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1. Introduction

Hypertension after kidney transplantation is an important factor for both graft and patient survival. Arterial hypertension in renal graft recipient is defined as the blood pressure higher than 140/90 mmHg. According to the recent guidelines, the target blood pressure should be less than 138/85 mmHg.[1]

Blood pressure in renal graft recipient is one of the most important factors with negative impact on the survival of kidney graft. Correlation between blood pressure and long-term graft survival is extremely significant.[2] The introduction of the calcineurin inhibitors into the post transplant immunosuppressive protocols has increased the prevalence of hypertension after kidney transplantation.

2. Epidemiology

Cardiovascular disease is the most frequent cause of morbidity and mortality after renal transplantation and remains a significant barrier to improve long-term outcomes. Although transplantation improves life expectancy compared with dialysis, survival remains well below general population estimates. Approximately 50% of patients die with a functioning transplant, with approximately 50% of these deaths from cardiovascular disease or stroke.[3] Cardiovascular death rates underestimate the full impact of this disease process given the large number of nonfatal events, including acute myocardial infarction, cardiac arrhythmias, heart failure, and stroke, that affect quality of life.

Transplant recipients are at an increased cardiovascular risk secondary to a variety of modifiable and non-modifiable factors, which should be early recognized, continuously monitored and, if possible, thoroughly treated. Blood pressure (BP) represents a non-immunological risk factor that should be readily amenable to intervention. Nevertheless, control rates are disturbingly poor and arterial hypertension is observed in the majority of
this patient population. The blood pressure frequently rises after kidney transplantation, as hypertension develops in up to 60 to 80 or more percent of renal allograft recipients.[4-6] Also, it is not unusual have poorly controlled blood pressure among kidney transplant recipients. In a single center study, for example, only 5 percent of kidney transplant patients were normotensive as defined by blood pressures less than 130/80 mmHg as measured by ambulatory blood pressure monitoring. [6]

3. Pathophysiology and causes

There are different factors that cause the appearance of hypertension: renal artery stenosis, immunosuppressive medications especially calcineurin inhibitors (cyclosporine and tacrolimus), corticosteroids, graft dysfunction, chronic allograft nephropathy (CAN), recurrent or “de novo” disease as well as genetic predisposition of donor and recipient.

Most transplant recipients have suffered from long-lasting chronic kidney disease (CKD) and have been treated with hemodialysis or peritoneal dialysis for a certain period. These patients exhibit structural and functional vascular abnormalities, as reflected by the high prevalence of elevated systolic BP and increased pulse pressure. BP in these patients is usually difficult to manage and often volume or salt-dependent. Older age, diabetes mellitus and a high cardiovascular disease burden are common comorbidities.

An association between hypertension and deterioration of renal function does not prove a causal relationship. Hypertension after transplantation might simply be the result of a deterioration in graft function rather than vice versa. Retrospective studies demonstrating an association between hypertension after transplantation and graft survival, cannot differentiate between cause and effect.[2, 7]

The first evidence that hypertension per se may lead to graft damage was the observation that not only hypertension after transplantation, but also hypertension before transplantation is associated with later CAN. Hypertension before transplantation increased the risk for later CAN by a factor of 3.4, the magnitude which was only surpassed by late (>60 days after transplantation) acute rejection episodes, which increased the risk for CAN by 5.5.[8]

Studies in animals support the concept of hypertension-induced graft damage. In two different hypertensive animal models (clipped native kidney plus allograft [9] or transplantation into spontaneous hypertensive rats [10]) it was shown that hypertension may aggravate graft damage.

Another elegantly designed study on rat allograft models explored the mechanisms by which hypertension contribute to CAN. [11] Rats were either left normotensive or were made hypertensive by treatment with deoxycorticosterone acetate (DOCA) and salt. Proteinuria was measured monthly, grafts were harvested at 3 and 6 months for semi-quantitative real time PCR for smooth muscle cell-growth factors PDGF and TGF-β and for
immunohistology. Systolic blood pressure was markedly elevated in rats receiving DOCA/salt. Proteinuria was elevated in untreated allografts compared to isografts and was further raised in hypertensive animals. Expression of mRNA for PDGF was higher in allografts than in isografts and was highest in hypertensive animals. Similarly, significantly more tubular cells expressing the ‘proliferating cell nuclear antigen’ as well as more extracellular matrix deposition were observed in hypertensive animals compared to untreated allografts. In addition, increased expression of MHC I and II was observed in hypertensive animals by both immunohistology and RT-PCR. Thus, hypertension may influence the immunogenicity of the graft.

These data indicate that hypertension of the recipient acts together with alloantigen-dependent factors on the expression of growth factors in the graft thought to be responsible for the morphological changes observed in CAN, particularly the vascular changes with proliferation of smooth muscle cells leading to neointimal proliferation.[12] Hypertension may initiate inflammatory pathways or act synergistically with alloantigen-dependent factors on graft injury.

### 3.1. Role of immunosuppressive drugs in development of hypertension

Immunosuppressive drugs have an important role in the development of hypertension in renal transplant patient. The majority of patients that use cyclosporine do have hypertension that usually normalizes after discontinuation of the incriminated immunosuppressant. Patients that have been using cyclosporine for more than a year develop a need for antihypertensive drug(s) in 20-100% of cases.[13] Most often, it is only a slightly elevated blood pressure that can be successfully controlled with antihypertensives. However, children can develop a serious hypertension combined with neurological complications including “grand mal” convulsions after transplantation, due to high doses of cyclosporine and vasoconstriction.[14]

Before cyclosporine A was introduced in 1983, 50% of the patients with transplanted kidney developed hypertension. After calcineurin inhibitors (cyclosporine and tacrolimus) were introduced the incidence of hypertension surged up to 70-90%.[15] The usage of cyclosporine and tacrolimus is associated with reduced production of nitrogen oxide and increased production of endothelin as well as reduced endothel function. These factors lead to the reduction of vasodilatation on one hand and the increase of vasoconstriction on the other hand, which consequently lead to hypertension. Cyclosporine nephrotoxicity and resulting chronic nephrosclerosis, thrombotic microangiopathy are probably caused by increased sympathetic activity, and reduced renal prostaglandin synthesis as well as stimulation of renin-angiotensin-aldosterone (RAAS) systems. [16]

Many authors agree that the influence of cyclosporine and tacrolimus on incidence of post-transplant hypertension is evident. However, the probability for developing a post-transplant hypertension in patients on tacrolimus, is at least 5% lower than in those on cyclosporine therapy. However, the others argue that tacrolimus in higher doses is no
different from cyclosporine in terms of risk for development of post-transplant hypertension. [17]

Calcineurin inhibitor (CNI) free immunosuppression has, therefore, been advocated due to the favorable cardio-metabolic profile. In patients receiving belatacept-based immunosuppressive regimens and the mammalian target of Rapamycin (mTOR) inhibitor sirolimus both systolic and diastolic blood pressure were lower compared with patients on CNI.[18]

Cyclosporine-induced hypertension was more of a problem in the early years of its widespread use in which target levels and treatment doses were significantly higher than today. However, in the modern era of individualized immunosuppression and after the publication of the results of the Efficacy Limiting Toxicity Elimination (ELITE)-Symphony study [19, 20] CNI minimization but not complete avoidance is being supported as the best available treatment strategy. Furthermore, findings that chronic humoral rejection may be a major cause of chronic allograft changes and late allograft failure annihilate the common perception that CNIs are responsible for interstitial fibrosis and tubular atrophy.[21] Thus, CNI-free combinations are reserved only for selected patients and CNIs are considered to be essential for the management of renal transplant recipients.

Corticosteroids as integral part of basic immunosuppressive protocols also have an important role as one of the possible causes for post-transplant hypertension. Volume retention caused by corticosteroids partially explains its hypertensive properties. It is proven that the decrease of corticosteroid dose leads to a significant decrease of post-transplant hypertension, as well as reduced body mass index that is considered to be one of the causes for the appearance of post-transplant hypertension.[22] Corticosteroids can deteriorate hypertension with their hemodynamic and hormone properties reflecting through salt and water retention. The usual steroid dose, 10 mg per day or less, however, does not present a significant cause of hypertension.[23]

The well known side-effects of corticosteroids have motivated interest in steroid-free immunosuppression for as long as these agents are available. Steroid withdrawal is possible in many transplant recipients with comparable patient and graft survival.[24, 25] Unfortunately, rejection rates are higher and allograft fibrosis seems to be more common. Still, there may be a advantageous trade-off in terms of reduction of cardiovascular risk factors including hypertension, diabetes and dyslipidaemia.[26] Corticosteroids may contribute more to hypertension early after transplantation or during pulse rejection therapy due to higher doses administered.[27] Glucocorticosteroid-mediated hypertension seems to result from increased peripheral vascular resistance through direct action on the vascular smooth muscle cells and not through the activation of the mineralcorticoid receptor.[28]

3.2. Role of allograft nephropathy in development of hypertension

It is accepted for a fact that chronic graft nephropathy is one of the main causes of hypertension after kidney transplantation.[29] Hypertension is quite often the first clinical
sign of chronic graft rejection. A great number of authors highlight the association between chronic graft nephropathy and hypertension more than the degree of tissue match (HLA), suggesting that hypertension is merely one of the causes of chronic graft nephropathy rather than its consequence.[8]

Hypertension is an independent risk factor for the graft dysfunction with the normal creatinine level, as well as with the patients that have been previously treated for acute rejection. The most frequent consequence of hypertension is hypertrophy of the left chamber, angina pectoris, myocardial infarction, stroke, heart weakness, arrhythmia, and sudden death.[15] With the appropriate treatment it is possible to induce regression of the left ventricle hypertrophy and reduce the risk of cardiovascular diseases. [30]

3.3. Donor and recipient related factors and the development of hypertension

Small increases in BP in donors after transplantation do occur and effects are more noticeable in donors with lower nephron mass.[31] However, apart from fetal programming, nephron mass declines continuously with age and prevalence of nephrosclerosis increases linearly and independently from other risk factors from 2.7% for patients aged 18-29 years to 73% for those aged 70-77 years.[32] Older kidney donors (>55 years) have slightly less than half the number of functioning glomeruli compared with younger ones according to a recent report.[33]

Apart from ongoing injury, congenital endowment and donor’s age appear to be critical determinants of transplant nephron mass. Therefore, it is not surprising that donor age and graft size are related to the development of posttransplant hypertension. Recipients of older deceased kidney donors are more likely to be hypertensive, whereas patients with low kidney transplant to recipient weight ratios are in need of more intense antihypertensive regimens.[34, 35]

Kidney recipients that have received kidney from donors with positive family history for hypertension have the higher possibility of developing artery hypertension than the recipients who have received the kidney from donors without family history. However, patients having primary hypertension as the cause of terminal renal insufficiency, become normotensive after bilateral nephrectomy and successful kidney transplantation from normotensive donor.[36]

Recipient’s native kidneys and pre-transplant hypertension are described as independent factor associated with post-transplant hypertension. They can cause hypertension in graft recipient via renin-angiotensin system.[29] Also, blood pressure in the recipient’s transplant can be influenced by re-emergence of primary disease, “de novo” glomerulonephritis and obstructive uropathy.

3.4. Posttransplant hypertension due to renal transplant artery stenosis

Incidence of renal artery stenosis falls within the range of 2-6% and it is comparably much lower than 80% incidence of developing post-transplant hypertension.[37] The donors
younger than 5 years, termino-terminal anastomosis with internal iliac artery as well as the implantation of right kidney are associated with frequent renovascular complications. In a retrospective study of 29 recipients with stenosis and a case-control group of 58 patients, an increased risk of stenosis was significantly associated with CMV infection and delayed function.[38] In contrast to termino-terminal anastomosis with the internal iliac artery, termino-terminal anastomosis with the external iliac artery, in children, decreases renal artery stenosis incidence.

Posttransplant hypertension due to renal transplant artery stenosis is important to identify because it is a correctable form of hypertension. Although it can present at any time, renal artery stenosis usually becomes evident between three months and two years posttransplant.[39]

Clinical suspicion for renal artery stenosis should be raised in situations when audible sound can be recorded during the graft auscultation or in the case of abrupt deterioration of graft function after administration of angiotensin-converting enzyme inhibitor. Hypertension caused by renal artery stenosis is frequently associated with the occurrence of diuretic resistant oedema without significant proteinuria, and with the reduced graft function. It is often associated with polycythaemia.

Stenosis can occur on the anastomosis, but also proximal or distal from anastomosis. Typical time of occurrence is 6-24 months after transplantation. Factors that can cause the renal artery stenosis are: artery injury during explantation and implantation, intimal injury during cannulation or weak technique of vascular suture.[40]

The prevalence of anastomotic renal transplant artery stenosis is difficult to assess. This is due in part to discrepancies in the definition of hemodynamically significant lesions and the use of different diagnostic modalities. It has been suggested that functionally significant stenosis occurs in up to 12 percent of transplant recipients with hypertension, with a range of incidence from 1 to 23 percent.[38]

As with other causes of bilateral renal artery stenosis or unilateral stenosis in a solitary kidney, the administration of an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) to a patient with transplant renal artery stenosis can lead to a reversible decline in glomerular filtration rate. [39, 41] Thus, an elevation in plasma creatinine concentration in this setting is suggestive but not diagnostic of renovascular disease in the graft. Persistent uncontrolled hypertension, flash pulmonary edema, and an acute elevation in blood pressure are other common features of this disorder.[42]

Although various different imaging techniques may be utilized to diagnose renal artery stenosis, arteriography is the preferred modality. However, since arteriography is invasive, magnetic resonance arteriography or CT angiography are increasingly utilized techniques to screen and/or diagnose transplant recipients for the presence of renovascular disease.[39, 43]

The options available to correct stenosis of the renal artery include angioplasty (with or without stenting) and surgery.
3.5. Consequences of posttransplant hypertension

Hypertension is one of the main risk factors for cardiovascular diseases and reduction of transplant and patient survival. Over the past ten years, the survival of kidney grafts and patients have been recording a significant improvement.

There is little doubt that uncontrolled posttransplant hypertension contributes considerably to graft failure and affects patient survival negatively. The Collaborative Transplant Study (CTS) group first demonstrated a strong and graded relationship between posttransplant BP and renal allograft failure [2], results that have also been validated in subsequent studies.[44] Furthermore, persistently poor controlled posttransplant hypertension (defined as SBP above 140 mm Hg) was found to be associated with poor outcomes, namely worse graft survival and increased cardiovascular mortality.[45]

The study of 29,000 kidney recipients confirms that the increase of systolic and diastolic pressure leads to the higher risk of graft failure. Chronic kidney failure is significantly associated with high blood pressure. It is proven that hypertension is an independent risk factor in kidney graft failure. It has been reported that in hypertensive recipients with systolic blood pressure higher than 150mmHg after the first year from transplantation, there is up to 15% better graft survival in four-years period, with prescribed antihypertensive therapy. [46]

4. Treatment of posttransplant hypertension

4.1. General considerations and principles

The target blood pressure is based in part upon the presence or absence of proteinuria and/or additional comorbid conditions, such as diabetes mellitus and/or atherosclerotic cardiovascular disease.[1, 5] The K/DOQI guidelines recommend that the target blood pressure should be less than 130/80 mmHg.[1] For those with significant proteinuria (greater than a spot urine total protein to creatinine ratio of 500 to 1000 mg/g), the K/DOQI work group suggests that a lower systolic blood pressure goal should be considered. The European best practice guidelines recommend a blood pressure goal of less than 125/75 mmHg for proteinuric patients. [47]

The recommended BP targets in renal transplant recipients do not differ from the BP targets of nontransplanted patients at high cardiovascular risk, such as diabetic patients and patients with CKD or established cardiovascular disease. It is important to note that the recommendation to lower systolic BP below 130 mmHg in high-risk hypertensive individuals of the (nontransplanted) general population is not even supported by consistent trial evidence [48] but also, a series of recent publications report no significant benefit or even potential clinical harm by targeting lower BP levels in those patients.

Posttransplant hypertension should be treated to protect against cardiovascular disease and against possible hypertensive injury to the graft. It has been suggested that long-term renal allograft survival may be negatively influenced by posttransplant hypertension. [7, 49]
There are also clinical data showing benefits with blood pressure control. This was best shown in a study of nearly 25,000 first deceased donor kidney recipients. Among patients with systolic blood pressures $>140$ mmHg at one year post-transplant, improved long-term allograft outcome was observed among patients with systolic pressures controlled to less than 140 mmHg at three years versus those with sustained increases in systolic pressure.

The goal of treatment is to protect graft function and reduce the risk of cardiovascular complications. By applying general lifestyle modifications such as weight control, limited salt and fat intake, moderate physical activity and smoking cessation it is possible to achieve better graft function.

No antihypertensive drug class is contraindicated in the renal transplant recipient and the selection of a specific agent depends mainly on the presence or absence of other comorbidities. The reluctance in the use renin-angiotensine-aldosterone system (RAAS) blockers and the ability of calcium channel blockers (CCBs) to counteract the systemic and renal vasoconstrictive effects of CNIs has influenced the choice of antihypertensive therapy. CCBs are currently considered the therapeutic standard for the treatment of posttransplant hypertension. A recent meta-analysis of a total of 60 randomized controlled trials enrolling nearly 4000 kidney transplant recipients showed that CCBs were the preferred first-line agents. Yet, in the majority of renal transplant recipients, multiple drugs must be given to effectively treat hypertension. As attaining BP targets is more important than selection of individual agents, every drug class may be appropriate after considering the individual contraindications and the patient’s risk profile.

It is necessary to determine the causes of post-transplant hypertension and then establish appropriate therapy. Hypertensive patients not taking cyclosporine or tacrolimus should be started on antihypertensive medications. Calcium channel blockers, ACE inhibitors, and beta-blockers all may be effective in this setting. A diuretic may also be necessary in patients with allograft dysfunction in whom volume expansion often contributes to the rise in blood pressure.

In patient on calcineurin inhibitor, an attempt should be made to reduce the calcineurin inhibitor dose in hypertensive patients receiving one of these agents. If the patient remains hypertensive, therapy with a calcium channel blocker or a diuretic (with concurrent salt restriction) should be begun. Other antihypertensive drugs can be added if the blood pressure is not controlled with a calcium channel blocker.

Patients with resistant hypertension should undergo renal arteriography to exclude renal artery stenosis unless there are findings (such as renal insufficiency and an active urine sediment) suggesting possible recurrence of the primary disease. Angioplasty (with or without stenting) or surgery is indicated if a significant stenosis is found. In the absence of renovascular disease, recurrent disease, or rejection, consideration should be given to removal of the native kidneys if there is no other way to control the hypertension.
4.2. Calcium channel blockers

Many physicians prefer a calcium channel blocker because in addition to proven antihypertensive efficacy, it minimizes cyclosporine-induced renal vasoconstriction.\[15, 58\] The influence on renal hemodynamics positively affects the reduction of fluids and also the acting of calcineurin inhibitors. Clinical studies show that the usage of calcium antagonists with calcineurin inhibitors is connected with the reduction of delayed graft function, with lower number of acute rejection episodes and improvement of long-term graft survival.\[59\]

A large number of studies have evaluated the efficacy of calcium channel blockers in kidney transplant patients. A 2009 systematic review of 29 studies with 2262 patients that compared calcium channel blockers to placebo or no treatment as well as seven studies with 405 patients that compared calcium channel blockers with ACE inhibitors found that calcium channel blockers were the most effective antihypertensive agent.\[53\] This systematic review included studies in which patients were not taking a calcineurin inhibitor.

CCBs and ACE inhibitors equally lower the blood pressure. However, in parallel head-to-head two year study which compared nifedipine and lisinopril, it was demonstrated that calcium antagonists improved renal function in 20% more patients than those taking lisinopril.\[46\]

Calcium channel blockers may have significant drug interactions with cyclosporine, tacrolimus, sirolimus or everolimus (Table 1). Verapamil, diltiazem, nicardipine, and amlodipine (to a minor extent), but not nifedipine or isradipine, slow cyclosporine/tacrolimus metabolism and elevate the plasma cyclosporine concentration.\[60, 61\] Some physicians have recommended the use of nifedipine to prevent this interaction, while others prefer verapamil or diltiazem since the inhibition of cyclosporine/tacrolimus metabolism permits the use of lower cyclosporine doses.

4.3. Beta blockers

Some authors argue that beta blockers should be first line of treatment in patients with posttransplant hypertension and co-existing heart disease.\[62\] Beta blockers may increase the triglyceride level, and decrease HDL cholesterol level and in already established dislipidemia in immunosupriminary patients may lead to the additional increase in lipid levels.\[63\] Beta blockers also contribute to the development of diabetes.

Nevertheless, in patients with heart disease and myocardial inarction they should be part of usual treatment. Left ventricle hypertrophy is an independent factor of mortality in 60 % of the patients with terminal kidney insufficiency while hypertension is a decisive factor in hypertrophy pathogenesis of the left chamber.\[64\]

4.4. ACE inhibitors and angiotensin II receptor blockers

The role of ACE inhibitors/angiotensin II receptor blockers in the transplant patient is incompletely defined. These drugs effectively lower the blood pressure and experiments in
animals suggest that they may partially protect against cyclosporine nephrotoxicity when compared to similar blood pressure control with hydrochlorothiazide, reserpine, minoxidil, hydralazine, or furosemide. [65, 66]

ACE inhibitors slow down chronic insufficiency of native kidney, and are used for a very long time as an alternative in hypertension treatment.[67, 68] The protective functioning effects of ACE inhibitor are founded on the decrease of both intraglomerular pressure and proteinuria. It is important to point out that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers inhibit the activation of transforming growth factor –β (TGF), which is included in pathogenesis of chronic kidney failure. The ability of angiotensin-converting enzyme inhibitor to slow down the development of chronic kidney failure is proven on animal experiments and it is documented in the recent report.[69]

However, there are several potential risks with ACE inhibitors/angiotensin II receptor blockers in calcineurin-inhibitor treated patients. The combination of ACE inhibition and

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AV-atrioventricular; CKD-chronic kidney disease; CNI-calcineurin inhibitor; COPD-chronic obstructive pulmonary disease; DHP-dihydropyridine; GFR-glomerular filtration rate; LVH-left ventricular hypertrophy; RAAS-renin–angiotensin–aldosterone system.

Table 1. Potential indications/benefits and side-effect/contraindications of various antihypertensive classes in treatment of hypertension after renal transplantation
cyclosporine-induced vascular disease can induce a modest decline in glomerular filtration rate via the same mechanism described above for renal artery stenosis [68],[70] Early after transplantation (within three to six months post-transplantation), the increase in serum creatinine concentration may confound the ability to accurately detect acute rejection.

Cyclosporine/tacrolimus tends to raise the plasma potassium concentration, primarily by decreasing urinary potassium excretion. This effect can be exacerbated by an ACE inhibitor, which reduces angiotensin II production and subsequent aldosterone secretion. Thus, ACE inhibitors should be avoided in patients who already have a plasma potassium concentration above 5.0 meq/L.

ACE inhibitors can induce anemia in transplant recipients, lowering the hematocrit by as much as 5 to 10 percent [69] via an effect that may be enhanced by cyclosporine.[71] Why this occurs is incompletely understood but a similar phenomenon probably accounts for the efficacy of ACE inhibition in posttransplant erythrocytosis.

To assess the safety and efficacy of ACE inhibitors and angiotensin II receptor blockers (ARBs) in kidney transplant recipients, a large number of retrospective and prospective studies have been performed. The magnitude of these effects was evaluated in a 2009 systematic review of 10 studies with 445 patients that compared angiotensin converting enzyme inhibitors to placebo or no treatment and of 7 studies with 405 patients that compared angiotensin converting enzyme inhibitors to calcium channel blockers.[53] Compared with calcium channel blockers, angiotensin converting enzyme inhibitors were associated with a decrease in GFR, proteinuria level, and hemoglobin value and an increased incidence of hyperkalemia.

No definitive conclusions with respect to GFR and allograft loss could be reached when angiotensin converting enzyme inhibitors were compared with placebo or no treatment. Several retrospective studies in patients with chronic allograft nephropathy have reported benefits with these agents in terms of slowing the progression of renal failure and possibly mortality.

4.5. Conclusion

In conclusion, a great number of patients after renal replacement treatment have poorly controlled blood pressure. Numerous studies bring evidence that poorly controlled hypertension poses a significant threat to both patient and graft which is why blood pressure control may be as equally important as tailoring the individualized immunosuppressive regime.

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