Hypertension in dialysis and kidney transplant patients

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For the first time, the Canadian Hypertension Education Program has studied the evidence supporting blood pressure control in people requiring renal replacement therapy for end-stage kidney disease, including those on dialysis and with renal transplants. According to the Canadian Organ Replacement Registry's 2008 annual report, there were an estimated 33,832 people with end-stage renal disease in Canada at the end of 2006, an increase of 69.7% since 1997. Of these, 20,465 were on dialysis and 13,367 were living with a functioning kidney transplant. Thus, it is becoming more likely that primary care practitioners will be helping to care for these complex patients. With the lack of large controlled clinical trials, the consensus recommendation based on interpretation of the existing literature is that blood pressure should be lowered to below 140/90 mmHg in hypertensive patients on renal replacement therapy and to below 130/80 mmHg for renal transplant patients with diabetes or chronic kidney disease.

Key Words: Antihypertensive drugs; Calcineurin inhibitors; Corticosteroids; Hemodialysis; Immunosuppression; Kidney transplantation; Peritoneal dialysis; Renal artery stenosis

Reports from the Canadian Organ Replacement Register (1) show that cardiovascular diseases remain the leading cause of death among patients on dialysis therapy and after renal transplantation. Hypertension is observed in approximately 80% to 90% of patients by the time chronic kidney disease (CKD) progresses to end-stage renal failure (stage 5), thereby favouring the development of left ventricular hypertrophy (LVH) (2). In addition, dialysis and transplantation patients often do not show the normal reduction in nocturnal blood pressures (BPs). This phenomenon increases the BP load and favours LVH, which is an independent risk predictor of cardiovascular complications in dialysis patients (3).

The present overview will not only underscore the importance of hypertension as a cardiovascular risk factor for dialysis and kidney transplant patients, but will also review mechanisms, diagnostic methods and management of hypertension.

HYPERTENSION IN DIALYSIS PATIENTS

Physiopathology

The most common pattern of BP in dialysis patients is systolic hypertension associated with a wide pulse pressure due to atherosclerotic arterial stiffness (4). The main pathogenic mechanisms of hypertension in dialysis patients are summarized in Table 1. Extracellular fluid overload is the most common feature in hypertensive dialysis patients. Indeed, insufficient volume removal is often the major factor responsible for dialysis-refractory hypertension (5). In many patients, there is also an abnormal relationship between extracellular fluid volume and

L'hypertension chez des patients en dialyse et greffés du rein

Pour la première fois, le Programme éducatif canadien sur l'hypertension a étudié les données probantes étayant le contrôle de la tension artérielle chez les personnes qui ont besoin d'une transplantation rénale en raison d'une insuffisance rénale chronique au stade ultime, y compris ceux qui sont en dialyse ou sont greffés du rein. D'après le rapport annuel 2008 du Registre canadien du remplacement d'organes, on estimait que 33 832 personnes étaient atteintes d'insuffisance rénale au stade ultime au Canada à la fin de 2006, une augmentation de 69,7 % depuis 1997. De ce nombre, 20 465 étaient en dialyse, et 13 367 vivaient avec une greffe d'organe fonctionnelle. Ainsi, il devient plus probable que les praticiens de premier recours contribueront aux soins de ces patients complexes. Étant donné l'absence de grand essai clinique contrôlé, la recommandation consensuelle fondée sur l'interprétation des publications existantes indique qu'il faudrait abaisser la tension artérielle à moins de 140/90 mmHg chez les patients hypertendus en voie de subir une transplantation rénale et à moins de 130/80 mmHg chez les patients greffés du rein atteints de diabète ou d'insuffisance rénale chronique.

the renin-angiotensin system (RAS) (6) – the circulating renin concentration is abnormally high for the exchangeable sodium levels. In addition, volume fluctuations such as plasma volume contraction during a dialysis session or interdialytic fluid overload result in activation of the sympathetic nervous system (7). Several additional factors also contribute to increase sympathetic outflow in this population including renal ischemia, increased activity of the RAS, nocturnal hypoxemia and prevalent comorbidities such as chronic heart failure.

Imbalance in endothelium-derived factors has also been reported in end-stage renal disease (8). In the 5/6 nephrectomy animal model, the vascular production of endothelin (ET)-1 is increased (9) and the expression of ET_B, an ET-1 clearance receptor, is reduced (10). The pressor effect of ET-1 is enhanced by the concomitant decrease of potent vasodilators such as prostacyclin and nitric oxide (NO). The production of NO by the blood vessel endothelium is inhibited by the accumulation (six- to 10-fold) of asymmetric dimethylarginine, which inhibits NO synthesis in CKD (11).

Erythropoietin (EPO) replacement therapy in anemic dialysis patients may also aggravate pre-existing hypertension (12). The precise mechanism underlying the development of hypertension following EPO therapy is still unclear. The pressor effect of EPO cannot only be accounted for by an increase in hematocrit and blood viscosity (12-14). Other potential mechanisms include an inappropriate increase in peripheral resistance (12), enhanced tissue renin activity (15) and an increase in angiotensin II receptor expression (16). Recent evidence also suggests that EPO accentuates a pre-existing

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TABLE 1
Mechanisms of hypertension in dialysis patients

Extracellular volume overload
Dysregulation of the renin-angiotensin-aldosterone system
Sympathetic overactivity
Imbalance in endothelium-derived vasoactive substances (endothelin-1 and nitric oxide)
Erythropoietin replacement therapy
Secondary hyperparathyroidism
Nocturnal hypoxemia and sleep disturbances

endothelial dysfunction. Blood vessel endothelial cells express EPO receptors (17) and these cells, when stimulated by EPO, release ET-1 (18). In vivo studies also demonstrate that EPO treatment can modulate ET-1 messenger RNA expression in the renal cortex of uremic rats (8), and can increase vascular and renal cortex ET-1 concentration in uremic rats (19,20), a phenomenon that can contribute to EPO-induced hypertension. Consistent with this, selective ET_A receptor blockade prevents the worsening of hypertension in EPO-treated uremic rats (21,22). A recent study (23) showed that EPO exerts a pleiotropic effect on the vascular endothelial ET-1/ET_B receptor system.

Secondary hyperparathyroidism can also contribute to hypertension in end-stage renal disease by favouring entry of calcium into vascular smooth muscle cells (24). Reports that showed that the treatment of hyperparathyroidism by vitamin D administration or parathyroidectomy in dialysis patients result in improved BP support this hypothesis (25).

Sleep disturbances are more frequent in end-stage renal disease than in the general population (26) and may contribute to hypertension in dialysis patients. Therefore, sleep apnea should be investigated in dialysis patients with resistant hypertension without other causes, mainly in those with compatible symptoms.

When and how to monitor BP?

Variation of blood fluid volumes in dialysis patients before, during and after hemodialysis cause marked fluctuations in BP. It remains unclear which BP recording (immediately predialysis or postdialysis) is more predictive of patient outcomes. Indeed, the predialysis systolic BP may overvalue and the postdialysis systolic BP may underrate the mean interdialytic BPs by 10/7 mmHg (27). Agarwal et al (28) recently demonstrated that the median BP, including predialysis, intradialytic and postdialysis BPs, provides improved sensitivity and specificity in diagnosing hypertension in hemodialysis patients. The role of 24 h ambulatory BP monitoring (ABPM) and home BP self-monitoring in hemodialysis patients is still being evaluated. An ABPM value seems reproducible and may be useful in evaluating systolic BP load, which is a key factor in the development of LVH (29). Approximately 70% of hemodialysis patients lack their circadian BP variation (ie, nondippers) and develop nocturnal hypertension (12), a phenomenon that contributes to increasing BP load. Interestingly, a significant correlation was observed between traditional supine mean BP readings after dialysis and 24 h ABPM interdialytic measurements (30). Similarly, Mitra et al (31) reported that the best representation of interdialytic ABPM values was the 20 min sitting postdialysis measure. Home BP self-monitoring also provides valuable information. Agarwal (32) observed a good correlation between average systolic and diastolic ABPM values and respective home BP self-monitoring readings.

What is the target BP in dialysis patients with hypertension?

Observational studies in hemodialysis patients have yielded paradoxical results on the relationship between BP level and cardiovascular morbidity and mortality risk. These relationships may be different from those observed in general populations. Low BP appears to be associated with higher mortality during the early years of dialysis, whereas high BP is associated with mortality in longer-term follow-up (33,34). Low predialytic BP in the dialysis population is likely not the result of overtreatment but may be a marker of congestive heart failure. Furthermore, other observational studies in

hemodialysis cohorts showed a reverse epidemiology phenomenon, with the highest mortality rate in patient groups with lower BPs (35,36). Similar results were reported in a retrospective analysis performed in peritoneal dialysis patients (37). In the absence of randomized controlled trials (RCTs), the Canadian Society of Nephrology guidelines (38) and the Canadian Hypertension Education Program (CHEP) (see the coming 2009 report) recommend a predialysis BP target of less than 140/90 mmHg.

Therapy

Nonpharmacological treatment of hypertensive dialysis patients:

Control of sodium and water balance with achievement of dry body weight with adequate dialysis prescription can either improve or even normalize BP in dialysis patients (39,40). An interdialytic weight gain as small as 2.5 kg is associated with a significant increase in BP (41). It is noteworthy that after achievement of dry weight, there may be a long period of time before BP improves, also denoted as the 'lag phenomenon' (42). To diminish large interdialytic weight gains, dialysis patients should be on a salt-restricted diet, which also reduces thirst, an important aspect of patient adherence. If the dialysate sodium concentration during hemodialysis is to be ramped to prevent intradialytic hypotension and cramping, normalization of the sodium level before the end of dialysis will also attenuate postdialysis thirst and interdialytic weight gain, and may result in a reduction of antihypertensive agents to control BP (43,44). The dialysis regimen is also an important factor in the control of BP in dialysis patients. Long duration hemodialysis treatments (three 8 h sessions/week) are associated with better BP control and reduction of cardiovascular complications (39). Nocturnal dialysis treatment (six 8 h sessions/week) increases arterial baroreflex sensitivity and normalizes BP (45,46). Long nocturnal home hemodialysis can also improve sleep apnea (47).

Antihypertensive drugs: The use of antihypertensive drugs is indicated for patients in whom hypertension remains despite seemingly proper volume control. High BP in dialysis patients can usually be controlled with the use of the same antihypertensive drugs used in nondialysis patients with CKD (48). The selection of antihypertensive agents is often dictated by the presence of coexisting diseases. An overly rapid intensification of the antihypertensive medication may result in dialysis-induced hypotension and inability to achieve dry weight.

Angiotensin-converting enzyme inhibitors: Angiotensin-converting enzyme (ACE) inhibitors are effective and usually well tolerated in dialysis patients. They can reverse LVH (49,50) and can reduce mortality (51). Dose adjustment is necessary for ACE inhibitors with renal elimination. They can also trigger anaphylactoid reactions in patients dialysed with AN69 membranes (52).

Angiotensin II receptor blockers: Although there is limited experience with angiotensin II receptor blockers (ARBs) in dialysis patients, they also seem well tolerated in this patient population. A recent open-label, randomized trial in 366 patients showed that an ARB may be effective in reducing nonfatal cardiovascular events in patients on long-term hemodialysis (53). Dose adjustment of ARBs in patients on hemodialysis is not necessary.

Calcium channel blockers: Calcium channel blockers (CCBs) are effective and well tolerated in dialysis patients, even in those who are volume expanded (54). Among dialysis patients with pre-existing cardiovascular disease, dihydropyridine CCBs and nondihydropyridine CCBs were associated with a significant reduction in cardiovascular mortality (55). A recent study (56) showed that amlodipine safely reduced systolic BP in a cohort of hemodialysis patients. Because of the negative chronotropic action of nondihydropyridine CCBs, combination with beta-blockers should be avoided.

Other antihypertensive drugs such as beta-blockers, alpha-1-adrenergic receptor blockers and centrally acting agents can be used in an association regimen to achieve BP targets. Beta-blockers are indicated in patients with coronary artery disease. In hemodialysis patients with dilated cardiomyopathy, a randomized trial (57) demonstrated that the vasodilating beta-blocker, carvedilol, significantly reduced morbidity and mortality over two years. Liposoluble beta-blockers

TABLE 2
Causes of post-transplant hypertension

	Examples
Immunosuppression	Cyclosporine Tacrolimus Corticosteroids
Graft disease	Delayed graft function Acute rejection Chronic allograft dysfunction Recurrent glomerular disease De novo glomerular disease Transplant renal artery stenosis
Recipient factors	Essential hypertension Original kidney disease Native kidney presence Excessive weight gain
Donor factors	Pre-existing donor hypertension Subarachnoid hemorrhage Prolonged cold ischemia time Advanced donor age Use of right kidney

(nadolol and atenolol) are cleared by the kidney and dose adjustment is necessary to prevent excessive bradycardia.

It is noteworthy that if volume overload is not properly corrected with dialysis, hypertension will remain despite the use of antihypertensive drugs.

Prospective RCTs are needed to determine the effect of antihypertensive drugs on cardiovascular outcomes in dialysis patients.

HYPERTENSION AFTER RENAL TRANSPLANTATION

The most common causes of kidney transplant failure are death with a functioning allograft and chronic allograft dysfunction (58,59). Cardiovascular disease is known to cause approximately 40% of deaths among renal transplant recipients and is its largest single cause (60). Thus, an understanding of the cardiovascular risk in renal transplant recipients is critical to the development of effective preventive and interventional strategies for this large population group. The epidemiology, diagnosis and management of postrenal transplant hypertension is reviewed in the following sections.

Prevalence, importance and etiology

Hypertension is widely prevalent following kidney transplantation (61), with rates of 67% to 90% since the introduction of cyclosporine in 1983 (62), compared with rates of 45% to 55% before then (61).

Post-transplant hypertension is a risk factor for cardiovascular disease (63) and chronic renal allograft dysfunction (64,65). There is a strong positive association between levels of BP control and risk for subsequent renal allograft failure (66), even after adjustment for baseline renal function (67). For each 10 mmHg rise in systolic BP, the risk for allograft loss is increased by 12% to 15% (67,68). A systolic BP of greater than 140 mmHg is associated with diminished long-term allograft survival, regardless of whether antihypertensive agents are used (66). An elevated BP also predicts acute rejection (69). Thus, adequate control of BP is an important goal for transplant recipients.

The etiology of hypertension following renal transplant includes ongoing essential hypertension, the presence of diseased native kidneys, allograft dysfunction due to acute tubular necrosis, acute rejection or chronic dysfunction, recurrent and de novo glomerular disease in the allograft, transplant renal artery stenosis, and immunosuppressive medication including calcineurin inhibitors (CNIs; cyclosporine or tacrolimus) or corticosteroids (68). Persistent post-transplant hyperparathyroidism is also a cause, and hypertension can also be caused by the donor organ (70). The etiology in a given patient is usually multifactorial (Table 2).

TABLE 3
Management of post-transplant hypertension

Investigations	Treatment
Measurement of renal function (serum creatinine, estimated glomerular filtration rate)	Lifestyle and dietary modification Calcineurin inhibitor dose reduction or substitution
24 h ambulatory blood pressure monitoring	Antihypertensive agents (all classes, often multiple agents)
24 h urine collection for protein and/or spot urine protein/creatinine ratio	Angioplasty for renal artery stenosis Surgical bypass
Hemoglobin	Bilateral native nephrectomy
Serum calcium	
Parathyroid hormone	
Calcineurin-inhibitor level	
Ultrasound of renal allograft with Doppler studies of graft vessels	
Angiography	
Renal allograft biopsy	

Both CNIs and steroids cause sodium retention and volume expansion, with associated low plasma renin levels (71). CNIs cause afferent arteriolar vasoconstriction by increasing sympathetic nervous system activity, intrarenal RAS activity and ET-1 synthesis and release; decreasing NO production and vasodilator prostaglandins; and increase vasoconstrictor cytokines (72-74).

Renal artery stenosis may manifest at any time, but is most common between three months and two years post-transplant (75). It has a frequency of 5% to 10%, is more common when the right kidney is used, and may be caused by rejection of the donor artery, clamp or perfusion pump cannulation injury, vessel size disproportion, inflammation from the suture material used, or extension of external iliac artery atherosclerosis (76,77).

Diagnosis and treatment targets

Diagnostic tools and methods used for renal transplant recipients are similar to those for the general population in the absence of evidence for a different approach. Diagnosing hypertension in the post-transplant clinic is often straightforward, although renal transplant recipients do exhibit masked hypertension and a white coat effect (78). As in other forms of CKD, ABPM has been found to be a stronger predictor of renal function (79) and LVH (80) than office BP. ABPM is an excellent tool to diagnose masked hypertension and white coat hypertension, and to assess the diurnal pattern of BP. A nondipping pattern of nocturnal BP has been found to have a prevalence of up to 90% in renal transplant recipients (81). Because office BP would have misdiagnosed 15% to 37% of hypertensive renal transplant recipients as being normotensive, this suggests that the prevalence of masked hypertension is likely high in this population (82,83).

The CHEP guidelines should be followed in the initial investigation of hypertension in renal transplant recipients akin to the general hypertensive population. However, given the unique characteristics of this patient group, a broad differential diagnosis must be entertained and the relevant investigations ordered where appropriate. These are summarized in Table 3. In addition to ABPM, other investigations, where indicated, include monitoring trends in renal function to detect new-onset dysfunction from conditions such as acute rejection and recurrent or de novo glomerular disease, and detecting proteinuria, which is strongly associated with elevated BP (84). An allograft biopsy may be required to establish the diagnosis. High serum calcium and parathyroid hormone levels may indicate persistent post-transplant hyperparathyroidism. A high hemoglobin level may indicate post-transplant erythrocytosis, and a high CNI blood level may be a reflection of chronic overexposure. If BP reduction is unusually difficult, particularly when it is accompanied by renal function compromise, an ultrasound of the renal allograft with Doppler interrogation of the renal vessels may establish a diagnosis of renal artery stenosis. Angiography with carbon

dioxide-containing contrast may be considered to avoid contrast-induced nephropathy.

The CHEP recommends that the treatment of hypertension in renal transplant recipients be the same as in other hypertensive patients. Unless specific comorbidities such as diabetes mellitus or CKD dictate specific targets (ie, less than 130/80 mmHg), a BP target of less than 140/90 mmHg is considered appropriate. In the absence of sufficient outcomes evidence, this recommendation is based on consensus opinion. European guidelines (85) provide a target of less than 130/85 mmHg for those without proteinuria and less than 125/75 mmHg for those with proteinuria, while American Society of Transplantation guidelines (63) prescribe a target of less than 140/90 mmHg. Although clinical trials are lacking, retrospective data demonstrated that achieving BP control was associated with improved allograft and patient survival (86). A decrease in nocturnal systolic BP was also associated with regression of LVH (87).

Management

Patients with renal transplants should also undergo nonpharmacological interventions including lifestyle modification and stress reduction therapy. Concurrent pharmacological intervention is advised if the BP is persistently above target and/or target organ damage is present (85). The BP-lowering effect of regular exercise and weight reduction, reducing salt and alcohol intake, and pursuing a less stressful lifestyle have not been systematically evaluated in the transplant population. Although CNIs cause salt retention and volume expansion, BP does not correlate with 24 h urine sodium excretion (84). Therapy for hyperlipidemia with statins may result in BP lowering (88).

Hypertension is very common in the immediate post-transplant period due to the use of higher doses of CNIs and steroids. As drug doses are lowered, the BP declines but is unlikely to reach the normotensive range. Some reports indicate that tacrolimus causes less hypertension than cyclosporine (89). In the Diabetes Incidence after Renal Transplantation: neoral C2 monitoring versus Tacrolimus (DIRECT) trial (90), both BP and the use of antihypertensive medication were not different between cyclosporine and tacrolimus at six months. The use of sirolimus instead of CNIs may result in better BP control (91), as demonstrated in the Rapamune Maintenance Regimen (RMR) trial (92). However, the Efficacy Limiting Toxicity Elimination-Symphony (ELITE-Symphony) study (93) of 1645 patients demonstrated no important difference in BP among four different immunosuppressive drug regimens. To date, steroid withdrawal has not been demonstrated to have a favourable impact on BP (94).

The use of antihypertensive agents is often dictated by comorbidities such as cardiovascular disease and proteinuria (63). Multiple agents are

typically required. There are no studies to date evaluating long-term renal and cardiovascular outcomes among different BP-lowering drug classes. CCBs reverse CNI-induced afferent arteriolar vasoconstriction and are associated with higher glomerular filtration rates than ACE inhibitors (95) in the short term, likely due to increased renal blood flow. The use of CCBs is associated with earlier allograft function recovery and better long-term allograft function when used with cyclosporine (71). Nondihydropyridine CCBs interact with CNIs through the hepatic cytochrome P450 system, thereby raising CNI levels; consequently, careful CNI blood level monitoring is required. Despite this, diltiazem has been used safely with both cyclosporine and tacrolimus (96). Beta-blockers increase the risk of dysglycemia and dyslipidemia to which renal transplant recipients are already prone. Alpha-blockers are theoretically beneficial because they reduce peripheral resistance without decreasing renal plasma flow. A long-term study has demonstrated their efficacy in the transplant population (97). Loop diuretics are helpful in states of volume expansion, but may exacerbate the prerenal azotemia caused by CNIs.

The RAS antagonists in the transplant population have been studied and shown to be safe and efficacious when used over long periods (98). A small RCT comparing nifedipine to lisinopril (95) showed a lower glomerular filtration rate in the lisinopril group after two years. A renal protective effect on 10-year allograft survival rate with an ACE inhibitor or ARB was found in a retrospective cohort study of 2031 renal transplant patients (99). However, this finding was not confirmed in another registry-based analysis (100). Presently, an RCT comparing ramipril with placebo in renal transplant recipients with proteinuria with the change in BP as a secondary end point is ongoing (101). Regular monitoring of allograft function, extracellular fluid volume status, and serum potassium levels is advised whenever RAS antagonists are prescribed or their dose is adjusted.

Clinically significant transplant renal artery stenosis can be treated by percutaneous transluminal angioplasty or surgical bypass. Although initial results are good, long-term follow-up studies are sparse. Selection of appropriate patients remains difficult (102). There is an approximately 20% restenosis rate with angioplasty (103). Intra-arterial stenting can also be performed, particularly in the event of recurrent stenosis (104). In a small series of six patients with recurrent RAS who received metallic stents, no further recurrence was reported after three years (105). Surgical repair, usually reserved for those with proximal recipient arteriosclerotic disease, is associated with a 10% stenosis recurrence rate and 30% allograft loss rate (103,106). In rare cases of resistant hypertension, in which the etiology is thought to be of native renal origin (eg, ischemia), bilateral native nephrectomy should be considered (107,108).

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