

Effect of Reduced Glomerular Filtration Rate on the Fractional Excretion of Urea in the Dog¹ (34139)

RICHARD PARK AND LAWRENCE RABINOWITZ
(Introduced by L. D. Carlson)

*Department of Human Physiology, University of California School of Medicine,
Davis, California 95616*

In studies on rats fed high protein diets, Kleinman *et al.* (1) found that the urine to plasma ratio of urea exceeded the urine to plasma ratio of inulin during periods of depressed glomerular filtration. This evidence for tubular secretion of urea has yet to be confirmed. The present study examines the effect of acute reductions in glomerular filtration rate (GFR) on the fractional excretion of urea $[(U/P \text{ urea})/(U/P \text{ inulin})]$ in the anesthetized, vasopressin treated dog.

Methods. Dogs were maintained on a standard diet (23% protein) for at least 2 weeks, then deprived of water and food for the 24 hr preceding an experiment. During an experiment, they were anesthetized with pentobarbital sodium and were infused intravenously with a solution containing vasopressin (0.5–1 mU/min/kg of body wt), inulin (75 mg/ml) and NaCl (0.6%) at 0.097–0.191 ml/min. A polyethylene catheter was inserted into a femoral artery and attached to an E & M Company pressure transducer and physiograph permitted measurement of arterial blood pressure in the lower aorta. A balloon embolectomy catheter was inserted into the same femoral artery and positioned in the aorta above the renal arteries.

In experiments on three female dogs, urine was collected from the bladder through an indwelling urethral catheter and blood was sampled from a femoral artery at the midpoint of urine collection periods. Urine was collected during four to six 20-min periods during antidiuresis, four 10-min periods during infusion of 6M mannitol at 4

ml/min, and four 5-min periods during infusion of 6 M mannitol at 20 ml/min. After initiation of a new rate of mannitol infusion, urine flow was allowed to stabilize before beginning collection. The balloon was inflated during the latter half of each series of collection periods.

In experiments on five male dogs, the ureters were catheterized for the collection of urine with a short length of polyethylene tubing at a level 2–3 cm below the renal pelvis. The catheter dead space was less than 1.0 ml. Blood was sampled from the femoral artery or jugular vein at the beginning and end of each collection period. No diuresis was produced in these experiments. During the six to fourteen 20-min collection periods in each experiment, the balloon was alternately deflated and inflated over two period intervals.

During inflation of the balloon in all experiments, the rate of inulin infusion was reduced to compensate for decreased inulin excretion. Inulin was determined by the diphenylamine method (2) and urea by the indophenol method (3). Data obtained during periods of the nondiuretic experiments in which plasma inulin varied by 20% were discarded. The significance of differences in the fractional excretion of urea at different levels of GFR (clearance of inulin) was determined by the unpaired variate analysis of Wilcoxon (4).

Results. During each experiment, fluctuations in GFR occurred during periods in which the balloon was deflated. The arterial balloon was inflated to produce and maintain a drop in arterial blood pressure of 50–70 mm Hg and a reduction in urine flow rate.

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TABLE I. Effect of Reduced GFR on the Fractional Excretion of Urea.

Exptl. procedure	Anti-diuresis	Mannitol (4 ml/min)	Mannitol (20 ml/min)
<i>P/U</i> inulin			
Deflated periods	0.0036 (0.0014–0.0121) ^a (18) ^b NS ^c	0.0571 (0.0415–0.1157) (6) NS	0.3278 (0.2577–0.4000) (6) NS
Inflated periods	0.0032 (0.0015–0.0181) (18)	0.0550 (0.0411–0.1035) (6)	0.2298 (0.1811–0.3389) (6)
<i>(U/P urea)/(U/P inulin)</i>			
Deflated periods	0.329 (0.140–0.660) (18) <i>p</i> < .01	0.624 (0.552–0.692) (6) NS	0.703 (0.649–0.848) (6) NS
Inflated periods	0.160 (0.029–0.450) (18)	0.580 (0.504–0.692) (6)	0.668 (0.625–0.727) (6)
% Highest GFR ^d			
Deflated periods	90.0 (74–100) (18)	83.0 (67–100) (6)	91.7 (80–100) (6)
Inflated periods	41.8 (15–70) (18)	52.0 (35–68) (6)	37.7 (24–44) (6)

^a Mean and range.

^b Number of collection periods.

^c Significance of difference between inflated and deflated periods.

^d Values for highest GFR in individual experiments (ml/min/kg of body wt): 2.44, 2.70, 3.28, 3.98, 4.46, 5.07, 5.86, and 5.93.

Inflation of the balloon led to sustained, large reductions in GFR that typically exceeded the spontaneous changes in GFR. All values for GFR from each experiment were expressed as a fraction of the highest GFR measured in that experiment. Because the fractional excretion of urea varies directly with the fractional excretion of water (*P/U* inulin), all comparisons of the effect of changes in GFR were made between data collected during periods in which the fractional excretion of water was similar.

Table I summarizes the results obtained in all experiments. During antidiuresis (mean *P/U* inulin: 0.0034), reductions of GFR to values equal to 70% or less of the highest GFR were consistently associated with large and significant reductions in the fractional excretion of urea. The average fractional excretion of urea during balloon inflation was less than half of the average obtained during deflation. During both levels of mannitol diuresis, no significant change in fractional ex-

cretion of urea was observed despite reductions in GFR comparable to those produced during antidiuresis.

Discussion. It has previously been shown that the fractional excretion of urea is directly related to the fractional excretion of water but is independent of large increases in the amount of urea filtered (5). In this study no evidence of secretion of urea during periods of reduced GFR was obtained. To the contrary, when GFR was reduced fractional reabsorption of urea increased at low urine flow rates (low *P/U* inulin ratios). Several explanations for the reduction in fractional urea excretion merit consideration. An increased but transient, passive reabsorption and accumulation of urea in the renal medulla (abatement) may occur during periods of abruptly reduced urine flow (6). However, it is unlikely that abatement played a major role in the present study since the duration of sustained, reduced fractional excretion, up to 40 min, exceeded the predicted duration of

abatement (6). Furthermore, in some periods, there was a reduction in the fractional excretion of urea when the urine urea concentration was depressed, a relationship opposite to that existing during abatement (6).

Increased fractional reabsorption may reflect an active urea reabsorptive process which, because of a low capacity (low T_m), contributed only slightly to the total fractional reabsorption when the filtered loads of urea were normal but which accounted for a larger proportion of the fractional reabsorption when filtered loads were reduced. The present data do not preclude a role for such an active transport process but absence of significant reductions in fractional urea excretion during periods of diuresis suggests that this explanation is not applicable.

Lastly, the increased fractional reabsorption may reflect increased reabsorption by diffusion throughout the nephron or any one of its segments due to increased transit time of tubular fluid. The hypothesis that tubular reabsorption of urea occurs primarily by diffusion is generally accepted and has been recently reinforced by the demonstration of Jones *et al.* (7) that urea reabsorption in the proximal nephron parallels transit time. If the observed reduction in GFR was paralleled by a reduction in GFR in all nephrons, increases in tubular fluid transit time are likely to have occurred (8) in the present experiments. Thus, increased urea reabsorption by diffusion appears to satisfactorily explain the observed reduced fractional excretion of urea.

Schmidt-Nielsen and co-workers have observed reductions in the fractional excretion of urea in sheep, dogs, and men fed low protein diets (6, 9). Small and variable reductions in GFR also occurred in their studies. Though the reductions in fractional excretion that we observed were similar in magnitude to those occurring during protein depletion, they appeared only with reductions in GFR which were far larger than any reported by Schmidt-Nielsen and co-workers. Our results would, therefore, support the

contention of Schmidt-Nielsen that the reductions in fractional excretion of urea that occurs in subjects fed low protein diets cannot be entirely explained by reductions in GFR.

If the depression in fractional urea excretion seen in our experiments is truly representative of changes present during chronic reductions in GFR in man, it would be expected that a chronic reduction in GFR would, by itself, lead to an increased fractional reabsorption and increased blood levels of urea.

Summary. In anesthetized dogs the fractional excretion of urea was measured during antidiuresis and mannitol diuresis when the glomerular filtration rate was either normal or reduced by inflation of a balloon in the aorta above the renal arteries. Reductions in glomerular filtration rate to 70% or less of normal values resulted in a significant reduction in the fractional urea excretion to 50% of normal values during antidiuresis but caused no significant changes during diuresis. Increased passive reabsorption of urea occurring as a result of increased transit time of tubular fluid is the proposed explanation for the changes in fractional urea excretion.

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