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. Exogenous administration of ANF at pharmacological concentrations increases sodium excretion and inhibits renin release. Tachydysrhythmias of atrial and ventricular origin have been shown to increase atrial pressures. Yet, while previous studies have documented increases in ANF during tachycardia, the integrated cardio-renal 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 (Po2 290-350; Pco2 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 retroperito-
nal 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 thermoladiation cath-
eter (model 93-131A, 7F, American Edwards Labo-
ratories, Inc, Santa Ana, California) was advanced
from the right external jugular vein through the
cardiac chambers with the tip positioned in a pulmo-
nary artery. Right atrial, pulmonary artery, and pul-
monary artery wedge pressures were measured. Car-
diac 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 (Extracor-
poral 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 mea-
surement of cardiac, renal, and systemic hemodynam-
ics and excretory function during each period. Arte-
rial 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 clear-
ance 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 endo-
crine 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 con-
tral mean arterial pressure. The experimental proto-
col was similar to that described above with two
15-minute control clearances followed by three 15-
minute clearances during which renal perfusion pres-
sure 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 immedi-
ately postconstriction and one 60 minutes postcon-
striction. 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 ventricu-
lar pacing. Arterial blood pressure was measured simultaneouly at sites proximal and distal to the
aortic clamp through catheters advanced retro-
gradely 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 previ-
ously described.10 The lower limit of detection was 3
pg/ml plasma. Glomerular filtration rate was deter-
mined by the clearance of inulin with plasma and
urine inulin concentrations measured by the anthrone
method.11 Plasma and urinary sodium concentrations
were quantified using ion-selective electrodes (sys-
tem 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. Plasma norepinephrine concentrations were measured by fractionation technique using high-pressure liquid chromatography quantitation after chromatographic purification.

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 increased with pacing, but was significantly reduced below control level in the recovery period.
changed from control level with pacing (21±5 to 16±4 μeq/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

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_{Na}+V, sodium excretion rate; FE_{Na}%, fractional excretion of sodium; FE_{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 ± 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.1 Previous studies in humans have reported that cardiac pacing increases circulating ANF only when atrial pressure is increased.15,16 Increased heart rate alone in humans, without increases in atrial pressure, does not appear to be sufficient to stimulate ANF in vivo.17 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>
<thead>
<tr>
<th></th>
<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>UNa+,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>FENa+ (%)</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 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; UNa+,V, urinary sodium excretion rate; FE Na+, fractional excretion of sodium; FE 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 by 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 tachydysrhythmias 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 polyuria. 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 arterial 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.²⁵ and demonstrates that the inhibition of renin activation with supraprenal aortic clamping is importantly associated with a maintenance of tubular sodium reabsorption.

Aldosterone has also been shown to be inhibited by ANF.²⁶⁻²⁸ The finding that aldosterone levels were not significantly changed during pacing could be interpreted as consistent with a suppression of aldosterone secretion mediated by the high ANF level.

Inhibition of vasopressin has been suggested as a mechanism contributing to the diuresis occurring with tachycardia.⁶,²⁹ ANF has been shown to inhibit vasopressin action on the collecting duct in vitro,³⁰ 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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**KEY WORDS** • atrial natriuretic factor • renal perfusion pressure • tachycardia • ventricular pacing • sodium excretion • renin-angiotensin-aldosterone system
Renal-endocrine adaptations to endogenous atrial natriuretic factor during tachycardia-induced reductions in renal perfusion pressure.
W L Miller, B S Edwards, R S Zimmerman and J C Burnett, Jr

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