On the Prevention of Acute Renal Failure (Vasomotor Nephropathy)

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Acute renal failure following severe trauma, shock, transfusion reactions, poisoning, and sepsis is characterized by prolonged oliguria, increasing azotemia, isothenuria, and a sodium concentration of 40-90 mEq/L. Despite the availability of intensive medical and surgical care, potent antibiotics, and dialysis, this syndrome still carries a mortality rate of approximately 50% and once established cannot be reversed by any known medical regimen. It is, however, often preventable, and the purpose of this paper is to evaluate the efficacy of the various prophylactic measures currently in vogue.

In searching for means of preventing acute renal failure, we should consider three pathophysiologic mechanisms involved that, historically, have received the greatest attention:

1. The passive backflow theory,
2. Tubular obstruction, and
3. Vasomotor factors.

According to the passive backflow theory, glomerular filtrate is formed at a normal or close to normal rate but is absorbed quantitatively and nonselectively across injured tubular epithelium. The tubular obstruction theory presupposes that cell swelling and tubular debris occlude the tubule lumen, raise intratubular pressure to the point that filtration is seriously reduced, and/or augment the driving force for passive backflow of the filtrate formed. The vasomotor theory suggests that acute renal failure is the result of a primary failure of glomerular filtration because of decreased glomerular capillary filtration pressure with or without reduced permeability of the filtration surface.

The renal cortical blood flow of human subjects with acute renal failure has been found almost invariably to be greatly decreased.\textsuperscript{1-4} If this decrease in blood flow relates only in part to an increased preglomerular vascular resistance as seems evident from angiography,\textsuperscript{6} glomerular filtration must be maximally suppressed. Although the possibility of inulin leakage casts some doubt on the validity of inulin clearance measurements which would confirm such a near cessation of filtration, micropuncture studies of experimental animals with acute renal failure have provided unequivocal proof that glomerular filtration does, indeed, fail.\textsuperscript{6} By and large, experimental models reveal proximal tubular pressure to be distinctly low, not elevated as might be suggested by the tubular obstruction theory. Although tubular leakage of glomerular filtrate has been described by some authors, tubular absorption has, for the most part, been shown to be markedly decreased, rather than increased as suggested by the passive backflow theory.\textsuperscript{7} Perhaps the most telling argument against this theory can be derived from studies of chronically salt-loaded rats poisoned with mercuric chloride. Such animals, allowed 1% saline solution in place of tap water for a month prior to mercury injection, are almost perfectly protected from renal failure. Their blood urea nitrogen concentrations and whole kidney inulin clearance values are close to normal 24 hours after the injection of mercury. Nevertheless, their kidneys show tubular necrosis which is just as severe...
as that displayed by their water drinking counterparts with virtually no renal function. If the passive back-flow theory is not applicable to kidneys with evident necrosis of the entire terminal portion of the proximal tubule, it is highly unlikely to be the major determinant of other types of acute renal failure in which tubular damage is far less severe. It is thus well to remember that the degree of tubular injury in the kidneys of patients with acute renal failure is highly variable. Finckh, Sevitt, and others have pointed out that classical acute renal failure may be found without any significant tubular injury, and that no correlation exists between the duration or severity of renal insufficiency and the degree of tubular injury which can be demonstrated. Similarly, acute renal failure in man may coexist with scant, if any, evidence of tubular obstruction with casts. In sum, the overwhelming bulk of evidence presently affirms that acute renal failure relates to a primary cessation of glomerular filtration.

Recently, Flores et al have proposed that filtration failure is caused by endothelial and renal interstitial cell swelling. Such swelling was said to be reversible, and renal failure prevented, by administering massive doses of mannitol. According to the data in that report, however, renal failure was not prevented by mannitol administration, merely somewhat blunted. In our laboratory, closely following the technique used by Flores, we could find no significant effect of mannitol therapy. Nor have we found a beneficial effect of hypertonic mannitol solutions in myoglobinuric acute renal failure other than that which could be achieved by volume expansion with saline or plasma alone. Mannitol clearly increases renal blood flow and helps maintain glomerular filtration in dogs subjected to limited hemorrhage; however, as their renal function generally returns to normal when renal perfusion pressure is restored after hemorrhage whether mannitol is given or not, one cannot presume from such studies that mannitol prevents acute renal failure. Aortic cross-clamping has also been reported to cause renal failure which is preventable with mannitol, but several investigators studying far larger numbers of animals have been unable to duplicate any renal abnormalities at all in similarly treated animals not given mannitol.

A number of clinical reports have suggested that mannitol prevents acute renal failure in man, although no prospective study of the efficacy of such treatment has appeared. Such a study would, however, be difficult indeed. Assuming a 1% overall incidence of renal failure in the total population of patients at risk after surgery, burns, trauma, or hemorrhage (a deliberate overestimate), at least 2,000 patients would need to be treated and a comparable number employed as controls before a statistically meaningful comparison of the two groups could be made. Powers et al have estimated that the syndrome occurs in 0.1% of patients at risk, a more realistic figure that would necessitate the inclusion of perhaps 20,000 patients in any controlled study of the efficacy of a prophylactic measure. While patients subjected to aneurysmectomy develop renal insufficiency more often than others subjected to less traumatic surgery, they still have a low risk of renal insufficiency unless the aneurysm has ruptured. In reviewing 1,659 cases of lower aortic surgery performed in ten centers, Kountz et al found an overall incidence of renal failure of only 3.8%. While the physician may be reassured that none of 20 or 50 patients subjected to major surgery and treated with mannitol will develop acute renal failure, there is little basis for assuming that mannitol infusions are responsible for his good luck. Similar considerations apply to the use of furosemide as a prophylactic agent.

The rationale for mannitol's usage rests with the suggestion that it maintains renal blood flow, reduces renal cell swelling, washes out tubular debris, serves to expand vascular volume, and induces urine output if filtration still persists. This is an impressive list of potential benefits, but the bulk of controlled experiments show cell swelling and tubular obstruction not to be critical to the development of acute renal failure. The syndrome can be induced readily in rats with congenital diabetes insipidus, excreting (and drinking) a volume equal to 80% of their body weight each day. Thus, the maintenance of urine volume and washout of tubular casts is not critical to the prevention of acute renal failure, whether this is achieved with furosemide or with mannitol. A response to either agent proves that acute renal failure does not yet exist, as urine can only be formed when filtration is ongoing.

Whether renal failure develops or not depends largely on the type, as well as on the severity, of the underlying injury sustained. Shock, for example, is a major factor. While brief and modest hypotension may, at times, lead to renal failure, the syndrome is far more likely to occur if shock is of long duration or poorly controlled. Volume depletion also plays a sig-
nificant pathogenetic role, adequate volume replacement being the most important single therapeutic modality available for the prevention of renal shutdown. The adequacy of fluid therapy cannot be merely assumed, however, but requires documentation of adequate weight gain, appropriate changes in urinary sodium concentrations and osmolality, and where needed, measurement of central venous pressure and blood volume. Sepsis may predispose to renal insufficiency not only on the basis of toxemia, but also by the activation of intravascular coagulation. With prompt and vigorous treatment of fluid volume deficits, the restoration of cardiac output to reasonable levels, and vigorous treatment of sepsis, the incidence of acute renal failure has become far lower than in previous times, a reduction which is as apparent in centers where mannitol and furosemide are not used as "preventive agents" as in those where they are.

While acute renal failure owing to trauma and shock is far less prevalent nowadays, a new threat has emerged with the widespread use of the aminoglycoside antibiotics. These agents are excreted essentially unchanged primarily by the kidney. Any impairment of glomerular filtration rate (GFR), whether because of organic disease or as a functional result of heart failure or dehydration, causes accumulation of these agents to a level which may be nephrotoxic. Unlike the idiosyncratic reactions to other antibiotics that occur in a very small percentage of the population, renal toxicity can be expected in any patient exposed to abnormally high concentrations of aminoglycosides. The setting in which these agents are used is one that so frequently results in some compromise in renal function that toxic levels are easily attained. Unlike other forms of acute renal failure, that following aminoglycoside overdosage may be irreversible.

How can we prevent this common and very serious complication? First, the aminoglycosides should be used only when less toxic antibiotics cannot be substituted. Second, renal function should be followed closely if these agents are to be given. Various formulae are used as guides to appropriate gentamicin dosage in the face of reduced renal function, and not one seems clearly superior to the others. All, however, rely on the reasonably accurate assessment of renal function. Normal serum creatinine concentrations in non-gravid adults range from 0.6 to 1.6 mg%. Thus, a value of 1.2 mg% in one patient may be normal; in another, it may be twice normal and indicative that the GFR is reduced by one half. If one abruptly loses all renal function, the serum creatinine obtained two days later will be perhaps 3 mg% and will rise progressively thereafter. It certainly would be erroneous to assume that a creatinine concentration of 3 mg% in such a patient means that the GFR is one third of normal and administer gentamicin (or the other aminoglycosides) accordingly, when, in fact, the GFR is almost nil. The way out of the dilemma is to routinely measure the serum creatinine concentration of any patient receiving these drugs on the day after treatment is started. Any significant increase should prompt a repeat determination 12 or 24 hours later, as should any circumstance likely to lead to worsening renal function. As serum creatinine concentrations truly reflect renal function only when they are stable, it is imperative that serum antibiotic levels be monitored to serve as the guide to dosage if the creatinine concentrations are rising.

Nephrotoxic renal damage may be superimposed on preexisting renal impairment and, as previously stated, may be irreversible. Only by treating the aminoglycosides with the greatest respect and closely monitoring the renal function of patients receiving these drugs can overdosage and the resultant renal failure be avoided.

To summarize, the best evidence available at present indicates that acute renal failure represents a sustained and severe decrease in GFR. Tubular factors are thus of secondary importance, and the term "acute tubular necrosis" (ATN) is not pathologically appropriate. Vasomotor nephropathy seems a better term, and one we have adopted for this syndrome which in many circumstances is largely preventable by the prompt and vigorous restoration of fluid deficits and cardiac output, as well as the treatment of sepsis. Unfortunately, such therapy may be only marginally successful in some instances (for example, overwhelming sepsis, acute hemorrhagic pancreatitis), but there is scant evidence that either mannitol or furosemide protects patients from renal failure. Rather than relying on such agents, efforts should be made to maintain normal fluid volume and cardiac output in all cases at risk of vasomotor nephropathy.

Renal failure owing to gentamicin and other aminoglycoside antibiotics is a result of improper attention to dosage relative to a patient's renal function. Close attention to renal function can largely
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eliminate this common cause of renal failure.

REFERENCES


