Treatment-Resistant Hypertension in the Transplant Recipient

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Summary: Treatment-resistant hypertension (TRH) is defined as follows: (1) the failure to achieve optimal blood pressure control to levels less than 140/90 mm Hg despite the concomitant use of 3 or more different classes of antihypertensive agents, one of which is a diuretic, or (2) the simultaneous use of 4 or more different classes of antihypertensive agents in a patient irrespective of blood pressure control and the exclusion of pseudoresistance. Patients with TRH constitute only a subset of patients with poorly controlled hypertension, which also includes other subsets of patients who are treated inadequately or who are noncompliant with prescribed pharmacologic and nonpharmacologic therapy. TRH does occur in kidney-transplant recipients. This may be related to a variety of factors including reduced renal function, renal artery stenosis, concurrent use of medications that increase blood pressure, lack of use or insufficient use of diuretics, noncompliance related to complex medication regimens, or activated neurohormonal pathways, especially aldosterone or the sympathetic nervous system. After kidney transplantation, normalization of blood pressure occurs only in a minority of patients, and it is estimated that 67% to 90% of kidney transplant patients have arterial hypertension and the improvement in glomerular filtration rate and fluid management offered by the kidney transplant may be offset by a wide array of factors. Epidemiologic studies that describe the prevalence of TRH in kidney transplant recipients are lacking.

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Treatment-resistant hypertension is not uncommon post-transplatation (Table 1).[1,2] The diagnosis of treatment-resistant hypertension (TRH) requires accurate blood pressure[3] measurement (Table 2) and correct technique, the exclusion of white-coat hypertension, and the confirmation of patient compliance with prescribed pharmacologic therapy.[3,4]

In the kidney transplant population, white-coat hypertension is common and the effect of physician presence on arterial blood pressure is more pronounced in transplant recipients compared with the general population, even in recipients suffering from allograft dysfunction and/or proteinuria.[5,6] Identifying white-coat hypertension avoids the cost and adverse effects of unnecessary antihypertensive medications. Wen and Gourishankar[7] highlighted the prevalence of white-coat hypertension through the comparison of office blood pressure (BP) measurement with ambulatory BP measurement (ABPM) in 244 prevalent kidney transplant recipients and found that office BP overestimates both 24-hour ABPM and daytime ABPM. Wadei et al[8] reported that ABPM-derived systolic and diastolic BP measurements were lower compared with the corresponding office values among 119 consecutive kidney transplant recipients who presented for their first annual evaluation; 29% had well-controlled hypertension using ABPM criteria compared with 41% who had office systolic BP levels greater than 140 mm Hg, indicating that some patients have white-coat hypertension.[9] Similarly, after ABPM data analysis among 868 patients recruited in the RETENAL study, 65% of patients diagnosed with true controlled hypertension were considered to have white-coat resistant hypertension. Beltran et al[10] evaluated ABPM in patients with office hypertension and identified 11 subjects with white-coat hypertension among 25 patients with well-controlled hypertension by ABPM and a small but important incident of masked hypertension. Agena et al[3] evaluated 183 kidney transplant patients with office BP, home BP monitoring, and ABPM, and concluded that optimally controlled BP was detected in 63.9% of subjects with ABPM, 55.2% with home BP monitoring, and 43.7% with office BP, leading once more to the same conclusion that some patients have white-coat hypertension.

Disturbance in circadian blood pressure rhythm is common after kidney transplantation[8,11–13] and the evaluation of such diurnal BP variations requires ABPM monitoring. Loss of the nocturnal systolic BP dip is associated with higher left ventricular mass index, increased cardiovascular events, lower allograft function, and increased risk of graft failure after kidney transplantation.[8,13,14] Wadei et al[8] reported that 1-year GFR was higher by 4.5 mL/min/1.73 m^2 for each 10% decrease in nocturnal systolic blood pressure (SBP). In recipients without rejection episodes, nondippers

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Table 1. Prevalence of Hypertension and Treatment Resistant Hypertension

Population	Hypertension	TRH
General population	28.6%	8.9%-12.8%
CKD population	70%-80%	15.8%-33.4% (% increases proportionately with reduction in GFR)12. 1%-48.3% (% increases proportionately with degree of albuminuria)
Kidney transplant recipients	67%-90%	

CKD, chronic kidney disease.

and reverse dippers had lower GFR at 1 year, and more accelerated kidney function loss 3 to 4 years after transplantation compared with dippers.[15] Other studies also have shown that ABPM values correlate with other manifestations of allograft dysfunction such as proteinuria, whereas office blood pressure had weak or no correlation.[12]

When ABPM is not readily available, self-measured home BP monitoring is a reasonable alternative because home blood pressure readings better correlate with ABPM-derived values than blood pressure values obtained in office settings.[3] Therefore, self-measured blood pressure should be encouraged in kidney transplant recipients.

ETIOLOGY AND PATHOGENESIS OF TRH IN THE KIDNEY TRANSPLANT RECIPIENT

Arterial hypertension or TRH in the kidney transplant recipient is generated and maintained by multiple factors relating to both recipient and donor, as well as pretransplant and post-transplant periods. Whether the risk profile of the kidney transplant recipient with TRH is similar to that of the nontransplant patient has yet to be evaluated thoroughly; however, with better, albeit limited, current knowledge of the latter from observational studies, it seems reasonable to extrapolate such a profile to the transplant recipient while exercising care to identify potential pitfalls.

The etiology of TRH in any given kidney transplant recipient usually is multifactorial; thus, a complete evaluation ought to include a work-up for secondary causes of hypertension also encountered in the non-kidney transplant patient such as obstructive sleep apnea (OSA),[16–18] primary hyperaldosteronism,[19,20] pheochromocytoma,[21,22] Cushing's syndrome,[23] coarctation of the aorta, and diabetes mellitus.[24] Kidney transplant recipients with OSA have higher levels of SBP despite taking more antihypertensive medications compared with those without OSA (147 ± 21 versus 139 ± 18 mm Hg; $P = .05$).[25]

More specific to the kidney transplant recipient, other causes of TRH also may include allograft dysfunction as a result of acute tubular necrosis, acute rejection, chronic dysfunction, recurrent and de novo glomerular disease in the allograft, transplant renal artery stenosis, persistent post-transplant hyperparathyroidism, and immunosuppressive medication including calcineurin inhibitors (CNIs) (eg, cyclosporine or tacrolimus) or corticosteroids; hypertension also can be caused by the donor organ. Some factors that potentiate arterial hypertension differ in the early and late post-transplant periods; these include the effects of volume changes, CNI use and trough level, high-dose steroids, poor or delayed allograft function, the development of proteinuria, and transplant renal artery stenosis.[26]

On a different note, the goal of identifying gene variants that are responsible for arterial hypertension and TRH in the general population or in transplant recipients remains elusive. It must be noted, however, that Genovese et al[27] described the finding of 2 risk alleles in the coding region of apolipoprotein A1 that are associated with hypertensive end-stage renal disease in African Americans subjects,[27] but there are no data yet as to the prevalence of these gene variants in African American patients with TRH.

Pretransplant advanced chronic kidney disease has been associated with functional and structural alterations in the arterial walls such as endothelial dysfunction, increased arterial stiffness, and evidence of vascular calcification[28–31]; the impact of this post-transplant arteriopathy seems to be dependent on length of time on dialysis and the severity of arterial damage present at the time of transplantation.[31] Bahous et al[28] showed that aortic pulse-wave velocity, a correlate of aortic stiffness, was higher in 101 living-donor kidney transplant recipients compared with healthy controls, and was related to increased post-transplant mean arterial blood pressure. Similarly, Delahousse et al[29] showed that recipient aortic stiffness was associated with arterial blood pressure at 3 and 12 months after transplant in 74 deceased-donor kidney

Table 2

Method of Measurement	Threshold (mm Hg)
Office or clinic	140/90
Overall ABPM average	125*-130/80
ABPM daytime	130*-135/85
ABPM night-time	120/70
Home	130-135/85

*According to the European best practice guidelines.