of CHF.

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