Clinical characteristics of resistant hypertension in renal transplant patients

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Abstract
Hypertension is a prevalent complication that occurs in 80–85% of all kidney transplant recipients. The pathogenesis of post-transplant hypertension is multifactorial and includes pre-transplant hypertension, donor hypertension, renin secretion from the native kidney, graft dysfunction, recurrent disease and immunosuppressive treatment. Hypertension negatively affects transplant and patient survival outcomes; cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic renal disease and after successful renal transplantation. Hypertension is a well-known risk factor for CVD and it is frequently associated with other CVD risk factors. Despite increased awareness of the adverse effects of hypertension in both graft and patient survival, long-term studies have shown that arterial hypertension in the transplant population has not been adequately controlled. Resistant hypertension (RH) is defined as office blood pressure (oBP) that remains above goal (oBP ≥140/90 or 130/80 mmHg) in patients with diabetes or chronic kidney disease despite the concurrent use of three antihypertensive agents, at full doses, one of them being a diuretic. Despite studies in the general population and the high prevalence of hypertension in renal transplant patients, data about RH are very scarce and the prevalence of RH in renal transplant patients is unknown and could be associated with a worse prognosis.

Keywords: ambulatory blood pressure monitoring; renal transplant; resistant hypertension

Introduction
Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic renal disease (CKD) and after successful renal transplantation. The burden of CVD in these patients exceeds by far that of the general population. The annual risk of fatal or non-fatal cardiovascular events in kidney transplant recipients is 3.5–5%, which is about 50-fold higher than in healthy individuals [1]. Several features unique to renal transplant patients deserve specific attention, and non-classical cardiovascular risk factors (i.e. inflammation, oxidative stress) may play a significant role in the increased incidence of CVD. However, many traditional CVD risk factors have been found to be associated with the increased incidence of posttransplant CVD. Among the many risk factors, a crucial role is played by hypertension, a condition affecting 80–85% of patients [2, 3].

Arterial hypertension
Hypertension negatively affects transplant and patient survival outcomes and is considered the major risk factor for the development of CVD [4, 5]. It is frequently associated with other CVD risk factors [6]. The cardiovascular risk of hypertension in the transplant population seems more or less comparable with the risk in the general population [7]. There are cogent arguments to consider blood pressure, particularly systolic blood pressure (SBP), as an important modifiable risk factor both for patient death and for allograft failure [4]. It has been noted that there is a continuous increment in risk for graft survival, patient survival and functional graft survival as a function of increasing systolic, and somewhat less, diastolic pressure [4]. Data from our group demonstrated the consequences that increased pulse pressure had on the outcomes of renal transplant patients, especially in terms of CVD. Thus, pulse pressure was an independent risk factor for increased cardiovascular morbidity and mortality in renal transplant patients [8].

The two major goals of antihypertensive therapy after transplant are preservation of kidney function (or slowing of kidney disease progression) and decreasing CVD risk. Treatment of hypertension in the general population lowers the risk of CVD by 20–30% and blood pressure should be reduced to at least below 140/90 mmHg (systolic/diastolic) [6, 9]. In this regard, adequate control of blood pressure in the transplant setting should help to preserve allograft function and improve long-term outcome. Opelz
et al. [4] found in 1998 that blood pressure control is suboptimal in clinical practice and as many as 50% of patients have a SBP of >140 mmHg. Recently, Opelz et al. [10] demonstrated that, although consistent control of SBP was associated with the best graft and patient outcome, lowering SBP even after several years of hypertension appeared to confer lasting benefit.

Lifestyle modifications, such as weight loss, increasing regular exercise and sodium restriction, may be helpful, although such a recommendation is not supported by clinical trial evidence after transplant. Calcium-channel blockers, diuretics, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors have all been used to reduce blood pressure after renal transplantation. Calcium-channel blockers are widely used to normalize blood pressure and appear to improve renal function soon after transplantation, although oedema is a common adverse effect of dihydropyridine calcium antagonists [11]. Despite the caveats regarding their use in patients with single kidneys, the administration of ACE inhibitors or angiotensin receptor blockers in the presence of stable allograft function is an attractive option, since these drugs have the potential to prevent the progression of chronic renal failure [12].

Resistant hypertension

Despite increased awareness of the adverse effects of hypertension in both graft and patient survival, long-term studies have shown that arterial hypertension in the transplant population has not been controlled adequately. Uncontrolled hypertension is not synonymous with resistant hypertension (RH). RH is defined as office blood pressure (oBP) that remains above goal (oBP ≥140/90 or 130/80 mmHg) in patients with diabetes or chronic kidney disease (CKD) despite the concurrent use of three antihypertensive agents, at full doses, one of them being a diuretic [13, 14]. Thus, the definition of RH is based on office measurements. RH is a common clinical problem in the general population, but the exact prevalence and prognosis is unknown. Clinical trials suggest that it is not rare, involving perhaps 20–30% of study participants. Factors that predispose to RH included population characteristics, such as increased life expectancy, higher obesity rates and decreased physical activity, as well as provider characteristics, including pseudo-resistance (inadequate measure of BP, inappropriate drug choices/doses, non-adherence to prescribed therapy or white coat effect) and secondary causes of RH (hyperaldosteronism, obstructive sleep apnoea, CKD, renal artery stenosis, pheochromocytoma, thyroid diseases, coarctation of the aorta and exogenous substances).

Despite studies in the general population and the high prevalence of hypertension in renal transplant patients, data about RH in such a population are very scarce. The only study showing RH in 6.8% of stable renal transplant patients was performed in our centre, and RH was mainly due to SBP elevation [15]. This hypertension was more usual in older age, in diabetic patients, in those with poor renal function and in patients who were receiving steroids as immunosuppressive therapy. Sub-optimal control in blood pressure is frequent in these patients and the failure to achieve it is multifactorial. Renal transplant patients are receiving a number of drugs, of the most important are the immunosuppressive drugs based on calcineurin inhibitors. These drugs produce widespread vasoconstriction and hypertension, particularly when combined with steroids. Volume expansion related to excessive dietary sodium, sodium retention secondary to CKD and/or failure to use diuretics appropriately can also contribute to RH.

Epidemiological and interventional studies in the general population have demonstrated that RH is a cardiovascular risk factor for CVD. Data from our group showed that RH represents an independent risk factor for increased cardiovascular morbidity and mortality in renal transplant patients [16]. The risk-modification strategies useful in the general population are likely to be also effective in transplant patients. Expanding our understanding of the causes of RH and thereby potentially allowing for more effective prevention and/or treatment will be essential to improve the long-term clinical management of this disorder in renal transplant patients.

Finally, there is a lack of literature comparing oBP with ambulatory blood pressure monitoring (ABPM) in the renal transplant population. It has been clear for some years now that ABPM is superior to casual oBP measurements as a predictor of target organ damage and morbidity cardiovascular events (left ventricular hypertrophy, hypertensive cerebrovascular disease, retinopathy, renal abnormalities and alterations in vascular compliance) in patients with arterial hypertension. There is no established definition of RH using ABPM, including patients with CKD. Normal values for 24 h average BP are lower than for oBP, i.e. <125–130 mmHg systolic and <80 mmHg diastolic blood pressure [15]. A multicentre, cross-sectional and observational study (REtenAL study) has been conducted in 30 nephrology/kidney transplant units from the Spanish public health system. Data were collected from consecutive unselected patients. Eligible patients included 868 hypertensive cadaveric kidney transplanted recipients aged <70 years, with functioning kidney for at least 1 year and with an estimated glomerular filtration ≥30 mL/min/1.73 m² and serum creatinine <2.5 mg/dL. Arterial hypertension was defined as oBP ≥130/80 mmHg or being on antihypertensive drug treatment [17]. This is the first multicentre study conducted in Spain analysing control rates of hypertension and prevalence of RH in a vast population of stable renal transplant patients followed up by nephrologists. This is the first analysis of RH using both oBP and ABPM in renal transplant recipients. The analysis shows that prevalence of RH is ~24%, using the current definition with oBP [14], and ~16% if we consider only patients with office BP ≥140 and/or 90 mmHg. The prevalence of true RH ascertained by ABPM is 19% [17].

In conclusion, posttransplant hypertension is often poorly controlled and undertreated. As this poses a significant threat to the survival of both the graft and the recipient, adequate BP control is as essential as immunological surveillance in the long-term transplant care. RH is frequent in renal transplant patients and represents a CVD risk factor. However, new longitudinal
studies are warranted to prove the prognostic value of BP control, based on ABPM, on target organ damage in the renal transplanted population.

Conflict of interest statement. None declared.

References


Received for publication: 14.9.12; Accepted in revised form: 14.9.12