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Diastolic dysfunction in end-stage renal disease patients

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Abstract

Cardiovascular disease is a significant cause of mortality and morbidity among patients with chronic kidney disease (CKD). CKD patients have a high burden of risk factors that are closely related to accelerated atherosclerosis, left ventricular (LV) systolic dysfunction, hypertrophy and dilatation, and high LV filling pressure. Left ventricular (LV) diastolic dysfunction in CKD patients frequently leads to the development of congestive heart failure and contributes to significant mortality and adverse clinical outcomes in CKD patients. Early identification of the diastolic dysfunction by echocardiography, before the onset of clinical heart failure, and intervention in CKD patients can lead to improved outcomes and can help in developing strategic treatments and in choosing patients most likely to benefit from these strategies. This review examines the diastolic dysfunction in end-stage renal disease patients, the underlying pathophysiological process, the risk factors, the diagnosis of diastolic dysfunction and the treatment options.

Keywords: diastolic dysfunction; end-stage renal disease; ESRD; echocardiography

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1. Introduction

Cardiovascular disease is a significant cause of mortality and morbidity among patients with CKD. Atherosclerosis, left ventricular (LV) systolic dysfunction, hypertrophy and dilatation, high LV filling pressure and LV diastolic dysfunction are the most frequent cardiovascular abnormalities in CKD patients.[1] These abnormalities may result from different mechanisms such as sodium and water retention, anemia, volume and pressure overload, uremia and hyperparathyroidism.[1,2] Primary disorders of the cardiac and renal system cause deterioration in each other via direct or indirect injuries through several complex mechanisms (cardiorenal syndrome).[2]

LV diastolic dysfunction affects mortality and morbidity in patients with CKD, and echocardiography enables the evaluation of the diastolic stiffness of the ventricle. The essential variables are the transmitral pulsed wave Doppler flow and the mitral annular tissue Doppler signal.[3,4] During diastole, transmitral Doppler flow can be categorized into four stages: isovolumic relaxation time (IVRT), early filling phase (E), diastasis, and atrial contraction. The ratio of E/e' is the most vital prognosticator in most cardiovascular disorders, including both systolic and diastolic heart failure, LV hypertrophy, myocardial infarction, cardiomyopathy, and subclinical myocardial diseases.[5] The E/e' ratio can predict mortality and cardiovascular events in CKD patients with diastolic dysfunction.[5]

2. Pathophysiology of diastolic dysfunction

The majority of patients with diastolic dysfunction exhibit abnormal active myocardial relaxation and passive ventricular stiffness that contributes to abnormal ventricular filling in diastole and shifts the normal ventricular pressure-volume curve upward and to the left, thereby resulting in a higher LV filling pressure for any given filling volume.[6] Additionally, neurohormonal mediated increases in venous tone and systemic arterial pressure may contribute to shifting blood to the central circulation and thereby further increase LV filling pressure.

When LV diastolic function is impaired, cardiac output is reduced, because the LV is not filled enough in diastole due to LV inflow obstruction. By contrast, to compensate for reduced cardiac output, increasing the inflow pressure to the LV and consequently, LV end-diastolic pressure becomes necessary, and that in turn increases left atrial pressure. As a result, LV dysfunction tends to cause pulmonary congestion.[7]

The end-systolic pressure-volume relationship is the same as a normal heart in diastolic heart failure (HF), but the end-diastolic pressure-volume relationship shifts upwards and leads to an increase in LV end-diastolic pressure.[7] When a sudden increase in blood pressure occurs in pathologies with diastolic dysfunction, the pressure-volume loop shifts to the upper right without decrease of the absolute index of contractibility. Therefore, pulmonary congestion is induced as a result of the significant increase in LV end-diastolic pressure.[7]

3. Echocardiography

Echocardiography provides a non-invasive assessment of cardiac function and structures. There is limited data on echocardiographic parameters predicting cardiovascular complications in patients with advanced CKD, including those who have not commenced dialysis.[6-9] In accordance with the European Society of Cardiology guidelines, the diagnosis of diastolic HF requires the following: (i) signs or symptoms of heart failure; (ii) normal or mildly abnormal LV systolic function (EF > 50%) and (iii) evidence of diastolic dysfunction.[10] Diastolic dysfunction can be graded as follows according to the diastolic filling pattern (**Table 1**). The grading of diastolic dysfunction and filling pattern is based on the mitral inflow, the mitral annulus velocity, the pulmonary vein velocity, and the color M-mode of mitral inflow.[11,12]

In grade 1 diastolic dysfunction (impaired myocardial relaxation), the E/A ratio is < 0.8, with a prolonged deceleration time (DT) (> 240ms). In the tissue Doppler assessment, e' is reduced with a resultant E/e' ratio (septal) <8, suggesting a normal LA pressure. The D-wave of the pulmonary venous

Table 1. **Grading scheme for diastolic dysfunction**[11,12]

	Normal	Grade I	Grade II	Grade III
E/A ratio	0.8–2.0	<0.8	0.8–2.0	≥2
e' (cm/sec)	>8	<8	<8	<8
E/e' ratio	<8	≤8	9–12	≥13
LAVi (ml/m2)	<28	<34	≥34	>34

Table 1. Grading scheme for diastolic dysfunction11,12

A: atrial mitral flow velocity, e': early mitral annulus velocity, E: early mitral flow velocity, LAVi: left atrium volume index

inflow is smaller than the S wave, and the atrial reversal (AR) wave is normal.[11,12]

In grade 2 diastolic dysfunction (pseudonormal pattern), when diastolic LV function deteriorates, LV compliance progressively decreases, and there is an increase in left atrial pressure and the diastolic filling pressure. The transmitral E wave velocity progressively increases, and the DT decreases. The pseudonormal pattern resembles a normal filling pattern. The E/A ratio is between 0.8 and 2.0, and the DT is between 160 and 240msec. This pseudonormal pattern is a transition pattern from impaired relaxation to restrictive filling and is a result of a moderately increased left atrial pressure superimposed on a relaxation abnormality. The following clues help distinguish this pattern from a normal filling pattern. The E/e' ratio (septal) is > 15 and the pulmonary venous flow AR is > 25cm/sec and longer than transmitral A wave.[11,12]

In grade 3 and 4 diastolic dysfunction (restrictive pattern), due to more severe diastolic dysfunction, the LV compliance reduces, and the left atrial pressure rises. The low compliance of the LV causes a rapid increase in the early LV pressure and a shortened inflow and DT. The E/A ratio is > 2. DT is < 160ms. The high left atrial pressure manifests as an E/e' ratio >15 at the septal annulus. The forward diastolic pulmonary vein flow stops in mid-late diastole, and during atrial contraction, there is a significant flow reversal.[11,12]

Diastolic HF is responsible for nearly half of HF hospitalizations and is seen more often in the elderly and women due to hypertension and anemia.[7] Comorbidity rate of obesity, diabetes, and CKD in diastolic HF is high, but not particularly higher than in systolic HF.[7] In general, both diastolic and systolic HF exhibit distinctive subjective symptoms and objective findings of HF including dyspnea, malaise, and edema.[7] Symptoms of diastolic HF typically include dyspnea due to pulmonary congestion, shortness of breath, paroxysmal atrial fibrillation (AF), and rapidly developing dyspnea induced by tachycardia, all of which are typical initial symptoms.[7] By contrast, in systolic HF, symptoms and signs due to general malaise and organ hypoperfusion associated with decreased cardiac output are frequently seen.[7]

The main differences between diastolic and systolic HF are the presence of contractile dysfunction and left ventricular remodeling.[7] In systolic HF, progressive ventricular dilatation, or eccentric cardiac hypertrophy, can be observed. By contrast, diastolic HF exhibits concentric ventricular remodeling without dilatation. The use of tissue Doppler E/e' ratio (early mitral inflow peak velocity/early diastolic mitral annular velocity) is an established and accurate diastolic function index that is not affected by hemodynamic load.[7]

4. Cardiovascular disease and end-stage renal disease

The pathophysiology of cardiac disease in end-

stage renal disease (ESRD) is related to the interaction of multiple factors including hypertension, chronic volume overload, anemia, the presence of an arteriovenous fistula (AVF) in patients on hemodialysis, as well as metabolic factors such as hypoxia, acidosis, hypocalcemia and increased levels of parathyroid hormone.[13,14]

In CKD patients, because of systemic hypertension, volume overload, renal anemia, and the presence of an AVF with high-flow rates, wall thickness, LV systolic and diastolic diameters, and cardiac output are increased, and indirectly ejection fraction is decreased.[13,14]

Anemia causes a chronic increase in cardiac output and leads to diastolic dysfunction.[13,14] The normalization of anemia can significantly improve the quality of life and physical function.[13,14]

The pathogenesis of hypertension in CKD patients is multifactorial. Hypervolemia is considered a major pathogenetic factor and other factors such as increased catecholamine, vasopressin, endothelin, a disturbed hormone profile with an activated renin-angiotensin system, and decreased nitrous oxide activity seems to play a crucial role in the high incidence of hypertension in CKD patients.[13,14]

After creation of an AVF in CKD patients, because of the increase in sympathetic nervous system activity, heart rate, and stroke volume, and reduction in peripheral resistance, there is a 10-20% increase in cardiac output. The long-term effects of an AVF creation are left ventricular hypertrophy, high-output cardiac failure, myocardial ischemia, and venous stenosis.[13,14]

High serum phosphorus levels also contribute to the high rates of cardiovascular mortality among CKD patients.[13,14] Hyperphosphataemia leads to calcification (due to increased calcium-phosphate product and secondary hyperparathyroidism) of coronary plaques, cardiac valves and myocardial tissue and inflammation.[13,14] The association with increased cardiovascular mortality further underlines the importance of adequately controlling hyperphosphataemia.

Lipid abnormalities are common in CKD patients, but their prevalence varies widely depending on the cause and stage of CKD.[13,14] CKD-related lipid disorders mainly consist of increased serum triglyceride levels (due to an enhanced production and accumulation of triglyceride-rich lipoproteins, such as very low-density lipoproteins and intermediate-density lipoproteins), low high-density lipoprotein cholesterol levels, increased amounts of small low-density lipoproteins, increased plasma concentrations of lipoprotein(a), and a number of qualitative changes in apolipoprotein(b) that impair the metabolism of several lipoprotein classes and thus ultimately contribute to progressive atherosclerosis.[13,14]

There is growing evidence that inflammation probably plays an essential role in the initiation and progression of the atherosclerotic process. This is the reason why atherosclerosis has been consequently defined as 'an inflammatory disease'.[13,14] A high percentage of CKD patients have serological evidence of an activated inflammatory response due to multiple potential factors, including the decreased renal clearance of pro-inflammatory cytokines, the accumulation of advanced glycation end-products, co-morbidities, and other factors related to the dialytic procedure (such as membrane bio-incompatibility, vascular access infections, contaminated dialysate).[13,14]

Hyperhomocysteinemia, which is now widely recognized as an independent predictor of cardiovascular disease in the general population, increases inversely with the reduction in renal function, is present from the earliest stages of CKD and is prevalent in > 85% of ESRD patients.[13,14]

The increased number of oxidative stress markers in CKD patients, indicates that CKD is a pro-oxidant state.[13-16] Although many factors directly related to CKD such as age and diabetes, uremia, inflammation and hyperhomocysteinemia or dialysis (bio-incompatible membranes and endotoxin-contaminated dialysate) potentially contribute toward the development of an imbalance between antioxidant defense mechanisms and excessive generation of oxidants. The exact mechanisms leading to the genesis of oxidative stress in CKD patients are not known.[13-16]

Diastolic dysfunction is closely associated with

left ventricular hypertrophy (LVH). LVH is known to occur in > 70% of incident ESRD patients and increases the risk for cardiovascular event. LVH has been shown to be an important independent predictor of cardiovascular outcome in ESRD patients. Furthermore, the change in LVH has been revealed to be a strong prognostic factor in these patients.[15,16]

Premature atherosclerotic coronary artery disease is driven by multiple risk factors, including dyslipidemia and oxidative stress.[15,16] Morphological changes in the heart include left ventricular hypertrophy, advanced coronary atherosclerosis, microvascular disease, and diffuse interstitial myocardial fibrosis.[15,16] These abnormalities are common in CKD patients and have been shown to be predictive of mortality.[17,18] The assessment of diastolic function by echocardiography has shown a high incidence of abnormalities in dialysis and non-dialysis CKD patients.[19,20]

ESRD patients treated with hemodialysis, experience a variety of metabolic and hemodynamic disturbances that predispose to changes in LV systolic and diastolic function parameters. Increasing myocardial calcium level, lipid peroxides level, oxidative stress and decreasing antioxidants may affect LV myocardial functions and loading conditions.[21]

Diastolic dysfunction is an abnormality of relaxation, filling, or distensibility of the left ventricle that is associated with augmented cardiovascular mortality.[13]

Therefore, early identification of patients with LV diastolic dysfunction might help in developing treatment strategies and in choosing patients most likely to benefit from these strategies. Developing a strategy to minimize large volume shifts (treatment with a high-dose loop diuretic use, salt and water restriction, more frequent hemodialysis, continuous peritoneal dialysis) and identification of the exact dry weight, particularly in hemodialysis patients, are most important. Blood pressure control is important and has a beneficial effect on LVH in CKD and ESRD patients. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) demonstrate not only an effect on the blood pressure but elicit a direct effect on the myocardium via the local renin-angiotensin system.[22,23]

The prevention of the development of LV diastolic dysfunction can also improve outcome and reduce the incidence of cardiovascular death in dialysis patients.[22,23]

5. Conclusions

Left ventricular diastolic dysfunction is common in hospitalized CKD patients and clinicians should evaluate them for left ventricular diastolic dysfunction. Further studies are required, in order to understand whether early identification and management of CKD patients with left ventricular diastolic dysfunction can help in improving the outcomes of these patients.

Diastolic dysfunction is a common and potentially harmful clinical condition in ESRD patients, particularly in hemodialysis patients who are more susceptible to shifts in fluid volume.The reasons for this high prevalence are related to the presence of traditional risk factors and the synergistic effects of these factors related to ESRD status and dialysis treatment. The underrecognition of diastolic dysfunction in dialysis patients may be linked to the underuse of simple methods such as echocardiography. A broader recognition of diastolic dysfunction and the development of clinical trials to investigate beneficial treatments, which are approaching risk factors both already applied in the general population and those specific to ESRD patients, may allow a significant reduction in the mortality and morbidity of ESRD patients.

Conflict of Interest

All authors declare no conflict of interest.

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Περίληψη

Διαστολική δυσλειτουργία σε ασθενείς με τελικού σταδίου νεφρική νόσο

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Η καρδιαγγειακή νόσος είναι η σημαντικότερη αιτία θνητότητας και θνησιμότητητας μεταξύ των ασθενών με χρόνια νεφρική νόσο (ΧΝΝ). Οι ασθενείς με ΧΝΝ έχουν διάφορους προδιαθεσικούς παράγοντες που σχετίζονται στενά με αθηροσκλήρυνση, διάταση και υπερτροφία της αριστερής κοιλίας, συστολική δυσλειτουργία και υψηλές πιέσεις πληρώσεως της αριστερής κοιλίας. Η διαστολική δυσλειτουργία της αριστερής κοιλίας σε ασθενείς με ΧΝΝ συχνά οδηγεί σε συμφορητική καρδιακή ανεπάρκεια, αυξάνοντας σημαντικά τη θνητότητα. Η πρώιμη διάγνωση της διαστολικής δυσλειτουργίας με την ηχωκαρδιογραφία, πριν την εκδήλωση συμπτωμάτων καρδιακής ανεπάρκειας, καθώς και η πρώιμη αντιμετώπιση των ασθενών με ΧΝΝ μπορεί να βοηθήσει στην ανάπτυξη στρατηγικών και θεραπειών που θα οδηγήσουν σε καλύτερα αποτελέσματα. Το άρθρο μελετά τη διαστολική δυσλειτουργία σε τελικού σταδίου ασθενείς με νεφρική νόσο, την παθοφυσιολογία της διαστολικής δυσλειτουργίας, τους προδιαθεσικούς παράγοντες καθώς και τη διάγνωση και τις θεραπευτικές επιλογές.

Λέξεις ευρετηρίου: διαστολική δυσλειτουργία, τελικού σταδίου νεφρική νόσος, ΧΝΝ, ηχωκαρδιογραφία

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