Role of Renal Na\textsuperscript{+},K\textsuperscript{+}-ATPase in the Regulation of Sodium Excretion Under Normal Conditions and in Acute Congestive Heart Failure

Margaret A. Lloyd, MD; Sharon M. Sandberg; and Brooks S. Edwards, MD

**Background.** Cardiac glycosides have traditionally been used as inotropic agents in the treatment of congestive heart failure (CHF). The renal actions of cardiac glycosides independent of inotropic effects are not characterized. The presence of endogenous digitalis-like factors (EDLFs) with characteristic Na\textsuperscript{+},K\textsuperscript{+}-ATPase activity has been postulated in volume-expanded states such as CHF, and recent studies have demonstrated that at least one EDLF shares structural homology with ouabain. This study was undertaken to evaluate the renal actions of ouabain in normal dogs and those with CHF.

**Methods and Results.** After surgical preparation, normal dogs (n=6) and dogs in pacing-induced CHF (n=6) received intrarenal ouabain in sequential doses of 0.167 μg/kg/min, 0.334 μg/kg/min, and 0.668 μg/kg/min. Hemodynamics and renal function were evaluated during the infusion. There was no change in heart rate or mean arterial pressure during the infusion compared with baseline in both groups. Sodium excretion and urine volume significantly increased in both groups. Plasma renin activity, activated by the onset of pacing in the CHF group, was inhibited by the administration of intrarenal ouabain in this group only.

**Conclusions.** These studies demonstrate that ouabain has diuretic and natriuretic actions independent of cardiac hemodynamics that are preserved in CHF. Furthermore, intrarenal ouabain suppresses activation of renin in CHF. (Circulation 1992;85:1912-1917)

**KEY WORDS** • ouabain • Na\textsuperscript{+},K\textsuperscript{+}-ATPase • endogenous digitalis-like factors • plasma renin activity

Congestive heart failure (CHF) represents a clinical syndrome characterized by a state of avid sodium retention with peripheral edema. Concurrently, there is activation of antinatriuretic systems, including the renin–angiotensin–aldosterone system (RAAS). In response to the volume overload associated with CHF, there is secondary stimulation of natriuretic factors including atrial natriuretic factor (ANF) and the putative endogenous Na\textsuperscript{+},K\textsuperscript{+}-ATPase inhibitors. deWardener and colleagues\textsuperscript{1-4} first demonstrated the existence of a circulating natriuretic factor that they speculated had Na\textsuperscript{+},K\textsuperscript{+}-ATPase inhibitory activity, the so-called “third factor.” Recent investigations have provided compelling evidence that at least one endogenous digitalis-like factor (EDLF), stimulated by mineralocorticoid-induced volume expansion, shares structural homology with the naturally occurring cardiac glycoside ouabain or an isomer.\textsuperscript{5-7} Bilateral adrenalectomy decreases the circulating levels of EDLF\textsuperscript{5}; therefore, the adrenal gland may represent one source of EDLF.

Standard medical therapy has traditionally included the use of a Na\textsuperscript{+},K\textsuperscript{+}-ATPase inhibitor, i.e., a cardiac glycoside, for the treatment of CHF. Extracts of the digitalis leaf were initially used by Withering as a means of treating dropsy (edema) associated with CHF.\textsuperscript{8} Withering reported his observations on the diuretic action of digitalis, and subsequent workers have emphasized the inotropic effects of the cardiac glycosides. In contemporary use, digitalis and its congeners are primarily considered inotropic agents.

The molecular basis for the actions of the cardiac glycosides resides in their unique ability to inhibit the membrane-bound Na\textsuperscript{+},K\textsuperscript{+}-ATPase enzyme system. This enzyme, found on all eukaryotic cells, represents the major pathway for sodium–potassium exchange across the cell membrane. On the α-subunit of the enzyme, there exists a receptor for the cardiac glycosides; binding to the receptor inhibits the enzyme system.\textsuperscript{9} Na\textsuperscript{+},K\textsuperscript{+}-ATPase is present on the basolateral aspect of renal tubular epithelial cells and may promote the renal tubular reabsorption of sodium. Recent studies have demonstrated that in CHF, there occurs an upregulation of Na\textsuperscript{+},K\textsuperscript{+}-ATPase activity within the proximal tubule.\textsuperscript{10} This increase in activity may be due in part to activation of the RAAS.

Administration of cardiac glycosides may result in a natriuresis; however, the mechanism by which digitalis

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From the Cardiorenal Research Laboratory, Department of Cardiovascular Diseases, Mayo Clinic and Foundation, Rochester, Minn.

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Address for reprints: Margaret A. Lloyd, MD, Cardiorenal Research Laboratory, Mayo Clinic and Foundation, 200 First Street, SW, Rochester, MN 55905.

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increases sodium excretion is not entirely clear. Yamamoto and colleagues have reported that high-dose ouabain increases circulating ANF; Covit and colleagues have reported that cardiac glycosides reduce plasma renin activity (PRA) and aldosterone in humans with CHF. It is not known whether this inhibition of the RAAS is dependent on an improvement in cardiac performance. Farber and colleagues in 1951 suggested that digitalis may directly enhance renal tubular sodium excretion.

The objective of the current study was to evaluate the renal actions of ouabain in the normal kidney and in the setting of acute, low-output CHF. Low-output CHF was induced by acute rapid ventricular pacing, an experimental state demonstrated in prior studies to be similar to clinical CHF with reduced cardiac output and mean arterial pressure, increased pulmonary pressures, activated RAAS, and markedly increased levels of circulating ANF.

**Methods**

Studies were performed in two groups of mongrel dogs (n = 6 per group) of either sex weighing 13–21 kg. Group 1 dogs received increasing doses of intrarenal ouabain only, and group 2 animals underwent ventricular pacing to induce acute CHF, followed by the administration of intrarenal ouabain. Dogs were fasted overnight before the study but allowed free access to water.

Animals were anesthetized with sodium pentobarbital (30 mg/kg) and maintained with supplemental doses as necessary. The trachea was intubated, and animals were mechanically ventilated (Harvard Apparatus, Millis, Mass.). Dogs were prepared by selective cannulation of a femoral vein and a femoral artery. The right internal jugular vein was isolated, and a 7.5 F balloon-tipped thermodilution catheter (American Edwards Laboratory, Santa Ana, Calif.) was advanced into the pulmonary artery. In group 2 animals, a left thoracotomy was performed and a ventricular pacing wire was sewn through the intact pericardium into the left ventricular epicardial surface. The thoracotomy incision was then closed in multiple layers. Ventricular pacing was initiated with a Medtronic 5320 pulse generator (Medtronic, Inc., Minneapolis, Minn.).

In both groups of dogs, the left kidney was exposed with a retroperitoneal flank incision. The ureter was cannulated (PE 200 tubing) for urine collection. A calibrated electromagnetic flow probe was placed around the renal artery (Carolina Medical Electronics, King, N.C.) for continuous monitoring of renal blood flow (RBF). The renal artery was cannulated with a 23-gauge needle for infusion of ouabain.

Through the femoral vein catheter, each dog received a priming dose of inulin (Nutritional Biochemicals, Cleveland, Ohio) and a continuous infusion at a rate of 1 ml/min in an effort to achieve a steady-state plasma inulin level of approximately 50 mg/dl. After preparation, the dogs were placed in the prone position. Both groups were allowed to stabilize for 1 hour after preparation.

Each clearance period consisted of a 15-minute urine collection, measurement of hemodynamic parameters, and withdrawal of 25 ml of blood for hormone analysis and electrolyte determination. In group 1, two sequen-
TABLE 1. Renal Data

<table>
<thead>
<tr>
<th></th>
<th>U vol (ml/min)</th>
<th>RBF (ml/min)</th>
<th>RVR (RU)</th>
<th>GFR (ml/min)</th>
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<td>Group 2</td>
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<td>0.668 µg/kg/min</td>
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<td>1.5±0.5†</td>
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<table>
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<tr>
<th></th>
<th>U\text{NaV} (mEq/min)</th>
<th>Fe\text{Na} (%)</th>
<th>U\text{K}V (mEq/min)</th>
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<td>251.9±71.5†‡</td>
<td>14.5±5.0€</td>
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</tbody>
</table>

U vol, urine volume; RBF, renal blood flow; RVR, renal vascular resistance; RU, resistance units; GFR, glomerular filtration rate; U\text{NaV}, absolute excretion of sodium; Fe\text{Na}, fractional excretion of sodium; U\text{K}V, absolute excretion of potassium.

*p<0.05 within group compared with prepacing baseline; †p<0.05 within group compared with preinfusion baseline.

Results

Renal Response

Results are summarized in Table 1. During ouabain infusion, urine flow rate increased by 316% (p<0.05) in group 1. In group 2, urine flow rate increased by 250% during ouabain administration (p<0.05). Urine flow rates were not significantly different between groups at the termination of the infusion.

In group 1, U\text{NaV} was increased by 298% during ouabain infusion. In group 2, sodium excretion decreased by 17% after the initiation of pacing, although this change did not achieve statistical significance. In this group, ouabain administration resulted in a 284% increase in sodium excretion compared with the preinfusion period. U\text{NaV} values between groups were similar at the termination of the infusion (see Figure 2).

Fe\text{Na} increased significantly, by 630% in group 1 during ouabain infusion (p<0.05). Fe\text{Na} did not significantly change in group 2 after the onset of ventricular pacing compared with the prepacing baseline. Fe\text{Na} increased by 345% in group 2 during ouabain infusion (p<0.05). At the termination of the infusion, Fe\text{Na} was similar in both groups.

Urinary potassium excretion was not significantly different within groups or between groups either at baseline or at any time during the infusion.

RBF decreased by 13% in group 1 during ouabain infusion (p<0.05). RBF significantly decreased by 33% after the onset of ventricular pacing in group 2. RBF decreased a further 30% compared with the preinfusion level during ouabain infusion; this reduction did achieve significance (p<0.05).

In the normal dog, RVR increased by 22% during ouabain infusion (p<0.05). After the onset of ventricular pacing in group 2, RVR did not change significantly. RVR increased during ouabain infusion in group 2 by 63% (p<0.05). RVR was similar in both groups at the end of the infusion.

GFR decreased by 57% in group 1 during ouabain infusion (p<0.05). In group 2, GFR did not significantly change after the onset of ventricular pacing. GFR remained unchanged in group 2 during ouabain administration compared with the preinfusion levels. GFR was not statistically different between groups at the termination of the infusion.

Hemodynamic Response

Hemodynamic changes are summarized in Table 2. MAP was unchanged by ouabain administration in group 1. MAP was reduced by ventricular pacing in group 2 and remained depressed throughout ouabain infusion.

Sodium Excretion

![Figure 2. Graph shows sodium excretion during intrarenal ouabain infusion in normal and pacing-induced congestive heart failure (CHF) dogs. U\text{NaV}, sodium excretion. *p<0.05 within group compared with prepacing baseline; †p<0.05 within group compared with preinfusion baseline; p<0.05 between groups.](http://circ.ahajournals.org/...
RAP was unchanged in group 1 animals during ouabain infusion. After the initiation of pacing in group 2, RAP was significantly higher than the prepacing baseline. In group 2, RAP remained significantly elevated during ouabain infusion. RAP was unaffected by ouabain administration.

PCWP was unchanged during ouabain infusion in group 1. PCWP increased significantly after the initiation of ventricular pacing in group 2. PCWP remained significantly elevated and unchanged during the duration of ouabain infusion in group 2.

In group 1, CO was unchanged during ouabain infusion. In group 2, CO declined significantly with the onset of pacing. CO remained significantly reduced during ouabain infusion and significantly different between the two groups.

**Endocrine Response**

Results are summarized in Table 3. ANF levels were unchanged in group 1 by ouabain. After initiation of CHF in group 2, ANF increased by 1,349% (*p<0.05). ANF was not further elevated by ouabain infusion.

PRA was unchanged during ouabain infusion in group 1. PRA increased by 56% after initiation of ventricular pacing (*p<0.05). Administration of ouabain

### Table 2. Hemodynamic Data

<table>
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<th>HR (beats per minute)</th>
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<th>RAP (mm Hg)</th>
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<td>Group 1</td>
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<td>Prepacing baseline</td>
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</tr>
<tr>
<td>Preinfusion baseline</td>
<td>137±6</td>
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<td>143±5</td>
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<tr>
<td></td>
<td>148±6</td>
<td>247±2*</td>
<td>130.8±8.6</td>
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<tr>
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<td>135±3</td>
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### Table 3. Endocrine Data

<table>
<thead>
<tr>
<th></th>
<th>ANF (pg/ml)</th>
<th>Endothelin (pg/ml)</th>
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<tr>
<td>0.668 µg/kg/min</td>
<td>3.98±2.41</td>
<td>3.88±1.39†</td>
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</table>

ANF, atrial natriuretic factor; PRA, plasma renin activity. *p<0.05 compared with prepacing baseline within group; †p<0.05 compared with preinfusion baseline within group; ‡p<0.05 between groups.
in acute CHF decreased PRA by 66% (p<0.05). PRA was not different between groups at the termination of the infusion (see Figure 3). Aldosterone levels were not significantly different between groups at baseline. Aldosterone was not suppressed by ouabain in group 1 and increased by 38% in group 2 (p<0.05).

Endothelin levels were similar in both groups at the preinfusion baseline. Endothelin levels were unchanged in group 2 by acute ventricular pacing and were not significantly different between groups during the infusion period.

Discussion

The current study demonstrates the profound natriuretic actions of ouabain in both the normal state and in acute CHF. We infused intrarenal ouabain at a rate ranging from 0.167 to 0.668 μg/kg/min for a total cumulative dose of 17.53 μg/kg, based on previous studies suggesting an initial dose in the human of 14.28 μg/kg. In both groups studied, intrarenal ouabain administration resulted in a significant increase in sodium excretion independent of an improvement in systemic hemodynamics. The natriuretic effects of ouabain were observed even under conditions in which renal perfusion declined significantly. Furthermore, the natriuresis observed in the normal dog was independent of an increase in circulating ANF or an inhibition of the RAAS. In acute CHF, natriuresis occurred without further activation of ANF and in the absence of an improvement in CO. Because aldosterone was not significantly inhibited by ouabain in either group, it is doubtful that the alterations observed in the RAAS accounted for the natriuretic action of ouabain. The responses observed suggest that the renal excretory effects of ouabain are mediated not by activation of ANF or the RAAS or by improved hemodynamics but by a direct renal action.

Na⁺,K⁺-ATPase is widely distributed throughout the nephron, with highest activity found in the proximal tubule, the thick ascending limb of the loop of Henle, and the distal convoluted tubule. Despite the well-recognized presence of Na⁺,K⁺-ATPase in the tubule, its contribution to the regulation of sodium excretion under normal conditions and in pathophysiological states has not been fully characterized in an in vivo model. Norepinephrine, which may be increased during acute CHF, has been associated with an increase in the activity of nonrenal Na⁺,K⁺-ATPase. Previous studies have demonstrated that in the kidney, norepinephrine results in no change or a slight decrease in the activity of Na⁺,K⁺-ATPase. The current studies demonstrate that in the normal kidney, inhibition of Na⁺,K⁺-ATPase activity resulted in an increased FeNa from a baseline value of 2.3±0.8% to 14.5±5.05% after ouabain administration. In acute CHF, inhibition of Na⁺,K⁺-ATPase activity decreased sodium reabsorption and increased FeNa from a baseline value of 2.2±1.3% to 7.6±2.6%, resulting in almost a fourfold increase in sodium excretion. Although anesthesia may alter autonomic control of the circulation, both groups of animals studied were anesthetized. Barbiturate anesthesia is not associated with alteration in renal sodium excretion. Although ouabain may inhibit Na⁺,K⁺-ATPase in vascular smooth muscle cells and thus alter RVR, the increase observed in FeNa suggests an important tubular site of action for ouabain. Although not directly assessed in this study, previous work by Tamaki and coworkers has demonstrated that ouabain impairs the autoregulatory curve both in the intact kidney and in the nonfiltering kidney. This suggests that tubuloglomerular feedback is not essential for the hemodynamic effects of ouabain.

In CHF, a number of antinatriuretic systems are activated to promote the renal tubular reabsorption of sodium. Na⁺,K⁺-ATPase is not the sole mediator of sodium reabsorption; however, its inhibition has major natriuretic effects. This observation not only enhances our understanding of the physiology of heart failure but suggests that there may be a noninotropic role for digitalis glycosides in the treatment of CHF.

Recent studies have mapped the distribution of Na⁺,K⁺-ATPase binding sites throughout the nephron. In severe CHF, there occurs an upregulation of binding sites within the proximal tubule. The ubiquitous presence of these high-affinity binding sites and their alteration in CHF support the hypothesis that natural EDLFS may participate in the regulation of volume-expanded states. Although the precise identity of all EDLFS remains unknown, investigations have demonstrated several characteristics shared with ouabain. These include 1) specific and reversible inhibition of canine kidney Na⁺,K⁺-ATPase activity, 2) inhibition of Na⁺,K⁺-ATPase noncompetitively with ATP, 3) inhibition of sodium pump activity in human red blood cells, 4) inhibition of serotonin uptake by human platelets, 5) reversal of Na⁺,K⁺-ATPase inhibition occurring with potassium, and 6) both induce diuresis and natriuresis in rat bioassay. Studies before the identification of ANF may have been confounded by the unrecognized effect of this hormone on natriuresis in the volume-expanded animal. ANF does not inhibit Na⁺,K⁺-ATPase, but its natriuretic effects may be similar.

As in clinical CHF, this model of heart failure is characterized by activation of PRA followed by activation of aldosterone. In acute CHF with the activation of renin, we observed an inhibitory effect of ouabain on PRA. In the unstimulated state, PRA was not further suppressed by exogenous ouabain. Previous studies have demonstrated that in the human with chronic CHF, digoxin administration results in a suppressed PRA. Similar reductions in PRA have been observed.
with administration of digoxin in normal subjects and those with essential hypertension.\textsuperscript{28} Although it was not the objective of the current study to evaluate the mechanism of this suppression, several alternative mechanisms could be considered. In states of CHF, an improvement in cardiac performance could suppress renin. In the current study with pacing-induced CHF, CO was not improved by ouabain, suggesting that ouabain-induced suppression of PRA is not dependent on an improvement in hemodynamics. Increased sodium delivery to the macula densa can suppress renin activity. Inhibition of Na\textsuperscript{+},K\textsuperscript{+}-ATPase activity in the proximal tubule should enhance delivery of sodium to the distal tubule and macula densa, thereby suppressing renin. Alternatively, ouabain may act by direct inhibition of juxtaglomerular cells. Finally, ouabain may suppress renin secretion by altering renal sympathetic nerve traffic. Ferguson and coworkers\textsuperscript{29} have demonstrated that cardiac glycosides may suppress muscle sympathetic nerve activity independently of their inotropic effects. Potentially, ouabain may suppress sympathetic nerve stimulation of renin. Further studies are required to precisely determine the mechanism of renin inhibition by ouabain.

Conclusions

This study evaluated the renal hemodynamic and excretory effects of intrarenal ouabain in both normal dogs and in those with acute CHF. Absolute and fractional excretion of sodium was increased significantly by ouabain in both groups of dogs, suggesting that the natriuretic effect of ouabain is preserved even in the presence of acute CHF with decreased renal perfusion. Unlike other diuretics, ouabain also has the beneficial potential to inhibit PRA in CHF. These studies not only provide insight into the therapeutic role of exogenous cardiac glycosides in CHF but also demonstrate the possible mechanisms by which endogenous glycosides may provide a protective role in volume-expanded states. As Withering suggested,\textsuperscript{8} the potent natriuretic activity of ouabain observed in the current study may represent an additional therapeutic and physiological action for the cardiac glycosides. We used ouabain as a pharmacological tool in this study to assess the role of intrarenal Na\textsuperscript{+},K\textsuperscript{+}-ATPase; however, further studies will be necessary to address the clinical relevance of these findings.

Acknowledgments

We acknowledge the assistance of Dr. John C. Burnett Jr. and Denise Heubein for performing the ANF and endothelin assays.

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M A Lloyd, S M Sandberg and B S Edwards

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