Hypertension in Post-renal Transplant Patients
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Abstract
Hypertension in renal transplant recipients is known to be a major risk factor for cardiovascular morbidity and mortality, as also reduced allograft survival. Importantly, hypertension in renal transplant patients is common and ranges from 50% to 80% in adult recipients and from 47% to 82% in pediatric recipients. Many patients experience a remarkable improvement in blood pressure (BP) control, requiring lesser medications within months of transplantation. However, the benefits of improved glomerular filtration rate (GFR) and fluid status may be negated by various donor and recipient factors, acute and chronic allograft injury, and immunosuppressive medications, thereby explaining some of the pathophysiology of post-transplant hypertension. Other contributory factors for hypertension after transplant, beyond a progressive decrease in GFR, include transplant renal artery stenosis and adrenal causes of hypertension, as noted in some patient cohorts. Notably, targets for hypertension management in renal transplant recipients remain an enigma, since there are not sufficient data from randomized controlled trials to support a benefit from targeting lower BP levels on graft and patient survival. Although no specific antihypertensive medications have been shown to be more effective than others at improving survival in this cohort, calcium channel blockers may be the most useful medication for mitigating calcineurin inhibitor-induced vasoconstriction, and their use may improve GFR. Use of inhibitors of the renin-angiotensin system remains an attractive strategy, but the potential for drug-drug interactions and altered pharmacokinetics and pharmacodynamics of the different antihypertensive medications need to be carefully considered. In conclusion, hypertension control affects both patient and long-term transplant survival, thereby necessitating the identification of the underlying pathophysiology and subsequent individualization of treatment goals.

Key words: Hypertension, Renal transplant, Renin angiotensin system

Introduction
Atherosclerotic cardiovascular (CV) disease is a significant cause of morbidity and mortality after renal transplant.[1] Hypertension is one of the most common clinical problems seen in renal transplant recipients and is a major “traditional” determinant of shortened allograft survival and increased CV events.[2] The major goals of antihypertensive therapy after transplant are the preservation of kidney function and reduction of CV disease risk. Recently published evidence-based guidelines recommend a goal blood pressure (BP) of 140/90 mmHg be adopted for the general population, regardless of risk factors.[3] Whether the same can be applied to renal transplant recipients is unclear. The BP frequently often rises early after kidney transplantation after saline loading interacts with initial high-dose immunosuppression.[4] Long-term BP is often easier to control after transplantation, as long as the individual achieves a good glomerular filtration rate (GFR).

Definition and Diagnosis
The relationship between BP and CV/renal events is continuous, making the distinction between normo- and hypertension based on BP cutoff values arbitrary to an extent. However, hypertension is defined as the level of BP at which the treatment benefits undoubtedly outweigh treatment risks, as demonstrated in clinical trials. Hypertension is defined by an office BP recording of >140/90 mmHg. BP is classified as optimal, normal, high

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normal, or Grades 1–3 hypertension in young, middle-aged, and the elderly. BP centiles are used in children and teenagers. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC 7) recommends that treatment is provided to achieve BP <130/80 mm Hg in patients with diabetes or chronic kidney disease (CKD). The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative has similar treatment target recommendations that have been endorsed recently by the Kidney Disease Improving Global Outcomes working group. In patients with significant proteinuria (defined as spot urine protein-creatinine ratio >500 mg/g), a European Best Practice Guideline suggests that the BP goal can be decreased to <125/75 mmHg. There are no targeted BP goals for the treatment of hypertension in post renal transplant patients.

Recent studies have assessed the correlation between ambulatory BP monitoring (ABPM), home BP monitoring (HBPM), and office clinic BP monitoring (CBP) in the post-transplant setting. The use of standardized techniques, as used in clinical trials of hypertension with >1 measurement of BP, can provide improved concordance rates between CBP and ABPM as seen in a study by Haydar et al. Other researchers have demonstrated that HBPM determinations had a significantly better agreement with ABPM than CBP (72% vs. 54%) even though both the CBP and the HBPM correlated with ABPM. The use of ABPM is being recommended more broadly in the transplant setting. The use of standardized techniques, as used in clinical trials of hypertension with >1 measurement of BP, can provide improved concordance rates between CBP and ABPM as seen in a study by Haydar et al. Other researchers have demonstrated that HBPM determinations had a significantly better agreement with ABPM than CBP (72% vs. 54%) even though both the CBP and the HBPM correlated with ABPM.

The use of ABPM is being recommended more broadly in the general population to better assess the clinical importance of nocturnal hypertension, masked hypertension, and white coat hypertension on the risk of vascular events. The diagnostic utility of ABPM should be considered in the kidney transplant recipient because it may prove helpful in guiding management decisions.

**Epidemiology and Outcomes**

Close to half of all renal transplant recipients had hypertension before the introduction of calcineurin inhibitors (CNIs). At present, the overall prevalence of hypertension is reported to be as high as 85%; however, it varies depending on the population studied and definition used. Even though it is generally accepted that hypertension negatively influences renal transplant outcomes, the precise effect of post-transplant hypertension on renal allograft outcomes is difficult to gauge because hypertension accelerates renal failure and declining allograft function worsens BP control. In a single-center observational study of deceased-donor transplant recipients, the odds ratio of allograft failure per 10 mmHg increase in BP measured at 1 year after transplantation (after adjustment for renal function) was 1.15 (95% confidence interval [CI], 1.02–1.30) for systolic pressure, 1.27 (95% CI, 1.01–1.60) for diastolic pressure, and 1.30 (95% CI, 1.05–1.61) for mean arterial pressure. The collaborative transplant study, a large cohort study of nearly 30,000 renal transplant recipients, demonstrated a graded association between systolic BP (SBP), diastolic BP (DBP), and allograft failure. In addition to decreased allograft survival, post-transplantation hypertension is associated with decreased patient survival as well. Each 10 mmHg increment of SBP >140 has been shown to be associated with a hazard ratio of death of 1.18 (95% CI, 1.12–1.23), and this risk persists after adjusting for allograft function. The association between hypertension and death in kidney transplant recipients is mediated by the increased risk of CV disease because uncontrolled hypertension post-transplant is associated with an increased risk of de novo congestive heart failure and ischemic heart disease. However, as with allograft failure, it has not been demonstrated in prospective studies that tight BP control mitigates the risks of CV disease and death in these patients. Nonetheless, strong observational data showing a relationship between higher BPs and worse outcomes warrant the treatment of post-transplant hypertension and the pursuit of prospective clinical trials to establish optimal BP targets.

**Pathophysiology**

In contrast to the general and CKD populations, risk factors for hypertension post-transplant include determinants of both donor and recipient origin and also factors that relate to the transplant process and immunosuppression. The interplay of such factors was demonstrated in a prospective observational study of 85 transplant recipients with stable renal function (without cyclosporine therapy), followed up for 8 years, by Guidi et al. Recipients without a family history of hypertension and who received a kidney from a hypertensive family developed hypertension more frequently compared to those with a kidney transplant from a normotensive family or recipients with familial hypertension (in whom the origin of the kidney did not influence the prevalence of post-transplant hypertension). During follow-up of these patients, it was noted that recipients of kidneys derived from hypertensive families developed higher DBPs and greater degrees of acute kidney injury during acute rejection than the other recipients.

**Donor Factors**

Donor factors independently associated with post-transplant hypertension include pre-existing hypertension, older age, and poor allograft quality. Recently, several genetic variants, including polymorphisms within genes that encode for ABC2, ABC1, CYP 3A5, and APOL-1, have been shown to be associated with early graft dysfunction and subsequent post-transplant hypertension. The size of the donor kidney relative to the recipient also plays a role in the development of post-transplant hypertension. A disparity between donor and recipient size can lead to a relative underdosing of nephrons and subsequent maladaptive hyperfiltration, glomerular hypertrophy, and intraglomerular hypertension.

**Acute Rejection and Chronic Allograft Injury**

Hypertension and GFR are intimately interrelated after renal transplant. Karthikeyan et al. demonstrated increasing...
requirements of antihypertensive medications from 0.7 in kidney transplant recipients with CKD Stage 1–2.3 in those with Stage 5 function. Kasiske et al. examined the impact of hypertension on transplant survival. After adjusting for the effects of rejection, kidney function, and other variables, each 10 mmHg rise of SBP was associated with an increased RR of transplant failure and death.\(^{[16]}\)

Any injury to a transplanted kidney can result in the initiation or worsening of post-transplant hypertension. The most common causes are acute rejection (cellular and antibody mediated), chronic allograft injury (including chronic antibody-mediated rejection and interstitial fibrosis/tubular atrophy), thrombotic microangiopathy, and recurrent glomerular disease.\(^{[2]}\) A renal transplant recipient with new-onset hypertension must be evaluated for an acute rejection, since this may be associated with RAAS stimulation and responds well to treatment of rejection. A recent report of patients with antibody-mediated rejection by non-DSA antibodies that bind to angiotensin II type I receptors suggests that AT1 receptor blockers might prevent this type of hypertension.\(^{[20]}\) Commonly, AT1 receptor-related vascular rejection occurs during the 1st week after surgery. Notably, hypertension related to chronic allograft injury is similar to that associated with CKD and occurs at least 3 months post-transplant in the absence of active acute rejection and CNIs. Recurrent disease commonly focal glomerulosclerosis that results in injury to the allograft also leads to hypertension. Rarely, a transplant renal artery kink confirmed by parvus tardus waveform on ultrasound Doppler and a page kidney caused by external renal compression due to hematoma, lymphocele, or urinoma can lead to early graft dysfunction and severe hypertension.\(^{[21]}\)

### Immunosuppressive Agents

These medications are known to be associated with post-transplant hypertension. Corticosteroids mediate hypertension through mineralocorticoid-induced sodium retention, increased responsiveness to vasoconstrictors, and decreased vasodilator production. The incidence of steroid-related hypertension is approximately 15%, especially in recipients with pre-existing hypertension.\(^{[22]}\) Transplant centers have tended to either lower the steroid dose or withdraw steroids to decrease the risk of post-transplant hypertension. Question arises whether such protocols result in tangible improvements in primary outcomes. In a 12-month open-label multicenter study, renal transplant recipients were randomly assigned to receive no steroids, steroids to day 7 post-transplant (steroid withdrawal), or standard steroid therapy, all in combination with cyclosporine, enteric-coated mycophenolate, and basiliximab. The study found no differences in terms of SBP or DBP between groups. However, there was a significantly higher incidence of rejection in the steroid avoidance or withdrawal groups. Most importantly, there were no differences in patient or transplant survival at the end of the study.\(^{[23]}\) Most likely, we are now seeing a practice of steroid-treated patients receiving much lower cumulative immunotherapy than their predecessors, and therefore, consequent impact of steroids on BP is negligible.

CNIs, particularly cyclosporine, are well-established causes of post-transplant hypertension. They have been shown to worsen BP control in HLA-identical renal transplants.\(^{[24]}\) The pathophysiology of cyclosporine-induced hypertension is related to direct vascular effects, through activation of the sympathetic nervous system, endothelin upregulation, and inhibition of nitric oxide, leading to potent vasoconstriction.\(^{[25]}\) The renal sodium retention stimulated by cyclosporine is also related to afferent glomerular arteriole vasoconstriction. Tacrolimus activates the renal sodium chloride cotransporter and causes a sodium sensitive forum of hypertension. Evidence suggests lower rates of post-transplant hypertension with tacrolimus as against cyclosporine.\(^{[26]}\) Decreasing the dose of cyclosporine by 50% at 1 year or longer post-transplant has been shown to decrease the risk of hypertension in patients treated with steroids and mycophenolate mofetil without increasing rejection risk.\(^{[27]}\) Given the importance of adequate immunosuppression to avoid rejection, decisions about adjusting immunosuppressive medications to facilitate BP control need to be carefully considered. It may be easier and safer to use lifestyle modifications or antihypertensive medication rather than modify immunosuppression.

### Recipient Factors

Recipients with prior longstanding hypertension have a loss of vascular compliance due to stiffening of vessels. These vascular changes can contribute to the hypertensive process, especially in the presence of volume excess. The genetic profile, age, body mass index, presence of obstructive sleep apnea syndrome (OSAS), and secondary causes of hypertension (either pre-existing or incident) are all important contributory factors to post-transplant hypertension.\(^{[2]}\) Transplant renal artery stenosis (TRAS), causing a form of renovascular hypertension, is the most common form of secondary hypertension. TRAS most commonly presents 3–24 months post-transplant, while risk factors include CMV infection, delayed transplant function, organ procurement complications, and surgical techniques. Incidence is also suggested to be higher in recipients of live donors and pediatric donors when compared to deceased donors.\(^{[28]}\)

TRAS has been reported in 1–23% of renal transplant recipients, mainly due to stenosis at the renal artery anastomosis, but it may also occur at more proximal sites, such as the recipient iliac artery.\(^{[29]}\) Presentation includes worsened hypertension, hypokalemia caused by secondary aldosteronism, a decline in allograft function, or worsening function with reduction in perfusion pressure, particularly with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blocker (ARB) therapy. Less commonly, flash pulmonary edema may occur in the setting of a single functioning transplant kidney with TRAS.\(^{[2]}\) Clinically evident bron, non-invasive imaging with renal artery Doppler is the initial diagnostic step. If inconclusive or suboptimal, then CT imaging with a small amount of contrast should be considered or even CO\(_2\) angiography. Magnetic
resonance angiography (MRA) with gadolinium may not be an option in the setting of reduced GFR; however, non-contract MRA is being used more frequently.[4]

Intravascular intervention for TRAS is indicated for either increased serum creatinine or worsened hypertension. Percutaneous intervention by angioplasty, with or without stenting, is considered as the treatment of choice if medical therapy is inadequate. Success rates are as high as 82–94%. Restenosis occurs in about 10% and transplant loss in up to 30% of recipients.[29] Surgical revascularization is reserved for lesions that are not amenable to percutaneous intervention or for recurrence after angioplasty. Whether platelet inhibitors should be used is unclear and, as with the native renal artery, stents are generally available for this site only as bare metal stents related to size requirements.[4]

Renin-dependent hypertension is likely to persist despite successful transplantation in rare cases. A high native kidney to transplant renal vein renin ratio can confirm the diagnosis. Bilateral native kidney nephrectomy[30] or ablation by embolization[31] has been found to be effective.

Secondary hypertension may be pre-existent and remain unrecognized, or it may present post-transplant. Primary hyperaldosteronism is a common cause of secondary hypertension in hypertensives, estimated to affect 20% of those with resistant hypertension. With this degree of penetrance and the common association of hypertension with CKD, prevalence rates are likely to be at least as high in the renal transplant population. Therefore, the presence of hypokalemia to any degree in association with severe hypertension should raise diagnostic suspicion, although registry data have suggested lower rates of post-transplant hypertension due to primary hyperaldosteronism.[3]

The association of primary hyperaldosteronism and OSA reported in patients with resistant hypertension should also be considered after renal transplantation, as it contributes to the development of pulmonary hypertension if not diagnosed and treated. The diagnosis depends on an elevated aldosterone-to-renin ratio, confirmed by the evidence of autonomous aldosterone production. Treatment is by suppressing the effect of aldosterone because of its potential vascular toxicity. A trial of spironolactone or eplerenone is reasonable and may even be helpful for facilitating BP control in patients on higher doses of corticosteroids.[2]

Management of Post-renal Transplant Hypertension

There is a lack of randomized controlled trials to examine optimal levels of BP in renal transplant recipients to prolong graft survival or limit the risk of CV events. There are also no data to define optimal treatment strategies. The target BP control for renal transplant recipients must be individualized based on all CV and renal risk factors. Lower BP goals (<140/90 mmHg) may be beneficial, given the epidemiologic data linking it to prolonged graft survival.[35]

The timing of the development of hypertension post-renal transplantation is an important consideration for effective management. In the initial few weeks to months post-transplantation, hypertension may be influenced by volume overload, higher doses of corticosteroids, and CNI levels and poor or delayed allograft function. Hence, their management requires achievement of ideal volume status and the employment of lower doses of both corticosteroids and CNIs while avoiding acute rejection episodes. Thiazide or loop diuretics should be considered. Beta blockers and calcium channel blockers (CCBs) can also be used if indicated. It is recommended to avoid ACEi and ARBs early post-transplantation due to their hemodynamic effect on GFR and potassium homeostasis.[32] Non-pharmacologic management with lifestyle modifications, including exercise, weight control, cessation of smoking, and dietary salt modification, must be an integral component of the management strategy as in the general population. The salutary effect of dietary sodium restriction in transplant recipients is supported by studies. In one study comprising relatively small number of kidney transplant recipients, a 3-month trial of an 80–100 mmol/day sodium-restricted diet resulted in a statistically significant drop in SBP and DBP compared with a control group on a non-restricted diet.[33]

Specific Classes of Antihypertensive Agents

A clinician has to choose antihypertensive medications in renal transplant recipients on the basis of efficacy, tolerability, lack of known drug-drug interactions, and medical comorbidity. CCB, diuretics, beta-blockers, alpha1 blockers, ACEi, and ARBs have all been used singly or in combination to reduce BP in the transplant population.

CCBs

CCBs act by inhibiting voltage-gated calcium channels in vascular smooth muscle cells and cardiac myocytes, thereby reducing contractility and inducing vasodilatation. Such drugs fall into two major classes: Dihydropyridine (e.g., amlodipine and nifedipine) and non-dihydropyridine (e.g., diltiazem and verapamil). It is well known that vasoconstriction is the dominant mechanism by which CNIs induce acute nephrotoxicity and hypertension. Therefore, vasodilatory CCBs have been an attractive option at least for the early management of hypertension after transplant, especially when target CNI levels are highest.[34] A large, prospective, randomized, comparative study found the following benefits of nifedipine compared to lisinopril, despite equivalent initial GFRs and attainment of similar BP levels. (1) At 1 year, GFR had significantly increased in those treated with nifedipine (56 vs. 46 mL/min at baseline) but was unchanged with lisinopril (44 and 43 mL/min, respectively); (2) at 2 years, improvement in GFR with nifedipine was maintained (10.3 mL/min; CI, 4.0–16.6); no such benefit was observed with lisinopril.[35] Non-dihydropyridines such as verapamil and diltiazem are potent inhibitors of cytochrome P450 and C3A4 and cause plasma levels of the immunosuppressive drugs to increase sharply soon after initiation. This is a transcriptional event and typically occurs during a 2–5 days’ period after initiation. Similarly,
discontinuation of CCB therapy leads to the decrease in the levels of immunotherapy; therefore, clinical acumen dictates that such drugs be used with caution and frequent monitoring. The dihydropyridine CCBs share these properties to a much lesser extent and therefore are easier to use in transplant recipients, although they are more likely to be associated with the development of edema. 

ACEI/ARB

The clinical benefits of RAS blockade have been clearly demonstrated in non-transplanted hypertensives with elevated CV risk. However, studies in transplant recipients have been inconclusive. Two systematic meta-analyses have attempted to consolidate the data on the use of ACEi/ARB in renal transplant recipients. Hiremath et al. [37] identified 21 randomized trials of ACEi/ARBs in three databases from 1966 to 2007 involving 1549 patients. With a 27-month median follow-up time, the use of ACE inhibition/ARBs was associated with significant reductions in GFR (−5.8 cc/min), hematocrit (−3.5%), and proteinuria (−0.47 g/dl), without a significant effect on serum potassium. Cross et al. published a Cochrane Database Systematic Review, which included 10 studies comparing ACEi with placebo with 445 patients and 7 studies comparing ACEi with CCBs with 405 patients. Compared with CCBs, the use of ACEi was found to be associated with a significant reduction in GFR (−11.49 cc/min), proteinuria (−0.28 g/dl), and hemoglobin (−1.3 g/dl), with a 2.74-fold elevated relative risk of hyperkalemia. [36] Heinz et al. [38] used the Austrian Dialysis and Transplant Registry and Eurotransplant databases and identified 2031 transplant recipients at a single center between 1990 and 2003. Compared with no ACEi/ARB therapy, any documented ACEi/ARB use was associated with improved 10-year patient (74% vs. 53%, P = 0.001) and graft (59% vs. 41%, P = 0.002) survival. However, another retrospective analysis of 17,209 patients transplanted between 1995 and 2004 from the collaborative transplant study was unable to show a difference in graft or patient survival at 6 years in those either on or off ACEi/ARB therapy. [35]

Therefore, definitive evidence of the benefit of ACEi/ARB therapy in transplant recipients is lacking. Several factors have to be considered when choosing such medications for kidney recipients.

- ACEi or ARB therapy can cause or exacerbate a decrease in GFR, and this effect may mimic or mask early signs of acute transplant rejection. Consequently, these drugs are difficult to use early after transplant when patients are at the highest risk of developing complications.
- Hyperkalemia is a frequent finding after renal transplant that is associated commonly with delayed transplant function and is an adverse effect of CNI (particularly tacrolimus) therapy. ACEi/ARB therapy can exacerbate the frequency and severity of hyperkalemia.
- ACEi can cause or exacerbate anemia in transplant recipients, decreasing hematocrit by as much as 5–10% through a mechanism that may be potentiated by cyclosporine. This incompletely understood phenomenon is believed to be caused by the inhibition of erythropoiesis and may be useful in the management of post-transplant erythrocytosis, a condition characterized by a progressive increase in hematocrit (>50%) and risk of atherothrombotic events. [4]

Apart from CCBs and ACEi/ARB, there are no or few published data on other classes of antihypertensives in post-renal transplant recipients.

Pharmacologic Principles in Post-transplant Therapeutics

Pharmacokinetic considerations are more significant in renal transplant recipients given the variability of renal function, comorbidities and large drug burden, and their interactions. Drug-drug interactions can be pharmacokinetic or pharmacodynamic in nature. Complete dose-response curves are rarely generated for antihypertensive drugs in renal transplant recipients. Hence, it is better to focus on the additive response with multiple drug combinations and not on titration of monotherapies. [12] Tachyphylaxis due to enzyme induction leading to increased drug metabolism does not usually occur in this patient population. Antihypertensive drugs are typically dosed till the desired effect is achieved and dosage reduction is only considered thereafter or if there are drug concentration-dependent adverse effects.

Conclusion

Renal transplant recipients commonly have hypertension post-transplantation. Many transplant recipients have poorly controlled BP despite evidence suggesting improved CV outcomes with good BP control. Much of the challenge arises from the complexity of multidimensional medical care that they require. The BP goals need to be lower than the general population and individualized to each patient. ABPM is a helpful tool to assess the adequacy of treatment and secondary causes of hypertension need to be considered in patients with resistant hypertension. Future clinical trials need to define optimal BP treatment goals and therapies in renal transplant recipients as also clearly demonstrate their influence on graft and patient survival.

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