PATHOPHYSIOLOGY OF THE KIDNEY IN ACUTE TUBULAR NECROSIS, WITH SPECIAL REFERENCE TO THE RENAL BLOOD FLOW

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Acute tubular necrosis is a reaction pattern of the kidney to certain types of injury. Three broad groups can be distinguished:

(*i*) *Ischaemic*, when the kidney has been ischaemic for sufficiently long to cause damage to tubule cells from anoxia—this occurs after clamping of the renal arteries, in severe oligaemic shock, or reflexly, as in concealed accidental haemorrhage of pregnancy.

(*ii*) *Toxic*, as in mercury, phenol or carbon tetrachloride poisoning, and

(*iii*) *A combined group*, when there is renal ischaemia plus the presence of certain less violent nephrotoxins. Often either factor alone is insufficient to cause damage. This occurs following haemolytic transfusion reactions, crush syndrome, abortions, etc. Haemolytic reactions occurring in 'cold' transfusions seldom cause trouble, but when they occur in shocked patients, renal damage is usual.

Course

The course of the illness is remarkably constant and can be divided into 4 phases:

Onset phase, when the patient is shocked or when a nephrotoxin is circulating.

Oliguric or anuric phase, which may last from a few hours up to 40 or even more days in severe cases.

Early diuretic phase, which is characterized by the passing of large volumes of urine with an almost constant composition approximating to that of half-isotonic extracellular fluid. This phase lasts for, on the average, as many days as the period of oliguria or anuria which precedes it.

Recovery phase. Provided that the patient has no condition other than acute tubular necrosis, almost complete recovery can be expected if he is kept alive during the earlier phases by avoidance of infection and by meticulous control of water and electrolyte balance.

FUNCTIONAL ORGANIZATION OF THE KIDNEY

Tubule Function

There is no doubt that there is tubular damage in both the oliguric and early diuretic phases. This has been shown histologically[1] and on testing of function.[2,3] There is some evidence that osmotic diuresis plays a role in the genesis of the polyuria in the early diuretic phase.[4]

Renal Blood Flow

A. Earliest reports. There is little doubt that during the onset phase, at least in those cases not caused by nephrotoxins, the renal blood flow is greatly reduced. The situation in the oliguric and early diuretic phases is more controversial and more interesting.

The earliest reports of renal blood flow determinations in patients with acute tubular necrosis were obtained by Sirota[5] and Bull, Joekes and Lowe[2] using the Fick method. The principle of the method was first described and placed on a sound theoretical basis by Wolf.[6] It is best described in algebraic terms. The following symbols are used:

A = Arterial inflow into the kidney in ml./min.
R = Renal venous outflow in ml./min.
V = Urine volume in ml./min.
L = Renal lymph volume in ml./min.
S_1 = Volume of the kidney at the start of a study in ml.
S_2 = Volume of the kidney at the end of a study in ml.
a = Arterial concentration of a substance in mg./ml.
r = Renal venous concentration of the same substance in mg./ml.
u = Urine concentration of the same substance in mg./ml.
l = Lymph concentration of the same substance in mg./ml.
s_1 = Concentration of the same substance in the kidney in mg./ml. at the start of a study.
s_2 = The same at the end of a study.
t = Time of study in minutes.

If we follow Wolf[6] and neglect lymph and also assume that the volume of the kidney and the concentration of the substance in it remain unchanged during a period of observation, then:

The volume of fluid entering the kidney per minute is equal to the volume leaving it per minute via the renal vein and as urine, i.e.

$$A = R + V$$

and, the quantity of any substance entering and leaving the kidney per minute is also equal

$$aA = uV + rR$$

but, since $A = (R+V)$ we may substitute

$$a(R+V) = uV + rR$$

from which we may derive

$$R = \frac{V(u-a)}{a-r}$$

Using similar arguments but different substitutions one may derive

$$A = \frac{V(u-r)}{a-r}$$

which is Wolf's formula[6] for determining renal arterial inflow.

Therefore, if we know V, the urine volume per minute, and u, a and r, the concentrations of the cleared substance in urine, arterial blood and venous blood, we may obtain an estimate of either the arterial inflow or the renal venous outflow.

Using this approach Sirota[5] and Bull, Joekes and Lowe[2] obtained all the necessary specimens in a number of patients at different stages of the illness and reported that during the oliguric and early diuretic phases the blood flow was extremely low—sometimes below 5% of normal. At the time there seemed to be no reason to doubt their validity, and Oliver[1] and myself[4] attempted syntheses of available pathological and functional evidence. In both, the gross reduction in renal blood flow played a central role in accounting for the severe oliguria because it was assumed that in the face of such a reduction in blood flow, glomerular filtration would be virtually at a standstill.

B. Later work. There was a gap in our knowledge of the blood flow in anuric patients because the Fick method required the collection of timed specimens of urine. In 1958, Munck[7] sought to fill this gap by using a different technique for measuring blood flow—a modification of the Kety-Schmidt[8] method, which did not require urine. In this method, the patient is suddenly made to breathe a foreign gas which dissolves in blood and tissues. For the next few minutes frequent arterial and renal venous blood samples are obtained and analysed for their content of the foreign gas. The concentration in arterial blood rises sharply, but the renal venous blood concentration lags behind because of the gas' passing into solution in the renal tissues. After some minutes an equilibrium is reached with the concentration in renal venous blood approximating to that in arterial blood and with the same concentration in the kidney. From the known solubility of the gas in renal tissue and from the arterio-venous gas differences integrated across the period of time during which there is a disequilibrium, it is possible to calculate the blood flow. This estimate of blood flow is, however, expressed differently from that of the Fick method. In the Kety-Schmidt method the figure is as ml. blood flow per 100 G of kidney, whereas in the Fick method it is as ml. blood flow per two kidneys per minute.

Munck's results[7] on patients with anuria and also in others with oliguria or in the early diuretic phase were quite different from those with the Fick technique. He found flows which were of the order of half normal instead of 5 - 20% of normal.

At the time it seemed to me that by far the most likely explanation of the discrepant results was that the kidneys were patchily perfused, some parts having a normal or only slightly reduced blood flow, while others were hardly perfused at all.

Picture a kidney perfused by two separate arteries of equal size. If we were to tie off one of these and then estimate the blood flow by the two methods, we would find with the Fick method a halving of blood flow but with the Kety-Schmidt technique a normal flow, because each 100 G of perfused kidney would have a normal flow. I therefore pictured the kidney as being largely without appreciable circulation except for small parts which were normally perfused. There was nothing I could see in the histological picture to confound this suggestion, and indeed stagnant circulation in some parts can be inferred from the appearance in the veins in some areas of an abnormally large number of nucleated cells.[9]

C. Most recent work. The position remained like this for some years except that Munck's findings[7] were confirmed by others.[10, 11] Then about 3 - 4 years ago Bálint and his colleagues,[12-15] working in Budapest on dogs in the oliguric phase of ischaemic tubular necrosis, applied yet another method to the estimation of blood flow. This was a much more direct one. They cannulated the renal vein and let the outflow from the kidney through tubing to the jugular vein as shown in Fig. 1.

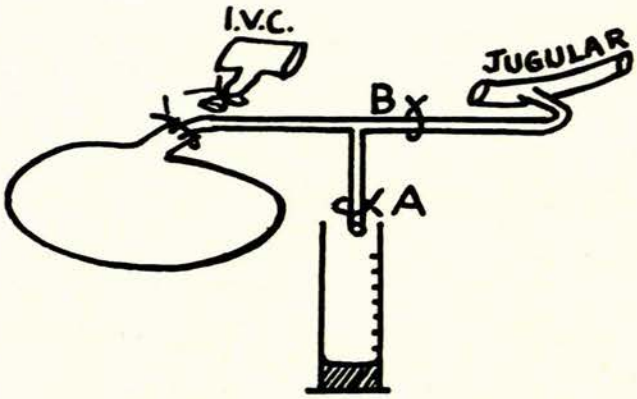

Fig. 1. See text.

By closing the tubing at B and opening A the blood could be caused to flow for a timed period into a measuring cylinder. At first glance it would seem that this method must give the correct answer, and the answer that Bálint *et al.* obtained agreed with Munck's and not with our Fick determinations.

The problem now was that three separate methods, each in itself seemingly theoretically sound, gave two different results. At this stage, Dr. Panos Metaxas was working with me and we decided to study the matter both theoretically and practically. We first examined the original clearance method and immediately realized that we had neglected to consider renal lymph flow. We rewrote the formula for determining blood flow to include a term for lymph.

$$A = V + R + L$$

$$\therefore \quad a(V+R+L) = uV + rR + lL$$

$$\therefore \quad R = \frac{V(u-a)}{a-r} + \frac{L(l-a)}{a-r}$$

It was conceivable that the term added to the old formula, namely, $\frac{L(l-a)}{a-r}$ might be large enough to account for the lower values we had obtained. We accordingly obtained renal lymph in dogs as well as the other values necessary, using two different methods. In the first, we exposed the kidney via the peritoneum, carefully clamping and tying the peritoneal surface and all areolar tissue as we proceeded. In so doing we obstructed most of the lymphatic outflow from the kidney, and the cortical lymphatics stood out clearly. The pedicle was similarly cleared leaving one major lymphatic, and from the cortical and hilar lymphatics we obtained our specimens.

In the second method we cut all the draining lymphatics from both the surface and the hilum and then allowed the lymph oozing from them to collect into a bowl which we placed under the kidney. In this method, of course, we could not examine hilar and cortical lymph separately, but the advantage was that we were not dealing with a kidney whose lymphatics were partly obstructed. In this way we were able to obtain estimates of the potential errors that might arise from neglect of lymph.[16] They proved to be small and certainly insufficient to account for the discrepancy between our results and Munck's.

Fortunately at about this time Professor Bálint spent a few days in our department and I later visited his. We had very fruitful discussions, and each followed the problem further. It immediately became evident that the direct method as carried out by Bálint was not as straightforward as it seemed at first sight. If the side-arm leading to the measuring cylinder is lowered, a siphoning effect occurs and can cause more blood than is actually flowing normally, to enter the cylinder. We made measurements with the tube lowered and also when it was held at a level to maintain the same pressure as was present when blood was flowing along the tube to the jugular vein. We found that the position of the tube to the measuring cylinder affected the measurement significantly, and in fact readings which were up to 50% too high could be obtained. This, however, was still insufficient to account for the discrepancy although it went some way towards explaining it.

Although we did not obtain quantitative measurements to prove it, we convinced ourselves that yet another possible error could arise in the direct method. The addition of a long, relatively indistensible tube between the renal vein and the jugular vein adds an appreciable resistance to flow so that the venous pressure inside the kidney is higher than it should be. When the side-arm to the measuring cylinder is opened, the pathway for the blood is shorter and the resistance less, so that even when the static pressure in the side-arm is maintained at the same level as it is when flow is along the jugular tube, its opening will cause a fall in venous pressure inside the kidney. Where the kidney is normal and the intrarenal tension normal this would not be important, but flow is critically affected by venous pressure when the renal tension is raised as it often is during such measurements. This might explain a further proportion of the discrepancy, but not the whole of it.

At the same time both Bálint and ourselves once again examined the theoretical background of the clearance procedure and we all realized that even the addition of a term for lymph was not enough. We should also consider storage or accumulation of the cleared substance in the kidney. We had to rewrite the clearance formula to take storage into account. The formula we arrived at was derived as follows:

$$aA = uV + rR + lL + \frac{s_2S_2 - s_1S_1}{t}$$

Since $\frac{S_2 - S_1}{t}$ is the change in kidney volume during the time of clearance,

$$A = V + R + L + \frac{S_2 - S_1}{t}$$

and, substituting the appropriate concentrations in each case as before, we derive:

$$R = \frac{V(u-a)}{a-r} + \frac{L(l-a)}{a-r} + \left[\frac{S_2(s_2-a)}{a-r} - \frac{S_1(s_1-a)}{a-r}\right] \Big/ t$$

Bálint and his colleagues undertook the estimation of the errors introduced by the neglect of the storage phenomenon and were able to show that at very low levels of urine flow the storage term in the equation accounted for a very substantial error.[17] Indeed the results of this study together with the others on the errors of the direct method now resolve the differences between the methods. It would seem, therefore, that in acute tubular necrosis the blood flow is *not* reduced as much as we had thought originally and probably lies between $\frac{1}{3}$ and $\frac{2}{3}$ of normal even in the oliguric or anuric phase.

PATHOGENESIS

I believe that the theoretical basis of clearance methods is now complete and that the differences between the three methods of determining blood flow are accounted for. The end result is an agreement that even in severely oliguric or anuric subjects there is a substantial blood flow probably of the order $\frac{1}{3}$ to $\frac{2}{3}$ of normal. With this knowledge and knowing the arterio-venous oxygen difference, it is now possible to make an estimate of renal oxygen consumption.

Bálint *et al.*,[18] who have studied the matter extensively in dogs, have shown that the basal oxygen consumption is normal but that that fraction of oxygen consumption which is probably related to tubular metabolic processes is reduced.

We can conclude from this that for practical purposes all the kidney is being perfused. There are no severely ischaemic areas. The reduction in non-basal oxygen consumptions is adequately explained by reduced oxygen demands of the damaged tubules.

If this is the correct interpretation we must now explain why, in the presence of a blood flow which would ordinarily be associated with appreciable glomerular filtration, there is little or no urine.

Three possibilities exist:

1. Filtration may be occurring, but the filtrate is virtually all being passively reabsorbed through damaged tubules.
2. The glomerular membrane may be so abnormal as to prevent filtration. This seems very unlikely on histological grounds.
3. The vascular tone of the afferent and efferent vessels or of a shunt path at the base of the glomerulus may be disturbed so that despite the adequate blood flow no filtration is occurring.

There is little to chose between hypotheses 1 and 3, but it is possible that further work may decide between them. Indeed, Dr. Taraba, one of Bálint's team, is at present with me and hopes to set up studies to this end. If hypothesis 3 is correct, there is a theoretical possibility that suitable vasoactive materials might be effective in treatment. I believe that there is some hope of this.

SUMMARY

The development of our knowledge of the renal blood flow in established acute tubular necrosis is outlined. Earlier reports based on determinations made by the Fick method suggested that the blood flow is very low, but later reports using a modification of the Kety-Schmidt method and by direct method show that the flow is only reduced to between $\frac{1}{3}$ and $\frac{2}{3}$ of normal. The reasons for the discrepancies of results between the methods are discussed and the implications of the findings considered in relation to the genesis of the anuria or oliguria.

REFERENCES

1. Oliver, J. (1953): Amer. J. Med., **15**, 535.
2. Bull, G. M., Joekes, A. M. and Lowe, K. G. (1950): Clin. Sci., **9**, 379.
3. Lowe, K. G., Moodie, G. and Thomson, M. (1954): *Ibid.*, **13**, 187.
4. Bull, G. M. (1956): *Modern Views on the Secretion of Urine*. London: Churchill.
5. Sirota, J. H. (1949): J. Clin. Invest., **28**, 1412.
6. Wolf, A. V. (1941): Amer. J. Physiol., **133**, 496.
7. Munck, O. (1958): *Renal Circulation in Acute Renal Failure*. Oxford: Blackwell.
8. Kety, S. S. and Schmidt, C. F. (1948): J. Clin. Invest., **27**, 476.
9. Dible, J. H. (1953): *Recent Advances in Pathology*, p. 299. London: Churchill.
10. Reubi, F. C., Gürtler, R. and Gossweiler, N. (1962): Proc. Soc. Exp. Biol. (N.Y.), **111**, 760.
11. Walker, J. G., Silva, H., Lawson, T. R., Ryder, J. A. and Shaldon, S. (1963): *Ibid.*, **112**, 932.
12. Bálint, P., Kiss, E. and Sturcz, J. (1959): Acta physiol. Acad. Sci. Hung., **15**, 237.
13. *Idem* (1959): *Ibid.*, **15**, 249.
14. Bálint, P. and Fekete, A. (1960): *Ibid.*, **17**, 277.
15. Bálint, P., Fekete, A. and Sturcz, J. (1960): *Ibid.*, **17**, 287.
16. Bull, G. M. and Metaxas, P. (1962): Clin. Sci., **23**, 515.
17. Bálint, P., Fekete, A. and Forgács, I. (1964): *Ibid.*, **26**, 345.
18. Bálint, P., Chatel, R., Fekete, A. and Forgács, I. (1964): *Ibid.*, **26**, 471.