

AD-A174 113

GLOMERULAR DYNAMIC STUDIES OF THE PATHOGENESIS OF ACUTE
RENAL FAILURE(U) VIRGINIA COMMONWEALTH UNIV RICHMOND
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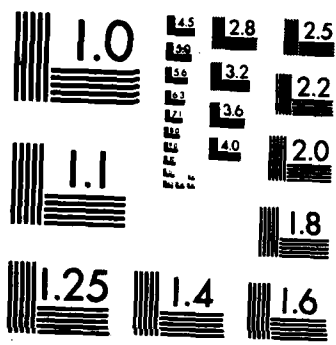
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<p>The aberrations in glomerular dynamic parameters attendant upon mercury induced acute renal failure have been evaluated in this study. As judged by several criteria, glomerular filtration is virtually totally abolished 16-26 hours after mercury injection. The majority of nephrons are totally collapsed and proximal tubule pressures are decidedly subnormal. The fall in glomerular filtration rate is not attributable to tubular obstruction but is directly related to alterations in pre- and postglomerular vascular resistances. The R_A/R_E ratio is markedly increased and probably represents preglomerular vasoconstriction concomitantly with an element of postglomerular vascular relaxation. Studies designed to determine the relative importance of this vascular change in these two vascular segments are continuing.</p> <p>The present results are in preparation for publication.</p>			
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**Glomerular Dynamic Studies of the
Pathogenesis of Acute Renal Failure**

Final Comprehensive Report

Donald E. Oken, M.D.

June 30, 1984

Supported by

**U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012**

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SUMMARY

The aberrations in glomerular dynamic parameters attendant upon mercury induced acute renal failure have been evaluated in this study. As judged by several criteria, glomerular filtration is virtually totally abolished 16-26 hours after mercury injection. The majority of nephrons are totally collapsed and proximal tubule pressures are decidedly subnormal. The fall in glomerular filtration rate is not attributable to tubular obstruction but is directly related to alterations in pre- and postglomerular vascular resistances. The R_A/R_E ratio is markedly increased and probably represents preglomerular vasoconstriction concomitantly with an element of postglomerular vascular relaxation. Studies designed to determine the relative importance of this vascular change in these two vascular segments are continuing.

The present results are in preparation for publication.

INTRODUCTION

This proposal was developed to examine the abnormalities in glomerular dynamics responsible for the development of failed filtration in experimental models of acute renal failure. As given in the initial proposal, the work was estimated to occupy a three-year period. The report concerns the research accomplished in the first year of support.

Although there have been many studies of glomerular dynamics in various physiologic and pathologic settings in the past, we could find no reports in which the various methodologies have been validated or the effect of internephron heterogeneity established. The degree of internephron and interanimal heterogeneity of each of the parameters measured in studies of glomerular dynamics in normal rats was examined here as a necessary requisite to subsequent studies in acute renal failure. In this aspect of the study, nephron glomerular filtration rate (SNGFR), glomerular capillary (P_g) Bowman's space (P_{BS}) and star vessel (P_{star}) hydrostatic pressures were measured along with nephron filtration fraction (SNFF) in quintuplicate in eleven normal Munich-Wistar rats. No correlation was found between the mean SNGFR values of the 11 animals and P_g , P_{star} or P_{BS} ($p > 0.2$ or higher). P_g for the individual rats did not correlate with P_{BS} or P_{star} ($p > 0.4$). The intraanimal coefficients of variation (SD/mean) for SNFF and SNGFR averaged $0.188 \pm SEM 0.013$ and 0.119 ± 0.010 , respectively ($n = 11$). P_g , P_{BS} and P_{star} showed rather less intra-animal variability, their coefficients of variation averaging $0.069 \pm SEM 0.007$, 0.087 ± 0.008 and 0.091 ± 0.006 , respectively. The interanimal coefficients of variation for these same parameters were: P_g 0.072; P_{BS} , 0.051; P_{star} , 0.054; SNGFR, 0.072; and SNFF 0.111, values which, with the exception of P_g , are significantly lower than the corresponding intra-animal coefficients of variation ($p < 0.001$). The intra- and interanimal coefficients of variation in both P_g , $COPE$ were not significantly different ($p > 0.2$).

As found in the earlier study of Arendshorst and Gottschalk, a large residual net filtration pressure left the animals in the present series far from filtration pressure equilibrium. The mean ultrafiltration coefficient was found to be notably lower than that in many (e.g. 2) but not all reports in the literature. Under this circumstance, glomerular plasma flow, rendering decreased plasma flow only a potential secondary role in the genesis of filtration failure, changes in the ultrafiltration coefficient and/or individual vascular resistances thus being essential to the development of near total cessation of filtration experimental renal failure (see below). Standard statistical equations were adapted to permit estimates of variances of the derived parameters of glomerular dynamics taking into account both the intra- and interanimal variances of the constituent measured parameters, information essential to the proper interpretation of glomerular dynamic alterations in the developmental phases of acute renal failure. A manuscript

describing these experiments will be submitted to Kidney International.

STUDIES OF EXPERIMENTAL ACUTE RENAL FAILURE

This study relates to the glomerular dynamic changes to be found in acute renal failure produced by subcutaneous injection of nephrotoxic doses (9 mg/kg B.W.) of mercuric chloride. Studies were performed 16-26 hours after mercury injection. The animals were anesthetized with sodium pentobarbital and the kidney was exposed for micropuncture in standard fashion. Cannulae were placed for arterial pressure measurement and the intravenous infusion of fluids prior to placement of a tracheostomy tube. The left kidney was isolated and embedded in agarose to minimize respiratory and pulsatile movement. As viewed through the dissecting microscope, the kidney surface was surveyed to determine the degree of tubular filling, the proportion totally collapsed tubules, the size of "star" vessels and the rapidity of blood flow in peritubular capillaries. The presence of tubular flow was determined qualitatively from the rate of progression of small oil droplets injected into proximal tubules. Nephron filtration rate was determined directly by quantitative fluid collection from the glomerulo-tubular junction. (SNGFR estimated in this way obviated the possibility that SNGFR values might be underestimated by tubular inulin leakage if measured in the customary fashion.) Nephron filtration fraction was estimated from the concentration of ^{125}I albumin in star vessel and systemic blood according to the equation $\text{SNFF} = (1 - I_A/I_E)$. Pressures in glomerular capillaries, "star" vessels, and in Bowman's space were measured by the Landis and servo-null methods in different series of rats.

Nephron filtration rate, estimated by direct quantitative collection of fluid at the glomerulo-tubular junction, was unmeasurably low in all but three of 79 nephrons studied in 23 rats. Nephron filtration fraction derived from 57 star vessels of 17 rats was $0.102 \pm \text{SEM } 0.05$, a value significantly greater than zero ($p < 0.01$) but less than control (0.29 ± 0.03 , $N = 55$).

Lissamine green injected iv as a bolus normally appears with fresh filtrate in Bowman's space and is seen to flow rapidly down the tubule. Injected in this fashion into rats with mercuric chloride induced acute renal failure, very faint staining of filtrate was seen in some glomeruli but this coloration disappeared within 5-20 seconds without ever passing the glomerulo-tubular junction into proximal tubules. Lissamine green did not appear at all in the majority of glomeruli. Injected in isotonic saline directly into Bowman's space until fluid just appeared in the most proximal segment of the proximal tubule, lissamine green became progressively more pale over a 2-4 minute period. In no instance, however, was it propelled down the tubule by the formation of new filtrate. After luminal occlusion with heavy mineral oil, fluid (i.e. fresh filtrate)

could be obtained from the glomerulo-tubular junction (GTJ) in measurable quantities (i.e. 5 nl or more) in only one of 44 attempts in 13 rats over a 3-5 minute period. (Normal fluid delivery rate at the GTJ is $28 \pm \text{SEM } 1.0$ nl/min). This value is indistinguishable from the SNGFR of 29.7 ± 0.6 nl/min) measured with ^{14}C inulin by conventional micropuncture methods ($p > 0.4$), $N = 55$). This, as manifest by failure of lissamine green to appear in Bowman's space in reasonable concentration after iv injection, failure of lissamine green injected directly into Bowman's space to enter the glomerulo-tubular junction and the absence of fluid entry into the tubular system as documented by direct collections from the glomerulo-tubular junction, glomerular filtration was virtually absent in virtually all surface nephrons. Further evidence for the near total cessation of filtration was obtained by injecting small droplets of low viscosity, stained silicone oil into 103 randomly selected proximal tubular segments of 23 animals. Normally, this injectate flows briskly along the proximal tubule and disappears from view almost instantaneously. In every instance, droplets injected into proximal tubules of rats with mercury poisoning remained totally stationary for up to 30 minutes with no tendency to forward propulsion.

Bowman's space and proximal tubule pressures averaged 9.7 ± 1.4 mmHg (control $11.6 \pm \text{SEM } 0.18$ mmHg). These values were obtained from the small minority of nephrons that contained sufficient fluid to permit pressure measurements. Pressure could not be measured accurately in the remaining nephrons but, since fluid could be injected into the proximal tubule of collapsed nephrons at hydrostatic pressures of 5-9 mmHg, elevated intratubular pressure cannot be incriminated as a major contributor to filtration failure in this model of ARF. With a mean glomerular capillary pressure of 25.6 ± 2.1 mmHg (control 49.2 ± 3.6 mmHg) and a mean colloid osmotic pressure in systemic arterial plasma of 11.4 ± 1.6 mmHg (versus control 15.6 ± 1.4 mmHg), $p < 0.001$), mean net afferent filtration pressure was thus 4.5 mmHg, a figure far lower than the value of 21.6 mmHg found in control rats ($p < 0.001$). Mean star vessel pressure was 8.4 ± 1.1 mmHg (control 12.6 ± 0.9 mmHg). Estimates of pre- (R_A) and postglomerular (R_E) require values for glomerular blood flow which cannot be determined with conventional techniques in the absence of glomerular filtration. Afferent and efferent blood flows, however, are equal when glomerular filtration is absent. Accordingly, when expressed as a ratio, R_A/R_E , the relative magnitudes of R_A and R_E can be assessed from the equation: $R_A/R_E = (\text{MAP} - P_g)/(P_g - P_{\text{star}})$. In the present study, the R_A/R_E ratio of mercury injected rats was found to be 4.5, a figure considerably higher than the control value of 1.8. Very marked heterogeneity in individual values was found, however, necessitating the extension of this study to include more data. In ongoing studies, moreover, renal cortical blood flow is being measured in each rat employing implanted cortical platinum electrodes and the hydrogen washout technique to facilitate interpretation of the R_A/R_E ratios by network modeling.

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