Atrial Natriuretic Peptide

Effects of synthetic atrial natriuretic peptide on renal function and renin release in acute experimental heart failure

Terry A. Scriven, B.A., and John C. Burnett, Jr., M.D.

ABSTRACT Studies were performed in anesthetized control dogs (n = 6) and in dogs (n = 6) with acute low-output heart failure produced by inflation of a balloon in the thoracic inferior vena cava. Studies were designed to determine the effects of synthetic atrial natriuretic peptide on renal function and renin release in this acute high-renin, sodium-retaining preparation. Intrarenal infusion of synthetic atrial natriuretic peptide (0.3 μg·kg⁻¹·min⁻¹) resulted in decreases in arterial pressure and renal blood flow in both groups. Glomerular filtration rate increased in both low-output (Δ + 10.7 ± 3.1 ml/min) and control (Δ + 8.7 ± 2.9 ml/min) groups. Fractional lithium excretion, a marker of proximal tubule reabsorption, also increased in both low-output (Δ + 12.0 ± 4.6%) and control (Δ + 14.3 ± 5.0%) groups. Renin secretory rate decreased in the low-output group from 852.8 ± 183.0 to 149.5 ± 73.7 ng/min and in the control group from 308.5 ± 84.5 to 44.5 ± 27.5 ng/ml. Intrarenal infusion of atrial natriuretic peptide resulted in an attenuated increase in both urinary sodium excretion (Δ + 42.3 ± 10.7 vs Δ + 201.2 ± 37.9 μeq/min) and fractional excretion of sodium (Δ + 0.48 ± 0.13% vs Δ + 2.85 ± 0.45%) in the low-output as compared with the control group. Our studies demonstrate that administration of synthetic atrial natriuretic peptide results in an increase in glomerular filtration rate and a decrease in proximal tubule reabsorption, as estimated by lithium excretion, in both control dogs and those with acute low-output heart failure. Furthermore, despite a decrease in arterial pressure, synthetic atrial natriuretic peptide markedly inhibits renin secretion under control conditions and in the high-renin state. Despite similar increases in glomerular filtration rate and decreases in proximal tubule reabsorption and renin release, the natriuretic response to synthetic atrial natriuretic peptide, although present, is markedly attenuated in this preparation of acute experimental heart failure.

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RECENT INVESTIGATIONS have established that mammalian atria possess specific secretory granules that synthesize and release natriuretic and vasoactive peptides that have a fundamental physiologic role in regulation of cardiovascular volume. These peptides have been referred to as atrial natriuretic factor, atrial natriuretic peptides, cardionatrin, atriopeptin, and auriculin. Previous studies from our laboratory have reported that intrarenal infusion of synthetic atrial natriuretic peptide results in a marked increase in urine volume and sodium excretion. This marked natriuretic response is associated with a significant increase in glomerular filtration rate and a decrease in whole-kidney proximal tubule reabsorption as determined by the clearance of lithium. These studies have also demonstrated that intrarenal administration of synthetic atrial natriuretic peptide results in marked inhibition of renin release despite a sustained decrease in arterial pressure.

Congestive heart failure is a syndrome characterized by sodium retention and activation of the renin-angiotensin system. To date, no studies have definitely investigated the renal hemodynamic and excretory response to atrial natriuretic peptide in a preparation of heart failure. Preliminary studies in dogs with experimental heart failure have reported that intravenous infusion of synthetic atrial natriuretic peptide is associated with a blunted natriuretic response. This blunted natriuretic response occurred despite an increase in creatinine clearance. Recent studies by Chimoskey et al. in hamsters with familial cardiomyopathy and congestive heart failure have demonstrated that intravenous infusion of synthetic atrial natriuretic peptide results in a marked increase in renal perfusion and filtration fraction.
gestive heart failure have shown a deficiency in atrial natriuretic peptide activity in these animals. These investigators speculated that the abnormalities in volume regulation accompanying heart failure could in part be mediated by an absence of atrial natriuretic peptide. The present study was therefore designed to test the hypothesis that exogenous administration of atrial natriuretic peptide to dogs with acute low-output heart failure, a preparation that produces the renal and neurohumoral adjustments characteristic of congestive heart failure, would correct defects in renal sodium handling and the renin-angiotensin system.

The present study investigates the effects of synthetic atrial natriuretic peptide on renal function and renin release in the presence and absence of acute low-output heart failure produced by inflation of a balloon in the thoracic inferior vena cava. Specifically, these studies focus on the effect of synthetic atrial natriuretic peptide on renal blood flow, glomerular filtration rate, proximal tubular reabsorption, renin secretion, and arterial pressure in this experimental preparation of heart failure.

Methods

Experiments were performed in two groups of 14 to 25 kg mongrel dogs: a control group and a group in which acute low-output heart failure was induced by balloon inflation. The low-output state was produced by introduction of a Bardex-Foley No. 16F catheter into the thoracic inferior vena cava via the right femoral vein, with subsequent inflation to increase inferior vena cava venous pressure approximately 8 to 10 mm Hg above baseline. The position of the balloon in the thoracic inferior vena cava was confirmed at the termination of the experiment by exploration of the vena cava through a thoracotomy incision. This preparation, extensively used in previous investigations of the pathophysiology of congestive heart failure, produces the systemic hemodynamic and neurohumoral adjustments that characterize this syndrome.10,11

Immediately before the experiment, each dog was anesthetized with pentobarbital (30 mg/kg iv). The femoral artery was catheterized for measurement of mean arterial pressure. Double cannulation of the left femoral vein was performed. One catheter was placed in the thoracic vena cava to measure venous pressure and the second was used for infusion of insulin in isotonic saline at a rate of 1 ml/min to achieve a plasma insulin concentration of 50 mg/dl. In the low-output group, the No. 16F Foley catheter was introduced into the right femoral vein and advanced into the thoracic inferior vena cava, as described above. Isotonic saline was perfused at 10 ml/hr through the catheter to maintain patency and to minimize thrombosis of the catheter tip. A left flank incision was then made and the left kidney was exposed. The ureter was cannulated with polyethylene tubing. The renal vasculature was isolated in situ. An angled 22-gauge needle was introduced into the renal vein for renal venous sampling, which was maintained patent with a 10 ml/hr heparinized saline infusion. A 22-gauge curved needle was placed in the renal artery for infusion of synthetic atrial natriuretic peptide. During non–atrial natriuretic peptide infusion periods of the experiment 1 ml/min isotonic saline was infused through the renal artery needle. Both needles were connected to Sage Instruments syringe pumps (Model 391A). An electromagnetic flow probe (Micron Instruments, Model MC-4025) was placed on the renal artery proximal to the needle and connected to a flowmeter (Micron Instruments, Inc., Model RC1008).

After completion of surgery, the balloon was inflated as described above in the low-output group; no inflation procedure was performed in the control group. The dogs were then allowed to stabilize for approximately 1 hr. During the control period, 15 min clearance was determined twice, followed by the intrarenal infusion of 26-amino acid (8-33) synthetic atrial natriuretic peptide (Peninsula Labs, Belmont, CA) at a rate of 0.3 µg/kg·min⁻¹·min⁻¹ for a total of 45 min. Fifteen minutes after initiation of the infusion of synthetic atrial natriuretic peptide, clearance was determined twice. Glomerular filtration rate was determined by the clearance of inulin. Plasma and urine levels of inulin were measured by the anthrone method. Plasma and urine sodium and potassium levels were determined by use of ion-selective electrodes (Beckman E 2A analyzer). Urine and plasma lithium concentrations were measured by flame-emission spectrophotometry (Instruments Lab, Model 357). Whole-kidney proximal tubular reabsorption of sodium was estimated by the lithium-clearance technique. This technique has been shown to be a reliable method for estimating proximal tubular handling of sodium, since lithium is reabsorbed exclusively by the proximal tubule.12,13 Thus, the fractional excretion of lithium serves as a measure of whole-kidney fractional delivery of sodium from the proximal tubule. Dogs were given 300 mg of lithium orally the night before each experiment. Samples for determination of plasma renin activity were obtained from arterial and renal vein catheters during each clearance period. Renin secretion rate was calculated from the product of renal plasma flow and the renal-arteriovenous plasma renin activity difference. For clarity of presentation, the renin secretion rate units of nanograms of angiotensin I per hour per minute were simplified to nanograms per minute. Plasma renin activity was measured by radioimmunoassay.14

All data on clearance during the control and atrial natriuretic peptide infusion periods were averaged and expressed as mean values ± SE. The data were analyzed with paired and unpaired t tests.

Results

Table 1 and figures 1 to 5 list the renal hemodynamic and excretory function data obtained at baseline and during the intrarenal infusion of synthetic atrial natriuretic peptide in the two groups of dogs.

Hemodynamics. A decrease in mean arterial pressure was observed during intrarenal infusion of synthetic atrial natriuretic peptide in both the control (120 ± 4 to 114 ± 4 mm Hg, p < .05) and low-output (113 ± 5 to 107 ± 4 mm Hg, p < .05) groups. Renal blood flow also slightly decreased in the control group (157 ± 24 to 146 ± 21 ml/min) and low-output group (143 ± 21 to 137 ± 23 ml/min) during administration of atrial natriuretic peptide; however, these decreases in renal blood flow were not significant. Renal vascular resistance did not change in either group in response to atrial natriuretic peptide. Glomerular filtration rate increased in the control group from 34.0 ± 3.9 to 45.3 ± 3.6 ml/min (p < .05) and glomerular filtration rate
similarly increased in the low-output group from 23.3 ± 4.4 to 33.9 ± 5.6 ml/min (p < .05).

**Excretory function.** When compared with the marked diuresis and natriuresis observed in control dogs, a significantly blunted natriuretic and diuretic response to intrarenal infusion of synthetic atrial natriuretic peptide was observed in the dogs with acute low-output heart failure. In control dogs urine flow increased from 0.47 ± 0.15 to 2.49 ± 0.44 ml/min (p < .005) and in the low-output group it increased from 0.11 ± 0.03 to 0.41 ± 0.10 ml/min (p < .05). Thus, the diuretic response was significantly blunted (p < .005) in the dogs in the low-output group (Δ +0.30 ± 0.08 ml/min) as compared with that in dogs in the control group (Δ +2.02 ± 0.37 ml/min).

Sodium excretion increased in the control group (29.9 ± 7.8 to 231.0 ± 42.5 μeq/min, p < .005) and in the low-output group (10.8 ± 2.3 to 46.2 ± 12.3 μeq/min, p < .02). Fractional excretion of sodium increased in the control dogs (0.57 ± 0.13% to 3.42 ± 0.54%, p < .005). A lesser increase in fractional excretion of sodium was observed in the low-output group (0.42 ± 0.16% to 0.90 ± 0.13%, p < .05). Thus, the natriuretic response to intrarenal administration of synthetic atrial natriuretic peptide was markedly attenuated (p < .005) in the dogs with acute low-output heart failure as compared with that in control dogs. Absolute urinary sodium excretion increased Δ +42.3 ± 10.7 μeq/min in the low-output group, compared with Δ +201.2 ± 37.9 μeq/min in the control group. The change in fractional sodium excretion with infusion of atrial natriuretic peptide was Δ +0.48 ± 0.13% in the low-output group, as compared with Δ +2.85 ± 0.45% in the normal group. Despite the blunted natriuretic response to atrial natriuretic peptide in the low-output group, fractional lithium excretion increased significantly in both the control dogs (29.8 ± 4.1 to 44.1 ± 4.6%, p < .05) and those with low-output heart failure (17.7 ± 3.1% to 30.2 ± 4.3%, p < .05).

Renin secretory rate was significantly elevated in dogs with acute low-output heart failure as compared with that in normal animals (852.8 ± 183.0 vs 308.5 ± 84.5 ng/min, p < .05). Nevertheless, the intrarenal infusion of synthetic atrial natriuretic peptide produced a significant decrease in renin secretory rate in both groups. Administration of synthetic atrial natriuretic peptide resulted in a decrease in renin secretory rate in

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**TABLE 1**

Renal hemodynamic and excretory response to intrarenal infusion of synthetic atrial natriuretic peptide in dogs in the control and acute low-output heart failure groups

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>IVCP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>GFR (ml/min)</th>
<th>RVR (ml/min·mm Hg⁻¹)</th>
<th>V (ml/min)</th>
<th>U₅ᵥV (μeq/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>120 ± 4</td>
<td>1.9 ± 0.4</td>
<td>157 ± 24</td>
<td>34.0 ± 3.9</td>
<td>0.88 ± 0.19</td>
<td>0.47 ± 0.15</td>
<td>29.9 ± 7.8</td>
</tr>
<tr>
<td>ANP</td>
<td>114 ± 4</td>
<td>1.8 ± 0.4</td>
<td>146 ± 21</td>
<td>45.3 ± 3.6</td>
<td>0.84 ± 0.13</td>
<td>2.49 ± 0.44</td>
<td>231.0 ± 42.5</td>
</tr>
<tr>
<td>Acute low-output group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>113 ± 5</td>
<td>10.8 ± 1.2¹</td>
<td>143 ± 21</td>
<td>23.3 ± 4.4</td>
<td>0.89 ± 0.16</td>
<td>0.11 ± 0.03</td>
<td>10.8 ± 2.3</td>
</tr>
<tr>
<td>ANP</td>
<td>107 ± 4¹</td>
<td>10.8 ± 1.3¹</td>
<td>137 ± 23</td>
<td>33.9 ± 5.6</td>
<td>0.91 ± 0.17</td>
<td>0.41 ± 0.10³,⁴</td>
<td>46.2 ± 12.3²,⁴</td>
</tr>
</tbody>
</table>

ANP = atrial natriuretic peptide; MAP = mean arterial pressure; IVCP = inferior vena cava pressure; RBF = renal blood flow; GFR = glomerular filtration rate; RVR = renal vascular resistance; V = urine flow; U₅ᵥV = urinary sodium excretion; FE₅ᵥ = fractional excretion of sodium; FE₅ᵥ = fractional excretion of lithium; RSR = renin secretory rate.

¹p < .05; ²p < .02; ³p < .005, by paired t test. ⁴p < .05 by unpaired t test.
normal dogs from 308.5 ± 84.5 to 44.5 ± 27.5 ng/min (p < .05). In the low-output group, intrarenal infusion of atrial natriuretic peptide decreased renin secretory rate from 852.8 ± 183.0 to 149.5 ± 73.7 ng/min (p < .005).

**Discussion**

The intrarenal infusion of synthetic atrial natriuretic peptide in control dogs and those with low-output heart failure resulted in a significant increase in glomerular filtration rate and a decrease in proximal tubule reabsorption as estimated by changes in lithium excretion. Intrarenal administration of the synthetic atrial natriuretic peptide significantly decreased arterial pressure as well as renin secretory rate in both groups. Despite similar alterations in glomerular filtration rate, proximal tubular reabsorption, and renin release in the two groups, the natriuretic and diuretic response to atrial natriuretic peptide was markedly attenuated in animals with acute low-output heart failure as compared with that in control dogs.

Glomerular filtration rate increased in both the control and low-output groups. The observed increase in glomerular filtration rate was consistent with previous reports of effects of synthetic atrial natriuretic peptide in normal dogs.\(^7\)\(^{-15}\) Previous studies have suggested that the increase in glomerular filtration rate observed with infusion of this substance may be the result of an increase in postglomerular arteriolar resistance or in the coefficient for ultrafiltration.\(^7\)\(^,\)\(^16\)

The present study revealed a significant increase in whole-kidney fractional excretion of lithium with intrarenal infusion of synthetic atrial natriuretic peptide in both groups. Previous studies from our laboratory, as well as others, have reported an action of atrial natriuretic peptide on proximal tubule reabsorption.\(^7\)\(^,\)\(^17\) However, the increased filtered load of lithium accompanying increased glomerular filtration in each group may have contributed to its increased excretion.

Despite a significant increase in glomerular filtration rate and a decrease in proximal tubule reabsorption, the natriuretic response to synthetic natriuretic peptide was markedly attenuated in the low-output group. Such a response is similar to the excretory response to acute volume expansion previously observed in animals with experimental heart failure.\(^18\) These latter studies in dogs with heart failure demonstrated that acute saline volume expansion, a physiologic maneuver recently reported to be associated with increased levels of immunoreactive atrial natriuretic peptide,\(^19\) is characterized by an increase in glomerular filtration.

**TABLE 1**

(Continued)

<table>
<thead>
<tr>
<th>FE(_{\text{Na}}) (%)</th>
<th>FE(_{\text{Li}}) (%)</th>
<th>RSR (ng/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.57 ± 0.13</td>
<td>29.8 ± 4.1</td>
<td>308.5 ± 84.5</td>
</tr>
<tr>
<td>3.42 ± 0.54(^C)</td>
<td>44.1 ± 4.6(^A)</td>
<td>44.5 ± 27.5(^A)</td>
</tr>
<tr>
<td>0.42 ± 0.16</td>
<td>17.7 ± 3.1</td>
<td>852.8 ± 183.0(^P)</td>
</tr>
<tr>
<td>0.90 ± 0.13(^R,D)</td>
<td>30.2 ± 4.3(^A)</td>
<td>149.5 ± 73.7(^C)</td>
</tr>
</tbody>
</table>

**FIGURE 3.** Individual data for absolute urinary sodium excretion (U\(_{\text{Na}}\)V) before and during administration of atrial natriuretic peptide in control and low-output groups.

**FIGURE 4.** Individual data for fractional excretion of sodium (FE\(_{\text{Na}}\)\(^{\text{+,}}\)) before and during administration of atrial natriuretic peptide in control and low-output groups.

**FIGURE 5.** Renin secretory rate (RSR) before and during administration of atrial natriuretic peptide in control and low-output groups.
rate and a decrease in proximal tubule reabsorption with a blunted natriuresis. The blunted natriuresis was attributed to enhanced solute reabsorption beyond the proximal tubule, perhaps in part mediated by enhanced circulating levels of aldosterone, which are known to be elevated in models of low-output heart failure, and/or alterations in physical factors, which occur during perturbations in renal perfusion and venous pressures. The present studies further support the hypothesis that the defect in the renal handling of sodium in heart failure may be mediated by factors that act beyond the proximal tubule and are therefore independent of the action of atrial natriuretic peptide on glomerular filtration rate and proximal tubular reabsorption. Thus, the present studies provide further insight into the understanding of heart failure by focusing on the importance of nephron segments beyond the proximal tubule in the pathophysiology of congestive heart failure.

Balloon inflation in the thoracic inferior vena cava resulted in an increase in renin secretion. The mechanism of the increase in renin release during balloon inflation may be multifactorial, with factors including decreased delivery of solute to the macula densa, increased renal nerve activity, and decreased distention of renal baroreceptors. Intrarenal administration of atrial natriuretic peptide nevertheless resulted in a decrease in renin secretory rate in both control dogs and those with low-output heart failure. This observation is consistent with previous reports that atrial natriuretic peptide decreases renin release despite a sustained decrease in arterial pressure. The mechanism by which atrial natriuretic peptide decreases renin secretory rate remains unclear. Previous investigations have reported an inverse relationship between sodium chloride delivery to the macula densa and renin release.

Probable enhanced delivery of sodium chloride to the macula densa during intrarenal infusion of atrial natriuretic peptide thus would be expected to signal the juxtaglomerular cells to decrease renin release. Recent studies by Oppeinorth et al. support a macula densa mechanism in the mediation of atrial natriuretic peptide–induced inhibition of renin release. However, the possibility of an additional direct suppression of renin release from the juxtaglomerular cells by this peptide cannot be excluded.

In summary, results of the present study demonstrate that the natriuretic response to atrial natriuretic peptide, although present, is markedly attenuated in the acute high-renin, sodium-retaining preparation of heart failure we used. This blunted natriuretic response occurs despite the unique ability of this peptide to increase glomerular filtration rate and decrease proximal tubule reabsorption. Furthermore, atrial natriuretic peptide serves as a potent inhibitor of the renin-angiotensin system in this high-renin state, despite a decrease in arterial pressure.

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References

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