Disproportionate Inhibition of Sodium Reabsorption in the Unilaterally Diseased Kidney of Dog and Man after an Acute Saline Load

FRANK D. GUTMANN and RICHARD E. RIESELBACH

From the Renal Section, Department of Internal Medicine, University of Wisconsin Medical Center, Madison, Wisconsin 53706

ABSTRACT Clearance studies were performed on 49 split-bladder dogs with a unilateral pyelonephritic or remnant kidney and three patients with unilateral kidney disease to examine the effects of an acute saline load on the diseased kidney (DK) as opposed to a simultaneously studied, contralateral control kidney (CK), which also served to maintain a nonuremic environment.

Before saline loading, base line studies in many of the dogs and the three humans were in agreement with previously published data. However, in dogs with a severe pyelonephritic lesion, a greater difference in DK vs. CK fractional excretion of sodium (FE_{Na}) and water was noted, whose magnitude was inversely correlated with the level of glomerular filtration rate (GFR) and maximum urine osmolality of DK compared to CK.

An acute saline load (75 ml/kg) resulted in an inhibition of fractional sodium and water reabsorption in the diseased dog kidney which was disproportionately greater than in the simultaneously studied CK, regardless of the type or severity of the lesion. While mean DK GFR for all dogs increased 15% more than CK GFR, failure of FE_{Na} to increase after induction of a disproportionate increase in DK GFR with parathyroid hormone suggested that the saline-induced disproportionate increase in GFR was not solely responsible for the exaggerated inhibition of fractional sodium and water reabsorption in the diseased dog kidney. Studies in the three patients after saline loading (25 ml/kg) revealed a similar disproportionate resetting of glomerulotubular balance.

Thus, regardless of base line function before expansion, the unilaterally diseased kidney of dog and man possesses unique characteristics in the *absence of uremia* which render it more reactive to the stimuli produced by acute saline loading. This suggests that the intrarenal environment of the kidney with a reduced nephron population may under some circumstances serve as a determinant of its function.

INTRODUCTION

The dog with an experimentally induced unilateral reduction in nephron population or the patient with unilateral pyelonephritis provides an opportunity to study the functional characteristics of a reduced nephron population in the absence of uremia. In addition to maintaining a normal internal environment, the contralateral intact kidney (CK) serves as an ideal control, in that it may be studied simultaneously with the diseased kidney (DK) under extrarenal environmental conditions which are theoretically identical. When the extracellular fluid volume (ECFV) is expanded in this setting, the nephrons of both kidneys should be exposed to identical humoral and physical stimuli, which appear to mediate ECFV homeostasis via regulation of sodium transport by the renal tubule (1).

In a recent redefinition of the intact nephron hypothesis, Bricker has emphasized that nephrons within the diseased kidney behave as if they were normal, in that they respond to the needs of the organism in an organized and directed fashion (2). Furthermore, Bricker and coworkers have suggested that regulation of sodium balance by chronically diseased kidneys may be mediated by a control system of extrarenal origin dependent upon an elevated level of a humoral factor during

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uremia which inhibits sodium transport (3, 4). In the presence of a unilaterally diseased kidney, one may assume that the response of the control kidney in resetting glomerulotubular balance following ECFV expansion is appropriate to the homeostatic needs of the organism. Thus, the response of DK should be proportionate to that of CK, unless DK possesses unique characteristics, even in the absence of uremia, which render it more responsive to the stimuli which inhibit sodium reabsorption in response to ECFV expansion.

The present studies were designed to investigate the response of DK as compared to CK to an acute saline load. First, extensive base line clearance data were obtained in the absence of ECFV expansion in 49 split-bladder dogs with unilateral remnant or pyelonephritic kidneys and in three patients with unilateral diseased kidneys. Then, a massive and acute expansion of the ECFV was accomplished via a rapid intravenous infusion of isotonic saline, 75 ml/kg in the dog and 25 ml/kg in man. The disproportionately greater inhibition of sodium reabsorption in DK as compared to CK observed in the dog and man in the *absence of uremia* suggest an intrinsic, increased reactivity of DK to the stimuli which serve to regulate ECFV via modulation of glomerulotubular balance.

METHODS

Dog studies

Preparation of experimental model. A unilateral reduction in nephron mass in the presence of a contralateral control kidney was induced in 49 female mongrel dogs weighing between 13 and 29 kg, in one of three ways. (*a*) In 35 dogs unilateral pyelonephritis was induced by ligating $\frac{1}{3}$ to $\frac{4}{5}$ of the arterial supply, as judged by the readily apparent infarction of the surface of the kidney. 250–750 punctures with a No. 25 electric cautery needle $\frac{5}{8}$ inch in length were evenly distributed throughout the remaining viable renal tissue. Approximately 4 hr later, 0.75 ml of a $3\frac{1}{2}$ hr broth culture of *E. coli* was injected intravenously. The foregoing produced a severely contracted, pyelonephritic kidney which on microscopic examination is indistinguishable from human chronic pyelonephritis (5). (*b*) In two dogs (Mr and Ke) unilateral pyelonephritis was induced in a manner similar to the foregoing 35 dogs, except that 1200 punctures alone were employed in the absence of partial arterial ligation, to avoid manipulation of the renal hilum. (*c*) In 12 dogs a unilateral remnant kidney was produced by ligating approximately $\frac{1}{3}$ to 39/40 of the arterial supply. No cautery injury or intravenous bacteria were employed in these 12 dogs. In all 49 dogs the experimental kidney was exposed through a flank incision; this invariably required disruption of perirenal mesenteric or peritoneal tissues which were adherent to the renal capsule. A mean of 13 wk was allowed to elapse in order to permit stabilization of the lesion in both the pyelonephritic (range 8–23 wk) and kidney remnant (range 5–31 wk) dogs; then, the urinary bladder was divided to permit separate, *simultaneous* urine collections from each kidney through bilateral indwelling cystostomy tubes, in the unanesthetized state (6).

Protocol for clearance and U_{max} studies. In all 49 dogs clearance studies were performed following 12–18 hr of water deprivation. All dogs were studied in the standing position. A constant infusion of 0.25 ml/kg per min of 3% mannitol was initiated in order to obtain adequate urine flow and was maintained throughout the study. A suitable priming dose of creatinine and *p*-aminohippuric acid (PAH) was administered intravenously as well as a sustaining dose via the constant infusion. Following a 45 min equilibration period, at least three base line clearance periods were obtained, each a minimum of 10 min. In order to obtain at least 3 ml of urine per clearance period, as long as 4 hr were required to obtain base line data in dogs with the most severe lesions, whereas less than 1 hr was required in the dogs with milder lesions. Immediately following these collections, the ECFV was expanded with 75 ml/kg of 0.85 sodium chloride over a period of 15–25 min. Then an additional three clearance periods were initiated immediately; these periods usually did not exceed 10 min each.

Additional studies were performed on some of the dogs on subsequent days. In nine of the dogs a similar protocol was employed except that the 0.85% sodium chloride volume expansion was replaced by a rapid intravenous injection of 400 mg of Diamox (acetazoleamide) followed by a 5 min equilibration period. In seven dogs, 400 U of parathyroid hormone (Eli Lilly & Co.) was rapidly injected intravenously after obtaining three to four base line clearance periods. 20 min later the first of three 15-min clearance periods was obtained. Then, the previously described volume expansion protocol was employed followed by three subsequent 10-min clearance periods.

Maximum urine osmolality (U_{max}) was determined in both kidneys simultaneously, usually 1 or 2 days before the first volume expansion study, and no sooner than 6 days after the bladder splitting operation. The dogs were water deprived 18–24 hr, then given 50 mU/kg of pitressin intravenously as a priming dose followed by an additional 10 mU/kg every 10 min intravenously until a minimum of 2 ml of urine was obtained from the diseased kidney. No clearance data were obtained on the day of a U_{max} study.

As depicted in Table I, the 49 dogs were divided into three groups. The pyelonephritic dogs were arbitrarily divided into a severe pyelonephritic group (DK/CK GFR ratio < 0.2, 18 dogs, DK GFR range 0.32–10.9 ml/min) and a moderate pyelonephritic group (DK/CK GFR ratio > 0.2, 19 dogs). The third group includes all of the remnant kidney dogs.

Human studies

A volume expansion protocol similar to that employed in the dogs was modified for studying three female patients who presented with X-ray evidence of a unilateral small kidney and a contralateral normal appearing kidney. In two patients (E. B. and N. F.) this study was performed as part of a hypertensive workup, and in the third (N. B.) as part of a vesicoureteral reflux workup. Food and water were withheld for 8 hr before a spinal anesthetic and no other medications except Demerol were administered for 24 hr before or during the test. Bilateral retrograde catheters (No. 6 or No. 7 French) were passed to approximately the middle third of the ureters. After an appropriate priming and sustaining infusion of inulin and PAH in 5% mannitol at 5 ml/min, and a 45–60 min equilibration period, two to three base line periods of at least 10 min in duration were obtained. Then 25 ml/kg of 0.9% sodium

TABLE I

Summary of Base Line Data (before Saline Load)

		GFR	C_{PAH}	V	U_{Na}	U_{Cr}	FE_{Na}	FE_{H_2O}	C_{H_2O}/GFR	FF	FE_K	U_{max}
		ml/min	*ml/min*	*ml/min*	*mEq/liter*	*mg/100 ml*	%	%	%	%	%	*mOsm/kg*
SP	DK	4.1 ±0.8	14.4 ±3.0	0.21 ±0.05	32.2 ±4.5	274 ±35	1.58 ±0.37	6.19 ±0.68	−1.14 ±0.40	29.7 ±1.3	19.2 ±3.1	579 ±66
	CK	57.1 ±3.0	189 ±14	1.81 ±0.20	14.7 ±3.6	481 ±48	0.44 ±0.14	3.40 ±0.36	−2.25 ±0.28	31.5 ±1.3	16.2 ±2.1	1581 ±97
	*				15/18	18/18	17/18	17/18	15/18	11/18	10/18	
MP	DK	16.9 ±1.5	56.2 ±4.4	0.39 ±0.04	28.2 ±3.9	541 ±46	0.52 ±0.13	2.66 ±0.35	−2.59 ±0.28	30.2 ±0.77	15.6 ±1.5	1140 ±73
	CK	49.5 ±2.7	161 ±9.9	0.91 ±0.07	25.8 ±4.7	651 ±44	0.35 ±0.07	2.07 ±0.22	−3.04 ±0.28	31.3 ±0.86	16.7 ±1.3	1660 ±107
	*				15/19	18/19	16/19	18/19	17/19	13/19	12/19	18/19
R	DK	5.7 ±1.2	20.0 ±3.4	0.21 ±0.06	35.1 ±4.6	412 ±47	0.83 ±0.19	3.52 ±0.55	−2.57 ±0.28	28.0 ±1.8	17.0 ±2.1	973 ±98
	CK	52.4 ±2.0	168 ±6.9	1.25 ±0.16	24.3 ±5.3	552 ±61	0.41 ±0.09	2.61 ±0.34	−2.74 ±0.33	31.6 ±0.94	16.6 ±2.0	1768 ±121
	*				11/12	10/12	12/12	10/12	9/12	9/12	5/12	
T	DK	9.4 ±1.1	32.0 ±3.5	0.28 ±0.03	31.3 ±2.5	411 ±29	0.99 ±0.16	4.16 ±0.38	−2.05 ±0.22	29.5 ±0.71	17.3 ±1.4	893 ±56
	CK	53.0 ±1.6	173.0 ±6.7	1.32 ±0.10	21.3 ±2.6	564 ±30	0.40 ±0.06	2.69 ±0.25	−2.67 ±0.17	31.5 ±0.61	16.5 ±1.0	1658 ±62
	*	49/49	49/49	49/49	41/49‡	46/49	45/49‡	45/49‡	41/49‡	33/49‡	22/49	48/49‡

* Fraction of dogs supporting the direction of the means.

‡ $P < 0.001$.

DK = diseased kidney; CK = control kidney; SP = severe pyelonephritis (DK/CK GFR < 20%); MP = moderate pyelonephritis (DK/CK GFR > 20%); R = remnant kidney; T = total (49 dogs); GFR = glomerular filtration rate; C_{PAH} = clearance of *para*-aminohippurate; V = urine flow rate; U_{Na} = urine sodium concentration; U_{Cr} = urine creatinine concentration; FE_{Na} = fractional excretion of sodium; FE_{H_2O} = fractional excretion of water; C_{H_2O}/GFR = free water clearance factored by GFR; FF = filtration fraction (GFR)/(C_{PAH}); FE_K = fractional excretion of potassium; U_{max} = maximum urine osmolality.

chloride was administered intravenously over 15 min; immediately thereafter an additional three clearance periods were obtained. The 5% mannitol constant infusion was changed to 0.45% sodium chloride at the onset of volume expansion.

Analytical technics and calculations

Venous blood was obtained from an indwelling needle and drawn into heparinized syringes during all studies in man and dog. Glomerular filtration rate in man was determined by inulin clearance. Inulin analyses were carried out according to the method of Roe, Epstein, and Goldstein (7). Exogenous creatinine clearance was employed in the dog as a measure of glomerular filtration rate. Creatinine concentration in urine and plasma was determined by the Jaffé reaction (8). Sodium analyses were performed on an Instrumentation Laboratories emission flame photometer. Urine osmolality was determined on an Advanced Osmometer by freezing point depression. PAH was measured by the method of Smith, Finkelstein, Aliminosa, Crawford, and Graber (9). Calcium and magnesium determinations were performed by atomic absorption spectrophotometry utilizing the Model 303 Perkin-Elmer instrument as previously described (10). Phosphate determinations were performed by means of the Auto-Analyzer methodology as recommended by Technicon Corp., Ardsley, N. Y. Uric acid determinations were performed by the enzymatic spectrophotometric method of Liddle, Seegmiller, and Laster (11).

In comparing the response of diseased and control kidney, we have used the following equation for parameters not expressed as a percentage, such as GFR, C_{PAH}, U_{Na}, U_{Cr}, and urine flow rate: (*a*) disproportionate response (%ΔDK − %ΔCK) = (DK$\bar{p}$ − DK$\bar{a}$)/(DK$\bar{a}$) − (CK$\bar{p}$ − CK$\bar{a}$)/(CK$\bar{a}$) × 100 (%) where DK = diseased kidney, CK = control kidney, $\bar{p}$ = post expansion, and $\bar{a}$ = base line before expansion. However, for those parameters expressed as a percentage, such as filtration fraction (FF), FE_{Na}, FE_{H_2O}, C_{H_2O}/GFR, FE_K, FE_{Ca}, FE_{Mg}, FE_{Phos}, and FE_{Ur} the following equation was used: (*b*) disproportionate response (ΔDK − ΔCK) = (DK$\bar{p}$ − DK$\bar{a}$) − (CK$\bar{p}$ − CK$\bar{a}$). The basis for this distinction is that those parameters expressed in milliliters per minute or milliequivalents per liter in these studies constitute a ratio scale whereas those parameters expressed as a percentage constitute an interval scale (12). For example, if values for FE_{Na} were converted to FR_{Na} (fractional reabsorption of sodium) the resultant answers would be quite inconsistent if the analysis appropriate to the interval scale were not used.

Values of *P* for evaluation of differences of means (paired samples) and correlation coefficients were obtained by using the Student's *t* test. All values of *P* are two-tailed. ±1 SEM was used as an index of dispersion. In the dogs and patients, base line data are derived from the means of all base line clearance periods; data following volume expansion, Diamox, and parathyroid hormone represent the means of the three clearance periods obtained following these experimental maneuvers.

RESULTS

Base line functional characteristics of the pyelonephritic or remnant dog kidney in the water-deprived state

In 48/49 dogs, the maximum urine osmolality (U_{max}) was lower in the experimental kidney; the mean DK/CK ratio was 893/1658. A smaller DK/CK U_{max} ratio tended to be associated with a smaller DK/CK ratio (Table I). The urine DK/CK creatinine concentration was less than 1.0 in 46/49 dogs with a mean ratio of 411/564. Similar to the U_{max} data, this ratio tended to be lower in those kidneys with the smaller DK/CK GFR ratio. In 41/49 dogs, the urinary sodium concentration (U_{Na}) was higher in the experimental kidney; the mean DK/CK ratio was 31.3/21.3. Although the filtration fraction (FF) was lower in the diseased kidney in 33/49 dogs, the mean difference (DK − CK)

for all 49 dogs was only (−)2.0%. The fractional excretion of sodium (FE_{Na}) was greater in the diseased kidney in 46/49 of the dogs. The mean differences (DK − CK) were 1.14% in the severe pyelonephritic group (SP), 0.17% in the moderate pyelonephritic group (MP), and 0.42% in the remnant kidney group (R) (Table I).

In an attempt to gain insight into why the diseased kidney consistently excreted a higher percentage of its filtered load of sodium during these base line studies, the absolute difference in FE_{Na} between the diseased and control kidney was plotted against the DK/CK GFR and DK/CK U_{max} ratios (Fig. 1). In order to introduce some degree of uniformity and thereby simplify interpretation of the data, only studies from those dogs were included in which the *control* kidney exhibited a reasonably great capacity for maximal urinary concentration in response to pitressin ($U_{max} > 1950$ mOsm/kg) and a reasonably maximal conservation of sodium (base line FE_{Na} of $< 0.35\%$). The foregoing data from these 12/49 dogs are depicted in Fig. 1. There was a curvilinear relationship between (DK − CK) FE_{Na} and (DK/CK) U_{max}, ($r = -0.804$) as well as between (DK − CK) FE_{Na} and (DK/CK) GFR, ($r = -0.674$).

The fractional excretion of water (FE_{H_2O}) was greater in the diseased kidney in 45/49 of the dogs. The mean differences (DK − CK) was 1.49% for all dogs. In 44/49 of the diseased kidneys and 47/49 control kidneys, the urine osmolality was greater than that

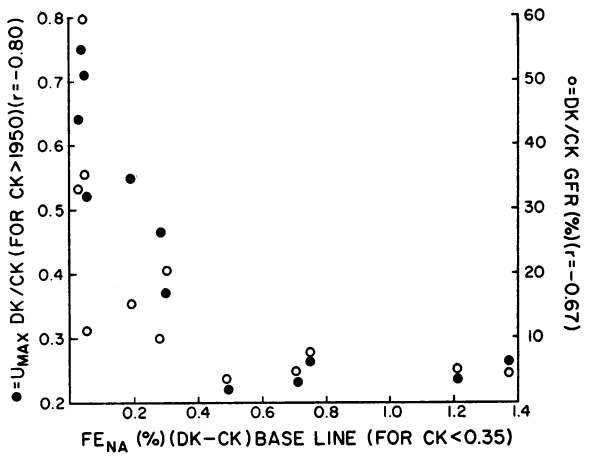

FIGURE 1 The relation of the difference in base line (*before* an acute saline load) fractional excretion of sodium (FE_{Na}) between the diseased (DK) and control (CK) kidneys, and either the DK/CK U_{max} (maximum urine osmolality) ratio, left ordinate, or the DK/CK GFR ratio, right ordinate. To simplify interpretation, only those dogs are included whose control kidney was capable of concentrating the urine above 1950 mOsm/kg *and* conserving sodium below a fractional excretion of 0.35% (12 dogs). U_{max} was determined during an isolated study, usually 1–2 days before obtaining GFR and FE_{Na} data, the latter being derived from the base line periods just before saline loading.

of the serum, i.e., negative free water clearance ($T^c_{H_2O}$) was observed. The seven exceptions occurred in five dogs; in three of these five dogs the diseased kidney was generating C_{H_2O} while the contralateral control kid-

TABLE II

Summary of Data after Saline Load

		GFR	C_{PAH}	V	U_{Na}	U_{Cr}	FE_{Na}	FE_{H_2O}	C_{H_2O}/GFR	FF	FE_K
		ml/min	*ml/min*	*ml/min*	*mEq/liter*	*mg/100 ml*	%	%	%	%	%
SP	DK	5.6 ±1.1	16.3 ±3.5	1.31 ±0.32	61.5 ±4.1	60.2 ±6.6	10.5 ±1.0	24.5 ±2.0	8.59 ±1.1	38.4 ±1.9	37.8 ±2.8
	CK	68.7 ±3.1	225 ±19	7.46 ±0.82	47.1 ±7.5	137 ±16.6	3.42 ±0.48	11.7 ±1.3	3.72 ±0.98	32.6 ±1.7	29.3 ±1.8
	disp. Δ*	20.0 ±5.1	−9.2 ±3.7				5.94 ±0.93	9.95 ±1.5	3.94 ±0.55	7.58 ±1.4	5.51 ±1.8
	‡	15/18	13/18						18/18	17/18	15/18
MP	DK	21.4 ±1.8	67.7 ±6.5	3.63 ±0.33	85.6 ±6.5	70.3 ±5.8	10.5 ±0.74	18.3 ±1.2	2.91 ±0.95	32.6 ±1.1	32.7 ±1.9
	CK	57.9 ±2.9	198 ±13	5.45 ±0.42	85.6 ±8.7	129 ±12	5.72 ±0.50	10.4 ±0.83	0.43 ±0.83	30.0 ±1.1	29.1 ±1.9
	disp. Δ	10.6 ±3.6	−5.1 ±3.7				4.59 ±0.57	7.28 ±0.66	2.04 ±0.36	3.78 ±0.95	4.77 ±1.1
	‡	15/19	13/19						17/19	15/19	15/19
R	DK	7.4 ±1.5	27.5 ±5.4	1.05 ±0.14	70.4 ±8.1	77.5 ±8.9	8.19 ±1.0	17.8 ±1.9	5.49 ±1.2	28.0 ±1.6	34.7 ±3.5
	CK	62.6 ±2.6	232 ±11	6.47 ±0.76	57.1 ±13	129 ±18	3.96 ±0.63	11.6 ±1.5	3.02 ±1.4	27.5 ±1.3	28.1 ±2.7
	disp. Δ	13.4 ±4.7	−6.5 ±5.5				3.81 ±0.72	5.32 ±0.98	2.32 ±0.67	4.02 ±1.4	6.04 ±2.2
	‡	10/12	7/12					11/12	11/12	11/12	10/12
T	DK	12.2 ±1.4	38.9 ±4.6	2.15 ±0.24	73.0 ±3.8	68.4 ±4.0	9.92 ±1.4	20.4 ±1.1	5.63 ±0.71	33.6 ±1.1	35.1 ±1.5
	CK	63.0 ±1.8	217 ±9.2	6.44 ±0.40	64.5 ±5.8	132 ±8.7	4.45 ±0.33	11.2 ±0.68	1.60 ±0.66	30.3 ±0.86	28.9 ±1.1
	disp. Δ	14.7 ±2.6	−6.9 ±2.3				4.89 ±0.45	7.78 ±0.60	2.81 ±0.31	5.23 ±0.72	5.35 ±0.93
	‡	40/49‖	33/49§				49/49	48/49‖	46/49‖	43/49‖	40/45‖

* = disproportionate change = (%ΔDK − %ΔCK) for those parameters which constitute a ratio scale (those to the left of center), where (%ΔDK) = (DK after − DK before)/(DK before) × 100, and (%ΔCK) = (CK after − CK before)/(CK before) × 100; however, for those parameters which constitute an interval scale (those to the right of center) *disproportionate change* = (ΔDK − ΔCK), where (ΔDK) = (DK after − DK before), and (ΔCK) = (CK after −CK before).

‡ Fraction of dogs supporting the direction of the means of disp. Δ.

§ $P < 0.005$.

‖ $P < 0.001$.

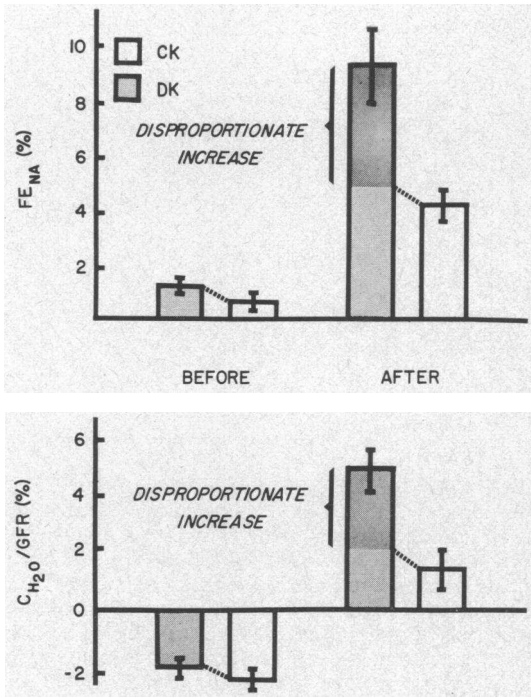

FIGURE 2 The disproportionate increase in fractional excretion of sodium (FE_{Na}) and free water clearance factored by GFR (C_{H_2O}/GFR) in the diseased kidney (DK) compared to a contralateral control kidney (CK) in 49 dogs after an acute saline load. *Before* saline loading the diseased kidney manifested a greater FE_{Na} and a lesser C_{H_2O}/GFR. This difference is delineated by the dashed lines connecting CK and DK in the left pairs of columns. If this difference persisted *after* acute saline loading, the response by DK would have been expected to be the height of the lightly hatched area in the right pair of columns. Any quantity greater than this anticipated discrepancy (broken line) has been termed *disproportionate* (heavily hatched area).

ney was generating $T^c_{H_2O}$. In 40/49 dogs the diseased kidney was generating either less $T^c_{H_2O}$ or more C_{H_2O} than the contralateral control kidney. The mean difference (DK − CK) in C_{H_2O}/GFR was 0.62% for all dogs.

The FE_K ranged between 5 and 34% for both kidneys in 48/49 dogs. There was considerable spread in the differences between the diseased and control kidneys. The mean difference (DK − CK) for all 49 dogs was less than 1%; the FE_K was greater in the diseased kidney in only 22/49 dogs.

Effect of acute saline loading in the dogs

FE_{Na}. Following volume expansion the FE_{Na} invariably increased in both the diseased and control kidney (Table II). Furthermore, the Δ FE_{Na} (FE_{Na} after expansion minus base line) was invariably greater in the diseased kidney. The mean disproportionate response (ΔDK −ΔCK) for all 49 dogs was 4.89% (Fig. 2). Thus the increment by the diseased kidney (ΔDK) in FE_{Na} (or alternatively, the inhibition of fractional reabsorption of sodium [FR_{Na}]) was more than twice the absolute increment in the control kidney (ΔCK) in response to volume expansion. In five of the dogs (Fe, Bt, Bm, An, and Ei) the mean $U_{Na}V$ *unfactored by GFR* was greater in the DK than the CK after saline loading, despite a marked discrepancy in GFR (mean DK/CK GFR ratio = 0.27).

To further characterize this disproportionate response in FE_{Na}, a comparison was made between DK and CK for each of the three consecutive clearance periods following acute saline loading. In nearly every instance, the peak FE_{Na} for each kidney, as well as the peak disproportionate FE_{Na} occurred during the first period, with a progressive decline thereafter. However, the rate of decline (absolute decrement) was greater in DK than CK in nearly every instance.

GFR. Following acute saline loading the GFR increased in 47/49 of the diseased kidneys, and 45/49 of the control kidneys, increasing in both kidneys in 43/49 dogs. The mean increase for all 49 diseased kidneys was 34.5%, while the corresponding mean increase for the control kidneys was only 19.8%. Thus, the mean disproportionate increase in GFR for all 49 dogs was 14.7%.

Since the GFR increased more in the diseased kidney than the control in 40/49 dogs, and a correlation of the disproportionate FE_{Na} and disproportionate GFR was significant ($r = 0.577$, $P < 0.001$), the influence of the disproportionate increase in GFR on the disproportionate increase in FE_{Na} was further investigated. Whereas the FE_{Na} *decreased* in the diseased kidneys from the first to the third period after expansion (from 12.3% to 7.9%), the concurrent GFR in these 49 diseased kidneys *increased* slightly (mean 11.8–12.4 ml/min, $P < 0.02$), thus demonstrating a dissociation between GFR and FE_{Na} following saline loading. Moreover, in 9/49 dogs in which GFR in the diseased kidney increased *less* than the control kidney following acute saline loading, there was nevertheless a substantial disproportionate increase in FE_{Na}. When GFR was elevated by an intravenous injection of parathyroid hormone (PTH) in separate clearance studies performed in six dogs (Table III), there was only a slight increase in FE_{Na}, and (DK − CK) FE_{Na} remained the same, despite an increase in GFR in both kidneys which was similar to that observed with volume expansion (ΔDK/ΔCK GFR ratio = 39%/27%). However, administration of an acute saline load following PTH administration induced a prominent natriuresis in DK and CK, with a disproportionate increase in FE_{Na} of 1.73% in the absence of any further increase in GFR.

FE_{H_2O}. Following saline loading the FE_{H_2O} invariably increased in both the diseased and control kidney.

Furthermore, the FE_{H_2O} was greater in the diseased kidney in 48/49 dogs. The increment by the diseased kidney (ΔDK) in FE_{H_2O} was also greater in 48/49 dogs. The mean disproportionate response for all 49 dogs was 7.8%. Thus, similar to the response in FE_{Na}, the increment in FE_{H_2O} by the diseased kidney (ΔDK = 16.3%) was nearly twice the absolute increase in the control kidney (ΔCK = 8.5%) in response to an acute saline load. Moreover, a correlation of the disproportionate increase in FE_{Na} and the disproportionate increase in FE_{H_2O} was highly significant ($r = 0.87$, $P < 0.001$, Fig. 3).

C_{H_2O}/GFR. Following the acute saline load, free water was generated by 40/49 diseased kidneys and 30/49 control kidneys. Thus, in 10/49 dogs the diseased kidney was generating free water while the contralateral control was simultaneously generating negative free water. In all dogs the C_{H_2O}/GFR was greater (or $T^c_{H_2O}$ lesser) by the diseased kidney than its contralateral control, and the increment in C_{H_2O}/GFR (or decrement in $T^c_{H_2O}$/GFR) was also greater by the diseased kidney in 46/49 dogs (Fig. 2, Table II). There was a poor relation between the disproportionate C_{H_2O}/GFR and disproportionate FE_{Na} ($r = 0.28$, $n = 49$).

FE_K. Following acute saline loading, FE_K increased in 48/49 diseased kidneys and all of the control kidneys.

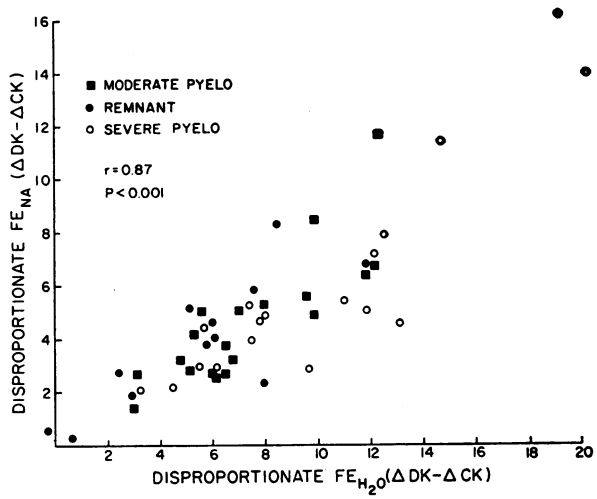

FIGURE 3 The relation between the disproportionate increase in fractional excretion of sodium (FE_{Na}) and the disproportionate increase in fractional excretion of water (FE_{H_2O}) after an acute saline load in 49 split bladder dogs with a unilateral diseased (DK) and control (CK) kidney.

However, whereas the FE_K was greater in the diseased kidney in only 23/49 of the dogs during the base line, it was greater in 41/49 dogs following saline loading.

TABLE III

GFR (ml/min) after Parathyroid Hormone and Then after Volume Expansion (VE)*

Dogs	Base line		After PTH				After VE			
	DK	CK	DK	CK	DK	CK	DK	CK	DK	CK
					% increase				% increase	
Ge	11.7	40.5	17.2	53.5	47	32	16.2	55.5	−6	4
Ra	12.3	40.2	17.5	56.9	42	42	20.3	62.8	16	10
Mr	42.1	62.7	49.9	68.3	19	9	41.6	58.5	−17	−14
Tr	15.9	32.7	21.3	40.7	34	25	24.0	41.8	13	3
Ke	8.37	38.8	12.4	48.8	48	26	12.0	49.7	−3	2
Cn	12.6	73.3	17.9	95.3	42	30	15.0	88.3	−16	−7
Mean	17.2	48.0	22.7	60.6	39	27	21.5	59.4	−2	0

FE_{NA} (%) after Parathyroid Hormone and Then after Volume Expansion

Dogs	Base line			After PTH			After VE		
	DK	CK	DK−CK	DK	CK	DK−CK	DK	CK	DK−CK
Ge	0.18	0.05	0.13	0.12	0.36	−0.24	5.66	3.93	1.73
Ra	0.47	0.27	0.20	0.51	0.35	0.16	5.14	4.62	0.52
Mr	0.36	0.28	0.08	0.88	0.45	0.43	2.54	1.31	1.23
Tr	0.39	0.22	0.17	0.37	0.26	0.11	6.79	4.66	2.13
Ke	0.69	0.39	0.30	0.87	0.39	0.48	8.82	4.08	4.74
Cn	0.04	0.03	0.01	0.68	0.68	0.00	3.33	2.42	0.91
Mean	0.36	0.21	0.15	0.57	0.42	0.16	5.38	3.50	1.88

* Parathyroid hormone (PTH) was employed to augment GFR.

The mean disproportionate response for all 49 dogs was only 5.35%.

Natriuretic response to Diamox by dog kidneys

Diamox was found to increase FE_{Na} in both the diseased and control kidney to a similar degree (Table IV), demonstrating that every stimulus to sodium excretion need not produce a disproportionate response in DK as compared to CK. Following Diamox, the increment in FE_{Na} by the diseased kidney was 3.35% as compared to 2.94% for the control kidney, in the presence of a degree of natriuresis by the control kidneys following Diamox similar to that induced in the *control kidneys* of these same dogs (under identical conditions on a different day) after saline loading. The results of the latter studies are included at the right of Table IV.

Effects of a saline load in man with a unilaterally diseased kidney

Contrary to the dog studies, there was little change in GFR (or C_{PAH}) following an acute saline load in either the diseased or control kidneys of three female patients (Table V). Despite the absence of a disproportionate increase in GFR there was a disproportionate increase in the FE_{Na} similar to that seen in the dogs (Fig. 2). The mean increase in FE_{Na} by the diseased kidneys was 4.6%, while that of the contralateral controls was 2.6%, resulting in a 2.0% disproportionate increase by the diseased kidneys. In addition, there was a considerable disporportionate increase in the fractional excretion of calcium, magnesium, phosphate, and uric acid. Although the mean increase in FE_{H_2O} (like that for FE_{Na}) following saline loading was much smaller (the degree of saline loading was only 1/3 on a per kilogram body weight basis) in the humans ($\Delta DK/\Delta CK = 5.5\%/3.0\%$) than in the dogs, the increase by the diseased kidney (ΔDK) in FE_{H_2O} (like that for FE_{Na}) was nearly twice as great as the increment by the control kidney after a saline load. In contrast to the dog studies, there was no disproportionate change in C_{H_2O}/GFR by the diseased human kidneys.

DISCUSSION

The primary goal of these studies was to determine if the kidney with a reduced nephron population (regardless of the type or severity of the lesion) displays a resetting of glomerulotubular balance following ECFV expansion which is proportionate to that observed in a simultaneously studied, contralateral control kidney. Also, base line observations before expansion provided an opportunity to reexamine parameters previously studied in this model, with particular reference to the type and severity of the lesion (5).

Base line data in the moderate pyelonephritic and remnant groups corresponded to previously published data, indicating a striking similarity in function per nephron between DK and CK. However, the functional pattern of the severe pyelonephritic kidney tended to be different for some parameters. The inverse relationship of the (DK − CK) FE_{Na} to the DK/CK U_{max} or GFR ratio (Fig. 1) is of particular interest in this regard. Malvin has previously proposed that a reduction of the osmotic gradient in the renal medulla might reduce the

TABLE IV

Effect of Diamox on FE_{Na} in "DK" vs. CK as Compared to Effect of Saline Load

	FE_{Na} (%)							$\frac{C_{H_2O}}{GFR}$,	FE_{Na} (%) after saline*	
	DK			CK						
Dog	Before	After	Δ	Before	After	Δ	ΔDK − ΔCK	ΔDK − ΔCK	ΔCK	ΔDK − ΔCK
Dw‡	0.21	4.05	3.84	0.08	2.94	2.86	0.98	−1.66	3.90	2.07
Ru‡	1.03	5.76	4.73	0.41	5.34	4.93	−0.20	−0.07	2.60	4.61
Cn	0.21	2.06	1.85	0.05	2.03	1.98	−0.13	1.23	2.63	1.33
Bl	0.19	1.76	1.57	0.11	1.34	1.23	0.34	−0.26	3.08	2.60
Je‡	0.12	3.65	3.53	0.10	3.60	3.50	0.03	−0.28	4.45	4.06
Ml	0.15	3.05	2.90	0.21	1.92	1.71	1.19	0.70	1.66	5.03
He	1.35	6.85	5.50	1.02	6.01	4.99	0.51	−0.08	7.03	3.65
Ho	0.14	3.69	3.55	0.09	2.94	2.85	0.70	0.49	6.16	5.48
Ge	0.19	2.86	2.67	0.02	2.43	2.41	0.26	0.36	5.65	4.99
$\bar{m}$	0.40	3.75	3.35	0.23	3.17	2.94	0.41	0.05	4.17	3.76

* Included to permit a comparison of the disproportionate response of DK vs. CK to saline, performed on a separate day, as compared to the similar response of DK and CK to Diamox in the same dogs.

‡ Received intramuscular DOCA during previous 18 hr.

Abbreviations are the same as in Table I and II.

TABLE V

Individual Data for Three Patients with Unilateral Pyelonephritis

Patient		GFR	C_{PAH}	V	U_{Na}	U_{In}	FE_{Na}	FE_{H_2O}	C_{H_2O}/C_{In}	FF	FE_K*	FE_{Ca}‡	FE_{Mg}‡	FE_{Phos}	FE_{Ur}*
		ml/min	*ml/min*	*ml/min*	*mEq/liter*	*mg/100 ml*	%	%	%	%	%	%	%	%	%
Before saline loading															
1 (EB)	DK	7.32	37.70	0.310	76.2	687	2.52	4.60	−2.06	20.9	9.62	0.94	2.19	6.08	10.30
	CK	58.80	264.00	2.340	69.5	738	2.14	4.27	−2.50	22.3	8.47	0.55	2.39	7.60	9.63
2 (NM)	DK	20.10	79.30	0.640	62.0	899	1.55	3.44	−3.42	25.7	12.30	0.97	1.38	9.45	11.60
	CK	60.30	267.00	1.570	49.3	1098	1.01	2.81	−3.84	22.6	11.20	0.59	0.78	10.50	10.40
3 (NF)	DK	1.00	5.55	0.037	79.3	670	2.37	4.11	−2.16	18.0	32.90	—	—	—	—
	CK	74.00	331.00	1.610	89.5	1149	1.53	2.35	−3.04	22.4	29.50	—	—	—	—
After saline loading															
1	DK	7.00	36.80	0.940	68.3	213	7.13	14.50	3.09	19.1	9.08	4.11	6.40	18.60	12.60
	CK	58.30	262.00	5.600	52.7	300	3.84	10.30	2.54	22.3	8.91	1.05	2.71	12.90	9.15
	disp. Δ§	4.20	7.10	64.000	—	—	2.90	3.90	0.10	−1.8	−1.00	2.70	3.90	7.20	2.80
2	DK	18.40	63.90	0.970	128.0	460	5.29	5.66	−3.96	28.8	17.80	3.62	5.48	21.10	14.20
	CK	62.30	216.00	2.070	131.0	726	3.44	3.60	−4.22	29.0	15.20	2.50	2.86	17.40	11.90
	disp. Δ	−11.80	−0.30	20.000	—	—	1.30	1.40	−0.20	−3.3	1.50	0.70	2.00	4.80	1.10
3	DK	0.97	5.33	0.075	126.0	299	7.78	8.45	−2.16	18.7	27.90	—	—	—	—
	CK	79.80	350.00	3.280	161.0	575	5.29	4.50	−3.69	22.8	22.10	—	—	—	—
	disp. Δ	−10.80	−9.70	−1.000	—	—	1.70	2.20	0.65	0.3	2.40	—	—	—	—
$\bar{m}$	%ΔDK or ΔDK	−5.30	−5.80	219.000	—	—	4.60	5.50	1.50	0.7	0	2.90	4.20	12.10	2.50
$\bar{m}$	%ΔCK or ΔCK	0.80	−4.80	192.000	—	—	2.60	3.00	1.30	2.3	−1.00	1.20	1.20	6.10	0.50
$\bar{m}$	disp. Δ	−6.10	−1.00	27.00	—	—	2.00	2.50	0.20	−1.6	1.00	1.70	3.00	6.00	2.00

U_{In}, urine inulin concentration; FE_{Ca}, fractional excretion of calcium; FE_{Mg}, fractional excretion of magnesium; FE_{Phos}, fractional excretion of phosphate; FE_{Ur}, fractional excretion of uric acid.

* It is recognized that this is not true fractional excretion, in view of bidirectional transport.

‡ Filtered load not corrected for protein binding.

§ See footnotes to Table II.

‖ See footnotes to Table II.

amount of water which diffuses passively from the descending limb of Henle's loop (13). This would result in the presentation of a greater volume of tubular fluid containing a decreased concentration of sodium to the ascending limb and distal nephron. Inability of these segments to reabsorb sodium as effectively under these circumstances would result in increased excretion of sodium. If the diminished U_{max} of the diseased kidneys in the present studies is a reflection of papillary osmolality, then it is conceivable that such a mechanism might result in a disparity of FE_{Na} in the diseased kidney (as compared to the contralateral control kidney) which is proportionate to the disparity in U_{max}. However, this thesis is not supported by studies in the rat with hereditary hypothalamic diabetes insipidus which have demonstrated that diminished papillary osmolality in that species does not alter the ability to conserve sodium (14). Another possible explanation for this disparity in function which occurs predominantly in the most severely diseased kidneys is that a greater decrease in nephron population unmasks the moderate degree of functional heterogeneity which is likely to be present within a kidney of this type, in contrast to the less severe pyelonephritic lesions in which the relatively few nephrons with glomerulotubular imbalance do not comprise a significant percentage of the total population. It is important to emphasize that in most of the animals, the diseased kidney was capable of reabsorbing greater than 99% of the filtered sodium (all but one reabsorbed > 96%) even in the absence of a strong challenge to conserve sodium and despite a marked urinary concentrating defect. Moreover, previously published studies have shown nearly identical function of the diseased and control kidney, when factored by GFR, for parameters other than fractional sodium and water excretion (2, 5).[1]

Regardless of the type of lesion in the diseased kidney,[2] its nephrons underwent a disproportionate or exaggerated resetting of glomerulotubular balance for some parameters following ECFV expansion. If the response by the control kidney to saline loading is taken as appropriate to the needs of the organism, then the exaggerated response by DK must be of intrinsic origin. A qualitatively similar pattern has been observed in our laboratory utilizing this model following several

[1] Unpublished data obtained on five of the dogs in the foregoing severe pyelonephritic group studied under similar conditions as during the base line periods for the present studies indicated that TM_{PAH}/GFR was the same for both DK and CK.

[2] Two diseased kidneys were not subjected to any surgical intervention in the hilar area, thereby militating against the influence of a disruption of renal innervation or lymphatic supply.

days of excessive oral NaCl intake,[3] thereby suggesting that this phenomenon is not merely due to an acute, massive expansion of the ECFV. That this difference was not artifactual was most clearly demonstrated in five of the dogs with milder lesions, in whom urinary sodium excretion in the diseased kidney exceeded that in the control kidney in spite of a mean DK/CK GFR ratio of 0.27. Moreover, the similar increase in FE_{Na} by both the diseased and control kidneys following Diamox suggests that every stimulus to sodium excretion need not produce a disproportionate response.

It became apparent during the early phases of this study that the disproportionate increase in FE_{Na} and FE_{H_2O} following acute saline loading might be attributed to the disproportionate increase in GFR manifested by most of the diseased dog kidneys. Despite a significant correlation ($r = 0.577$, $P < 0.001$) of the disproportionate FE_{Na} and disproportionate GFR, a greater inhibition of FR_{Na} by the diseased kidney independent of the changes in GFR was subsequently supported by: (*a*) the dissociation of FE_{Na} and GFR during consecutive clearance periods after saline loading, (*b*) the absence of a disproportionate increase in DK sodium excretion despite induction of a disproportionate increase in DK GFR (by administration of commercially prepared parathyroid hormone) of a similar magnitude to that observed following saline loading, (*c*) the disproportionate FE_{Na} in the three human studies in the absence of a disproportionate increase in GFR, and (*d*) the disproportionate increase in DK FE_{Na} in the dogs without a disproportionate increase in DK GFR.

Of special interest is the disproportionate increase in C_{H_2O}/GFR which occurred in most of the dogs. One might interpret this as evidence that the enhanced inhibition of FR_{Na} in these diseased kidneys occurs proximal to the diluting segment of the nephron. However, there is a poor correlation between the disproportionate C_{H_2O}/GFR and FE_{Na}. The fact that in 10/49 dogs the DK was generating free water while the CK was generating negative free water suggests to us that it is difficult to differentiate the cause of the disproportionate increments in C_{H_2O}/GFR among the following possibilities: (*a*) enhanced C_{H_2O}/GFR by the DK due to greater delivery of solutes from a more proximal site in the nephron to the diluting segment, (*b*) decreased transit time through the distal nephron associated with a solute diuresis (as seen during a mannitol diuresis in the dog) permitting insufficient time (compared to the contralateral control kidney) for reabsorption of generated free water, or (*c*) decreased reabsorption of free water in the collecting ducts secondary to a diminished osmotic driving force in the medulla of the diseased kidney compared to the control kidney, a possibility supported indirectly by the diminished U_{max} of the DK. The absence of a disproportionate increase in C_{H_2O}/GFR in the three human studies sheds further doubt on the possibility that the enhanced C_{H_2O}/GFR by the DK of the dog is simply due to enhanced generation of free water by the diluting segment in response to increased delivery of sodium. On the other hand, it seems unlikely that any defect in end-organ response to endogenous antidiuretic hormone (ADH) is involved.

The elucidation of the basis for this exaggerated inhibition of sodium reabsorption in the diseased kidneys of nonuremic man and dog following an acute saline load might contribute to an understanding of the mechanism whereby ECFV is regulated in the presence of advanced bilateral disease and uremia. If this regulation were totally under the influence of an extrarenal control system, with the efferent limb mediated via a humoral factor which inhibits sodium transport, then one must postulate an increased sensitivity of DK to this factor in order to explain the present data.

An alternative explanation is based upon the observations initially described by Martino and Earley relating to the influence of Starling forces upon the rate of sodium transport (15). The marked architectural derangement evident within both remnant and pyelonephritic kidneys suggest that even minimal changes in these forces within the intrarenal environment of these kidneys could be markedly exaggerated in the presence of hemodynamic perturbations induced by ECFV expansion.

Other possible explanations for this phenomenon include (*a*) the survival in DK of an inordinate number of outer cortical "salt losing nephrons" whose hemodynamics are particularly influenced by changes in ECF volume[4] (17) or (*b*) disruption of peritubular capillaries, which would decrease effectiveness of sodium removal from the interstitium under the stress of volume expansion, thereby producing enhanced backleak of sodium in these regions. However, these latter two alternatives are difficult to reconcile with the fact that an exaggerated inhibition of FR_{Na} occurs in the remnant kidneys.

While the mechanism underlying these observations remains to be elucidated, these data do suggest that the diseased kidney possesses an enhanced intrinsic capacity to respond to extracellular fluid volume expansion by decreasing fractional reabsorption of sodium, which is independent of the presence of uremia or any associated humoral factor. This *intrinsic* functional alteration of the diseased kidney could be an important

[3] In preparation.

[4] In this regard, the fact that furosemide, a renal cortical vasodilator, causes a similar disproportionate increase in GFR and FE_{Na} by the diseased kidney is of particular interest (16).

factor which enables man with advanced bilateral renal disease to maintain ECFV homeostasis without substantially reducing the dietary sodium intake (3).

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