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Mordecai M. Popovtzer, … , Mario Villamil, Charles R. Kleeman

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Research Article

The renal handling of phosphorus was evaluated in rats with acute renal failure (ARF) induced by injection of mercuric chloride ($HgCl_2$). Clearances of endogenous creatinine (Ccr) and of phosphorus (Cp) were measured in the following groups: 1. Intact animals (control); 2. Parathyroidectomized rats (PTX) with normal kidney function (PTX control); 3. Animals with mercury-induced acute renal failure (Hg-ARF); 4. PTX rats with Hg-ARF; 5. Rats with Hg-ARF maintained normophosphatemic with dietary phosphate restriction; 6. Animals with oliguric ARF following renal artery constriction; 7. Rats with unilateral Hg-ARF. In addition, radioinulin clearances were measured in 6 normal and in 14 azotemic animals and correlated with simultaneously recorded endogenous Ccr. Radioinulin clearance was also used as an estimate of GFR (glomerular filtration rate) in the animals of group 7.

The Cp/GFR in the intact animals (group 1) was 0.25 ±0.06 (mean ±SD). PTX (group 2) caused a subsequent decrease in Cp/GFR to 0.11 ±0.04 $P < 0.0005$. The ARF animals in group 3 were classified either as oliguric (U_{vol} [urine volume] <2 ml/24 hr, Ccr 0.008 ±0.005 ml/min) or nonoliguric (V_{vol} >2 ml/24 hr, Ccr 0.136 ±0.12). The Cp/GFR in the oliguric animals (0.16 ±0.09) was lower than that in group 1, $P < 0.0005$, and failed to increase following administration of exogenous parathyroid hormone. The Cp/GFR in the oliguric animals in […]

Renal Handling of Phosphorus in Oliguric and Nonoliguric Mercury-Induced Acute Renal Failure in Rats

MORDECAI M. POPOVTZER, SHAUL G. MASSRY, MARIO VILLAMIL, and CHARLES R. KLEEMAN

From Cedars-Sinai Medical Research Institute and Departments of Medicine, Cedars-Sinai Medical Center and University of California Medical School, Los Angeles, California 90048

ABSTRACT The renal handling of phosphorus was evaluated in rats with acute renal failure (ARF) induced by injection of mercuric chloride ($HgCl_2$). Clearances of endogenous creatinine (Ccr) and of phosphorus (Cp) were measured in the following groups: 1. Intact animals (control); 2. Parathyroidectomized rats (PTX) with normal kidney function (PTX control); 3. Animals with mercury-induced acute renal failure (Hg-ARF); 4. PTX rats with Hg-ARF; 5. Rats with Hg-ARF maintained normophosphatemic with dietary phosphate restriction; 6. Animals with oliguric ARF following renal artery constriction; 7. Rats with unilateral Hg-ARF. In addition, radioinulin clearances were measured in 6 normal and in 14 azotemic animals and correlated with simultaneously recorded endogenous Ccr. Radioinulin clearance was also used as an estimate of GFR (glomerular filtration rate) in the animals of group 7.

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INTRODUCTION

The fractional tubular reabsorption of phosphorus is depressed in chronic renal insufficiency (1–5). This finding has been the subject of numerous investigations both in humans and in animals with chronically diseased kidneys (2–4, 6–8). The information derived from above studies has established the importance of secondary hyperparathyroidism in maintaining the high fractional excretion of phosphorus (Cp/GFR)[1] in chronic renal failure. However, the renal handling of phosphorus in acute renal insufficiency has received minimal attention.

In a previous study serial determinations of urinary phosphorus in patients with acute renal failure disclosed a characteristic excretory pattern (9, 10). In the oliguric

Dr. Popovtzer's present address is University of Colorado Medical Center, Denver, Colo. 80220.

Drs. Massry and Villamil are Established Investigators of the American Heart Association.

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[1] *Abbreviations used in this paper:* ARF, acute renal failure; Ccr, endogenous creatinine clearance; Cin, radioinulin clearance; Cp, phosphorus clearance; GFR, glomerular filtration rate; PTX, parathyroidectomized rats.

phase the per cent of the filtered phosphorus excreted (Cp/GFR) was either unchanged or lower than normal, whereas during the diuretic phase the fractional excretion reached values considerably higher than normal. Secondary hyperparathyroidism has been documented in rats with acute renal failure (11–14); its presence in humans with acute renal failure could account, at least partly, for the augmented Cp/GFR during the diuretic phase. In the oliguric phase a profound decrease in the perfusion of individual nephrons with a reduced filtered load of phosphorus and relatively well preserved tubular reabsorptive capacity could lead to an enhanced fractional reabsorption of phosphorus. The present study was designed to evaluate the role of above-mentioned and other mechanisms in renal handling of phosphorus in acute renal failure.

METHODS

White female rats weighing 180–220 g were fed Purina pellet chow diet with tap water ad lib. The animals were housed individually in metabolic cages and daily urine outputs were collected and measured. Blood samples were drawn from the tail vein at the beginning, the midpoint, and the end of each 24 hr collection. Urine and serum specimens were analyzed for phosphorus (15), creatinine, and calcium by methods previously reported from this laboratory (16). The mean of the three consecutive serum concentrations was used for the determination of clearance rates. In addition to the 24 hr collections short term urine collections were employed in radioinulin clearance experiments, The latter were designed to assess the value of creatinine clearance as an indicator of glomerular filtration rate, both in normal and in azotemic animals.

Inulin-carboxyl-^{14}C clearance studies

These experiments were conducted between 10:00 a.m. and 2:00 p.m. Under light ether anesthesia the animals were water loaded with an orogastric tube. The load consisted of 15% ethyl alcohol in tap water in an amount equal to 5% of body weight. The same water load was repeated 30 min later. The above treatment induced a smooth and prolonged anesthesia with a brisk water diuresis. The animals were subsequently placed on a heated board. Femoral artery and vein were exposed and cannulated with PE-10 tubing.[2] The arterial cannula was used for withdrawing blood samples while the venous one served as an infusion line. Each animal received intravenously a priming dose of inulin-carboxy-^{14}C,[3] 1.5 μCi per 100 g body weight, followed by a sustaining infusion (Cobe pump)[4] delivering 1 ml normal saline with 4 μCi of radioinulin per hr. The sustaining dose was reduced in animals with impaired kidney function, whereas animals with oliguric acute renal failure received a single priming dose of radioinulin without sustaining infusion. Both ureters were approached through a suprapubic incusion and individually catheterized with PE-10 catheters. Urine from both ureters drained either into a single or into two separate graduated tubes in experiments with unilateral acute renal failure. 45 min were allowed for equilibration before two to three consecutive, timed urine samples were collected, at 20–30 min intervals. At the midpoint of each collection period, 0.2 ml of blood was withdrawn, whereas about 5 ml was obtained at the end of each experiment. In animals with oliguric acute renal failure in which only single urine specimen was available, two to three blood samples were obtained during a collection which continued for 4–6 hr. Plasma and urine specimens were diluted (200 ×) and measured for inulin-^{14}C activity in a Nuclear-Chicago liquid counter.[5] All urine specimens, and the plasma specimens obtained at the end of the experiments, were analyzed for creatinine and phosphorus.

Control studies

Group 1. 16 animals with intact kidneys served as the principal control group.

Group 2. 12 animals underwent parathyroidectomy 24 hr before the clearance study. The surgical procedure consisted of a median neck incision, separation of the anterior cervical muscles, and exposure of the thyroid gland. Both parathyroid glands were identified at the posterolateral aspects of the upper poles of the thyroid and destroyed with hot-wire cautery (Light Duty Cautery).[6] The success of the parathyroidectomy was ascertained by a drop in serum calcium to a level of 6 mg/100 ml or less.

Renal failure studies

Group 3. Acute renal failure was induced in one group of rats with an intramuscular injection of 0.3 mg mercuric chloride ($HgCl_2$) per 100 g of body weight.

Group 4. The above-mentioned treatment was given to another group of animals that had been parathyroidectomized earlier.

Group 5. 18 animals were fed low-phosphorus diet[7] supplemented with aluminum hydroxide gel (Amphojel)[8] for 1 wk. Acute renal failure was induced in 12 animals on the 8th day.

Group 6. Acute oliguric renal failure was induced in this group with a partial occlusion of one renal artery combined with removal of the contralateral kidney. Left paravertebral incision exposed the left kidney and its artery. The artey was carefully dissected and a steel wire (0.02 mm in diameter) was applied in a parallel fashion to the longitudinal axis of the artery. A silk ligature tied together both the vessel and the steel wire. The latter was pulled out gently leaving a residual arterial lumen approximately equal to the diameter of the wire. Upon completion of this procedure the contralateral kidney was removed and the clearance studies were started 24 hr later.

Unilateral acute renal failure

Group 7. This lesion was produced by a direct injection into the renal artery of 0.1 ml 30 mg% $HgCl_2$. The left renal artery and its continuation into the aorta were exposed and well visualized under a dissecting microscope. A purse string suture was placed on the aorta opposite the

[2] Clay-Adams, Inc., Parsippany, N. J.
[3] New England Nuclear Corp., Boston, Mass.
[4] Cobe Laboratories, Inc., Denver, Colo.
[5] Nuclear-Chicago, Des Plaines, Ill.
[6] V. Mueller Surgical Products, Inc., subsidiary of American Hospital Supply Corp., Evanston, Ill.
[7] Nutritional Biochemicals Corporation, Cleveland, Ohio.
[8] Wyeth Laboratories, Division of American Home Products Corporation, Philadelphia, Pa.

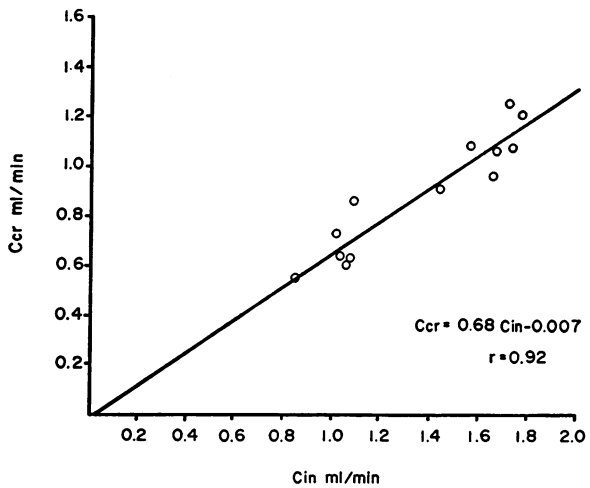

FIGURE 1 The relationship between the clearances of endogenous creatinine (Ccr) and radioinulin (Cin) in normal rats.

origin of the left renal artery. A 30 gauge needle was passed through the area confined by the suture and thereafter introduced into the lumen of the renal artery. Following slow injection of $HgCl_2$ into the renal artery the needle was withdrawn quickly and the puncture site was occluded by tightening the purse string suture.

Group 7A. The above protocol was applied to another group of animals except for the substitution of the mercuric chloride solution with 0.1 ml of normal saline.

In both groups 7 and 7A individual kidney function studies were performed using radioinulin for the determination of glomerular filtration rate.

RESULTS

Fig. 1 shows a close relationship between the radioinulin (Cin) and creatinine clearances (Ccr) in six animals of group 1. In these animals 24-hr Ccr as well as short Cin and Ccr rates were measured. The linear equation: $Ccr = 0.68\ Cin + 0.007$, $r = 0.94$, $P < 0.001$, indicates that Ccr is smaller than Cin by a factor equal to 0.68. On the basis of above information in all determinations of fractional clearances of phosphorus (Cp/GFR) in animals with intact kidneys in whom only Ccr was obtained, the ratio Ccr/0.68 was arbitrarily used as GFR.

The serum levels of calcium and phosphorus as well as the excreted fraction of filtered phosphorus in group 1 (Table I) were compared with corresponding determinations in group 2 (Table I) and were found to be significantly different ($P < 0.0005$).

Animals with acute renal failure were classified as either oliguric or nonoliguric on the basis of urine flow per 24 hr; nonoliguric: more than 2 ml/24 hr; oliguric: less than 2 ml/24 hr.

The nonoliguric animals presented with variable degrees of renal insufficiency with a GFR ranging from 0.37 to 0.03 ml/min (Table I). The mortality rate was low. The kidneys in vivo were pink and bled profusely from incision sites. The clearances were measured during 1 of 5 consecutive days following the toxic injury. In 6 of 14 animals radioinulin clearances were measured and correlated with simultaneous creatinine clearances (Fig. 2). The equation $Ccr = 0.95\ Cin + 0.007$, $r = 0.98$, $P < 0.001$, indicated close relationship between Ccr and Cin with a slope near unity. On the basis of above findings, Ccr rates were used to substitute GFR in all animals with acute renal failure in which Cin was not available. The fractional excretion of phosphorus in the nonoliguric rats was remarkably high (Table I) Cp/GFR 0.94 ±0.29, and in 5 of 14 animals the excreted fraction exceeded unity. The effect of parathyroidectomy on Cp/GFR in nonoliguric acute renal failure is shown in Table I. PTX caused a marked decrease in Cp/GFR (0.27 ±0.08 as compared to 0.94 ±0.29). The fraction 0.27 did not differ significantly from 0.25 of the normal animals (group 1) but it was significantly higher than the Cp/GFR in the PTX animals with normal kidney function in group 2 ($P < 0.0005$).

The effect of phosphate deprivation on Cp/GFR in five normal animals and eight rats with nonoliguric renal failure is shown in Table I. In the normal animals urinary calcium concentrations were measured as well. Cp/GFR decreased drastically in normal animals following phosphorus depletion whereas the fractional excretion of diffusible calcium reached extremely high values (Cca/GFR 0.41 ±0.17). Serum concentrations of total calcium were elevated above 11 mg/100 ml in two animals. In the azotemic animals mean serum concentration of phosphorus (S[P]4.30 ±1.1 mg/100 ml) was comparable with that in the normal animals of group 1 (S[P]4.67 ±0.98 mg/100 ml). In four of eight animals

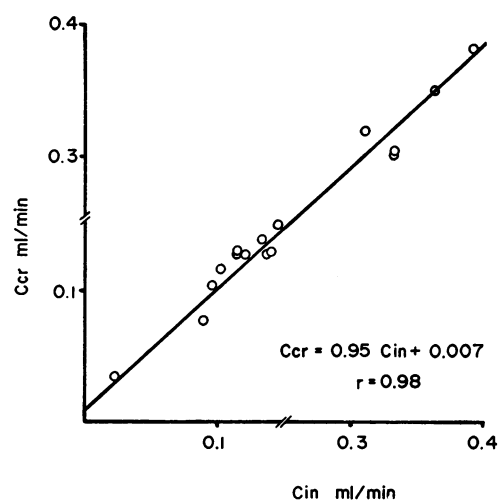

FIGURE 2 The relationship between the clearances of endogenous creatinine (Ccr) and radioinulin (Cin) in rats with mercury-induced nonoliguric acute renal failure.

TABLE I

Serum and Urine Values (Mean ±SD) in All Groups of Animals

Group	No. of rats	U_{vol}*	SCR‡	SCA§	SP‖	GFR	CP¶	CP/GFR
		ml/24 hr	*mg/100 ml*	*mg/100 ml*	*mg/100 ml*	*ml/min*	*ml/min*	
Control rats	16	19.10 ±23.10	0.67 ±0.22	9.32 ±0.69	4.57 ±0.98	1.2600 ±0.3400	0.3100 ±0.1100	0.2500 ±0.0600
Rats with normal kidney function after parathyroidectomy	12	9.50 ±5.00	0.71 ±0.05	5.45 ±0.55	8.60 ±1.90	1.1400 ±0.3500	0.1400 ±0.0700	0.1100 ±0.0400
Rats with nonoliguric acute renal failure	14	20.20 ±15.60	4.38 ±1.58	9.31 ±0.91	12.30 ±5.00	0.1320 ±0.0950	0.1140 ±0.0650	0.9400 ±0.2900
Parathyroidectomized rats with nonoliguric acute renal failure	12	8.00 ±5.00	2.76 ±1.14	4.92 ±0.62	16.7 ±0.08	0.1350 0.1210	0.0320 ±0.0230	0.2700 ±0.0800
Normal rats after phosphate deprivation	5	23.40 ±5.46	0.67 ±0.08	11.14 ±1.00	1.98 ±0.08	0.9000 ±0.0600	0.0030 ±0.0007	0.0040 ±0.0010
Phosphate-depleted rats with nonoliguric acute renal failure	12	22.9 ±9.8	4.07 ±2.85	12.10 ±2.60	4.30 ±1.10	0.1990 ±0.1890	0.1530 ±0.1450	0.8200 ±0.3600
Rats with oliguric Hg induced acute renal failure	12	1.35 ±0.39	5.47 ±1.88	9.10 ±2.30	19.20 ±5.40	0.0076 ±0.0054	0.0012 ±0.0006	0.1600 ±0.0930
Rats with oliguric Hg induced acute renal failure with exogenous parathyroid hormone	4	1.65 ±0.43	3.82 ±0.66	10.30 ±2.70	25.90 ±3.60	0.0110 ±0.0050	0.0022 ±0.0014	0.1520 ±0.0660
Rats with oliguric renal failure due to renal artery constriction	7	0.93 ±0.31	2.70 ±0.48	—	27.70 ±4.69	0.0032 ±0.0008	0.0004 ±0.0000	0.0900 ±0.0030

* Urine volume.
‡ Creatinine concentration in serum.
§ Calcium concentration in serum.
‖ Phosphorus concentration in serum.
¶ Phosphorus clearance.

in which serum concentration of calcium was measured, hypercalcemia was present. The fractional excretion of phosphorus (Cp/GFR 0.82 ±0.36) was not significantly different from that found in animals that were not on phosphate restriction (group 3 Cp/GFR 0.94 ±0.28), indicating that the hyperphosphatemia in the azotemic animals was not an important factor in causing the rise in Cp/GFR. The individual Cp/GFR values for each kidney in animals with nonoliguric unilateral acute renal failure (group 7) are shown in Fig. 3. In animals that were subjected to sham operation (group 7A) there was no significant difference between both kidneys with regard to any measurable function. In group 7 the filtration rate on the injured side (GFR 0.21 ±0.07) was lower than that (GFR 0.64 ±0.2) on the intact side. The fractional excretion of phosphorus in the affected kidney (Cp/GFR 0.51 ±0.17) was significantly higher than that in the untreated contralateral one (Cp/GFR 0.24 ±0.07, $P < 0.0005$). The nature of the lesion produced by intra-arterial injection of mercury is presented in Fig. 4.

In the oliguric animals glomerular filtration rates were inordinately reduced (GFR 0.02 ml/min or less). In eight oliguric animals radioinulin clearances were measured and correlated with simultaneous endogenous creatinine clearances (Fig. 5). The equation $Ccr = 0.92\ Cin + 0.0007$, $r = 0.96$, $P < 0.001$, indicated intimate relationship between Ccr and Cin with a slope near unity. On the basis of above findings, Ccr rates were used to substitute GFR in all oliguric animals. The vast majority of the animals in this group succumbed within 24–48 hr following the nephrotoxic insult. In vivo in-

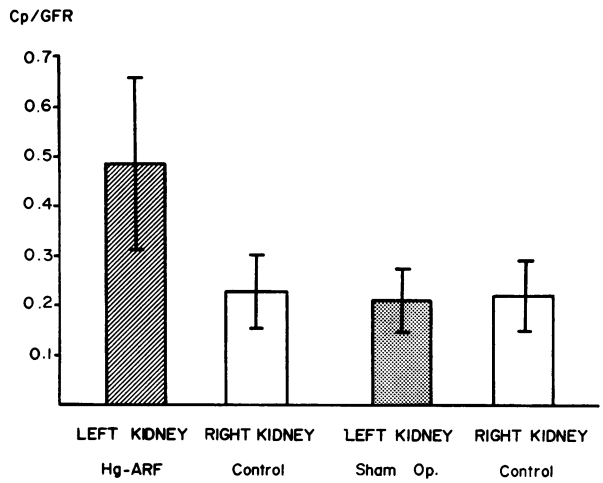

FIGURE 3 Divided fractional excretion of phosphorus (Cp/GFR) in unilateral mercury-induced nonoliguric acute renal failure (Hg-ARF) compared with unilateral sham operated kidney. The results are presented as mean ±SD values for the respective groups.

spection of the kidneys displayed pale cortical surfaces with poor bleeding response to a sharp injury. The clearances were measured 24–72 hr after the onset of oliguria. The duration of oliguria at the time of clearance studies had no appreciable effect on the results. In this group the Cp/GFR (0.16 ±0.08) was lower than that in the normal animals (group 1) (Table I). Four animals with acute oliguric renal failure were given exogenous parathyroid hormone (parathyroid extract)[9] in two intramuscular doses of 80 U during the clearance study. The mean Cp/GFR in these four rats was comparable with that in the animals that received no exogenous hormone (Table I), indicating inability of the hormone to augment the reduced Cp/GFR in the oliguric animals.

The animals with primary renal ischemia (group 6) were oliguric with severely reduced GFR. Similarly to the animals with mercury-induced oliguria these ani-

[9] Lilly, Eli, & Co., Indianapolis, Ind.

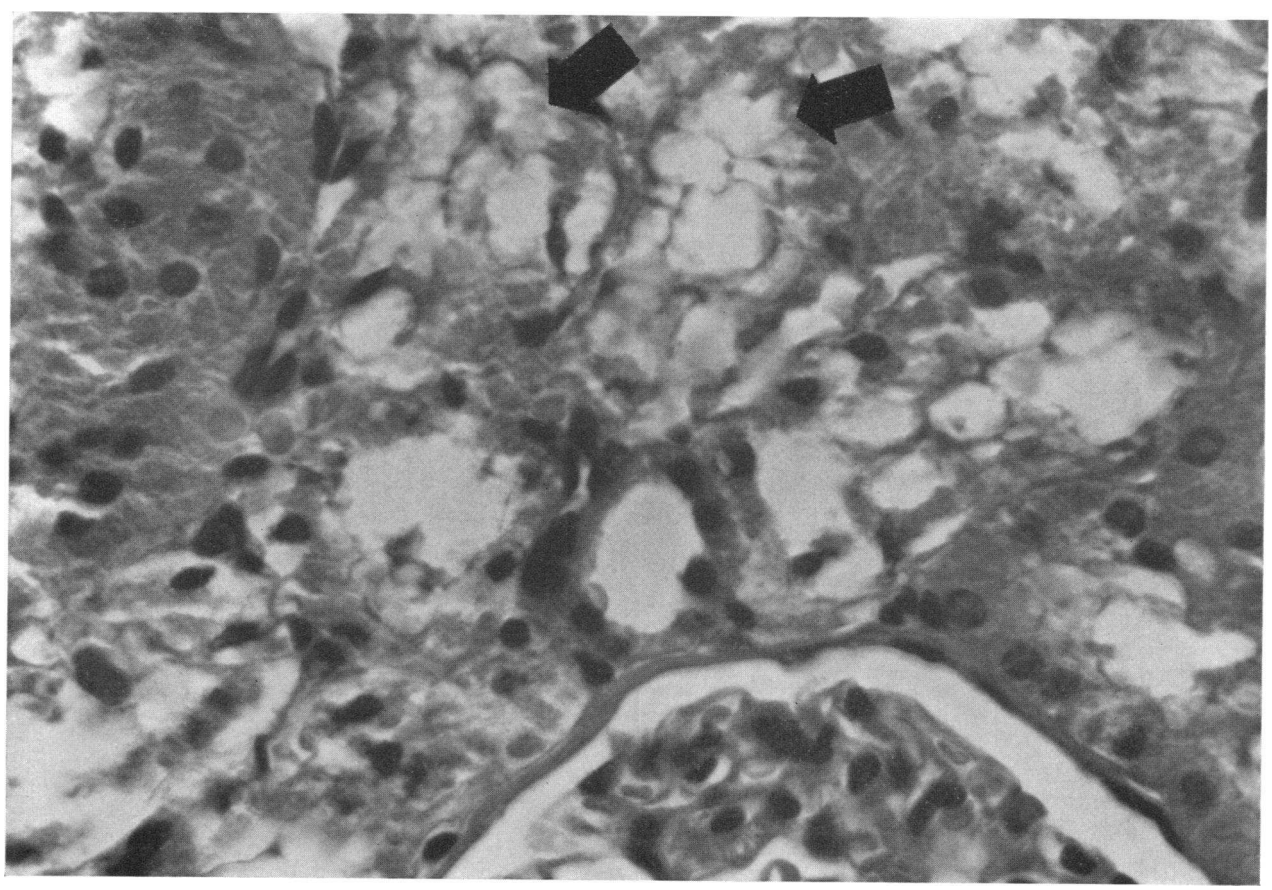

FIGURE 4 The changes produced by intrarenal arterial injection of mercury consisted of severely damaged proximal tubules with well-preserved glomerular structure. Proximal tubules (arrows) show extensive necrosis and vacuolar degeneration. A portion of an unaffected glomerulus is also seen. × 400.

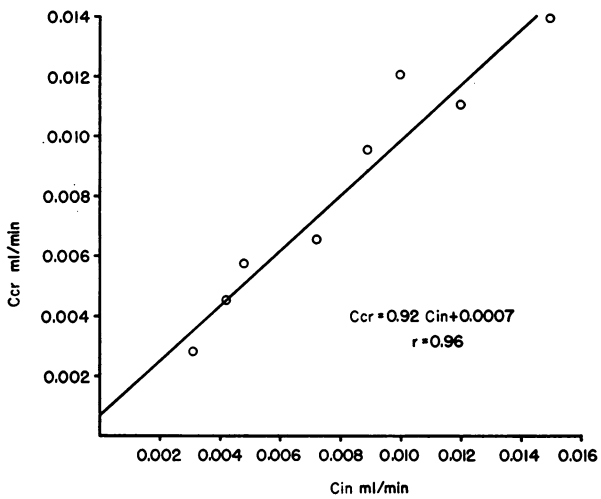

FIGURE 5 The relationship between the clearances of endogenous creatinine (Ccr) and radioinulin (Cin) in rats with mercury-induced oliguric acute renal failure.

mals exhibited very low fractional excretion of phosphorus[10] (Cp/GFR 0.09 ±0.02) (Table I).

In the animals with oliguric unilateral renal failure, the injured kidney behaved similarly to the kidneys in animals with bilateral oliguric renal failure. In vivo inspection also revealed a pale kidney indicating possible cortical ischemia. The urine flow from the injured kidney was severely reduced (0.15 ±0.05 μl/min) as compared with contralateral intact kidney (16.5 ±4.4 μl/min). The mean GFR of the injured kidney was 2.5 ±1.3 μl/min and of the contralateral 715 ±137 μl/min. Similarly to bilateral oliguric renal failure the Cp/GFR of the diseased kidney was low (Cp/GFR 0.074 ±0.006) whereas it was normal in the contralateral kidney (Fig. 6).

DISCUSSION

The results of the present study demonstrated that the renal handling of phosphorus in the rats with experimental renal failure was similar to that previously reported in humans with acute renal disease (9, 10). In both cases the presence or absence of oliguria was the principal factor which determined the direction in which the Cp/GFR was altered. The various mechanisms controlling renal handling of phosphorus which were evaluated in our experimental model could also apply to the human disease.

The fractional excretion of phosphorus was decreased in three experimental conditions associated with oliguria: (*a*) Hg-ARF (group 3), (*b*) unilateral Hg-ARF (following intrarenal arterial injection of mercury) and (*c*) ARF due to unilateral renal artery constriction with contralateral nephrectomy (group 6).

The etiology of oliguria associated with ARF is a subject of continuing debate. However, the preponderance of evidence, mainly derived from micropuncture studies, favors the view that the major factor leading to oliguria in ARF is reduction of glomerular filtration rate per nephron, secondary to cortical hypoperfusion, the latter probably due to an increased preglomerular resistance (17–21). Opposed to this concept is the contention that structural and functional tubular changes are primarily responsible for the oliguria (22, 23). Recent studies in humans support the notion that a diffuse reduction in renal cortical perfusion represents a common pathway accounting for the suppression of renal function in acute renal failure resulting from a diversity of basic etiologic factors (24, 25). The marked pallor of the surface of the kidneys in the oliguric ARF animals may also be interpreted as reflecting a state of cortical hypoperfusion. It seems most likely that the cortical ischemia and the reduced GFR per nephron are responsible for both the oliguria and the reduced Cp/GFR in oliguric ARF. Because of the marked decrease in the filtration rate per nephron the phosphorus load which is delivered to the tubules may be well below the maximum reabsorptive capacity ($TmPO_4$) leading to an almost complete reabsorption of the filtered phosphorus (26).

Considering passive tubular back-flow as an alterna-

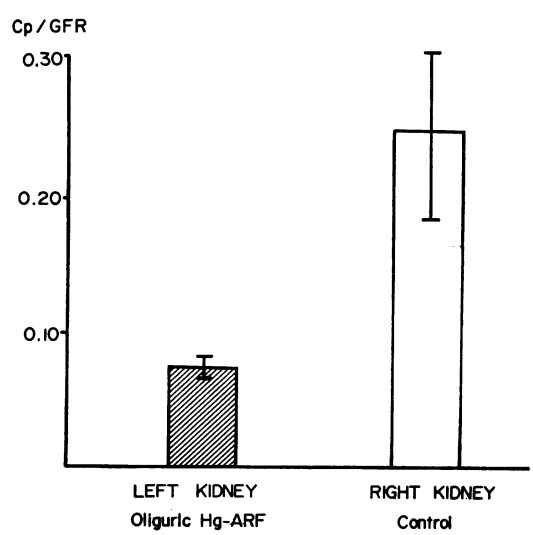

FIGURE 6 Divided fractional excretion of phosphorus (Cp/GFR) in unilateral mercury-induced oliguric acute renal failure. The results are shown as mean ±SD values for the whole group.

[10] We have recently observed in three elderly patients with renal failure (Ccr < 10 ml/min) secondary to atheromatous narrowing of main renal arteries fractional excretion of phosphorus (Cp/GFR ≅ 0.20) considerably lower than the values noticed in other patients with parenchymal kidney disease.

tive mechanism responsible for oliguria (22, 23) one may argue that the exceedingly low Cp/GFR reflects a passive back-flow of phosphorus across more severely injured epithelium. However, passive back-flow probably should not result in differential reabsorption of phosphorus and creatinine (inulin) to give very low Cp/GFR. The inability of the exogenous parathyroid hormone to increase Cp/GFR is evidence against the possibility that an acquired parathyroid hypofunction contributes to the low Cp/GFR of the oliguric state. The observation that the fractional excretion of phosphorus was also decreased in the unilateral oliguric ARF excludes a possible effect of the uremic state per se on renal handling of phosphorus in oliguria.

Oliguria accompanied by a decreased fractional excretion of phosphorus was also observed in unilateral renal vein hypertension (27). In the cited study partial occlusion of one renal vein in dogs resulted in a unilateral reduction of kidney function associated with oliguria and with a mean decrease in Cp/GFR from 0.19 to 0.10 on the affected side. The above changes in Cp/GFR were similar to our present findings in unilateral oliguric renal failure.

In contrast to the low fractional excretion of phosphorus observed in the above-mentioned states of oliguria, the Cp/GFR in end stage chronic renal failure with oliguria has been shown to be very high (28). This dissimilarity in renal handling of phosphorus could be related to diverse underlying mechanisms of oliguria in the acute and chronic renal disease; in the first case, hypoperfusion of individual nephrons seems to be the unifying etiology whereas in the latter, diminution of nephron population appears to be primarily responsible for the loss of kidney function and for the terminal oliguria (29, 30).

Nonoliguric ARF. Micropuncture studies in rats with nonoliguric acute renal failure demonstrated normal filtration rates of individual nephrons (31, 32) in variance to the low filtration rates in oliguric acute renal failure. The present data show that a functional discrepancy between these two forms of renal failure exists also with regard to renal handling of phosphorus. High fractional excretion of phosphorus was observed in all rats with nonoliguric acute renal failure. Several factors which could contribute to the increased Cp/GFR were given particular consideration. (*a*) Parathyroid hyperfunction was well documented immediately in the early course of acute renal failure in rats (11–14). Our observations that the fractional excretion of phosphorus was significantly lower in the azotemic rats without parathyroid glands than in those with intact glands emphasizes the importance of parathyroid hyperfunction in decreasing tubular reabsorption of phosphorus. However, the fact that Cp/GFR in the azotemic parathyroidectomized animals was higher ($P < 0.0005$) than the Cp/GFR of the control group (parathyroidectomized animals with intact kidneys) suggested presence of additional important factors contributing to the rise in Cp/GFR. (*b*) Hyperphosphatemia was a striking finding in all rats with acute renal failure. The possible role of this abnormality in causing elevation of Cp/GFR was tested with dietary phosphate restriction. Maintenance of normal serum phosphorus levels in the uremic rats did not affect significantly the marked rise in Cp/GFR. (*c*) Intrinsic tubular damage: the individual kidney function studies in unilateral nonoliguric acute renal failure demonstrated a decreased fractional reabsorption of phosphorus in the affected kidney, in the absence of azotemia, and probably in the absence of secondary hyperparathyroidism. This observation is consistent with acute tubular injury per se leading to an impaired tubular reabsorption of phosphorus.

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