

Review Article

Hypertension: The Neglected Complication of Transplantation

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Received 10 March 2013; Accepted 11 April 2013

Academic Editors: A. A. Noorbala, R. S. Padwal, and D. G. Romero

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Arterial hypertension and transplantation are closely linked, and its association may promote impaired graft and overall survival. Since the introduction of calcineurin inhibitors, it is observed in 50–80% of transplanted patients. However, many pathophysiological mechanisms are involved in its genesis. In this review, we intend to provide an updated overview of these mechanisms, dealing with the causes common to all kinds of transplantation and emphasizing special cases with distinct features, and to give a perspective on the pharmacological approach, in order to help clinicians in the management of this frequent complication.

1. Introduction

Arterial hypertension (AH) occurs frequently after transplantation, and the association of both has been a well documented fact since many years. It may begin early or late after the procedure, or even in an accelerated fashion from a preexistent hypertension, and may appear in all forms of transplant, that is, solid organ (renal, cardiac, pancreatic, hepatic, and pulmonary) as well as nonsolid (bone marrow) transplants. Once the mechanism/s leading to AH are unleashed, a very deleterious situation may arise, because it has been demonstrated that its presence is associated to impaired graft and overall survival [1].

The incidence of AH in transplant recipients has increased notoriously, above all since the introduction of calcineurin inhibitors (cyclosporine, tacrolimus). With the use of these two drugs AH is observed with varying degrees in 50–80% of the patients [2]. Moreover, there are many more pathophysiological mechanisms involved in the genesis of AH which are basically dependent on the transplanted organ.

There are also at least two main issues to take into account in this group of patients: first, that calcineurin inhibitors and corticosteroids are used jointly, which in turn may increase the hypertensive response; and second, that the use

of cyclosporine and tacrolimus leads invariably to nephrotoxicity, which along with renal insufficiency predispose to AH independent of the direct effect of calcineurin [3].

We will outline in this review the main causes of AH in the transplanted patients, with a special focus on the pathophysiological mechanisms and emphasizing the causes common to all kinds of transplantation. Renal transplantation will be dealt apart due to the fact that it possesses some distinct features regarding etiology [4, 5]. After this, we will focus on the characteristics of the most widely used drugs in order to clarify the pharmacological approach.

2. Methods

The search in the literature was by retrieving the most relevant articles indexed in the major databases: Medline and Embase. We used keywords such as “transplant,” “hypertension,” “calcineurin inhibitors,” “transplantation,” “liver,” “cardiac,” “renal.”

3. Causes Common to All Transplants

3.1. Calcineurin Inhibitors (CNIs). Over the past decades, CNIs (cyclosporine, tacrolimus) have become the cornerstone of transplant immunosuppression, but unfortunately they are frequently related to AH and other complications,

most importantly nephrotoxicity and thrombotic microangiopathy [6]. The majority of protocols include one of these two agents, usually combined with corticosteroids and an added third drug such as mycophenolate, azathioprine, or sirolimus.

The prevalence of systemic AH in transplanted patients treated with CNIs is high, ranging 70–90% [4, 7].

The mechanisms by which they produce AH are manyfold and complex, and they are favored by certain features of this family of drugs such as its high liposolubility and easy penetration in vascular smooth muscle cells. Most of them are not mutually exclusive and may potentiate each other.

The preponderance of one mechanism over the other has not been established yet, but we know that vasoconstriction and increased peripheral resistance constitute the main hemodynamic effect associated to these drugs.

We propose to summarize the main mechanisms involved in the genesis of CNI-induced hypertension as follows.

- (i) Endothelial dysfunction: CNIs impair vasodilatory response by diminishing prostacyclin levels (PGI₂), endothelium derived relaxing factor, and nitric oxide activity [8–10].
- (ii) Production of vasoconstrictor substances: Chiefly endothelin-1 [11], which is thought to be involved in the process of tissue damage, fibrosis, and stimulation of proinflammatory cytokines. It is not clear yet whether endothelin contributes to CNI-induced hypertension through renal or systemic vasoconstriction [12–14].
- (iii) Sodium sensitivity: CNIs reduce glomerular filtration rate and increase sodium reabsorption, a fact which may be corroborated in vivo by the presence of volume expansion in bioimpedance measurements. Therefore, greater pressure levels are required to maintain natriuresis. This is thought to occur due to increased sodium-chloride cotransporter (NCC) activity in the distal convoluted tubule. At least in part, CNI-induced AH may be a salt-sensitive form of hypertension mediated by the WNK/SPAK kinases—NCC pathway, and bare a resemblance to familial hyperkalemic hypertension (Gordon Syndrome) [15–21].
- (iv) Renin-Angiotensin-Aldosterone System (RAAS): early after transplantation plasma renin is low, but over time CNIs induce direct and/or indirect RAAS stimulation, that is, at a renal and/or peripheral vascular level. This increase in RAAS levels may demand a variable time since the procedure, which has a practical consequence when deciding the correct moment to begin the use of RAAS-inhibiting drugs. This time-varying delay is due to the fact that RAAS activation depends on several conditions such as type of transplant (renal, cardiac, liver or bone marrow), use of concomitant drugs, and hemodynamic status after the procedure. For instance, increased renin serum levels have been observed in patients with liver transplantation and established

hypertension thirteen months after the procedure, but in the same population low renin levels have been observed during the first four months, even in those who would develop hypertension afterwards [22, 23]. In contrast, the use of diuretics in cardiac transplantation increases circulating renin levels within the first months, theoretically paving the way for early administration of RAAS inhibitors [24, 25]. Therefore, the efficacy of drugs which act by inhibiting the angiotensin converting enzyme, blocking the angiotensin (AT₁) receptor, or directly inhibiting renin, will be high or low depending on the circulating renin levels at a given time. The general consensus is that these drugs have limited efficacy as monotherapy during the early posttransplant period but gradually acquire relevance when one year posttransplantation approaches or with concomitant diuretic use. Long-term ACE inhibitors may confer benefits in the presence of proteinuria and ameliorate adverse cardiovascular outcomes independently from their blood pressure-lowering effect [26, 27].

- (v) Sympathetic activation: a preponderant role of the sympathetic nervous system in long-term blood pressure rises in patients under CNIs has not been established yet. There seems to be a lack of response to adrenergic inhibitors and persistence of vasoconstriction immediately after renal or cardiac transplantation in denervated individuals [2]. Cyclosporine, when administered acutely, seems to rise blood pressure partly by activating sympathetic activity, that is, either by increasing renal afferent signaling through vasoconstriction of the vascular bed or by central modulation of glutaminergic neurotransmission [28, 29]. But this effect has been observed neither with sustained cyclosporine treatment nor with tacrolimus [30]. Consequently, the use of alpha-adrenoceptor antagonists (alpha-blockers) may not provide benefits beyond those that could be obtained with any other antihypertensive drug class in this scenario [31].

3.2. Corticosteroids. The relationship between corticosteroid use and AH is well known, although the mechanism of action has not been completely unraveled. Contrary to the original belief that sodium retention and volume expansion explained the rise in blood pressure, it seems that the predominant mechanism would be an increased pressor response [32].

These drugs may impact on the development of post-transplant AH so much for the received daily dose as for the accumulative doses, including treatments for graft rejection with intravenous bolus. The relative importance of corticosteroids when compared to CNIs is a minor one, taking into account that there is usually a progressive dose tapering, but they may play a greater role when used in high doses, above all during the first months after the procedure [7]. The incidence of posttransplant corticosteroid-related hypertension has been estimated in around 15% [33].

3.3. Other Associated Conditions. There are a myriad of conditions which may worsen outcome and alter blood

pressure measurements after transplantation, to name a few, elevated body mass index, pheochromocytoma, primary hyperaldosteronism, hyperparathyroidism, drug abuse, and smoking status.

4. Transplanted Organ-Related Causes (Renal)

The following list summarizes causes and predisposing factors for AH which are related to kidney transplantation, a procedure with distinctive characteristics [7, 34–36]:

- (i) primary renal disease in native kidneys,
- (ii) elderly and female donor,
- (iii) hypertensive donor,
- (iv) use of right-sided donor kidney,
- (v) prolonged ischemia time,
- (vi) delayed graft function,
- (vii) chronic rejection,
- (viii) stenosis of the transplanted renal artery,
- (ix) blockage along the transplanted urinary tract (lymphocele, ureteral obstruction),
- (x) chronic allograft nephropathy,
- (xi) recurrent and de novo glomerulonephritis in the renal allograft.

5. Diagnosis of Hypertension in Transplant Patients

Hypertension may be diagnosed on the basis of persistently elevated office blood pressure values ($\geq 140/90$ mmHg). A single reading $\geq 180/100$ mmHg sometimes is enough to make a diagnosis [37, 38]. When poor quality manual measurements and/or office-induced increases in blood pressure are suspected, the use of fully automated oscillometric sphygmomanometers capable of multiple readings with the patient resting alone may be an alternative in order to minimize office AH overdiagnosing [39]. In the latter case the cut-point for defining AH should be 135/85 mmHg, the same as in Home Blood Pressure Monitoring [40].

At home monitoring with automated validated devices may be suitable to better define blood pressure profile especially when white-coat effect or masked hypertension is suspected [41–44].

A 24-hour ambulatory blood pressure monitoring provides additional information beyond that obtained by clinic and home-based readings and should be considered in the initial evaluation and during treatment controls [45–47]. An altered circadian rhythm is frequent in transplant recipients and nocturnal blood pressure increases may be unmasked by this method [48, 49] (Figure 1). In kidney transplant, a non-dipping pattern at one-year postprocedure may identify patients at risk for increased kidney function loss and lower glomerular filtration rate [50].

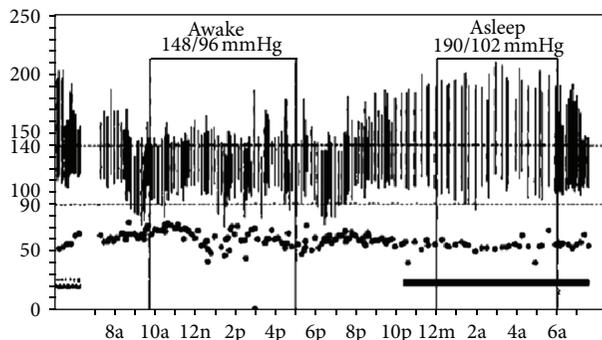


FIGURE 1: 24-hour ambulatory blood pressure measurement of a 25-year-old patient several months after liver transplantation and immunosuppression with cyclosporine. Circadian rhythm is altered (nocturnal rise). Extracted from [2] with permission.

6. Initial Approach to the Transplanted Hypertensive Patient

Once the diagnosis of hypertension has been made the search does not need to be very extensive, and it should be basically adjusted to the general recommendations for hypertensive patients [37]. A comprehensive medical history should be included, with information regarding use of drugs such as NSAIDs, contraceptives, erythropoietin, nasal decongestants, and ergot-derived medications.

Initial laboratory testing should include a liver panel, serum creatinine, blood urea nitrogen, ionogram and 24-h urine for creatinine clearance, proteinuria, and 24-h urinary sodium (the latter in order to establish sodium intake).

In patients subjected to kidney transplantation, early doppler ultrasound may reveal transplant renal artery stenosis, a recognized cause of AH which may lead to allograft dysfunction [51, 52], and conventional renal ultrasound may detect causes of blockage along the urinary tract as in the case of ureteral obstruction or peritransplant fluid collections (hematomas, lymphoceles, and urine leak) [53].

7. Blood Pressure Goals

Since there are no treatment guidelines for the transplanted population [7], blood pressure goals may be extrapolated from the 2007 guidelines of the European Society of Hypertension (ESH) [54] (reappraised in 2009 with no changes regarding this point) [37], the European Society of Cardiology (ESC) [55], the 2002 European Best Practice Guidelines for Renal Transplantation (EDTA) [56], the 2004 Kidney Disease Outcomes Quality Initiative K/DOQI (NKF) [57], the 2003 JNC7 [58], and the 2012 KDIGO Guidelines for Management of Blood Pressure in CKD [59]. The proposed blood pressure goals for transplanted patients in general are similar to those in patients with high cardiovascular risk:

Transplanted patients in general: $< 130/80$ mm Hg.

Although the European Best Practice Guidelines for Renal Transplantation 2002 recommended a target BP $\leq 125/75$ mm Hg in proteinuric patients, there is still no strong evidence, and the new KDIGO guidelines avoided this

recommendation [56, 59]. The proposed target BP levels are based on observational data.

8. Nonpharmacological Management

In general, lifestyle changes should be emphasized to reduce global cardiovascular risk, much in the same fashion as in the general population. Therefore, general rules apply such as smoking cessation, low sodium diet, and fostering aerobic exercise during 30–45 minutes for at least five days a week in order to avoid overweight with a BMI goal of $<30 \text{ Kg/m}^2$. If possible, a DASH-type diet with low saturated fat should be recommended, along with an increase in fruits, vegetables, fish, and seafood consumption [34].

9. Management of Immunosuppressive Therapy

Steroid withdrawal or minimization is being increasingly used in new transplantation protocols. This is due to the fact that reducing the dose of corticosteroids or suspending treatment altogether may ameliorate blood pressure control and other factors such as diabetes and hyperlipidemia, although the value of this strategy has been questioned by many factors; for instance, sometimes the beneficial effect is transient [33, 60, 61], many patients have a total lack of response, graft survival may be compromised due to increased rates of acute rejection, and it is not clear whether to initiate steroid downtitration or discontinuation early (<3 months) or late (between 3 and 12 months) after the procedure. In a retrospective analysis late steroid withdrawal in liver transplant recipients was associated with better long-term graft survival without increasing the rates of cardiovascular events, hyperlipidemia, or diabetes [62]. It has been suggested also that rapid discontinuation of steroids (≤ 7 days) does not significantly increase acute rejection episodes and late graft loss, with 80% of the recipients remaining steroid-free long term [63, 64], and there are reports associating steroid withdrawal after year-long treatment with reductions in mortality and cardiovascular events risk, at least in renal transplant patients [65, 66]. However, some studies showed no significant impact of steroid withdrawal on posttransplant BP control [67, 68], and in a recent prospective, randomized trial of complete steroid avoidance in liver transplantation there was a trend towards decreased graft and recipient survival, supporting the use of at least a short course of steroids [69].

Reducing the doses of cyclosporine and/or tacrolimus is followed by a reduction in blood pressure, being cyclosporine comparatively stronger in its prohypertensive power [70–72]. However, the benefits of this reduction must be weighed carefully against maintaining acceptable acute rejection rates [73].

It is difficult to choose only one course of action when substituting or changing the combination of immunosuppressive drugs, a matter which is still under debate. CNIs may be reduced and/or substituted and/or combined with mammalian target of rapamycin (mTOR) inhibitors such as sirolimus or everolimus, or mycophenolic acid derivatives,

taking into account the limitations of each drug and their adverse effects profile. It remains to be seen whether newer CNI-sparing drugs such as belatacept prove to be an option, given that the initial tests compared to cyclosporine in renal transplant patients showed a good safety profile and allowed a reduction in antihypertensive medication [74–76].

Overall, when changes are made in the management of immunosuppressive therapy outside the usual protocols, they should be reinforced with a close clinic and laboratory-based followup. The experience of the Institution in charge of the patient with one scheme or the other is an important fact to be taken into account [77–82].

10. Pharmacological Treatment

When choosing the right antihypertensive medication for the transplanted patient, some considerations may be taken into account. First, that antihypertensive drug administration [35, 36, 83, 84] in this population should contemplate possible interactions that might increase serum levels of immunosuppressors, particularly cyclosporine, tacrolimus, and/or mTOR inhibitors, whose metabolism depends on the CYP 450 3A4 enzymatic pathway, the same used by other drugs [85]. Diltiazem [86] and Verapamil [87], for instance, are antihypertensives which inhibit this pathway and have potential for increasing serum levels of immunosuppressors. Secondly, basic principles apply, which are also valid for essential hypertension therapy, such as monitoring renal function, sodium and potassium levels, and watching for usual adverse reactions such as hypotension or edema. Figure 2 intends to provide a basic algorithm for therapeutic approach. Table 1 summarizes drugs used in CNI-induced AH.

Calcium-Channel Blockers. This group of drugs is still of choice and is particularly attractive due to its vasodilatory effect which counteracts the final CNI action on the vascular smooth muscle, thus decreasing peripheral resistance with an acceptable profile of adverse events. Within this group, dihydropyridines such as amlodipine, felodipine, nifedipine, or lercanidipine are preferred (nicardipine interferes with cyclosporine). Non-dihydropyridines (diltiazem and verapamil) and nicardipine should be used with caution, measuring serum levels of cyclosporine and eventually adjusting the dose [88–92].

Beta-Blockers (BBs). BBs are commonly used in transplanted patients and are useful in normalizing cardiac output especially in those with a hyperdynamic circulatory pattern. They may be used in patients with renal insufficiency and somehow mitigate the tachycardizing effects of dihydropyridinic calcium channel blockers. The new BBs are suitable for once-daily administration for better compliance and have higher β_1 -adrenoceptor affinity. In this group we find Bisoprolol and Nebivolol, the latter of which has intrinsic endothelial NO-releasing properties making it particularly attractive [26, 93, 94].

Diuretics. They counteract the sodium-retaining effects of CNIs, although at the expense of a rise in serum creatinine levels which should be taken into account when

TABLE 1: Drugs used for the treatment of calcineurin inhibitor-induced arterial hypertension.

Class of Drug	Name	Characteristics	Adverse effects	Interaction with Cyclosporine (CyC)
Calcium Channel Blockers				
Dihydropyridines	Nifedipine	Counteract CyC (and possibly TAC) induced vasoconstriction	Edema, Headache, tachycardia, erythema, gingival hyperplasia	--
	Isradipine	Idem	Idem	--
	Felodipine	Idem	Idem	--
	Amlodipine	Idem	Idem	±
	Nicardipine	Idem	Idem	++
	Lercanidipine	Idem	Less edema	±
Nondihydropyridines	Diltiazem HCL	Moderate power, reduces coronary vasculopathy after heart transplant	Edema, headache	++
	Verapamil HCL	Less vasodilatory power, potentiates immunosuppression?	Constipation, bradycardia, AV block	++
Beta Blockers	Atenolol	May reduce Cyc-induced headache	Bradycardia, bronchospasm	--
	Bisoprolol	Useful when concomitant cardiac disease is present		
	Metoprolol			
Alpha-beta blockers	Nebivolol	Idem + Nitric Oxide release vasodilation		
	Labetalol	Effective oral and intravenous administration	Bradycardia, Orthostatic hypotension	--
	Carvedilol	Extended release formulation allow once daily use	Bradycardia, bronchospasm	--
ACE Inhibitors	Enalapril	Limited efficacy with once daily use	Hyperkalemia, Hyperazotemia Nongap Metabolic Acidosis Dry Cough	--
	Lisinopril	Effective along with diuretics may limit renal fibrosis	Idem	--
	Perindopril	Idem + allow once daily use	Prerenal azotemia, Hyperuricemia Hypokalemia Hyponatremia	--
	Zofenopril			
Thiazide or Thiazide—like diuretics	Hydrochlorothiazide	Counteract sodium retention, potentiate other anti-AH drugs		
Loop Diuretics	Indapamide	Idem + better 24-h profile, lowers nocturnal BP	Idem	--
	Furosemide	Strong, short action	Hypokalemia, hypomagnesemia	--
	Torsemide	Sustained action	Idem	--
Centrally acting vasodilators	Minoxidil	K-channel opener. Use with loop diuretics and BBs to minimize adverse effects	Pericardial effusion, Tamponade, Angina pectoris	--
	Clonidine	Alpha-2 adrenergic and imidazoline-1 receptor agonist	Sedation, dry mouth	--
	Moxonidine	Imidazoline type 1 receptor agonist. Promotes natriuresis	Sedation, dry mouth.	--

titrating cyclosporine and/or tacrolimus doses. In general they are considered safe, especially loop diuretics such as furosemide or torsemide due to better metabolic profile compared to thiazides. Hypokalemia and hypomagnesemia may occur. Torsemide allows a single-dose regimen for better compliance. The role of aldosterone antagonists is not yet defined [34].

Alpha-Blockers. These drugs are generally well tolerated and may be associated with other groups of drugs in order to reach blood pressure targets. There is more experience with doxazosin [95, 96].

ACEIs, ARBs. The benefit is limited when used early post-transplantation due to low serum renin levels during this

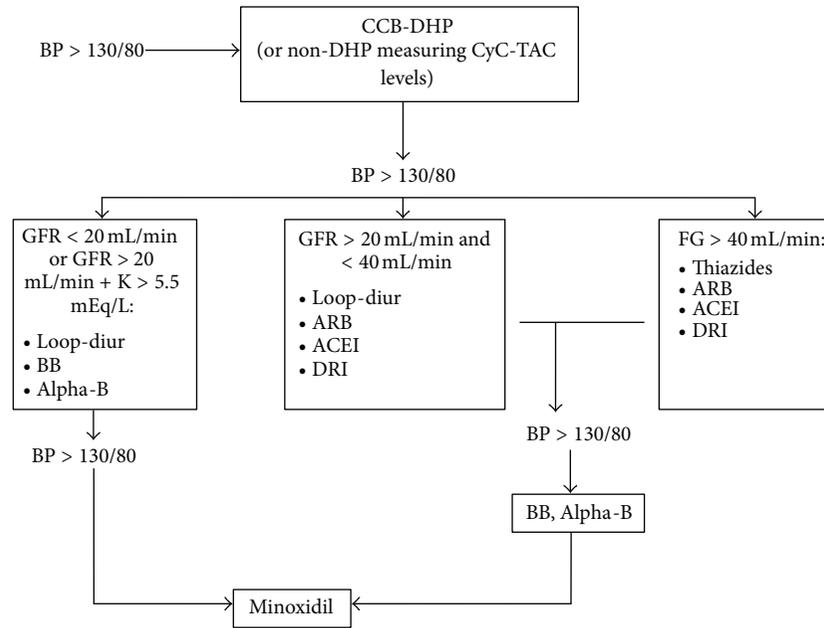


FIGURE 2: Algorithm for therapeutic approach in transplant patients with hypertension.

period. They are also usually avoided within the first 3 to 4 months because they are known to have acute hemodynamic effects leading to increased serum creatinine levels, making interpretation difficult in a time when acute rejection is a strong possibility. However, they grow gradually in importance when ~12 months have elapsed. At this time, these drugs may ameliorate the profibrotic effects of CNIs and reduce microalbuminuria. Some unwanted effects may take place such as hyperkalemia, metabolic acidosis, and a mild usually transient glomerular filtration fall due to efferent arteriole vasodilation [97, 98].

Renin Inhibitors. There is no experience with aliskiren use, but theoretically low renin levels during the first phase posttransplant rise the assumption that no desired effect should be expected at least after a period of ~12 months.

Other Antihypertensive Drugs. Individuals with difficult-to-treat AH and renal impairment are candidates for third line antihypertensive drugs. There is some experience with the use of direct vasodilators such as Minoxidil (limited by risk of tamponade/pericardial effusion), central α -agonists (methyl-dopa, clonidine), and imidazolinic receptor-acting drugs (moxonidine) [34].

11. Conclusions and Perspectives

AH in transplanted patients, regardless of type (solid or nonsolid), is an important issue, above all due to its high prevalence and its association with reduced graft and overall survival. Thus, clinical suspicion should always be present, and diagnosis should be made as early as possible after the procedure.

Adequate diagnosis methods should be peremptorily implemented, beyond the classical office BP readings; 24-hour

ABPM allows very valuable information on circadian rhythm and nocturnal blood pressure, and Home Blood Pressure Monitoring (HBPM) has established itself as a very useful method for daytime BP diagnosis and followup in this population of patients [43]. Future studies will enable us to understand more about the utility of HBPM and other noninvasive cardiovascular methods for the evaluation of hypertensive transplanted patients, such as central blood pressure measuring (at office and 24-h ambulatory), pulse wave velocity, and dysautonomic assessment via heart rate variability, to quote a few.

From the therapeutic point of view, we should realize that some pathophysiological mechanisms common to immunosuppressive agents promote the occurrence of hypertension, but we should also understand that there are mechanisms involved in AH that are related to the type of transplanted organ. Essential hypertension and secondary causes may be exacerbated by the use of transplant-related medication, but the condition may appear also in prior normotensive subjects. Time after transplantation is crucial when deciding which kind of antihypertensive agent should be used, since serum renin behavior varies during the first months. The more we understand about these hypertension-leading mechanisms the more we are going to be able to recognize the adequate treatment.

Today, there are a myriad of therapeutic options available ranging from drug type, different combinations, dosages, and time-to-treat when it comes to using steroids and immunosuppressants, as well as diverse antihypertensive medications and nonpharmacological approaches. There are also invasive therapeutic options in the fields of dialysis, hemodynamics, and surgery when anatomic and functional causes cannot be managed adequately with a more conservative treatment. Future therapeutic options such as catheter-based renal

denervation by radiofrequency ablation and subcutaneous carotid stimulation are promising but were not studied yet in this population.

Updated consensus statements from the different International Societies are needed to determine common blood pressure objectives with data supported by strong evidence from randomized clinical trials rather than observational. Deciding optimal BP targets and first line medication treatment should be focused on clinically important outcomes such as graft survival, cardiovascular disease, and mortality.

Finally, multidisciplinary team work in a high complexity hospital should be encouraged for the better management of this complex group of patients.

Acknowledgments

The authors would like to acknowledge the expert assistance of Dr. José Boggia and Ms. Silvia Yeha.

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