

## Role of Hemodynamic Changes in the Increased Cation Excretion after Acute Unilateral Nephrectomy in the Anesthetized Dog

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### Research Article

Studies were carried out in anesthetized dogs to characterize the increase in cation excretion which occurs after acute unilateral nephrectomy (AUN). 60 min after AUN, cation excretion had increased from  $31.5 \pm 2.7$  to  $66.3 \pm 12.0$   $\mu\text{eq}/\text{min}$  ( $P < 0.005$ ) and fractional cation excretion had increased from  $0.56 \pm 0.05$  to  $1.03 \pm 0.14\%$  ( $P < 0.005$ ), as the glomerular filtration rate was unchanged and renal blood flow fell. The increased cation excretion was accompanied by an increase in fractional phosphate excretion, no change in chloride excretion, and a fall in renin secretion. These alterations in renal function were associated with marked changes in systemic hemodynamics: cardiac output fell from  $2.52 \pm 0.24$  to  $1.85 \pm 0.16$  liters/min ( $P < 0.001$ ), as diastolic pressure rose without an overall increase in mean arterial pressure, and heart rate fell.

To assess the importance of these hemodynamic changes in the renal response, AUN in a separate group of dogs was accompanied by the simultaneous opening of a surgically created femoral artery-to-vein fistula at flow matching the blood flow to the removed kidney. When this was done, no alterations in systemic or renal hemodynamics were observed, and cation excretion did not differ from control. Subsequent closure of the fistula then caused a fall in cardiac output from  $2.15 \pm 0.25$  to  $1.77 \pm 0.20$  liters/min ( $P < 0.05$ ), and an increase in cation excretion from  $34.6 \pm 9.5$  to  $52.3 \pm 13.7$   $\mu\text{eq}/\text{min}$  [...]

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# Role of Hemodynamic Changes in the Increased Cation Excretion after Acute Unilateral Nephrectomy in the Anesthetized Dog

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**ABSTRACT** Studies were carried out in anesthetized dogs to characterize the increase in cation excretion which occurs after acute unilateral nephrectomy (AUN). 60 min after AUN, cation excretion had increased from  $31.5 \pm 2.7$  to  $66.3 \pm 12.0$   $\mu\text{eq}/\text{min}$  ( $P < 0.005$ ) and fractional cation excretion had increased from  $0.56 \pm 0.05$  to  $1.03 \pm 0.14\%$  ( $P < 0.005$ ), as the glomerular filtration rate was unchanged and renal blood flow fell. The increased cation excretion was accompanied by an increase in fractional phosphate excretion, no change in chloride excretion, and a fall in renin secretion. These alterations in renal function were associated with marked changes in systemic hemodynamics: cardiac output fell from  $2.52 \pm 0.24$  to  $1.85 \pm 0.16$  liters/min ( $P < 0.001$ ), as diastolic pressure rose without an overall increase in mean arterial pressure, and heart rate fell.

To assess the importance of these hemodynamic changes in the renal response, AUN in a separate group of dogs was accompanied by the simultaneous opening of a surgically created femoral artery-to-vein fistula at flow matching the blood flow to the removed kidney. When this was done, no alterations in systemic or renal hemodynamics were observed, and cation excretion did not differ from control. Subsequent closure of the fistula then caused a fall in cardiac output from  $2.15 \pm 0.25$  to  $1.77 \pm 0.20$  liters/min ( $P < 0.05$ ), and an increase in cation excretion from  $34.6 \pm 9.5$  to

$52.3 \pm 13.7$   $\mu\text{eq}/\text{min}$  ( $P < 0.01$ ), thus mimicking the findings with AUN alone.

These results demonstrate that AUN causes hemodynamic changes resembling those seen on closure of a chronic arteriovenous fistula. Prevention of these hemodynamic changes after AUN also prevents the functional adjustment of the remaining kidney, suggesting that they may be important in initiating the renal response. The increased electrolyte excretion after AUN may occur through mechanisms similar to that seen on closure of an arteriovenous fistula.

## INTRODUCTION

Exclusion of one kidney from the circulation initiates a poorly understood process of enlargement of the other kidney called compensatory hypertrophy. This results ultimately in increases in renal size and function to compensate partially for the lost renal mass. Studies of this phenomenon in the period immediately after nephrectomy have shown that increases in electrolyte excretion can occur very quickly in the remaining kidney, usually without measurable increase in glomerular filtration rate (GFR)<sup>1</sup> and frequently with a fall in renal plasma flow (RPF) (1-4). Additional studies have shown that proximal tubular reabsorption is depressed after clamping of the contralateral renal artery (5-7), although increases in sodium and water excretion did not regularly occur in these studies.

The present experiments were undertaken in order

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<sup>1</sup>Abbreviations used in this paper: A-V, arteriovenous; AUN, acute unilateral nephrectomy; FE, fractional excretion; GFR, glomerular filtration rate; PRA, plasma renin activity; RBF, renal blood flow; RPF, renal plasma flow;  $U_{Cl}V$ , urinary chloride excretion;  $U_{K}V$ , urinary potassium excretion;  $U_{Na}V$ , urinary sodium excretion.

to examine more closely the consequences of acute uninephrectomy on systemic hemodynamics and function of the remaining kidney. The results of these studies demonstrate that acute nephrectomy is followed by a fall in cardiac output and heart rate and an increase in diastolic blood pressure, as cation excretion by the remaining kidney rises. When these hemodynamic changes are prevented, uninephrectomy is not accompanied by an increase in cation excretion, suggesting that the alterations in hemodynamics that accompany acute uninephrectomy may be important determinants of the natriuretic response of the remaining kidney.

## METHODS

Experiments were carried out in 24 mongrel dogs of either sex and weighing between 18 and 26 kg. Food was withheld for 18 h before surgery but the dogs were allowed free access to water. They were anesthetized with intravenous sodium pentobarbital (30 mg/kg) and were ventilated via a cuffed endotracheal tube attached to a Harvard respirator (Harvard Apparatus Co., Inc., Millis, Mass.). The kidneys were approached through subcostal flank incisions, and catheters placed in each renal vein and ureter. Catheters were also placed in the superior vena cava via the right external jugular vein for injection of indocyanine green, and in the brachial artery for recording of arterial blood pressure and heart rate, blood sampling, and blood withdrawal for cardiac output determinations. In three dogs, an adjustable Blalock screw clamp was placed around the aorta above the renal arteries and adjusted to maintain constancy of renal perfusion pressure after nephrectomy; in these experiments, renal perfusion pressure was measured by a catheter inserted into the distal aorta via a femoral artery. In all experiments, a maintenance solution of isotonic saline was infused via a foreleg vein at 0.5 ml/min; this solution contained sufficient inulin and sodium *p*-aminohippurate to achieve plasma concentrations of 25 and 1 mg/dl, respectively.

Experiments were conducted according to two protocols. (a) In 16 dogs, control clearance and hemodynamic measurements were followed by complete surgical uninephrectomy. The renal artery and vein were isolated, doubly ligated and severed, and the kidney removed. After this, the maintenance infusion was slowed in half, and observations repeated starting 30–60 min after the nephrectomy. 11 of these dogs received intramuscular injections of desoxycorticosterone acetate in oil, 5 mg, during surgical preparation, and in 4 animals, acute renal denervation was accomplished by stripping the renal artery and vein of all visible nerves and coating the renal pedicle with absolute alcohol. (b) In another eight dogs, catheters were additionally placed in a femoral artery and vein and attached to tubing led through a calibrated, occlusive roller pump. Blood flow to the kidney to be extirpated was measured *in situ* with an electromagnetic flow meter (Biotronex Laboratories, Inc., Silver Spring, Md.). At the time of nephrectomy, flow was initiated through the femoral fistula, and the pump flow rate adjusted to match flow that had been measured in the kidney that was removed. After a suitable intermediate period to allow for equilibration to occur, repeat clearance and hemodynamic measurements were made. After these, the pump was then turned off, and a final set of observations were taken under conditions that now dupli-

cated the circumstances after acute nephrectomy alone. Each of these dogs received intramuscular injections of desoxycorticosterone.

Clearance periods were 10 or 15 min in length; three to five such periods were averaged to yield a single figure for each dog for each experimental period. Arterial and renal venous blood samples were obtained at the midpoints of alternate periods. Cardiac output was also measured in alternate periods by the dye dilution technique. After injection of 3.75 mg indocyanine green dye into the superior vena cava, arterial blood was withdrawn from the brachial artery at a constant rate through a densitometer (Gilford Instrument Laboratories Inc., Oberlin, Ohio), the output from which was recorded with a chart recorder (Honeywell Visicorder, Honeywell, Inc., Test Instruments Div., Denver Colo.). Cardiac output was calculated by planimetry from the dye dilution curve using a programmable calculator.

Blood samples were immediately placed in chilled, heparinized tubes, centrifuged in the cold, and frozen until later analysis. Samples for measurement of plasma renin activity (PRA) were obtained in tubes containing EDTA and analyzed by using a radioimmunoassay for angiotensin I (8, 9). Plasma and urine were analyzed for concentrations of inulin, *p*-aminohippurate sodium, potassium, chloride, and osmolality by methods previously described for this laboratory (10, 11). Inorganic phosphorus was measured by the method of Alabaster and Evans on the autoanalyzer (12). GFR was calculated from the clearance of inulin, renal blood flow (RBF) from the clearance and extraction of *p*-aminohippurate and the arterial hematocrit, and renin secretory rate from RPF and the difference in PRA in renal venous compared with arterial blood. Fractional excretion (FE) of  $\text{PO}_4$  was calculated from  $C_{\text{PO}_4}/C_{\text{inulin}} \times 100$  and  $\text{FE}_{\text{cation}}$  from  $C_{\text{Na+K}}/C_{\text{inulin}} \times 100$ .<sup>2</sup> Values are the means  $\pm 1$  SE, and the statistical significance of differences between periods was assessed using Student's *t* test for paired observations.

## RESULTS

Uninephrectomy uniformly resulted in small increases in urine flow and cation excretion by the contralateral kidney in the 30–60 min after organ extirpation. These increases were observed as soon as measurements were begun (15 min after nephrectomy) and could be detected as long as 180 min after nephrectomy. The increase in cation excretion consisted of increments in both urinary sodium excretion ( $U_{\text{NaV}}$ ) and urinary potassium excretion ( $U_{\text{KV}}$ ) (Table I), although the increase in  $U_{\text{NaV}}$  did not achieve significance ( $0.10 > P > 0.05$ ) because of variations among the different experiments.  $\text{FE}_{\text{cation}}$  increased from  $0.56 \pm 0.05$  to  $1.03 \pm 0.14\%$  of the filtered load, as GFR was unchanged (Table I). These changes in cation excretion were accompanied by a significant increase in  $\text{FE}_{\text{PO}_4}$ , but no overall change in urinary chloride excretion ( $U_{\text{ClV}}$ ). RBF decreased from 260

<sup>2</sup> Urinary potassium reflects secretion of potassium in the distal nephron in a process related to sodium reabsorption at this site, and bears little relationship to filtered potassium. However, for consistency  $\text{FE}_{\text{cation}}$  has been determined by means of the filtered cation load.

**TABLE I**  
Effect of AUN on Renal Hemodynamics, Electrolyte Excretion, and Renin Secretion by the Remaining Kidney\*

	Urine flow	GFR	RBF	$U_{Na}V$	$U_KV$	$U_{Na+K}V$
	ml/min	ml/min	ml/min	$\mu\text{eq/min}$	$\mu\text{eq/min}$	$\mu\text{eq/min}$
Control	0.24 $\pm 0.04$	39.5 $\pm 3.7$	260 $\pm 29$	6.9 $\pm 1.5$	24.6 $\pm 2.2$	31.5 $\pm 2.7$
60 min after uninephrectomy	0.49 $\pm 0.12$	40.1 $\pm 3.8$	228 $\pm 31$	21.4 $\pm 7.8$	44.9 $\pm 5.7$	66.3 $\pm 12.0$
<i>P</i> §	<0.05	NS	<0.02	<0.10	<0.001	<0.005
	$FE_{\text{cation}}$	$U_{Cl}V$	$FE_{PO_4}$	PRA	Renin secretory rate	
	%	$\mu\text{eq/min}$	%	ng A-I / ml/h	ng A-I / min	
Control	0.56 $\pm 0.05$	11.2 $\pm 3.0$	2.6 $\pm 1.5$	23.8 $\pm 3.3$	960 $\pm 242$	
60 min after uninephrectomy	1.03 $\pm 0.14$	15.4 $\pm 7.7$	13.0 $\pm 4.8$	12.3 $\pm 1.9$	316 $\pm 83$	
<i>P</i>	<0.005	NS	<0.05	<0.001	<0.02	

\* Values are means  $\pm 1$  SE of measurements before and 60 min after AUN in 16 dogs.

‡ Cation excretion.

§ Level of statistical significance using Student's *t* test for paired data. Renin measurements were made in seven dogs.

<sup>||</sup> Angiotensin I.

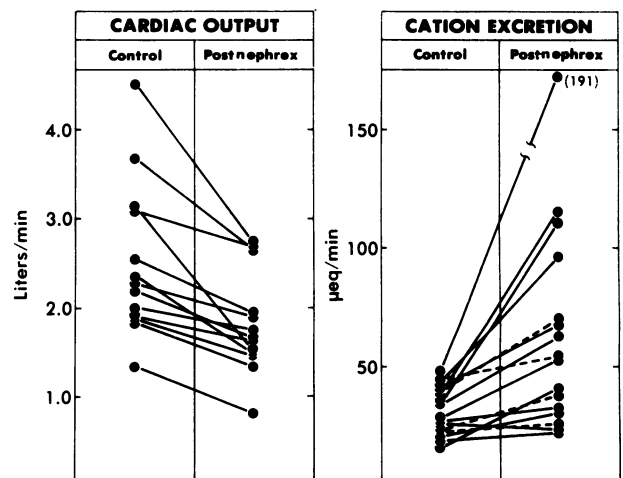
$\pm 29$  to  $228 \pm 31$  ml/min ( $P < 0.02$ ); inasmuch as mean arterial pressure was on the whole unchanged (Table II), renal vascular resistance rose from  $0.483 \pm 0.044$  to  $0.581 \pm 0.061$  mm Hg/ml per min ( $P < 0.05$ ). Similarly, constancy of GFR in the face of a decrease in RBF resulted in a rise in filtration fraction from  $0.30 \pm 0.02$  to  $0.35 \pm 0.01$  ( $P < 0.005$ ). Renin secretory rate and arterial PRA were measured in seven of these experiments; each fell significantly (Table I).

Acute renal denervation was performed in four studies; the response of these denervated kidneys to contralateral nephrectomy was identical to that seen in innervated kidneys (Fig. 1). Similarly, treatment with exogenous mineralocorticoid did not alter the response. In three experiments, uninephrectomy produced increases in mean aortic pressure of  $>10$  mm Hg. In these studies, renal perfusion pressure was kept at or below control levels by constriction of an aortic clamp. Cation excretion in these three studies increased by 26.1, 10.4, and 15.2  $\mu\text{eq/min}$ . Thus, acute unilateral nephrectomy resulted in increased cation excretion and decreased renin secretion, by

**TABLE II**  
Effect of AUN on Systemic Hemodynamics, Hematocrit, and Plasma Total Protein Concentration\*

	Cardiac output	Mean arterial pressure	Diastolic pressure	Heart rate
	liters/min	mm Hg	mm Hg	beats/min
Control	2.52 $\pm 0.24$	112 $\pm 4$	94 $\pm 5$	150 $\pm 4$
60 min after uninephrectomy	1.85 $\pm 0.16$	116 $\pm 4$	102 $\pm 5$	137 $\pm 9$
<i>P</i>	<0.001	NS	<0.025	<0.05
	Total peripheral resistance	Arterial hematocrit	Total protein concentration	
	$\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$	vol%	g/100 ml	
Control	3,634 $\pm 352$	46.5 $\pm 1.4$	5.18 $\pm 0.18$	
60 min after uninephrectomy	5,229 $\pm 661$	46.5 $\pm 1.3$	4.93 $\pm 0.15$	
<i>P</i>	<0.005	NS	<0.05	

\* Values are means  $\pm 1$  SE of multiple observations in each dog before (control) and 60 min after complete surgical nephrectomy. Hematocrit and protein concentration were measured in 16 dogs; hemodynamic measurements were made in 13 dogs. Total peripheral resistance was calculated in only 10 studies because of the presence of an aortic clamp in three experiments.



**FIGURE 1** Changes in cardiac output and cation excretion ( $U_{Na+K}V$ ) 60 min after AUN. Each point is the average of two or three measurements of cardiac output and three to five measurements of cation excretion before and after uninephrectomy; points connected by dotted lines in the right panel are from acutely denervated kidneys.

the contralateral kidney despite renal vasoconstriction and increased filtration fraction. This response was not dependent on the renal nerves, occurred in the presence of exogenous mineralocorticoid administration, and was observed in the face of constant renal perfusion pressure.

The alterations in systemic hemodynamics caused by acute uninephrectomy are shown in Table II and Fig. 1. Mean arterial pressure tended to rise, but the increase was not significant. On the other hand, diastolic pressure rose, in association with a consistent fall in cardiac output from  $2.52 \pm 0.24$  to  $1.85 \pm 0.16$  liters/min ( $P < 0.001$ ). Heart rate also fell. Because of this fall in cardiac output with unchanged mean aortic pressure, calculated total peripheral resistance rose (Table II). The fall in cardiac output was significantly greater than the blood flow to the removed kidney ( $668 \pm 146$  vs.  $249 \pm 18$  ml/min,  $P < 0.02$ ).

To distinguish the importance of these changes in systemic hemodynamics from some other consequence of uninephrectomy in the increased cation excretion, additional studies were carried out in a separate group of animals. In these studies, a femoral arteriovenous (A-V) shunt was opened at the time of nephrectomy at blood flow matching flow to the removed kidney. The effect of this maneuver on systemic hemodynamics is shown in Table III. When acute nephrectomy was accompanied by opening of the femoral fistula, only minimal changes in cardiac output,

TABLE III  
*Effect of Acute Uninephrectomy Accompanied by Simultaneous Opening of a Femoral Fistula, and Subsequent Closure of the Fistula, on Systemic Hemodynamics in the Dog\**

	Control	Uninephrectomy + fistula open	Close fistula
Cardiac output, liter/min	2.30 $\pm 0.28$	2.15 $\pm 0.25$	1.77 $\pm 0.20$
<i>P</i>	NS	<0.05	
Mean arterial pressure, mm Hg	98 $\pm 6$	98 $\pm 6$	104 $\pm 7$
<i>P</i>	NS	<0.05	
Diastolic pressure, mm Hg	88 $\pm 6$	86 $\pm 6$	95 $\pm 7$
<i>P</i>	NS	<0.05	
Heart rate, beats/min	146 $\pm 8$	140 $\pm 6$	145 $\pm 4$
<i>P</i>	NS	NS	
Total peripheral resist- ance, $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$	3,713 $\pm 384$	3,954 $\pm 419$	5,194 $\pm 727$
<i>P</i>	NS	<0.05	

\* Presentation of data the same as in Table II ( $n = 8$ ).

TABLE IV  
*Effect of Acute Uninephrectomy Accompanied by Simultaneous Opening of a Femoral Fistula, and Subsequent Closure of the Fistula, on Renal Function in the Dog\**

	Control	Uninephrectomy + fistula open	Close fistula
GFR, ml/min	32.1 $\pm 3.6$	32.7 $\pm 4.1$	36.2 $\pm 4.9$
<i>P</i>	NS	NS	
RBF, ml/min	244 $\pm 28$	232 $\pm 20$	189 $\pm 19$
<i>P</i>	NS	<0.05	
$U_{Na}V$ , $\mu\text{eq}/\text{min}$	6.1 $\pm 1.3$	5.0 $\pm 1.9$	10.3 $\pm 3.4$
<i>P</i>	NS	<0.05	
$U_KV$ , $\mu\text{eq}/\text{min}$	18.4 $\pm 2.6$	29.7 $\pm 7.7$	42.1 $\pm 10.7$
<i>P</i>	NS	<0.01	
$U_{Na+K}V$ , $\mu\text{eq}/\text{min}$	24.6 $\pm 3.3$	34.6 $\pm 9.5$	52.3 $\pm 13.7$
<i>P</i>	NS	<0.01	
$FE_{\text{cation}}$ , %	0.61 $\pm 0.16$	0.77 $\pm 0.12$	1.11 $\pm 0.19$
<i>P</i>	NS	<0.05	
$U_{Cl}V$ , $\mu\text{eq}/\text{min}$	12.4 $\pm 3.4$	9.0 $\pm 4.1$	10.3 $\pm 6.3$
<i>P</i>	NS	NS	
$FE_{PO_4}$ , %	4.3 $\pm 2.4$	5.5 $\pm 2.0$	11.8 $\pm 3.3$
<i>P</i>	NS	<0.05	

\* Presentation of data the same as in Table I. Data are from the same eight dogs in which the hemodynamic measurements in Table III were made.

mean and diastolic blood pressure, and total peripheral resistance were observed, suggesting that this maneuver was successful in abolishing the hemodynamic consequences of nephrectomy. Subsequent closure of the fistula, by turning off the pump in the nephrectomized animal, duplicated the situation seen with uninephrectomy alone. This reproduced many of the hemodynamic changes described in Table II: cardiac output fell from  $2.15 \pm 0.25$  to  $1.77 \pm 0.20$  liters/min, as both mean arterial and diastolic blood pressures rose significantly (Table III). In contrast to the earlier studies, no fall in heart rate was observed.

The results of this sequence of maneuvers on function and electrolyte excretion of the remaining kidney are shown in Table IV. No significant changes in GFR were seen after nephrectomy and opening of the fistula, or then after fistula closure. RBF was not altered when nephrectomy was accompanied by fistula

opening, but fell significantly from  $232 \pm 20$  to  $189 \pm 19$  ml/min when the fistula was then closed ( $P < 0.05$ ). Electrolyte excretion likewise was unchanged in the period after nephrectomy and opening of the fistula (Table IV). However, when the pump controlling fistula blood flow was turned off, small but significant increases in both  $U_{Na}V$  and  $U_KV$  occurred, and total cation excretion increased from  $34.6 \pm 9.5$  to  $52.3 \pm 13.7$   $\mu\text{eq/min}$  ( $P < 0.01$ ). These changes in absolute cation excretion were reflected by similar changes in  $FE_{\text{cation}}$  and were paralleled by the changes observed in  $FE_{\text{PO}_4}$ . However,  $U_{Cl}V$  was not altered either by nephrectomy with simultaneous fistula opening or by subsequent fistula closure (Table IV). PRA was not measured in these experiments.

Thus, the hemodynamic changes seen after acute nephrectomy could be prevented by the opening of a femoral A-V fistula. When this was done, the changes in renal hemodynamics and electrolyte excretion did not occur. When the femoral fistula was then closed, thereby reproducing the circumstances of acute uninephrectomy alone, the characteristic changes in systemic and renal hemodynamics and electrolyte excretion occurred.

## DISCUSSION

These studies confirm that acute unilateral nephrectomy (AUN) results in a prompt increase in electrolyte excretion by the contralateral kidney. This consisted chiefly of an increment in  $U_KV$  because the increase in  $U_{Na}V$  was small and achieved statistical significance in only one group of dogs. Previous studies of contralateral kidney clamping in the dog have demonstrated a significant depression of proximal tubular reabsorption without an increase in  $U_{Na}V$ , suggesting that increased distal reabsorption occurred to prevent natriuresis (5-7). Studies in volume-expanded animals indicate that natriuresis after acute uninephrectomy is more pronounced (4, 13); the present experiments were carried out in hydropenic animals, thereby minimizing the natriuretic consequences of this maneuver. As seen in Fig. 1, animals with higher basal rates of cation excretion tended to show a greater increment after AUN. It is known that  $U_KV$  is dependent in part on the amount of sodium reaching the distal potassium secretory site (14), so that increased  $U_KV$  may reflect increased delivery, and reabsorption, of sodium at this site, despite only small increases in  $U_{Na}V$ . Another factor influencing potassium secretion, and  $U_KV$ , is the anionic composition of fluid reaching the distal convolution (14). The delivery of significant quantities of relatively nonreabsorbable anions such as bicarbonate and sulfate accelerate potassium secretion and lead to increased  $U_KV$ . In this regard, earlier studies have shown that con-

tralateral kidney clamping causes an increase in urinary sodium bicarbonate excretion (13, 15). For these reasons, it seems logical to interpret the increased cation excretion after uninephrectomy in the present studies as resulting from decreased proximal reabsorption, and increased distal delivery, of filtered sodium bicarbonate, leading to increased distal potassium secretion. Increased cation excretion, chiefly potassium, then results, accompanied presumably by bicarbonate (13). The constancy of  $U_{Cl}V$  in these experiments is consistent with this formulation. Depressed proximal reabsorption may be inferred from the increased  $FE_{\text{PO}_4}$  observed in these studies, to the extent that this reflects depression of proximal phosphate reabsorption.

The major findings of the present studies were the consistent alterations in systemic hemodynamics observed after AUN. These alterations consisted of significant falls in cardiac output and heart rate and a rise in diastolic pressure without change in mean aortic pressure. These alterations are identical to those that occur on closure of a chronic A-V fistula (16, 17) and have long been known to be natriuretic when produced as a result of this maneuver (18). Because each kidney receives  $\approx 10\%$  of the cardiac output as its blood flow, it is perhaps not implausible to consider acute uninephrectomy as being analogous to closure of a chronic A-V fistula. Such an analogy would suggest that the induced hemodynamic changes after uninephrectomy play an important role in the natriuretic response of the opposite kidney, and that some other consequence of acute reduction in renal mass is not responsible for the natriuresis. To test this point, studies were done in which the hemodynamic perturbations caused by uninephrectomy were prevented by the simultaneous opening of a femoral A-V fistula. Flow through this fistula closely matched the blood flow to the removed kidney, with the consequence that no significant change occurred in any of the measured hemodynamic variables (Table III). Under these conditions, nephrectomy failed to alter function or electrolyte excretion of the contralateral kidney. Although the slight rise in  $U_KV$  in this group (Table IV) suggested an effect related to the nephrectomy, this change was nevertheless not statistically significant. These results thus demonstrated clearly that nephrectomy per se was not responsible for the changes seen in the remaining kidney through some unidentified neural or humoral pathway. Moreover, the results implicated even more strongly a central role of the hemodynamic changes resulting from AUN in initiating the response of the remaining kidney. This was further supported by the finding that closure of the femoral fistula in the nephrectomized dog then reproduced virtually all the hemodynamic changes originally observed after

simple nephrectomy alone, and also resulted in increased cation excretion. A strong relationship therefore was established between the systemic hemodynamic changes and the response of the remaining kidney to AUN.

The precise hemodynamic signal that constitutes the afferent limb of this circulatory reflex is not known. The natriuresis after closure of an A-V fistula has been analyzed in terms of an increase in "effective" blood volume (18). The effect definition of "effective" blood volume has, however, remained elusive. In the present studies, the kidney to be extirpated could be considered as a resistance circuit in parallel with nonrenal vascular resistance. Nephrectomy would result in an increase in total peripheral resistance and a consequent rise in blood pressure, albeit small. This, in turn, could lead to activation of baroreceptors, subsequently producing reflex cardiovascular changes and increased cation excretion. Closure of an A-V fistula could be analyzed similarly. If AUN causes only trivial changes in right-sided cardiac pressures, as has been reported to be the case on closure of an A-V fistula (16, 17), then antinatriuretic stimuli arising from activation of right atrial receptors would be minimal or absent (19–21). A further parallel between these two maneuvers is the observation of decreased RPF on closure of an A-V fistula (22). The pattern of anion excretion seen on closing a fistula is not known, but would have to include phosphaturia and bicarbonaturia without chloruresis in order to be consistent with the observations after AUN.

The present studies show clearly that the renal nerves or changes in mineralocorticoid activity are not necessary for the response, in accord with earlier observations (2, 6, 14). The natriuresis also occurs despite continuous infusions of vasopressin (6, 14). Although mean arterial pressure rose slightly in these experiments, the increase was not significant, consistent with previous findings (2, 6). In addition, changes in hematocrit or plasma protein concentration cannot account for the increased cation excretion. Thus, no known circulating or compositional change in the blood appears adequate to explain the increased cation excretion. A striking feature of these studies was the fall in RBF, and consequent increases in filtration fraction and renal vascular resistance. Under most circumstances, these changes are antinatriuretic and would be expected to increase rather than decrease proximal reabsorption (23). Deen and associates (24) have developed a model of proximal reabsorption in which sufficiently low rates of postglomerular plasma flow are associated with decreases in absolute proximal reabsorption, despite increases in filtration fraction and postglomerular protein concentration. The predictions of this model were subsequently verified experimentally by Myers and colleagues (25),

who found that reductions in postglomerular plasma flow produced by norepinephrine infusion led to reduced proximal reabsorption in the rat despite an increase in single nephron filtration fraction. Such a mechanism does not seem likely to account for decreased proximal reabsorption after AUN: the fall in RPF in these studies was only 12%, and estimated whole-kidney postglomerular plasma flow (RPF-GFR) fell only 18%, far less than the 40% reduction in efferent arteriolar plasma flow observed by Myers et al. (25), and insufficient to overcome the increased postglomerular plasma protein concentration and to decrease proximal reabsorption as in the model proposed by Deen and associates (24). Whether the fall in RBF in the present studies was associated with a redistribution of blood flow to lead to natriuresis is not known; earlier reports failed to demonstrate measurable blood flow redistribution after AUN (2, 26). On the other hand, redistribution of GFR to superficial cortical nephrons has been observed 15 h after uninephrectomy (27) and immediately on closure of an A-V fistula (22). How such redistribution occurs, and its consequences on proximal tubular sodium, bicarbonate, and phosphate reabsorption, remain questions for further study. The possibility that a humoral substance is involved in the natriuresis after AUN has been suggested (27); in one study, prostaglandin infusion prevented the decrease in proximal reabsorption normally observed after contralateral kidney clamping (28).

The mechanism for the decreased renin secretion observed after acute uninephrectomy cannot be determined from these studies. Natriuretic states in general are associated with decreased renin secretion, whether through vascular, tubular, or neurohumoral pathways. Evidence has been presented that chloride may play an important role in the suppression of PRA which accompanies volume expansion, possibly through a tubular mechanism (29). Although  $U_{ClV}$  was not increased after AUN, delivery of chloride to the macula densa could have been increased along with the increase in sodium and bicarbonate, and have resulted in decreased renin release. Alternatively, renin secretion could have diminished through vascular or neurohumoral mechanisms. Regardless of the exact mechanism, the observation is consistent with an increase in effective circulating blood volume after uninephrectomy (18).

In summary, AUN is associated with a marked decrease in cardiac output and an increase in total peripheral resistance as cation excretion by the remaining kidney increases. Prevention of these hemodynamic changes prevents the increase in cation excretion, demonstrating that removal of renal mass per se is not the factor responsible for the compensation by the remaining kidney. Whether these hemodynamic changes play any role in the long-term increase in

renal mass that follows uninephrectomy is an important issue for subsequent investigation.

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