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Acute Renal Failure: Structural-Functional Correlation (38210)

CARL J. RICHARDS AND GERALD F. DIBONA

Department of Internal Medicine, University of Iowa College of Medicine and Veterans Administration Hospital, Iowa City, Iowa 52240

Although there are many renal pathologic features common to human cases of oliguric acute renal failure, the correlation between structural renal damage and renal function is poor (1–3). To explain this, investigators have studied the pathophysiology of experimental animal models of oliguric acute renal failure. In both the mercuric chloride (4) and glycerol (5) models in the rat, it has been shown that the major factor resulting in oliguria is a profound decrease in glomerular filtration rate related to afferent glomerular arteriolar vasoconstriction.

While there seems to be no unique pathologic feature which directly reflects this pathophysiologic change, the degree of functional impairment as estimated by nitrogen retention correlates roughly with the extent of certain nonspecific pathologic features, namely renal tubular epithelial cell necrosis and plugging of tubular lumens. In the mercuric chloride model, saline loading resulted in a reduction in the degree of functional impairment which was reflected in slightly less extensive (i.e., less widespread) histologic damage as compared to animals on a regular sodium diet (6).

Saline loading has also been shown to have a protective effect on renal function in the glycerol model of acute renal failure in the rat (7, 8). The purpose of this study was to determine whether the functional protection afforded by saline loading in the glycerol model has its structural correlate in a reduced degree of pathologic change.

Methods. Twelve 175–250 g female Sprague–Dawley rats were divided into 3 dietary groups of four rats each and placed on a low, normal or high sodium diet for 4 weeks before sacrifice. Those on a low sodium diet received Hartroft sodium-deficient test diet (Nutritional Biochemicals Corporation, Cleveland, Ohio) and distilled water *ad libitum*. Rats on a normal sodium diet received Purina lab chow pellets (sodium = 200 mEq/kg, potassium = 185 mEq/kg) and distilled water *ad libitum*. Rats on a high sodium diet received Purina lab chow pellets and 0.9% NaCl *ad libitum*. The animals were kept in individual metabolic cages and allowed free access to food and drinking fluid.

After four weeks the animals were injected with 50% glycerol intramuscularly (10 ml/kg body wt) (5) and sacrificed 24 hr later. Blood was taken from the aorta in these rats and others treated identically for determination of blood urea nitrogen (BUN) by an automated method (9). The kidneys were removed, bisected in the frontal plane and fixed immediately in 10% buffered formalin. They were later embedded in paraffin, sectioned and stained with hematoxylin and eosin. The specimens were coded by a table of random numbers and evaluated independently by 2 observers on 2 occasions each for a total of four readings. The coding of the specimens, the BUN levels and the dietary groupings were unknown to the observers.

As previously reported (6), the sections were judged on a scale of 0 to 4+ with zero representing no involvement and 4+ representing the greatest change seen among all the sections. A 4+ reading did not necessarily mean extreme involvement on an absolute scale but rather the greatest involve-

ment of the groups on a comparative scale. Parameters evaluated included: (1) tubular patency and (2) epithelial cell necrosis. These parameters were judged according to their appearance in the outer and inner cortex and recorded separately.

The 4 readings for each parameter for each section were averaged to give a single value. The coding sequence was broken and the 4 values in each group were averaged for each parameter judged. Data are presented as mean ± standard error. Statistical evaluation was performed using Student's *t*-test for unpaired data between each group.

Results. I. *Functional data.* As noted in Fig. 1, the 3 dietary groups were distinctly separate with respect to their degree of renal functional impairment 24 hr after glycerol injection. There appeared to be a gradation of renal functional impairment in proportion to the amount of sodium in the diet, the high sodium animals having the best function: high sodium group BUN 43 ± 6 mg%; normal sodium group 75 ± 14 mg%; low sodium group 165 ± 21 mg%. Each of these groups differs from the other 2 groups by $P < 0.01$.

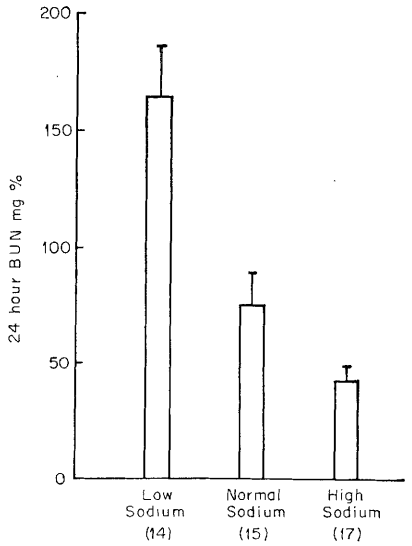


FIG. 1. Blood urea nitrogen concentrations 24 hr after glycerol administration in the 3 dietary groups. Data are shown as the mean ± standard error; figures in parenthesis are the numbers of rats in each dietary group.

II. *Pathologic data.* No glomerular abnormalities were noted in any of three dietary groups.

A. *Outer cortex* (Fig. 2). The incidence of plugged tubules in the outer cortex in the low sodium group was markedly increased in comparison with either the normal sodium or high sodium group ($P < 0.001$). There was also a significant difference between the normal sodium and high sodium group ($P < 0.02$).

Tubular cell necrosis was also inversely proportional to dietary sodium intake with a significant difference between all 3 groups. The difference between high sodium and low sodium animals was marked ($P < 0.001$).

B. *Inner cortex* (Fig. 2). The changes observed in the inner cortex were almost identical to those seen in the outer cortex with a significant difference in the incidence of plugged tubules and epithelial cell necrosis noted between each dietary group ($P < 0.01$).

Figure 3 shows low power views of the outer renal cortex in each of the 3 dietary groups. The extent and severity of renal tubular epithelial cell necrosis and plugging of tubular lumens is greatest in the low dietary sodium group and least in the high dietary sodium group.

Discussion. Glycerol injection in the rat

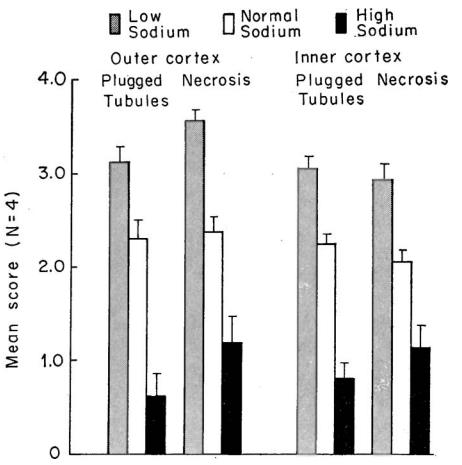
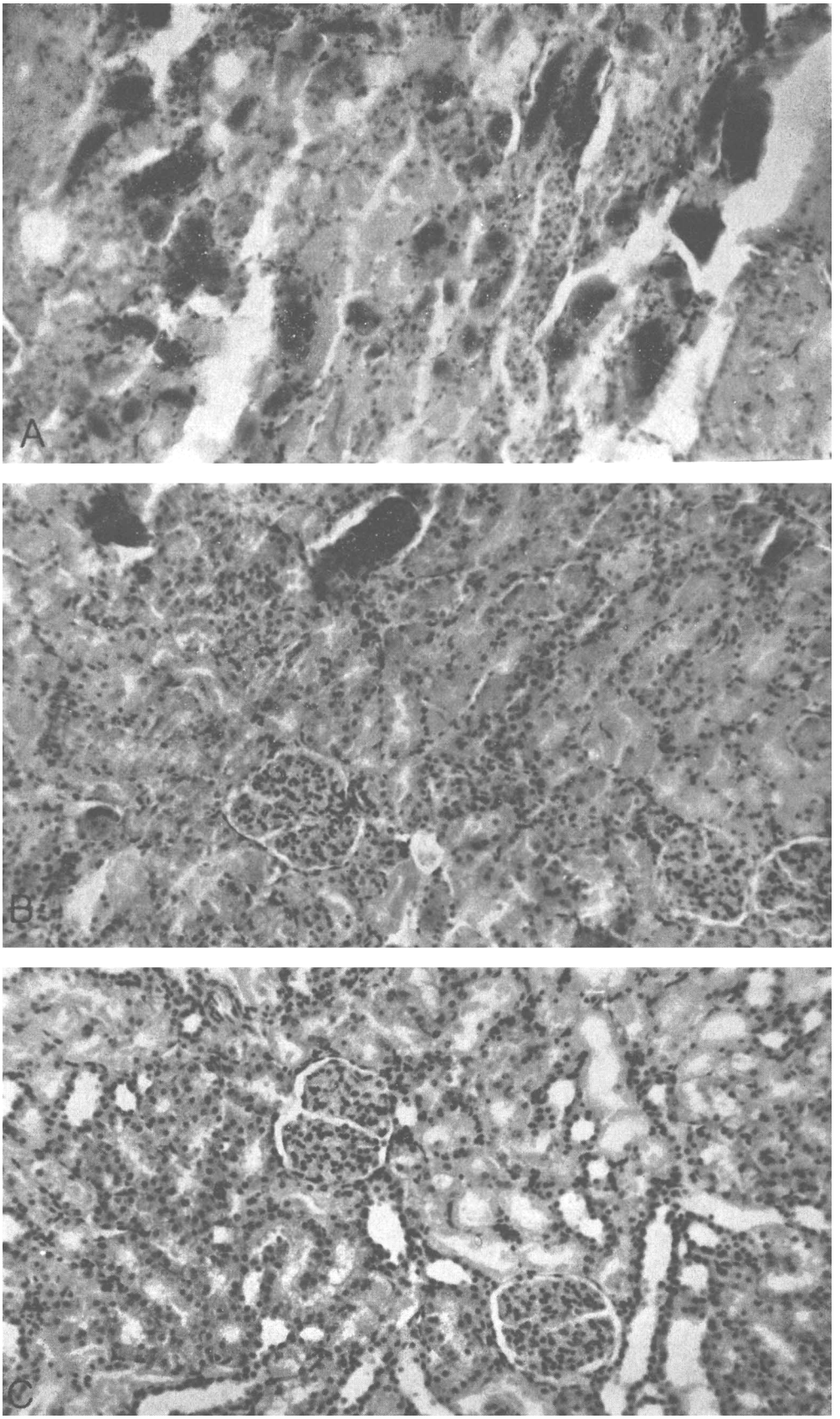


FIG. 2. Renal pathologic scores 24 hr after glycerol administration in the 3 dietary groups. Data are shown as the mean ± standard error.


A
B
C

was originally developed as a model for studying hemolytic transfusion reaction (10). The striking hemoglobinuria which accompanied the intravascular hemolysis led to the appreciation of this as a model for acute renal failure. In 1957 Finckh carefully documented the serial pathologic changes in the rat kidney after subcutaneous injection of glycerol (1.75 ml of 50% glycerol/100 g body wt (11)). The characteristic appearance 24 hr after injection was that of renal tubular epithelial cell necrosis involving the majority of proximal convoluted tubules. The necrotic tubular epithelial cells were eosinophilic and largely devoid of nuclei with many cellular fragments shed into the tubular lumina. Many casts were noted in the loops of Henle and distal convoluted tubules. The animals were allowed a regular diet and water *ad libitum* and no attempt was made to control dietary sodium.

Since then others have used the glycerol model to study the pathophysiology of oliguric acute renal failure (12). Earlier theories suggested that the oliguria might be related to the pathologic lesions noted, either to tubular obstruction from necrotic tubular epithelial cells or leakage of glomerular filtrate out of the damaged tubules into the interstitium. However, detailed micropuncture studies have shown that neither of these factors contribute significantly to the oliguria. The glomerular filtration rate of single surface nephrons is reduced; this, in conjunction with the finding of a low intratubular pressure, indicates a decrease in glomerular capillary pressure. This can occur via afferent arteriolar vasoconstriction which may be mediated via the renin-angiotensin system. Evidence in support of this theory derives from studies showing a protective effect on renal function of renal renin depletion via high sodium intake in this and other experimental models of acute renal failure (7, 8).

Given this interaction between afferent glomerular arteriolar tone, the renin-angiotensin system and sodium intake, one might anticipate a good correlation between renal functional impairment and structural damage in experimental acute renal failure. A prior study from this laboratory (8) showed a good correlation between dietary sodium intake, plasma renin activity and renal functional impairment; animals on a high sodium diet had less functional impairment after glycerol than did those on a low sodium diet. Plasma renin activity was suppressed in the high dietary sodium group and elevated in the low dietary sodium group. The correlation between dietary sodium intake and renal functional impairment is again confirmed by these studies. Furthermore, the extent of renal structural alterations were in parallel with functional impairment, in agreement with similar observations in the mercuric chloride model.

The failure to observe a structural–functional relationship in human cases of acute renal failure probably relates to the multiple etiologies routinely observed in large clinical series. In addition, other variables such as state of sodium and water balance, involvement of related organ systems, nutritional balance and timing of renal biopsy undoubtedly have an unpredictable influence on the results of such a clinical–pathological study.

Summary. This study evaluates the correlation between renal structural alterations and renal functional impairment 24 hr after induction of oliguric acute renal failure in the rat by intramuscular glycerol injection. The major structural alterations were renal tubular epithelial cell necrosis and plugging of tubular lumens; these were graded as to severity in a blind fashion. Renal functional impairment was estimated by blood urea nitrogen (BUN) measurements. The rats were studied under conditions of varied dietary sodium content resulting in different levels of activity of the renin-angiotensin system which is known to be involved in the pathophysiology of this disorder. Renal structural alterations were severe in the low dietary sodium group, modest in the normal dietary sodium group and least in the high dietary sodium group. Renal functional im-

FIG. 3. Low power (100×) photomicrographs of the outer renal cortex in each of the 3 dietary groups: A. low sodium, B. normal sodium, C. high sodium. See text for description.

pairment followed a similar pattern, BUN: low dietary sodium group 165 ± 21 mg%, normal dietary sodium group 75 ± 14 mg%, high dietary sodium group 43 ± 6 mg%. When conditions known to influence the severity of glycerol-induced oliguric acute renal failure were varied, a good correlation was observed between renal structural alterations and renal functional impairment.

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