Left ventricular hypertrophy after renal transplantation: new approach to a deadly disorder

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Introduction

Renal transplantation (RT) is the treatment of choice for end-stage renal failure, but all-cause mortality is high in these patients [1]. The cardiovascular death rate is higher than in the general population, even after stratifying for age, gender and race. Moreover, left ventricular hypertrophy (LVH) is extremely common in kidney transplant recipients (50–70%) and appears to be an important determinant of survival [2]. In general, correction of the uraemic state by RT leads to regression of LVH, but in many patients cardiac growth persists, even in normotensive recipients [3]. Many risk factors of volume and pressure overload concur after RT. Additionally, other risk conditions inherent to RT, such as immunosuppressive therapy and possibly genetic factors, may contribute to perpetuate this complication. The renin–angiotensin system (RAS) plays an important role in the pathogenesis of cardiac growth. Blockade of this system by angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type 1 (AT1) receptor antagonists (ARAs) leads to significant regression of LVH, independently of other risk factors [4]. However, whether it decreases long-term mortality in this population is unclear.

This review summarizes current knowledge on pathogenesis, clinical aspects and treatment of LVH following RT.

Clinical significance

Regardless of blood pressure, LVH is predictive of cardiac complications in both the general population and chronic kidney disease patients [5,6], including renal transplant recipients. Persistent or de novo LVH is a risk factor for death and congestive heart failure following RT [7]. Cardiac growth limits compliance of the left ventricle, increases coronary vascular resistance and decreases capillary length density, so that there is a reduction in the ratio of capillary perfusion to myocardial supply. As a consequence, the hypertrophic myocardium becomes more sensitive to ischaemia and more vulnerable to arrhythmias, congestive heart failure and sudden death.

From this perspective, it is easy to understand the importance of detecting LVH early during follow-up in order to apply the most appropriate therapeutic measures in these patients.

Pathophysiology of LVH: Role of immunosuppression

LVH is primarily an adaptive response to volume and pressure overload with the aim of minimizing ventricular wall stress. Two models of adaptation may develop depending on the patterns of stress imposed. Pressure overload causes parallel addition of sarcomeres, thickening of myofibres and concentric hypertrophy. This allows the generation of greater intraventricular pressure to overcome the outflow impedance. In contrast, volume overload produces lengthening of myofibres and eccentric hypertrophy, leading to an increased cardiac stroke volume by Starling mechanism [8]. Both processes lead to an acceleration of myocardocyte apoptosis and fibrosis. This type of cardiac change differs significantly from exercise-related cardiac remodelling. The clinical importance of modified LV geometric patterns relies on the fact that they are associated with poorer prognosis and are modifiable by antihypertensive therapy [5,9].

Renal transplant patients have numerous risk factors for both volume and pressure overload. Cardiac geometry at the time of RT is the product of...
age, diabetes, blood pressure, anaemia, vascular access, duration of the uraemic state as well as genetic factors. Following RT, the persistence or evolution of such risk factors and others inherent to RT may promote LVH further, predisposing to congestive heart failure and death. In addition, hypoalbuminaemia and ischaemic heart disease may also contribute to myocytes apoptosis and ventricular remodelling [10]. Finally, cytokines and growth factors such as angiotensin II may also alter the balance among cardiac hypertrophy, apoptosis and fibrosis (Figure 1).

Although the mechanisms by which LVH develops are incompletely understood, the local RAS probably plays a crucial role in the cardiac remodelling process. Mechanical stretch directly increases angiotensin II release from cardiac myocytes, which acts in an autocrine fashion stimulating intracellular protein synthesis [11]. The fact that blockade of this system by ACEIs or ARAs significantly decreases LVH independently of blood pressure [4] is further indirect evidence for this mechanism.

Immunosuppressive therapy may also modulate cardiac growth. Steroid-induced sodium and water renal retention contributes to cardiac hypertrophy regardless of systemic RAS and blood pressure [12]. Furthermore, glucocorticoids induce ACE expression in vascular smooth muscle, which could increase blood pressure [13]. Steroid withdrawal has been associated with lower blood pressure and the need for reduced antihypertensive medication [14]. Consequently, regression of LVH can also be expected with this therapeutic approach.

The activation of the calcium-dependent phosphatase, calcineurin, plays a critical role in the development of LVH [15]. Calcineurin inhibitors (cyclosporin A and FK506) may, therefore, minimize this complication although these substances induce hypertension. An elegant study demonstrated that early administration of FK506 to Dahl salt-sensitive rats attenuated the development of LVH [16]. However, the high doses required in this animal strain to achieve such an effect and the persistence of myocardial fibrosis argue against their use in kidney transplant patients for this aim. In the future, a more specific blockade of cardiac calcineurin action might be a promising therapeutic option to prevent LVH.

The mammalian target of rapamy cin (mTOR) plays a key role in regulating cell growth. Interestingly, rapamycin, a specific inhibitor of mTOR, has been shown to attenuate load-induced cardiac hypertrophy in mice [17]. Because rapamycin is a widely used immunosuppressant for solid organ transplantation, its early prescription might suppress cardiac hypertrophy in the transplant population. Obviously, future studies are required to clarify these aspects.

**Can diabetes influence cardiac growth?**

The present prevalence of diabetes at the time of transplantation is ~15–20% and approximately an additional 20% of patients develop this complication following RT [18]. Cardiac growth is associated with diabetes in both the general population and chronic kidney disease patients [19,20]. Although the mechanisms are not well understood, hyperglycaemia increases intracellular Ca$^{2+}$ and thereby stimulates LVH-related
Protein synthesis [21]. Moreover, advanced glycation end-products (AGEs) may play a key role in the pathogenesis of cardiomyopathy. Inhibition of AGE formation leads to attenuation of diabetes-associated cardiac abnormalities in rats, mainly via decreased collagen III gene and protein expression [22]. Therefore, it is plausible to assume that optimal metabolic control induces a marked reduction of LV mass in diabetic patients.

In keeping with this view point, a recent study in type 1 diabetes recipients revealed that pancreas transplantation led to significant regression of cardiac mass after optimal control of HbA1c levels during 6 months of follow-up [23]. Likewise, strict glycaemic control was associated with a significant LV mass reduction in type 2 diabetic patients [24]. Thus, close post-transplant monitoring of glycaemia or HbA1c levels should be a key objective in this population to minimize cardiovascular complications and to improve long-term outcome. The fact that higher survival rates have been observed in type 1 diabetic recipients of a simultaneous kidney–pancreas transplant compared with kidney transplant alone [25] further supports this argument.

Role of ACE gene polymorphism

Angiotensin II is a powerful stimulus for cardiac growth, and myocardial ACE activity depends, at least in part, on the ACE gene polymorphism. The ACE/DD genotype, which is associated with the highest tissue and plasma ACE levels, may be a major risk factor for LVH [26]. The trophic effect of angiotensin II may be more pronounced when the heart is under stress [27] or when the RAS system is also stimulated by other factors such as immunosuppressive therapy [13]. In other words, the ACE/DD genotype may play a permissive role in the development of LVH when the cardiac growth machinery is activated. Accordingly, the increased risk related to DD genotype has also been extended to renal transplant patients [28], which might explain the persistence of LVH in some patients following RT. Whether other RAS polymorphisms increase the risk of LVH in this population remains to be proven. In any case, these findings may be useful for targeting therapeutic interventions after RT.

Preventive and therapeutic options to minimize LVH

Given that patients with LVH are at increased risk of morbidity and mortality, early consideration of this complication may help prevent LVH-related cardiac events. There is consensus that echocardiography is the gold standard for diagnosing LVH. However, the ideal timing to perform serial echocardiographic studies in renal transplant recipients is not well known. LVH is common after RT and may be modifiable by antihypertensive treatment, as pointed out above. At present, therefore, it is reasonable to perform an echocardiogram to assess LV mass at the time of transplantation and, thereafter, once every 12–24 months. Undoubtedly, this allows an appropriate selection of antihypertensive therapy in order to minimize life-threatening complications.

Obviously, an optimal control of risk factors for LVH such as overweight, anaemia, arteriovenous fistula and blood pressure will lead to regression of cardiac hypertrophy and, consequently, a better outcome after RT. Whether the use of immunosuppressants such as rapamycin, new calcineurin inhibitors or steroid-free immunosuppressive protocols may also ameliorate cardiac outcome remains to be elucidated.

Brain natriuretic peptide (BNP) is a cardiac neurohormone predominantly released from the cardiac ventricle in response to LV volume expansion and pressure overload. Previous studies have suggested the usefulness of BNP as a marker of LVH and systolic dysfunction in both the general population and chronic kidney disease patients [29,30]. This may also be true for renal transplant recipients, but needs be confirmed in further studies.

In principle, all major classes of antihypertensive agents can cause LVH regression, but not to the same degree. There is evidence that ACEIs and ARAs provide the most pronounced reduction in cardiac mass, in part independently of their effects on blood pressure [4]. In addition, chronic AT1 receptor blockade with losartan is associated with regression of myocardial fibrosis [31], which is a common finding in renal patients. In this respect, several clinical trials have also demonstrated a similar clinical pattern in renal transplant patients who were treated with ACEIs or ARAs [32,33]. Interestingly, a greater reduction of cardiac mass was observed in kidney transplant recipients with the ACE/DD genotype compared with other genotypes (ID or II) [32].

Aldosterone has been shown to stimulate cardiac collagen synthesis and fibroblast proliferation via activation of local mineralocorticoid receptors, leading to excessive cardiac growth. Spironolactone, an aldosterone receptor antagonist, has been reported to reduce LV mass as well as BNP plasma levels [34]. Spironolactone might therefore be a good therapeutic option not only for LVH but also for congestive heart failure in renal transplant patients. Future studies are required to investigate the cardiac effects of this agent in the transplant population.

Lastly, it has been suggested that a more aggressive therapy or more selective usage of drugs that reverse LVH may lead to better outcome, since regression of LVH has been associated with an improvement in cardiovascular risk [35]. However, such a beneficial effect has not been proven yet in the transplant population. Undoubtedly, longer follow-up studies will provide better information on this issue.
LVH is common after RT and may contribute to high mortality. Although a variety of pathogenetic mechanisms have been proposed for this process, angiotensin II plays a key role for LVH. In addition, the ACE/DD genotype, which has the highest circulating and tissue ACE levels, has been associated with higher risk for LVH in renal transplant patients. Other risk factors related to RT include diabetes and immunosuppressive therapy which also may modulate cardiac architecture. Finally, antihypertensive therapy, mainly ACEIs or ARBs, significantly reduces LVH, but whether it also decreases mortality in transplant recipients is presently unknown.

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References
