Hypertension after kidney transplantation: are treatment guidelines emerging?

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Introduction

Hypertension after renal transplantation is a strong predictor of patient and graft survival, but European guidelines for treatment of post-transplant hypertension have not yet been put forward. However, with the present knowledge, including data from recent intervention studies, there is a basis for future therapy guidelines. Here we address some important aspects of hypertension and its treatment after kidney transplantation.

Definition of post-transplant hypertension

In transplant recipients, hypertension is usually defined as blood pressure \(140/90 \text{ mmHg}\) or likewise if a patient is treated with antihypertensive drugs [1,2]. A cut-off at 150/90 mmHg has also been proposed [3]. We prefer the first definition, which is probably the most widely accepted cut-off value for primary hypertension in the general population [4]. Some centres use the blood pressure criteria of the World Health Organization/International Society of Hypertension (>130/85 mmHg) [5].

Incidence and pathophysiology of post-transplant hypertension

Prior to the introduction of cyclosporine as a maintenance immunosuppressant in 1983, post-transplant hypertension was seen in less than half of all patients; since the introduction of calcineurin inhibitors, however, systemic hypertension is now found in 70–90% of recipients [6–8].

Corticosteroid therapy is not a major contributor to chronic hypertension in transplant recipients due to the rapid tapering of the dose, but steroids may contribute early after transplantation (in high doses) or during pulse rejection therapy. In a review of the literature, Veenstra et al. [9] estimated the incidence of corticosteroid-related hypertension to be \(\sim 15\%\).

Besides calcineurin inhibitors and steroids a variety of pre- and post-transplant factors have been shown to predict occurrence of hypertension following renal transplantation. The major factors are listed in Table 1.

Impact of post-transplant hypertension

For many years it has been known that hypertension as a potent cardiovascular risk factor is associated with impaired patient and graft survival, although the nature of this relationship has not been clearly delineated. The survival of grafts and patients has improved considerably during the last decade, but the long-term results have not been as encouraging. Opelz et al. [10] demonstrated a striking association between

Table 1. Causes of post-transplant hypertension

<table>
<thead>
<tr>
<th>Pre-transplant factors</th>
<th>Post-existing hypertension and LVH</th>
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<tbody>
<tr>
<td>Body mass index</td>
<td>Primary kidney disease (native kidneys)</td>
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<tr>
<td>Donor related</td>
<td>Hypertensive donor</td>
</tr>
<tr>
<td>Elderly and female donor</td>
<td>Use of right-sided donor kidney</td>
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<td>Transplantation related</td>
<td>Prolonged ischaemia time</td>
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<tr>
<td>Delayed graft function</td>
<td>Immunosuppressive therapy</td>
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<tr>
<td>Renal transplant artery stenosis</td>
<td>Calcineurin inhibitors (CyA and tacrolimus)</td>
</tr>
<tr>
<td>Renal outflow obstruction (lymphocele, ureteral stenosis)</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Renal transplant dysfunction (CAN, GN)</td>
<td>LVH, left ventricular hypertrophy; CyA, cyclosporin A; CAN, chronic allograft nephropathy; GN, glomerulonephritis (recurrent or de novo).</td>
</tr>
</tbody>
</table>

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systolic and diastolic blood pressure levels 1 year after a successful transplantation and kidney graft survival. In their follow-up study of >29,000 cadaveric renal transplant recipients, they found that increasing levels of systolic and diastolic blood pressure post-transplant were associated with a graded increase of subsequent graft failure ($P<0.0001$). Chronic graft failure was also significantly associated with blood pressure, even when patient death was censored ($P<0.0001$). Cox regression analysis established increased blood pressure as an independent risk factor for graft failure. Whether substantial lowering of blood pressure improves long-term transplant outcome remains unknown. However, a review of the data, focusing on those who were hypertensive ($>150$ mmHg) at 1 year but were subsequently successfully treated to achieve a lower blood pressure ($<150$ mmHg) after 3 years, showed that graft survival improved by $\sim15\%$ during the following 4 years when compared with patients who remained hypertensive (G. Opelz, personal communication).

**Drug treatment of hypertension after transplantation**

Initially, the cause of hypertension should obviously be evaluated and causal treatment implemented whenever possible (Table 1). Otherwise, the optimal drug treatment of post-transplant hypertension has been a matter of debate.

Angiotensin-converting enzyme (ACE) inhibitors have emerged as an attractive alternative for hypertension treatment, slowing the progression of native chronic renal disease [11–14]. The 'protective' effects of ACE inhibitors have been attributed, among several other factors, to a reduction in intraglomerular pressure. This may be of particular interest since it has been proposed that progressive graft failure resulting from chronic allograft dysfunction may be associated with glomerular hyperfiltration and hypertension due to an inadequate nephron mass. Another factor of importance is that both ACE inhibitors and angiotensin-II receptor antagonists may inhibit the activation of TGF-$\beta$, which is one of several growth factors involved in the pathogenesis of chronic allograft dysfunction. The ability of ACE inhibitors to slow the progression of chronic allograft dysfunction does remain, however, unproven.

Besides the blood pressure lowering effect of calcium channel antagonists (CCA), these drugs also efficiently counteract the intrarenal vasoconstriction associated with CaA treatment (and possibly tacrolimus) [15]. Their effect on renal haemodynamics may also reduce long-term CaA nephrotoxicity [16]. Clinical studies have suggested that use of CCAs in renal transplant patients receiving CaA may be associated with a reduction in both delayed graft function and acute rejection episodes, and possibly also a better long-term graft function. However, a meta-analysis of

![Fig. 1. GFR at 3 weeks (control), 1 year and 2 years after transplantation.](Image)

21 studies published in 1994 concluded that results were conflicting [17]. CCAs and ACE inhibitors reduce blood pressure to a similar extent in renal transplant recipients [18].

In order to evaluate the effect of CCA and ACE inhibitors on renal allograft function we performed a double-blind randomized study comparing nifedipine with lisinopril, where the primary aim was to examine graft function (glomerular filtration rate (GFR), 99 mTc-DTPA) during a 2-year treatment period [19]. The results clearly showed that controlled-release nifedipine significantly improved renal function by $\sim20\%$ during this time period and that in this context it was superior to lisinopril in the treatment of post-transplant hypertension (Figure 1) [19]. These findings are in agreement with those of another large randomized study recently published by Rahn *et al.* [20].

Treatment with $\beta$-blockers reduces morbidity and mortality after myocardial infarction and is also of benefit in heart failure patients. Some investigators have therefore suggested that these agents should be considered as possible first-line therapy for post-transplant hypertension in patients with concomitant heart disease [21]. Many $\beta$-blockers, however, increase triglyceride levels and decrease HDL cholesterol levels [22,23]. It is well known that dyslipidemia is worsened by standard immunosuppressive treatment [23]. Moreover, a recent report also found a significantly greater risk of developing diabetes among patients taking $\beta$-blockers than among untreated controls [24]. The risk of developing impaired glucose tolerance or diabetes after transplantation is high on a drug regimen consisting of calcineurin inhibitors and corticosteroids [25]. In other words, $\beta$-blockers may not be the best choice for the majority of transplant recipients but may certainly be so in some conditions, as mentioned above.

**Left ventricular hypertrophy and combination therapy**

Left ventricular hypertrophy (LHV) is an independent determinant of mortality [26–28] and is found in $\sim60\%$ of patients with end-stage renal disease. Blood
pressure plays a pivotal role in the pathogenesis of LVM. We evaluated the effect of different antihypertensive regimens (lisinopril, n = 76; nifedipine, n = 78) on morphological and functional cardiac parameters after transplantation [29]. Echocardiography was performed at baseline and after 1 year (follow-up). At baseline, 65% of the patients had LVH. After 1 year of treatment the myocardial mass was considerably and similarly reduced by 15% (P<0.0001) in both groups, from ~150 g/m² to ~125 g/m². Nevertheless, >40% of these patients still had LVH at the end of 1 year of treatment. However, further regression of LVM occurred during the second year of randomized treatment (data not published). To obtain such an effect on blood pressure and LVM, a combination therapy with other antihypertensive drugs had to be given in 80% of the patients during the first 3 months, and in two-thirds of the patients in the long run [18]. Consequently, the choice of drug therapy usually implies a combination therapy with two or more drugs, which must be individually designed to obtain optimal efficacy and tolerance in each patient.

Treatment goals

European guidelines for the treatment of post-transplant hypertension have yet not been put forward. The National Kidney Foundation Task Force on cardiovascular disease recommended that the goal for therapy should probably be ≤135/85 mmHg for renal patients without proteinuria and possibly ≤125/75 mmHg for patients with proteinuria [30]. Blood pressure values of <120 mmHg (systolic) and <80 mmHg (diastolic) are considered optimal in non-transplanted renal patients [4]. We found good results with respect to GFR and LVH by reducing blood pressure to about 135/85 in renal transplant patients [19,29] with a CCA-based combination therapy. Treatment of isolated systolic hypertension has not been evaluated in this patient group. Randomized trials for the evaluation of hard end-points will probably never be performed in this patient population.

Summary

Despite improvements in patient and graft survival, transplant patients continue to die prematurely due to accelerated cardiovascular disease. Calcineurin inhibitors and corticosteroids induce hypertension in most transplant recipients. Post-transplant hypertension appears to be a major risk factor for graft and patient survival. Hypertension following renal transplantation must be treated as strictly as in patients with essential hypertension, diabetes mellitus or chronic renal failure. An adequate treatment goal may be a blood pressure of <135/85 mmHg. A strong case can be made for treating hypertensive renal transplant recipients with a CCA. In the early post-transplant period, antihypertensive treatment should in our opinion normally include a CCA. We are not willing to go as far as Dudley in his recent editorial in Transplantation [31], where he concludes that ‘a strong case can be made for adding controlled release nifedipine to the initial drug regimen of all renal transplant recipients receiving cyclosporin-based immunosuppression, whether hypertensive or not’. In any case, we propose that the time has come for the ERA/EDTA to develop guidelines for the treatment of hypertension after renal transplantation.

References

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