Effects of kidney transplantation on cardiac morphology and function

Efeito do transplante renal na morfologia e função cardíaca

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ABSTRACT

Cardiac involvement is very frequent in patients with chronic kidney disease on dialysis. Kidney transplantation results in reducing morbidity and mortality compared to patients on dialysis. The objective of this review was to address the effect of renal transplantation in cardiac structure and function assessed by echocardiography. Since the 1980s, studies have demonstrated a trend towards improvement in cardiac parameters after kidney transplantation. With the improvement of the Doppler imaging methods, the new studies, although with conflicting results, demonstrated improvement in systolic and diastolic function and reduction of left ventricular mass, especially in the first two years after renal transplantation with stabilization of the parameters in subsequent years. Overall, the body of evidence has demonstrated significant impact of renal transplantation on left ventricular hypertrophy, systolic and diastolic function, but the results are not uniform.

Keywords: Kidney transplantation. Echocardiography, doppler. Hypertrophy, left ventricular. Chronic kidney disease. Ventricular function, left.

RESUMO

O envolvimento cardíaco é muito frequente nos portadores de doença renal crônica em diálise. O transplante renal resulta em redução da morbidade e mortalidade em relação aos pacientes em diálise. O objetivo desta revisão foi abordar o efeito do transplante renal na estrutura e função cardíaca avaliada pela ecodopplercardiografia. Desde a década de 1980, os estudos já demonstravam tendência à melhora nos parâmetros cardíacos após o transplante renal. Com a melhora dos métodos de imagens ao ecodopplercardiograma, os estudos, apesar de alguns resultados conflitantes, demonstravam melhora na função sistólica e diastólica e redução da massa ventricular esquerda, principalmente nos primeiros dois anos após o transplante renal com estabilização dos parâmetros nos anos subsequentes. De forma geral, o corpo das evidências tem demonstrado impacto importante do transplante renal na hipertrofia ventricular esquerda, função sistólica e diastólica, porém os resultados não são uniformes.

Palavras-chave: Transplante de rim. Ecocardiografia doppler. Hipertrofia ventricular esquerda. Insuficiência renal crônica. Função ventricular esquerda.

INTRODUCTION

Cardiac structural and functional impairment is very frequent in patients with chronic renal disease (CRD), chiefly those on dialysis. According to Foley *et al.*,[1] approximately 73.4% of CRD patients who are started on dialysis present left ventricle hypertrophy (LVH), 35.8% have left ventricle (LV) dilatation and 14.8% have reduced LV shortening fraction, cardiac abnormalities which are progressive, chiefly during the first year on dialysis.[2] Besides, impairment of diastolic function is also frequent in these patients,[3] progressing parallel to the increase of LV mass.[4]

With better surgical techniques and immunosuppressive therapy, renal transplantation is now considered standard treatment for patients with end-stage CRD, resulting in mortality reduction, compared with dialysis.[5] Recent data from the United State Renal Data System showed the gender and race-adjusted mortality rate for patients on dialysis to be 6.7 to 8 times higher than that for the general population, whereas mortality for transplanted patients with working grafts was 1.3 to 1.6 times higher than that of the general population.[6]

The aim of this review was to describe, based on the main published international studies, the effects of renal transplantation on cardiac structure and function, including the studies which used Doppler echocardiography to assess LV mass, as well as systolic and diastolic functions.

Role of Doppler echocardiography

Doppler echocardiography is a non-invasive, widely used technique to assess cardiac structure and function, through the reunion of several ultrasound techniques in a single examination. Traditionally, M and bi-dimensional modes allow assessment of the ventricular mass and volumes, with excellent accuracy for the diagnosis of LVH, definition of the geometric pattern (concentric remodeling, concentric or eccentric hypertrophy) and estimate of the systolic function (qualitatively or quantitatively). Furthermore, Doppler-derived techniques may generate indirect information about ventricular relaxation and its filling dynamic, which underlie the physiology of diastole.

In the past few years, Doppler echocardiography has markedly advanced, with new parameters and concepts used to assess LV systolic and diastolic functions. Modern quantitative methods of myocardial disease assessment, including the estimate of tissue velocity, have allowed identification of subclinical LV dysfunction.[7] Doppler tissue imaging, for example, allows real-time assessment of the longitudinal velocity inside the myocardium, with the use of pulsed Doppler, being less sensitive to pre-load changes, and turning out to be an important instrument for categorization of LV diastolic function.[8] In addition to information obtained from analysis of the Doppler tissue curve, the E/e' ratio (ratio between the amplitude of the E wave from the conventional pulsed Doppler curve and the amplitude of the e' wave from the Doppler tissue curve) has been useful for assessing LV diastolic function, once it maintains a direct relationship with the filling pressure of this chamber.[9] More recently, Rakhit *et al.*[10] demonstrated that the e' wave from tissue Doppler was an independent predictor of death and cardiovascular events in patients with CRD.

Tei[11] described a myocardial performance index that encompasses systolic and diastolic parameters, reflecting global heart function. A number of studies have demonstrated its clinical usefulness as a sensitive indicator of myocardial dysfunction severity[12,13] and prognostic predictor in several cardiac diseases.[14,15]

On the other hand, left atrium assessment, through conventional echocardiography, has been recently valued, as it has been widely demonstrated that it is important to diagnose the severity of LV diastolic dysfunction, which is known to reflect on the pressure and size of that chamber.[16] Likewise, a simple estimate of the left atrial volume has been demonstrated to have a good correlation with previously validated methods, such as computerized tomography.[17] Moreover, left atrial volume estimate has been an important predictor of cardiovascular disease in population studies.[18] When stage 5 CRD patients are specifically assessed, left atrial volume is an independent predictor of cardiovascular events.[19,20]

Structural and functional cardiac abnormalities after renal transplantation

Early investigations of post-transplantation cardiac abnormalities, using uni-dimensional echocardiography (M-mode), were published in the 1980 decade. In spite of the small samples involved, those studies already pointed to a trend towards decreased cardiac volumes after the procedure,[21] as well as improved parameters of systolic function[22] and early regression (three weeks) of LV mass index.[23] Specifically assessing a group of patients with juvenile diabetes, Larsson *et al.*[24] observed a significant 37% reduction of the ventricular mass, 44 months after renal transplantation, besides a reduction of the LV systolic and diastolic volumes, with consequent increase of the ejection fraction and better LV distensibility and filling patterns.

Yet, with the introduction of bi-dimensional echocardiography, more robust studies were published, with conflicting results. One of these, assessing more than 40 patients, showed a significant reduction of the ventricular mass and cardiac volumes, although without any impact on the diastolic function, about 18 months after renal transplantation.[25] At the same time, however, Hüting,[26] in a more prolonged follow-up study (> 40 months), assessing 24 patients on hemodialysis, could not demonstrate any reduction of the ventricular mass, in spite of having reported improved ejection fraction.

In spite of the technological breakthrough represented by the incorporation of Doppler into bi-dimensional echocardiography in the 1990 decade, conflicting results continued to be published. Peteiro *et al.*[27] demonstrated significant reduction of the LV mass and volumes, 10 months after renal transplantation, chiefly in the subgroup with better arterial pressure control, although without any impact on the systolic and diastolic functions. Two recent studies have also demonstrated significant cardiac alterations after renal transplantation. One, assessing 50 individuals before and 3 months after renal transplantation, demonstrated significant improvement of the ejection fraction and reduction of the chamber diameters.[28] Another retrospective study of 30 patients demonstrated significant reduction of LVH and diastolic dysfunction 1 year after renal transplantation.[29] A larger study, involving more than 100 patients, demonstrated reduction of the left ventricular mass index and of LV diastolic volume, during renal transplantation follow-up, in addition to normalization of the shortening fraction in the subgroup of patients with systolic dysfunction.[30] As for children, Alvares *et al.*[31] observed a trend towards reduction of chamber volumes and of ventricular mass, as well as improvement of the systolic function.

On the other hand, other studies have failed to demonstrate any cardiac alteration after renal transplantation. De Lima *et al.*[32] did not observe any significant reduction of ventricular hypertrophy, or any impact on LV systolic and diastolic functions during a 30-month follow-up after renal transplantation, another study even showing increased ventricular mass in the transplanted group, in comparison with patients on dialysis and controls without renal disease.[33] It is noteworthy, however, that the latter study compared independent groups, which might not have been homogeneous.

In studies of early evaluation after renal transplantation, reduction of the chamber volumes and improvement of the systolic function, without any impact on myocardial thickness have generally been demonstrated. Assessing 67 patients, 4 months after renal transplantation, McGregor *et al.*[34] observed an increase of the LV shortening fraction and reduction of its end-systolic diameter, without any significant alteration of the ventricular mass. Two studies, which evaluated a small number of transplanted patients through serial echocardiography, demonstrated early reduction of LV volumes and mass index up to three months after transplantation, without any additional alteration up to 1 year after the transplantation, and without any impact on myocardial thickness during the study period.[35,36] Those authors believed that reduction of the ventricular mass was associated with reduction of the ventricular diameter, chiefly due to improvement of volume overload which occured after renal transplantation, once there was no reduction of myocardial thickness.

Rigatto *et al.*[37] highlighted the fact that reductions of the LV mass and volume, which occur after renal transplantation, are generally restricted to the first 2 years, there being stabilization of these echocardiographic parameters in the third and fourth years after renal transplantation.

Evaluation of the diastolic function after renal transplantation became more accurate after the introduction of cardiac flow analysis with Doppler flow measurement. In the first study including only children and adolescents, in which transplanted patients were compared with those on dialysis, only the latter showed diastolic dysfunction. The same authors demonstrated an association between ventricular relaxation abnormality and overload, anemia and arteriovenous fistula (AVF).[38] More recently, Dudziak *et al.*[39] demonstrated progression of diastolic function after renal transplantation, during an average follow-up time of 30 months, observing an association between this deterioration and the use of cyclosporin.

With the use of tissue Doppler imaging, Oflaz *et al.*[40] demonstrated significant alterations in the biventricular diastolic function parameters among transplanted patients, compared with healthy individuals. A recent study involving children showed an increased E/e' ratio in those who had undergone renal transplantation (E/e' = 9.49) and those on peritoneal dialysis (E/e' = 11.9), compared with healthy children (E/e' = 8.0).[41] Although the E/e' ratio was higher in the renal transplantation group than in the healthy children, there was a significant difference in comparison with the peritoneal dialysis group. The only study which assessed the evolution of tissue Doppler imaging before and after renal transplantation showed a significant increase of the e' wave, from 5.6 to 6.5 cm/s, during a 4.2-year follow-up period.[10] Tissue Doppler imaging has shown an impact of renal transplantation on diastolic function, with improvement of the parameters.

LV systolic function may have sub-clinical alterations, below the threshold of the ejection fraction determination on Doppler echocardiography. Pirat *et al.*[42] demonstrated that the systolic indices of both ventricles, as assessed with tissue Doppler imaging, were similar in transplanted patients and controls, but increased in patients on dialysis. Mesocardial shortening fraction, measured in the ventricular wall middle segment thickness, is a more accurate assessment of myocardial performance in the presence of LVH. The prevalence rate of sub-clinical systolic dysfunction with this method was higher in children on hemodialysis and those with LVH, than in healthy children or transplanted ones.[43]

Factors responsible for cardiac alterations after renal transplantation

Factors associated with echocardiographic alterations after renal transplantation have not been clarified. Polymorphism of the angiotensin-converting enzyme (ACE) gene has been associated with LVH. Likewise, Hernandez *et al*.[44] demonstrated that patients with the DD genotype of the ACE gene, undergoing renal transplantation, did not show LVH reduction or improvement of their ejection fraction, compared with individuals with other genotypes, such as II and ID. It is thus possible that genetic factors may influence cardiac structural and functional alterations after renal transplantation.

The presence of an AVF is another factor that may influence the cardiac alterations after renal transplantation, chiefly LVH. A study of 20 transplanted patients, 4 months after closure of the AVF, observed reduction of the LV diastolic diameter and mass index, although the intensity of the AVF flow before the occlusion did not have an impact on the improvement of these parameters.[45] Unger *et al*.,[46] in a 21-month follow-up study after AVF closure, also demonstrated a significant reduction of the LV mass index, although with an increase of the relative thickness. This increased relative thickness, however, might be accounted for by a more marked reduction of the end-diastolic diameter than of the wall thickness. In a recent case-control study, Cridlig *et al*.[47] demonstrated that a patent AVF has a significant impact on LV mass and dimensions, in disagreement with the findings of Sheashaa *et al*.,[48] who did not observe any impact of spontaneous AVF closure on the evolution of LVH and systolic and diastolic functions.

Immunosuppressants, which represent a breakthrough in organ transplantation, may be associated with cardiac alterations after renal transplantation. In a recent study, which closely monitored the serum levels of cyclosporine, a lower prevalence of diastolic dysfunction at lower drug levels was demonstrated.[49] Paoletti *et al*.,[50] through a non-randomized, single center study, demonstrated that conversion from calcineurin inhibitor to sirolimus may favor LVH regression after renal transplantation, regardless of alterations in the arterial blood pressure.

Among other factors, possibly related to post-transplantation cardiac alterations, there is evidence that control of systolic blood pressure, preserved graft function (assessed through serum creatinine), [51,52] normal hemoglobin level, and adequate nocturnal systolic blood pressure fall[53] are also significantly associated with LVH regression. In children and adolescents, as well as in adults, post-transplantation LVH is independently associated with duration of pre-transplantation dialysis, anemia, and post-transplantation hypertension.[54,55] A recent study showed a significant and independent association between LVH persistence and the high incidence of clinical infections and chronic rejection.[56]

Conclusion

Cardiac alterations are highly prevalent in CRD individuals on dialysis. Echocardiography has an important role in the evaluation and follow-up of these individuals after renal transplantation.

In general, the body of evidence has demonstrated an important impact of renal transplantation on LVH and systolic and diastolic functions, although the results are not uniform. Other factors, such as genetic alterations, AVF, type of immunosuppressant, arterial blood pressure, anemia and graft function are likely to play a role in post-transplantation cardiac alterations, and may account for the conflicting results reported.

There is a need of well designed studies involving significant numbers of individuals, and with serial echocardiographic follow-up, using the new parameters (Doppler tissue imaging, myocardial performance index and left atrial volume), to better evaluate this population of renal transplantation patients.

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