Echocardiographic Alterations in Patients with Chronic Kidney Failure Undergoing Hemodialysis

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Abstract
Changes in cardiac structure and function detected by echocardiography are common in patients with chronic kidney disease undergoing hemodialysis, and have been recognized as key outcome predictors. This review attempts to summarize recent evidence pointing to the usefulness of the method in the detection of clinical and subclinical cardiac dysfunction, stratification of cardiovascular risk and assessment of intervention strategies.

Chronic Kidney Disease and Cardiopathy
Cardiovascular complications are the main cause of death in patients with chronic kidney disease (CKD) undergoing hemodialysis therapy. The cardiovascular mortality in these individuals is 10- to 20-fold more frequent than in the general population. Although more than 50% of the individuals starting a dialysis program present some type of pre-existent cardiovascular disease, the traditional risk factors for cardiovascular disease do not completely explain this excess risk, which seems to be influenced by the so-called non-traditional risk factors associated with CKD. This set of factors accelerates the course of coronary artery disease (CAD) and is associated with a higher prevalence of ventricular hypertrophy, myocardial fibrosis, valvulopathies, arrhythmias and sudden death. The cardiomiopathy of the patient undergoing dialysis is mainly due to the presence of ischemic cardiopathy (by critical obstruction of the coronaries, decrease in coronary reserve or microvascular alterations) and morphofunctional alterations of the left ventricle (LV) in response to pressure and volume overload. The physiopathology of the transformations induced by uremia in the left ventricular chamber is complex and multifactorial.

The volume overload originates from the hydro-saline retention, anemia and arteriovenous fistula, leading to LV eccentric hypertrophy (mass increase secondary to the increase in myocyte length and increase in the ventricular volume, with normal relative wall thickness). Anemia, in particular, deserves special attention in this group of patients. The association between anemia, congestive heart failure and kidney failure led Silverberg et al to propose the term “cardio-renal syndrome.” Affections of the heart and kidney can have a common etiology and the heart failure (HF) can lead to pre-renal uremia; subsequently, the decrease in the renal function can cause anemia, which leads to more cardiac damage. The correction of the hematocrit using erythropoietin generated clinical (improvement in the functional class and decrease in the need for diuretics) and morphophysiological benefits (improvement in the LV remodeling and function).

The overload of pressure can result from arterial hypertension, arteriosclerosis and, occasionally, aortic stenosis, causing LV concentric hypertrophy (increase in mass secondary to the increase in myocyte thickness, without significant alteration in the ventricular volume and increased relative thickness). In the absence of interventions that decrease the left ventricular overload, an impairment in the chamber adaptation occurs, with a consequent increase in cell death and myocardial fibrosis, which lead to capillary density decrease, diastolic dysfunction, intraventricular conduction disorders, dilatation and further compensatory hypertrophy.

Such phenomena predispose to ventricular remodeling by neurohumoral activation and increase in the electrical excitability, elements that are progressively associated to a higher incidence of sudden death in this group of patients. Even after optimized pharmacological treatment and coronary revascularization procedures, some patients undergoing hemodialysis die of sudden death, suggesting that other factors, in addition to myocardial ischemia, can have an important role in the triggering of lethal arrhythmias.

Potential substrates for the genesis of arrhythmias in this clinical scenario include metabolic alterations, systolic and/or diastolic dysfunction, LV hypertrophy and volume overload. In parallel, there is a displacement of LV pressure-volume curve to the left, meaning that small volume increases can trigger large pressure elevations, with clinical manifestations of congestive heart failure. The myocyte death induced by the combined injury of hemodynamic overload and risk factors inherent to uremia, such as anemia, hyperparathyroidism, malnutrition, oxidative stress, chronic inflammation and others, makes the prognosis poorer. Although the clinical diagnosis of heart failure (HF) can be attained with relative safety, the interpretation of clinical signs is a problem in the daily practice. It is known that clinically manifested HF represents the method in the detection of clinical and subclinical cardiac dysfunction, stratification of cardiovascular risk and assessment of intervention strategies.

Key Words
Echocardiography, Doppler; Renal Dialysis; Risk Assessment.

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complementary assessment methods, of relative low cost and with good reproducibility brings an important contribution to the development of knowledge of the physiopathology of the disease and the evaluation of potential treatment strategies.

The Role of Echocardiography

The diagnosis of LV abnormalities by Doppler echocardiography is an important step for the characterization of individuals with higher cardiovascular risk, estimating the prevalence of primary heart disease in a population to study its predisposing factors, prognostic impact and the effect of therapeutic interventions. The Doppler echocardiogram is a complementary, non-invasive examination, broadly used in the assessment of heart structure and function, bringing several ultra-sound techniques together in a single examination.

Traditionally, the M-mode and the two-dimensional Doppler echocardiogram allow the assessment of ventricular mass and volumes, with excellent accuracy for the diagnosis of hypertrophy, definition of its geometric pattern (concentric or eccentric) and systolic function estimate (qualitative or quantitatively). Additionally, the techniques derived from the Doppler can generate indirect information regarding the ventricular relaxation and its filling dynamics, which constitute the physiology of diastole. A Canadian study that followed a cohort of 432 patients starting hemodialysis therapy showed that only 16% had a normal Doppler echocardiogram. The finding of echocardiographic alterations, such as hypertrophy, dilatation and systolic dysfunction triples the risk of HF, regardless of age, diabetes and coronary failure.

Left Ventricular Hypertrophy

The left ventricular hypertrophy (LVH) is highly prevalent in CKD and is associated to a clearly unfavorable prognosis. More than 2/3 of the patients undergoing dialysis with LVH die of congestive heart failure or sudden death, which is the reason why it is one of the main targets of therapeutic intervention, together with coronary artery disease.

The incidence of LVH increases with the progressive decline in renal function, with an inverse linear correlation between the LV mass and the glomerular filtration rate. Thus, the prevalence of LVH varies from 16-31% in individuals with CKD and glomerular filtration > 30 ml/min., from 38-45% in those with more compromised renal function, from 60-75% in those starting renal substitution therapy, and up to 70-90% in patients undergoing regular dialysis therapy.

The LV mass is proportional to body size and, traditionally, the indexation by body surface has been used for this correction in the classic studies. Different values of partition have been employed in several prospective studies to define the presence of LVH. As examples, Silverberg et al. used 125 g/m² as reference value, whereas Parfrey et al. used values employed by Framingham (132 g/m² for men and 100 g/m² for women). In spite of this variation, all had similar results, demonstrating the clear effect of increased ventricular mass in the adverse prognosis. However, the individual undergoing hemodialysis is subject to large body weight alterations, either caused by alterations in volemia or by the nutritional status impairment, which can lead to assessment errors based on the indexation by body surface. Thus, the indexation by height to the power of 2.7, proposed by de Simone et al., seems to be the most accurate to estimate LV mass in this group of patients. Applying this concept to patients undergoing hemodialysis, it was demonstrated that the method based on height has a slight superior value for the prediction of general and cardiovascular mortality than the one based on body surface. It is important to recognize that part of the alterations in the LV geometry in uremic patients might be related to the moment when the echocardiogram is performed. Soon after the hemodialysis session, a reduction in the LV diastolic diameter is common as well as increased wall thickness as the pure consequence of the volume depletion by ultrafiltration. Similarly, the assessment carried out right before the hemodialysis session can diagnose LV dilatation with eccentric hypertrophy, which will be “converted” to concentric at the end of the session. Such fluctuations can lead to evaluation errors, which can be minimized by performing the examination on interdialytic days (Tuesday or Thursday), preferably between 12 PM and 6 PM.

Although the LVH diagnosed at the echocardiogram is a universally acknowledged independent predictor of mortality, it is important to emphasize that this onus is attained after a period of at least two years of dialytic therapy. Additional stratification can be obtained through the categorization of the geometric pattern of the myocardial hypertrophy, that is, whether it is concentric or eccentric. A multicentric prospective study with a cohort of 432 patients starting hemodialysis showed a median time of survival of 48 months for patients with concentric LVH and 56 months for those with eccentric LVH.

The mass monitoring through seriate echocardiogram is an additional clinical tool of great importance for the assessment of prognosis and degree of success of interventions aiming at the regression of the LVH. Evidence indicates that the progression of LVH in individuals with CKD is predictive of cardiovascular events, regardless of the basal LV mass values. On the other hand, the regression of myocardial hypertrophy can be obtained with vigorous pharmacological treatment, especially with angiotensin-II converting enzyme inhibitors, resulting in the decrease in the number of cardiovascular events and longer survival.

Other LVH regression strategies in terminal CKD, such as the treatment with erythropoietin, restricted control of volemia by aggressive ultrafiltration and renal transplant can also have their effects monitored through echocardiography.

Left Ventricular Systolic Dysfunction

In studies using different methodologies, the prevalence of the LV systolic dysfunction varied from 15% to 18% in patients undergoing dialysis (starting the treatment or undergoing regular chronic therapy, respectively), reaching 28% in individuals assessed at the moment of the renal transplant. The LV systolic dysfunction is a powerful unfavorable prognostic indicator for individuals undergoing hemodialysis as well as for those submitted to renal transplant. The accountable mechanisms are multifactorial, including coronary failure, anemia, hyperparathyroidism, uremic toxins, malnutrition...
and prolonged hemodynamic overload. The analysis of the LV systolic function by the echocardiogram is performed annually, usually by methods that evaluate the ejection phase, especially the percentage of shortening and ejection fraction (EF). These techniques, based on measurements carried out in the endocardium, can overestimate the contractility in patients with LVT. Alternatively, a method based on the measurement of the myocardial wall shortening fraction, the midwall fractional shortening, proposed as a measurement of the systolic function regardless of the LV geometry, can be used in this context, diagnosing a lower systolic performance in individuals with normal EF.

In spite of such considerations, the LV systolic function diagnosed by any of the aforementioned methods was independently associated with fatal and non-fatal cardiovascular events, with no difference being demonstrated regarding the predictive power among them.

It is interesting to mention that, although the adverse effect of the systolic dysfunction is independent from the left ventricular mass, these alterations interact in the prediction of cardiovascular outcomes, with the maximal risk being reached by patients that present an association of both.

**Left Ventricular Diastolic Dysfunction**

The diastolic dysfunction is characterized by alterations in the ventricular relaxation and compliance, frequently coursing with a compensatory increase in the filling pressures at more advanced phases. From a hemodynamic point of view, the increase in the left intraventricular diastolic pressure is the phenomenon responsible for the manifestation of HF, whatever the underlying cause is. Studies of necropsies and experimental uremia pointed to the presence of specific diffuse intermyocardiac fibrosis in the heart of uremic individuals, not observed in hypertensive, non-nephropathic individuals, which could imply in electrical instability (predisposing to sudden death) and alterations in the diastolic properties of the myocardium (predisposing to the increase in the filling pressures). Among the physiological mechanisms related to prominent myocardial fibrosis, one can postulate the activation of humoral factors associated to hypertrophy (high plasma levels of angiotensin II, parathyroid hormone, endothelin, aldosterone and catecholamines) and the presence of underlying myocardial ischemia. The increase in the stiffness and the decrease in the relaxation (secondary to fibrosis) lead to the exacerbation of the volmic variation effects on the LV filling. Thus, even in patients with normal EF, a small increase in LV volume can generate pulmonary congestion, whereas the volmic depletion can induce the decrease in the chamber filling, causing arterial hypotension and hemodynamic instability.

Studies with small sample sizes reported a prevalence of LV diastolic dysfunction in uremic patients varying from 50 to 65%, including pre-dialysis populations, those undergoing dialysis and post-transplant ones. Although the alterations in LV filling are frequently detected in patients undergoing hemodialysis, the prevalence of diastolic dysfunction and its prognostic meaning are not completely known in this group.

The limitations of the use of Doppler echocardiographic parameters derived from the mitral transvalvular flow in previous studies are due to the fact that these parameters are highly dependent on the pre-load conditions. Such approach can produce false-negative results in patients undergoing hemodialysis, diagnosing as normal individuals with a pseudonormalization of the mitral flow (high filling pressures masking the LV relaxation alterations).

In this context, the Doppler echocardiographic parameters employed in the assessment of cardiac function represent an important advancement regarding diagnosis. In the last years, the tissue Doppler (TD) of the mitral annulus was introduced in the clinical scenario as an important method of assessment of the LV diastolic function, segmental and global. The early diastolic velocity of the mitral annulus (E') is well correlated with the relaxation indices measured by invasive methods. Some researchers demonstrated that the diastolic velocities derived from the mitral annulus tissue Doppler (E' and A') are “relatively” independent from the pre-load, presenting no significant variation after a hemodialysis session, providing that certain “physiologic” limits of volmic decrease are respected, that is, that they are incapable of triggering alterations in the heart rate and arterial pressure. For that reason, E' seems to be particularly useful in patients undergoing hemodialysis, identifying relaxation alterations independent from the LV filling pressures and, consequently, differentiating the pseudonormalization from the actual normal pattern of diastolic function. A recent Australian study followed a cohort of 129 patients with terminal CKD (with no evidence of LV ischemia at the stress echocardiogram) for more than 2 years, demonstrating that the tissue diastolic velocity added an independent prognostic value to the clinical parameters. The ratio between the early diastolic velocity of the mitral flow (E) and E' (known as the E/E' ratio) was the best non-invasive predictor of increase in the filling pressures in the comparison of multiple Doppler echocardiographic indices with the final diastolic pressure (measured by hemodynamic catheter), either by using the septal E' or the mean between the septal and the lateral E'. Hence, the E/E' ratio is an especially interesting index for the diagnosis of advanced diastolic dysfunction. The possibility of indicating an increase in intraventricular pressure through this method allowed, in parallel, the demonstration of its important prognostic value in two recent studies with terminal CKD patients. A study carried out with 125 candidates to renal transplant demonstrated that the E/E' > 15 was an independent predictor of the increase in the LV diastolic pressure (> 15 mmHg) and was associated to a higher general mortality in this group.

Another study of 220 individuals with terminal CKD followed for 4 years, concluded that the E/E' ratio was an independent predictor of general and cardiovascular mortality, adding prognostic information above and beyond the clinical and biochemical data, ventricular mass and systolic function.
Left Atrial Dilatation

Strong evidence indicates the left atrium (LA) dilatation as a robust predictor of cardiovascular outcomes in the general population and in several clinical scenarios. Recent directives recommend that the adequate quantification of the LA size be obtained by the estimate of the chamber volume in the two-dimensional mode and not by the traditional measurement of the anteroposterior diameter in the M-mode. In addition to being superior in the prediction of cardiovascular events including atrial fibrillation, cerebrovascular accident, heart failure, myocardial infarction, and cardiac death, the LA volume is related to the severity and duration of the LV diastolic dysfunction. Differently from the elevated indices derived from the conventional (mitral flow) or tissue Doppler (mitral annulus, which provide momentary and transient information on the left ventricular filling, the LA volume functions as a chronic marker of the diastolic function, reflecting the “historical” mean of the increased filling pressures. A recent study with hemodialysis patients in sinus rhythm and no mitral valvulopathy demonstrated that the LA volume indexed for body surface > 35 ml/m² was the most accurate parameter for the detection of pseudonormalization of the mitral flow in comparison with the several indices that were previously tested. Extending the clinical value of the LA, two recent publications, using different indexation methods (body surface or height to the power of 2.7), found that the index was an independent predictor of mortality in patients receiving substitutive renal therapy. The finding of the indexed LA volume > 32 ml/m² provided complementary information to the traditional clinical and echocardiographic data, including EF, E/E' ratio and left ventricular mass. Although new observational and interventional studies are needed to validate these findings and to define the best indexation method in patients with nephropathies, it is advisable that the measurement of the LA be incorporated to the routine echocardiographic assessment of these patients, considering that the consensus of the American Society of Echocardiography recommends it for the general population.

As the LV diastolic function seems to be chronically compromised in most patients undergoing hemodialysis, even in those who are asymptomatic, the LA volume can offer the opportunity to identify the individuals at higher risk to present HF, atrial arrhythmias and poor clinical evolution.

Valvular Calcifications

The calcification of cardiac valves is frequent in patients chronically treated with dialysis. Some data suggest that the valvular calcification is not only a consequence of natural aging and calcium-phosphorus metabolism disorders, but also caused by inflammation, similar to what is seen in atherosclerosis. In addition to presenting a clinical effect by determining valvular stenosis and/or reflux, its importance lies in the association that has been reported between the valvular calcification and higher risk of mortality and cardiovascular events in the uremic patient. A study carried out in 192 patients undergoing peritoneal dialysis found calcification in at least one valve, mitral or aortic, in 32% of the population. After a mean follow-up of 18 months, the cardiovascular mortality was 22% versus 3% in individuals with and without valvular calcification, respectively. Such association was independent from the usual clinical and demographic variables, C-reactive protein and concomitant atherosclerotic vascular disease.

Another interesting study proposed a score for prognosis prediction after renal transplant based on the echocardiogram. After the follow-up of 203 transplanted patients (mean age 47 ± 12 years, 93% undergoing dialysis), independent predictors of mortality were age ≥ 50 years, LV systolic dimension ≥ 35 mm, wall thickness ≥ 14 mm and presence of calcification in the mitral annulus. Patients aged ≥ 50 years and two of the other three predictors had a 5-year mortality of 82%. In contrast to these findings, a study carried out with 202 patients undergoing hemodialysis (with a prevalence of 23% of valvular calcification) did not demonstrate an independent prognostic value after adjustment for risk factors and LV mass.

Pericardial Disease

Acute pericarditis can occur in approximately 20% of the uremic patients, before the start of dialysis or during the chronic dialysis treatment. Uremia and/or inefficient dialysis are the most frequent causes. Individuals undergoing maintenance hemodialysis with significant pericardial effusion usually do not respond satisfactorily to the intensification of the dialysis and may be referred to early elective pericardial drainage with the objective of preventing hemodynamic complications. Constrictive pericarditis occurs less frequently in patients undergoing hemodialysis.

Stress Echocardiography

The use of pharmacological stress echocardiography in patients with terminal CKD is an attractive strategy, as it allows the assessment of myocardial ischemia without demanding from the patient the capacity to exercise and, moreover, it provides the estimate of the LV basal systolic function. Furthermore, the presence and extension of the ischemia during the assessment have a prognostic value that is independent for general mortality in this group of individuals. A larger volume of evidence was generated with the use of dobutamine as the stressor agent. The set of available information does not indicate significant differences in accuracy and negative predictive value in comparison to Nuclear Medicine when assessing obstructive coronary disease in candidates to renal transplant (including those undergoing dialysis). Alternatively, two small studies suggested the usefulness of the stress echocardiogram with dipyridamole in the diagnosis of ischemia and the prognosis prediction. Although patients with CKD and normal stress echocardiogram results have a better prognosis than those with abnormal results, the mortality rate remains considerable in the first group, when compared to the excellent prognosis conferred by the normal test results in the general population. This can be explained by the high-risk profile inherent to the individual with nephropathy. Moreover, a national study showed that the assessment has a limited sensitivity in the presence of coronary uniarterial disease and obstructions between 50 and 70% of the vessel lumen. Thus, an individualized approach must be considered in individuals.
at higher risk, as the coronary angiography can still be of crucial importance in the detection of clinically relevant coronary artery disease.

**Conclusion**

The set of evidence indicates the extraordinary role of the Doppler echocardiography in the improvement of the global clinical assessment quality of the patient with CKD undergoing dialysis. The literature and the clinical practice have emphasized the usefulness of the method in the diagnosis of subclinical heart dysfunction, in the refinement of the clinical diagnosis of heart failure, in the cardiovascular risk prediction and when establishing the course and follow-up of the treatment strategies. The Doppler echocardiographic outcomes have shown to be useful substitute markers for prognosis and intervention studies. North-American directives recommend the Doppler echocardiogram for all patients undergoing dialysis one to three months after the start of the substitutive renal therapy and at three-year intervals subsequently, regardless of symptoms. Our opinion is that all patients initiating dialytic therapy must be submitted to an echocardiogram. However, shorter intervals between evaluations can be of clinical value in individualized therapies. It has been demonstrated that the follow-up with seriate echocardiograms adds prognostic value beyond the basal assessment, enabling the monitoring of the regression or not of the LV alterations. In the future, new Doppler echocardiographic methods with the capacity to investigate subclinical myocardial disease (such as strain, strain rate and ultrasonic tissue characterization) will further benefit this group of patients at excessive cardiovascular risk.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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**Referências**


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