The Pattern of Recovery of Renal Function Following Renal Artery Occlusion in the Dog

By SYDNEY M. FRIEDMAN, M.D., R. L. JOHNSON, M.D., AND CONSTANCE L. FRIEDMAN, PH.D.

The pattern of recovery of renal function following two hours of complete ischemia was studied in a series of dogs. A marked functional ischemia persisted for several hours after release of the clamp, but restoration of blood flow was substantially complete in 24 hours. Other renal functions returned slowly over a period of weeks, reflecting the rate of repair of damaged tubules. Two important phases of recovery are thus to be considered: (a) a brief but significant period of continuing ischemia immediately following the trauma, and (b) a period of slow repair of those nephrons damaged but not destroyed in the first phase of the insult.

The confusion surrounding the nature of the acute nephropathies associated with traumatic and toxic injuries has recently been considerably dispelled by the elegant work of Oliver and his colleagues.1 As a result of these studies, it is now understood that interruption of the arterial blood supply to the kidney either directly by clamping of the renal artery, or indirectly by the induction of extreme systemic hypotension, provides the investigator with a valid experimental tool for the study of traumatic renal injury. The demonstration of the validity of such procedures seemed to us to clear the way for a direct experimental attack on some therapeutic problems. As a necessary prelude to such studies it is essential to know the pattern of response to acute renal injury in the untreated animal. Clamping the renal artery seemed to be an acceptable procedure, and the dog the animal of choice.

The pattern of recovery of glomerular and tubular function following two hours' occlusion of the renal artery had already been studied in three dogs by Roof and colleagues.2 In our work on the subject of acute renal failure in the rat3,4 we had been impressed with the variability of response in different animals and with the necessity for use of large groups. The dog is no less variable in its responses than the rat. Accordingly, the present study was undertaken in an effort to provide a sufficient body of basic data for the study of experimental therapy which was to follow. Further, Roof and her co-workers2 had obtained renal vein blood samples for the correction of flow data in only two of their dogs. This essential procedure was followed in all of our dogs and, as will be shown, proved essential for the interpretation of the functional studies.

METHODS

Female mongrel dogs were used throughout. The following procedures formed the general basis for this study.

1. Right nephrectomy and left renal subcutaneous transplantation were performed followed by a recovery period of at least three weeks. Renal transplantation followed the method of Page and Corcoran6 and of Rhoads.0

2. The renal artery was clamped for two hours using a rubber covered sernrefine; the kidney was completely exposed for this procedure.

3. Data were obtained concerning renal function (a) in the uninephrectomized state with the kidney explanted, (b) within three to four hours of removal of the clamp, (c) 24 hours after clamping, (d) five to eight days after clamping, and (e) two weeks and later after clamping.

4. Renal function was studied using standard technics for creatinine and para-aminohippurate as described by Selkurt.7 Three accurately timed periods were used for each datum. When extraction fractions were to be determined, clearance periods were carried out in the usual manner except that simultaneous midpoint renal vein and femoral artery samples were drawn into heparinized syringes. These were immediately centrifuged, but since no facilities were available for refrigerated centrifuging, the error of this omission8 is present in our para-aminohippurate data as given.

Because parts of the procedure required the use of anesthesia, Nembutal (20 to 30 mg. per kilo-
gram intravenously) was used for all determinations in order to secure uniformity. All data are referred to surface area using the formula of Cowgill and Drabkin. Blood pressure was obtained by direct femoral artery puncture with an 18 gauge needle recording through a Sanborn electromanometer.

**Observations**

All the findings are presented as group data in table 1.

**Renal Function in Uninephrectomized Dogs.** Renal function was studied in all dogs prior to clamping the renal artery. Uninephrectomy followed by subcutaneous explantation of the remaining kidney had been carried out at least three weeks prior to these control determinations.

The removal of one kidney followed by a period sufficient to allow some compensation by the remaining kidney produced the expected result. Filtration rate ($C_{cr}$), renal plasma flow ($C_{PAH}$) and functioning tubular mass ($Tm_{PAH}$) were all reduced to about 75 per cent of their prenephrectomy value. At least part of the functional compensation was referable to a relatively large blood flow to each unit of functioning tissue; that is, a relative hyperemia of the kidney.

In seven of the dogs used, simultaneous sampling of renal venous and femoral arterial blood was carried out. It was therefore possible to determine renal plasma flow ($RPF_{cr}$) from the extraction of creatinine ($RPF_{cr}$) and, independently, from the extraction of para-aminohippurate ($RPF_{PAH}$).

**Renal Function Three to Four Hours after Clamping the Renal Artery.** Clearance and extraction studies were carried out in four dogs three to four hours after removal of the clamp. In all cases the renal artery was observed to be completely patent and functional immediately after release of the clamp. At this time the clearance of creatinine was at a negligible level. This is not to say, however, that the filtration rate was actually depressed to this marked degree. There was ample evidence to indicate marked tubular damage and it is impossible to estimate the amount of creatinine diffusing back to the blood through injured tubules.

The clearance of para-aminohippurate was likewise negligible and undoubtedly reflected the fact that the tubular mechanisms for transferring para-aminohippurate were only operating at about 5 per cent efficiency, judging by the value for para-aminohippurate extraction. With $C_{cr}$ and $C_{PAH}$ thus complicated by tubular damage, the derived filtration fraction is

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>3 wks. postnephrect.</th>
<th>3-4 hrs.</th>
<th>24 hrs.</th>
<th>5-8 days</th>
<th>2 wks. or more</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Av. S.E. No. of dogs</td>
<td>Av. S.E. No. of dogs</td>
<td>Av. S.E. No. of dogs</td>
<td>Av. S.E. No. of dogs</td>
<td>1 at 1 wk. 1 at 1 mo. 1 at 3 mos.</td>
</tr>
<tr>
<td>$C_{cr}$ cc./min./M²</td>
<td>59.0 17.5 9</td>
<td>1.9 0.15 4</td>
<td>8.6 3.8 7</td>
<td>13.5 8.3 6</td>
<td>12.7 61.0 63.0</td>
</tr>
<tr>
<td>$C_{PAH}$ cc./min./M²</td>
<td>182.0 40.0 9</td>
<td>5.2 4.2 4</td>
<td>27.9 13.7 7</td>
<td>44.7 18.9 6</td>
<td>62.5 163.0 174.0</td>
</tr>
<tr>
<td>FF as %</td>
<td>32.0 2.3 9</td>
<td>47.0 5.3 4</td>
<td>39.8 4.6 7</td>
<td>20.9 5.1 6</td>
<td>20.3 37.5 36.6</td>
</tr>
<tr>
<td>$Tm_{PAH}$ mg./min./M²</td>
<td>13.8 1.0 9</td>
<td>1.4 0.5 6</td>
<td>3.17 1.1 5</td>
<td>3.23 5.58 6.0</td>
<td></td>
</tr>
<tr>
<td>$RPF_{cr}$ cc./min./M²</td>
<td>254.0 28.7 7</td>
<td>27.0 24.9 4</td>
<td>93.7 58.0 7</td>
<td>96.0 40.4 6</td>
<td>96.0 82.0</td>
</tr>
<tr>
<td>$RPF_{PAH}$ cc./min./M²</td>
<td>240.6 12.1 6</td>
<td>36.631.5 4</td>
<td>147.7 37.0 7</td>
<td>157.0 19.8 6</td>
<td>102.0 213.0 207.0</td>
</tr>
<tr>
<td>$E_{PAH}$ %</td>
<td>65.9 3.7 6</td>
<td>4.8 2.6 4</td>
<td>14.2 6.5 7</td>
<td>26.3 7.8 6</td>
<td>32.7 79.0 84.9</td>
</tr>
</tbody>
</table>

S.E. = \( \sqrt{\frac{\sum x^2 - [n(\bar{x})^2]}{n(n - 1)}} \)
similarly difficult to interpret as an absolute value.

Renal plasma flows estimated from para-aminohippurate and creatinine extractions did not agree closely. Nor would they be expected to, for at these low levels of extraction, technical errors in sampling time and small errors in the analytic determination assume relatively large proportions. The two sets of data under discussion, however, do agree in indicating a very low renal plasma flow of the approximate order of 20 per cent of normal. When it is recalled that the values tabulated are the maximal ones obtained in the period extending up to four hours after clamping, and in view of the gross patency of the renal artery, the conclusion seems unavoidable that there is a continuing ischemia extending several hours after clamping. Since this ischemia largely disappears over the next 12 to 18 hours, it would seem that a functional ischemia supersedes the mechanical ischemia of the clamp.

Renal Function 24 Hours after Clamping the Renal Artery. Clearance and extraction studies were carried out in seven dogs 24 hours after release of the clamp. At this time Cr and CrPAH were both considerably improved as compared with the immediate postclamping period. Both were, however, still extremely depressed at about the 10 per cent level of normal function. Similarly, TmPAH was about 10 per cent of the average preclamping value.

Renal plasma flow showed a remarkable improvement, so that at this stage the continuing ischemia noted after release of the clamp had probably in large measure disappeared. There was still, however, a marked discrepancy between RPFcr and RPFPAH with the latter value being considerably higher. A possible explanation for this might be that para-aminohippurate is vicariously cleared from the extracellular fluid by those nephrons which are still functional, a concept developed by Corcoran, Taylor and Page. If this explanation is correct, then RPFcr more truly represents the plasma flow.

Renal Function Five to Eight Days after Clamping the Renal Artery. Clearance and extraction studies were carried out one week after release of the clamp in five dogs and five days after release in one dog. Although Cr and CrPAH were somewhat improved over the previous period, both values were still markedly depressed, this time at about the twenty per cent level of normal function. The amount of functioning tubular tissue showed a marked increase, although it was still far below normal.

Renal plasma flow showed no change from that observed 24 hours after clamping, indicating that a maximal value had been reached at this earlier stage. There was still a marked discrepancy between RPFPAH and RPFcr of the same degree as noted previously.

Renal Function Two Weeks to Three Months after Clamping the Renal Artery. Clearance and extraction studies were carried out two weeks, one month and three months after clamping, one dog being used for each of these periods.

Dog 1, studied two weeks after clamping, showed a still further improvement in all renal functions. The degree of unrecovered function was still indicated by the lack of correspondence between CrPAH and RPFPAH owing to the poor extraction of para-aminohippurate at approximately 40 per cent of normal.

Dog 11, studied one month after clamping, by contrast showed values for Cr, CrPAH and filtration fraction which all fall within the normal range. RPFPAH at this stage agreed closely with CrPAH, the difference between them being referable to the 70 per cent extraction of para-aminohippurate, a value which is in the lower range of normal. It is noteworthy that TmPAH was almost identical with the preoperative level in this same dog. Indeed, judging by the preclamping data for this animal, renal function had now been completely restored.

Dog 4, studied three months after clamping, had likewise recovered, although TmPAH had not returned to the preclamping level, reflecting the destructive obliteration of some tubules.

DISCUSSION

Several interesting facts which we have not hitherto seen reported emerge from these data. In the first place, all renal functions with the exception of renal plasma flow improve in parallel fashion after damage due to renal is-
chemia. The recovery rate in general is slow in the first two weeks. If all functions increase in parallel, it seems unreasonable to suppose that multiple injuries are involved. Functional and anatomic destruction of the tubule is the only injury which one might postulate. Such an injury, which we know to exist anatomical, explains in the first instance the low TmPAH and the low E_PAH. Tm_PAH cannot return to the original normal level since some nephrons are undoubtedly completely destroyed. E_PAH, by contrast, returns to normal, for it represents only the ability of functioning nephrons to transfer para-aminohippurate. According to this view, C_PAH is low when E_PAH is low. Similarly, Cer is depressed in parallel with E_PAH, since the damaged tubules probably permit the back transfer of creatinine to the tubular perfusate.

The second interesting finding is that the recovery rate for renal plasma flow is entirely different from the others. It is characterized by a rapid restoration in the first day after clamping and only minor improvement thereafter. In part, this result is expected, for if the vascular channels are intact and patent, renal plasma flow should at once return to normal upon removal of the clamp. Most interesting, however, is the fact that renal plasma flow does not recover immediately after removal of the clamp. This can only mean that, while the vessels are restored to almost full patency some hours later, and hence must be anatomically intact, they remain partially shut down immediately after the clamp is removed. We conclude, therefore, that in addition to the clamping ischemia, a functional ischemia is present. This ischemia extends the damage caused by the clamp.

Throughout the data for renal plasma flow after clamping, there is a discrepancy between RPF, and RPF_PAH with the latter being consistently greater. Further, while RPF, attains a stable value 24 hours after removal of the clamp, a value which remains substantially unchanged in all subsequent periods, RPF_PAH continues to increase moderately at each succeeding interval. The explanation of vicarious clearance of para-aminohippurate from interstitial fluid by undamaged nephrons appears very likely. This would explain the higher value of RPF_PAH obtained 24 hours after clamp-
ing, and further, as partially damaged tubules slowly recovered, the vicarious clearance would be augmented, with still higher values of RPF_PAH being obtained. That there are partially damaged tubules which do recover with time seems evident both from the observed increase in Tm_PAH and in E_PAH.

If this explanation for the values of renal plasma flow is accepted, however, it implies that RPF, more truly represents plasma flow through the kidney. If so, one must conclude that plasma flow through a previously clamped kidney does not exceed approximately one-third of the preclamping value. Direct proof for such an assertion would be mandatory.

Regardless of interpretation, it seems clear that a functional ischemia supersedes the clamping ischemia. Such an ischemia undoubtedly contributes to further structural damage of the kidney. Accordingly, it seems reasonable to suggest as a working hypothesis that therapy of acute nephropathy associated with traumatic and toxic injury might well be divided into two phases. In the first phase, attempts to improve the inadequate renal circulation as early as possible would be made. In the second phase, attempts would be made to increase the rate at which partially damaged nephrons return to functional integrity. Further work is in progress to test the potential usefulness of therapeutic agents in these two phases.

SUMMARY

Data are presented showing the rate of recovery of renal function in the dog following two hours of complete renal ischemia. Renal function is depressed to negligible levels for almost 24 hours, then slowly improves over the following two weeks. The functional depression is apparently entirely referable to tubular damage.

The tubular damage which follows renal ischemia is partly reversible since, apparently, some nephrons are not completely disrupted.

The damage referable to renal ischemia of mechanical origin is aggravated by a functional ischemia which seems to continue for several hours after release of the clamp.

It is suggested that therapy might be aimed at alleviating the immediate post-traumatic
functional ischemia in the early phase and accelerating the rate of tissue repair in the late phases of treatment.

REFERENCES


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