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CKJ REVIEW

Diastolic function in chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) is characterized by clustered age-independent concentric left ventricular (LV) geometry, geometry-independent systolic dysfunction and age and heart rate–independent diastolic dysfunction. Concentric LV geometry is always associated with echocardiographic markers of abnormal LV relaxation and increased myocardial stiffness, two hallmarks of diastolic dysfunction. Non-haemodynamic mechanisms such as metabolic and electrolyte abnormalities, activation of biological pathways and chronic exposure to cytokine cascade and the myocardial macrophage system also impact myocardial structure and impair the architecture of the myocardial scaffold, producing and increasing reactive fibrosis and altering myocardial distensibility. This review addresses the pathophysiology of diastole in CKD and its relations with cardiac mechanics, haemodynamic loading, structural conditions, non-haemodynamic factors and metabolic characteristics. The three mechanisms of diastole will be examined: elastic recoil, active relaxation and passive distensibility and filling. Based on current evidence, we briefly provide methods for quantification of diastolic function and discuss whether diastolic dysfunction represents a distinct characteristic in CKD or a proxy of the severity of the cardiovascular condition, with the potential to be predicted by the general cardiovascular phenotype. Finally, the review discusses assessment of diastolic function in the context of CKD, with special emphasis on end-stage kidney disease, to indicate whether and when in-depth measurements might be helpful for clinical decision making in this context.

LAY SUMMARY

This review briefly explains mechanisms of diastole, i.e. the phase in the cardiac cycle when the left ventricle fills with blood to be pumped in the arterial system, providing nourishment to body organs and systems. The focus of the review is the analysis of alterations of diastole associated with chronic kidney disease and the causes underlying the abnormality of diastolic function. Thus, causes for those abnormalities are explained. The methods for measurements of diastolic abnormalities are briefly reported and indications are provided on whether assessment of diastolic function can benefit patient management.

Keywords: atrial fibrillation, chronic haemodialysis, heart failure, inflammation, left ventricular hypertrophy

INTRODUCTION

Ventricular diastole is the phase of the cardiac cycle when ventricular chambers fill with blood that is then pumped into the arterial tree during systole. Diastole begins physiologically when myocardial contraction ends and is conventionally set at the aortic valve closure [1]. Physiologically, the ability of the ventricles to increase chamber volume receiving blood from the atria

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depends on different physiological mechanisms interacting during the cardiac cycle, which for convenience will be examined one at the time. Whatever abnormality occurs in one of these mechanisms, during any phase of diastole, should be classified as diastolic dysfunction [2].

In the present review we will briefly address the pathophysiology of diastole and its relations with cardiac mechanics, haemodynamic loading and structural conditions, non-haemodynamic factors, metabolic characteristics, with specific attention on chronic kidney disease (CKD) in general and special focus on end-stage kidney disease (ESKD). We will also provide some methods of quantification of diastolic function. Additionally, we will discuss whether diastolic dysfunction represents a distinct characteristic in CKD or rather is a proxy for the severity of the cardiovascular condition, including abnormalities of chamber geometry, hypertrophy, myocardial mechanics, haemodynamic loading conditions and metabolic and electrolyte abnormalities. Finally, we will provide suggestions on whether and when assessment of diastolic function might be useful in CKD, to help in decision making.

Pathophysiology and assessment of left ventricular filling

The physiology of ventricular diastole can be divided into three mechanisms that are closely linked and overlap each other. Any abnormality of one or more of these mechanisms results in diastolic dysfunction.

Elastic recoil

The ventricle dissipates the potential energy accumulated during squeezing, through elastic recoil, beginning at the end of contraction. After contraction, during elastic recoil, the cardiomyocyte tends to resume its physical resting state. The magnitude of the elastic recoil strictly depends on the magnitude of systolic wall deformation, depending on the spatial orientation of cardiomyocytes, and their cross-fibre shortening/thickening interplay [3–5]. More than a pure marker of diastolic function, elastic recoil is an expression of global ventricular mechanics.

Elastic recoil can be measured using cardiovascular imaging techniques such as echocardiographic 3D strain imaging (speckle tracking) [6, 7] or cardiac magnetic resonance imaging (CMRI) [8, 9], by tagging deformation of speckles through the ventricular wall. These methods can visualize apical twisting and untwisting. Like almost all other measures of diastolic function, elastic recoil depends on loading conditions [3, 10].

A complete physiologic cardiomyocyte resting state is not sufficient to promote efficient ventricular filling, because a resting state occurs between the minimal end-systolic length and the maximal end-diastolic stretch, depending on the loading conditions and electrolyte balance between extra- and intracellular concentrations of sodium (Na^+), potassium (K^+), calcium (Ca^{++}) and magnesium (Mg^+). Thus cardiomyocytes need energy to actively force distention beyond the resting state to reach full diastolic distension.

Active relaxation

Most of diastole is in fact characterized by the active elongation of cardiomyocytes, an adenosine triphosphate (ATP)-dependent phase that needs energy expenditure to be implemented, because it relies on active pumping of Ca^{++} ions outside cardiomyocytes. A reduction of intracellular Ca^{++} concentration allows inhibition of the interaction of actin–myosin bridges, promoting left ventricular (LV) relaxation and chamber filling in diastole [11]. Conventionally, active relaxation begins right after aortic valve closure, although actually, contraction stops before end-ejection [12].

The very early phase of active relaxation occurs without changes in ventricular volume (isovolumetric relaxation), because, at the aortic valve closure, ventricular chamber pressure is still elevated (aortic diastolic pressure) and needs to decrease to equal the atrial pressure to allow mitral valve opening. The rapidity of this decay is an important marker of relaxation and can be estimated by calculating the ventricular relaxation time constant (τ). τ is ideally calculated by direct measure of LV pressure, but can also be estimated by a complex calculation from non-invasive procedures, giving reliable estimates [13]. τ is the only measure of relaxation that is independent of preload [13].

LV relaxation promotes ventricular filling, which starts when the mitral valve opens, initially taking advantage of the highest atrioventricular gradient (rapid filling; Fig. 1). Thereafter, chamber filling continues more slowly (slow filling; Fig. 1), promoted only in part by the residual persistent atrioventricular gradient and substantially limited by myocardial stiffness (see the next paragraph). It is intuitive that during slow filling, active relaxation strongly interacts with myocardial stiffness.

Relaxation-dependent LV filling predominates in normal hearts, and in young normal subjects, the atrioventricular gradient is low at the time of atrial contraction and, in normal conditions, LV filling can be completed at a low atrial pressure.

Passive late diastolic filling

The third mechanism influencing diastolic filling is related to the elasticity of the myocardium and its intrinsic distensibility. Myocardial compliance increases in importance once the atrioventricular gradient decreases during rapid filling. When myocardial stiffness increases, the decrease of the atrioventricular gradient is faster and atrial ejection force is reduced, due to the higher pressure in the ventricular chamber [14].

Both alteration of myocardial tissue composition and LV chamber remodelling are responsible for a decrease in LV compliance [15] that affects, in particular, the late part of diastole (passive filling). In an attempt to overcome myocardial rigidity and maintain LV filling, LV filling pressure increases, requiring increased atrial pressure. This pattern of LV filling is characteristic of restrictive physiology.

In restrictive physiology, the atrial contribution declines and most LV filling occurs during the first part of diastole, before equalization of atrial and ventricular pressure, which occurs very rapidly due to decreased myocardial distensibility. In addition to increased myocardial stiffness, extrinsic factors also play a role in reduced LV chamber compliance, such as pericardial function, intrathoracic pressure and left to right ventricular interaction [16].

Increased LV filling pressure, particularly LV end-diastolic pressure (LVEDP), always indicates heart failure (HF), but the development of high LVEDP is different in systolic or diastolic HF (Fig. 2) [17]. In systolic HF the normal relation between filling pressure and increasing diastolic volume does not change, because LV chamber volume increases with increasing LV filling pressure, with a consistent decline in LV distensibility, parallel to the volume increase. In diastolic HF, an increase in LV filling pressure is not accompanied by ‘normal’ increasing chamber volume, due to increased myocardial stiffness. However, at end-diastole, LVEDP is increased in either situation (Fig. 2). Thus, HF is invariably characterized by increased LVEDP, diastolic

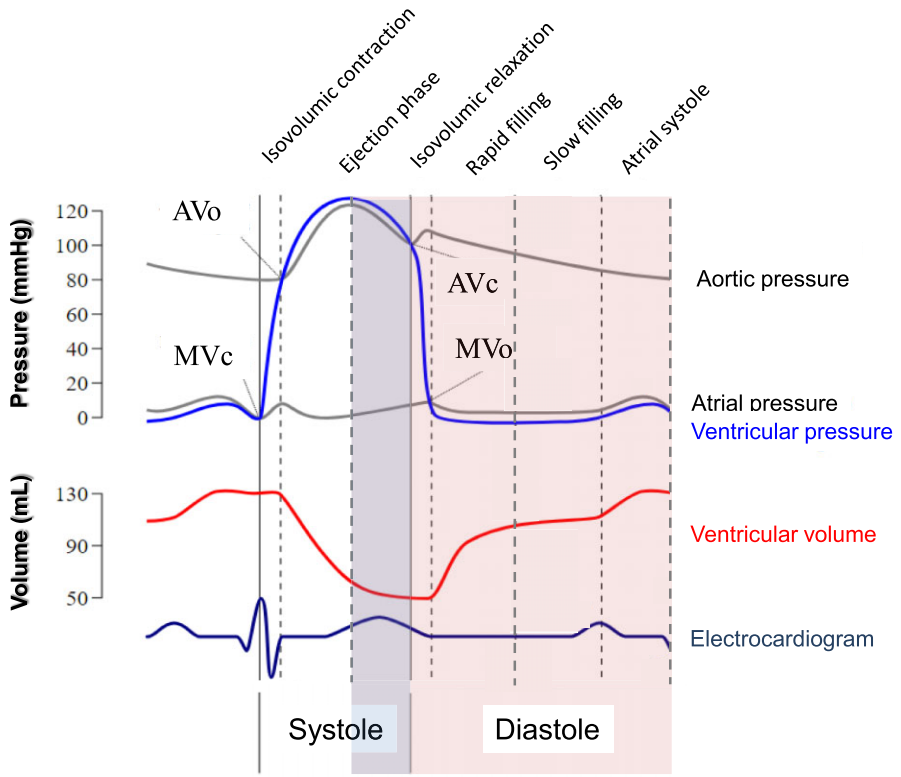

Figure 1: Pressure–volume phases of the cardiac cycle, from isovolumetric contraction to atrial systole. Diastole is represented as the pink area, beginning at the aortic valve closure (AVc). The grey area is the transition between the peak pressure and the beginning of diastole, when contractility gives way to elastic recoil, which ends at mitral valve opening (MVo). MVc: mitral valve closure; AVo: aortic valve opening.

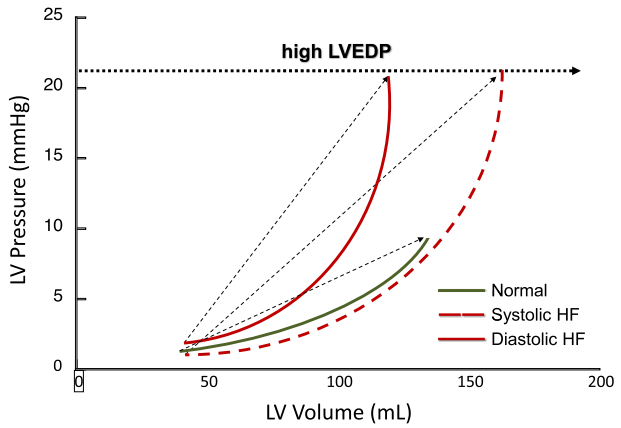

Figure 2: Magnification of the diastolic pressure–volume relationship in normal conditions (green line), systolic HF (dashed red line) and diastolic HF (continuous red line). Tiny dotted black lines indicate progression to LVEDP. Tick dotted line indicates LVEDP.

dysfunction is always present and the normal paradigm of considering diastolic HF as a sort of special condition should be changed, because HF occurs in every condition in which LV filling needed to sustain stroke volume is achieved by a marked increase in filling pressure, irrespective of LV systolic dysfunction.

The best way to assess restrictive physiology is through the ventricular pressure/volume loop (as shown in Fig. 2), which is obtained invasively. However, we have developed, and externally validated, a model to estimate the pressure–volume loop non-invasively, which might be useful to explore pump mechanics [18].

LV filling pressure can be estimated by the ratio between transmitral E velocity and tissue Doppler E′ velocity recorded at the mitral annulus. There are equations that can help in estimating LV filling pressure in different conditions [19, 20], which might be useful in the presence of signs and symptoms of HF, especially when ejection fraction is about normal.

Eventually, diastolic dysfunction occurs every time active relaxation is inappropriate and/or chamber stiffness is increased, requiring a higher pressure to fill properly.

Left atrium

Every abnormality of LV filling rapidly impacts on left atrial (LA) dimensions and function, because the LA is extremely sensitive to changes in pressure, due to its thin wall thickness. Wall stress in the LA (i.e. the ratio between wall tension and wall thickness) is strictly dependent on wall tension (i.e. the product of LA chamber pressure and volume). Accordingly, in the absence of significant mitral regurgitation, LA dilatation would be the hallmark of any abnormalities related to atrial emptying, characterizing diastolic dysfunction [21].

A limitation for the simple use of LA volume as a marker of diastolic dysfunction is the routine indexing of the value for body surface area. This estimation of body size, based on geometrically inconsistent assumptions [22], is in general misleading [23]. This is especially true in conditions such as CKD, which is associated with rapid changes in total body water and body

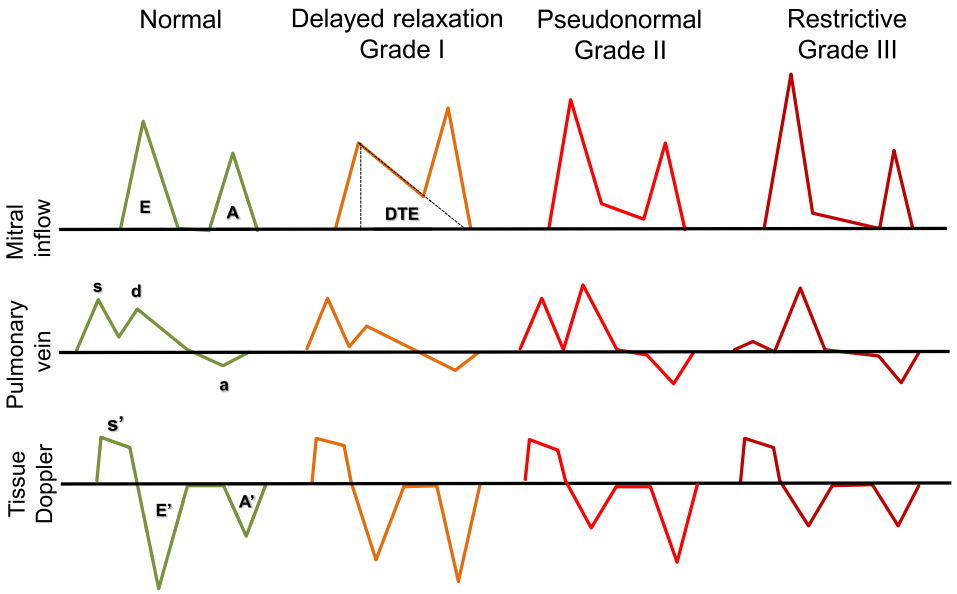

Figure 3: Grading of diastolic dysfunction base on schematic Doppler spectral characteristics of LV filling pattern at the level of mitral valve inflow, pulmonary vein and tissue Doppler of the mitral annulus. Grading is determined by the level of LV filling pressure. E: transmitral early diastolic velocity; A: transmitral late diastolic velocity; DTE: deceleration time of peak E velocity; s: pulmonary vein peak systolic velocity; d: pulmonary vein peak diastolic velocity; a: pulmonary vein velocity at the atrial systole; s′: tissue Doppler systolic velocity; E′: tissue Doppler early diastolic velocity; A′: tissue Doppler late diastolic velocity.

weight, as well as with abnormalities of the balance between intra- and extracellular water content [24]. Unfortunately, there is no consolidated indication on allometric normalization of LA volume like what has been done for LV mass, except an indication from an epidemiological study suggesting normalization of LA volume for the square of height [25, 26]. Thus, in the absence of externally validated cut-offs for LA volume normalized for body size, if needed, LA volume is better used as a raw value, especially for within-patient comparison.

Measurements of diastolic function

Doppler echocardiographic interrogation of mitral and aortic flow velocities, together with pulmonary vein flow and tissue Doppler of the mitral annulus, provides several parameters associated with diastolic dysfunction (Fig. 3) [27, 28]. However, flow measures are very sensitive to loading conditions [29, 30], in addition to age and heart rate [31]. The most used measures are:

- The time between aortic valve closure and mitral valve opening, when LV internal volume remains unchanged [isovolumetric relaxation time (IVRT)]. Prolonged IVRT is an important sign of delayed relaxation. Similarly, short IVRT might be the sign of increased LA pressure, but many confounders should be considered [32].
- The ratio of mitral inflow early peak velocity (E) to the late peak velocity, induced by atrial systole (A), measurable at the level of the mitral valve leaflet (E/A ratio). When relaxation is impaired, the atrial contribution to complete LV filling is greater (Fig. 3; grade I diastolic dysfunction). In contrast, when LV filling pressure increases, the LA contribution progressively decreases, initially simulating a normal flow pattern (grade II, pseudonormal filling pattern). Eventually, participation to completeness of LV filling can become almost irrelevant when LV filling pressure is high (grade III, restrictive filling pattern). The difference between normal and grade II cannot be appreciated at the mitral level, while it is evident comparing tissue Doppler of the mitral annulus and the pulmonary vein flow pattern (Fig. 3).
- Deceleration time of transmitral E velocity (DTE). Impaired relaxation implies slower LV filling and therefore prolongation of DTE (Fig. 3). In contrast, when LV filling pressure increases, DTE becomes progressively shorter. The LV filling pattern is defined as restrictive (Fig. 3) when a prominent E-velocity is present together with rapid DTE, short IVRT and disproportionately low tissue Doppler E′ velocity.
- The ratio of DTE to peak E velocity (DTE index) is a more precise estimate than unadjusted DTE [33].

For an extensive review of methods to assess diastolic function, refer to the 2016 combined European and American guidelines [2].

Assessment of diastolic dysfunction by CMRI is not yet a clinical routine. CMRI is a gold standard approach for the accurate assessment of biventricular function, ventricular geometry and mass, valvular pathologies, pericardial effusion, and myocardial structure, including localization and quantification of myocardial scars and inflammation. Like Doppler echocardiography, CMRI is also able to quantify transmitral flow using phase contrast imaging techniques and has been demonstrated to be a useful tool to identify patients with diastolic dysfunction [34, 35]. However, CMRI for the assessment of diastolic dysfunction is far from being a routine exam in clinical practice, due to the cost, availability and lack of clear advantages compared with Doppler echocardiography.

CKD and diastolic dysfunction

Diastolic dysfunction is a CKD characteristic, even in the early stages [36]. In patients with CKD, the complex haemodynamic and neurohormonal interplay between the heart and kidney is directly involved in diastolic dysfunction [37, 38]. However,

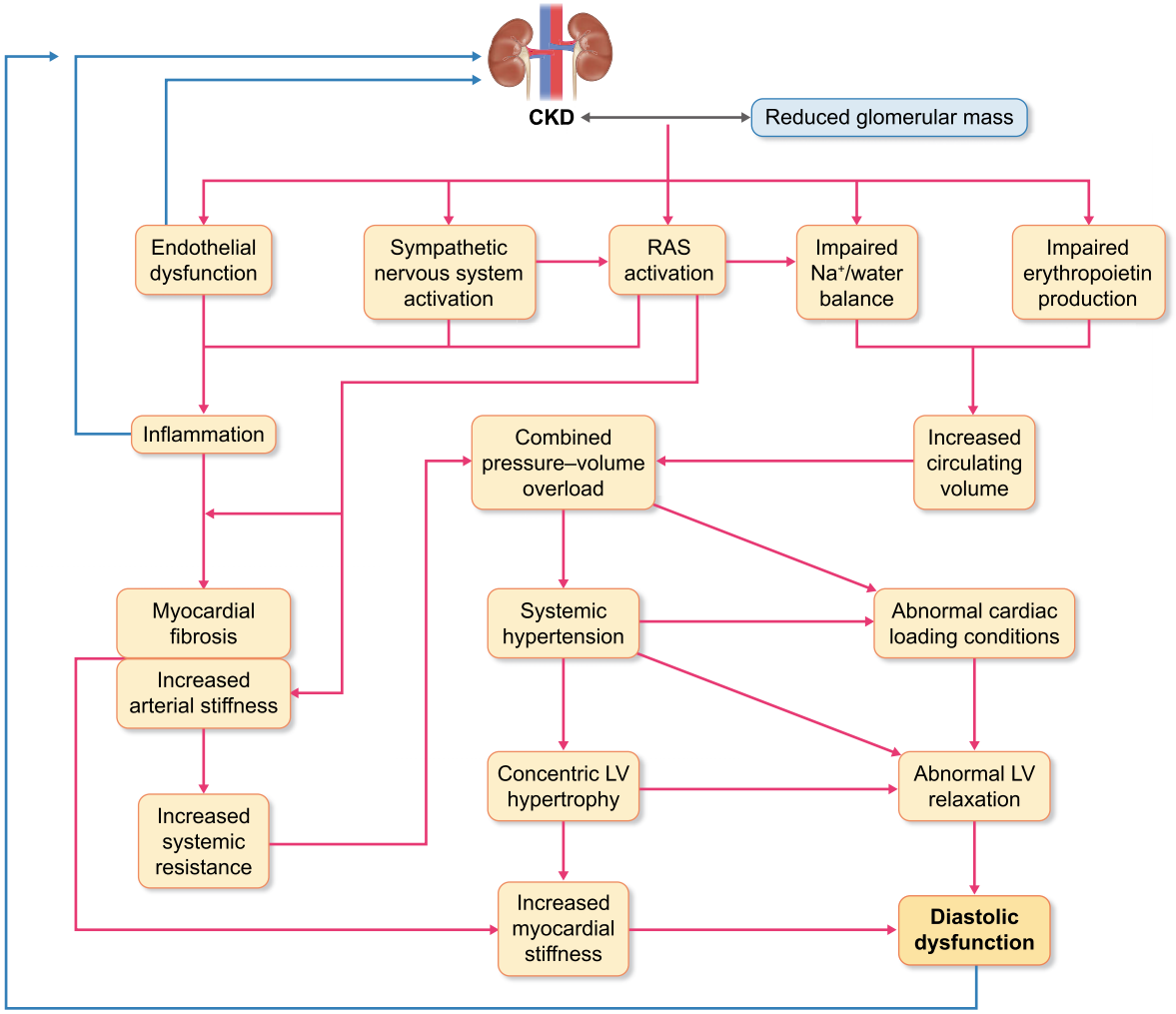

Figure 4: Schematic sequence of CKD-related pathophysiologic structural and haemodynamic changes linked to diastolic dysfunction. The red arrows represent the pathways through which CKD participates in development and progression of diastolic dysfunction. The blue lines represent mechanisms causing progression loops aggravating CKD. CKD: chronic kidney disease; RAS: renin angiotensin system; LV: left ventricle.

whether diastolic dysfunction is a direct consequence of CKD or a proxy of several cardiovascular structural and functional abnormalities causally associated with CKD is unclear. CKD is linked with many haemodynamic, structural, metabolic, energetic and electrolytic abnormalities that converge to largely explain diastolic dysfunction.

Diastolic dysfunction influences atrial afterload, stretching and wall stress, producing atrial fibrosis and dilatation and ion channel remodelling, with a high risk of atrial fibrillation [39], which is in fact frequent in CKD patients [40], especially in ESKD [41]. Symptoms related to paroxysmic atrial fibrillation might be catastrophic in patients with profoundly altered active relaxation, whose LV filling mostly depends on the atrial contribution, while they might be haemodynamically irrelevant in restrictive physiology.

Although cardiovascular effects are generally thought to become significant at CKD stage 3a [42, 43], there is increasing evidence that the relation between the decline of kidney function and cardiovascular risk is continuous from less severe degrees of impaired glomerular filtration rate (GFR) to frank uraemic cardiomyopathy [44]. Hereafter, we will examine cofactors of diastolic dysfunction in the context of CKD (Fig. 4).

Haemodynamic load and structural changes

Due to pathophysiological changes in the arterial system and fluid balance, CKD is a condition associated with the greatest level of haemodynamic overload, combining volume and pressure components [45, 46]. The greatest level of LV hypertrophy is in fact found in CKD, also independent of prevalent cardiovascular disease [47–49], especially at the end-stage. Combined volume and pressure overload cause remarkable structural and geometric alteration [50, 51], with important pathophysiological effects on systolic and diastolic function. In clinical practice, the recently reported geometric pattern of dilated concentric LV hypertrophy [51] is often found in ESKD. The frequency of concentric LV geometry in CKD is also associated with profound structural abnormalities characterized by progressive fibrosis and extracellular matrix disarray, not only related to haemodynamic overload, but also to the activation of different pathways,

including mammalian target of rapamycin signalling and a direct tissue angiotensin II effect [52, 53].

Concentric LV geometry is also the characteristic of conditions in which the magnitude of LV mass substantially exceeds the level needed to sustain normal stroke work (called 'inappropriate LV mass'), even independent of clear-cut established LV hypertrophy [54, 55]. Inappropriate LV mass is a specific modification of LV geometry in the context of CKD [56]. Compared with a definition of LV hypertrophy close to the one proposed by the 2018 European Guidelines on Arterial Hypertension [57], and based on the LV mass index, inappropriate LV mass exhibited higher sensitivity (0.89 versus 0.54) and specificity (0.82 versus 0.62) in the identification of patients with clustered age-independent concentric LV geometry, geometry-independent systolic dysfunction and age and heart rate–independent diastolic dysfunction (prolonged relaxation) [54].

Concentric LV geometry is consistently related to echocardiographic markers of abnormal LV relaxation (including prolonged IVRT, E/A ratio with dominant A velocity and delayed DTE), whereas the presence of increased LV mass adds little to this association [58]. However, coexistence of LV hypertrophy and concentric LV geometry (i.e. concentric LV hypertrophy) is associated with a lower DTE than when LV hypertrophy is absent [58]. This suggests that together with a dominant (and more explorable) abnormal relaxation pattern, elements of restrictive physiology are present in concentric LV hypertrophy. This is particularly important in the context of CKD stage 4 and 5, given the high prevalence of concentric LV hypertrophy in these stages. In clinical practice, the observation of concentric LV hypertrophy with a dominant abnormal relaxation pattern but inconsistent value of DTE may suggest abnormal LVEDP.

Non-haemodynamic mechanisms

In addition to haemodynamic mechanisms, CKD causes metabolic and electrolyte abnormalities and activation of biological pathways that can directly influence intrinsic mechanisms of diastolic function [52, 53, 59]. Many markers of inflammation, including CRP, fibrinogen and members of the interleukin family have been shown to be negatively correlated with measures of kidney function and positively correlated with albuminuria [60]. Abnormal haemodynamic load can directly induce pro-inflammatory reactions [61]. In CKD, chronic exposure to cytokine cascade, activation of the myocardial macrophage system and specific electrolyte abnormalities can impact the myocardial structure and alter the architecture of the myocardial scaffold [62–65], increasing reactive fibrosis and altering myocardial distensibility. Inflammation is also linked to protein energy wasting in CKD, altering energy storage [66, 67], and complicates energy handling, already difficult in stressed conditions, impairing both the systolic and diastolic myocardial workload. Hyperparathyroidism might play a key role as both an indirect factor, sustaining arterial hypertension, and a direct promoter of inflammation and fibrosis [68, 69].

As already previously discussed [70], the heart needs to rapidly generate very large amounts of ATP, but the ATP turnover is also extremely fast [71]. In normal conditions, this turnover is supported by energy produced from fatty acid oxidation [72], a stable pathway of energy production. However, a fat-free acid pathway results in a substantial increase in myocardial oxygen consumption to sustain a given external workload [71, 72] and in a large amount of dissipated energy [73]. In conditions in which efficiency must be high, such as haemodynamic overload and other stress conditions [74], glucose and lactate oxidation (which is 30–50% in normal conditions) has to be greater, because the amount of oxygen used to produce each ATP molecule utilizable for cardiac mechanics is substantially lower than with fatty acid oxidation [72, 75].

In CKD, the coexistence of high levels of LV hypertrophy favours greater utilization of glucose substrate, but highly prevalent insulin resistance [76] blunts this mechanism of preservation of mechanical efficiency, in a condition in which fatty acid oxidation might not be efficient, when protein energy wasting is present [66, 67]. The energy required for contraction and relaxation might be substantially decreased in ESKD. Inhibition of sodium–glucose co-transporter 2 (SGLT2) may partially overcome this energetic imbalance, especially, but not only, in conditions of insulin resistance or deprivation [77–79], through their ketogenic activity [80, 81], by providing a convenient way to produce energy [73], which is not affected by insulin resistance. The effect of SGLT2 inhibitor on slowing the progression of CKD is well documented [82].

Eventually, the electrolyte imbalance often found in the most advanced stages of CKD [83] can influence cardiac mechanics, especially through effects on the pattern of activation [84] and repolarization. Na^{+}, K^{+}, Ca^{++} and Mg^{++} are the key ions regulating depolarization and repolarization. The duration of the action potential is not the same across the wall thickness. Depolarization first occurs at the endocardial level traveling toward the epicardium, and repolarization travels in the opposite direction due to the intrinsic difference in the activity of the various ion channels among the layers [85]. Every condition increasing this 'repolarization dispersion' can favour desynchrony and alter diastolic mechanics [86–88].

Cardiorenal syndrome (CRS)

CRS is a group of disorders characterized by a reciprocal relationship between acute or chronic cardiac and renal injuries. In the pathophysiology of CRS, diastolic dysfunction plays a pivotal role, by leading to the development of HF [89]. In a large clinical series, assessment of diastolic function and evaluation of LV filling pressure has been indicated to be helpful in predicting the development of acute kidney injury [90]. The LA dimension and estimated systolic pulmonary artery pressure are the main echocardiographic markers of a bad prognosis in patients with CRS [89, 91, 92].

Diastolic dysfunction and decision making

According to what is reported in the previous paragraphs, the clinical need to accurately assess diastolic function in CKD remains elusive. Easily measurable structural and functional variables (i.e. LV mass index, relative wall thickness, LV systolic performance), even considering the methodological caveats, largely predict the LV filling pattern and should accompany every in-depth evaluation of diastolic function. According to a general criterion [93], even suggested by the 2018 European Society of Cardiology/European Society of Hypertension guidelines on arterial hypertension [57], echocardiographic evaluation should be performed when results can modify or address clinical decision making. This criterion is valid also for in-depth assessment of diastolic function in the context of CKD. Other techniques can help in non-invasive evaluation, including myocardial two- or three-dimensional strain imaging [28, 94] and especially pulmonary ultrasound using palm-held ultrasound devices [95, 96], but their efficacy for decision making is questionable in the context of CKD [95].

Assessment of diastolic dysfunction has been recently suggested to be a useful tool for predicting the development of adverse renal outcomes, defined as a >50% decrease in estimated GFR from baseline, doubling of serum creatinine, dialysis initiation and/or kidney transplantation [97], although no adjustment for LV geometry and geometry-independent systolic function was considered (only ejection fraction was used as a measure of systolic function). However, this has also been demonstrated in patients with preserved systolic function (defined as an ejection fraction >50%), further demonstrating that diastolic heart dysfunction is a risk factor for CKD progression, also after adjusting for the presence of body surface area–based LV hypertrophy [98], but not for other factors that might influence disease progression for both the heart and kidney (Fig. 4).

What may be recommended is looking at the general picture, especially in patients with ESKD. Cardiovascular phenotypes of LV geometry characterized by concentric LV geometry and abnormal relaxation, especially when increased LV stiffness is present, should be taken into consideration, especially in the ESKD patients on dialysis [99]. As commented previously [99], as a consequence of severe myocardial fibrosis found in ESKD, severe diastolic dysfunction occurs, involving all diastolic phases. To complete effective LV filling and achieve sufficient end-diastolic volume, providing adequate stroke volume, the left ventricle needs adequate preload to recruit Starling forces. In the case of concentric LV remodelling, preload needs to be sustained by adequate LV filling pressure in addition to volume. During dialysis, LV filling pressure decreases to a variable extent because of subtraction of central circulating volume [100, 101], depending on the ultrafiltration rate [102]. Because of increased LV stiffness, a reduction of LV filling pressure also implies a decrease in LV end-diastolic volume [101]. The combination of these changes causes a reduction of Starling forces recruitment that cannot be easily compensated for by increasing contractility, due to the impaired contractile reserve in the presence of concentric LV hypertrophy [103], largely due to myocardial stunning [101]. A decrease in preload can be mild–severe and might cause different degrees of hypotension. If the time of volume subtraction is prolonged enough to allow oncotic forces to restore circulating volume and preserve LV preload and coronary microcirculation, hypotension might be prevented.

Thus, in the presence of concentric LV geometry (and severe diastolic dysfunction), slow dialysis sessions might be needed to prevent hypotension. In this case, combined, detailed assessment of LV geometry and at least a qualitative estimate of LV filling pressure might be clinically useful, as well as preliminary assessment of contractile reserve [104].

There is no specific management for diastolic dysfunction in CKD. A reduction of heart rate might result in increased diastolic filling and improved stroke volume, which is energetically convenient. The use of β-blockers has been shown to improve outcome in ESKD [105, 106]. Improvement of diastolic function can be achieved by managing structural, haemodynamic and biological conditions impairing mechanisms of active relaxation and passive filling. A reduction of LV mass, whenever this is possible, optimization of haemodynamic loading conditions, preservation of optimal energy-producing mechanisms and electrolyte balance have positive effects on diastolic function.

Box 1 presents key questions of interest for the management of patients with CKD, relative to diastolic dysfunction, and suggestions based on current evidence. Assessment of diastolic function is certainly useful for studying mechanisms, but it does not have great relevance in daily clinical practice and decision making.

Box 1

Question	Answer
Should nephrologists screen CKD patients for the presence of diastolic dysfunction?	Not necessarily. In terms of clinical decision making, assessment of diastolic function will add little to information provided by LV geometry, systolic performance and metabolic and electrolyte balance.
Why assess diastolic dysfunction in CKD?	Assessment of diastolic dysfunction might be useful to estimate LV filling pressure in patients with dyspnoea, as a quantitative measure of pulmonary congestion.
Is there a need for follow-up of patients with diastolic dysfunction?	Follow-up might be primarily useful for the evolution of abnormalities in LV geometry and systolic performance. Evolution toward any form of HF may be monitored by estimating LV filling pressure.
Is there a specific recommendation in terms of medical treatment?	Prudent use of β-blockers to control heart rate might be useful to improve LV filling and energetics if it results in improved stroke volume.

CONCLUSIONS

LV diastolic dysfunction is closely tied to cardiovascular phenotypes in CKD and involves all mechanisms implicated in the efficiency of diastole. LV diastolic dysfunction may be assessed and monitored whenever it is useful to orient management, although information on LV geometry, systolic function and performance are already sufficient for clinical decision making. Information on diastolic dysfunction might be useful especially in ESKD, most often characterized by severe degrees of concentric LV geometry, and both delayed relaxation and increased LV stiffness if/when information on LV geometry and systolic performance are considered insufficient. During dialysis, LV filling pressure decreases to a variable extent because of subtraction of central circulating volume, depending on the ultrafiltration rate. The combination of functional and geometric changes causes a reduction of Starling forces recruitment that cannot be easily compensated by increasing contractility, due to the impaired contractile reserve and myocardial stunning in the presence of concentric LVH and hypotension. The time of volume subtraction should be calibrated based on the individual cardiovascular phenotype.

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AUTHORS' CONTRIBUTIONS

G.d.S. and C.M. contributed to the design and implementation of the paper, to the writing and critical review of the manuscript. G.d.S. prepared figures and tables.

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No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

None declared. No part of this article has been previously published elsewhere.

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