Hypertension After Renal Transplantation

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ABSTRACT

Hypertension is a frequent complication after organ transplantation in both children and adults and is a significant risk factor for the development of cardiovascular disease and graft dysfunction. There are multiple mechanisms responsible for the development of posttransplant hypertension. In the pre-cyclosporine era, chronic rejection was the most common cause. The introduction of cyclosporine A has increased the prevalence of hypertension in solid organ transplant recipients. Cyclosporine increases renal vascular resistance by causing vasoconstriction of the afferent arteriole. From a pathophysiologic point of view, a calcium channel blocker should be used as the initial therapy in patients with cyclosporine-associated hypertension. Hypertension needs to be treated aggressively in all transplant recipients in an attempt to minimize allograft and cardiovascular damage.

Key Words: Renal transplantation, hypertension, cyclosporine A, steroids, renin, calcium channel blockade, angiotensin-converting enzyme inhibition

INCIDENCE OF POSTTRANSPLANT HYPERTENSION

In the pre-cyclosporine era, hypertension occurred in approximately 40 to 50% of kidney transplant patients (5–11). The introduction of cyclosporine A has increased the prevalence of hypertension in solid-organ transplant recipients (7–13) and has been reported in 60 to 70% of adult renal and up to 90% of extrarenal transplant recipients (14–20). In the University of Texas Medical School study (7), the prevalence of hypertension after renal transplantation was examined in 150 cyclosporine A/prednisone-treated transplant recipients and 50 concurrently treated prednisone/azathioprine patients. At 1 yr, the prevalence of hypertension (diastolic blood pressure ≥90 mm Hg) was 63% in the cyclosporine A/prednisone group versus 42% in the prednisone/azathioprine group (P < 0.01). The higher incidence of hypertension in the cyclosporine A/prednisone group was sustained at 2 yr (61 versus 38%; P < 0.05). The mean number of drugs used to control hypertension was significantly higher in the cyclosporine A/prednisone cohort at 1, 6, and 12 months posttransplantation, but there was no difference in the number of drugs used in the two groups at 24 months (7). In the study from Cambridge University (10), the incidence of hypertension was 67% in cyclosporine-treated patients compared with 46% in azathioprine-treated renal transplant recipients. In addition, two studies have reported that the conversion of renal transplant recipients from cyclosporine to azathioprine resulted in a significant decrease in blood pressure (12,13). Hypertension is common in patient and graft survival in the 1980 to 1990 decade was principally the result of fewer infectious deaths and fewer cases of graft loss due to acute rejection, respectively. Improvement in graft and patient survival in the 1980s was minimal because of the two leading causes of failure, chronic rejection and cardiovascular deaths, respectively, emphasizing the need for prevention of cardiovascular deaths (3). In addition, posttransplant hypertension is a major risk factor for graft survival (4). It has not been established whether this is because of the deleterious effects of hypertension on graft structure and function or whether the hypertension is a marker of underlying renal disease (4). Normotension is a good prognostic marker for long-term graft survival, and effective and appropriate treatment of hypertension is likely to slow the progression of allograft parenchymal disease (4).
children after renal transplantation with a prevalence of 70 to 80% (2, 21–25). In the most recent report of the North American Pediatric Renal Transplant Cooperative Study, hypertension was present in 80% of cadaver and 61% of living related donor allograft recipients 1 month after transplantation (25). There was a resolution of hypertension with time, so that 1 and 2 yr posttransplant, hypertension was present in 67 and 65% of cadaveric recipients and in 57 and 53% of living related donor recipients, respectively. Moreover, the majority of patients (72, 66, and 62% at 1, 12, and 24 months, respectively) required multiple drug therapy to control the hypertension (25).

In cardiac transplant recipients, hypertension has been an infrequent occurrence in patients treated with azathioprine and prednisone. However, with the introduction of cyclosporine, hypertension has been reported as a complication in up to 90% of patients (14–17). Both the incidence and severity of hypertension have been more pronounced in cardiac, lung, bone marrow, and liver transplant recipients than in kidney transplant recipients (11, 14–20).

**CAUSES OF HYPERTENSION AFTER RENAL TRANSPLANTATION**

The cause and pathogenesis of posttransplant hypertension is multifactorial. The causes of sustained hypertension after renal transplantation are listed in Table 1. The most frequent causes currently observed are cyclosporine-induced hypertension and chronic rejection (4). In patients with stable renal allograft function and cyclosporine blood levels, the degree of hypertension has been shown to neither abate nor increase over a 3-yr study period (26). Steroids may have a synergistic effect with cyclosporine in causing hypertension, but once the maintenance dose of prednisone has been reduced to <10 mg/day, steroids appear to have little if any role in contributing to the genesis of hypertension after transplantation (4, 26). Converting from daily to alternate-day steroid therapy while maintaining the same total dose significantly reduces the mean arterial pressure (27). Steroid withdrawal has been shown to have a beneficial effect on the prevalence and severity of hypertension in children and adults (24, 28).

In the precyclosporine era, chronic rejection was the most common cause of posttransplant hypertension. This condition is characterized by progressive deterioration in renal function, the development of hypertension and proteinuria, and histologic evidence of microvascular and tubulointerstitial disease. Cyclosporine-induced hypertension has now become the main cause of posttransplant hypertension. Acute cyclosporine nephrotoxicity is characterized by renal vasoconstriction, and this may progress to chronic changes in the renal microvasculature.

The development of functionally significant transplant renal artery stenosis is characterized by an acute deterioration in renal function in association with the sudden onset of hypertension or deterioration in preexisting hypertension and the appearance of a new bruit over the transplant. Functionally significant renal artery stenosis can be diagnosed by the demonstration of a reduction in RBF and GFR after the administration of an angiotensin-converting enzyme inhibitor (ACEI) (9); however, the use of this test is not valid in patients receiving cyclosporine (4). Diagnosis should be confirmed by angiography, and if confirmed, the majority of cases can be successfully treated by percutaneous transluminal angioplasty (29), reserving bypass surgery for cases in which this procedure is not successful.

The development of recurrent or de novo glomerulonephritis or recurrent diabetic nephropathy in the transplant may be associated with the development of hypertension, although these conditions are not important causes of posttransplant hypertension.

Renin-dependent hypertension may be responsible for persistent hypertension in a small percentage of dialysis patients and is likely to persist despite successful transplantation. It can usually be controlled with antihypertensive therapy, but in rare cases, it may be the cause of severe hypertension after transplantation. Diagnosis may be confirmed by a high native kidney-to-transplant renal vein renin ratio. If severe, bilateral native kidney nephrectomy (30) or ablation by embolization (31) has been shown to be effective.

**TABLE 1. Causes of persistent hypertension in the renal allograft recipient**

<table>
<thead>
<tr>
<th>Immunosuppressive Therapy</th>
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<tbody>
<tr>
<td>Steroids</td>
<td></td>
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<tr>
<td>Cyclosporine (A or G)</td>
<td></td>
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<tr>
<td>Tacrolimus (FK506)</td>
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<td>Disease in the Renal Allograft</td>
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<tr>
<td>Chronic rejection</td>
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<tr>
<td>Cyclosporine nephrotoxicity</td>
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<tr>
<td>Tacrolimus nephrotoxicity</td>
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<tr>
<td>Transplant renal artery stenosis</td>
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<tr>
<td>Recurrent or de novo glomerulonephritis</td>
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<tr>
<td>Recurrent diabetic nephropathy</td>
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<tr>
<td>High Renin Output From Native Kidneys</td>
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<tr>
<td>Recurrent Essential Hypertension</td>
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<tr>
<td>Recurrent systemic disease</td>
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<tr>
<td>Transplantation of a predisposed allograft</td>
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<tr>
<td>Miscellaneous</td>
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<tr>
<td>Coexistent cause of secondary hypertension</td>
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<tr>
<td>Primary aldosteronism</td>
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<tr>
<td>Pheochromocytoma</td>
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<td>Hypercalcemia</td>
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Adapted from Luke (4).

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It is possible that recurrent or de novo essential hypertension may develop after renal transplantation. However, this is very difficult to document. Likewise, it has been difficult to document an increased prevalence of posttransplant hypertension in recipients of cadaveric allografts from donors with a family history of essential hypertension (4). However, requirements for antihypertensive therapy have been shown to be significantly higher in recipients of cadaver kidneys from donors with a history of familial hypertension (32).

Infrequent causes of posttransplant hypertension include the coexistence of a secondary cause of hypertension, such as primary aldosteronism or pheochromocytoma, and persistent hypercalcemia.

**PATHOGENESIS OF CYCLOSPORINE A-INDUCED HYPERTENSION**

Cyclosporine A has been shown to decrease RBF and GFR and cause an increase in mean arterial pressure and renal vascular resistance in experimental animals (33) and in humans (13). The rapidity of onset of these changes indicates that they are brought about by the vasoconstrictive effect of cyclosporine on the renal vasculature. Photographs of the renal microcirculation before and after the administration of cyclosporine have graphically demonstrated vasoconstriction of the afferent arteriole (34). The vasoconstrictive effect of cyclosporine on the afferent arteriole produces a form of hypertension that is more volume dependent than renin dependent (35). In renal transplant recipients not receiving cyclosporine, blood pressure does not fall in response to a low-salt diet, indicating the presence of renin-dependent hypertension, whereas hypertensive patients on cyclosporine exhibit a significant fall in blood pressure on a low-salt diet (4,35). The volume-dependent nature of cyclosporine-induced hypertension has been confirmed by the response to a test dose of the ACEI drug captopril. Azathioprine-treated patients had a significant fall in blood pressure after captopril, but the cyclosporine-treated patients did not, and the increment in plasma renin activity was greater in the azathioprine-treated patients (4,35). Diabetic patients receiving both a kidney and a bladder-drained pancreas transplant have a low incidence of hypertension (36). This has been attributed to the loss of sodium (as both sodium chloride and sodium bicarbonate) from the pancreatic excretion, thereby confirming the volume-dependent nature of cyclosporine-induced hypertension. In cardiac transplant recipients, the plasma volume has been shown to be higher in hypertensive patients than in non-hypertensive patients receiving cyclosporine (37). Catecholamines (38), prostaglandins (39), endothelin (40), and the renin-angiotensin system (41,42) have all been implicated as possible mediators of vasoconstriction of the afferent arteriole. Studies in dogs have indicated that chronic cyclosporine administration activates the renin-angiotensin-aldosterone system, suppresses circulating atrial natriuretic factor, and results in chronic sodium retention (42). However, most human studies have shown that plasma renin is not elevated in cyclosporine-treated patients (43,44), a finding that is consistent with volume expansion.

Cyclosporine may also cause hypertension by its effects on renal nerves. It has been shown that the infusion of cyclosporine into rats increases genitofemoral nerve traffic and causes an increase in sodium retention (45). Supportive evidence of the role of renal nerves comes from the demonstration that cyclosporine-induced decreases in RBF can be mitigated by the denervation of the kidney or by the α-1 antagonist prazosin (38). The fact that renal allografts are denervated could explain why more severe hypertension and nephrotoxicity occur in nonrenal transplants as compared with kidney allograft recipients (11). However, an alternative explanation for the lower incidence of hypertension in kidney transplant recipients may be that kidney transplant programs generally use a lower dose of cyclosporine than is used in nonrenal transplant recipients. In pediatric renal transplant recipients, cyclosporine dose requirements are generally higher than in adult patients; this may explain the higher prevalence of hypertension in young kidney transplant recipients (21,22).

Nonrenal mechanisms may also be implicated in cyclosporine-induced hypertension. Cyclosporine has a generalized vasoconstrictor effect on smooth muscle and may affect the systemic circulation and total peripheral resistance, independent of its effects on renal tissue (46). Hypertension has been shown to develop in cyclosporine-treated normotensive renal transplant recipients after exercise (47). Despite being normotensive at rest, cyclosporine-treated patients had evidence of a vasopressor effect, with inappropriately high systemic vascular resistance developing after exercise, whereas azathioprine-treated patients had a response similar to that observed in normal controls. Cyclosporine therapy also results in mild hypomagnesemia, which may contribute to hypertension (48) and may also affect intracellular calcium-binding proteins, which may cause increased vascular tone (49).

**MANAGEMENT OF CYCLOSPORINE-INDUCED HYPERTENSION**

The initial approach involves the use of nonpharmacologic measures to control blood pressure and to minimize premature cardiovascular morbidity and
mortality in patients with functioning allografts. These measures include weight control, a diet with a moderate sodium restriction and a low saturated fat intake, exercise, and cessation of smoking. The concept that the pathophysiology of cyclosporine-induced hypertension is volume dependent indicates that modest salt restriction is an appropriate therapeutic maneuver. However, too severe salt restriction, especially if coupled with diuretic therapy, might result in a drop in GFR because of an impairment in the autoregulatory capacity of the transplanted kidney (3). In patients with sustained blood pressures of >140/90 mm Hg, antihypertensive agents should be started.

Although high cyclosporine levels correlate poorly with hypertension, the dosage should be adjusted downward if the drug levels are high (9). In patients with normal cyclosporine levels, small decreases in the cyclosporine dose should be considered. If significant proteinuria is present and the serum creatinine level is greater than 2 mg/dL, an allograft biopsy should be performed to exclude chronic rejection or recurrent disease. Hypertension in chronic rejection often mediated through the renin-angiotensin system, and therapy should be directed at both control of vascular volume and inhibition of angiotensin. Hypertension secondary to recurrent disease should be managed as in the original disease. In patients with renal artery stenosis, angioplasty or surgical correction should be performed. In the unlikely event that medical therapy is ineffective and if other causes of hypertension have been excluded, bilateral nephrectomy or host kidney ablation by embolization should be considered (9,30,31).

The treatment of cyclosporine-associated hypertension is initially directed at the control of GFR. These acute studies on the effects of a CCB on renal hypoperfusion strengthen the argument that calcium antagonists, because of their predominant effect at the preglomerular level, appear to be ideal candidates for the long-term treatment of cyclosporine-associated hypertension. Similar effects have been observed with verapamil (54), isradipine (55), nifedipine (56), felodipine (57), and diltiazem (58). Cyclosporine levels in blood need to be monitored carefully when agents that block its metabolism are used. Calcium antagonists may also have an immunosuppressive effect (59). Thus, the use of a CCB may have multiple beneficial effects; they decrease blood pressure, reduce the cyclosporine dose requirement (with certain agents), and may have an immunosuppressive effect of their own.

The use of an ACEI in cyclosporine-treated patients remains controversial. Lisinopril has been reported to reduce protein excretion in renal transplant recipients with heavy proteinuria, while maintaining stable renal function (60). In another study, lisinopril was effective in controlling blood pressure during 2.5 yr of follow-up, without having an adverse effect on renal function (61). The main adverse effect of lisinopril was a significantly lower hematocrit when compared with that in patients treated with a CCB. A fall in hematocrit has been reported with other ACEI drugs (62,63). However, in other studies, both enalapril (56), and captopril (64) have been shown to cause a significant fall in RPF and GFR. Reversible acute renal failure has been reported in renal transplant recipients treated with an ACEI (65, 66). Given the proposed pathophysiology of cyclosporine-induced hypertension, this is not surprising. If cyclosporine constricts the afferent arteriole and reduces perfusion of the efferent arteriole, ACEI-induced dilation would be maintained by constriction of the efferent arteriole, dependent on angiotensin II. The administration of an ACEI in cyclosporine-treated patients would be clinically significant, and only small changes in serum creatinine would result (64). For the majority of cases, it is unlikely that this fall in GFR would be maintained by constriction of the efferent arteriole (64, 65). However, in the occasional patient, acute renal failure has been reported in renal transplant recipients treated with an ACEI (65, 66). Given the proposed pathophysiology of cyclosporine-induced hypertension, this is not surprising. If cyclosporine constricts the afferent arteriole and reduces renal hypoperfusion (53). These acute studies on the effects of a CCB on renal hypoperfusion strengthen the argument that calcium antagonists, because of their predominant effect at the preglomerular level, appear to be ideal candidates for the long-term treatment of cyclosporine-associated hypertension. Similar effects have been observed with verapamil (54), isradipine (55), nifedipine (56), felodipine (57), and diltiazem (58). Cyclosporine levels in blood need to be monitored carefully when agents that block its metabolism are used. Calcium antagonists may also have an immunosuppressive effect (59). Thus, the use of a CCB may have multiple beneficial effects; they decrease blood pressure, reduce the cyclosporine dose requirement (with certain agents), and may have an immunosuppressive effect of their own.

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CONCLUSION

Posttransplant hypertension is a complicated problem with multiple contributing factors. Although cyclosporin A has unequivocally resulted in a highly significant improvement in transplant outcome, it has become an important cause of iatrogenic hypertension. The hypertension is associated with increases in renal vascular resistance due to constriction of the afferent arteriole. This results in sodium retention in the proximal tubule. From a pathophysiologic point of view, treatment with a CCB in association with moderate sodium restriction and/or a small dose of a diuretic appears to be the most appropriate form of therapy.

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