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CYCLOSPORIN-INDUCED HYPERTENSION

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Introduction: Hypertension has emerged as a serious adverse effect of immunosuppression with cyclosporin, which has become the mainstay of immunosuppression in organ transplantation. Improved survival rates with cyclosporin compared to previous regimens based on corticosteroids and azathioprine were established and have led to an expansion of solid organ transplantation. Cyclosporin has also been used at lower dosages for the treatment of autoimmune disease.

Cyclosporin is a macrolide antibiotic structurally different from the newer immunosuppressive agent tacrolimus, although both share final pathways that inhibit cytokine release from lymphocytes. Both cyclosporin and tacrolimus induce widespread vasoconstriction of systemic circulation and an increase in arterial blood pressure. Vasoconstriction in the kidney results in a decreased renal blood flow and is the basis for the nephrotoxicity observed with both agents. The consequence is newly developed hypertension or deterioration of existing hypertension. The prevalence of post-transplant hypertension with cyclosporin and tacrolimus is similar by one year after transplantation.

Incidence of hypertension associated with cyclosporin therapy: The introduction of cyclosporin increased the prevalence of hypertension in all indications (Table 1).

Table 1. Hypertension before and after introduction of cyclosporin

Indication	Hypertension (%)	
	Before cyclosporin	After cyclosporin
Transplant		
Bone marrow	5-10	33-60
Cardiac	10	71-100
Liver	n.a.	65-85
Renal	45-55	67-86
Non-transplant		
Rheumatoid arthritis	n.a.	42-45
Uveitis	n.a.	23-29
Myasthenia gravis	n.a.	81
Psoriasis	n.a.	30

n.a. = not applicable

The prevalence rates in patients receiving cyclosporin for non-transplant indications such as psoriasis or uveitis range from 23 to 54% while the rates for heart, liver or kidney transplant recipients treated with the combination of cyclosporin and corticosteroids range from 65 to 100%.

Clinical features of cyclosporin-induced hypertension: *Blood pressure rises within days of cyclosporin administration* before changes in renal function or sodium balance can be detected. When corticosteroids are added, blood pressure may further increase to levels requiring antihypertensive therapy within the first weeks or months.

In patients after *heart transplantation*, hypertension is nearly universal. It is associated with a high incidence of left ventricular hypertrophy. Allograft vasculopathy leads to accelerated coronary injury. A subgroup of patients may develop progressive renal failure.

In *liver transplant* recipients, there is a clinically significant rise in blood pressure, usually over a period of several weeks.

Kidney transplant candidates have hypertension in roughly 50% before the procedure. Transplant-related complications such as rejection, organ preservation injury, or transplant renal artery stenosis can impair renal function and worsen hypertension.

Bone marrow recipients usually develop severe hypertension during acute cyclosporin administration, which later resolves. Total body irradiation may accelerate renal vascular injury. There were some complications reported like intracerebral hemorrhage, encephalopathy, or seizures.

Cyclosporin in *non-transplant indications* increases blood pressure less rapidly, and progression to hypertension is less common.

Complications: Hypertension after organ transplantation is characterized by a *disturbed circadian rhythm* with the absence or reversal of the normal nocturnal fall in blood pressure. *Nocturnal headaches* and increased *nocturnal urination* are commonly noted by patients. The highest blood pressure values within a 24-hour period may be recorded at night occasionally producing retinal hemorrhages and CNS symptoms. Early studies in cardiac transplant recipients raised the possibility that changes in the circadian rhythm of blood pressure reflect cardiac denervation. However, there is an identical loss of normal pressure variation after cardiac transplantation, and also a smaller fall in cardiac output and a rise in systemic vascular resistance during the night. The loss of the nocturnal blood pressure fall is associated with a higher incidence of left ventricular hypertrophy, lacunar stroke, and microalbuminuria. Nocturnal blood pressure elevations may predispose transplant recipients to accelerated atherosclerotic complications. *Corticosteroids* have also been *associated with a loss of the nocturnal blood pressure fall* in other situations such as in Cushing's syndrome.

Cyclosporin and renal dysfunction attributable to cyclosporin commonly co-exist. Cyclosporin nephrotoxicity alone does not explain cyclosporin-induced hypertension. Several studies indicate that cyclosporin-induced hypertension is sodium-sensitive and may be modulated by sodium intake.

Remarkably, *hypertension persists later after transplantation despite reductions both in cyclosporin and corticosteroid dosages.* Occasionally, there is a reversal of post-transplant hypertension to normal levels of blood pressure during long-term follow-up.

Pathogenesis of hypertension after transplantation: The precise mechanism remains to be elucidated. During cyclosporin administration, there is an increased systemic vas-

cular resistance. The activity of the renin-angiotensin system is suppressed by cyclosporin even during restriction. This explains why ACE inhibitors have a limited antihypertensive efficacy early after transplantation.

Microneurographic studies of adrenergic nerve traffic in cardiac transplant recipients and myasthenia gravis indicate that cyclosporin enhances nerve activity although circulating catecholamine levels are normal. Studies in liver transplant recipients report a decrease in sympathetic nerve activity during cyclosporin administration. Some data support impaired endothelium-dependent vasodilation mediated by nitric oxide pathways in cyclosporin-induced vasoconstriction.

Management of hypertension during cyclosporin administration: The choice of antihypertensive therapy should take into account the reduced glomerular filtration rate and renal vasoconstriction universally present in all patients treated with cyclosporin. The patients usually have elevated uric acid, and cyclosporin partially inhibits renal potassium and hydrogen ion excretion predisposing to hyperkalemic metabolic acidosis. To prevent worsening of azotemia and hyperuricemia, diuretics are often avoided. Potassium-sparing agents must be used with caution. ACE inhibitors and angiotensin II antagonists, when used alone, have limited efficacy early after transplant, and may aggravate both hyperkalemia and acidosis. The gradual increase in plasma renin activity after transplantation provides clinical support to use *ACE inhibitors later. Dihydropyridine calcium antagonists are preferred,* mostly due to their ability to reverse cyclosporin-mediated vasoconstriction. Verapamil is a less potent vasodilator potentiating immunosuppression, thereby allowing to reduce cyclosporin doses. Beta-blockers have also been successfully used, either alone or in combination with dihydropyridines. *Labetalol*, an a-ß-blocker, is effective both intravenously and orally.

References

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