Echocardiography in Chronic Kidney Disease: Diagnostic and Prognostic Implications

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Key Words

Echocardiographic evaluation · Chronic kidney disease · Myocardial pathy

Abstract

Most of the recent advances in the understanding of chronic kidney disease (CKD)-related cardiovascular disease have focused on atherosclerosis and arteriosclerosis, and much less effort has been dedicated to unveil and evaluate the mechanisms and impact of interventions related to myocardial dysfunction. Hence, echocardiographic evaluation plays a pivotal role in establishing the diagnosis of myocardial pathy as well as in stratifying risk and defining the impact of interventions. The aim of this review is to examine the profile of myocardial pathy in CKD, and to identify how the echocardiogram can be useful in diagnostic and prognostic clinical approaches.

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Introduction

Cardiovascular complications are the main cause of death in patients with chronic kidney disease (CKD) on renal replacement therapy [1]. Although many individuals starting dialysis treatment present some form of pre-existing cardiovascular disease (CVD), the traditional risk factors for CVD do not fully explain this increased risk, which appears to be influenced by non-traditional (inflammation and oxidative stress) and CKD-related (anemia, disorders of mineral metabolism) risk factors

[1]. The combination of these factors accelerates the progression of arterial disease and is associated with a greater prevalence of ventricular hypertrophy, myocardial fibrosis, valvopathy, arrhythmia, and sudden death [2].

Most of the recent advances in the understanding of CKD-related CVD have focused on atherosclerosis and arteriosclerosis, and much less effort has been dedicated to unveil and evaluate the mechanisms and the impact of interventions related to myocardial dysfunction. Hence, echocardiographic evaluation plays a pivotal role in establishing the diagnosis of myocardial pathy as well as in stratifying risk and defining the impact of interventions. The aim of this review is to examine the profile of myocardial pathy in CKD, and to identify how the echocardiogram can be useful in diagnostic and prognostic clinical approaches.

Characterization of CKD-Related Cardiomyopathy

Cardiomyopathy in hemodialysis (HD) patients is primarily due to the presence of a critical obstruction of coronary vessels, reduction of coronary reserve and/or microvascular alterations, and left ventricular (LV) morpho-functional alterations in response to the overload of pressure and volume [3]. In the absence of interventions that reduce LV overload, adaptation in the chamber is triggered, leading to an increase in cell death and myocardial fibrosis. As a consequence, there is a decrease in capillary density, diastolic dysfunction, and disturbances in intraventricular conduction, dilatation, and more compensatory hypertrophy [3]. Such phenomena predis-

pose to an increase in electric excitability, which is related to a greater incidence of sudden death in this group of patients [2].

It is known that clinical manifestation of cardiac failure represents an independent predictor of mortality in patients beginning HD treatment [4]; however, discerning the subjacent cause can be essential in defining the most efficient therapeutic approach. A few questions are relevant in the diagnosis and most importantly in the management of this high-risk population: is there simple volume overload or primary cardiac disease? In the presence of cardiomyopathy, is the systolic and/or diastolic function compromised? Can we estimate the LV filling pressure? In this context, the application of diagnostic methods of low relative cost and a good reproducibility can contribute significantly to the knowledge of the physiopathology of the disease and to the definition of potential strategies for treatment.

Importance of Doppler Echocardiography in CKD-Related CVD

The Doppler echocardiogram allows for the evaluation of ventricular mass and volume, and has an excellent accuracy for the detection of hypertrophy, definition of its geometric pattern (concentric or eccentric), and quantification of systolic function. In addition, Doppler-derived techniques can generate information regarding ventricular relaxation and its dynamics of filling, as well as concerning the presence of abnormalities in the cardiac valves and the pericardium. In a Canadian study following a cohort of 432 patients starting dialysis, only 16% presented a normal echocardiogram [5]. In this group of patients, the presence of hypertrophy, dilatation or systolic dysfunction can triple the risk of cardiac failure, independently of age, diabetes, or coronary disease [5]. In the following section, we will display specific cardiac alterations that can be detected by echocardiography and discuss their impact on morbidity and mortality in patients with CKD.

Left Ventricular Hypertrophy

LV hypertrophy (LVH) is highly prevalent in CKD and is associated with a clearly unfavorable prognosis; therefore, it is a major target for intervention. The incidence of LVH increases with a progressive decline in renal function [6]. Accordingly, the prevalence of LVH varies between 16 and 31% in individuals with CKD and a glomerular filtration rate of >30 ml/min, increases to 60–75% in those beginning renal replacement therapy, and

reaches 70–90% in patients on regular dialysis [4, 7, 8]. In this latter group, LVH is more frequent in those who are diabetic and in older subjects [9].

LV mass is proportional to body size and traditionally, indexing body surface was utilized for correction in classic studies. Different cutoff values were employed in several prospective studies in order to define the presence of LVH. For instance, Silberberg et al. [10] used a reference value of 125 g/m^2 , while Parfrey et al. [5] used the values employed in the Framingham study (132 g/m^2 for males and 100 g/m^2 for females). Despite this, studies presented similar results, demonstrating a clear effect of increased LV mass in an adverse prognosis [5, 10, 11]. However, an individual on HD is subject to large variations in body weight, be it an alteration of volemia or a compromised nutritional state, which can thus lead to erroneous evaluation by body surface indexation. A proposed indexation by height to the 2.7 power [12] appears to be the most accurate estimate of LV mass in this group of patients. Upon application of this concept in HD patients, it was possible to show that the method based on height has a slightly superior value for predicting general and cardiovascular mortality in comparison to that using body surface [13].

It is important to recognize that part of the alteration in the geometry of LV in CKD patients can be related to the moment at which the echocardiogram was performed. Shortly after the dialysis session, it is common to see a reduction in diastolic diameter of the LV and an increase in the thickness of the LV wall as a pure consequence of volume depletion by ultrafiltration. Similarly, the exam performed shortly before beginning the session can present a diagnosis of LV dilatation with eccentric hypertrophy that will be ‘converted’ into concentric at the end of the session. Such fluctuation can lead to incorrect evaluation that could be minimized by performing the echocardiogram during the interdialytic period [5].

The monitoring of mass by serial echocardiogram is an additional clinical tool of great importance in the evaluation of prognosis and success of interventions that result in regression of LVH [14]. Evidence indicates that progression of LVH in individuals with CKD is predictive of cardiovascular events, independent of basal values of LV mass. An increase in mass of $1 \text{ g/m}^{2.7}$ /month was associated with a 62% increase in the incident risk of fatal and non-fatal cardiovascular events in a study with dialysis patients [15]. This study suggested that changes in LV mass index represent a stronger predictor for mortality and cardiovascular complications than LV mass itself and that periodic echocardiographic studies may be useful in clinical practice. Another interesting study found

Fig. 1. Representative images of echocardiographic findings commonly observed in dialysis patients and associated with poor outcome. **a** Parasternal longitudinal view showing a pattern of concentric left ventricular hypertrophy. **b** Parasternal transversal view of the same patient. **c** Classic pattern of abnormal relaxation, pointing to a mild diastolic dysfunction (left: early (E) and late (A) diastolic mitral flow velocities showing inversion of the E/A ratio; right: early (E') and late (A') mitral annulus velocities confirming the abnormal relaxation). **d** Mitral annulus calcification. LV = Left ventricle; RV = right ventricle; AO = aorta; LA = left atrium.

that improvements in LV mass index and systolic function over a 1-year period after inception of dialysis therapy were associated with a subsequently reduced likelihood of cardiac failure, but not with less ischemic cardiac events and death [14]. On the other hand, London et al. [8] showed that intensive treatment of risk factors for LVH produces a clear regression in LV mass index and reduces all-cause and cardiovascular mortality (but this was a multifactorial intervention study, not an observational study, which better reflects the real world of everyday clinical practice). Whether the reversal of LVH is linked to a parallel decrease in major cardiovascular complications in the dialysis population (as it occurs in the general population) is still not completely elucidated. Therefore, it remains to be demonstrated that repeated LV mass measurements have an unquestionably favorable impact in the management of CKD.

Left Ventricular Systolic Dysfunction

In studies using different methodologies, the prevalence of systolic dysfunction of LV varies from 15 to 28% in patients on dialysis [7, 9, 16]. LV systolic dysfunction is a powerful indicator of unfavorable prognosis in patients on HD [11] as well as those in the post-renal transplant phase [7]. The analysis of systolic function by echocardiogram is usually performed by methods evaluating ejection phase, in particular the fractional shortening and

the ejection fraction. These techniques, based on measures taken in the endocardium, can overestimate the systolic function in patients with LVH. Alternatively, a method based on the measure of the myocardial midwall fractional shortening, proposed as a geometry-independent index of LV systolic function [17], can be employed in this context, diagnosing lower systolic performance in patients with normal ejection fraction. Despite these observations, LV systolic dysfunction, diagnosed by any of the previously cited methods, is independently associated with fatal and non-fatal cardiovascular events, and therefore does not demonstrate a difference in predictive power among the methods [18]. It is interesting to highlight that although the adverse effect of systolic dysfunction is independent of LV mass, these alterations interact in the prediction of cardiovascular outcome, reaching a maximum risk in patients with an association of both [18].

Left Ventricular Diastolic Dysfunction

Diastolic dysfunction is characterized by alterations in ventricular relaxation and compliance, frequently followed by a compensatory increase in filling pressure in more advanced stages. The latter phenomenon is usually responsible for the manifestation of cardiac failure, whatever the subjacent cause may be. Small studies have reported a prevalence of LV diastolic dysfunction in CKD patients varying from 50 to 65%, including pre-dialysis,

dialysis, and post-transplant populations [19]. Although alterations in LV filling are frequently detected in CKD patients, their prognostic impact is not well known for this group. Doppler parameters derived from mitral inflow are highly load dependent [20], and might have produced false-negative results in previous studies with HD patients (pseudonormalization of mitral flow being diagnosed as normal).

In recent years, tissue Doppler imaging (TDI) of mitral annulus or myocardial walls was introduced to the clinical setting as an important method of evaluation of segmental and global diastolic function. TDI-derived diastolic velocities (early E' and late A') are 'relatively' preload independent, without significant variation after 1 HD session, given that certain 'physiological' limits of volemic reduction were established (in other words, incapable of triggering alterations in heart rate and blood pressure) [20]. Consequently, E' (which is an index of relaxation) can be particularly useful for HD patients in differentiating pseudonormalization from the true normal profile of diastolic function [20]. A recent Australian study followed a cohort of 129 patients with end stage CKD (without evidence of LV ischemia on stress echocardiogram) for more than 2 years, demonstrating that E' added independent prognostic value to clinical parameters [21]. The ratio between early diastolic velocity of mitral flow (E) and E' (known as the E/E' ratio) was the best non-invasive predictor of elevated LV filling pressure in the comparison between multiple echocardiographic indices and final diastolic pressure (measured by hemodynamic catheter), using either septal E' [22] or a mean of septal and lateral E' [23]. In this manner, the E/E' ratio is of particular interest for diagnostics of advanced diastolic dysfunction, characterized by elevated intraventricular pressure. The possibility of estimating ventricular filling pressure by this method allowed, in parallel, for the demonstration of its prognostic importance in 2 recent studies [24, 25] in patients with CKD. A study with 125 transplant candidates demonstrated that an E/E' of >15 was an independent predictor of increased LV diastolic pressure (>15 mm Hg) and was associated with a greater general mortality in this group [24]. Another study with 220 CKD patients followed for 4 years concluded that an E/E' of >15 was an independent predictor of general and cardiovascular mortality, supplying prognostic information above and beyond clinical and biochemical data, ventricular mass, and systolic function.

Another form of evaluating diastolic function is the measurement of left atrial (LA) volume. In contrast to the Doppler-derived indices, which supply us with momentary and transitory information regarding the LV filling,

the LA volume acts as a chronic marker of diastolic function, reflecting the long-term effect of increased filling pressure. A study of HD patients in sinus rhythm without mitral valvopathy demonstrated that LA volume indexed for body surface of >35 ml/m² was the most accurate parameter for detection of pseudonormalization of mitral flow in comparison to several previously tested indices [25]. Broadening the clinical value of LA volume, 2 recent publications reported, utilizing different indexation methods (body surface [16] or height^{2.7} [26]), that this index was an independent predictor of mortality in patients on renal replacement therapy. The finding that an indexed LA volume of >32 ml/m² supplied information complementary to the clinical and traditional echocardiographic data, including ejection fraction, E/E' ratio and LV ventricular mass [16]. In parallel, a study of patients with advanced CKD found an independent association between LA volume and C-reactive protein, suggesting that inflammation may contribute to LA dilatation relation to increased risk [27]. Although new observational and interventional studies are necessary for validation of these findings and definition of the best method of indexation in renal patients, it is advisable that the assessment of LA volume is incorporated into the routine echocardiographic evaluation of these patients.

Summary and Conclusions

There is increasing evidence of the pivotal role of echocardiography in the improvement of quality of global clinical evaluation of advanced CKD patients. Current literature and clinical practice have emphasized the usefulness of the method for the diagnosis of clinical and subclinical cardiac dysfunction, the prediction of cardiovascular risk, and in the orientation and follow-up of treatment strategies. Guidelines recommend the echocardiogram for all dialysis patients 1–3 months after the start of renal replacement therapy and in intervals of 3 years subsequently, despite the symptoms [28]. Our opinion is also that all patients starting dialysis therapy should have a comprehensive echocardiogram; however, follow-up with serial studies at closer intervals of 12–18 months seems to add prognostic value [14, 15] and should be considered for most dialysis patients. In addition, we believe it is a reasonable approach to repeat an echocardiogram in each patient with changes in symptoms, new clinical event, or a treatment likely to affect cardiac function. The exam should be scheduled on a non-dialysis day (days between, not the longest day), preferably between 12 and 18 h [5].

As a final point, it is worth mentioning the value of cardiac biomarkers, such as troponin T and brain natriuretic peptide, which are useful for diagnostic and prognostic purposes in advanced CKD. Although they do not replace echocardiography, these surrogate markers may progress to play an adjunctive role to echocardiography

in assessing cardiovascular risk of CKD subjects [29]. In the future, new echocardiographic methods presenting investigative properties in subclinical myocardial disease could render an even greater benefit for these patients at high cardiovascular risk.

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Editorial Comment

M. El Nahas, Sheffield

The minireview by Pecoits-Filho and Barberato is an update on the role of echocardiography in defining risk and prognosis in CKD. Emphasis is on the range of structural and functional abnormalities detectable by echocardiography. The diagnostic and prognostic value of echocardiography is growing in end-stage renal disease. It also sheds light on the pathophysiology of the heart response to strain in uremia as LV hypertrophy in advanced CKD is often inappropriate and characterized by a simul-

taneous increase of LV wall thicknesses and diameters. Changes in left atrial size are also of prognostic significance. These changes may be reflected in the parallel increase in myocardial-derived circulating biomarkers such as troponin T and natriuretic peptides (BNP and NT-proBNP). Longitudinal intervention studies will show whether changes in myocardial geometry or the circulating levels of associated biomarkers affect CVD morbidity and mortality in end-stage renal disease.