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A look at the upper heart chamber: the left atrium in chronic kidney disease

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ABSTRACT

Altered left ventricular (LV) mass and function are classical hallmarks of cardiomyopathy in chronic kidney disease (CKD). The left atrium (LA), a heart chamber exquisitely sensitive to volume overload and diastolic function, is an independent predictor of death and adverse cardiovascular (CV) events in high-risk patients such as those with hypertension and/or with heart failure. In this review we focus on the relationship of LA size with LV diastolic function, and the association between LA enlargement and CV and renal outcomes in patients with CKD, including patients with end-stage renal disease. Increased LA size emerges as a powerful predictor of mortality and major adverse CV events in both end-stage and early CKD, and some studies also show a close association between enlarged LA and renal disease progression. Secondary analyses of clinical trials suggest that the LA has the potential to be elected as a surrogate end point in CKD patients but the issue remains to be tested in specifically designed clinical studies.

Keywords: cardiomyopathy, CKD, clinical outcome, diastolic function, left atrium

INTRODUCTION

Cardiomyopathy, which is defined in anatomical terms as left ventricular hypertrophy (LVH) or as a functional alteration in left ventricular (LV) systolic and/or diastolic function, is the most prevalent cardiovascular (CV) disorder in chronic
kidney disease (CKD) [1]. A large survey in the USA [2] recently confirmed earlier observations in relatively smaller studies [3], which reported that the prevalence of LVH is progressively higher across CKD stages of increasing severity, reaching ~80% in patients with end-stage renal disease (ESRD) [2, 4]. Cardiomyopathy in CKD is characterized by marked interstitial fibrosis [5], an alteration that was confirmed in vivo in ultrasound studies based on video densitometry [6, 7]. Collagen deposition in the myocardium stiffens the left ventricle, thereby impairing LV relaxation during diastole. Along with systolic dysfunction, diastolic dysfunction has now emerged as a major risk factor for death and CV events both in the general population [8] and in patients with CV disease [9], as well as in CKD [10]. The left atrium (LA) is profoundly affected by altered diastolic function and the pathophysiological link between diastolic dysfunction and LA volume and function has been solidly established [11]. A large, patient-based meta-analysis established LA size to be a powerful predictor of mortality in patients with heart failure [12]. Since LA enlargement may reflect both volume expansion and alterations in diastolic function, the studies focusing on LA size are of great interest in CKD. The issue has now been investigated in a series of observational studies of varying breadth and quality and in a limited number of experimental studies. Herein we provide a narrative review which briefly recapitulates the link between LA size and LV diastolic function and findings in selected studies in CKD describing the relationship of LA size with the diastolic dysfunction and with health outcomes in the specific setting of this condition.

The search for relevant original articles for this review was carried out by accessing PubMed in May 2013 applying the terms ‘left’ and ‘atrium’ associated with three target populations (CKD or ESRD or Dialysis). This search produced a list of 184 papers. From this list we selected 22 pertinent papers in CKD patients reporting information on the mechanism(s), prevalence, predictive power or modifiability of left atrial enlargement in the target population. Furthermore, we extracted 51 papers dealing with the LA in diseases other than CKD or with technical or methodological issues from personal (EP and CZ) databases.

THE PATHOPHYSIOLOGICAL LINK BETWEEN THE LA AND LV DIASTOLIC DYSFUNCTION

In the normal heart, the diastolic phase starts with the isovolumic relaxation, during which the LA acts as a reservoir that receives blood from the pulmonary circulation. After mitral opening, the LA acts as a conduit for transmural blood flow to the LV along a pressure gradient in the early phase, and then passively from the pulmonary veins. Last, in the late LV diastolic phase, LA contraction contributes to ~20% of LV diastolic filling [13]. Impairment of LV relaxation resulting from increased collagen deposition can increase LV end-diastolic pressure. After mitral valve opening, the LA chamber is directly exposed to the elevated pressure of the LV [14], and this translates into an increase in the pressure in the LA to maintain the ventricular filling [15] (Figure 1). The result of this increase in LA parietal tension is progressive atrial dilation [14]. Thus, the size of the LA is affected by the same factors that influence ventricular filling [15], and can therefore be considered a reliable parameter of both lusitropic properties and diastolic function of the LV.

Left atrial size can be estimated by measuring the anteroposterior diameter of the LA, which is quite a simple echocardiographic measurement. However, since the LA is not a symmetrically shaped structure, this parameter provides an inaccurate estimate of LA size. More accurate metrics of the LA have now been developed and validated in various populations. Among them, the LA volume index measured by 2-D echocardiography proved to be quite a reproducible and accurate metric of LA size in studies which adopted cardiac nuclear magnetic resonance (CMR) or computed tomography (CT) scans as the gold standard [13]. Due to its substantial cost advantage and simpler logistics, The American Society of Echocardiography now formally recommends measuring LA volume using biplane 2-D echocardiography [16]. Even though LA volume underestimates the true LA volume when compared with CMR or CT, this imprecision is fully acceptable in clinical practice. Compared with Doppler mitral inflow velocities that reflect filling pressures at the time of measurement, LA volume can be considered as the integrated effect of LV filling pressure over time [17], and as such an additional

![Diagram](https://via.placeholder.com/150)

**FIGURE 1:** Factors influencing left atrial volume. Reduced capacity of the LV to relax, an active process regulated by catecholamines and other factors (lusitropism) or LV rigidity due to LV wall thickening and myocardial fibrosis results in LV dysfunction, an alteration that increases LV end-diastolic pressure. High diastolic pressure demands a higher LA pressure to maintain LV filling and this haemodynamic adaptation goes along with LA enlargement. Blood volume returning to the heart via the pulmonary veins is another fundamental determinant of LA volume.
Left atrium in CKD

Due to volume expansion and malnutrition, appropriate indexing of echocardiographic parameters is fundamental in patients with CKD [1, 4]. In this respect the superiority of indexing by height powered to 2.71 (h^{2.71}) over indexing by body surface area (BSA, m²) is well demonstrated in stage 5D CKD [4] and the application of this indexing has now been adopted in studies in pre-dialysis patients [2]. There are currently no formal studies comparing the predictive power of LA indexed by h^{2.71} to that indexed by BSA in pre-dialysis CKD patients. However, given the strong association of LA size with LV mass and the superiority of the h^{2.71} indexing for LV mass measurement, it makes sense to use the same indexing for LA in CKD patients. Both indexes have been used in studies in CKD patients and therefore attention should be paid to the marked difference in the two scales when comparing different studies.

The prevalence of diastolic dysfunction in CKD patients of varying severity (from stage 3 to 5 CKD) is ~75% [2]. A left atrial volume index (LAVI) is increased in the vast majority of stage 5 CKD patients approaching the start of dialysis treatment [20] and in stage 5D CKD patients as well [21].

Volume expansion and left atrial enlargement

As alluded to above, the increased LA size can also be the effect of volume overload [18, 21]. Accordingly, a close direct relationship has been reported between LAVI and elevated plasma ANP and BNP, i.e. two biomarkers that in part reflect volume expansion [22]. Extracellular fluid excess occurs at a very early stage of CKD and is independently associated with cardiac remodelling, an anatomical adaptation which includes left atrial enlargement. In a study involving 104 patients with mild-to-moderate CKD [23], 66% exhibited an LAVI >32 mL/m², a threshold beyond which there is a progressive increase in the risk of mortality [24]. Of note, in stage 5D CKD patients with reduced or abolished nocturnal BP dipping, a functional hallmark of volume expansion [25], this alteration was associated with LA enlargement and this association was largely independent of BP load [26].

Inflammation and left atrial enlargement

Among the non-haemodynamic factors that correlate with LA size in CKD, inflammation is undoubtedly the most consistently observed one. In a mixed population including patients on regular dialysis treatment and patients with stage 3–5 CKD, a strong direct relationship has been reported between enlarged LA and high sensitivity C-reactive protein, which went along with a parallel association between the LA with carotid intima-media thickness, an established marker of atherosclerosis [27]. This finding in CKD patients is consistent with observations in patients with permanent atrial fibrillation (AF) where an association between CRP and interleukin-6, atrial size and the duration of AF was identified [28]. Interestingly, in patients with severe heart failure due to dilated cardiomyopathy, upregulation of metalloproteinase-2 and subsequent atrial extracellular matrix remodelling with increased type I collagen fraction were found to be associated with increased left atrial size and the development of sustained AF [29]. This finding is consistent with previous observations indicating that left atrial remodelling is accompanied by histological evidence of inflammation and fibrosis in myocardial biopsies of patients with AF [30]. Even though there are no anatomo-pathological studies documenting the same phenomenon in CKD, it appears most likely that findings in patients with LA enlargement and AF also apply to CKD patients. In this respect, the tight correlation between atrial size and the presence of malnutrition [31], a disorder almost always associated with inflammation and protein wasting in haemodialysis (HD) patients [32], goes along with the previously discussed association between increased LA size and high CRP in CKD patients [27]. Malnutrition frequently underlies hidden volume expansion in CKD, i.e. a major factor impacting upon LA volume and this phenomenon is of particular relevance in ESRD patients [33, 34]. Inflammation in the LA walls may be the expression of persistent wall stress by high endo-cavitary pressure or the effect of raised systemic inflammatory mediators [35]. Thus, volume overload and inflammation in CKD patients may contribute to promoting damage at the tissue level in the left atrial walls both because systemic inflammation may exert a harmful effect on the LA and because LA wall stress incited by volume expansion triggers local inflammatory changes. Persistent LA enlargement is a well-known risk factor for AF and therefore the high prevalence of AF in stage 5D CKD patients [36] is a predictable sequel of the adverse effects of two dominant risk factors in this population, namely hidden or manifest volume expansion and inflammation.

Intriguingly, for the first time, a recent study on stage 3–5 CKD patients reported a very high prevalence of subclinical LA enlargement and a strong independent relationship between plasma sodium concentration and subclinical LA enlargement in this population [37]. There are still no clear clues for interpreting these stimulating findings, nonetheless they are of potential interest because alterations in plasma sodium are frequent in CKD patients and include hypernatraemia (serum Na >145 mmol/L) which developed at least once in 7% of CKD patients in a study with a 5-year follow-up [38, 39]. A better understanding of the mechanism(s) generating mild hypernatraemia in CKD as well as studies considering the functional relationship between arginine vasopressin and LA volume are needed to interpret the LA volume–plasma sodium relationship in the CKD population [40]. The hypothesis that mild hypernatraemia induced by sodium excess may trigger LA enlargement should be tested in interventional studies of
salt intake modification in CKD patients. Furthermore, mechanistic studies considering LA function and mechanics are needed to shed light on this potentially important link. LA function is indeed an important physiological parameter and a predictor of adverse clinical outcomes in a high-risk condition like myocardial infarction with ST elevation [41].

**LA as a Predictor of Death and Adverse CV Outcome in CKD**

Studies in high-risk populations like patients with CV disease [12, 42–45] and in hypertensive patients [46] and in the general population [47] have repeatedly confirmed that increased LA volume signals a high risk for adverse CV outcomes. Of note, studies in a large cohort of subjects with a preserved LV systolic function documented that this association is independent of the underlying LV geometry pattern, since it is evident both in patients with normal geometry and in those with concentric or eccentric remodelling [48].

In the past few years several cohort studies investigated the hypothesis that LA size may predict all-cause mortality and CV outcomes in patients with CKD of varying severity (Table 1). Initial studies were carried out in ESRD patients on dialysis. In a cohort of 249 HD patients without heart failure at the time of enrolment, LA volume indexed by height$^{2/7}$ held prognostic value above and beyond what was provided by LV mass and LV function for the risk of nonfatal CV events and death over a 3-year observation period [21]. Furthermore, in another study by the same investigators, progressive LA volume changes over 15 months predicted the risk of incident fatal and non-fatal CV events regardless of baseline LV mass index and geometry [49]. More recently, a CMR study in a cohort of ESRD patients on a waiting list for kidney transplantation confirmed these findings [50]. LA volume emerged as the only echocardiographic index independently associated with mortality in a low-risk dialysis population in whom strict volume control was achieved by dietary salt restriction [51]. By the same token, LA volume was an independent death predictor in a reasonably large cohort ($n = 216$) of CAPD patients [52]. In this study the application of discrimination analysis (ROC curve analysis) showed that LA volume is a better prognostic factor for all-cause and CV mortality than other echocardiographic parameters of cardiac morphology and function.

Information on the predictive power of LA size for health outcomes at a pre-dialysis stage is still very limited. In a study based on the measurement of LA diameter (a less accurate metric of LA size than LA volume) in a cohort of patients with advanced CKD, preserved LV systolic function and no history of ischaemic heart disease [53], the LA diameter significantly increased the predictive power for CV mortality of a model that also included relevant clinical variables and information on cardiac ischaemia as assessed by a stress test by single-photon emission computed tomography. Similarly, observations in a larger cohort of patients with stage 3–5 CKD [54], showed that an LA diameter >4.7 cm was associated with a 2-fold increase in the hazard ratio (HR) of CV events regardless of LVH and LV systolic dysfunction.

Collectively, metrics of LA size including the LA diameter and LA volume are undoubtedly independent predictors of mortality and CV risk over a wide range of GFR values, including moderate and severe CKD and kidney failure. The usefulness of measuring LA size in patients with CV diseases during echocardiography is beyond question [16]. The predictive power of LA metrics in CKD patients suggests that the same may hold true even in this high-risk population. However, it should be clearly acknowledged that the HR of increased LA volume (or diameter) for death and CV complications, although high in terms of public health, is too modest to allow considerable gains in prognostic ability, a consideration that also applies to LV mass index [56].

AF, an established consequence of LA enlargement, is highly prevalent in subjects with non-dialysis CKD [57] and in dialysis patients [36, 58]. Like in the general population, left atrial enlargement in CKD is a predictor of the risk of AF in patients with renal disease [36, 57, 58].

**LA as a Predictor of Adverse Renal Outcomes**

Experimental studies in the rat demonstrated that myocardial infarction of moderate degree leads to proteinuria and focal glomerulosclerosis in uni-nephrectomized rats [59]. This observation suggests that the link between the kidney and the heart may be bi-directional in nature. Renal impairment may not only amplify the risk of CV disease but it may also be the consequence of cardiac disease [60]. Subclinical cardiac damage predicts the progression of CKD and, in theory, there is a possibility that such a link may be causal in nature [61] even in man. LVH has been associated with progressive worsening of renal function in hypertensive subjects [62, 63] and in stage 3–5 CKD patients in studies by Paolletti et al. [64] and Chen et al. [65]. Of interest, in the study by Chen et al. [65] an enlarged LA diameter rather than LVH remained significantly associated with progression to ESRD at multivariate analysis, implying that LA enlargement is a stronger predictor than LVH of the risk of CKD progression. These findings were confirmed in another study in Japanese patients with more advanced stage 4–5 CKD [66]. In this latter study, LA volume together with systolic BP and serum albumin was the most significant predictor of the risk of more rapid progression to end-stage requiring dialysis, both in diabetic and non-diabetic subjects. Remarkably, the predictive power of LA enlargement for adverse renal outcomes apparently extends to residual function in peritoneal dialysis (PD) patients as well. Indeed, in a cohort of 121 incident PD patients, an LA volume >32 mL/m² proved to be significantly associated with more rapid residual renal function loss [67]. In general, PD patients are more volume expanded and exhibit a larger atrial size than HD patients [68] and volume expansion is considered the main reason why PD patients maintain residual renal function longer than HD patients [69]. Thus, findings by Kim et al. [67] suggest that volume expansion, i.e. a main determinant of LA volume, rather than favouring residual renal function maintenance, actually accelerates the rate of loss of residual
A three-level classification of quality of reporting was developed considering the completeness of reporting of title/abstract, introduction, methods, results, discussion and other information, as indicated in the STROBE checklist of 22 items [55]. By this scale, all studies reported in Table 1 classify as being of good quality.

Table 1. Left atrial size as a predictor of CV outcome in predialysis and dialysis CKD patients

<table>
<thead>
<tr>
<th>Author (year) [ref.]</th>
<th>Study population</th>
<th>Sample size</th>
<th>LA size assessment</th>
<th>Study outcome</th>
<th>HR (each mL)</th>
<th>Comparison with other predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tripepi (2006) [21]</td>
<td>HD</td>
<td>249</td>
<td>2-D echo LA volume/height2.7 changes</td>
<td>CV events/death</td>
<td>1.02</td>
<td>Independent of LVMI, EF, superior to BP</td>
</tr>
<tr>
<td>Tripepi (2007) [49]</td>
<td>HD</td>
<td>191</td>
<td>LA volume/height2.7 changes</td>
<td>CV events</td>
<td>2.99 (+1.68 mL/years)</td>
<td>Independent of LVMI, EF, LV geometry</td>
</tr>
<tr>
<td>Patel (2010) [50]</td>
<td>Dialysis</td>
<td>201</td>
<td>Magnetic resonance LA volume /BSA</td>
<td>all-cause mortality</td>
<td>1.06 (each mL)</td>
<td>Independent of LV systolic dysfunction and previous IHD; superior to LVMI and BP</td>
</tr>
<tr>
<td>Ozdogan (2010) [51]</td>
<td>HD</td>
<td>576</td>
<td>2D-echo LA volume/BSA</td>
<td>All-cause mortality</td>
<td>1.025 (each mL)</td>
<td>Independent of PP ; superior to E/A ratio, LVMI, LV volume</td>
</tr>
<tr>
<td>Kim (2011) [52]</td>
<td>PD</td>
<td>216</td>
<td>2D-echo LA volume/BSA</td>
<td>All-cause/CV mortality</td>
<td>1.05–1.08 (each mL)</td>
<td>Independent of IHD; superior to LVMI and E/E’ ratio</td>
</tr>
<tr>
<td>Chan (2008) [53]</td>
<td>CKD</td>
<td>200</td>
<td>M-mode LA diameter/BSA</td>
<td>CV mortality</td>
<td>1.20 (each mm/m²)</td>
<td>Independent of IHD; superior to EF</td>
</tr>
<tr>
<td>Chen (2012) [54]</td>
<td>CKD</td>
<td>505</td>
<td>M-mode LA diameter</td>
<td>CV events</td>
<td>2.14 (LAD &gt; 4.7 cm)</td>
<td>Independent of IHD, AF, LVMI and EF ; superior to E/A ratio</td>
</tr>
</tbody>
</table>

LVMI, left ventricular mass index; EF, left ventricular ejection fraction; IHD, ischaemic heart disease; BP, blood pressure; PP, pulse pressure; E/E’ ratio, the ratio of transmirtal Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; EA, atrial fibrillation; EA, ratio of the early (E) to late (A) ventricular filling velocities.

GFR in these patients. A likely interpretation of this phenomenon is that LA enlargement triggered by LV dysfunction and volume overload heralds heart failure which in turn reduces renal blood flow and precipitates complete loss of renal function.

Overall, it should be emphasized that although LA enlargement is consistently associated with progression of CKD, the strength of such a link is statistically too weak to be exploited for prognostic purposes. Risk factors of the same strength as LA volume or of even greater strength do not possess sufficiently high discrimination power to identify patients that go on to develop relevant clinical events and therefore are unlikely to qualify as valid prognostic factors [70]. As to the possibility that the same relationship is the expression of a causal link whereby cardiac disorders may favour CKD progression we still lack solid experimental evidence to support this intriguing hypothesis. The opportunity now opened by the omics technologies [71] represents an unprecedented chance to decipher the pathophysiological and clinical relevance of this fascinating heart (LA)–kidney connection.

**Modification of Left Atrial Volume in Interventional Studies**

The randomized clinical trial is the definitive test for attributing a causal role to any purported risk factor implicated in the risk of adverse health outcomes. In theory LA volume could represent a surrogate of clinical events and as such it could be used as a study outcome in clinical trials, as has been done with LV mass in studies testing the efficacy of nocturnal dialysis [72]. So, we may apply interventions aimed at modifying left atrial volume enlargement (e.g. extracellular volume reduction or interventions aimed at improving LV diastolic dysfunction) and use changes in LA volume as a surrogate of the risk of all-cause and CV death mortality or progression to ESRD. However, establishing a biomarker as a surrogate is a tantalizing undertaking [73] and in this respect there is still no evidence derived from specifically designed clinical studies to prove that LA volume is a valid surrogate of clinical events in CKD.

In ESRD, the patients’ pre-load reduction by HD reduces LA volume [74] which is in line with the notion that extracellular volume is a main determinant of LA size [18]. Improvement in diastolic dysfunction by ACE inhibition in patients with an enlarged atrium and isolated diastolic dysfunction goes along with LA volume reduction [75]. This finding, which was observed in the context of a randomized clinical trial in patients without CKD, supports the contention that LA volume is a reliable index of diastolic function over-time. No similar studies have been performed in CKD patients.

Intriguingly, a recent post hoc analysis of the Paricalcitol Capsule Benefits in Renal Failure–Induced Cardiac Morbidity Trial [76], an RCT designed to evaluate the effect of paricalcitol on LVH in stage 3–4 CKD patients, documented a highly significant reduction in LA volume after 48 weeks of treatment but no change in LV mass or in the classical parameters of LV diastolic function like the E/E’ ratio [77]. Since there was no evidence of volume expansion in paricalcitol treated patients when compared with placebo patients in this trial, this phenomenon clearly suggests that this form of vitamin D has lusitropic effects and thus that LA volume may be a more sensitive indicator of diastolic function than the E/E’ ratio.
CONCLUSIONS AND PERSPECTIVES

LA size and especially so LA volume qualify as reliable indexes of diastolic function and represent sensitive biomarkers of CV and perhaps renal outcomes in CKD patients. Furthermore, the prediction power of these metrics may be even greater than that of LV mass thus highlighting their potential value in CV assessment. Well-designed, adequately powered, clinical trials are still needed to assess whether LA metrics may be adopted as surrogate markers in clinical trials.

CONFLICT OF INTEREST STATEMENT

None declared.

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