Renal Cortical Intermediary Metabolism in the Recovery Phase of Postischemic Acute Renal Failure in the Dog (43363)

INMACULADA MONTAÑÉS, ALFREDO BADÍA, MANUEL A. RÉNGEL, AND JOSÉ M. LÓPEZ-NOVOA[1]

Laboratory of Renal Physiopathology, Fundación Jiménez Diaz-Consejo Superior de Investigaciones Científicas, Madrid, Spain and Department of Physiology and Pharmacology, University of Salamanca, Salamanca, Spain

Abstract. **Renal metabolism has been studied in eight dogs before and 48 hr after a 60-min period of renal ischemia induced by clamping the left renal artery with the simultaneous removal of the right kidney, and in 12 sham-operated animals. The study involved the measurement of renal uptake and production of lactate, glutamine, glutamate, alanine, ammonium, and oxygen, and the measurement of the tissue concentrations of ATP, glutamine, lactate, α-ketoglutarate, aspartate, and alanine in the renal cortex. Two days after a temporary renal ischemia, the remaining kidney showed a 22% decrease in glomerular filtration rate (GFR) and a 25% decrease in renal plasma flow. Fractional sodium and potassium excretions were similar to those of control dogs. Renal production or extraction of glutamine, glutamate, alanine, ammonium, and oxygen (all expressed by 100 ml of GFR) was not significantly different in basal conditions or 2 days after ischemia, but lactate extraction was reduced in postischemic kidneys (−101 ± 29 vs −204 ± 38 μmol/100 ml GFR in control dogs). The cortical concentrations of glutamine and glutamate were lower in postischemic than in control kidneys. No differences were found in cortical concentration of α-ketoglutarate, aspartate, lactate, pyruvate, or ATP, but total nucleotides and inorganic phosphate were decreased in postischemic kidneys. It is concluded that in the recovery phase of the ischemia, a decreased lactate uptake is the main metabolic change, and total ATP production is adapted to the decrease of GFR and sodium reabsorption.** [P.S.E.B.M. 1992, Vol 199]

Acute renal failure (ARF) in human subjects, associated with acute damage of the renal parenchyma and with loss of excretory function, is frequently initiated by an ischemic episode. The damage is generally reversible (1). In the last years a number of studies have been devoted to analyzing the changes in cell energetics after acute renal failure (2). However, most of these studies have been devoted to analyzing only ATP synthesis and turnover, and they have focused only on the initial phase of the ARF. The purpose of the present study was to analyze the changes in intermediary metabolism of the kidney during the recovery phase of postischemic ARF in the dog. In rats, Preuss *et al.* (3) showed that acute renal failure is associated with decreased oxidative metabolism and impaired transport functions. In addition, it has been shown that ammoniogenesis and gluconeogenesis from glutamate *in vitro* are decreased in the early (4) and late (5) stages of glycerol-induced ARF in rats.

The aim of the experimental design used in the present work was to reproduce in dogs the acute renal failure and its uremic milieu and thereby simulate the clinical condition seen in humans. In addition, we were able to study in the same dog one normal kidney and a kidney with acute renal failure in a uremic milieu, thus avoiding the enormous difference between individuals that exists in mongrel dogs.

Methods

Studies were carried out in 20 normal mongrel dogs (17–34 kg). The dogs were placed in individual metabolic cages that allowed collection of urine without contamination by food and feces for 4 days. Dogs were allowed free access to standard dog food pellets and

[1] To whom requests for reprints should be addressed at Departamento de Fisiología, Facultad de Medicina, Universidad de Salamanca, Avenida del Campo Charro s/n, 37007 Salamanca, Spain.

Received February 11, 1991. [P.S.E.B.M. 1992, Vol 199]
Accepted October 15, 1991.

0037-9727/92/1993-0321$3.00/0

water. Urine was collected daily under mineral oil to prevent evaporation. After an overnight fast, each dog was anesthetized with intravenous sodium pentobarbital (30 mg/kg body wt). A Harvard respirator was used to ventilate the dogs through a cuffed endotracheal tube. The rate and depth of respiration were initially adjusted to maintain carbon dioxide tension (PCO_2) around 35 mm Hg. An isotonic saline solution (pH 7.4) was infused at 2 ml/min through a peripheral vein. In eight dogs, the abdominal cavity was opened and the dogs were injected with 5000 IU of heparin. After careful dissection of the left renal pedicle to make sure that only one artery supplied the left kidney, the renal artery was clamped with an atraumatic vascular clamp for 60 min. In the meantime, the right kidney was dissected free from the perirenal fat. After an appropriate equilibration, a tissue sample of the right kidney cortex was obtained and freeze-clamped between two aluminum blocks cooled to the temperature of liquid nitrogen, according to the technique of Wollemberg *et al.* (6). The interval between removal of a portion of the superficial renal cortex and freeze-clamping was always less than 5 sec. The right renal pedicle was ligated immediately after this procedure and the right kidney was removed.

Once the period of renal ischemia was completed, the clamp was removed and blood reflow to the kidney was verified visually. The surgical wounds were closed, and the dogs were allowed to recover from the anesthesia in a warm, quiet environment. When the dogs showed the first signs of alertness, they were replaced in metabolic cages, and urine was collected daily as described previously. A blood sample was obtained daily by peripheral vein puncture for creatinine and electrolyte measurements.

Two days after the renal ischemia, the left renal function was studied. The surgical preparation has been described previously (7). In brief, after an overnight fast, each dog was anesthetized with intravenous sodium pentobarbital (30 mg/kg body wt) and received additional small doses whenever necessary during the experiments. The rate and depth of respiration were adjusted to maintain PCO_2 and PO_2 at the levels measured before anesthesia.

After a priming dose of creatinine (20 mg/kg body wt), a 5% mannitol solution containing 2 g of creatinine and 1 g of *p*-aminohippurate per liter, adjusted to pH 7.4, was infused into a jugular vein at a constant rate of 2 ml/min. The abdominal cavity was opened with a midline incision and the left renal vein was catheterized through the left ovarian or spermatic vein. An isotonic saline solution was infused slowly through the catheter inserted in the renal vein. The left ureter was also catheterized and urine was collected under mineral oil in graduated cylinders. During the experiment, blood was drawn anaerobically through a femoral artery catheter and analyzed immediately for acid base parameters.

Following a 30-min equilibration period, the renal ammoniagenesis and the renal utilization or production of glutamine, glutamate, α-ketoglutarate, alanine, lactate, and pyruvate by the left kidney were measured by three determinations of blood arteriovenous differences, and four consecutive, 10-min urine collections. At the end of the clearance periods, a slice of the left renal cortex was obtained and rapidly freeze-clamped as described above.

The tissue concentration of glutamine, glutamate, α-ketoglutarate, aspartate, alanine, lactate, pyruvate, ATP, ADP, AMP, and inorganic phosphate was measured in a neutralized perchloric extract of the kidney cortex (8).

In the remaining 12 dogs, that served as control group, the same experimental procedures, except for the renal ischemia, were performed in the same way as in the experimental group.

Analytical Methods. The pH, PCO_2, and PO_2 of blood and urine were measured anaerobically at 38°C with a digital, acid base analyzer (pH/blood gases analyzer model 168; Corning Medical, Corning Glass Works, Medfield, MA). Analytical methods used to determine plasma creatinine and *p*-aminohippurate, as well as glutamine, glutamate, α-ketoglutarate, malate, citrate, lactate, pyruvate, alanine, aspartate, NH_4^+, ATP, ADP, AMP, and inorganic phosphate, were the same as those described previously (8).

Calculations. Plasma bicarbonate concentrations were calculated from the Henderson-Hasselblach equation, as described previously (7). Blood oxygen content was calculated from the PO_2, pH, PCO_2, body temperature, hemoglobin, and hematocrit, as described by Kelman (9). Endogenous or exogenous creatinine clearance was used to estimate glomerular filtration rate (GFR). Renal blood flow was calculated from the *p*-aminohippurate clearance (corrected for renal extraction) and the hematocrit value. Renal utilization or production of each metabolite and oxygen was calculated by Woolf's equation modified by Cohen (10), taking into account the net urinary losses. In order to express the renal utilization or production of metabolites at similar rates of sodium filtration, these parameters were also expressed per 100 ml GFR. The rationale for this calculation was explained fully by Halperin *et al.* (11), in a previous publication.

Statistical Analysis. Data are expressed as mean ± SE. Unless otherwise specified, the term "significant" is used to describe a difference with a *P*-value of less than 0.05. One way analysis of variance for repeated measurements, followed by multiple means comparisons by the Scheffé's test, or the paired or unpaired Student's *t* test were used to analyze the differences between means.

Results

The urinary data reveal that the right uninephrectomy and left renal artery occlusion induced a 50% decrease in GFR on the first day and a 30% decrease on the second day after renal ischemia (Table I). Renal ischemia also produced a marked increase in fractional sodium excretion on the day after renal ischemia, but only minimal changes were observed on the second day after ischemia.

The data on arterial blood parameters before and 2 days after ischemia are shown in Table II. The only significant change observed after ischemia was an increase in plasma creatinine. Acid base parameters were not modified by the ischemia.

Table III shows data on arterial blood parameters during clearance studies in control dogs and in dogs 2 days after ischemia. No significant differences in arterial acid base parameters or plasma metabolite concentrations were observed between postischemic and control dogs.

Table IV shows data on left renal function in control dogs and in dogs 2 days after renal ischemia. Dogs after renal ischemia showed, compared with controls, a 25% reduction in GFR and renal blood flow and a small increase in the fractional excretion of sodium and chlorine.

Table I. Effect of Renal Artery Clamping on GFR and Electrolyte Excretion[a]

	Days after ischemia		
	Before (two kidneys)	1 Day (one kidney)	2 Days (one kidney)
Urinary flow	0.49 ± 0.06	0.46 ± 0.12	0.28 ± 0.04[b]
GFR (ml/min)	64 ± 10	16 ± 3[b]	22 ± 3[b]
UNaV (mEq/day)	48 ± 8	40 ± 12	13 ± 14[b]
UKV (mEq/day)	40 ± 6	24 ± 5[b]	18 ± 3[b]
UClV (mEq/day)	47 ± 8	36 ± 14	12 ± 7[b]
FENa (%)	0.56 ± 0.06	1.67 ± 0.33[b]	0.57 ± 0.74
FEK (%)	16.7 ± 3.7	36.7 ± 3.1[b]	23.4 ± 7.0[b]
FECl (%)	0.67 ± 0.22	2.10 ± 0.61[b]	0.75 ± 0.6

[a] Values are means ± SE (n = 8). Abbreviations used in table: UNaV, urinary sodium excretion; UKV, urinary potassium excretion; UClV, urinary chloride excretion; FE, fractional excretion.
[b] Significant difference ($P < 0.05$) from the values on the day before ischemia (Student's t test for paired data).

Table II. Effect of Renal Artery Clamping on Arterial Blood Parameters[a]

	Days after ischemia		
	Before	1 Day	2 Days
Hematocrit (%)	50 ± 1	49 ± 2	47 ± 5
Creatinine (mg/dl)	0.78 ± 0.09	1.55 ± 0.19[b]	1.80 ± 0.54[b]
Na (mM)	146 ± 2	143 ± 2	148 ± 2
K (mM)	3.9 ± 0.1	4.0 ± 0.2	3.7 ± 0.8
Cl (mM)	111 ± 1	109 ± 1	113 ± 2
Bicarbonate (mM)	20 ± 1	19 ± 1	18 ± 1
pO_2 (mm Hg)	74 ± 3	79 ± 2	79 ± 2
pCO_2 (mm Hg)	33 ± 2	32 ± 3	30 ± 1
pH	7.40 ± 0.01	7.38 ± 0.01	7.39 ± 0.01

[a] Values are means ± SE (n = 8).
[b] Significant difference ($P < 0.05$) from the values on the day before ischemia (Student's t test for paired data).

Table III. Effect of Renal Ischemia on Arterial Blood Parameters[a]

	Control dogs	Postischemic dogs
pH	7.38 ± 0.01	7.39 ± 0.02
pCO_2 (mm Hg)	33.3 ± 3.5	30.1 ± 1.1
Bicarbonate (mM)	20.6 ± 1.5	18.4 ± 0.14
PO_2 (mm Hg)	74.3 ± 9.8	79.5 ± 1.5
Na (mM)	143.7 ± 0.4	142.8 ± 3.8
K (mM)	3.0 ± 0.4	3.7 ± 0.4
Cl (mM)	106.2 ± 1.9	112.0 ± 2.2
Ammonium (mM)	0.07 ± 0.01	0.11 ± 0.01[b]
Glutamine (mM)	0.44 ± 0.04	0.30 ± 0.02
Glutamate (mM)	0.04 ± 0.01	0.04 ± 0.01
Alanine (mM)	0.24 ± 0.02	0.25 ± 0.04
Lactate (mM)	1.50 ± 0.24	1.56 ± 0.11
Pyruvate (mM)	0.09 ± 0.01	0.15 ± 0.01
Lactate/pyruvate	17	11
Urea (mg/dl)	24.2 ± 1.5	72.1 ± 8.1[b]

[a] Values are means ± SE (n = 12 control and eight postischemic dogs).
[b] Significant difference ($P < 0.05$) from the values of the control dogs. Student's t test for unpaired data.

Table IV. Effect of Renal Ischemia on Urinary Parameters of the Left Kidney[a]

	Control dogs	Postischemic dogs
Urine flow (ml/min)	2.0 ± 0.4	1.32 ± 0.69
Urine (pH)	7.04 ± 0.21	6.01 ± 0.08
Urine NH_4	16.2 ± 0.67	11.92 ± 0.92
$FEHCO_3$ (%)	2.4 ± 0.5	0.72 ± 0.14[b]
FENa (%)	1.8 ± 0.3	1.6 ± 0.4
FEK (%)	21.7 ± 4.7	19.2 ± 2.1
FECl (%)	1.8 ± 0.2	1.8 ± 0.6
FELac (%)	0.8 ± 0.2	3.3 ± 0.7[b]
FEPyr (%)	1.6 ± 0.5	5.0 ± 0.9[b]
GFR (ml/min)	32.8 ± 3.0	25.9 ± 2.6[b]
Renal blood flow (ml/min)	253 ± 25	185 ± 15[b]

[a] Values are means ± SE (n = 12 control and eight postischemic dogs) and were calculated from the means of four urinary clearance values. Abbreviation used in table: FE, fractional excretion.
[b] Significant difference ($P < 0.05$) from the values of control dogs. Student's t test for unpaired data.

Table V shows the renal utilization or production of critical metabolites in kidneys from control animals and in those submitted to renal ischemia. Data from control animals are similar to those published previously for the dog kidney (7, 8, 11). No significant differences in the renal utilization or production of glutamine, glutamate, α-ketoglutarate, or alanine were observed between normal and ischemic dogs. Although the increase in ammonia production was not significant, the ratio of ammonia production to glutamine utilization increased from 1.6 to 1.95. There was a striking reduction in lactate utilization, as well as a

Table V. Effect of Renal Ischemia on Renal Utilization or Production of Metabolites[a]

	Control dogs	Postischemic dogs
Total NH_4 production	87 ± 20	101 ± 23
Glutamine utilization	−51 ± 9	−63 ± 6
Glutamate production	5.6 ± 2.3	11 ± 5
Alanine production	29 ± 6	36 ± 7
Lactate utilization	−204 ± 38	−101 ± 29[b]
Pyruvate production	5.5 ± 4.3	16 ± 5
Oxygen consumption	−725 ± 165	−601 ± 124

[a] Values are means ± SE (n = 12 control and eight postischemic dogs) in micromoles per 100 ml GFR and were calculated from the means of four urinary clearance values.
[b] Significant difference ($P < 0.05$) from the values of control dogs. Student's t test for unpaired data. + = production; − = utilization of metabolites.

Table VI. Effect of Renal Ischemia on Metabolite Profile in the Renal Cortex[a]

	Control kidney	Postischemic kidney
Glutamine	0.67 ± 0.09	0.38 ± 0.04[b]
Glutamate	3.02 ± 0.39	2.12 ± 0.23[b]
α-Ketoglutarate	0.55 ± 0.29	0.59 ± 0.38
Aspartate	0.98 ± 0.14	1.08 ± 0.12
Lactate	0.81 ± 0.10	0.95 ± 0.17
Pyruvate	0.08 ± 0.02	0.11 ± 0.03
Lactate/pyruvate	9.47	8.21
Alanine	0.95 ± 0.11	0.75 ± 0.13
ATP	1.17 ± 0.03	1.17 ± 0.04
ADP	0.64 ± 0.07	0.52 ± 0.07[b]
AMP	0.17 ± 0.02	0.13 ± 0.02[b]
Inorganic phosphate	1.45 ± 0.25	2.00 ± 0.38[b]
Total nucleotides	1.98 ± 0.09	1.83 ± 0.09[b]

[a] Data are expressed as μmol/g wet wt.
[b] Statistically significant differences ($P < 0.05$; paired Student's t test) between control and postischemic kidneys (n = 8).

small, nonsignificant increase in ammonia production by the postischemic kidneys. Renal oxygen consumption was 232 ± 56 μmol/min in control animals and 151 ± 31 μmol/min in postischemic dogs. However, if oxygen consumption is expressed by 100 ml GFR, the postischemic dogs show a renal oxygen consumption only 17% lower than that of control animals.

Table VI shows the concentration of critical metabolites in the renal cortex of the right kidney in control conditions, and in the left kidney, 48 hr after a 60-min period of renal ischemia. Data from control kidneys are similar to those published previously (7, 8, 11). Postischemic kidneys showed lower tissue concentrations of glutamine and glutamate than did control kidneys, with no significant differences in α-ketoglutarate, aspartate, lactate, pyruvate, or alanine. The lactate to pyruvate ratio did not show significant changes. No differences in ATP concentration were observed between control and postischemic kidneys, but both ADP, AMP, and total nucleotide concentrations were decreased in postischemic kidneys. The ATP to ADP ratio increased from 1.95 ± 0.55 to 2.37 ± 0.56 ($P < 0.05$). Water content was similar in slices taken from postischemic (7.81 ± 0.71%) and control kidneys (7.77 ± 0.54%; P = NS).

Discussion

The acute course of acute renal failure in the present model, reproduced an abbreviated and nonoliguric form of acute renal failure, similar to that observed in volume-expanded humans after an isolated ischemic insult associated with cardiovascular surgery (12). Profound changes in glomerular and tubular function were evident after 24 hr of recovery of renal function, with a marked decrease in urine flow, GFR, and renal blood flow, and an increase in fractional sodium excretion. However, GFR and renal blood flow recovered 48 hr after renal ischemia. This pattern is very similar to that shown by Yagil *et al.* (13) in the conscious, uninephrectomized rats after a 45-min renal ischemia. Our present data, showing that 48 hr after renal ischemia, the ability of the cortical renal cells to obtain energy through the major metabolic routes (lactate and glutamine oxidization measured by lactate and glutamine uptake) and by oxygen extraction is only slightly impaired in relationship with the amount of fluid filtered and reabsorbed, strongly support an excellent recuperation of the main metabolic pathways of the kidney after ischemia.

In the present studies, postischemic dogs showed a 17% reduction in oxygen extraction when corrected by 100 ml GFR, which agrees with the decreased lactate uptake. Calculation of ATP turnover from oxygen consumption (according to Ref. 20) gives about 1390 μmol/min in control and 906 μmol/min in postischemic kidneys. ATP required for Na reabsorption (according to Ref. 11) represents 1100 μmol/min (80% of the ATP turnover) in control and 815 μmol/min (90% of the ATP turnover) in postischemic kidneys. Thus, the relationship between renal ability to extract oxygen, glutamine, and lactate and the renal reabsorption of sodium, previously demonstrated by Vinay *et al.* (14), is maintained in postischemic dogs.

Our data demonstrate nonsignificant differences in renal production of ammonium in both groups of animals. These data agree with those of Lenhart *et al.* (15) showing no differences in renal tissue ammonia 24 hr after renal ischemia in rats. These data are in variance with those of McFarlane-Anderson *et al.* (5) showing an increased ammoniagenesis and renal glutamine uptake by renal slices obtained from rats 36 hr after inducing ARF by glycerol. In addition, renal arteriovenous differences for glutamine concentration were also increased. However, the interpretation of these data

is difficult. Increased glutamine uptake and ammonia production could be explained by an ARF-associated acidosis, and data on acid base equilibrium were not provided in the study of McFarlane-Anderson *et al.* (5).

Our data also reveal that, 2 days after renal ischemia, there is a slight increase in plasma ammonia concentration. This slight hyperammonemia is neither of renal origin, because renal ammonia production is not increased 48 hr after renal ischemia, nor does it seem to be related to the muscle trauma due to the surgery, because surgical procedures were identical in both groups of dogs. Hyperammonemia could perhaps be explained by the accelerated release of amino acid from muscle and the increased hepatic amino acid uptake and catabolism already associated with uremia (16).

The decrease in lactate utilization agrees with recent data from our laboratory demonstrating that when proximal tubules were isolated from dog kidneys 48 hr after a 60-min period of renal ischemia, and were incubated with a mixture of glutamine and lactate (1 m*M* each) (including glutamate and pyruvate, 0.1 m*M* each), in which the main substrates used as fuel from the proximal tubules are present in the same order of concentration as in plasma, tubules from postischemic kidneys extracted significantly less lactate than those from the control kidney (17). The mechanism responsible for the decrease in lactate utilization by the ischemic kidney cannot be easily deduced from the present experiments. One could hypothesize that lactate uptake could be decreased due to an increased lactate concentration in the renal cortex caused by anaerobic glycolysis. However, blood and cortical lactate concentrations were not different in control and postischemic dogs. One possible explanation is the reduction of lactate utilization by thick ascending limbs (TAL) of Henle's loop. Indeed, lactate is the preferred substrate for this nephron segment, and lactate extraction by the kidney is largely determined by the ATP turnover of TAL. If the reduction of lactate uptake was related to a reduction in proximal tubules metabolism, one would have expected a simultaneous reduction of alanine synthesis. This was not the case, alanine production being, in fact, slightly increased. A fall in ATP turnover in TAL would not be accompanied by a change in alanine production (a feature largely due to proximal metabolism). Thus, our observation is compatible with a residual effect of ischemia on TAL. Another possibility is that the activity of the lactate transport system present in the renal tubule is impaired due to the cell damage secondary to ischemic insult. This contention agrees with the increased lactaturia of animals with ARF. In addition, a decrease in renal cortical brush border membrane fluidity has been demonstrated for dogs with acute renal failure (P. Perez-Rodrigo, I. Montañés, and J. M. López-Novoa, unpublished data), and this fact has been related to decreased ionic transport (18).

Cellular levels of ATP are not different in postischemic and control kidneys, in spite of decreased levels of total adenine nucleotides. This latter observation can be explained by the stepwise degradation of ATP to adenosine, which is converted to inosine via adenosine deaminase, thus decreasing the total adenine nucleotide pool (19). In fact, the total adenine nucleotide seems to be a main determinant for cell function recovery (19).

Our data demonstrate that 48 hr after renal ischemia in dogs, the major metabolic routes by which the renal cortex obtains energy, mainly used for sodium reabsorption, seem to be adapted to the decrease in GFR and, thus, to the sodium filtered and reabsorbed by these animals.

Part of this work was presented at the 23rd Annual Meeting of the European Society of Clinical Investigation (Athens, Greece, April 1989) and published as an abstract. This research was supported in part by grants from the Dirección General de Investigación Científica y Técnica (DGICYT PM88-0013-C02). We acknowledge the collaboration of Dr. Carlos Castilla and the staff of the Department of Experimental Surgery and the Services of Clinical Biochemistry and Hematology of the Jiménez Diaz Foundation.

1. Finn WF, Chevalier RL. Recovery from postischemic acute renal failure in the rat. Kidney Int **16**:113–119, 1979.
2. Bonventre JV, Leaf A, Malis CD. Nature of the cellular insult in ischemic acute renal failure. In: Brenner BM, Lazarus JM, Eds. Acute renal Failure, 2nd ed. New York: Churchill-Livingstone, pp4–43, 1988.
3. Preuss HG, Turkantonis A, Hsu CH, Shim PS, Barzyk P, Tio F, Schreiner GE. Early events in various forms of experimental acute tubular necrosis in rats. Lab Invest **32**:286–294, 1975.
4. Preuss HG. Tubular function in experimental acute tubular necrosis in rats. Kidney Int **10**:551–557, 1976.
5. McFarlane-Anderson N, Hortelano P, Alleyne GO. Renal metabolism of glutamine in rats with acute renal failure. Kidney Int **27**:640–642, 1982.
6. Wollemberg A, Ristau O, Schoffa G. Eine einfache technik der extrem schnellen abkülung großerer gewebestucke. Pflugers Arch **270**:399–412, 1960.
7. Rengel MA, Gougoux A, Vinay P, López-Novoa JM. Effect of valproate on intact metabolism in the intact dog. Kidney Int **34**:645–654, 1988.
8. Gougoux A, Vinay P, Cardoso M, Duoplain M, Lemieux G. Immediate adaptation of the dog kidney to acute hypercapnia. Am J Physiol **243**:F227–F234, 1982.
9. Kelman GR. Digital computer subroutine for the conversion of oxygen tension into saturation. J Appl Physiol **21**:1375–1376, 1960.
10. Cohen JJ. High respiratory quotient of dog kidney in vivo. Am J Physiol **199**:560–568, 1960.
11. Halperin ML, Vinay P, Gougoux A, Pichette C, Jungas RL. Regulation of the maximum rate of renal ammoniogenesis in the acidotic dog. Am J Physiol **248**:F607–F605, 1985.
12. Myers BD, Miller DC, Mehigan JT, Olcott C, Golbetz H, Robertson CR, Derby G, Spencer R, Friedman S. Nature of the renal injury following total renal ischemia in man. J Clin Invest **73**:329–341, 1984.

13. Yagil Y, Myers BD, Jamison RL. Course and pathogenesis of postischemic acute renal failure in the rat. Am J Physiol **255**:F257–F264, 1988.
14. Vinay P, Lemieux G, Gougoux A, Halperin M. Regulation of glutamine metabolism in the dog kidney in vivo. Kidney Int **29**:68–79, 1986.
15. Lenhart M, Skapars J, Areas J, Razavy MH, García G, Preuss HG. Role of renal ammonium accumulation on ischemic acute renal failure and acute tubular necrosis in rats. Contrib Nephrol **64**:28–32, 1989.
16. Wesson DE, Mitch WE, Wilmore DW. Nutritional considerations in the treatment of acute renal failure. In: Brenner BM, Lazarus JM, Eds. Acute Renal Failure. Philadelphia: WB Saunders, pp618–642, 1983.
17. Montañes I, Badía A, Rengel MA, López-Farré A, López-Novoa JM. Intermediary metabolism in renal proximal tubules in the recovery phase of the experimental renal ischemia in dogs. Ren Fail **13**:77–86, 1991.
18. Molitoris BA. Membrane fluidity: Measurement and relationship to solute transport. Semin Nephrol **7**:61–71, 1987.
19. Stromski ME, VanVaarde A, Avison MJ, Thulin G, Gaudio KM, Kashgarian M, Shulman RG, Siegel NJ. Metabolic and functional consequences of inhibiting adenosine deaminase during renal ischemia in rats. J Clin Invest **82**:1694–1699, 1988.