Renal-Endocrine Adaptations to Endogenous Atrial Natriuretic Factor During Tachycardia-Induced Reductions in Renal Perfusion Pressure

Wayne L. Miller, Brooks S. Edwards, Robert S. Zimmerman, and John C. Burnett Jr.

Atrial pressure, atrial natriuretic factor (ANF), the renin-angiotensin-aldosterone system, and renal hemodynamic functions were examined during and after right ventricular pacing in anesthetized dogs (n=9). Mean arterial pressure, cardiac output, and renal blood flow decreased during tachycardia while right and left atrial pressures increased. ANF markedly increased during tachycardia but urinary and fractional excretion of sodium were unchanged from control. Plasma renin activity was not increased during pacing despite the decrease in renal perfusion pressure. After tachycardia and restoration of mean arterial pressure to control, ANF declined but remained elevated above control despite a return of atrial pressure to control level. After tachycardia, urinary and fractional sodium excretion increased significantly in the absence of an increase in glomerular filtration rate. These findings support the following conclusions: 1) tachycardia increases ANF in association with increased atrial pressure; however, an elevation of ANF persists following tachycardia despite the absence of the persistent stimulus of elevated atrial pressures; 2) the increase in ANF during tachycardia may contribute to the absence of a decrease in sodium excretion and activation of the renin-angiotensin system that occurs with reduction in renal perfusion pressure; and 3) tachycardia-induced natriuresis may be dependent on an increase in ANF and the maintenance of renal perfusion pressure. (Circulation Research 1990;66:76–83)

Atrial natriuretic factor (ANF) is a potent hormone of cardiac origin that is released in response to an increase in atrial pressure with associated atrial stretch.1,2 Exogenous administration of ANF at pharmacological concentrations increases sodium excretion and inhibits renin release.3 Tachydyssrhythmias of atrial and ventricular origin have been shown to increase atrial pressures.4-6 Yet, while previous studies have documented increases in ANF during tachycardia,4,7-9 the integrated cardiorenal and endocrine responses to tachycardia are conflicting. The current study was, therefore, designed to determine the effect of tachycardia and associated cardiac hemodynamic changes on circulating concentrations of ANF and consequent changes in sodium excretion and plasma renin activity. Rapid right ventricular pacing in the dog was employed as a model of tachycardia. The specific hypotheses tested were 1) circulating concentrations of ANF parallel changes in atrial pressure during and following tachycardia, 2) sodium excretion parallels circulating concentrations of ANF during and following tachycardia, and 3) an inverse relation exists between plasma ANF concentration and plasma renin activity during and following tachycardia. To test further the relation between elevated ANF upon renin activity during reductions in renal perfusion pressure as observed during tachycardia graded constriction of the suprarenal aorta in the presence and absence of exogenous ANF was also performed in a separate group of dogs.

Materials and Methods

Surgical Preparation

Twenty-four mongrel dogs weighing 16–22 kg were studied. The pacing group comprised nine dogs; each of these dogs received one oral dose of lithium carbonate (300 mg) 12–18 hours before the acute study. The aortic clamping group comprised the
remaining 15 dogs. The dogs were fasted but allowed water ad libitum until the time of the study. Dogs were anesthetized with sodium pentobarbital (30 mg/kg i.v.) with additional anesthetic given as needed to maintain a constant level of anesthesia. Pulmonary ventilation was accomplished by a positive-pressure respirator (model 6070, Harvard Apparatus, South Natick, Massachusetts) with room air enriched with 100% oxygen. Blood gases and pH were monitored and adjustments made as necessary to maintain acceptable ranges (PO$_2$ 290–350; PCO$_2$ 27–40; pH 7.36–7.46). Respiratory rate and tidal volume were adjusted to body weight.

A polyethylene catheter was advanced from the left femoral artery to the level of the abdominal aorta for measurement of arterial blood pressure and blood sampling. Two polyethylene catheters were advanced through the left femoral vein. One venous catheter was used to infuse isotonic saline at 1 ml/min, and the second was used to infuse inulin in isotonic saline to attain a plasma inulin concentration of approximately 50 mg/dl. Syringe pumps (model 391A, Sage Instruments, Cambridge, Massachusetts) were used to maintain saline and inulin infusions during the experimental period. A left retroperitoneal flank incision was made and the left ureter was calculated with polyethylene tubing. A calibrated electromagnetic flow probe was placed around the left renal artery and connected to a flow meter (model FM 5010, Carolina Medical Electronics, King, North Carolina). Both renal blood flow and arterial pressure were recorded on a strip chart recorder (model 2200, Gould Instruments, Cleveland, Ohio).

A flow-directed balloon-tipped thermocatheter (model 93-131A, 7F, American Edwards Laboratories, Inc, Santa Ana, California) was advanced from the right external jugular vein through the cardiac chambers with the tip positioned in a pulmonary artery. Right atrial, pulmonary artery, and pulmonary artery wedge pressures were measured. Cardiac output was determined in triplicate by thermodilution technique (model 9510-A, American Edwards Cardiac Output Computer). In addition, cardiac pacing was accomplished by the transvenous placement of a 6F bipolar pacing catheter (Extracorporeal Medical Specialties, Inc, King of Prussia, Pennsylvania) into the right ventricular cavity. An electrocardiogram (lead II) was continuously recorded. During the experimental period, the dogs were held prone in a metal frame.

Experimental Protocols

Rapid right ventricle pacing. After completion of the surgical preparations and initiation of intravenous infusions, the dogs were allowed to stabilize for approximately 60 minutes. Data were collected during four experimental phases: control, pacing, post-pacing, and recovery. The control phase consisted of two consecutive 15-minute clearances with the measurement of cardiac, renal, and systemic hemodynamics and excretory function during each period. Arterial blood samples were drawn to measure selected renal-endocrine concentrations as described below. After control clearances, right ventricular pacing was initiated at 200 beats/min for 45 minutes. During the pacing period, three 15-minute clearances were obtained with hemodynamic, renal, and endocrine measurements completed midway through each clearance period. The postpacing period consisted of the 45 minutes immediately after the pacing period and was divided into three 15-minute clearances with measurements of hemodynamic, renal, and endocrine function data during each clearance. After the 45-minute postpacing period, a second 45-minute stabilization period without data collection was observed. A final 15-minute recovery clearance was then completed with all measurements obtained as in the previous periods. The total duration of the pacing experiment was 180 minutes.

Suprarenal aortic clamping. Mean renal perfusion pressure was reduced by graded clamping of the aorta proximal to the renal arteries by an adjustable Blalock clamp placed above both the right and left renal arteries. Renal perfusion pressure was reduced to an extent comparable to that observed with right ventricular pacing—approximately 15% below control mean arterial pressure. The experimental protocol was similar to that described above with two 15-minute control clearances followed by three 15-minute clearances during which renal perfusion pressure was reduced by aortic clamping (n = 9). At the completion of this 45-minute period, the clamp was removed and all parameters were again monitored during two 15-minute recovery periods, one immediately postconstriction and one 60 minutes postconstriction. In an additional group of six dogs, ANF was infused systemically (10 ng/kg/min i.v.) beginning 1 minute before and continuing through the period of reduced renal perfusion pressure. The dose of exogenous ANF infused was designed to elevate plasma levels within a physiological range and not to exceed the levels we observed with right ventricular pacing. Arterial blood pressure was measured simultaneously at sites proximal and distal to the aortic clamp through catheters advanced retrogradely from the femoral artery. Hemodynamic, renal, and endocrine parameters were measured during each of the clearance periods.

Analytical Procedures

Extracted arterial plasma levels of ANF were measured by a radioimmunoassay procedure previously described. The lower limit of detection was 3 pg/ml plasma. Glomerular filtration rate was determined by the clearance of inulin with plasma and urine inulin concentrations measured by the anthrone method. Plasma and urinary sodium concentrations were quantified using ion-selective electrodes (System E2A, Beckman Instruments, Brea, California). Plasma and urine lithium concentrations, however, were measured by flame-emission spectrophotometry (model 357, Instruments Lab, Lexington, Massachu-
setts). Plasma renin activity, plasma aldosterone and arginine vasopressin concentrations were measured by radioimmunoassay.\textsuperscript{12,13} Plasma norepinephrine concentrations were measured by fractionation technique using high-pressure liquid chromatography quantitation after chromatographic purification.\textsuperscript{14}

All data from the individual 15-minute clearances were combined for the control, ventricular pacing, and postpacing periods (the recovery period consisted of only one 15-minute clearance) and the mean values calculated. Data from the aortic constriction groups were combined for the two control periods, while data from each of the aortic constriction and recovery periods are expressed separately. Data are expressed as mean±SEM. Statistical analysis of data was completed by the Student's t test for paired and unpaired observations. Statistical significance was accepted for $p<0.05$.

**Results**

**Rapid Right Ventricular Pacing**

*Hemodynamic data.* Figures 1 and 2 and Table 1 depict the cardiovascular responses to ventricular pacing. Heart rate was increased with pacing to 200±2 beats/min from a control of 143±2 beats/min. In the postpacing period, heart rate (149±2) remained above control but had returned to control by the recovery period. Mean arterial pressure and cardiac output were significantly decreased from control with pacing (112±4 to 92±4 mm Hg and 3.2±0.2 to 2.4±0.2 l/min, respectively), while right and left atrial pressures were elevated above control. Renal blood flow was reduced from control (171±11 to 144±12 ml/min) during ventricular pacing. Renal vascular resistance, however, was not altered during pacing, but was significantly elevated in the postpacing periods. Mean arterial pressure returned to control level during the immediate postpacing and recovery periods. Cardiac output did not return to control level in the postpacing periods, but was maintained at the lower pacing-induced level for the remainder of the experimental periods. Peripheral vascular resistance was increased by approximately 40% above control by the time of the recovery phase.

*Endocrine data.* Endocrine responses to ventricular-paced tachycardia are shown in Figure 3 and Table 3. ANF concentrations increased significantly above control (54±5 pg/ml) with pacing (268±8 pg/ml). ANF then declined during the immediate postpacing period, but remained elevated (83±10 pg/ml) above control despite the return of atrial pressure to control levels. Control ANF level was restored, however, during the recovery period.

Despite the significant decrease in renal perfusion pressure during tachycardia, plasma renin activity (PRA) was not significantly elevated from control (3.0±0.5 ng/ml/min) with pacing and remained unchanged throughout the protocol. Aldosterone was unchanged from control (6.3±0.6 ng%) with pacing, but was elevated during the postpacing periods. In contrast, vasopressin decreased from control (6.2±0.5 pg/ml) during ventricular pacing and was then elevated above control in the postpacing period. Plasma osmolalities, however, were unchanged with tachycardia or in the recovery period. Norepinephrine plasma concentration (control, 85±13 pg/ml) was elevated with ventricular pacing to 166±15 pg/ml, and while the norepinephrine level declined in the postpacing period, the concentration remained significantly above control level (125±14 pg/ml).

*Renal function data.* Renal function responses to ventricular-paced tachycardia are shown in Figure 4 and Table 3. Glomerular filtration rate decreased significantly from control with pacing (28±2 to 22±1 ml/min) and remained depressed during the immediate postpacing period, but returned to control level in the recovery period. Sodium excretion was not

**FIGURE 1.** Hemodynamic response to right ventricular pacing in the dog. Asterisk indicates significant difference from control. MAP, mean arterial pressure; CO, cardiac output.

**FIGURE 2.** Hemodynamic response to right ventricular pacing in the dog. Asterisk indicates significance difference from control. L(AP), pressure; RBF, left renal arterial blood flow; RVR, left renal artery vascular resistance.
changed from control level with pacing (21±5 to 16±4 \(\mu\)eq/min) above control as well as above the level observed during pacing. Fractional excretion of sodium also was unchanged with pacing, but increased significantly in the postpacing period. After pacing, both urinary and fractional sodium excretion increased in the absence of increases in glomerular filtration rate. Fractional excretion of lithium, which reflects whole kidney proximal tubule sodium delivery, was not significantly altered from control (28±3%) during ventricular pacing or in the postpacing periods. Filtration fraction also did not change from control during pacing or in the postpacing periods. Serum sodium concentration was unchanged from control (144±0.4 meq/l) during and after pacing.

**Suprarenal Aortic Constriction**

**Hemodynamic data.** Figure 5 shows the effects of ANF infusion on proximal and distal aortic blood pressure and renal blood flow with clamping of the suprarenal aorta. Renal perfusion pressure as reflected by mean distal aortic blood pressure was uniformly reduced during clamping in both groups (with and without ANF infusion). In contrast, proximal aortic pressure was increased during aortic clamping in the absence of ANF infusion. An increase in proximal arterial pressure with aortic clamping, however, was not observed with the simultaneous infusion of ANF; mean proximal arterial pressures remained at control level. Renal blood flow was significantly reduced during aortic clamping in the absence of exogenous ANF but was preserved in the presence of ANF infusion.

**Endocrine data.** Endogenous ANF levels were elevated with aortic clamping alone and remained elevated, although decreasing, in the recovery periods (Figure 5). Plasma levels of ANF with exogenous infusion and aortic clamping were elevated to approximately two times that observed with aortic clamping alone. The maximum level of 148±28 pg/ml, however, was below that observed with right ventricular pacing (269±24 pg/ml). In this group, ANF levels returned to control during recovery.

PRA was elevated with aortic clamping alone. Despite the maintenance of reduced renal perfusion pressure from the first period of clamping, PRA

### Table 1. Hemodynamic Response to Right Ventricular Pacing in the Dog

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Pacing</th>
<th>Postpacing</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>143±2</td>
<td>200±0</td>
<td>149±2*</td>
<td>146±4</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>112±4.3</td>
<td>92±3.5*</td>
<td>109±2.5</td>
<td>114±4.7</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.15±0.17</td>
<td>2.43±0.15*</td>
<td>2.46±0.16*</td>
<td>2.39±0.24*</td>
</tr>
<tr>
<td>(L)AP (mm Hg)</td>
<td>4.4±0.36</td>
<td>11.2±0.67*</td>
<td>4.0±0.28</td>
<td>3.78±0.43</td>
</tr>
<tr>
<td>(R)AP (mm Hg)</td>
<td>0.06±0.36</td>
<td>-2.15±0.22*</td>
<td>-0.56±0.25</td>
<td>-0.89±0.45</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>171±11</td>
<td>144±12*</td>
<td>155±14</td>
<td>146±25</td>
</tr>
<tr>
<td>RVR (mm Hg/ml/min)</td>
<td>0.73±0.072</td>
<td>0.780±0.119</td>
<td>0.996±0.142*</td>
<td>1.071±0.233*</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. MAP, mean arterial pressure; CO, cardiac output; (L)AP, left arterial pressure; (R)AF, right atrial pressure; RBF, renal blood flow; RVR, renal vascular resistance.

*p<0.05 vs. control, n=9.

**FIGURE 3. Endocrine responses to right ventricular pacing in the dog.** Asterisk indicates significant difference from control. ANF, atrial natriuretic factor; PRA, plasma renin activity; ALDO, aldosterone; AVP, arginine vasopressin; NE, plasma norepinephrine.

**FIGURE 4. Renal response to right ventricular pacing in the dog.** Asterisk indicates significant difference from control. GFR, glomerular filtration rate; \(U_{\text{Na}^+}V\), sodium excretion rate; \(FE_{\text{Na}^+}\), fractional excretion of sodium; \(FE_{\text{Li}^+}\), fractional excretion of lithium.
showed a delayed response and was not elevated until the third 15-minute period of aortic clamping. In contrast, PRA in the presence of exogenous ANF was unchanged from control level but was significantly reduced when compared with PRA in the same period (third) of aortic clamping alone. PRA returned to control level during the recovery periods in both groups.

Renal function data. Sodium excretion was reduced with aortic clamping alone but not to a statistically significant extent (29.6±8.6 to 16.0±7.2 μeq/min). In the presence of ANF infusion, sodium excretion was maintained at control level during aortic clamping (57.6±11.6 to 67.0±19.8 μeq/min). With the discontinuation of both aortic clamping and ANF infusion, sodium excretion was significantly elevated above control (123±41 vs. 58±12 μeq/min) during the immediate postconstriction recovery period. Sodium excretion then returned to control level in the subsequent recovery period (51.0±23.3). In contrast, sodium excretion was unchanged from control in the recovery periods of the group with aortic clamping alone (29.6±8.6 to 34.3±14.3 μeq/min).

Gomerular filtration rate was unchanged from control with aortic clamping in the presence (35±3 vs. 33±3 ml/min) and absence (31±4 to 35±3 ml/min) of exogenous ANF. During the recovery periods, glomerular filtration rate was elevated immediately postpacing in the group with aortic clamping alone (31±4 vs. 43±3 ml/min) but remained unchanged from control in the group that had received exogenous ANF (35±3 to 42±5 ml/min).

**Discussion**

The present study demonstrates that tachycardia produced by rapid ventricular pacing 1) results in parallel increases in atrial pressures and ANF; 2) despite the marked increases in ANF during tachycardia, a natriuresis was observed only after tachycardia when mean arterial pressure was restored to control level; and 3) despite the tachycardia-induced decrease in renal perfusion pressure, the renin-angiotensin-aldosterone system was not stimulated. In addition, suprarenal aortic clamping to reduce renal perfusion pressure without comparable increases in ANF was associated with increases in PRA that could be suppressed by physiological concentrations of ANF.

The tachycardia produced significant increases in circulating ANF presumably by the increase in atrial pressures and atrial stretch. Previous studies in humans have reported that cardiac pacing increases circulating ANF only when atrial pressure is increased. Increased heart rate alone in humans, without increases in atrial pressure, does not appear to be sufficient to stimulate ANF in vivo. Despite the parallel increases in atrial pressures and ANF during pacing, and the prompt return of atrial pressures to control, ANF did not return to control level immediately after tachycardia in the present study. While alterations in ANF clearance cannot be excluded as during tachycardia, the results of this study suggest that the time course of ANF activity persists despite cessation of the stimulus of atrial pressure for ANF release from the atria.

A contribution of atrial stretch and reflex-mediated renal and hemodynamic effects of rapid right ventricular pacing and systemic hypotension cannot be excluded by this study. The modulation by ANF of arterial and cardiopulmonary baroreceptor activity would reflect potentially an indirect mechanism whereby ANF could attenuate the sodium retention effects of renal sympathetic nerve stimulation associated with a decrease in mean systemic arterial pressure. In addition, a buffering effect of ANF on renal hemodynamics is suggested by the absence in

### Table 2. Endocrine Response to Right Ventricular Pacing in the Dog

<table>
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<th>Control</th>
<th>Pacing</th>
<th>Postpacing</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANF (pg/ml)</td>
<td>154.1±4.80</td>
<td>268.8±24.2*</td>
<td>83.4±10.44*</td>
<td>44.3±4.76*</td>
</tr>
<tr>
<td>PRA (ng/ml)</td>
<td>2.99±0.54</td>
<td>3.54±0.326</td>
<td>2.86±0.423</td>
<td>2.42±0.96</td>
</tr>
<tr>
<td>ALDO (ng/dl)</td>
<td>6.28±0.60</td>
<td>6.70±0.39</td>
<td>8.76±0.85*</td>
<td>11.94±3.05*</td>
</tr>
<tr>
<td>AVP (pg/ml)</td>
<td>6.23±0.49</td>
<td>4.83±0.405*</td>
<td>7.68±0.77*</td>
<td>7.99±1.41</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>84.8±12.66</td>
<td>166.0±15.09*</td>
<td>124.7±14.07*</td>
<td>123.4±24.04</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. ANF, atrial natriuretic factor; PRA, plasma renin activity; ALDO, aldosterone; AVP, arginine vasopressin; NE, plasma norepinephrine.

* *p<0.05 vs. control, n=9.*

### Table 3. Renal Responses to Right Ventricular Pacing in the Dog

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Pacing</th>
<th>Postpacing</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td>27.8±1.74</td>
<td>21.8±1.44*</td>
<td>23.9±1.84*</td>
<td>26.4±3.97</td>
</tr>
<tr>
<td>U\textsubscript{Na+}\textsuperscript{+}V (μeq/min)</td>
<td>20.8±5.2</td>
<td>15.9±3.8</td>
<td>35.5±7.8*</td>
<td>17.8±5.6</td>
</tr>
<tr>
<td>FE\textsubscript{Na+} (%)</td>
<td>0.50±0.13</td>
<td>0.44±0.09</td>
<td>0.88±0.19*</td>
<td>0.42±0.14</td>
</tr>
<tr>
<td>FE\textsubscript{Li+++} (%)</td>
<td>27.6±2.95</td>
<td>26.6±2.75</td>
<td>34.5±3.67</td>
<td>31.1±6.67</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. GFR, glomerular filtration rate; U\textsubscript{Na+}\textsuperscript{+}V, urinary sodium excretion rate; FE\textsubscript{Na+}, fractional excretion of sodium; FE\textsubscript{Li+++}, fractional excretion of lithium.

* *p<0.05 vs. control, n=9.*
our study of a significant increase in renal vascular resistance during pacing despite the stimulus of decreased renal perfusion pressure.

Previous studies have demonstrated that exogenous infusion of ANF to simulate changes in ANF plasma levels within the physiological range results in significant and dose-dependent increases in sodium excretion. Also, studies that abolished the natriuresis to volume expansion by the use of ANF antibodies or partial right atrectomy support a physiological role for ANF in the regulation of sodium excretion. In the current study, despite marked increases in ANF during tachycardia, sodium excretion did not increase. This renal hyporesponsiveness, however, occurred in association with tachycardia-induced reduction in arterial pressure. During the posttachycardia period in association with an elevated plasma concentration of ANF and a restoration of arterial pressure, a natriuresis was observed. Taken together, these findings would indicate that a natriuretic response develops only if renal perfusion pressure is sustained in association with elevated circulating ANF. A similar conclusion can be drawn from the data of the aortic clamping experiments where a natriuresis was observed only after renal perfusion pressure was restored in kidneys previously exposed to elevated levels of exogenous ANF. The natriuresis occurred in this setting despite the return of plasma ANF to control level, which again suggests a protracted time course of ANF activity.

The clinical findings in patients with tachydyssrhythmias and congestive heart failure are relevant to the present study. Wood observed that patients with preexistent heart failure who developed paroxysmal tachycardia with impairment in cardiac output did not develop a postarrhythmic polycuria. Congestive heart failure and cirrhotic patients with clinical syndromes associated with reduced arterial pressure have been shown to have an attenuated renal response to elevated ANF levels. In addition, Scriven and Burnett demonstrated a blunted renal response to the infusion of synthetic ANF in dogs with experimental heart failure. In contrast, Edwards et al reported an exaggerated natriuresis to ANF in dogs with angiotensin II hypertension. Therefore, a compromise of renal perfusion pressure may limit the renal natriuretic response to the elevated ANF levels associated with these conditions as well as with the pacing-induced tachycardia as demonstrated in this study.

In the current study, PRA was not increased during tachycardia despite the marked decrease in arterial pressure which has been shown to be a potent stimulus for renin release. The elevated level of ANF during tachycardia and the relative inhibition of renin release during tachycardia-induced decreased renal perfusion pressure suggests the inhibition of renin secretion by ANF. This conclusion is consistent with other data demonstrating the inhibition of renin secretion by ANF. In addition, our control study with aortic clamping demonstrates that the exogenous infusion of physiological concentrations of ANF inhibits the elevation of PRA that occurs when renal perfusion pressure is decreased in the absence of elevations in atrial pressures. Endogenous ANF levels were also elevated with aortic clamping alone but were not sufficiently elevated to inhibit renin activity; levels were approximately 50% of those obtained with exogenous ANF infusion. The ANF levels with infusion, however, were within the physiological range of those observed with ventricular pacing in the present study. This would support a physiological role for ANF as a counter-regulatory hormone to the renin-angiotensin system. Exogenous ANF infusion appeared to prevent the rise in proximal mean arterial pressure with aortic clamping, a response also observed by others. This may be related to the inhibition of the renin-angiotensin system observed with elevated ANF levels. A systemic effect of ANF may also in part explain this response in that ANF has been shown to reduce cardiac output by reducing venous return, which would attenuate an arterial
constrictor response to clamping of the aorta. The present study also further extends the previous report of Sheuer et al. and demonstrates that the inhibition of renin activation with suprarenal aortic clamping is importantly associated with a maintenance of tubular sodium reabsorption.

Aldosterone has also been shown to be inhibited by ANF. ANF has been shown to inhibit vasopressin action on the collecting duct in vitro, but an ANF effect to inhibit vasopressin production or release remains controversial. The findings of the current study indicate that vasopressin was decreased during ventricular pacing in association with elevated ANF levels. Vasopressin levels then increased in the postspacing periods. These results suggest that high ANF levels may participate in the inhibition of vasopressin release; however, other mechanisms such as cardiac baroreceptor reflex-mediated decreases in the neurohypophyseal release of vasopressin are known to be activated by elevated atrial pressures and could contribute to the observed reduction in vasopressin with pacing. It is also evident from these data that the decrease in vasopressin during tachycardia was not in itself sufficient to effect a diuretic response.

In summary, the present findings demonstrate the integrated cardiorenal-endocrine response to tachycardia. These studies confirm the hypothesis that circulating concentrations of ANF increase in association with atrial pressure during tachycardia. However, the failure of ANF to normalize following tachycardia despite normalization of atrial pressure suggests atrial peptide release may occur in the absence of sustained increases in atrial pressure. These studies also demonstrate an attenuated natriuresis to ANF during tachycardia and aortic clamping despite a marked increase in circulating concentrations of the atrial peptide. The natriuresis during the posttachycardia and aortic clamping period when arterial pressure was restored suggests that renal perfusion pressure is an important modulator of the renal response to ANF. Lastly, these studies are consistent with the hypothesis that ANF may inhibit the activation of the renin-angiotensin-aldosterone system during tachycardia despite reductions in arterial and renal perfusion pressures.

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References


KEY WORDS • atrial natriuretic factor • renal perfusion pressure • tachycardia • ventricular pacing • sodium excretion • renin-angiotensin-aldosterone system
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