Cyclosporine and Posttransplant Hypertension

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ABSTRACT
Prevalence studies suggest that hypertension is present in more than 50% of kidney transplant patients. It is more prevalent in pediatric patients, and cyclosporine has added to the rates in both children and adults. Hypertension is an important risk factor for cardiovascular disease, which remains the leading cause of death for recipients of renal transplants. Fortunately, posttransplant hypertension is commonly mild to moderate in nature (transplant artery stenosis hypertension being the exception) and can be treated medically. However, the removal of native kidneys and the correction of arterial stenosis are two surgical interventions that are more common in the transplant population than in the general population. In posttransplant hypertension that is primarily due to cyclosporine, one must balance the risks of reduced cyclosporine dosage against the risks of the hypertension. Both diuretic and calcium channel blocker therapy are believed to be useful in cyclosporine-induced hypertension. Other vasodilators also may be effective, although they may have undesired effects on RBF and glomerular filtration.

Key Words: Cyclosporine, posttransplant, hypertension

Cyclosporine is usually a factor in posttransplantation hypertension (1). Cyclosporine may not always be the the most important factor, but its effect on renal hemodynamics adds to the elevation of arterial pressure. This is obvious in heart transplant programs (2), which had a low prevalence of hypertension before the widespread use of cyclosporine. In kidney transplant programs, there has always been a high prevalence of hypertension (3). That high prevalence of hypertension has increased, but not dramatically so, with the nearly universal use of cyclosporine. Pediatricians report a higher prevalence of hypertension in young recipients of kidney transplants than prevalence reported for adults (4). Cyclosporine requirements are generally higher in pediatric recipients. Thus, cyclosporine-associated hypertension is an especially important issue in pediatric renal transplantation (5).

Cyclosporine increases renal vascular resistance (6). The site of this increase in vascular resistance is the afferent arteriole (7). Interestingly, this is the site of increased renal vascular resistance most suspected in essential hypertension (8). The vasoconstrictive effect of cyclosporine on the afferent arteriole produces a form of hypertension that is more volume dependent than renin dependent (9). The evidence that cyclosporine-induced hypertension is a volume-mediated hypertension comes from several studies in humans and animals.

We compared 15 renal transplant patients on cyclosporine therapy with therapeutic blood levels with 15 equally hypertensive transplant patients on only azathioprine and prednisone. In these studies, 4 days of severe sodium restriction (9 mEq/24 h) resulted in marked decreases in blood pressure in the cyclosporine patients but not in the azathioprine patients. Sodium balance studies showed that cyclosporine patients tended to retain more sodium on both a low- and high-sodium intake. We also noted a tendency to sodium retention in normotensive transplant patients receiving cyclosporine (10). Others have also suggested that the excretion of sodium is impaired in cyclosporine-treated patients and animals (11,12).

Recently, we have observed a group of diabetic patients treated with the transplantation of both a kidney and a pancreas. We treated these patients with high doses of cyclosporine but did not note hypertension (13). A group of diabetic patients who had received only a kidney transplant during the same interval did have a rate of hypertension normally expected. On closer study, we suggested that the loss of sodium (as both sodium chloride and sodium bicarbonate) from pancreatic excretion explains the difference in blood pressure in the groups. This again suggests that hypertension associated with cyclosporine may be favorably affected by sodium loss.

Most human studies suggest that plasma renin is not elevated in cyclosporine patients, which is also consistent with volume expansion (14–16). Unfortunately, the results in human studies and some animal studies (17,18) differ on this point. This may repre-
sent differences in animal studies, which are usually done acutely after starting cyclosporine (hours to weeks), and human studies, which are often done after patients are on cyclosporine for months or years. Therefore, we and others have looked for acute effects of cyclosporine on renin in humans and have not found any evidence of stimulation (19,20).

Thus, in humans (as in sheep [21,22]), there is little evidence that the renin-angiotensin system is involved either chronically or acutely in hypertension associated with cyclosporine. In the rat, however, renin may be stimulated. In both humans and animals, cyclosporine appears to result in sodium retention. Thus, the hypertension associated with cyclosporine might well respond to diuretic therapy and not be markedly influenced by therapy aimed at the renin-angiotensin system. This has been our clinical experience.

The most important factor leading to volume expansion is the vasoconstriction of the afferent arteriole. The mechanism of this vasoconstriction remains a subject of debate, but recently, Kon and associates have suggested that endothelin may be an important mediator (23). Endothelin is a potent renal vasoconstrictor that, unlike most renal vasoconstrictors, does not stimulate the renin-angiotensin system. Other frequently mentioned vasoconstrictors that may mediate cyclosporine nephrotoxicity and hypertension are thromboxane (24), sympathetic nerve stimulation (25), and the renin-angiotensin system. None of these possible mediators are proven to be of critical importance, and all may play a role.

Once one views cyclosporine as a potent constrictor of the (preglomerular) afferent arteriole, despite mechanism, one can draw an analogy to the hemodynamic changes that might be seen in transplant renal artery stenosis. Thus, such patients would have a prerenal type of effect on renal function. They would tend to have enhanced proximal tubular reabsorption of sodium, urea, and uric acid. Eventually, they would become volume expanded and would not stimulate the renin-angiotensin system. We believe these are all established features of cyclosporine-associated hypertension.

In patients with solitary kidneys and stenosis of the (preglomerular) blood supply, a syndrome of converting enzyme, inhibitor-induced acute renal failure has been described (26). If the analogy of cyclosporine-induced hypertension having hemodynamic effects similar to those seen with transplant renal artery stenosis holds, then one might expect to see a fall in GFR in patients put on converting enzyme inhibitors. Such reports have appeared in the literature (27,28). We have seen a small (5- to 10-mL/min) decrease in GFR in hypertensive renal transplant patients put on captopril for several days (29). This fall in GFR has not been observed in the same patients treated with calcium channel blockers with the same decrease in blood pressure. Thus, cyclosporine-associated posttransplant hypertension does appear to have a prerenal vasoconstrictive picture that mimics the lesion of transplant renal artery stenosis.

The treatment of cyclosporine-associated hypertension might be directed at the reversal of the renal vasoconstriction and natriuresis. Calcium channel blockers appear to be effective agents. Calcium channel blockers seem to have preferential effects on the afferent arteriole (30). They are also mildly natriuretic (8). In our hands, they appear to decrease renal vascular resistance more effectively than converting enzyme inhibitors in this specialized form of hypertension. Another approach to cyclosporine hypertension is to reduce or stop cyclosporine. This should be considered in closely matched, living related transplant patients for whom other causes of hypertension are not identified. On the other hand, in most series, if cyclosporine is discontinued in recipients of a cadaveric renal transplant, the recipients risk acute rejection and even graft loss. The risks of such an approach, I believe, seldom match the possible benefits. On the other hand, reducing the dose of cyclosporine is less risky than discontinuing the drug entirely and is more often an approach that I would consider.

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