Effects of dietary sodium chloride intake on renal function and blood pressure in cats with normal and reduced renal function

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Objective—To determine effects of variations in dietary intake of sodium chloride (NaCl) on systemic arterial blood pressure (ABP) in cats with normal and reduced renal function.

Animals—21 adult cats (7 with intact kidneys [control cats; group C], 7 with unilateral renal infarction with contralateral nephrectomy [remnant-kidney model; group RK], and 7 with unilateral renal infarction and contralateral renal wrapping and concurrent oral administration of amlodipine [remnant-wrap model; group WA]).

Procedure—All cats were sequentially fed 3 diets that differed only in NaCl content (50, 100, or 200 mg of Na/kg); each diet was fed for 7 days. The ABP was recorded continuously by radiotelemetry, and renal function (glomerular filtration rate [GFR]) was determined on the sixth day of each feeding period.

Results—Dietary supplementation with NaCl did not affect ABP, but it increased GFR in groups C and WA. The renin-angiotensin-aldosterone axis was activated in groups RK and WA at the lowest NaCl intake, but supplementation with NaCl suppressed this activation in group WA. The lowest NaCl intake was associated with hypokalemia and a high fractional excretion of potassium that decreased in response to supplementation with NaCl. Arterial baroreceptor resetting was evident after chronic hypertension but was not modified by dietary supplementation with NaCl.

Conclusions and Clinical Relevance—Low NaCl intake was associated with inappropriate kaliuresis, reduced GFR, and activation of the renin-angiotensin-aldosterone axis without evidence of a beneficial effect on ABP. Therefore, this common dietary maneuver could contribute to hypokalemic nephropathy and progressive renal injury in cats. (*Am J Vet Res* 2004;65:620–627)

Chronic kidney disease (CKD) is a common problem in cats.[1-4] Cats with reduced **glomerular filtration rate (GFR)** reportedly[5-7] have a high prevalence of systemic hypertension. Changes in renal function can alter **arterial blood pressure (ABP)** through effects on **sodium chloride (NaCl)** concentrations and homeostasis of body fluids.[8] In cats with renal insufficiency, NaCl retention may result from a rightward shift of the renal pressure-natriuresis relation. Thus, dietary supplementation with NaCl could aggravate hypertension in cats with renal insufficiency through enhanced, unregulated volume expansion.

The possibility exists of an increase in lability of ABP in hypertensive cats[9] and rats[10] with induced renal insufficiency. An increase in variability of ABP in hypertensive cats could pose a risk for end-organ injury caused by bouts of heightened ABP or ischemia during periods of low ABP. Baroreflex control of ABP may be altered during chronic systemic hypertension, a phenomenon known as baroreflex resetting, and supplementation with NaCl may affect baroreflex activity and thus alter variability of ABP.[11,12] In baroreceptor-denervated dogs, ABP was slightly increased, compared with values for clinically normal dogs, but analysis of 24-hour frequency distribution curves for ABP revealed a 2-fold increase in variability in the denervated dogs.[13] Thus, the baroreflex is essential for maintenance of stability of ABP, and resetting during CKD could predispose an affected animal to end-organ injury.

The renin-angiotensin-aldosterone axis may be involved in the generation or maintenance of systemic hypertension in cats with naturally developing renal disease, as evidenced by increased plasma renin activity, concentrations of angiotensinm or aldosterone, or both in some affected cats.[7,14-17] Furthermore, the volume-contracting effects of dietary restriction of NaCl may be expected to activate the renin-angiotensin-aldosterone axis. Because the renin-angiotensin-aldosterone axis is a major regulator of renal hemodynamics and ABP, dietary supplementation with NaCl may affect ABP and renal function in a complex, interrelated manner. Unfortunately, the effects of dietary supplementation of NaCl in cats with renal impairment have not yet been fully characterized.

The objectives of the study reported here were to determine the lability of ABP in 2 groups of cats with experimentally induced CKD and evaluate the effects of dietary supplementation with NaCl on renal function and ABP in clinically normal cats and cats with renal impairment attributable to the remnant-kidney model[18-21] and remnant-wrap model[22] for induction of hypertensive renal insufficiency. Furthermore, we intended to assess baroreceptor responsiveness in these cats.

Materials and Methods

Animals—Twenty-one male and female cats that were 1 to 1.5 years old and weighed (mean ± SD) 2.75 ± 0.14 kg were used in the study. All cats were initially screened and classified as healthy on the basis of results for physical exam-

Received August 1, 2003.
Accepted September 23, 2003.
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ination and serum concentrations of **creatinine (Cr)**, BUN, albumin, electrolytes, and bicarbonate; anion gap; and urine protein-to-creatinine ratio. All cats were treated for endoparasites, vaccinated against common viral diseases, and had negative results when tested for FIV and FeLV infection by use of immunologic tests. A microchip[a] was aseptically inserted in the subcutaneous tissues at the base of the tail of each cat for identification purposes. The cats were housed separately in isolated rooms maintained at 21° to 23°C. All cats were maintained on equal amounts of light (7 AM to 7 PM) and darkness (7 PM to 7 AM) throughout the study. All animal experiments were conducted in accordance with established procedures[23] and approved by an institutional animal care committee.

Surgical procedure—Cats were randomly assigned to 1 of 3 groups. Group C (control group) consisted of cats with intact renal function, whereas cats with induced renal insufficiency included cats with renal impairment attributable to the remnant-kidney model (group RK) or the remnant-wrap model (group WA). Cats of group RK had renal insufficiency induced by ligation of branches of the renal artery that caused infarction of approximately five-sixths of the left kidney, followed by nephrectomy of the right kidney approximately 2 weeks later.[20] Renal insufficiency was induced in cats of group WA via partial ablation of the right kidney by sharp resection of the cranial and caudal poles, followed by wrapping with silk and cellophane.[21] These procedures were performed approximately 3 months before the cats entered the study reported here. To reduce the prevalence of hypertensive encephalopathy,[21] amlodipine besylate[b] was administered (0.25 mg/kg, PO, q 24 h) to all cats in groups RK and WA for 25 days after the initial surgical procedure and again to cats in group WA starting at least 1 week before the study reported here and continuing throughout the remainder of the study. A radiotelemetric catheter and transducer[c] were surgically implanted into the right femoral artery of each cat 2 weeks before recording of ABP, as described elsewhere.[24]

Experimental protocol—Each cat was sequentially fed diets containing 3 amounts of sodium (**low NaCl [LS]** intake, **medium sodium [MS]** intake, and **high sodium [HS]** intake). During the first feeding period (ie, LS intake), all cats were fed a measured quantity of a commercially available food[d] that contained 0.282 g of protein and 8.6 mg of NaCl/g of food on a dry-matter basis, which provided 50.5 mg of sodium/kg on an as-fed basis. During the second feeding period (ie, MS intake), 50 mg of sodium/kg was added (in the form of NaCl[e]) to a small amount (approx 5 g) of canned food.[f] During the third feeding period (ie, HS intake), 150 mg of sodium/kg was added to the canned food.[f] Each feeding period was 7 days in duration.

The ABP was recorded in each cat continuously throughout the study. Reported mean values for ABP and **heart rate (HR)** represented mean values for the last 3 days of each feeding period. Variability in ABP and HR were determined as the SD of the mean ABP and HR obtained for a 24-hour duration on the sixth day of each period. On the sixth day of each period, blood samples were collected from 5 randomly selected cats of each group to determine the serum concentration of aldosterone, plasma renin activity, and concentrations of atrial natriuretic peptide and arginine vasopressin. Samples were stored at –80°C for 1 to 4 weeks prior to assay. Data on ABP were not obtained during or for approximately 1 hour after collection of blood samples. On day 7 of each period, analysis of renal clearance was conducted.

Radiotelemetry measurements—The radiotelemetry system[g] has been described elsewhere.[24] It allowed radiotelemetric data to be obtained from ambulatory, undisturbed cats by continuous recording for a duration of 20 seconds every 2 minutes for 24 hours. In 1 cat of group C, the ABP implant failed, and data (including variability) for ABP for this cat were excluded from statistical analyses. Prior to implantation and following removal of implants at the end of the study, the accuracy of each implant was verified with the aid of a mercury manometer and pressure chamber.

Measurement of renal clearance—On day 7 of each period, urine and blood samples were collected for determination of urinary concentrations of protein and creatinine; serum concentrations of Cr, BUN, albumin, electrolytes (sodium, chloride, and potassium), and bicarbonate; anion gap; and osmolarity. Analysis of urinary clearance was then conducted[20] to determine renal clearance of exogenously administered inulin (ie, GFR) and **para-aminohippuric acid (PAH**; ie, **renal plasma flow [RPF]**).

Biochemical analyses—Concentrations of inulin and PAH in plasma and urine were analyzed by methods that involved the use of anthrone and ethylenediamine, respectively.[20] Osmolarity was determined by the freezing-point depression method by use of a microosmometer.[h] Biochemical analyses of plasma and urine samples were conducted with the aid of a semiautomated analyzer.[i] Plasma or serum concentrations of aldosterone,[j] arginine vasopressin,[k] and atrial natriuretic peptide[l] and plasma renin activity[m] were determined by radioimmunoassay performed at a commercial laboratory.[n]

Data analysis—Variability of ABP and HR were determined by time-series analysis by use of the SD of the mean ABP and HR obtained from measurements at 2-minute intervals during a 24-hour interval on day 6 of each feeding period. The GFR and RPF were determined by use of standard urinary clearance equations for inulin and PAH, respectively. Filtration fraction was the quotient of GFR divided by RPF. Renal electrolyte-to-inulin clearance ratio was used to determine fractional electrolyte excretions. Osmolar clearance was calculated by standard clearance equations by use of urinary and plasma osmolarity. Free-water clearance was calculated as the difference between the urinary flow rate and osmolar clearance.

Statistical analysis—Values were reported as mean ± SEM. Statistical analyses were performed with the aid of a commercially available software program.[o] Values were compared among groups by use of an ANOVA, whereas values were compared within each group for the dietary treatments by use of repeated-measures ANOVA. When a significant overall treatment effect was detected, pairs of group means were compared by use of the Student-Newman-Keuls test to examine group effects. The Dunn test was used to compare mean values for ABP when the sample size differed among groups. When the normality test was not met, the Kruskal-Wallis ANOVA or Friedman repeated-measures ANOVA were used to determine significant differences in mean values. Values were considered significant at $P < 0.05$.

Results

ABP—Systolic blood pressure of group RK was significantly higher than the corresponding value for group C for all dietary NaCl intakes (**Table 1**). Group WA had intermediate values for systolic blood pressure that were not significantly different from values for groups RK or C. Similar patterns were found for mean ABP and diastolic blood pressure. Variations in dietary NaCl intake had no effect on ABP or HR in any group.

Body weight—Body weight did not differ among groups (**Table 2**). Variations in body weight during the

Table 1—Mean ± SEM arterial blood pressure (ABP) and heart rate (HR) in clinically normal cats (control cats; group C) and cats with renal insufficiency induced by use of the remnant-kidney method (group RK) or the remnant-wrap method (group WA) during low-sodium (LS), medium-sodium (MS), and high-sodium (HS) dietary intake

Variable	Diet	Group C	Group RK	Group WA
Systolic ABP (mm Hg)	LS	119.1 ± 2.3[a]	141.9 ± 4.9[b]	135.6 ± 8.8[a,b]
	MS	120.5 ± 1.6[a]	140.6 ± 3.9[b]	134.8 ± 8.6[a,b]
	HS	119.7 ± 1.8[a]	142.8 ± 4.9[b]	136.6 ± 8.6[a,b]
Mean ABP (mm Hg)	LS	100.4 ± 2.1[a]	123.3 ± 5.4[b]	114.7 ± 8.3[a,b]
	MS	100.6 ± 1.5[a]	122.1 ± 4.8[b]	114.2 ± 8.5[a,b]
	HS	100.3 ± 1.0[a]	125.7 ± 6.7[b]	115.1 ± 8.7[a,b]
Diastolic ABP (mm Hg)	LS	84.7 ± 2.2[a]	108.3 ± 5.8[b]	99.0 ± 8.4[a,b]
	MS	84.2 ± 1.8[a]	107.3 ± 5.7[b]	98.4 ± 8.5[a,b]
	HS	83.7 ± 0.9[a]	111.0 ± 8.0[b]	98.4 ± 8.5[a,b]
HR (beats/min)	LS	181.0 ± 6.0	194.0 ± 3.0	190.0 ± 4.0
	MS	178.0 ± 6.0	191.0 ± 3.0	186.0 ± 7.0
	HS	179.0 ± 5.0	191.0 ± 3.0	184.0 ± 7.0

[a,b]Within a row, values with different superscript letters differ significantly ($P < 0.05$) among groups.

study did not follow a consistent pattern among groups because it was unaltered in group C during feeding of NaCl-supplemented diets, decreased slightly in group RK during feeding of NaCl-supplemented diets, and increased slightly in group WA during the HS intake.

Biochemical analyses—During the LS intake, plasma osmolarity did not differ among groups. For group C, plasma osmolarity decreased significantly during the MS and HS periods (Table 2). Consequently, the osmolarity of group C was lower than that in groups RK or WA during the MS and HS periods.

As expected, serum concentrations of BUN and Cr for groups RK and WA were significantly higher than the corresponding values for group C. The BUN concentration decreased significantly for groups C and RK after feeding the NaCl-supplemented diets (ie, MS and HS periods). For group WA, BUN concentration decreased slightly, but not significantly, after feeding the NaCl-supplemented diets. Serum concentration of Cr for group C decreased significantly during the MS and HS periods. We did not detect significant differences in serum Cr concentration after feeding the NaCl-supplemented diets for groups RK and WA, although it was slightly decreased. There was not an apparent difference in the degree of azotemia between groups RK and WA for any dietary treatment.

Serum sodium concentration was also similar among all groups during the LS and HS periods. Serum sodium concentration increased slightly but significantly in all groups after consumption of the NaCl-supplemented diets in both the MS and HS periods. Serum potassium concentration did not differ significantly among groups during the LS and MS periods. For group C, plasma potassium concentration increased significantly during feeding of NaCl-supplemented diets. We did not detect changes in serum potassium concentration for groups RK and WA after feeding the NaCl-supplemented diets. Serum chloride concentration for group WA was slightly lower than the concentrations for groups C and RK during the LS

Table 2—Mean ± SEM body weight and serum biochemical variables in clinically normal cats (group C) and 2 groups of cats with reduced renal function (groups RK and WA) during LS, MS, and HS dietary intake

Variable	Diet	Group C	Group RK	Group WA
Body weight (kg)	LS	2.81 ± 0.13	2.82 ± 0.34[x]	2.52 ± 0.24[x]
	MS	2.79 ± 0.14	2.73 ± 0.33[y]	2.52 ± 0.22[x]
	HS	2.82 ± 0.12	2.76 ± 0.32[y]	2.63 ± 0.21[y]
Osmolality (mOsm/kg)	LS	322.9 ± 2.7[x]	321.0 ± 2.9[x]	331.1 ± 3.2
	MS	311.0 ± 1.1[a,y]	341.9 ± 4.8[b,y]	321.1 ± 1.6[c]
	HS	309.1 ± 1.3[a,y]	327.4 ± 2.5[b,x]	323.1 ± 3.4[b]
BUN (mg/dL)	LS	24.43 ± 1.11[a,x]3	8.71 ± 2.46[b,x]	47.00 ± 8.13[b]
	MS	21.29 ± 1.58[a,y]	32.14 ± 1.33[b,y]	34.57 ± 2.83[b]
	HS	19.14 ± 1.35[a,y]	30.29 ± 1.06[b,y]	34.29 ± 2.96[b]
Creatinine (mg/dL)	LS	1.34 ± 0.04[a,x]	2.27 ± 0.13[b]	3.03 ± 0.56[b]
	MS	1.20 ± 0.06[a,y]	2.26 ± 0.12[b]	2.37 ± 0.11[b]
	HS	1.14 ± 0.04[a,y]	2.16 ± 0.14[b]	2.34 ± 0.10[b]
Albumin (g/dL)	LS	2.67 ± 0.08[x,y]	2.79 ± 0.05	2.90 ± 0.08[x]
	MS	2.57 ± 0.08[a,x]	2.69 ± 0.08[a]	2.83 ± 0.06[b,x]
	HS	2.73 ± 0.09[y]	2.71 ± 0.06	2.60 ± 0.06[y]
Sodium (mEq/L)	LS	150.6 ± 0.6[x]	151.1 ± 0.5[x]	150.9 ± 0.7[x]
	MS	152.9 ± 0.1[a,y]	153.6 ± 0.5[a,y]	154.7 ± 0.4[b,y]
	HS	152.4 ± 0.5[y]	153.0 ± 0.3[y]	153.9 ± 0.4[y]
Potassium (mEq/L)	LS	3.34 ± 0.17[x]	3.23 ± 0.18	3.00 ± 0.10
	MS	3.61 ± 0.17[y]	3.16 ± 0.09	3.21 ± 0.14
	HS	3.77 ± 0.17[a,y]	3.31 ± 0.07[b]	3.01 ± 0.18[b]
Chloride (mEq/L)	LS	115.9 ± 0.7[a]	116.1 ± 0.6[a]	111.9 ± 1.3[b,x]
	MS	117.4 ± 0.4	116.1 ± 0.7	116.1 ± 0.9[y]
	HS	116.9 ± 0.6[a]	117.4 ± 0.6[a]	114.9 ± 0.6[b,y]
Bicarbonate (mmol/L)	LS	18.00 ± 0.87[a]	21.14 ± 0.91[b,x]	19.00 ± 0.72[a]
	MS	18.14 ± 0.70	17.71 ± 0.47[y]	18.00 ± 0.93
	HS	18.43 ± 0.43	20.43 ± 0.90[x]	18.29 ± 0.87
Anion gap (mEq/L)	LS	20.00 ± 0.62[a]	17.00 ± 0.95[b,x]	22.71 ± 1.02[c]
	MS	21.00 ± 0.62[a]	22.86 ± 0.80[a,b,y]	23.71 ± 0.42[b]
	HS2	1.00 ± 0.38[a]	18.43 ±1.02[b,x]	23.71 ± 0.75[c]

[a,b,c]Within a row, values with different superscript letters differ significantly ($P < 0.05$) among groups.[x,y,z]Within a variable within a column, values with different superscript letters differ significantly ($P < 0.05$) among dietary treatments.
See Table 1 for key.

period but increased significantly during the MS and HS periods.

During the LS period, group RK had a significantly higher serum bicarbonate concentration and lower anion gap, compared with values for groups C and WA. Serum bicarbonate concentration was not affected by feeding NaCl-supplemented diets, except for group RK during the MS period in which it decreased while the anion gap increased.

Renal function—As expected, the GFR during the LS period was lower for groups RK and WA, with mean differences of 25.8% (group RK) and 47.2% (group WA), respectively (**Fig 1**). The GFR of group WA was significantly lower than that of group RK during the LS period. Similar patterns for differences among groups were observed during the MS and HS periods. The GFR increased significantly for group C during the MS and HS periods. Similarly, there was a significant increase in GFR of group WA during the MS period. However, there were no significant alterations of GFR for group RK during feeding of the NaCl-supplemented diets.

Mean values for RPF of group C were significantly greater (by 52.3% to 57.1% and 56.4% to 68.4%) than corresponding values for groups RK or WA, respective-

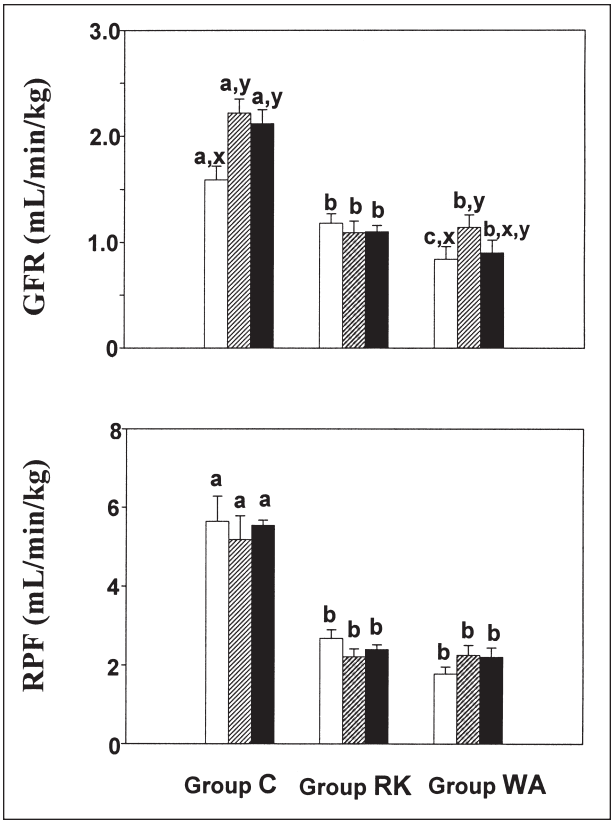

Figure 1—Mean ± SEM glomerular filtration rate (GFR; top) and renal plasma flow (RPF; bottom) in clinically normal cats (control cats; group C; n = 7) and cats with renal insufficiency induced by use of the remnant-kidney method (group RK; 7) or the remnant-wrap method (group WA; 7) sequentially fed 3 diets that provided 50 (low-sodium diet; white bars), 100 (medium-sodium diet; cross-hatched bars), or 200 (high-sodium diet; black bars) mg of sodium/kg. Each diet was fed for 7 days. Notice that the GFR and RPF were significantly ($P < 0.05$) decreased in both groups of cats with renal insufficiency. The GFR, but not RPF, for group C was significantly ($P < 0.05$) lower during feeding of the low-sodium diet, compared with values during feeding of the other diets. For group WA, the GFR was also significantly ($P < 0.05$) lower during feeding of the low-sodium diet, compared with GFR during feeding of the medium-sodium diet. a,b,c—For a variable within the same diet, values with different letters differ significantly ($P < 0.05$) among groups. x,y,z—For a variable within the same group, values with different letters differ significantly ($P < 0.05$) among diets.

Table 3—Mean ± SEM renal water and electrolyte excretion in clinically normal cats (group C) and 2 groups of cats with reduced renal function (groups RK and WA) during LS, MS, and HS dietary intake

Variable	Diet	Group C	Group RK	Group WA
Urine flow (mL/min/kg)	LS	0.044 ± 0.005	0.054 ± 0.010	0.048 ± 0.001[x]
	MS	0.037 ± 0.005[a]	0.044 ± 0.005[a]	0.077 ± 0.015[b,y]
	HS	0.044 ± 0.003	0.033 ± 0.002	0.047 ± 0.010[x,y]
Osmolar clearance (mL/min/kg)	LS	0.084 ± 0.013	0.075 ± 0.010	0.083 ± 0.014
	MS	0.076 ± 0.012[a]	0.053 ± 0.006[a]	0.129 ± 0.017[b]
	HS	0.072 ± 0.009	0.053 ± 0.007	0.077 ± 0.011
Free-water clearance (mL/min/kg)	LS	–0.040 ± 0.012	–0.021 ± 0.016	–0.051 ± 0.008[x,y]
	MS	–0.039 ± 0.008[a]	–0.010 ± 0.005[b]	–0.049 ± 0.008[a,x]
	HS	–0.028 ± 0.010	–0.019 ± 0.006	–0.029 ± 0.003[y]
Urinary protein-to-creatinine ratio	LS	0.20 ± 0.06[a]	0.17 ± 0.04[a]	0.56 ± 0.15[b]
	MS	0.24 ± 0.11	0.17 ± 0.04	0.53 ± 0.16
	HS	0.15 ± 0.02[a]	0.18 ± 0.05[a]	0.39 ± 0.07[b]
Fractional excretion (%)				
Sodium	LS	1.71 ± 0.34[a]	2.86 ± 0.40[b]	6.52 ± 1.25[c]
	MS	1.16 ± 0.30[a]	2.39 ± 0.31[a]	5.60 ± 0.62[b]
	HS	1.21 ± 0.23[a]	1.92 ± 0.37[a]	3.96 ± 0.34[b]
Potassium	LS	32.26 ± 2.54[a,x]	41.31 ± 4.18[a,x]	107.52 ± 21.04[b]
	MS	17.07 ± 1.67[a,y]	31.64 ± 4.74[b,y]	97.16 ± 21.23[c]
	HS	19.27 ± 2.55[a,y]	25.62 ± 3.67[a,y]	60.14 ± 8.35[b]
Chloride	LS	1.87 ± 0.37[a,x]	3.75 ± 0.48[b,x]	7.33 ± 1.11[c]
	MS	2.68 ± 0.30[a,y]	5.18 ± 0.56[b,y]	7.71 ± 1.02[c]
	HS	1.89 ± 0.21[a,x]	3.46 ± 0.29[b,x]	6.04 ± 0.59[c]

[x,y]Within a variable within a column, values with different superscript letters differ significantly ($P < 0.05$) among dietary treatments.
See Table 1 and 2 for remainder of key.

Table 4—Mean ± SEM variability of mean systemic ABP and mean HR in clinically normal cats (group C) and 2 groups of cats with reduced renal function (groups RK and WA) during LS, MS, and HS dietary intake

Variable		Group C	Group RK	Group WA
ABP variability (mm Hg)	LS	7.10 ± 0.55	6.43 ± 0.49	6.60 ± 0.84
	MS	6.98 ± 0.56	7.50 ± 0.93	5.41 ± 0.42
	HS	7.50 ± 0.84	6.91 ± 0.85	6.40 ± 0.55
HR variability (beats/min)	LS	14.2 ± 2.1	10.9 ± 1.6	10.8 ± 1.3
	MS	14.6 ± 2.3	11.6 ± 1.2	11.6 ± 1.6
	HS	15.0 ± 2.4	11.3 ± 1.2	11.9 ± 1.3

See Table 1 for key.

ly (Fig 1). There was not a significant difference for RPF between groups RK and WA. We did not detect significant effects of feeding NaCl-supplemented diets on RPF in any group.

Urine flow, osmolar clearance, or free-water clearance did not differ among groups during the LS period (**Table 3**). Mean values for the urinary protein-to-creatinine ratio of groups C and RK were not significantly different, but a significantly higher value was observed for group WA during the LS period. Urinary protein-to-creatinine ratio was apparently not altered by dietary supplementation with NaCl.

Fractional excretion rate for sodium during the LS period was significantly higher for groups RK and WA, compared with the rate for group C. Supplementation with NaCl had little effect on fractional excretion of sodium, tending to depress the rate in all 3 groups (Table 3). Fractional excretion of chloride in both groups of cats with renal insufficiency was significantly higher than the corresponding value for group C during the LS period, and feeding NaCl-supplemented diets did not consistently affect this variable. Fractional excretion of potassium was greatest during the LS period for group WA and decreased in all 3 groups during feeding of NaCl-supplemented diets, although it decreased significantly reduced only for groups C and RK.

Variability of ABP and HR—Variability of mean ABP and HR was not significantly different among groups or dietary periods (**Table 4**).

Hormone concentrations—Plasma renin activity was increased for group WA but was not significantly altered by feeding of NaCl-supplemented diets in any group (**Table 5**). During the LS period, serum aldosterone concentration was greater for groups RK and

Table 5—Mean ± SEM hormone values in clinically normal cats (group C) and 2 groups of cats with reduced renal function (groups RK and WA) during LS, MS, and HS dietary intake

Hormone	Diet	Group C	Group RK	Group WA
Plasma renin activity (ng/mL/h)	LS	0.72 ± 0.13[a]	1.40 ± 0.22[a,b]	4.06 ± 1.74[b]
	MS	1.20 ± 0.17	1.20 ± 0.09	3.79 ± 1.61
	HS	0.98 ± 0.41	1.44 ± 0.49	3.46 ± 1.49
Aldosterone (ng/dL)	LS	1.0 ± 0.0[a]	8.5 ± 4.3[b]	31.9 ± 18.1[b,x]
	MS	1.0 ± 0.0[a]	4.1 ± 0.8[b]	25.1 ± 13.5[c,y]
	HS	1.0 ± 0.0[a]	3.9 ± 1.3[a,b]	18.2 ± 11.3[b,y]
Atrial natriuretic peptide (pg/mL)	LS	169.0 ± 20.0	187.0 ± 59.0	186.0 ± 49.0
	MS	162.0 ± 24.0	241.0 ± 54.0	184.0 ± 35.0
	HS	156.0 ± 22.0	178.0 ± 49.0	208.0 ± 49.0
Arginine vasopressin (pg/mL)	LS	28.0 ± 12.7[a]	65.5 ± 4.5[b]	18.9 ± 8.7[a]
	MS	29.2 ± 6.2	61.0 ± 5.8	52.7 ± 11.5
	HS	50.5 ± 11.1	32.3 ± 19.0	24.5 ± 5.8

See Tables 1 and 3 for key.

WA than for group C. Increasing dietary NaCl intake depressed the aldosterone concentration of group WA, although it remained increased. Dietary supplementation of NaCl reduced, but not significantly, the serum aldosterone concentration of group RK. Mean ± SEM aldosterone-to-renin ratio (absolute value) was 1.05 ± 0.20 for group C and was significantly increased for groups WA (6.61 ± 0.82) and RK (4.15 ± 1.09). Feeding NaCl-supplemented diets reduced, but not significantly, the aldosterone-to-renin ratio (absolute value) similarly in all groups (mean values for all cats were 6.71 ± 1.76 for the LS period, 4.74 ± 0.83 for the MS period, and 3.85 ± 0.62 for the HS period). Plasma concentrations of atrial natriuretic peptide did not differ significantly among groups during the LS period, and dietary supplementation with NaCl had no apparent effect on this variable. Plasma arginine vasopressin concentration was significantly increased for the RK group during the LS period. Dietary supplementation with NaCl had no significant effect on plasma arginine vasopressin concentration.

Discussion

The remnant-kidney and remnant-wrap methods for induction of renal insufficiency in cats caused systemic hypertension consistent with that reported in other studies[20,22] and with observations in cats with naturally developing CKD that also commonly develop systemic hypertension.[5-7] Although dietary NaCl restriction may be used clinically in the management of affected cats, variations in dietary NaCl intake had no effect on ABP in clinically normal cats or in either group of cats with renal insufficiency in the study reported here.

Effects of dietary NaCl on blood pressure have been studied in other species. In rats with reduced renal mass, high NaCl intake increases mean blood pressure.[25] However, experiments in clinically normal dogs revealed that increasing NaCl intake from 8 to 120 mmol/kg causes an increase in total body water, but blood pressure and HR remain unchanged.[26] Results of our study are consistent with those for clinically normal dogs. Taken together, analysis of the results of these studies suggests that neither blood pressure nor systemic hypertension associated with renal insufficiency is sensitive to the effects of NaCl in either species.

Variability of blood pressure is limited by the arterial baroreceptor reflex.[13] In chronic hypertension, the baroreceptor reflex can play a causal role in the increase of blood pressure, or it can be reset as indicated by normalization of HR even though blood pressure is still high. Analysis of results of our study documented that impaired renal function increased blood pressure but did not have a significant effect on HR. This suggests that there is baroreceptor resetting in cats after renal impairment. Furthermore, the degree of variability in blood pressure and HR were unchanged by the amount of renal function or dietary NaCl intake. We conclude that the increase in blood pressure observed in cats with renal impairment does not involve a baroreceptor defect and that dietary NaCl does not alter blood pressure or baroreflex activity in clinically normal cats or cats with renal insufficiency.

During the MS period, the GFR of groups C and WA was significantly increased without a change in ABP or RPF. Although this result was also observed during the HS period in the clinically normal cats, the HS diet did not sustain the increase in GFR of group WA. These results for GFR are supported by parallel patterns of decreases in serum Cr concentrations in response to feeding NaCl-supplemented diets. Dietary NaCl intake did not alter GFR in the RK group, which is consistent with results of a study[27] of the remnant kidney model in dogs in which an abrupt change in dietary NaCl intake did not cause variations of renal function. Analysis of these results suggests that feeding supplemental NaCl led to efferent arteriolar vasoconstriction, alone or in combination with afferent vasodilation, in response to NaCl loading in cats of groups C and WA. The decrease in plasma osmolarity for group C may have reflected volume expansion. Thus, increased GFR with NaCl loading could have been attributable to a tubuloglomerular feedback-mediated arteriolar response to this volume expansion.[28] Alternatively, changes in renal arteriolar tone could have been caused by suppression of the intrarenal renin-angiotensin system or activity of renal sympathetic nerves. In certain experimental settings in rodents, dietary salt loading can enhance GFR, but this has generally been associated with suppression of an activated renin-angiotensin-aldosterone axis,[29,30] a situation clearly not operative in the clinically normal cats of our study. Unfortunately, our results do not allow us to distinguish among these possibilities for the cats of the study reported here, although the systemic renin-angiotensin system, as reflected by plasma renin activity, was apparently unaltered by dietary NaCl in the group of clinically normal cats.

Mean serum aldosterone concentrations in both groups of cats with renal insufficiency were increased, compared with the concentration of group C, with serum aldosterone concentrations being greatest for group WA. High plasma renin activity was also apparent in this group. This method has been characterized as causing greater activation of the renin-angiotensin-aldosterone system than is seen with the remnant-kid-

ney model.[22] In 1 study,[15] clinically normal cats and cats with hypertension associated with various naturally developing renal diseases did not have overall differences in plasma renin activity and concentrations of angiotensin I, whereas the aldosterone concentration was significantly greater in hypertensive cats with renal disease. Cats with polycystic kidney disease tend to have low-to-normal plasma renin activity, as well as serum aldosterone concentrations within the reference range, but increased aldosterone-to-renin ratios.[17] Similarly, cats with induced renal insufficiency by each of the 2 methods used here had higher ratios indicative of a more consistent increase in aldosterone concentrations.

An increase in aldosterone concentration in cats with renal insufficiency could have been attributable to an increase in plasma renin activity, hyperkalemia, altered sensitivity to stimuli for aldosterone release (eg, plasma renin or potassium concentrations), reduced aldosterone degradation rate, or a combination of these factors. It should be mentioned that cats of group WA also received amlodipine besylate, an antihypertensive agent that may have played a role in activation of the renin-angiotensin-aldosterone axis in those cats. Clearly, the low serum potassium concentrations argue against a contribution of this factor, indicating that plasma potassium concentration is not a critical factor in the regulation of aldosterone secretion in cats. Our results do not allow us to distinguish the relative contribution of other factors in aldosterone overproduction.

In the study reported here, dietary NaCl affected aldosterone concentrations in cats with renal impairment. A 50% suppression of aldosterone as a result of feeding NaCl-supplemented diets was evident in both groups of cats with reduced GFR, whereas changes could not be evaluated in clinically normal cats because the basal aldosterone concentrations in control cats were at the lower end of assay sensitivity during the LS period. In general, plasma renin activity was less sensitive to NaCl intake, compared with the sensitivity of aldosterone concentrations to NaCl intake. Dietary salt loading in certain experimental models of hypertension in rodents can suppress an activated renin-angiotensin-aldosterone axis while having no effect on blood pressure or actually delaying the onset of hypertension.[29,30] The finding that feeding NaCl-supplemented diets can suppress the renin-angiotensin-aldosterone axis without increasing blood pressure while maintaining or increasing GFR in cats with renal insufficiency is interesting. Given the potentially deleterious effects of this hormonal system on renal function and structure,[22,31] such manipulations may have clinical use to preserve renal structure and function and slow the progression of CKD.

It should be mentioned that the concentrations of serum aldosterone in animals with chronic renal failure may be falsely increased when measured by radioimmunoassay without prior dichloromethane extraction.[32] Furthermore, plasma from human patients with chronic renal failure may contain a polar substance that cross-reacts with anti-aldosterone antibodies.[32] We cannot exclude possible interference or cross-reaction in the assays used to measure aldosterone concentrations in our study, although the increases in aldosterone concentrations in cats with renal impairment were generally parallel to observed changes in plasma renin activity and were in all likelihood primarily a result of a true increase in aldosterone concentrations.

Amlodipine besylate was administered to cats in group WA to control blood pressure. Without antihypertensive treatment, this method of induced renal insufficiency causes persistent increases of systolic blood pressure of > 180 mm Hg and a substantial incidence of hypertensive encephalopathy.[22] The nature of this experimental group (ie, combining the remnant-wrap model plus antihypertensive treatment) did not allow us to determine whether effects observed in this group were attributable to the method (remnant-wrap), amlodipine besylate, or a model-by treatment interaction. Nonetheless, results obtained for this group were of interest because of the widespread use of this antihypertensive agent in cats with hypertensive renal insufficiency.[21,33-35] Importantly, our study documented that dietary supplementation with NaCl suppressed the renin-angiotensin-aldosterone axis without adversely affecting blood pressure in this group.

Baseline sodium intake in the study (LS period) was 50 mg/kg/d, and we sequentially added NaCl to the diet to yield intakes of 100 and 200 mg of sodium/kg/d; these intakes were equivalent to total daily sodium intakes of 2.2, 4.4, and 8.7 mmol/kg, respectively. Other studies[36,37] suggest that the minimal sodium requirement for maintenance in cats is 0.4 to 0.9 mmol sodium/kg/d. Our baseline diet during the LS period provided 2.2 mmol sodium/kg and was referred to as a low-salt diet because this amount of intake is similar to that commonly used in commercially available diets denoted as having a reduced salt content. However, the LS diet provided sodium intake that was several fold in excess of the published values for minimum requirements. Thus, our study was not designed to address the effects of extremely low amounts of sodium intake that approach minimum requirements.

For all dietary NaCl intakes, fractional excretion of sodium was appropriately higher in cats with reduced GFR. However, fractional excretion of sodium did not increase, and the serum sodium concentration was significantly, albeit only slightly, higher in all groups after feeding NaCl-supplemented diets. This is somewhat surprising and could not be explained by changes in aldosterone or atrial natriuretic peptide concentrations in the cats. Clearance and excretion evaluations were conducted after food was withheld overnight, and diurnal variations in urinary sodium metabolism may have been responsible for the lack of anticipated effects of feeding NaCl-supplemented diets. Nonetheless, this finding was unexpected; poorly understood factors appear to be affecting the regulation of sodium metabolism by the kidneys of cats.

Serum potassium concentrations were comparatively low in all groups of cats during the reduced NaCl diet (LS period), a time when the fractional excretion of potassium was inappropriately high. Fractional excretion rates for potassium appeared to be directly related to aldosterone concentrations in our study, sug-

gesting a contribution of this hormone to the inappropriate excretion of potassium. Fractional excretion of potassium seemed to respond appropriately to feeding NaCl-supplemented diets in all groups, changes probably mediated by a decrease in sodium reabsorption in the distal tubules, which would reduce the electrical gradient driving potassium secretion at that site.[38] This reduction in sodium reabsorption was probably mediated primarily by suppression of plasma aldosterone concentrations[39] and, perhaps, also a reduction in catecholamine concentrations[40] or other local factors[39] that modulate renal sodium transport at this site. We did not investigate these other factors.

The study reported here had several limitations. In addition to activation of the renin-angiotensin-aldosterone system, catecholamine synthesis or increased activity of renal nerves may have played a role in the development of hypertension, especially during surgical reduction of renal mass.[41] Clinically normal humans have a change in adrenergic responses after high NaCl intake.[42] Thus, changes in NaCl intake may have affected the response of blood pressure and renal hemodynamics in the cats of our study, although we cannot evaluate this proposal because we did not measure plasma catecholamine concentrations. A second potential limitation is the duration of each dietary period, which was 7 days to provide ample time for chronic volume and hormonal adjustments to the dietary changes, as determined on the basis of the evaluation of sodium homeostasis in other species.[43] Although unlikely, we cannot exclude the possibility that responses may have differed somewhat with longer durations of dietary NaCl intake. Furthermore, it is reasonable to propose that some of the effects caused by variations in dietary NaCl intake in the study reported here, particularly the lowest salt intake, could have caused adverse long-term consequences for the cats with renal insufficiency, and our study did not address this hypothesis. We examined the effect of feeding NaCl-supplemented diets and thus did not randomize the order of exposure to variations in dietary NaCl. In addition, we did not measure variables during a final LS time-control period. We cannot completely eliminate the possibility of a carryover effect of sequential NaCl loading or the possibility that NaCl restriction would have caused unexpected results in cats that contrasted from those predicted by the LS treatment in this study. However, our results are consistent with results of similar studies in dogs in which the order of dietary treatment did not affect the response of GFR[26,27] or blood pressure[26] to variations in NaCl intake.

In the study reported here, the lowest NaCl intake was associated with the lowest values for GFR. Low NaCl intake was also associated with inappropriate hypokalemic kaliuresis and activation of the renin-angiotensin-aldosterone system in cats with renal insufficiency. These findings of sodium insensitivity on blood pressure were remarkably similar in clinically normal cats and cats with renal insufficiency induced by the remnant-kidney method (group RK) or the remnant-wrap method with concurrent administration of amlodipine besylate (group WA). These results are cause for concern because potentially deleterious effects of the lowest NaCl intake were evident despite the lack of a beneficial effect on blood pressure in any group of cats.

[a]IMI-1000 implantable micro identification, BMDS, Seaford, Del.
[b]Norvasc, Pfizer Inc, New York, NY.
[c]Model TA11PA-C40, Data Sciences International, St Paul, Minn.
[d]Prescription diet feline K/D dry, Hills Petfoods, Topeka, Kan.
[e]Sodium chloride AR, Sigma Chemical Co, St Louis, Mo.
[f]Prescription diet feline A/D dry, Hills Petfoods, Topeka, Kan.
[g]Dataquest advanced research technology, version 2.2, Data Sciences International, St Paul, Minn.
[h]Osmette model 5004 microosmometer, Precision Systems Inc, Natick, Mass.
[i]Spectrum CCX, Abbott Diagnostics, Irving, Tex.
[j]Aldosterone Immunoassay, Diagnostic Systems Laboratories Inc, Webster, Tex.
[k]Quest advantage arginine vasopressin assay, Nichols Institute Diagnostics, San Juan Capistrano, Calif.
[l]Atrial natriuretic peptide radioimmunoassay, Research & Diagnostic Antibodies, Berkeley, Calif.
[m]GammaCoat, Incstar Corp, Stillwater, Minn.
[n]LabCorp, Laboratory Corporation of America, Burlington, NC.
[o]Sigmastat 2, SPSS Inc, Chicago, Ill.

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