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Cyclosporin-Induced Hypertension
Incidence, Pathogenesis and Management

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Abstract

Blood pressure increases soon after administration of immunosuppressive regimens using cyclosporin. Characteristic vascular changes lead to systemic and renal vasoconstriction. Changes in blood pressure are commonly associated with disturbed circadian regulation and may promote the rapid development of target organ injury, including intracranial haemorrhage, left ventricular hypertrophy and microangiopathic haemolysis. The mechanisms underlying this disorder are complex and include altered vascular endothelial function. Vasodilators such as prostacyclin and nitric oxide are suppressed, whereas vasoconstrictors, including endothelin, are increased. Changes in the kidney include vasoconstriction, reduced glomerular filtration and sodium retention. Effective therapy depends upon rigorous blood pressure control by administration of vasodilating agents, with attention to potential interactions with cyclosporin.

For more than a decade, cyclosporin has been a mainstay of immunosuppression in organ transplantation. Improved survival rates with cyclosporin as compared with previous regimens limited to corticosteroids and azathioprine are well established and have led to broad expansion of solid organ transplantation, to include liver, heart, lung, and kidney-pancreas combinations.[1] Cyclosporin also has been used at lower dosages for the treatment of autoimmune diseases. Cyclosporin is a macrolide antibiotic, structurally different from a newer immunosuppressive agent tacrolimus although both share final pathways that inhibit cytokine release from lymphocytes. Cyclosporin is available as a lipid suspension in a cremaphor vehicle and more recently, in a new microemulsion formulation with enhanced bioavailability and absorption.

Both cyclosporin and tacrolimus have prominent effects on blood vessels, leading to wide-

spread vasoconstriction of the systemic circulation and an increase in arterial blood pressure. Vasoconstriction in the kidney results in decreased renal blood flow and is the basis for the nephrotoxicity observed with both agents.[2-5] These effects result in the appearance of new or the exacerbation of existing hypertension in virtually every clinical situation in which cyclosporin is used. Prevalence rates of post-transplant hypertension with cyclosporin and tacrolimus are similar by 1 year after transplant, although early severity and time of onset may differ.[6] Cyclosporin has been more extensively studied and is the focus of this discussion.

This review will summarise current understanding of the clinical features of hypertension that develops with cyclosporin-based regimens, the pathogenesis of post-transplant hypertension and recommendations for treatment.

1. Incidence of Hypertension Associated with Cyclosporin

Representative incidence rates for clinical hypertension before and after the introduction of cyclosporin are summarised in table I. Compared with the pre-cyclosporin era, cyclosporin is associated with increases in both the incidence and severity of hypertension in the transplant setting. Serial studies in patients treated with cyclosporin document a universal increase in systemic vascular resistance within days to weeks of administration

Table I. Prevalence of hypertension before and after cyclosporin administration (after Textor et al.,[7] with permission)

Indication	Hypertension (%)	
	before cyclosporin	after cyclosporin
Transplant		
Bone marrow	5-10	33-60
Cardiac	10	71-100
Liver	NA	65-85
Renal	45-55	67-86
Nontransplant		
Rheumatoid arthritis	NA	42-45
Uveitis	NA	23-29
Myasthenia gravis	NA	81
Psoriasis	NA	30

NA = not applicable.

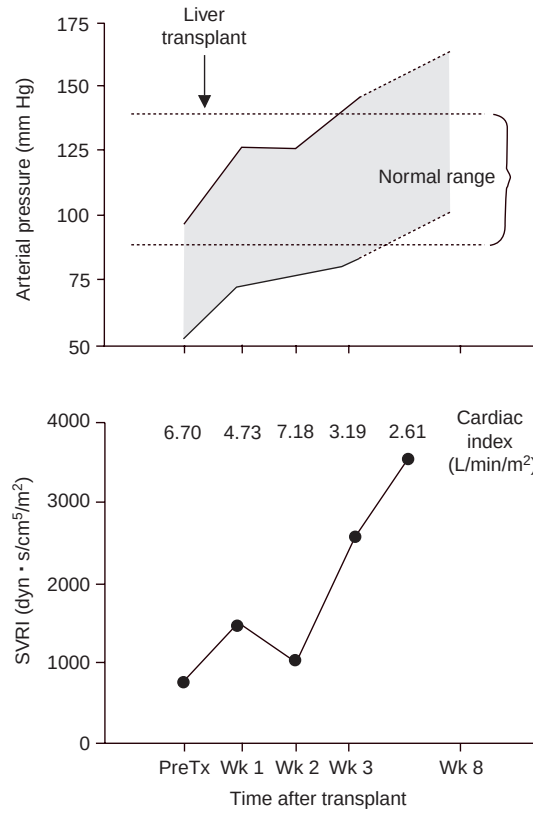

Fig. 1. Blood pressure, cardiac index and calculated systemic vascular resistance index (SVRI) in a patient followed serially during development of *de novo* hypertension after liver transplantation. Blood pressure was low before transplantation (see top graph) because of widespread splanchnic vasodilation associated with hyperdynamic cardiac output in end-stage liver disease. Blood pressures increase immediately and progressively after transplantation mediated by a rise in systemic vascular resistance. The patient received immunosuppression with azathioprine, cyclosporin and a tapering regimen of prednisone from the time of transplantation (reproduced from Textor et al.,[7] with permission). **PreTx** = pre-transplant.

(fig. 1).[7] Whether such increases reach 'hypertensive' levels depends on threshold pressures defined as abnormal. Prevalence rates in patients receiving cyclosporin for nontransplant indications such as psoriasis or uveitis range from 29 to 54%,[8] while rates for heart and liver transplant recipients treated with the combination of cyclosporin and cortico-

steroids range from 71 to 100%. In the latter situations, hypertension typically occurs *de novo* in previously normotensive individuals. Features of cyclosporin-associated hypertension specific to the type of organ transplant are described in table II.

Renal transplant recipients treated with cyclosporin present a special challenge in isolating the hypertensive and nephrotoxic effects of cyclosporin. Most patients with renal failure are hypertensive before transplantation. Transplant complications such as rejection, organ preservation injury and transplant renal artery stenosis can impair renal function and worsen hypertension. Nevertheless, aggravation of hypertension by cyclosporin has been confirmed by blood pressure reductions seen with the later withdrawal of cyclosporin.

The role of corticosteroids in cyclosporin-induced hypertension is complex. While glucocorticoids alone rarely have major effects on blood pressure in individuals with normal renal function, corticosteroids administered in immunosuppressive doses to patients with impaired renal function commonly aggravate hypertension. The association of higher corticosteroid dose regimens during tacrolimus administration in liver transplant recipients with higher incidence rates of hypertension suggests that higher corticosteroid doses profoundly affect the rate and severity of blood pressure change.[6] Recent efforts to withdraw corticosteroids indicate that blood pressure falls despite continued cyclosporin administration.[9,10] Hence, it is likely that both cyclosporin and corticosteroid dose in combination are major elements in the prevalence and severity of post-transplant hypertension.

2. Clinical Features of Cyclosporin-Induced Hypertension

Arterial pressure rises within days of cyclosporin administration, before changes in renal function or sodium balance can be detected.[7,11] When corticosteroids are added, the blood pressure may increase further to levels that prompt antihypertensive therapy within the first weeks or months. Serial studies in liver transplant recipients indicate that the rise in blood pressure progresses to clinically significant levels over several weeks, sometimes rising 40 to 50mm Hg. Between 1 and 6 months after transplant, 70 to 100% of heart and liver transplant recipients have blood pressure levels which merit the initiation of antihypertensive therapy (>140/90mm Hg).[7]

Hypertension developing after organ transplantation is characterised by disturbed circadian rhythm, with absence or reversal of the normal nocturnal fall in blood pressure (fig. 2). Nocturnal headaches and increased nocturnal urination are commonly noted by patients. The highest pressures within a 24-hour period may be recorded at night (fig. 3), occasionally producing accelerated hypertension with retinal haemorrhages and CNS symptoms. Early studies in cardiac transplant recipients raised the possibility that changes in circadian rhythm of blood pressure reflect cardiac denerva-

Table II. Clinical features of cyclosporin-induced hypertension by type of organ transplant

Type of transplant	Features
Heart	*De novo* hypertension is nearly universal. Higher rates of left ventricular hypertrophy. Allograft vasculopathy leads to accelerated coronary injury. Subset with progressive renal failure
Liver	*De novo* hypertension. Marked rise in blood pressure with transition from pretransplant systemic vasodilation to vasoconstriction. Reported complications: haemolytic uraemic syndrome, intracranial haemorrhage
Kidney	Majority with pretransplant hypertension. Multiple causes post-transplant include rejection, organ preservation injury, transplant renal artery stenosis. Sodium sensitive
Bone marrow	Severe hypertension during acute cyclosporin therapy, later resolves. Total body irradiation may accelerate renal vascular injury. Reported complications: microangiopathic haemolysis, intracerebral haemorrhage, encephalopathy, seizures
Nontransplant uses	Less rapid rise in blood pressure. Progression to hypertension is less common. Higher prevalence in those with hypertension before cyclosporin. Reversible changes in GFR out to 2.5 years after initiation of therapy

GFR = glomerular filtration rate.

tion.[12,13] However, identical loss of normal pressure variation after renal and liver transplantation argues against this mechanism.[14] Haemodynamic measurements after cardiac transplantation demonstrate an attenuated fall in cardiac output with a rise in systemic vascular resistance during the night.[15] In patients with essential and secondary hypertension, loss of nocturnal blood pressure fall is associated with a higher incidence of left ventricular hypertrophy, lacunar stroke and microalbuminuria.[16-18] By the same token, nocturnal blood pressure elevations may predispose transplant recipients to accelerated atherosclerotic complications. Serial studies in cardiac and liver transplant recipients suggest that a portion of patients will regain more normal circadian blood pressure patterns by 1 year after transplantation.[19,20] Corticosteroids have also been associated with loss of nocturnal blood pressure fall in other situations such as Cushing's syndrome.[21,22] As corticosteroid dosages are routinely tapered at later times after transplantation, it is difficult to separate effects of corticosteroid dosage from the effects of other time-related mechanisms after transplant.

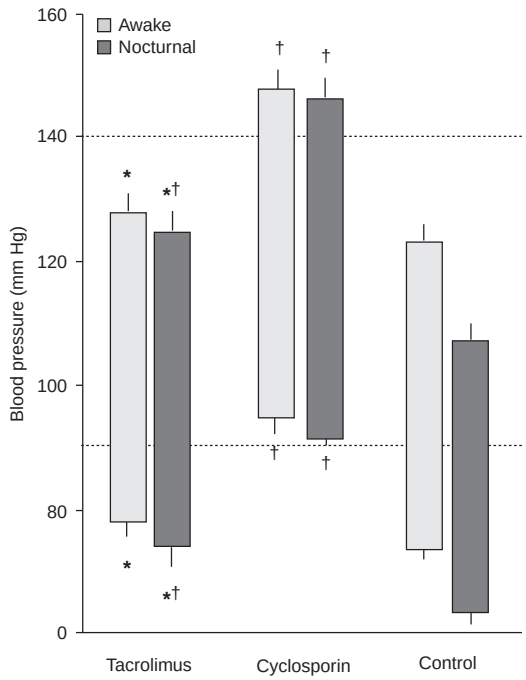

Fig. 2. Awake and nocturnal blood pressure readings taken by ambulatory blood pressure monitoring 1 month after liver transplantation. Both cyclosporin and tacrolimus-treated patients failed to demonstrate a nocturnal pressure fall, in contrast to control patients. Nocturnal heart rates fell to a similar degree in all groups. * = $p < 0.01$ compared with cyclosporin recipients; † = $p < 0.01$ compared with control patients.

Cyclosporin-induced hypertension can lead to significant target organ damage after transplantation. It may progress to an accelerated phase with vascular injury, including microangiopathic haemolysis, encephalopathy and seizures.[7] Intracranial haemorrhage has occurred. Most severe manifestations occur in children and patients who were previously normotensive. Distinguishing between the effects of high blood pressure and direct vascular toxicity from cyclosporin may be difficult.

Hypertension and renal dysfunction attributable to cyclosporin commonly co-exist. Both conditions reflect vasoconstriction and have been considered different facets of a single problem.[7,23] It is clear that cyclosporin nephrotoxicity alone does not explain cyclosporin-induced hypertension.[7] Several studies indicate that cyclosporin hypertension is sodium sensitive and may be modulated by sodium intake.[24] Initial changes in renal blood flow, glomerular filtration and sodium reabsorption are haemodynamically mediated and reversible upon withdrawal of cyclosporin. Pathological changes in the kidney may become irreversible after long term exposure, both in humans and in animal models.[25] Studies in vascular smooth muscle and in experimental models indicate that disturbances of endothelial substances including nitric oxide, endothelin and interactions with angiotensin may favour cytokine production and local stimulation of mitogenesis and collagen production leading to permanent scarring.[25]

The natural history of hypertension related to cyclosporin is not well known primarily because patients are treated, to prevent the complications mentioned above. Frequently, other cardiovascular risk factors also change after transplantation with increases in cholesterol and triglyceride levels and bodyweight gain. Cardiovascular events are a ma-

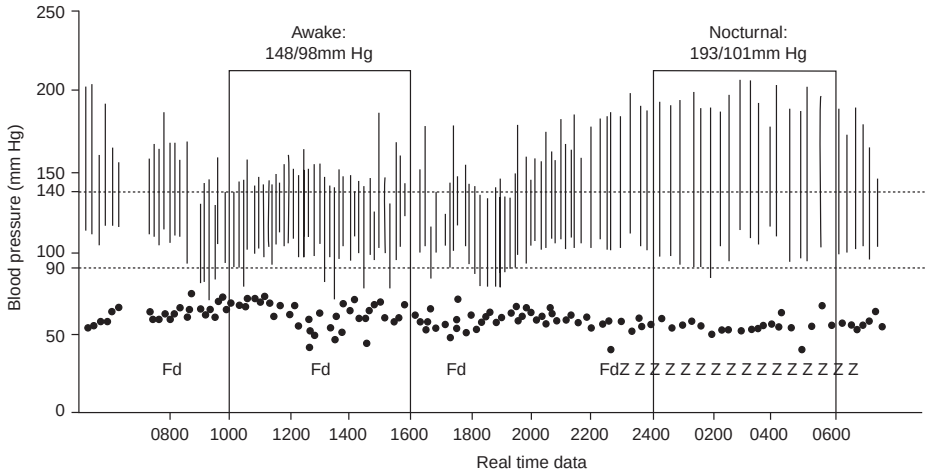

Fig. 3. Ambulatory blood pressure monitoring for 24 hours recorded within 2 months after orthotopic liver transplantation in a 35-year-old woman treated with cyclosporin-based immunosuppression. Although day-time pressures were modestly elevated, the highest pressures occurred during the nocturnal period (marked by ZZZ). Nocturnal hypertension has been associated with rapid development of target organ damage. **Fd** = food.

jor cause of late mortality after renal and cardiac transplantation.[26-28] Hence, management of coexisting cardiovascular risk factors, such as hypertension, is likely to be an important element in determining ultimate outcomes after organ transplantation.

Remarkably, hypertension persists late after transplant, despite reduction in cyclosporin and corticosteroid dosages. In the transplant hypertension unit of the Mayo Clinic, Rochester, US, more than 75% of liver transplant recipients remain on antihypertensive medications for more than 3 years following transplantation.[29] Antihypertensive medication dosage requirement are highest in the first year and decline slightly thereafter. Occasionally, we have observed reversal of post-transplant hypertension to normal levels of blood pressure during long term follow-up (5% of patients).[7] This occurs despite equally severe renal dysfunction in patients whose hypertension 'resolves'. Cyclosporin-induced changes in blood pressure and renal function are usually reversed by withholding the drug or decreasing the dosage. Reports from patients who undergo transition from cyclosporin to azathioprine therapy after renal transplantation indicate that reversal of these effects may occur several years after transplantation.[30]

3. Pathogenesis of Hypertension After Transplantation

The precise mechanisms underlying cyclosporin-induced hypertension remain to be elucidated. Study of this problem has been difficult because results from animal studies differ substantially from those in humans. Most experimental models of cyclosporin administration demonstrate renal and vascular changes, but fail to manifest hypertension. Thus, major species differences have been reported related to cardiovascular and neuroendocrine effects of cyclosporin. In this review, we focus primarily on data from human studies.

The haemodynamic basis for elevated arterial pressure during cyclosporin administration is increased systemic vascular resistance. This parameter has been measured in sequential studies during the first weeks after administration of cyclosporin and after several years.[5,31] The primary focus of current research efforts is to elucidate the mecha-

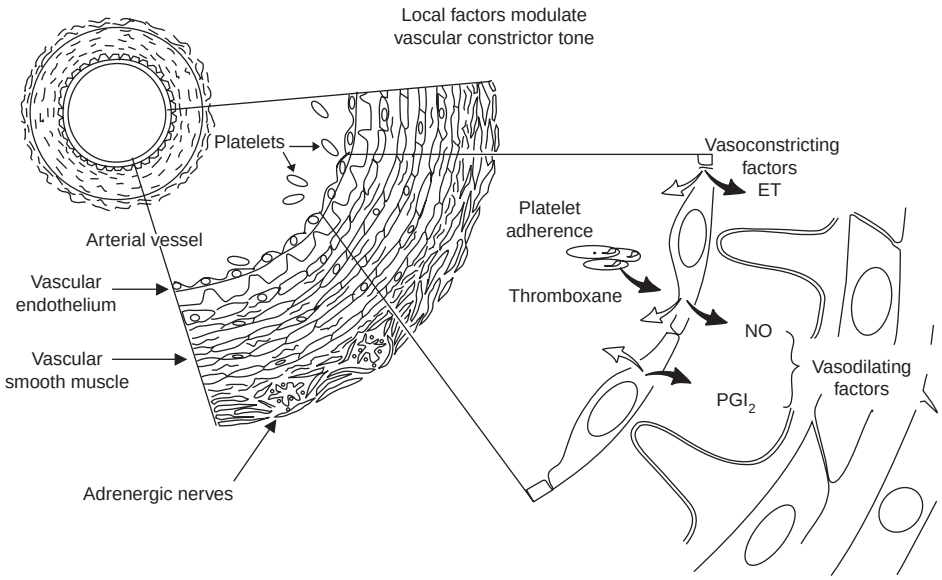

Fig. 4. Schematic diagram of blood vessel wall and several local mechanisms that regulate smooth muscle tone. After transplantation, vasoconstriction with cyclosporin coincides with abnormalities of locally induced vasoconstrictors, such as endothelin (ET) and thromboxane, in combination with impaired vasodilation from suppression of prostacyclin [prostaglandin I_2 (PGI_2)] and nitric oxide (NO). Such changes interact with altered systemic adrenergic and hormonal stimuli (reproduced from Textor et al.,[7] with permission).

nisms responsible for cyclosporin-induced vasoconstriction.

Unlike studies in the rat and dog, human studies indicate that activity of the renin-angiotensin system is suppressed after cyclosporin administration even during sodium restriction.[32,33] When used alone, ACE inhibitors have limited antihypertensive efficacy early after transplant.[34] These observations suggest that the circulating renin-angiotensin system is a minor participant in the development of post-transplant hypertension. Plasma renin activity rises gradually in liver transplant recipients over the first 2 years after transplant.

The role of adrenergic mechanisms in post-transplant hypertension remains uncertain. Experimental studies indicate a major role for the renal nerves in modulating cyclosporin-induced renal vasoconstriction and sodium retention.[35] These effects are reversed by renal denervation or adrenergic blocking agents. Human renal transplants, however, demonstrate cyclosporin-induced vasoconstriction and hypertension immediately after transplantation despite being surgically denervated. Hence, renal nerves are not essential for cyclosporin mediated vasoconstriction in humans. Microneurographic studies of adrenergic nerve traffic in cardiac transplant recipients and myasthenis gravis patients indicate that cyclosporin enhances nerve activity, although circulating catecholamine levels are normal.[36] Other studies have not confirmed these results.[37] Similar studies in liver transplant recipients report a decrease in sympathetic nerve activity during cyclosporin administration.[38]

To add to the confusion, vascular reactivity to adrenergic stimuli may be altered in the presence of cyclosporin. Some studies report increased sensitivity to pressor stimuli whereas others report diminished responsiveness.[7] Intravenous methyldopa is ineffective in reducing arterial pressure in hypertensive bone marrow transplant recipients.[34] Hence, a primary role for adrenergic mechanisms in cyclosporin hypertension is questionable.

Numerous potential mechanisms for vascular smooth muscle constriction may account for re-

sponse to cyclosporin (fig. 4). Cyclosporin is highly lipophilic and freely permeates cell membranes, including endothelial cells. As is widely recognised, local production of vasoactive materials, such as nitric oxide, prostacyclin and endothelin, may profoundly alter vasomotor tone. These mediators have been the focus of recent studies.

Endothelin is a potent vasoconstrictor and mitogenic stimulant, stimulated both *in vitro* and *in vivo* by cyclosporin. Circulating levels are elevated modestly after transplantation,[32,39] but are regulated independently from levels from regional vascular beds, such as urinary endothelin.[40] Urinary endothelin levels increase after cyclosporin administration and remain elevated indefinitely.[40] Animal studies suggest that some, but not all, vasoconstriction during cyclosporin administration may be related to endothelin.[41,42] Subpressor doses of endothelin modify the effects of other vasoactive stimuli, such as the effects of norepinephrine (noradrenaline) or inhibition of nitric oxide.[43] Studies of renal transplant recipients receiving long term cyclosporin therapy demonstrate major decreases in renal plasma flow and glomerular filtration rate transiently 4 to 6 hours after administration of the cyclosporin.[44] While plasma endothelin levels were unchanged, urinary endothelin levels increased in parallel with the renal haemodynamic changes (fig. 5). Whether endothelin is an important vasoactive modulator after human transplantation is not yet known.

The role of thromboxane after cyclosporin exposure has not been established. While animal models indicate increased thromboxane levels after cyclosporin administration, human studies indicate that urinary thromboxane excretion falls after cyclosporin administration.[32] Use of thromboxane synthase inhibitors in renal transplant recipients produces only minor changes in renal blood flow and glomerular filtration.[45] Fish oil supplements, administered to divert prostaglandin pathways away from thromboxane, have variable effects, and initial benefits regarding nephrotoxicity and blood pressure have not been confirmed.[46,47] Fish oil supplementation has numerous potential effects, including enhancement of endothelium-dependent vasodilation and thus must be considered nonspecific. Taken together, few data support a role for thromboxane in cyclosporin-induced vasoconstriction in humans.

Could vasoconstriction and hypertension reflect withdrawal of tonic vasodilatory mechanisms? Experimental studies suggest that prostacyclin, a vasodilatory prostaglandin, is

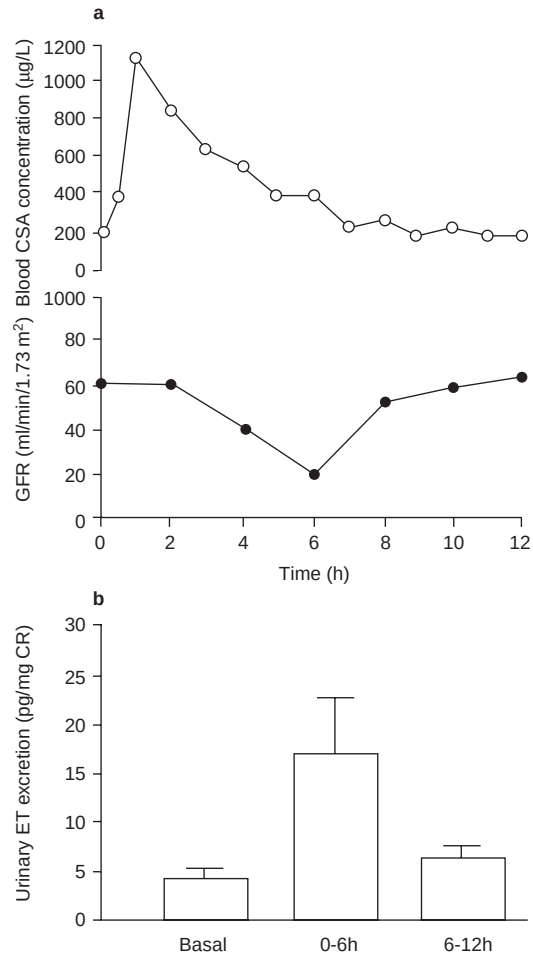

Fig. 5. Transient reduction in glomerular filtration rate (GFR) occurring 6 hours after administration of oral cyclosporin (CSA) dose in a representative kidney transplant recipient (**a**). Urinary excretion of endothelin (ET) rose within the first 6 hours after peak cyclosporin concentrations (**b**) (reproduced from Perico et al.[44] with permission). **CR** = creatinine.

increased during exposure to cyclosporin.[48,49] Results from human studies, however, demonstrate sustained reduction in prostacyclin excretion in cyclosporin-treated liver transplant recipients.[32,50] Similar results have been observed in isolated vascular smooth muscle cells and in patients with non-transplant applications of cyclosporin.[51] Studies using dopamine, an agent purported to require prostacyclin production for renal vasoactive effects in humans, demonstrate restoration of prostacyclin and partial restoration of blood flow in the kidney when infused in cyclosporin-treated volunteers.[52]

Considerable data support a role for impaired endothelium-dependent vasodilation mediated by nitric oxide pathways in cyclosporin-induced vasoconstriction. Inhibition of nitric oxide synthase in normal rats produces widespread vasoconstriction, pressure elevations and changes in urinary electrolyte handling similar to those observed with cyclosporin. Studies in renal transplant recipients indicate that urinary nitrates are reduced and vasodilatory response to infused *L*-arginine (the substrate for nitric oxide production) is reduced in cyclosporin-treated patients as compared with control individuals.[53] Human subcutaneous vessels obtained from patients treated with cyclosporin demonstrate impaired endothelium-dependent vasodilation *in vitro*.[54] Further study of nitric oxide in humans has been limited by the evanescent characteristics of nitric oxide and inherent difficulty in accurately measuring levels of activity of this system in the intact organism.

Some authors have proposed that alterations in intracellular calcineurin by cyclosporin and other immunosuppressive agents including tacrolimus mediate both vasoconstriction and immunosuppressive mechanisms.[36] These authors[36] suggest that other immunosuppressive agents that do not

Table III. Therapy for cyclosporin-induced hypertension (after Textor et al.,[7] with permission)

Class of drug	Features	Adverse effects	Cyclosporin disposition
Calcium antagonists	Potent vasodilators		
Dihydropyridine			
Nifedipine	Reverses cyclosporin-mediated vasoconstriction	Oedema, headache	–
Isradipine			–
Felodipine			–
Amlodipine			±
Nicardipine			++
Diltiazem HCL	Moderate potency reduces coronary vasculopathy after heart transplantation	Oedema, headache	++
Verapamil HCL	Least potent vasodilator, potentiates immunosuppression?	Constipation, slow heart rate, atrioventricular block	++
β-Blockers	May diminish cyclosporin-induced headache	Slow heart rate, bronchospasm	–
α-β Blockers			
Labetolol	Effective intravenously and orally	Slow heart rate, postural hypotension	–
ACE inhibitors			
Enalapril	Limited efficacy alone	Aggravates hyperkalaemia, azotaemia	–
Lisinopril	Effective with diuretics may limit renal fibrosis	Non-anion gap metabolic acidosis	–
Diuretics			
Thiazide-class: e.g. indapamide	Counteracts sodium retention potentiate other antihypertensive medications	Aggravates pre-renal azotaemia, hyperuricaemia	–
Loop diuretics: e.g. furosemide (frusemide)	Potent, short acting	Magnesium and potassium losses	–

HCL = hydrochloride; **–** signifies no reported effect on the concentration or disposition of cyclosporin; ± signifies possible slight interference with the disposition of cyclosporin; + signifies interference with the disposition of cyclosporin; ++ signifies strong interference with the disposition of cyclosporin.

require interaction with calcineurin, such as rapamycin, may lack the vascular effects that result in nephrotoxicity and hypertension.

It is likely that the abovementioned mechanisms are interdependent. Cyclosporin alters function of the endothelium in general. As supported by studies in the dog, vasomotor tone depends finally on the relative balance of vasodilatory pathways such as nitric oxide and prostacyclin and vasoconstrictive pathways such as endothelin and thromboxane. Effects of low doses of endothelin are magnified in many vascular beds during simultaneous inhibition of nitric oxide using *L*-nitromonomethyl-arginine ester.[43]

Collectively, multiple lines of evidence indicate that vascular regulation changes profoundly after transplantation using immunosuppressive regimens based on cyclosporin and corticosteroids. In severe instances, cyclosporin vascular toxicity leads to release of endothelium-derived factor VIII antigen, intravascular haemolysis and fibrin deposition.[7] In less severe instances, this alteration is reflected as a shift of vascular regulation in favour of regional and often widespread vasoconstriction.

4. Management of Hypertension During Cyclosporin Administration

Relatively few studies systematically address the optimal treatment of hypertension during cyclosporin administration. Based on a decade of experience with the use of cyclosporin, certain general principles have emerged to guide selection of antihypertensive therapy. Table III summarises features of several drug classes commonly used.

Several principles merit emphasis. The choice of antihypertensive agent should take into account the reduced glomerular filtration rate and renal vasoconstriction universally present in all patients who receive cyclosporin either for transplant immunosuppression or for nontransplant indications. Uric acid levels are elevated, sometimes profoundly. Cyclosporin partially inhibits renal potassium and hydrogen ion excretion, predisposing patients to hyperkalaemic metabolic acidosis. Diuretic therapy is often avoided to prevent worsening of azotaemia and hyperuricaemia. Potassium sparing agents must be used with caution. ACE inhibitors and angiotensin II receptor antagonists, when used alone, have limited efficacy early after transplant and may aggravate both hyperkalaemia and acidosis.

In the selection of antihypertensive agents, it is also necessary to consider the effects of agents on cyclosporin disposition and blood concentrations. Several calcium antagonists, particularly verapamil, nicardipine and to a lesser extent diltiazem, interfere with cyclosporin metabolism and lead to accumulation of the drug.[7] The withdrawal from the market of mibefradil, a selective 'T-type' calcium antagonist was prompted by reports of numerous cytochrome P450–mediated drug interactions, including a 2-fold rise in cyclosporin and tacrolimus concentrations. While this property has been used to reduce cyclosporin dosage requirements and hence drug costs, if not recognised and monitored closely, this effect can lead to unexpected episodes of cyclosporin-related toxicity.[55]

In the Mayo Clinic Transplant Hypertension unit, dihydropyridine calcium antagonists are relatively 'preferred' agents for cyclosporin-related hypertension. This choice is related partly to their efficacy at smooth muscle vasodilation. The dihydropyridine class in particular can overcome even potent vasoconstriction produced by endothelin. Nifedipine, isradipine and felodipine have negligible effects on cyclosporin disposition and are potent vasodilators. All 3 drugs have been used successfully in transplant settings. Amlodipine has minor effects on cyclosporin disposition and has been studied in renal transplant recipients with good results.[56-59] During systemic administration of both nifedipine and isradipine, vasodilation translates into reduced systemic vascular resistance during blood pressure reduction. However, at antihypertensive dosages used clinically, no change in glomerular filtration rate or renal blood flow has been demonstrated in more than 250 patients treated sequentially.[60]

Other antihypertensive agents may also be effective. β-Blockers have been used successfully,

Table IV. Effect of diuretics on blood pressure (BP) and renal function after liver transplantation.[a] All values are given as mean ± standard error of the mean

	Diuretic-treated patients (n = 39)		Matched control participants (n = 39)	
	time I[b]	time II[c]	time I[b]	time II[c]
Systolic BP (mm Hg)	146 ± 3	132 ± 2[d]	135 ± 3[e]	137 ± 2
Diastolic BP (mm Hg)	92 ± 2	83 ± 1[d]	82 ± 2[e]	86 ± 2[f]
Serum creatinine level (μmol/L)	119 ± 7	141 ± 6[d]	119 ± 7	129 ± 4
GFR (ml/sec/1.73m^3)	1.00 ± 0.06	0.92 ± 0.06	1.02 ± 0.08	1.08 ± 0.06[g]

a Blood pressure decreased in liver transplant recipients treated with a diuretic. While there was a small decline in renal function compared to transplant recipients who did not receive diuretics, this reduction did not progress with duration of therapy, out to 15 ± 2 months after transplant.

b Time I is before diuretic therapy (mean time 3.2 ± 0.6 months after transplant).

c Time II is during diuretic therapy (mean time 10.9 ± 1.4 months after transplant).

d $p < 0.01$ *vs* time I.

e $p < 0.05$ *vs* diuretic patients at time I.

f $p < 0.05$ *vs* time I.

g $p < 0.01$ *vs* diuretic patients at time II.

GFR = glomerular filtration rate.

either alone or in combination with dihydropyridines.[7] The gradual increase in plasma renin activity after transplant, provides clinical support for use of ACE inhibitors during later time periods. Several trials indicate that ACE inhibitors may be used safely, particularly when combined with diuretics.[61]

Diuretics are commonly withheld after transplantation out of fear of worsening cyclosporin-induced nephrotoxicity. To define the magnitude of their effects on renal function and blood pressure, we compared 39 liver transplant recipients treated with a diuretic [thiazide type or furosemide (frusemide)] with 39 liver transplant recipients not receiving diuretics, matched for serum creatinine level and time after transplant. Measurements of blood pressure and renal function were examined before (mean time 3.2 ± 0.6 months after transplant) and during diuretic treatment (mean time 10.9 ± 1.4 months after transplant) and at similar time-points in the matched group. Blood pressure fell with diuretic therapy (table IV). While there was a small decline in renal function of 9% detectable by serum creatinine level measurement and iothalamate clearance, the reduction in glomerular filtration rate did not progress with longer duration of diuretic therapy, with a follow-up of up to 15 months after transplant. In our experience, the addition of diuretics rarely poses problems and potentiates the efficacy of most antihypertensive regimens.

Review of the Mayo unit experience with *de novo* hypertension related to cyclosporin in liver transplant recipients, indicates that one-third of patients achieve acceptable blood pressure control with a dihydropyridine calcium antagonist alone and one-third of patients will achieve acceptable blood pressure control with labetalol alone.[29] The remaining patients will require treatment with a second agent. Noteworthy here is the observation that even moderate doses of antihypertensive agents commonly produce intolerable oedema, fatigue or postural symptoms in more than 30% of patients. These patients often change regimens completely, more often than patients with essential hypertension managed by the same nursing personnel. We attribute the sensitivity of transplant recipients to adverse medication effects to the additional burdens of postoperative recovery, resumption of physical activity after prolonged disability and interactions with other medications.

With the gradual taper of cyclosporin and corticosteroid dosages, treatment of hypertension may require less medication over time. However, the majority of patients continue to require treatment. The recent introduction of a microemulsion formu-

lation of cyclosporin claimed to offer increased bioavailability and a more predictable pharmacokinetic profile[62] and continued efforts to taper corticosteroids early may change the course of post-transplant hypertension in the future even with continued use of cyclosporin. Calcium antagonists have been studied as adjuvants to immunosuppression in experimental settings. Recent clinical trials suggest these agents may offer protection from graft failure in renal transplant recipients[63-65] and may slow development of the atypical coronary vascular lesions observed after cardiac transplantation.[66] Calcium antagonists have been used to promote renal vasodilation and thereby prevent cyclosporin-induced nephrotoxicity after renal transplantation.[59,67-69] To date, efforts to prevent cyclosporin related hypertension with calcium antagonists have not been effective. Oral supplementation with omega-3 fatty acids has been reported to prevent hypertension and reduce the extent of blood pressure rise by systemic vasodilatation after cardiac transplant and has been recommended as an adjuvant to antihypertensive therapy.[70]

5. Conclusion

Development of hypertension is almost universal during treatment with cyclosporin-based immunosuppression and occurs in both transplant and nontransplant settings. Particularly in transplant patients, the underlying mechanism of altered vascular reactivity and systemic and renal vasoconstriction results in impaired glomerular filtration and sodium retention, magnified by the effects of corticosteroids. Management requires anticipation of these changes and intervention to avoid serious adverse consequences.

Acknowledgements

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