

# Arterial hypertension in renal transplantation: Clinical implications, pathogenesis and current management strategies

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## Abstract

Renal transplantation is the treatment of choice in end-stage kidney disease patients. Cardiovascular disease is the main cause of death in dialysis patients. The cardiovascular risk sharply declines after successful renal transplantation, but still death with a functioning graft due to cardiovascular disease is the leading cause of death in renal transplant recipients. Conventional cardiovascular risk factors such as hypertension, diabetes and hyperlipidemia which are common in transplant recipients and are associated with adverse outcomes, are accentuated by the effects of immunosuppressive drugs. More specific, arterial hypertension is a major problem in renal transplantation due to its high prevalence as well as due to its associations with cardiovascular disease and chronic allograft nephropathy. Some of the parameters implicated in the pathogenesis of post-transplant hypertension are donor and recipient factors, acute and chronic allograft injury, and immunosuppressive drugs. A significant and potentially remediable cause of resistant hypertension in renal transplant recipients is renal artery stenosis. Treatment of arterial hypertension in renal transplant patients is challenging due to the lack of established blood pressure goals, the association with multiple comorbidities and the complex immunosuppressive treatment. The aim of this review is to describe the clinical implications of increased blood pressure in renal transplant recipients, the specific settings underlying the pathogenesis of arterial hypertension in this patient population and current management strategies.

**Key words:** Arterial Hypertension; renal transplantation; immunosuppression; renal artery stenosis; cardiovascular disease

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## Introduction

Renal transplantation is the gold standard of treatment for patients with end-stage kidney disease (ESRD). Hemodialysis patients have a ten to twenty times higher risk of premature cardiovascular disease (CVD) compared to the general population. The risk sharply declines after successful renal transplantation, but still remains three to five times higher compared to that of the general population [1]. Death with a functioning graft due to CVD is the leading cause of death following renal transplantation. Conventional cardiovascular risk factors such as hypertension and diabetes are common in renal transplant recipients (RTRs) and are associated with adverse outcomes, and are also accentuated by the effects of immunosuppressive drugs [1, 2].

Arterial hypertension in patients with chronic kidney disease (CKD) remains a major challenge due to its high prevalence within this patient population as well as due to its associations with CVD and progression of CKD [3]. Following renal transplantation, arterial hypertension remains a prevalent disorder ranging from 50% to 80% [4, 5]. Although blood pressure (BP) targets are more easily achieved in RTRs, especially in those with preserved glomerular filtration rate (GFR) [4], adequate control of BP has been reported in as few as 5% of RTRs [6]. The aim of this review is to describe the clinical implications of increased BP in RTRs, the specific settings underlying the pathogenesis of arterial hypertension in this patient population and current management strategies.

## Clinical outcomes

Arterial hypertension in RTRs is considered one of the major risk factors for the development of CVD, including both ischemic heart disease and congestive heart failure [7-10]. Accordingly, higher levels of systolic BP and lower levels of diastolic BP have been significantly and independently associated with an increased risk of cardiovascular events and all-cause mortality, without evidence of a J-shape correlation [8]. Arterial hypertension is a major determinant of left ventricular hypertrophy and heart failure following transplantation [7, 10].

The association of arterial hypertension with allograft dysfunction is bidirectional, as arterial hy-

pertension accelerates renal damage and on the other hand is, itself, aggravated by declining allograft function. Several observational studies have shown that BP during the first post-transplant year was independently associated with renal allograft survival with a pattern of a graded relationship between systolic and diastolic BP values and allograft loss [11, 12]. Finally, post-transplantation hypertension is associated with decreased patient survival, which should most probably be ascribed to the increased risk of CVD [13].

## Pathogenesis and risk factors for post-transplant hypertension

The pathogenesis of arterial hypertension following renal transplantation is multifactorial with the implication and interplay of donor, peri-transplant, and recipient factors. Several experimental models of renal cross-transplantation which investigated the genetics of arterial hypertension, have shown that the inherited predisposition to hypertension resides primarily in the kidneys [14]. Thus, transplanting kidneys from deceased-donors with a family history of hypertension is associated with an increased incidence of post-transplant hypertension. Accordingly, in recipients without a history of familial hypertension, the transplantation of a «hypertensive» kidney has been associated with a tenfold increased requirement of antihypertensive drugs than the transplantation of a «normotensive» kidney, so as to achieve similar levels of blood pressure control [15]. Although it has been reported that transplantation of a kidney from normotensive donors with a negative family history of hypertension led to prolonged normotension in recipients with end-stage renal disease (ESRD) due to hypertensive nephrosclerosis and resistant hypertension while on dialysis, it seems that in recipients with familial hypertension, the origin of the kidney does not influence the prevalence of hypertension after transplantation [15, 16]. Other donor related factors include older donor age, and poor allograft quality as occurs with extended criteria donors, as well as several genetic variants, including polymorphisms within genes that encode for APOL-1, ABCC2, ABC1 and CYP3A5 [4].

A major recipient related factor which contributes to post-transplant hypertension is already established vascular stiffening and loss of compliance due to long-standing CKD [4]. Moreover, secondary hypertension may develop both prior to or following renal transplantation, such as in the setting of primary aldosteronism or obstructive sleep apnea [4]. However, the most common etiology secondary hypertension is transplant renal artery stenosis, occurring in 1-3% of RTRs and manifesting as a form of renovascular hypertension [17, 18]. Nevertheless, several reports suggest that functionally significant stenosis occurs in up to 12% of RTRs with hypertension [18]. Identification of renal artery stenosis as a potential cause of arterial hypertension following renal transplantation is of paramount importance as it is a correctable form of hypertension [17]. Delineation of the risk factors for renal artery stenosis, such as difficulties in organ procurement and operative techniques, atherosclerotic disease, or cytomegalovirus (CMV) infection, are beyond the scope of this review [19]. The diagnostic and therapeutic approach is similar to patients with suspected renovascular hypertension and a single functioning kidney, with angioplasty remaining the gold standard of treatment [17-19].

Immunosuppressive medications are associated with post-transplant hypertension, with corticosteroids and calcineurin inhibitors (cyclosporine and tacrolimus) bearing the greater burden. Accordingly, immunosuppressive protocols utilizing alternate day steroids or complete steroid withdrawal result in improved BP control, albeit at an increased risk for acute allograft rejection [20]. Cyclosporine causes hypertension via direct vascular effects leading to afferent glomerular arteriole vasoconstriction with subsequent sodium retention, whereas tacrolimus activates the renal sodium chloride cotransporter, causing salt sensitive hypertension [21, 22].

Clinical trials have suggested lower rates of post-transplant hypertension with tacrolimus compared to cyclosporine and there is benefit of switching patients from a cyclosporine-based to tacrolimus-based regimen in terms of BP control [23].

Finally, both acute and chronic allograft injury are associated with emergence or worsening of post-transplant hypertension. The pathophysiology

of hypertension associated with chronic allograft injury is similar to that associated with CKD [4].

### **Diagnosis and therapeutic goals**

The diagnosis and management of hypertension rely on office BP measurements. However, patients with CKD present with abnormal BP patterns with home and ambulatory BP monitoring. Thus, the ESC/ESH and ACC/AHA 2017 blood pressure guidelines suggest application of home BP monitoring (HBPM) and ambulatory BP (ABPM) monitoring in order to confirm arterial hypertension, detect white-coat and masked hypertension, as well as during patient follow-up so as to evaluate BP control during treatment [24, 25]. According to the latest ESC/ESH guidelines when hypertension is suspected, the diagnosis should be confirmed either by repeated office BP measurements during several visits or BP measurement using 24h ABPM or HBPM [24]. Renal transplant recipients display abnormal BP patterns as well, including a 16% rate of masked hypertension and 24% rate of white-coat hypertension, whereas the proportion of nondippers reaches nearly 70% [26]. Although there is a paucity of data regarding optimal means of hypertension detection and follow-up in RTRs, recent studies have shown that daytime and night-time systolic BP predict the risk of GFR loss after kidney transplantation, with night-time BP being the strongest indicator of the risk of renal function loss [27]. Although multiple hypertension guidelines have been published during the last 10 years, the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the care of RTRs, specifically address hypertension management in renal transplantation and recommend that target BP levels should be less than 130/80 mmHg [28]. These findings underscore the necessity of more intensive research with regard to identification of abnormal BP patterns and adequacy targets in RTRs in order to improve clinical outcomes.

### **Management of arterial hypertension in renal transplant recipients**

The main targets of treatment of arterial hypertension are cardiovascular protection and prevention of hypertensive allograft injury. Immunosuppres-

sive therapy should be adjusted to optimal levels so as to provide maximum allograft protection against rejection on one hand and avoid treatment complications on the other. Glucocorticoid dose should be reduced to a low maintenance level whereas calcineurin inhibitor blood levels should be monitored on a regular basis so as to be maintained within the desired target range [29]. Dihydropyridine calcium channel blockers are generally considered the first line treatment of choice, as apart from antihypertensive effects, they attenuate cyclosporine-induced renal vasoconstriction [4, 30-32]. Several studies which evaluated the efficacy of calcium channel blockers in kidney transplant patients, have shown clear benefits with regard to renal allograft protection [30-32]. A systematic review of studies comparing calcium channel blockers with placebo or no treatment as well as with ACE inhibitors, showed that calcium channel blockers were the most effective antihypertensive agents in terms of nephrotection and prevention of GFR decline [32]. On the other hand, it should be noted that the non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are cytochrome inhibitors (CYP3A/4) and concurrent use with calcineurin and mammalian (mechanistic) target of rapamycin (mTOR) inhibitors results in increased immunosuppressive drug levels [33, 34]. Thus, tight monitoring of immunosuppressive levels and possible dosage adjustments might be necessary so as to avoid drug side effects.

Despite the undisputable cardiovascular benefits of renin-angiotensin system blockade (RAS) in the general population, including patients with arterial hypertension, diabetes mellitus, heart disease and proteinuric CKD, the protective role of RAS blockade remains to be further clarified in RTRs. Accordingly, a recent metanalysis of randomized trials failed to show that RAS blockade significantly affects clinical outcomes, in terms of all-cause mortality, transplant failure, or creatinine level doubling [35]. Moreover, a recent study in RTRs with proteinuria, did not show a significant reduction in doubling of serum creatinine, ESRD, or death, in patients treated with ramipril compared to placebo [36]. Thus, according to the until now available evidence, that larger

trials enrolling more than 10,000 patients are needed to definitively answer whether RAS blockade is associated with improved clinical outcomes in this patient population. Additionally, treatment of renal transplant recipients with ACE inhibitors/ARBs carries potential risks, including a mild decline in the GFR, increased incidence of hyperkalemia and anemia [4, 37]. Thus, most clinicians postpone the initiation of an ACE inhibitor or an ARB if indicated, three to six months post-transplantation so as to avoid potential side effects and confounding with acute rejection in the setting of increased creatinine concentration.

Finally, all the armamentarium of available antihypertensive agents, (including  $\beta$ -blockers, diuretics, vasodilators and centrally acting antihypertensives), might be utilized in the difficult hypertensive patient or in the setting of resistant hypertension, after excluding secondary causes and associated aggravating factors. Nevertheless, the clinician should be cautious and bear in mind the pharmacokinetic properties of each agent, drug-drug interactions and medication dose adjustment in the setting of allograft dysfunction, so as to minimize adverse events.

The true prevalence of resistant hypertension in RTRs has not been determined, however excluding potential causes such as renovascular disease, recurrence of the primary disease, or rejection remains the mainstay of the diagnostic approach. Removal of the native kidneys has been suggested as the ultimate therapeutic strategy, in the rare setting of truly resistant hypertension [38].

## Conclusions

Arterial hypertension is a common, major cardiovascular risk factor in RTRs. Treatment of arterial hypertension in RTRs is challenging due to the associated multiple comorbidities and complex medical treatment, while established BP goals still lack in this population. Future clinical trials are needed to define the goals of ideal BP levels, optimization of therapeutic strategies as well as find out how they translate into improved cardiovascular and graft outcomes and patient survival.  $\blacklozenge$

## Conflict of interest

There is no conflict of interest.

## Περίληψη

# Αρτηριακή υπέρταση στη νεφρική μεταμόσχευση: Κλινικές επιπτώσεις, παθογένεια και τρέχουσες στρατηγικές διαχείρισης

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Η μεταμόσχευση νεφρού αποτελεί θεραπεία εκλογής για τους ασθενείς με νεφρική νόσο τελικού σταδίου. Η καρδιαγγειακή νόσος είναι η κύρια αιτία θανάτου στους ασθενείς υπό εξωνεφρική κάθαρση. Ο καρδιαγγειακός κίνδυνος μειώνεται κατακόρυφα μετά από την επιτυχή μεταμόσχευση νεφρού, αλλά ο θάνατος με λειτουργόν (το) μόσχευμα λόγω καρδιαγγειακής νόσου παραμένει το συχνότερο αίτιο θανάτου των λήπτων νεφρικών μοσχεύματος. Οι παραδοσιακοί παράγοντες κινδύνου όπως η υπέρταση, ο διαβήτης και η υπερλιπιδαιμία οι οποίοι είναι συχνοί στους λήπτες νεφρικού μοσχεύματος σχετίζονται με κακή έκβαση, ενώ η ανοσοκατασταλτική θεραπεία αποτελεί επιπρόσθετο παράγοντα κινδύνου. Πιο συγκεκριμένα, η αρτηριακή υπέρταση αποτελεί μείζον πρόβλημα για τη μεταμόσχευση νεφρού λόγω της υψηλής επίπτωσης καθώς και της σύσχετισης αυτής με την καρδιαγγειακή νόσο και τη χρόνια νεφροπάθεια του μοσχεύματος. Μερικοί από τους παράγοντες οι οποίοι εμπλέκονται στην παθογένεια της αρτηριακής υπέρτασης μετά τη μεταμόσχευση νεφρού είναι παράγοντες που σχετίζονται με τον δότη και τον λήπτη, η οξεία και η χρόνια βλάβη του μοσχεύματος και τα ανοσοκατασταλτικά φάρμακα. Μία σημαντική και εν δυνάμει αντιμετώπιση αιτία ανθεκτικής υπέρτασης στους μεταμοσχευμένους ασθενείς είναι η στένωση της νεφρικής αρτηρίας. Η θεραπεία της αρτηριακής υπέρτασης στους λήπτες νεφρικού μοσχεύματος αποτελεί πρόκληση εξαιτίας της έλλειψης σαφών θεραπευτικών στόχων, του συσχετισμού της με πολλαπλή συνοουρότητα και της συνδυαστικής ανοσοκατασταλτικής αγωγής. Ο σκοπός της ανασκόπησης αυτής είναι η περιγραφή των κλινικών επιπτώσεων της αυξημένης αρτηριακής πίεσης στους μεταμοσχευμένους ασθενείς, οι ιδιαίτερες αναφορικά με την παθογένεια της αρτηριακής υπέρτασης σε αυτόν τον πληθυσμό ασθενών και οι τρέχουσες στρατηγικές αντιμετώπισης.

**Λέξεις ευρετηρίου:** Αρτηριακή Υπέρταση, μεταμόσχευση νεφρού, ανοσοκαταστολή, στένωση νεφρικής αρτηρίας, καρδιαγγειακή νόσος

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