Effect of Bilateral Atrial Appendectomy on Postprandial Sodium Excretion in Conscious Monkeys (43721)

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Abstract. **We have shown that bilateral atrial appendectomy attenuates the increase in atrial natriuretic factor and sodium excretion that occurs after acute blood volume expansion. These findings suggest that the atrial appendages influence renal sodium excretion. The purpose of the present study was to determine whether atrial appendectomy alters the increase in sodium excretion that occurs postprandially. One to two weeks after surgery, conscious monkeys (*Macaca fascicularis*) were given a meal through a nasogastric tube. The meal consisted of water (20 ml/kg), sodium (2.5 mmol/kg), carbohydrate (2.65 g/kg), protein (0.68 g/kg), and fat (0.89 g/kg). Postprandial changes in renal function were monitored for 210 min after the meal was started. In the sham animals, urine flow increased from 0.23 ± 0.04 to 0.55 ± 0.05 ml/min, sodium excretion increased from 28.6 ± 7.8 to 84.4 ± 12.3 μmol/min and fractional sodium excretion increased from 1.35 ± 0.38% to 3.06 ± 0.43%. Bilateral atrial appendectomy (ATX) significantly attenuated the renal responses to the meal. Urine flow in the ATX animals increased from 0.19 ± 0.03 to 0.30 ± 0.02 ml/min, sodium excretion increased from 26.5 ± 5.8 to 45.8 ± 15.2 μmol/min, and fractional sodium excretion increased from 0.99 ± 0.02% to 1.53 ± 0.34%. Postprandial changes in renal and systemic hemodynamics were also monitored and were similar in both groups. Plasma levels of atrial natriuretic factor were also similar in both groups and did not increase postprandially. These findings demonstrate that bilateral atrial appendectomy attenuates postprandial-induced increases in sodium excretion by mechanisms that do not involve an increase in atrial natriuretic factor.** [P.S.E.B.M. 1994, Vol 206]

Renal adjustments in salt and water excretion play an important role in maintaining fluid/electrolyte homeostasis. These mechanisms are under the control of multiple regulatory systems and involve numerous factors (see 1 and 2 for review). These include intrinsic renal mechanisms as well as extrinsic neural and humoral pathways.

The cardiac atria contain components of two systems capable of influencing renal function: neural receptors and peptide hormones (3). Our laboratory has been interested in aspects of both of these atrial control systems, in particular, the role of renal sympathetic nerves and atrial natriuretic factor (ANF). Using renal denervation, we have found an important role of the renal nerves in mediating the renal response to volume expansion in conscious monkeys (4, 5). However, the role of endogenously released ANF in mediating changes in renal sodium excretion has been difficult to determine because of the absence of an analogue capable of blocking its renal actions. Several approaches have been used to overcome this problem, including atrial appendectomy (ATX) (6–8), active immunization (autoimmunity) or passive immunization (9–13), and heparin administration (11). We have used the surgical approach and shown that bilateral atrial appendectomy attenuates volume expansion-induced increases in ANF and sodium excretion (6) in conscious monkeys. This finding suggests that endogenously released ANF participates in fluid/electrolyte

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Received October 18, 1993. [P.S.E.B.M. 1994, Vol 206]
Accepted January 5, 1994.

0037-9727/94/2061-0045$10.50/0

balance. On the other hand, these conclusions must be made with caution since acute volume expansion is a laboratory technique that does not necessarily mimic physiologic conditions because of the magnitude and abruptness of the change in volume.

Physiologic increases in extracellular fluid volume occur postprandially. The renal response is variable and depends to a large extent on the composition of the meal (14). High sodium intake increases urine flow and sodium excretion (15). In contrast, low salt meals increase urine flow with little or no change in sodium excretion (15). Since high-salt meals are associated with increases in extracellular fluid volume, atrial pressure, and sodium excretion, it is reasonable to propose that the atrial appendages participate in the regulation of postprandial sodium excretion.

The purpose of the present experiment was to test the hypothesis that the atrial appendages influence sodium excretion under physiologic conditions, i.e., after intake of a meal high in sodium content. The results demonstrated that bilateral atrial appendectomy attenuates postprandial sodium excretion. However, in contrast to acute volume expansion (6), ANF remained constant in the atrial intact animals postprandially. In addition, atrial appendectomy decreased sodium excretion without affecting ANF levels. These findings indicate that ATX attenuates postprandial sodium excretion by mechanisms that do not necessarily involve an increase in ANF.

Materials and Methods

General Preparation. Experiments were carried out in 11 adult male monkeys (*Macaca fascicularis*) that were maintained on a standard diet with water *ad libitum*. Two groups of animals were studied: atrial appendectomy (ATX, $n = 6$) and sham operated controls ($n = 5$). Procedures used in this study were in accordance with guidelines in the Public Health Service *Guide for Care and Use of Laboratory Animals* and were approved by the Institution's Animal Care and Use Committee.

Before surgery, the animals were trained to sit quietly in a primate restraint chair (Primate Products, Woodside, CA) by use of the pole and collar technique (6, 16). In addition, the monkeys were conditioned to tube feeding via a nasogastric tube. After the training protocol, the monkeys underwent sham or ATX surgery followed by a 1–2-week recovery. The postprandial experiment was carried out with the monkeys in the conscious state.

Surgical Preparation. Technical aspects of the atrial appendectomy surgery have been documented in an earlier publication (6). In brief, the monkeys were anesthetized with ketamine HCl (5 mg/kg, im) and removed from their cage. An indwelling catheter was placed in the saphenous vein, and the monkeys further anesthetized with sodium pentobarbital (25 mg/kg, iv). Maintenance doses of pentobarbital were given when necessary. A cuffed endotracheal tube was inserted, and the lungs ventilated with a respirator. A left thoracotomy was performed through the fourth intercostal space using aseptic technique. The pericardium was opened and both atrial appendages were removed. As much tissue was removed as possible without distorting the junction of the pulmonary veins and vena cava with the atria. The cut edges of the pericardium were approximated, and a chronic catheter was implanted in the descending thoracic aorta to later measure blood pressure and draw arterial blood samples. The aortic catheter was exteriorized through the fifth intercostal space, tunneled subcutaneously, and exited the skin between the scapulae. After catheter placement, the chest was closed and evacuated. Two venous catheters were implanted: one into the inferior vena cava through the femoral vein to measure central venous pressure and the other through the internal jugular vein for intravenous infusions. These catheters were also exteriorized between the scapulae. The catheters were filled with heparin (1000 U/ml) and chloromycetin (100 mg/ml), and protected by placing the animal in a standard primate jacket (Alice King Chatham, Medical Arts, Los Angeles, CA). Postoperatively, the animals were treated with antibiotics (Longicil: 100,000 U im) on alternating days for 1 week. The chronic catheters were routinely flushed with heparin and antibiotics every 3–5 days.

Sham operated controls underwent the same surgical procedures and postoperative treatment except the atrial appendages were not removed. The time required to complete the surgical procedures was adjusted to match the appendectomy group.

Experimental Procedures. The postprandial experiment was carried out 1–2 weeks postoperatively. The weight of the animals on the day of the postprandial experiment was the same as their presurgical weight. This was true for both groups of animals. The sham animals weighed 5.2 ± 0.4 kg before surgery and 5.3 ± 0.4 kg on the day of the experiment. The atrial appendectomized animals weighed 4.9 ± 0.3 kg both before surgery and on the day of the experiment.

Each animal was sedated with ketamine HCl (5 mg/ml) and removed from its cage. The outer orifice of the urethra was cleansed, painted with providone-iodine (Betadine), and 2% xylocaine jelly instilled into the urethra. An 8 Fr. feeding tube was inserted through the urethra into the bladder for timed urine collection. A nasogastric tube was advanced into the stomach to administer the meal, its position verified by aspiration of stomach contents. The monkeys were placed in the restraint chair to recover from the ketamine, and the central venous and arterial catheters were connected to transducers to continuously record

pressure. A priming dose of creatinine (33 mg/kg) and p-aminohippurate (PAH, 8 mg/kg) was then given to each animal, followed by a maintenance infusion (0.50 ml/min) containing 1.6 g/liter of both creatinine and PAH in 0.9% saline solution. After a 60-min equilibration period, consecutive 10-min urine samples were collected. At the midpoint of alternate urine collection periods, a 4-ml blood sample was withdrawn to determine plasma sodium, creatinine and PAH concentrations, and plasma osmolality. Red blood cells were resuspended in 6% high molecular weight dextran in isotonic saline and reinfused into the animal. After 30–40 min of constant urine flow the monkeys were given a liquid meal through the nasogastric tube. The meal consisted of water (20 ml/kg), sodium (2.5 mmol/kg), carbohydrate (2.65 g/kg), fat (0.89 g/kg), and protein (0.68 g/kg). Urine was collected for an additional 210 minutes postprandially. Plasma samples to measure ANF were drawn at the midpoint of the control urine collections and at 30-min intervals after the meal was started. At the end of the experiment the animals were euthanized with an overdose of sodium pentobarbital, and the kidneys removed and weighed.

Analyses. Arterial and central venous pressures were measured with Statham P23ID pressure transducers and were recorded with a Grass Model 7D polygraph. Plasma and urine concentrations of creatinine and PAH were determined by the methods described by Brod and Sirota (17) and Smith (18), respectively. Clearances of creatinine and PAH were used to estimate changes in glomerular filtration rate and renal plasma flow, respectively. Sodium and potassium concentrations in the plasma and urine samples were measured by using an IL 643 Flame Photometer and osmolality was determined by freezing point depression (Advanced Instruments, Model 3DII).

Plasma ANF concentrations were determined by radioimmunoassay using a rabbit antibody to rat ANF_{1-28} (Peninsula Labs, Belmont, CA) as previously described (6). In brief, blood samples were collected in chilled tubes containing ethylenediaminetetraacetic acid (EDTA) and aprotinin and were centrifuged to obtain plasma for later analysis. ANF samples were extracted using a C_{18} reverse phase column (Waters Associates, Milford, MA). The samples were eluted from the columns using acidified methanol (4 ml glacial acetic acid/100 ml) and were dried overnight under a stream of air. The dry residue was dissolved in assay buffer and ANF levels determined in duplicate. The data were reduced using a log-logit plot after correction for nonspecific binding. Results were not corrected for recovery.

Statistics. A two-way analysis of variance with repeated measures design for one factor (time) was used to test for differences across time and between groups (19). If the analysis of variance showed that significant differences ($P < 0.05$) were present, Dunnett's test was used for comparing the control mean with each of the postprandial means across time (within groups comparison). Group differences (appendectomy vs sham) were tested by using an unpaired t test. Probability values less than 0.05 were considered significant.

Results

The time course for the changes in urine flow, sodium excretion and fractional sodium excretion are shown in Figure 1. The shaded areas shown in the upper panels (urine flow and sodium excretion) represent the mean ± standard error of the mean for three time control experiments. Urine flow and sodium excretion remained constant in the control experiments for the entire observation period. The mean significantly increased salt and water excretion in the sham animals. Urine flow increased from 0.23 ± 0.04 ml/min before the meal to a peak of 0.55 ± 0.05 ml/min post-

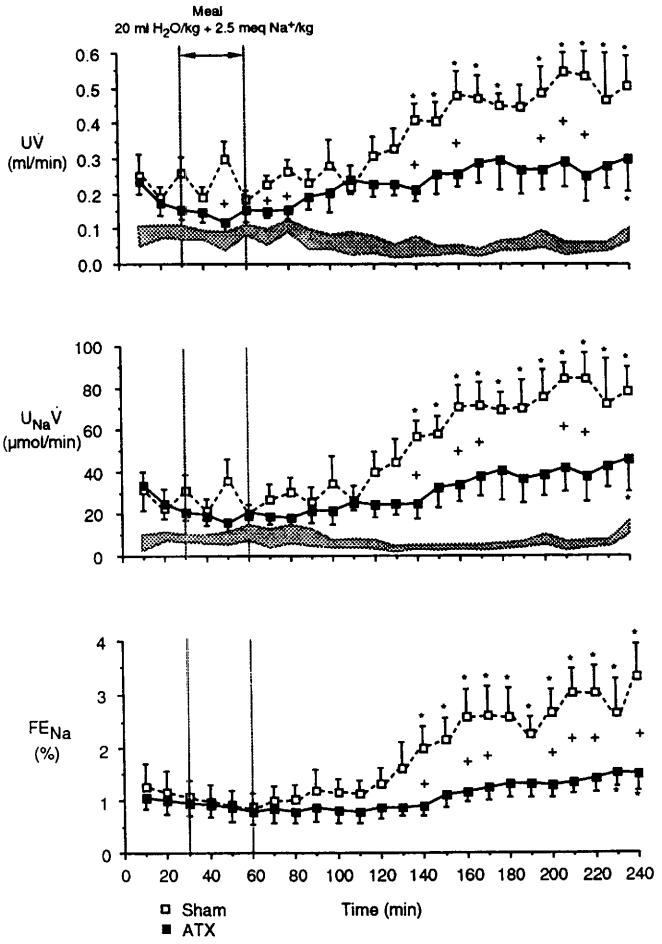

Figure 1. Postprandial changes in urine flow (V̇), sodium excretion ($U_{Na}V̇$), and fractional sodium excretion (FE_{Na}) in sham and atrial appendectomized monkeys. Values are means ± SE for continuous 10-min periods. The shaded areas represent the mean ± SEM for three time control experiments. *Significantly different from average control value, $P < 0.05$. †Significant group differences, $P < 0.05$.

prandially. Sodium excretion increased from 28.6 ± 7.8 to 84.4 ± 12.3 μmol/min and fractional sodium excretion increased from 1.35 ± 0.38% to 3.06 ± 0.43%. The increase in renal salt and water excretion was significant 80 min after the meal in the sham animals. ATX significantly attenuated the increase and delayed the onset of these changes. In the ATX animals, urine flow increased from 0.19 ± 0.03 to 0.30 ± 0.02 ml/min, sodium excretion increased from 26.5 ± 5.8 to 45.8 ± 15.2 μmol/min, and fractional sodium excretion increased from 0.99 ± 0.02% to 1.53 ± 0.34%. The increase in the ATX group was not significant until 180 min after the meal was given. During the 3 hr of observation after the meal, the sham animals excreted approximately 72% of the sodium load compared with 39% in the ATX animals. A similar pattern was observed for changes in osmolar clearance (data not shown in figure). In the sham animals, osmolar clearance increased from 0.45 ± 0.06 to 0.92 ± 0.05 ml/min ($P < 0.05$). ATX significantly attenuated the increase, which rose from 0.45 ± 0.07 to 0.59 ± 0.11 ml/min. Free water clearance (not shown) did not change significantly in either group.

We evaluated renal (Fig. 2) and systemic hemodynamics (Fig. 3) to determine whether changes in these parameters could have influenced renal function postprandially. A slight but statistically significant increase in creatinine (CR) and PAH clearances (Fig. 2) occurred in the sham animals after the meal was given which returned back to control levels. There were no significant differences in CR or PAH clearance between the sham and the ATX animals at any time during the experiment. Figure 3 shows changes in systemic hemodynamics. Mean arterial pressure decreased slightly while heart rate remained constant or tended to increase slightly in both groups after the meal. There was no difference in arterial pressure between groups. Central venous pressure (CVP), also shown in Figure 3, remained relatively constant for the duration of the experiment in both groups. There was a tendency for CVP to be lower in the sham group. The functional significance of this trend is questionable, however, because technical problems limited the number of observations to three in the ATX group and four in the sham group. The above findings indicate that the attenuated diuretic and natriuretic response in the ATX group was not due to postprandial differences in renal or systemic hemodynamics between the two groups.

Plasma ANF levels (Fig. 4) remained constant in the sham and the ATX animals after the meal was given. The ANF levels tended to be slightly lower in the ATX animals but this difference was not statistically significant. Collectively, these findings indicate that ATX does not alter basal secretion of ANF and

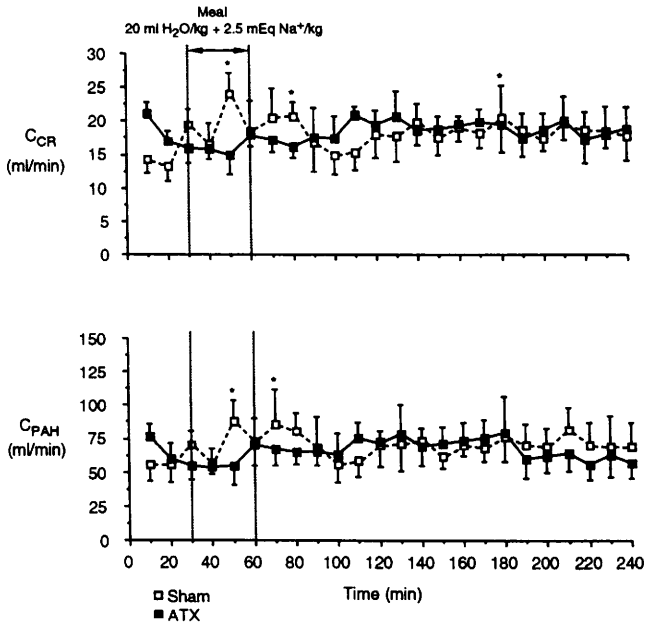

Figure 2. Postprandial changes in creatinine clearance (C_{CR}) and PAH clearance (C_{PAH}) in sham and atrial appendectomized animals. Same format as Figure 1.

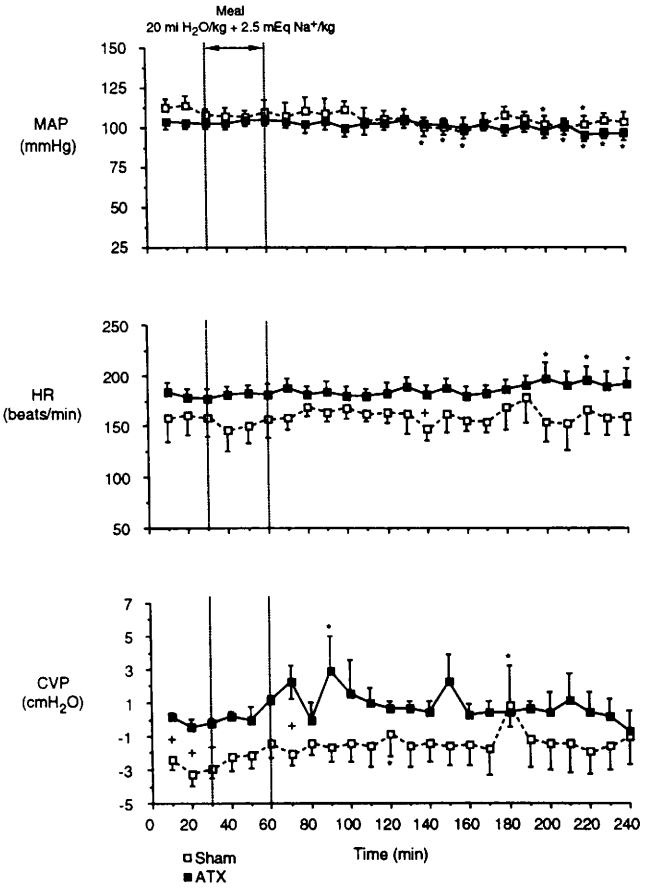

Figure 3. Postprandial changes in mean arterial pressure (MAP), heart rate (HR), and central venous pressure (CVP) in sham and atrial appendectomized monkeys. Same format as Figure 1.

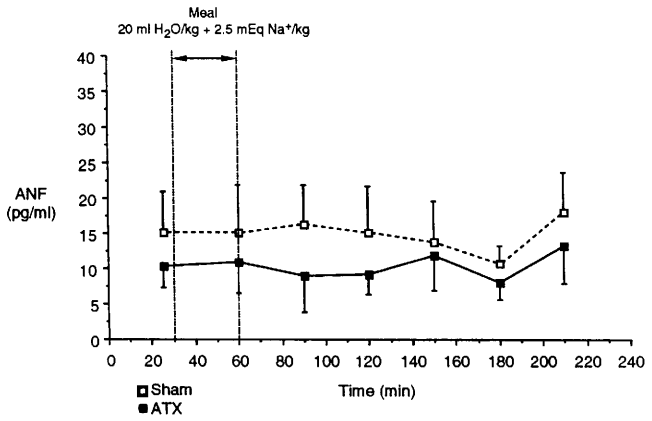

Figure 4. Postprandial changes in atrial natriuretic factor (ANF) in sham and atrial appendectomized animals. Same format as Figure 1.

that administration of a mixed meal containing carbohydrate, protein, fat, and salt does not increase the release of ANF.

At the end of the study, a bolus of veratrine (60 μg) was administered through the central venous line to determine if the surgical procedures interrupted cardiac afferents. Veratrine activates cardiopulmonary afferents and causes a reflex decrease in blood pressure and heart rate. In the sham operated control animals, blood pressure decreased from114 ± 11 to 70 ± 10 mm Hg and heart rate decreased from 180 ± 20 to 136 ± 8 bpm. In the appendectomized group, the decreases observed after veratrine were similar to those in the intact animals. Blood pressure and heart rate decreased from 101 ± 6 to 57 ± 8 mm Hg and from 183 ± 18 to 139 ± 20 bpm, respectively. These results indicate that atrial appendectomy did not significantly interrupt cardiac afferents.

Discussion

Renal sodium excretion is an important determinant of extracellular fluid volume and is regulated by a variety of factors. We have shown that the atrial appendages participate in this regulation since bilateral atrial appendectomy significantly attenuates sodium excretion during acute volume expansion (6). The purpose of the present experiment was to determine whether the atrial appendages influence sodium excretion under physiologic conditions, i.e., after a meal high in sodium content. Results from these studies demonstrate that bilateral atrial appendectomy attenuates postprandial sodium excretion without altering renal or systemic hemodynamics, that ANF remains constant postprandially, and that ATX does not reduce ANF levels postprandially. These findings indicate that under physiologic conditions the atrial appendages are capable of influencing renal sodium excretion by a mechanism that does not necessarily involve an increase in ANF.

Postprandial changes in ANF have been evaluated in other studies, with conflicting results. Verburg *et al.* (20) investigated postprandial changes in ANF and sodium excretion in conscious dogs. They found that ANF and sodium excretion increased after a meal containing 125 mmol of sodium. ANF increased from 33 to 48 pg/ml while sodium excretion increased from ~20 to 170 μmol/min. In a similar study with human subjects, Solhaug and Granger (21) determined that postprandial levels of ANF are influenced by the preexisting level of dietary sodium intake. ANF was elevated postprandially only in subjects that were on a high sodium intake, increasing from 32 to 37 pg/ml 30 min after the meal. Saville *et al.* (22), on the other hand, found that consumption of a high salt meal (100 mmol sodium) increased sodium excretion without a change in plasma ANF concentration.

Other experiments, also carried out in humans, focused on the contribution of ANF in mediating the increase in glomerular filtration rate that occurs after a meal high in protein. Rodriguez-Iturbe *et al.* (23) and Solomon *et al.* (24) found that dietary protein increased glomerular filtration rate and sodium excretion. In the former study (23), ANF levels increased 2-fold (5–10 fmol/ml) while in the latter (24), ANF levels did not change. The reasons for these differences in ANF responses are not clear. Interestingly, neither group felt that ANF was important in mediating the increase in sodium excretion that accompanied the high protein meal. Rodriguez-Iturbe *et al.* (23), in particular, considered the increase in ANF levels to be subnatriuretic.

The renal response of the monkeys in the present study is similar to other postprandial experiments in that administration of a high salt meal caused sodium excretion to increase (20–24). The fact that ANF remained constant in the monkeys suggests that the magnitude of change in extracellular fluid volume was not great enough to induce the release of ANF. We tried to address this possibility in the design phase of the experiment by giving a meal that was physiologically relevant, yet sufficient to adequately activate the system. Daily sodium intake for the monkeys was maintained at 2.5 mmol of sodium/kg body weight, which is considered normal for these animals. The meal for the postprandial experiment provided a mixed diet of carbohydrate, protein, and fat with the total 24-hr complement of sodium (2.5 mmol/kg). We reasoned that if ANF is important in regulating postprandial sodium excretion, then administration of the total sodium load for 24 hr in a single meal should provide an adequate stimulus for ANF release. The meal caused a clear increase in sodium excretion (Fig. 1). However, the fact that ANF remained constant postprandially suggests that ANF may not be an important regulator of postprandial sodium excretion.

Verburg *et al.* (20) studied dogs that were given more than twice the sodium than our monkeys received, which may explain why plasma ANF levels increased in their experiments and not in ours. It is not clear whether a meal containing less sodium (~2.5 mmol/kg) would increase atrial pressure and stimulate ANF release in conscious dogs. Another consideration is species differences; i.e., dogs are quadrupeds, and primates are bipeds. The difference in body position between dogs and monkeys may be important since the distribution of extracellular fluid volume in the body can be influenced by gravity and the functional compliance of the limbs. For example, as water and electrolytes are absorbed from the gut, gravity may cause a greater percentage of this volume to distribute to the legs of primates compared with dogs. This would cause a relative reduction of atrial stretch in nonhuman primates and man and diminish the stimulus for ANF release.

Circulating levels of ANF are functionally related to stretch-induced ANF release and tissue extraction/metabolism. We, like many investigators, have focused on ANF release and have minimized the metabolic component that influences plasma ANF concentrations. That is, we assume that metabolism of ANF is constant under most circumstances. In this regard, Henriksen *et al.* (25) found that splanchnic extraction of ANF increases after a meal and that the increase in hepatic clearance is due to increased splanchnic blood flow. These authors (25) hypothesized that increased splanchnic removal of ANF may attenuate postprandial increases in plasma ANF. The significance of this observation in the present study is unknown although altered extraction could provide another mechanism to modify the concentration of ANF in the blood.

The question remains, what mechanism caused the attenuated postprandial sodium excretion in the ATX group? Clearly, ANF remained constant and is not responsible for this result. Alterations in renal and systemic hemodynamics also seem unlikely because postprandial changes in creatinine and PAH clearances, and arterial pressure were also similar in both groups. Cardiopulmonary baroreceptors can influence renal sodium excretion through reflex changes in renal nerve activity (26) and/or the release of other natriuretic hormones (27, 28). Surgical damage to this pathway could attenuate sodium excretion. However, this possibility is unlikely because (i) the reflex response to veratrine was normal in the control and ATX groups; (ii) cardiac denervation does not decrease postprandial sodium excretion in dogs (29); (iii) cardiopulmonary stimulation in monkeys influences renal function to a lesser extent than the dog (30, 31); and (iv) the minor changes in central venous pressure that occurred in our experiment suggests that cardiopulmonary baroreceptors were minimally activated postprandially. Therefore, it is unlikely that nonspecific changes in cardiac afferents account for the diminished sodium excretion in the ATX animals.

Extracellular fluid volume is regulated by multiple control systems (1, 2). One system that plays a critical role is the renin-angiotensin system. Our findings of reduced sodium excretion in the ATX group could be explained, in part, by an increase in the baseline activity of this system. Although plasma renin activity was not measured in this experiment, we feel that our results cannot be explained solely by a change in the renin-angiotensin system. Our reasoning is based on several experimental observations. First, baseline sodium excretion and fractional sodium excretion were the same in the sham and ATX groups. If renin and angiotensin II levels were elevated in the ATX group, then the relationship between arterial pressure and sodium excretion would shift to the right causing an increase in arterial pressure; however, arterial pressure was not elevated in the ATX animals. Second, body weights in the sham and ATX groups were the same before and after surgery which suggests that fluid electrolyte balance was not chronically altered by ATX. Finally, we found that other variables capable of influencing plasma renin activity were equal in both groups including: renal perfusion pressure (arterial pressure), renal hemodynamics (C_{CR} and C_{PAH}), and ANF levels. The above findings indicate that during the control period (0–30 min) renin levels were probably similar in the sham and ATX groups. Nevertheless, since we did not measure renin levels, we cannot rule out the possibility that plasma renin activity was elevated in the ATX group.

Another explanation for the attenuation in sodium excretion in the ATX group is that atrial appendectomy indirectly reduced the responsiveness of the kidney to ANF. Results from this experiment do not directly exclude this possibility; however, we believe that this explanation is unlikely. We base this on observations from a previous experiment (6) where we volume expanded an ATX monkey and started a replacement infusion of ANF (10 ng/kg/min) at the start of volume expansion. Without ANF replacement, sodium excretion increased from a control of 14.8 to 17.7 μmol/min after volume expansion. When ANF was infused, sodium excretion increased from 5.2 to 134 μmol/min. The increase in sodium excretion demonstrates that the kidneys of the ATX animals are responsive to ANF.

It is possible that the atrium releases a circulating factor, other than ANF, that is capable of influencing renal sodium excretion. If this is the case, then ATX may have attenuated the release of this factor. This hypothesis is supported by other investigations (10, 27, 28). Cowley *et al.* (27, 28) found that ANF did not increase after acute saline expansion and that bilateral

atrial resection attenuated the increase in sodium excretion. They also found that atrial resection attenuated the increase in sodium excretion in cardiac denervated animals (28). This latter finding demonstrates that the release of the natriuretic factor is not dependent on cardiac nerves (28). Furthermore, Cowley *et al.* (27, 28) could not account for the attenuation in sodium excretion by changes in renin, aldosterone, or vasopressin. They concluded that an unidentified factor, with diuretic and natriuretic capabilities, is released after volume expansion, and that the release of this factor is removed by atrial resection. Sakata *et al.* (10) carried out a similar experiment in conscious rats and demonstrated that ATX attenuated volume expansion-induced increases in sodium excretion. Volume expansion also did not increase ANF in these animals. These authors speculated that the attenuated renal response may be due to alterations in sympathetic tone, plasma renin activity or vasopressin release. They also suggested that another factor with natriuretic capabilities may be present in the atria. The nature of this factor is unknown and its existence remains highly speculative. The results from the present experiment, like those of Cowley *et al.* (27) and Sakata *et al.* (10), are consistent with the hypothesis that the atria release multiple natriuretic hormones. Our data does not exclude the possibility that the atria influence the release of other natriuretic hormones via cardiac neural reflexes or that the atria may release a factor that circulates to other tissues which may contain a natriuretic hormone. Furthermore, this cardiac factor could modulate the activity of other systems capable of regulating renal sodium excretion. Further experiments will address these possibilities.

In summary, bilateral atrial appendectomy attenuated postprandial sodium excretion in conscious monkeys without altering renal or systemic hemodynamics. In addition, ANF did not increase postprandially and was not altered by ATX. These findings indicate that ATX attenuates postprandial sodium excretion by a mechanism that does not necessarily involve an increase in ANF.

We gratefully acknowledge the assistance of Dr. Craig Metzler in analyzing plasma atrial natriuretic factor levels, as well as the technical assistance of Nancy Hurst, Terry Hurst, and Peggy Abel.

This work was supported by grants from the American Heart Association, Texas Affiliate (85G-027) and the National Institutes of Health HL41028, HL31987, and HL35879. T.V. Peterson was a recipient of National Heart, Lung and Blood Institute Research Career Development Award HL01383.

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