REVIEW ARTICLE

Hypertension and renal transplantation

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Hypertension after renal transplantation contributes significantly to the cardiovascular death of adults and children [1,2]. Initially there was a debate about the effect of hypertension on renal graft survival [3-5]. Recently, however, it has been proved that there is a significantly negative correlation between the levels of systolic and diastolic arterial blood pressure and the long term graft survival [6]. The negative effect of systolic blood pressure was present even if the diastolic blood pressure was less than 90 mmHg. The prevalence of hypertension is 75-80 % among renal transplant recipients in the immediate post transplant period in the cyclosporine era, while in the precyclosporine era it was 45-50% [7,8]. The factors causing hypertension after renal transplantation can be discriminated in graft endogenous and exogenous. Hypertension of renal graft recipients is multifactorial and usually these patients have more than one cause of hypertension [7]. During the immediate post transplant period, the positive balance of sodium and water, the acute tubular necrosis, the acute obstruction of the ureter, the acute rejection and the hypercalcemia[9] have been incriminated as causes of hypertension. Hypertension after the first transplant trimester is related to cortico-steroid, cyclosporine and FK506 use as well as chronic allograft rejection [10-12].
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A. Causes and mechanisms leading to hypertension after renal transplantation

I. Graft endogenous causes of hypertension

Hypertension related to the kidney of the donor

Many data demonstrate that hypertension can be caused by the kidney of the donor. Donor hypertension and death due to of subarachnoid hemorrhage have been connected with higher blood pressure of the recipient [13-15]. Patients with nephrosclerosis and end stage renal failure because of essential hypertension were cured of their hypertension after renal transplantation from a donor with normal blood pressure [16]. The amount of transplanted renal tissue and the differences between body weight of the donor and body surface area of the recipient have been incriminated for the development of hypertension after renal transplantation [17].

Recurrence or de novo development of renal parenchymal disease

Recurrence of primary renal disease in the graft has been considered responsible for hypertension after renal transplantation. Focal segmental glomerulosclerosis and IgA nephritis recurring in the graft have been connected with hypertension [18,19]. Recurrent or de novo hemolytic uremic syndrome has been encountered to cause severe hypertension accompanied by progressive loss of renal function[20].

Rejection

Hypertension is very common and is almost always present during hyperacute or acute vascular rejection. Acute rejection usually impairs renal excretory function and causes hypertension via volume expansion and glomerular ischemia.

Chronic allograft rejection is accompanied by the development of ischemia and fibrosis with secondary renin production and it is possibly the main cause of transplant hypertension. Hypertension due to chronic rejection is liable

to respond to treatment with angiotensin converting enzyme inhibitors and this fact supports the idea that there is a mechanism related to renin production.

Higher incidence and worse severity of hypertension has been observed with declining renal graft function. It has been supported that salt and water retension are the major factors contributing on the pathogenesis of hypertension of these patients [18].

II. Causes of transplant hypertension not related to the graft

Hypertension related to native kidneys

The incidence of hypertension is lower among anephric transplanted patients. The surgical removal of native kidneys can restore patient's blood pressure to normal levels, even if nephrectomy takes place a remote time from transplantation. It has been suggested that the native kidneys continue to produce renin, which elevates the intrarenal vascular resistance, lowers the intrarenal plasma flow and cause systemic arterial hypertension [21]. There are references which show that nephrectomy of native kidneys is followed by a steady fall of arterial blood pressure and a lowering of intragraft vascular resistance [21]. In spite of this, it has been reported recently, that the benefit of nephrectomy is short lived and in the late phase of transplantation other factors dominate blood pressure regulation [22,23]. So far, there are no firm data which show a positive effect of bilateral nephrectomy on patient and graft survival. For this reason, this procedure should be reserved for patients with uncontrollable hypertension and after other reversible causes of hypertension have been excluded. The native kidney embolism under X-ray guidance is safe, effective and can be done instead of bilateral nephrectomy.

Native kidneys can also contribute to hypertension by an uncontrolled production of erythropoietin, leading to polycythaemia [24].

Renal artery stenosis

The incidence of significant renal artery stenosis (70-80% occlusion of the lumen), which should be readily detectable with duplex sonography, has been described in 2-6% of renal grafts [25]. Renal artery stenosis may be located at the point of anastomosis or in the donor artery. The stenoses manifest usually during the first six months after renal transplantation, but they may appear at any time during the two years after it. Lower donor age (<5 years), end to end anastomosis to the internal iliac artery and the use of the right kidney have been found to be associated with increased renovascular problems [26-28]. We should suspect renal artery stenosis when there is persistent hypertension not responding to antihypertensive drugs. It may be accompanied by edema resistant to diuretics without serious proteinuria. Renal function is usually impaired and may influenced by patients' fluid balance or without obvious reason. Angiotensin converting enzyme inhibitors may change the autoregulation of the ischemic kidney and cause sudden fall of glomerular filtration rate (GFR), especially if there is loss of body fluids at the same time. The co-existence of polycythaemia with hypertension and impaired renal function suggests renal artery stenosis. The auscultation of a bruit is not a specific finding but the appearance of a new bruit or the existence of bruits with diastolic element are findings suggestive of renal artery stenosis.

Renal artery stenosis due to atherosclerotic lesions usually occurs months or years after transplantation. Preanastomotic stenosis of the external or internal iliac artery may also occur[29]. Another rare cause of transplant artery stenosis is fibromascular dysplasia of the donor artery[30]. The diagnosis of renal artery stenosis can be done with sonography by an experienced radiologist especially if a color doppler is used. Sometimes the results of the doppler are equivocal. In these cases renal angiography or digital subtraction angiography is needed. In this case oblique views are indispensable since stenosis may be missed. Renal artery stenosis can not be diagnosed by radioisotope scanning in the case of renal transplantation and captopril renography can not be used in single kidneys.

Percutaneous transluminal angioplasty (PTA) is the treatment of choice for renal artery stenosis. Good results have been attained also with surgical bypass. Surgical intervention is preferred when the stenosis is located at the point of anastomosis, whereas renal angioplasty is preferred when there is distal stenosis [31,32]. Surgical repair of the stenosis is difficult and the loss of the graft is not rare. Successful results, with a fall of blood pressure and/or response to lesser amounts of antihypertensives, have been reported in 60-85%

of cases but there is a 30% relapse of stenosis. The relapse of stenosis is a possibility that must be kept in mind during the follow up of the patient. PTA in combination with stenting after PTA using expandable metallic stents has been successfully used for recurrent stenosis[33].

The influence of the number of renal arteries on short and long term vascular complications in a large group of adult recipients failed to find difference in the outcome, when grafts with single versus grafts with multiple renal arteries were compaired[34]. In spite of this, we must suspect stenosis in transplants with technical proplems such as the cases with more than one vessel when delayed graft function was combined with hypertension.

Corticosteroids and calcineurine inhibitors

High cortisol doses and pulses have been connected with hypertension via sodium retension and increase of plasma volume [35]. It has been proved that the daily steroid dose as well as the cumulative steroid dose are significantly correlated to blood pressure [36]. On the other hand, low steroid doses for the long term immunosuppression are not possibly related with hypertension [37-39] but steroid withdrawal has been connected with lower arterial blood pressure [40].

Cyclosporine causes hypertension to patients transplanted or not. Cyclosporine induced hypertension is not related to the level of renal function [41,42]. Cyclosporine A can induce the whole spectrum from simple to malignant hypertension or HUS/thrombotic microangiopathy [43,44]. It is due to direct vasospasm and the increased sympathetic nervous system activity [45]. The direct effect on the vasculature is due to the impact of CyA on endotheline, nitric oxid and protaglandin synthesis. Cyclosporine also causes sodium and fluid retention [46]. Normal or low plasma renin activity (PRA) has been observed in patients on cyclosporine A[47], but it may be inappropriately high in the presence of hypertension and sodium retension. Tissue and subtype – specific modulation of angiotensin II receptors has been noticed by chronic cyclosporine A treatment[48]. There is no correlation between these actions and the dose or levels of the drug in the blood. It is of interest that the vascular lesions caused by cyclosporine could be diminished by angiotensin receptor blockers but not by other antihypertensive agents and interstitial fibrosis was decreased by losartan and enalapril[49,50]. There is improvement of the blood flow in the kidney, fall of the level of blood pressure and remission of the vessel resistance in patients converted from cyclosporine to azathioprine. Patients on cyclosporine present higher frequency of hypertension compared to patients taking azathioprine[7,51]. In humans sodium restriction reduces blood pressure only in CsA treated recipients and not in patients treated with convensional immunosuppression[52,53]. Patients under long term treatment with CsA exhibit hyperplasia of the juxtaglomerular apparatus which is reversible once the immunosuppressive regimen is switched to azathioprine[54].

Weight gain

It is known that renal patients usually gain considerable amount of weight during the first year after transplantation [55]. The body mass index was significantly higher in the patients with hypertension than in normotensive control individuals.

B. Effect of hypertension on heart mass

It has been found that there is a significant correlation between systolic blood pressure and left ventricular mass index by echocardiography[56]. In graft recipients the correlation was even more pronounced than in patients with essential hypertension. This finding is important since left ventricular mass is a potent independent predictor of cardiac mortality. An attenuated decrease of nighttime blood pressure in renal transplant recipients has been observed in many studies. This possibly plays a significant role in the augmentation of left ventricular mass[57].

C. Hypertension and long term renal allograft function

In a long-term analysis in renal transplant recipients, hypertension along with HLA missmatch and rejection episodes was found to be a strong predictor of adverse graft function[58]. The effect of hypertension on graft function was further illustrated by the data of the collaborative transplant study[59]. A highly significant correlation between blood pressure and long term graft function was found. A factor which appears to be hypertension related is urinary albuminuria[60]. Patients with microalbuminuria had higher daytime systolic blood pressure, higher left ventricular mass and inferior graft outcome[56,61].

D. Treatment of hypertension after renal transplantation

Treatment of elevated blood pressure in renal transplant recipients significantly reduces morbidity and mortality[62,63]. When the systolic blood pressure is greater than 200 mm Hg and diastolic blood pressure is greater than 120 mm Hg, rapid reduction of blood pressure is imperative in order to prevent vital organ damage. The initial therapeutic goal for blood pressure management in the the early post-transplant period is a systolic blood pressure less than 160 mm Hg and a diastolic blood pressure less than 90 mm Hg. The final regulation of blood pressure should be managed on an outpatient basis only in a stable transplant recipient. Many factors play important role in the fluctuation of blood pressure levels so the treatment of hypertension is individualized. No single antihypertensive agent has been found to be more effecacious or better tolerated than the others used in the treatment of posttransplant hypertension. The initial antihypertensive therapy must aim at the patient's risk factors.

Calcium antagonists

Calcium channel blockers are usually well tolerated and it has been proved that they reduce mean arterial pressure and total renal vascular resistance, increase renal blood flow and GFR, reduce cyclosporine toxicity, decrease perfusion injury and the grade of acute tubular necrosis immediately after transplantation[64-67]. These drugs inhibit the entrance of calcium through voltage dependent channels into the smooth muscles of vasoconstricted arterioles. For the above reasons, It has been reported that calcium antagonists are the drugs of choice. However, in a comparative clinical trial, it was found that a calcium antagonist, an ACE inhibitor and an a-blocker were equally effective in reducing blood pressure[68] and patient and graft survival did not show difference with the use of b-blockers and / or calcium antagonists in a 5-year follow up[69].

The long acting nifedipine and isradipine are probably the most effective drugs among calcium channel antagonists and do not increase cyclosporine levels as it happens with diltazem, verapamile, nicardipine and amlodipine[70-72]. These drugs are potent vasodilators and may cause dizziness, flushing, headeache, leg edema and gum hyperplasia[73-75]. These adverse effects can be minimised by the use of slow release formulations or agents with a slow onset of action. It has been reported that short – acting calcium antagonists, given in non-transplanted patients, may increase the mortality rate in those with a recent history of acute myocardial infarction or coronary heart disease[76]. So, caution is advised in the use of short – acting calcium antagonists for the treatment of post-transplant hypertension (table 1).

Angiotensin converting enzyme inhibitors (ACE)

The basic haemodynamic effect of ACE inhibitors is vasodilation via suppression of angiotensin II production and inhibition of bradykinin inactivation. Also, it has been suggested that ACE inhibitors retard the evolution of glomerulosclerosis and chronic decline of renal function, by normalizing arterial blood pressure and possibly intraglomerular hemodynamics[77,78].

The use of ACE inhibitors in post-transplant hypertension had been a matter of debate for a long time. In recent clinical studies with a long term follow up in renal transplant patients, ACE inhibitors have been shown to be effective in the treatment of post-transplant hypertension. There was no difference between the antihypertensive effect, ACE inhibitors and calcium antagonists. Also renal plasma flow and GFR were similar in both groups of patients[79,80]. Mourad compared nifedipine plus atenolol with lisinopril plus furosemide and found no differences between the two groups as far as the antihypertensive efficacy, the adverse drug reaction profile, the effect on plasma renal flow and GFR. It has been shown that ACE inhibitors reduce significantly the proteinuria of transplanted patients with chronic allograft nephropathy[81].

The decline of renal function that may be seen after treatment with ACE inhibitors is possibly related with the existence of renal artery stenosis or it may happen in grafts with normal parenchyma when the patient is dehydrated[82-84]. The use of these drugs has been connected with hyperkalemia, especially in, patients with diabeties and anemia[85] (table 2).

Diuretics

The mechanism by which diuretics reduce blood pressure is not known. The first period after starting diuretic therapy, the control of blood pressure is by volume depletion. Later there is

Table 1. Dose, renal effects, dosage adjustment and toxicity of the most commonly used calcium antagonists in renal transplantation.

Calcium antagonist	usual dose mg/d	renal effects GFR RBF RVR	percentage of normal dosage in renal failure >50	10-50	<10	toxicity
Nifedipine	30-120	improve GFR, RBF, decrease RVR	100	100	100	gingival hyperplasia, headace, oedema, flushing
Felodipine	5-20	»	100	100	100	»
Amlodipine	5-10	»	100	100	100	»
Isradipine	2.5-10	»	100	100	100	»
Nicardipine	60-120	»	100	100	100	»
Diltiazem	60-350	»	100	100	100	and conduction abnormality
Verapamil	180-240	»	100	100	100	»

Table 2. Dose, renal effects, doasage adjustment in renal failure and toxicity of most commonly used ACE in renal transplantation.

ACE inhibitors	usual dose mg/d	renal effects GFR RBF RVR	percentage of normal dosage in renal failure >50	10-50	<10	toxicity
Captopril	50-100	No/_ No/_ _	100	75	50	conduction abnormality, cough, angioedema, hyperkalemia, leucopenia
Enalapril	2.5-20	»	100	75	50	»
Lisinopril	10-20	»	100	50	25	»
Fosinopril	20-40	»	100	100	75	»

Table 3. Dose, renal effects, doasage adjustment in renal failure of the more commonly used diuretics in renal transplantation

Diuretics	usual dose mg/d	renal effects GFR RBF RVR	percentage of normal dosage in renal failure >50	10-50	<10	toxicity (most frequent)
Furosemide	20-320	acytely decrease and RBF	100	100	100	hypercholesterolemia hyperglycemia hypokalemia hyperuricaemia
Hydrochlorothiazide	12.5-50	»	100	100	avoid	»
Chlorothiazide	125-500	»	100	100	avoid	»
Ethacrynic acid	25-200	»	100	q12hr	avoid	»
Bumetanide	0.5-10	»	100	100	100	»
Amiloride	2.5-10	»	100	100	avoid	»
Indapamide	1.25-25	improve GFR	100	100	avoid	»

possibly a vascular hyporesponsiveness to the sympathetic nervous system[86]. Diuretics are the best choice in patients with edema and sodium overload. Sodium load, food-drug interactions and drug-drug interactions may lessen or ablate the effectiveness of diuretic therapy[87-89]. Loop diuretics can cause hypokalemia, hypocalcemia and exacerbate hyperparathyroidism. The extended use of diuretics and calcinurin inhibitors may require close electrolyte monitoring to avoid gout and cardiac mortality associated with low magnesium levels[90]. On the contrary, thiazide diuretics may induce hypercalcemia and potassium sparing agents may induce hyperkalemia. The use of cyclosporine, FK506, ACE inhibitors, b-blockers and cotrimoxazole has been connected with hyperkalemia. Hyperuricemia and hypomagnesaemia are complications of cyclosporine and tacrolimus therapy[91] (table 3).

Table 4. Dose, renal effects, dosage adjustment in renal failure and toxicity of most commonly used ß-blockers in renal transplantation

ß-blockers	usual dose mg/d	renal effects GFR	RBF	RVR	percentage of normal dosage in renal failure >50	10-50	<10	toxicity
		_	_	_				bradycardia hypertriglyceridaemia depression mask hypoglycaemia bronchospasm
Atenolol	50-100				100	50-75	30-50	
Nadolol	40-320				100	50	25	
Propranolol	120-320				100	100	100	
Metoprolol	50-200				100	100	100	
Labetalol	400-1200	No change GFR, RBF and RVR			100	100	100	

Table 5. Dose, renal effects, dosage adjustment in renal failure and toxicity of Ag II receptor antagonists in renal transplantation.

Ang II rec antagonist	usual dose mg/d	renal effects GFR	RBF	RVR	percentage of normal dosage in renal failure >50	10-50	<10	toxicity
Losartan	50-100	No/_	No/_	_	100	100	75	anemia
Valsartan	80-320	»			100	100	75	»
Irbersartan	150-300	»			100	100	100	»
Candesatan	4-32	»			100	100	75	»
Eprosartan	200-400	»			100	100	75	
Telmisartan	40-120	»			100	100	100	

ß-Blockers

The precise mode of action of ß-blockers in reducing blood pressure is not known. In a small study of the effect of ß-blockers on hypertensive renal transplant recipients, a blood pressure reduction was noted only in hypertensive patients with their native kidneys in situ[92]. Native kidneys may play an important role in activation of renin and angiotensin system mediated by activation of the sympathetic nervous system. In a randomized study renal transplant recipients received atenolol or quinapril. In both groups blood pressure control was achieved. However quinapril lowered significantly albumin excretion[93].

ß-Blockers may mask the symptoms of hypoglycemia and thyrotoxicosis and cause sexual dysfunction, muscle weakness, tiredness and fatigue. They can also complicate the lipid profile in renal transplant recipients. The beneficial effect of ß-blockers in transplant recipients with a history of myocardial infarction or coronory heart disease outweight the risk of their adverse effects. ß-Blockers should be considered as a first choice treatment for patients with a renal transplant and a history of CHD. Abrupt discontinuation of ß-blockers may cause rebound hypertension and so the dosage should be reduced slowly over a 1- to 2-week period (table 4).

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists reduce the blood pressure by blocking the physiological response to angiotensin II[94,95].

The recent successful use of angiotensin II receptor antagonists type I has added a new group of drugs in the treatment of renal transplant hypertension[96-98]. These agents show a significant control on the blood pressure, reduce the need for other antihypertensive agents[97,98] and reduce statistically significantly proteinuria of patients with chronic allograft disease[99]. These agents do not seem to interfere with any of the immunosuppressive agents.

Stimulation of AT1 receptors of erythroid progenitor cells by Ag II is believed to increase

red blood cell mass independently from circulating erythropoietin. AT1 blockers cause statistically significant fall of Ht and Hb and are very useful in hypertensive patients with erythremia[97,98]. It is believed that the blockade of AT1 receptors results in a decrease of red blood-cell mass independently of erythropoietin and initial haemoglobin levels[100,101]. They do not cause hyperkalemia or hyperuricemia and raise slightly but significantly the levels of serum creatinine.

These drugs have the ability to lower significantly the levels of TGF-ß1 in the plasma of transplanted patients with chronic allograft nephropathy[102]. The drugs of this category could be proved valuable not only for the treatment of hypertension of renal transplant recipients but also for the intervention in the evolution of chronic allograft nephropathy (table 5).

Miscellaneous

Phlebotomy has also been found to ameliorate hypertension[103]. On the other hand ACE inhibitors, apart from lowering blood pressure also lower Hb values as do the new AT-1 receptor blockers[97,98]. Hb values are also lowered by theophylline, but because of its side effects is not a suitable theraputic option.

ΠΕΡΙΛΗΨΗ

Γ. Βέργουλας. **Υπέρταση και μεταμόσχευση νεφρού.** Ιπποκράτεια 2001, 5 (2): 51-60

Η υπέρταση αποτελεί σημαντικό παράγοντα κινδύνου για την επιβίωση ασθενών και μοσχευμάτων στις μεταμοσχεύσεις νεφρού. Η συχνότητα της υπέρτασης μετά τη μεταμόσχευση νεφρού κυμαίνεται από 75 έως 80% και μπορεί να διακριθεί σε ενδογενή και εξωγενή του μοσχεύματος και είναι συνήθως πολυπαραγοντική. Κατά την άμεση μεταμοσχευτική περίοδο οφείλεται σε θετικό ισοζύγιο νατρίου και ύδατος, σε οξεία σωληναριακή νέκρωση, σε οξεία απόφραξη του ουρητήρα, σε οξεία απόρριψη και σε υπερασβεστιαιμία. Μετά το πρώτο τρίμηνο σχετίζεται με τα κορτικοστεροειδή, την κυκλοσπορίνη, το FK506, και τη χρόνια νεφροπάθεια μοσχεύματος. Η θεραπεία της μειώνει σημαντικά τη νοσηρότητα και θνητότητα των μεταμοσχευμένων νεφροπαθών. Τα συνηθέστερα αντιυπερτασικά που χρησιμοποιούνται μόνα τους ή σε συνδυασμό είναι οι ανταγωνιστές του ασβεστίου, τα διουρητικά, οι β-αδρενεργικοί αποκλειστές, οι ανταγωνιστές του μετατρεπτικού ενζύμου της αγγειοτενσίνης και οι αποκλειστές των υποδοχέων τύπου 1 της αγγειοτενσίνης ΙΙ.

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