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A Practical Guide to the Management of Hypertension in Renal Transplant Recipients

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Abstract

Hypertension as well as hypotension can be harmful to a newly transplanted renal allograft. Elevated blood pressure is also a major risk factor for cardiovascular death, which is a frequent occurrence despite successful renal transplantation. Renal artery stenosis, immunosuppressive drugs, chronic rejection, retained native kidneys, and excessive extracellular fluid volume may all contribute to post-transplant hypertension. Antihypertensive agents are widely used in the management of post-transplant hypertension. Careful clinical judgement and knowledge of the pharmacology, pharmacodynamics, pharmacokinetics, adverse drug reaction profiles, potential contraindications, and drug-drug interactions of antihypertensive agents are important when therapy with antihypertensive drugs is initiated in renal transplant recipients. Since blood pressure elevation in any individual is determined by a large number of hormonal and neuronal systems, the effect of antihypertensive agents on the allograft should be considered a critical factor in the management of hypertension in renal transplant recipients. Most renal transplant recipients have other risk factors for premature cardiovascular death such as diabetes mellitus, hypercholesterolemia, insulin resistance, obesity, left ventricular hypertrophy and ischaemic heart disease. Initial antihyperten-

sive therapy should be tailored individually according to the patient's risk factors. A realistic therapeutic goal for blood pressure management in the initial post-operative state is a systolic blood pressure <160mm Hg and a diastolic blood pressure <90mm Hg with lower pressure targets becoming applicable late post-transplantation.

Cardiovascular and cerebrovascular diseases are major causes of mortality in renal transplant recipients with functioning allografts.[1-5] The association of hypertension with stroke, congestive heart failure, peripheral arterial disease and coronary heart disease (CHD) has been investigated in several collaborative prospective and observational studies in nontransplant populations. A higher incidence of primary and secondary cerebrovascular and cardiovascular events were observed among patients with hypertension compared with normotensive individuals.[6,7] According to recent data from United States Renal Data System, in 1997 the mortality from cardiac arrest, acute myocardial infarction (MI) and other cardiac causes account for 46% of all deaths in patients with diabetes mellitus and functioning allografts.[1]

Hypertension is a common complication in renal transplant recipients.[8,9] It has been estimated that 60 to 70% of all renal transplant recipients become hypertensive, or have increased blood pressure over their baseline levels, after transplantation.[10,11] As many as 90% of extra-renal transplant recipients also have a rise in blood pressure after successful engraftment.[12-14] Since well designed clinical studies have provided strong evidence supporting a correlation between hypertension and mortality in nontransplant patients, it is logical to assume that renal allograft transplant recipients have at least the same or greater risk for premature cardiovascular morbidity and mortality associated with hypertension. Reduction of diastolic blood pressure (DBP) of 5 to 10mm Hg in a nontransplant patient with hypertension may decrease the risk of stroke by 42% and CHD by 14%.[15]

Treatment of elevated blood pressure in renal transplant recipients significantly reduces morbidity and mortality.[4,5] Post-transplant hypertension has been recognised as an independent risk factor for allograft survival.[16] In a recent study, Opelz et al.[16] investigated the influence of high blood pressure on renal allograft survival in 29 751 renal transplant recipients over a 7-year period. A negative correlation was noted between chronic kidney allograft failure and hypertension. Interestingly, this negative correlation was observed in both cadaveric and living donor allograft kidneys.

The introduction of cyclosporin into the immunosuppressive regimens of transplant recipients has increased allograft and patient survival;[17] however, its use is associated with hypertension. Hypertension after renal transplantation in patients receiving cyclosporin is associated with impaired glomerular filtration rate (GFR), decreased renal blood flow, increased intrarenal vascular resistance, salt sensitivity and suppressed plasma renin activity.[18-20]

Blood pressure is regulated by a number of hormonal and neuronal systems. The effect of antihypertensive agents on the allograft is a critical factor in the management of hypertension in renal transplant recipients. Most renal transplant recipients have several risk factors such as diabetes mellitus, hypercholesterolaemia, insulin resistance, obesity, left ventricular hypertrophy, and ischaemic heart disease. The effect of antihypertensive drugs on pre-existing conditions also should be considered. In addition, immunosuppressive drugs may accentuate coronary artery risk factors and these risk factors should be screened and monitored routinely.[22,23]

In general, blood pressure should be lowered slowly and gradually so that the patient is able to tolerate antihypertensive therapy optimally. Too rapid or intense a reduction in blood pressure may produce signs and symptoms of organ ischaemia with serious consequences.

When the systolic blood pressure (SBP) is

>200mm Hg and the DBP is >120mm Hg, hypertension may precipitate a medical emergency requiring rapid reduction of blood pressure to prevent vital organ damage. The initial therapeutic goal for blood pressure management in the early post-transplant period is a SBP of <160mm Hg and a DBP <90mm Hg. Multiple factors such as extracellular fluid volume, graft dysfunction and intensity of immunosuppressive therapy may have an important role in the fluctuation of blood pressure. The fine tuning of blood pressure should be managed on an outpatient basis only in stable transplant patients.

The objective of this review paper is to discuss the pathophysiology and treatment of post-transplant hypertension, and provide clinicians with a database necessary to improve pharmacotherapeutic outcomes in renal transplant recipients.

1. Pathophysiology of Post-Transplant Hypertension

1.1 Renal Artery Stenosis

Renal artery stenosis in renal allograft has been recognised as a prevalent cause of systemic arterial hypertension after successful kidney transplantation. Because of the lack of sensitivity and specificity of non-invasive diagnostic methods, the true incidence of this problem is largely unknown, with estimates varying from as low as 1% to as high as 23%.[24] Data applying renal allograft artery angiography as a screening procedure are lacking in the literature.

The clinical presentation of renal artery stenosis-induced hypertension is similar to that of renal artery stenosis in solitary-native kidney (one-kidney, one-clip Goldblatt model). Hypertension of recent onset, which is difficult to control, or in association with allograft dysfunction (as measured by serum creatinine levels), should raise the suspicion of renal allograft artery stenosis. Reports of acute renal insufficiency induced by the use of ACE inhibitors, and the presence of audible bruits over the graft implantation area are present in the literature.[25] However, the true sensitivity and specificity of these findings are unknown.

The use of colour Doppler ultrasonography as a diagnostic method has gained much popularity as the resolution of transducers and expertise of sonographers have improved over the past decade. However, it is still an operator-dependent technique, and as such is subject to a wide variation in reproducibility. Similarly, nuclear renogram with or without captopril enhancement suffers from lack of standardisation. Magnetic resonance angiogram and 3D spiral computed tomography (CT) imaging have been used more recently, yet no large series comparing these techniques with the conventional ones have been reported. Selective renal allograft artery angiography is considered the gold standard. However, it involves the risks of iodine contrast-induced nephropathy, arterial puncture and cannulisation of small vessels with potential for bleeding or dissection of the intimal layer. The recent development and clinical application of CO_2 angiography could result in high-resolution images without the hazard of contrast nephropathy.[26]

Renal artery stenotic lesions can be classified as diffuse or focal. Focal lesions can be present at the site of anastomosis or apart from it. Aetiological factors described are:[27,28] 1) pre-existing donor renal stenosis (not diagnosed prior to procurement); 2) microscopic tears of the intima of the arteries during procurement, perfusion or implantation; or 3) surgical technique used for artery anastomoses (end-to-end anastomosis most commonly described as a risk factor). Vascular risk factors in the recipient, such as dyslipidaemia, diabetes mellitus and the presence of a hypercoagulable state have not been extensively addressed in the literature. The role of immunological factors post transplant has been suggested.[29]

Percutaneous transluminal angioplasty (PTA) is the treatment of choice for most patients with focal lesions. It is the least invasive of the interventional therapies, and it carries a high rate of short-term success when conducted in experienced centers. Large studies addressing the response rate in different types of lesions, the use of expandable

stents, and long term (>2 years) patency of those vessels are lacking in the literature. Surgical correction of allograft renal artery stenosis is the next step in therapy. It is a demanding procedure with high rate of graft loss, requiring a highly experienced surgical team. Again, the long term patency and function of those grafts are unknown. Medical treatment has traditionally been reserved for high-risk surgical recipients, and for those patients with unchanged serum creatinine, in whom blood pressure can be easily controlled with minimal adverse effects from medications.

In summary, the detection of renal artery stenosis in renal allograft requires a high index of suspicion and the use of sophisticated and expensive diagnostic techniques. The importance of a correct diagnosis is paramount as it could lead to therapeutic interventions that may result in normalisation of blood pressure and creatinine levels, and hopefully increase kidney graft and patient survival.

1.2 Native Kidneys

The exact role of retention of native kidneys in the incidence of systemic hypertension in recipients of a well-functioning renal allograft is not known. Clinical studies investigating the incidence of hypertension in renal allograft recipients with or without native nephrectomy indicates that the native kidney may play an important role in the pathogenesis of hypertension in some patients following transplantation.[30-32] The benefits of native nephrectomies and embolisation in terms of blood pressure control were described more than a decade ago.[30,31] The poor applicability of peripheral renin level measurement as a screening test is well known.[33] Imaging studies are not well described in this setting. The impact of hypertension induced by native kidneys, diagnostic testing availability, expenses involved and outcomes of surgical or medical nephrectomies have not been extensively studied. To date, it is reasonable to consider investigation only in younger patients without history of hypertension pre-transplant, and with a severe and uncontrollable systemic hypertension without other identifiable aetiologies following renal transplantation.

1.3 Allograft Rejection

Experimental and clinical evidence suggests that allograft rejection may affect the pathological processes associated with the onset of post-transplant hypertension. A retrospective clinical study[34] of the incidence of hypertension following transplantation has demonstrated a higher incidence of hypertension when chronic allograft rejection is present. In a clinical study by Kirkman and co-workers,[35] 72% of transplant recipients with chronic allograft rejection had hypertension. Chronic rejection was identified as the leading cause of post-transplant hypertension during the pre-cyclosporin era. Chronic rejection is a slow, progressive arteriolopathy and/or nephrosclerosis. Vascular morphological changes associated with chronic rejection have been implicated in the pathogenesis of post-transplant hypertension in patients with chronic rejection.[36]

1.4 Calcineurin Inhibitors

Cyclosporin produces hypertension in healthy individuals as well as in a high percentage of renal and extra-renal allograft recipients.[37,38] The mechanisms for increased blood pressure during immunosuppression with cyclosporin therapy are multiple and overlapping. In experimental animals, it can be shown that there are direct vasoconstrictive effects of cyclosporin on resistance size vessels.[12,39] Associated with the rise in blood pressure in experimental animals is an increase in endothelial release of endothelin. In addition, there is a decrease in the responsiveness of these vessels to nitric oxide and acetylcholine, and various studies have shown a decrease in vasodilator prostaglandins.[12] Cyclosporin has also been shown to impair endothelial nitric oxide response to vasoconstrictive stimuli in coronary blood vessels.[40]

In healthy volunteers, a single, oral dose of cyclosporin 10 mg/kg has been shown to cause an increase in blood pressure with a rise in peripheral vascular resistance. Associated with increases in

blood pressure during cyclosporin therapy has been a loss of the normal nocturnal decline in blood pressure.[21] This impairment was reversed when the volunteers were switched to azathioprine. It has also been shown in cyclosporin-treated renal allograft recipients that plasma renin activity is depressed despite pathological evidence for activation of the intrarenal renin angiotensin system.[41] The hypertension associated with cyclosporin is volume dependent since sodium retention and cautious use of diuretics can improve blood pressure.[20] This is distinctly different from renin-mediated forms of hypertension. The pathophysiology of cyclosporin-associated hypertension, then, is similar to the one-kidney, one-clip model of experimental hypertension. Furthermore, when cyclosporin is given to mice for 2 to 3 weeks and then withdrawn, subsequent salt loading will produce salt-dependent hypertension in a normotensive animal even though the renal injury caused by the cyclosporin was produced prior to blood pressure elevation.[42] There are also data suggesting that the sympathetic nervous system is activated both centrally and peripherally when individuals are given cyclosporin.[43] More recent data have suggested that enhanced sympathetic activity, although commonly associated with cyclosporin-induced hypertension, is not dependent on such activation since the blood pressure effects can be dissociated from sympathetic overactivity.[13,44] Another physiological abnormality induced by cyclosporin which contributes to hypertension is afferent arteriolar vasoconstriction, leading to vascular damage that impairs autoregulatory ability.[45] Thus, the response to both hypotension produced by diuretics or hypertension may be transmitted to the renal parenchyma, resulting in tubulointerstitial damage. Experimentally, denervation of the kidney does not abrogate cyclosporin-induced renal histopathological changes.[10,11]

Tacrolimus is generally thought to be less likely than cyclosporin to produce rises in mean arterial pressure, since it appears to have less dramatic effects on afferent arteriolar resistance in the kidney. In addition, when it is compared with cyclosporin in clinical trials, tacrolimus has produced less dramatic hypertension.[46] In a series of liver transplant patients, tacrolimus produced less systemic vasoconstriction than did cyclosporin while affecting the renal circulation to the same extent.[14] Thus, while tacrolimus may produce relatively less hypertension than cyclosporin, hypertension is still common. Therapy of the elevated blood pressure *per se* is of critical importance in preventing cardiovascular death.

1.5 Corticosteroids

Hypertension is common in patients with Cushing's syndrome. The incidence of hypertension in patients with Cushing's disease is approximately 70%, while the incidence of hypertension in recipients of therapeutic doses of synthetic corticosteroids is approximately 20%.[47,48] This difference has been attributed to secretion of different steroid analogues with different activities from the adrenal glands. Adrenocorticosteroids are mainly classified as glucocorticoid or mineralocorticoid. Cortisol is a naturally occurring hormone which exhibits mostly glucocorticoid activity, whereas aldosterone exhibits virtually pure mineralocorticoid activity.[48] Glucocorticoid and mineralocorticoid production and secretion are regulated by corticotropin (adrenocorticotropic hormone; ACTH) and the renin-angiotensin system, respectively. The mineralocorticoid activities of corticosteroids include sodium retention, volume expansion and hypokalaemia. Glucocorticoid activities include shifting of fluids from interstitial to intravascular compartments and hyperinsulinaemia.[48,49]

Since the introduction of synthetic corticosteroids into clinical practice, hypertension has been described as a major adverse drug reaction associated with their therapeutic use.[50] The excessive production and secretion of mineralocorticoids such as aldosterone in Conn's syndrome or glucocorticoids in Cushing's disease can lead to hypertension.[51-53] The precise sequence of events and pathogenesis of steroid-induced hypertension is not clear. The long term impact of glucocorticoids on hypertension has been the subject of con-

Table I. Usual dose, renal effects, dosage adjustment in renal failure and toxicity of most commonly used antihypertensive agents in renal transplantation[109,110]

Drug	Usual dose (mg)	Renal effect			Percentage[a] of normal dosage in renal failure			Toxicity
		GFR	RBF	RVR	>50[b]	10-50[b]	<10[b]	
Diuretics		No	No	↓				Hypercholesteraemia, hyperglycaemia, hypokalaemia, hypomagnesaemia, hypercalcaemia/hypocalcaemia (loop diuretics), hyperuricaemia and pancreatitis. Only loop diuretics are effective with low GFR (30 ml/min) Ototoxicity with loop diuretics
Chlorothiazide	125-500	Acutely decrease both GFR and RBF, but no long term effect on GFR or RBF. Decrease RVR. Indapamide improve GFR and RBF			100	100	Avoid	
Hydrochlorothiazide	12.5-50				100	100	Avoid	
Chlorthalidone	12.5-25				100	100	Avoid	
Metolazone	2.5-10				100	100	100	
Indapamide	1.25-5				100	100	Avoid	
Furosemide	20-320				100	100	100	
Bumetanide	0.5-10				100	100	100	
Ethacrynic acid	25-200				100	q12hr	Avoid	Non-sulfonated diuretic
Torasemide	5-100				100	100	100	
Spironolactone	25-200				100	100	Avoid	Hyperkalaemia
Triamterene	50-200				100	100	Avoid	Hyperkalaemia
Amiloride	2.5-10				100	100	Avoid	Hyperkalaemia
β-Blockers		↓	↓	↑				Bradycardia, hypertriglyceridaemia, depression, may mask symptoms of hypoglycaemia and bronchospasm. May causes rebound hypertension if stop abruptly
Nadolol	40-320	Increase RVR and decrease GFR and RBF			100	50	25	
Propranolol	120-320				100	100	100	
Timolol	20-80				100	100	100	
Atenolol	50-100				100	50-75	30-50	
Metoprolol	50-200				100	100	100	
Labetolol	400-1200	No changes in GFR, RBF and RVR			100	100	100	
Calcium antagonists		↑	↑	↓				Gingival hyperplasia, headache, oedema, flushing
Amlodipine	5-10	Improve GFR, RBF and a decrease in RVR			100	100	100	
Felodipine	5-20				100	100	100	
Isradipine	2.5-10				100	100	100	
Nicardipine	60-120				100	100	100	
Nifedipine	30-120				100	100	100	
Diltiazem	60-360				100	100	100	Conduction abnormality

Table I contd

Drug	Usual dose (mg)	Renal effect			Percentage[a] of normal dosage in renal failure			Toxicity
		GFR	RBF	RVR	>50[b]	10-50[b]	<10[b]	
Verapamil	180-240				100	100	100	Conduction abnormality
ACE inhibitors		No /↓	No/↓	↓				Cough, angioedema, hyperkalaemia, leucopenia
Benazepril	10-40	No changes or decrease in GFR, RBF and a decrease in RVR			100	50-75	50	
Captopril	50-100				100	75	50	
Enalapril	2.5-20				100	75	50	
Fosinopril	20-40				100	100	75	
Lisinopril	10-20				100	50	25	
AII receptor antagonists		No /↓	No/↓	↓				
Losartan	50-100	No changes or decrease in GFR, RBF and a decrease in RVR			100	100	75	
Valsartan	80-320				100	100	75	
Irbesartan	150-300				100	100	100	
Others		No	No	No				
Doxazosin	2-8	No changes in GFR, RBF and a decrease in RVR			100	100	100	
Prazosin	4-12				100	100	100	
Terazosin	10-20				100	100	100	
Clonidine	0.2-0.9	Acutely decrease both GFR and RBF, but no long term effect on GFR or RBF. Decreased RVR			100	100	100	
Guanabenz	8-24				100	100	100	
Minoxidil	5-10 bid				100	100	100	Fluid retention, hirsutism
Hydralazine	25 to 100 qid				q6-8hr	q6-8hr	q6-8hr	Drug-induced lupus

a Unless otherwise indicated.

b Estimated creatinine clearance (ml/min).

AII = angiotensin II; **bid** = twice daily; **GFR** = glomerular filtration rate; **qid** = 4 times daily; **RBF** = renal blood flow; **RVR** = renal vascular resistance; ↑ indicates increase; ↓ indicates decrease.

troversy. The results of experimental studies in dogs, sheep, and other animals have shown that increased plasma volume, sodium retention and increased vascular responsiveness to catecholamines are independent of the mineralocorticoid or glucocorticoid activities of corticosteroids.[48] The suggested mechanism for the hypertensive effect of corticosteroids is multifactorial. The factors involved in steroid-induced hypertension include: changing electrolyte balance, increased sensitivity to endothelin-1 and angiotensin, increased density of glucocorticoid receptors in the vascular smooth muscle cells, and decreased production of vasodilator prostaglandins.[48] During initial corticosteroid therapy, a profound increase in plasma volume and sodium retention occurs, which leads to an increase in blood pressure and cardiac output. Glucorticoids may increase plasma volume by shifting fluids from the intracellular to the extracellular compartment.[54,55]

The biochemistry and structural pathology of steroid-induced hypertension remains unknown.

However, over the last decade a number of reports have confirmed the correlation between both the incidence of post-transplant hypertension and the use of antihypertensive drugs to the dose and use of corticosteroids.[56-58] A fall in SBP and DBP or a decrease in the dosage of antihypertensive agents required have been reported in several randomised, prospective studies of elective corticosteroid withdrawal after kidney and liver transplantation.[59-61] In a liver transplant setting, the incidence of post-transplant hypertension was significantly greater in patients who were treated with higher dosages of prednisone in the first 4 months following transplantation compared with patients treated with lower dosages.[62] Hricik et al.[57] discontinued antihypertensive drugs in 15% of transplant patients who were enrolled in an elective corticosteroid withdrawal protocol.

2. Treatment of Post-Transplant Hypertension

The ideal antihypertensive agent for treatment of post-transplant hypertension should:

- reduce blood pressure
- be safe when combined with immunosuppressive agents without increasing the risk of adverse drug reactions associated with these necessary agents
- reduce the risks associated with hypertension such as strokes, MI and other cardiovascular disease
- be free of hepatotoxic and nephrotoxic effects
- be effective regardless of patient ethnicity
- not adversely affect blood glucose levels, lipid profile and heart rate
- be easily titratable
- not induce tolerance to antihypertensive effects and
- be inexpensive.

A single ideal agent has yet to be discovered.

Over 100 antihypertensive agents have been approved by the US Food and Drug Administration (FDA), and none of these agents fulfills the ideal antihypertensive agent characteristics. No single agent has been shown clearly to be more efficacious and well tolerated compared with other agents in the treatment of post-transplant hypertension in renal transplant recipients. The choice of antihypertensive agent is an area of controversy, although large clinical studies have demonstrated most of the antihypertensive agents do have a positive impact on the risks associated with hypertension in the non-transplant population.

The pharmacoeconomics of antihypertensive agents is attracting more attention.[63] The economic impact of a treatment should include cost of monitoring, compliance and adverse drug reactions. Cost-effectiveness studies based on acquisition cost of the drug without considering cost and benefits/outcomes are misleading. The initial antihypertensive therapy should be tailored individually according to the patient's risk factors. When new antihypertensive agents are initiated or added to the therapy of an individual renal transplant recipient, potential contraindications, adverse drug reactions and drug interactions must be considered (table I).

2.1 Calcium Antagonists

Calcium antagonists, in theory, have been considered the drugs of choice for the treatment of post-transplant hypertension. The major vascular and/or renal haemodynamic effects of calcium antagonists include decreased mean arterial pressure and total renal vascular resistance, and increased renal blood flow and GFR. In addition to reducing blood pressure, verapamil and diltiazem also decrease heart rate and cardiac output. Calcium antagonists inhibit entrance of calcium into the smooth-muscle of vasoconstricted arterioles through voltage potential-dependent channels. There are several theoretical reasons why calcium antagonists are considered the drugs of choice for the treatment of post-transplant hypertension. These include a decrease in perfusion injury, protective effect on cyclosporin-induced nephrotoxicity, a decrease in the incidence of delayed graft function, and better long-term graft survival.[66-70] However, in a comparative clinical trial, a calcium antago-

nist, an ACE inhibitor and an α-blocker were equally effective in reducing blood pressure.[71]

In animal models of ischaemia, calcium influx into the smooth muscle may lead to the generation of free radicals, mitochondrial dysfunction and calcium accumulation.[72,73] The exact mechanism by which calcium antagonists ameliorate ischaemic injury is unknown. Calcium antagonists may modulate the influx of calcium into vascular cells and prevent acute tubular necrosis during an ischaemic insult.[72,73] This hypothesis was tested in a prospective study by Wagner et al.[74] The influence of diltiazem on the incidence of acute tubular necrosis after transplantation was studied in 20 patients. Diltiazem was added to Euro-Collin's solution and was given pre- and post-operatively. The incidence of acute tubular necrosis or delayed graft function was 10% in the treatment group (n = 20) and 41% in the control group. Calcium antagonists also reduced nephrotoxicity associated with the use of cyclosporin. Administration of calcineurin inhibitors causes a reduction in GFR and renal plasma flow. Hypoperfusion and reduction of GFR associated with cyclosporin may result in vasoconstriction due to an increase in angiotensin II and norepinephrine plasma levels.[75,76] The use of calcium antagonists [felodipine (n = 10) and verapamil (n = 10)] in renal transplant recipients was associated with improved renal plasma flow and GFR, lower serum creatinine levels and greater urine output.[77-79] However, in a 5-year follow-up study by Morales and co-workers[80] patient (n = 17) and graft survival was similar with the use of β-blockers and/or calcium antagonists.

Improved graft survival associated with the use of calcium antagonists may be the result of direct immunosuppression. Palmer et al.[81] compared 17 renal transplant recipients who were discharged from hospital and maintained on calcium antagonists with patients who never received calcium antagonists. In a 1-year follow-up period, the incidence of rejection was significantly less, serum creatinine levels were lower and the GFR higher in these patients compared with the group not receiving calcium antagonists. Calcium regulates several intracellular functions including the signal that increases proliferation of T lymphocytes. *In vitro*, calcium antagonists modulate levels of calcium influx and ultimately inhibit T cell activation.[82,83] The concentration of calcium antagonists required to produce immunosuppression is almost 100-fold higher than the therapeutic range. Therefore, it has been postulated that the immunosuppressive properties of calcium antagonists must be via mechanisms other than the direct inhibition of T lymphocytes.[82,83]

Calcium antagonists are potent vasodilators, and may cause dizziness, flushing and headache. Dihydropyridine calcium antagonists have been associated with a higher incidence of oedema of the extremities than other calcium antagonists, which is not related to sodium and water retention.[84] Clinically, significant headache and flushing have been reported with the use of short acting calcium antagonists. These adverse effects can be minimised with the use of slow release formulations or with agents possessing a slow onset of action, such as amlodipine, which do not induce a reflex tachycardia.[85] Recent reports in non-transplant patients indicate that short-acting calcium antagonists may increase mortality in some patients with a recent history of acute MI or CHD.[86,87] Thus far there is no clinical evidence to suggest that short-acting or long-acting calcium antagonists increase the mortality in renal transplant recipients. Because compelling data indicates that calcium antagonists are beneficial in the treatment of post-transplant hypertension, these agents can be used safely in patients without a history of CHD, unless information becomes available to dispute these beneficial findings. However, caution is advised in the use of short-acting calcium antagonists for the treatment of post-transplant hypertension. Verapamil and diltiazem slow atrioventricular (AV) nodal conduction and should be used with some caution in patients with impaired AV nodal function. Constipation has been reported in renal transplant patients taking verapamil in the early stage of the treatment.[71] This adverse drug reaction is probably due to inhibition of calcium channels in

the intestinal tract, resulting in relaxation of the smooth muscle. Diltiazem has also been reported to cause constipation in a small number of patients with hypertension.[84] Diltiazem, amlodipine, nicardipine and verapamil inhibit the metabolism of calcineurin inhibitors. Therefore, cyclosporin and tacrolimus blood concentrations should be monitored closely.[45,88,89]

2.2 β-Blockers

The precise pharmacological and pharmacodynamic effects of β-blockers in reducing blood pressure are unknown.[90] These agents have no clinically important effect on GFR, renal blood flow or renal vascular resistance in nontransplant patients.[84] Regardless of cardioselectivity, intrinsic sympathomimetic activity (ISA), membrane-stabilisation activities or lipid solubility, all β-blockers are effective in equipotent doses in reducing SBP. In general, patients who fail to respond to 1 β-blocker, will not respond to another β-blocker.[84] In a small study of the effect of β-blockers (propranolol, atenolol and metoprolol) by Huysmans et al.,[91] a blood pressure reduction was noted only in 10 hypertensive renal transplant recipients with the native kidney *in situ*. These observed differences in response to β-blockers were explained based on the role of the native kidney in induction of post-transplant hypertension. Native kidneys may play an important role in activation of renin and the angiotensin system mediated by activation of the sympathetic nervous system. Therefore, a β-blocker may be indicated for reduction of blood pressure if the native kidney is *in situ*.[91] In addition, cyclosporin may increase sympathetic activity resulting in tachycardia and hypertension, and β-blockers are known to antagonise the action of catecholamines at β-adrenergic receptors. In a recent study, Hausberg and co-workers[92] randomised 75 renal transplant patients to quinapril or atenolol. After 24 hours months of therapy, the serum creatinine levels did not change significantly in either group from baseline. In both groups excellent blood pressure control was achieved without any significant adverse drug reactions. However, patients treated with quinapril had significantly lower urinary albumin excretion.

The most common adverse effects of β-blockers are the diminution or masking of the symptoms of hypoglycaemia and thyrotoxicosis, sexual dysfunction, muscle weakness, and tiredness/fatigue. Blunting the clinical signs and symptoms of hypoglycaemia may complicate the treatment of hypertension in renal transplant recipients with diabetes mellitus. The pharmacodynamic adverse interactions on lipid profile may further complicate hyperlipidaemia disorders in renal transplant recipients. Many reports have documented the favourable benefit of β-blockers in reducing morbidity and mortality following acute MI.[93,94] These benefits of β-blockers in transplant patients who have a history of MI or CHD outweigh the risk of adverse drug reactions or potential synergistic toxicity with other immunosuppressive drugs. β-Blockers should be considered as the first line of treatment in patients with post-transplant hypertension and a history of CHD. Abrupt discontinuation of β-blockers may exacerbate rebound hypertension and so the dosage should be reduced slowly over a 1- to 2-week period.

2.3 ACE-Inhibitors and Angiotensin II Receptor Antagonists

The primary haemodynamic effect of ACE inhibitors is vasodilatory via suppression of production of angiotensin II (AII) and inhibition of the inactivation of bradykinin (accumulation of bradykinin in plasma and tissue). AII receptor antagonists reduce the blood pressure by blocking physiological response to angiotensin II.[95,96] Newer angiotensin II receptor antagonists (e.g. eprosartan) have higher affinity for the AT1 receptor subtype.[97] However, the clinical significance of this property is unknown.

The use of ACE inhibitors in post-transplant hypertension has been the subject of much debate. Because of potential complications with these agents in the early post-transplantation, the routine use of ACE inhibitors has been discouraged in renal transplant recipients. Renal autoregulation plays a

vital role in maintaining a constant effective renal plasma flow and GFR over different ranges of blood pressure. In conditions where transplanted allografts have a low intra-renal pressure, such as renal artery stenosis, chronic vascular rejection and nephrotic syndrome, ACE inhibitors may significantly compromise effective allograft blood flow as is evidenced by a rise in serum creatinine levels in some patients receiving these agents.[98] Acute allograft dysfunction and decline in the GFR may be further worsened by sodium depletion and the use of diuretics.[61,99] Concerns about low plasma renin activity and hyperkalaemia which are associated with both cyclosporin and ACE inhibitors have provided further argument for the avoidance of ACE inhibitors in the treatment of post-transplant hypertension.

In normotensive and hypertensive nontransplant patients with diabetes mellitus, ACE inhibitors reduce proteinuria.[100] In these settings, ACE inhibitors have been shown to reduce intraglomerular hypertension and hyperfiltration. This characteristic of ACE inhibitors was studied by Bochicchio and colleagues in renal transplant recipients.[100] A decrease in proteinuria was observed after 12-months treatment with fosinopril in renal transplant recipients with chronic rejection. Similarly, when the effect of lisinopril in proteinuria was studied in 12 renal transplant recipients with hypertension, a similar result was obtained.[98] After 3 months treatment with oral lisinopril 2.5 mg/day, heavy proteinuria decreased in 11 of 12 patients, without a major reduction in the GFR.

The efficacy and safety of losartan potassium was studied by del Castillo et al.[101] in 67 renal transplant patients. After 12 weeks' therapy, proteinuria was decreased significantly at 4 and 12 weeks especially in patients with proteinuria greater than 300 mg/24 hours. Losartan was well tolerated and effective in reducing blood pressure and did not interfere with any of the immunosuppressive agents.

In recent clinical studies with a long term follow-up in renal transplant patients, ACE inhibitors have been shown to be effective in the treatment of post-transplant hypertension. In 1 study the ACE inhibitor perindopril was as effective as the calcium antagonist amlodipine in reducing blood pressure in 10 patients.[102] The renal plasma flow and GFR were similar in the both groups. Mourad et al.[103] compared nifedipine plus atenolol with lisinopril plus furosemide with a 3-year follow-up period in 14 patients. This study showed no differences in antihypertensive efficacy, adverse drug reactions profile or clinically significant effect on the renal plasma flow or GFR between treatment groups. Similarly, shorter studies comparing amlodipine with lisinopril[104] and nifedipine with perindopril[105] failed to show any differences. A smaller trial comparing enalapril with nifedipine was also inconclusive.[106-107]

In an animal model of chronic allograft nephropathy, losartan potassium improved renal function, preserved renal structure and reduced proteinuria.[108] Transforming growth factor (TGF)β-1 is an important fibrogenic growth factor in the development of chronic rejection. In animal models of chronic cyclosporin nephropathy, when salt-depleted animals were given placebo, nilvadipine, hydralazine/hydrochlorothiazide, enalapril or losartan potassium, the same antihypertensive effect and reduction in GFR was achieved in all groups. However, only losartan potassium and enalapril attenuated the expression of TGFβ-1 and ameliorated the lesions of chronic cyclosporin nephropathy.[109] There is some evidence to suggest that plasma renin levels are low after renal transplantation, however, cyclosporin activates synthesis and accumulation of intra-renal renin.[76] This increase in the intra-renal renin content may play an important role in fibrinogenesis and chronic cyclosporin nephropathy. Like diabetes mellitus, the effect of cyclosporin on renin and the angiotensin system is associated with low plasma renin activity, a high incidence of hypertension, and nephrotoxicity with evidence of afferent arteriopathy.[76,109]

Finally, angiotensin II receptors reside on erythrocyte progenitor cells. ACE inhibitors or AII receptor antagonists are effective agents for the treat-

ment of post-transplant erythrocytosis. These agents should be considered the drug of choice for treatment of hypertension in transplant patients with co-existing post-transplant erythrocytosis.[110]

In summary, ACE inhibitors or AII receptor antagonists are effective but underutilised classes of antihypertensive drugs for the treatment of post-transplant hypertension. The main advantages of this class of antihypertensive drugs are a high rate of efficacy, lack of metabolic adverse effects, preservation of the renal structure, reduction of proteinuria, and, potentially, a reduction in the production of growth factors associated with chronic rejection and/or cyclosporin-induced chronic progressive nephropathy.

2.4 Diuretics

Unfortunately, there are no comparative or placebo-controlled clinical studies to suggest that diuretics are effective and the best agents for treatment of post-transplant hypertension. It is important to note that diuretics have repeatedly been evaluated, tested and shown to prevent the incidence of cardiovascular events and mortality associated with hypertension in the non-transplant setting.[6,7,15] The exact mechanism by which diuretics reduce blood pressure is unknown. Initially in the first 4 to 6 weeks after starting diuretic therapy, reduction of blood pressure is by volume depletion. But long term pharmacodynamic effects of diuretics mostly correlate with a decrease in vascular responsiveness to the sympathetic nervous system.[111] These agents are excellent choices in transplant patients with excess fluid and sodium overload. Sodium load, food-drug interactions and drug-drug interactions (nonsteroidal anti-inflammatory drugs) may lessen the effectiveness of diuretic therapy in the treatment of hypertension or even result in resistance to the natriuretic and antihypertensive effects of diuretics.[112-114]

Loop diuretics can cause hypocalcaemia and thiazide diuretics can induce hypercalcaemia. Loop diuretics may exacerbate the hyperparathyroidism which can complicate post-transplant bone disease associated with prednisone use and renal failure.[115,116] Potassium-sparing agents may result in hyperkalaemia, while thiazide and loop diuretics reduce potassium reabsorption. The use of cyclosporin, tacrolimus, ACE inhibitors, cotrimoxazole, and β-blockers are also associated with hyperkalaemia. Hyperuricaemia and hypomagnesaemia are frequent complications of both cyclosporin and tacrolimus therapy. In a study by West et al.[117] the incidence of hyperuricaemia was 55% in the cyclosporin group and 25% in the azathioprine group. The extended use of both diuretics and calcineurin inhibitors may require close electrolyte monitoring to avoid gout and cardiac mortality associated with low levels of magnesium.[118] Whereas ethacrynic acid is the only diuretic that can be used safely in patients with a history of a true 'sulfa' hypersensitivity reaction, this restriction is probably unnecessary in most patients.

In summary, diuretics should be considered the preferred agents for treatment of post-transplant hypertension in patients with evidence of sodium and extracellular fluid overload.

2.5 Treatment Strategies

Calcium antagonists, ACE inhibitors, diuretics and β-blockers can be used for the treatment of hypertension following renal transplantation. A management guideline for the treatment of post-transplant hypertension is suggested in figure 1. Patients with severe hypertensive episodes may require aggressive treatment. Like any other treatment modality, the short and long term risks and benefits should be assessed very closely. In a stepped care model of the treatment of hypertension, if the first drug is not effective, a second drug would be added. However, if a given drug is not effective in controlling elevated blood pressure, solely adding another antihypertensive agent is not justified. The drug that was not effective should be substituted with another class of antihypertensive drug. In this treatment strategy a lower number of antihypertensive agents will be administered to control blood pressure with fewer possible adverse drug reactions.

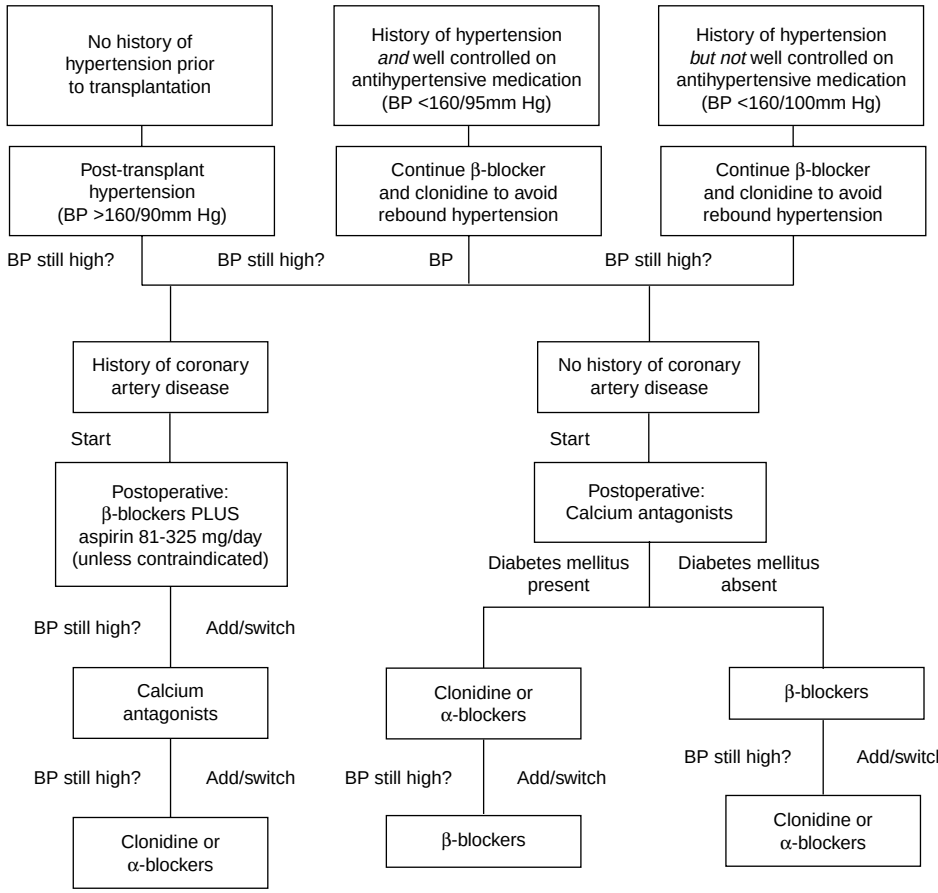

Fig. 1. Algorithm for the treatment of hypertension in renal transplant recipients.
Whenever you are using this algorithm in an individual patient, consider potential contraindications, adverse drug reactions and drug-drug interactions. Remember, as the number of antihypertensive agents used increases, the number of potential drug-drug interactions and adverse drug reactions also increases. Continue diltiazem and verapamil for patients with a history of atrial fibrillation or other conduction disorders, however, start cyclosporin at 5 mg/kg/day and tacrolimus (FK-506) at 0.1 mg/kg/day. **BP** = blood pressure; **PRN** antihypertensive medications: Nifedipine 10mg orally every 3 to 4 hours as needed; Clonidine 0.1mg orally every 1 to 2 hours as needed; Labetalol 20mg intravenously every 3 to 4 hours as needed.

The primary objective of the treatment of hypertension is to reduce blood pressure without any significant harm to the allograft. This algorithm starts post transplantation, if patients with a sustained SBP of >160mm Hg or DBP >90mm Hg require pharmacological treatment. If a patient has no history of hypertension before transplantation, start with a low dose of a long-acting or slow release formulation of a calcium antagonist, (such as amlodipine) and slowly titrate the dose to achieve a specific therapeutic goal. This strategy is based on the results of several studies described in section 2.1. Because of the nephroprotective effect against cyclosporin-induced nephrotoxicity, less delay in graft function and reduced ischaemic injury, slow-acting calcium antagonists (such as amlodipine) remain the drugs of choice in most circumstances following renal transplantation. However, β-blockers are especially useful in transplant patients with co-existing CHD. β-Blockers

should be considered in patients with a previous MI. If only a partial clinical response is attained, an agent from a different class of antihypertensive drugs should be added. If patients experience unacceptable adverse drug reactions, substitute to another class of antihypertensive agents; an agent with favorable effects on co-morbid conditions. If the patient has a history of hypertension and was well controlled by clonidine or a β-blocker, continue these agents to avoid rebound hypertension unless contraindicated. If blood pressure is not at the target goal, add or substitute a calcium antagonist. Since most renal transplant recipients have several risk factors such as diabetes mellitus, hypercholesterolemia, insulin resistance, obesity, left ventricular hypertrophy and/or ischaemic heart disease, the effect of antihypertensive drugs on pre-existing conditions also should be considered. The choice of antihypertensive agents in a transplant setting are similar to that of the primary care provider in the treatment of essential hypertension. Antihypertensive agents should be tailored to the individual patient according to the pre-existing co-morbid condition. For example, for patients with symptoms associated with urinary tract blockage from prostatic hypertrophy, an α-blocker should be considered. Or, as discussed in section 2.3, ACE inhibitors should be considered the drug of choice for treatment of hypertension in transplant patients with co-existing post-transplant erythrocytosis, or chronic allograft nephropathy. When new antihypertensive agents are initiated or added in an individual renal transplant recipient, potential contraindications, adverse drug reactions and drug interactions must be considered.

3. Conclusion

Post-transplant hypertension has been identified as a risk factor for allograft failure, and cardiovascular morbidity and mortality among renal allograft recipients with a functioning allograft. The interactions between multiple factors such as native kidney, renal artery stenosis, chronic rejection, immunosuppressive drugs and other medications may contribute to post-transplant hypertension. Recognition and optimal treatment of hypertension after renal transplantation may decrease risk factors for premature cardiovascular events. A rapid decrease in blood pressure is inappropriate for most patients because this may result in a possible reduction in blood flow to the allograft causing allograft thrombosis or dysfunction. Hypertension following renal allograft transplantation is commonly resistant to monotherapy and most patients require multiple antihypertensive drugs. As the number of antihypertensive agents increase, the number of potential drug-drug interactions and adverse drug reactions increase. The management of hypertension in the setting of renal transplantation is extremely important since cardiovascular disease is a major cause of morbidity and mortality even in successful renal transplant patients. Thus, the totality of the data available now suggests that blood pressure lowering is the most important aspect of hypertension following renal transplantation, regardless of how that goal is achieved. While some theoretical advantages remain with calcium antagonists, these have not been shown to be clinically relevant. In fact, since chronic nephrotoxicity secondary to immunosuppressive drugs may be due to activation of the intrarenal renin angiotensin system, and since chronic rejection may also be abrogated by blockade of this system, there may be advantages to the use of ACE inhibitors or AII receptor antagonists for their renoprotective effects. However, no studies have addressed these issues directly.

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