

Background

Left atrial diameter (LAD) or volume is an independent predictor of mortality in the community, and recent evidences had emerged focusing on the importance of its assessment as an adjunctive, relevant parameter which may enrich the prognostic stratification also on patients with CKD undergone renal replacement therapy. Nevertheless, as many determinants of changes on left atrium, such as extracellular volume expansion, alterations in ventricular mass, and impairments on left ventricular diastolic relaxation and filling are common in CKD patients, it is still unclear its real prognostic value on this patient population.

Objective

We sought to evaluate the associations of LAD with a range of traditional and uremic related risk factors, as well as to text its prognostic value in a carefully phenotyped cohort of non-dialysis dependent CKD stages 3 to 5 patients.

Methods

In a cross-sectional study, we included 288 patients (61, [53-68] years; 63% men). LAD, left ventricular mass index (LVMI), and left ventricular ejection fraction (EF) were assessed by echocardiography. Patients were followed for 34 (21 - 41) months for overall mortality and cardiovascular events.

Results

✓ General characteristics of the studied population as well as patient's characteristics according to tertiles of LAD distribution are summarized in **Tables 1 and 2**. Across increasing tertiles, patients were more often men, had a higher prevalence of ischemic heart disease and peripheral vascular disease, as well as a higher Charlson comorbidity index, and were using more antihypertensive drugs. Regarding body composition parameters, increments on LAD was associated with higher BMI and fluid overload (i.e. an increased amount of extracellular water). Whereas C-reactive protein (CRP), cardiac troponin I and brain natriuretic peptide (BNP) concentrations were increased, total cholesterol and triglycerides were incrementally reduced across increasing LAD tertiles. In addition, augmentations on LAD associated with poorer echocardiography findings (left ventricular mass index [LVMI] and worse left ventricular geometry and function), as well as increased coronary artery calcification and myocardial ischemia.

✓ The multivariate correlates of LAD (logarithm transformed) are shown in **Table 3**. Male sex, ischemic heart disease, plasma BNP, as well as LVMI and extracellular water emerged as independent predictors of left atrium diameter.

✓ During a follow-up of 34 (21-41) months, 77 patients died and we computed 62 CV events (fatal and non-fatal). Cox proportional hazards models in **Table 4** explore the etiological association between LAD and the outcomes. Increased LAD was associated with higher hazards for all-cause mortality and CV events in crude and adjusted models, which included, among others, LVMI and LVEF. However, after a further adjustment for extracellular water, it lost the significance in the prediction of both outcomes.

Results

Table 1. Clinical and anthropometric data of the 288 CKD stages 3 - 5 patients, overall, and according to the left atrium diameter.

	All Patients (n = 288)	Low LAD (n = 98)	Middle LAD (n = 94)	High LAD (n = 96)	P for trend
Clinical and anthropometric parameters					
Age (years)	62 (53 - 68)	60 (52 - 68)	61 (54 - 68)	62 (57 - 71)	0.074
Men (n, %)	182 (63%)	48 (49%)	63 (67%)	71 (74%)	< 0.001
Smoking (n, %)	165 (57%)	56 (57%)	54 (57%)	55 (57%)	0.983
Diabetes (n, %)	146 (51%)	43 (44%)	61 (65%)	42 (44%)	0.998
Ischemic heart disease (n, %)	99 (34%)	23 (24%)	33 (35%)	43 (45%)	0.002
Peripheral arterial disease (n, %)	124 (43%)	28 (29%)	46 (49%)	50 (52%)	0.001
Systolic BP (mmHg)	150 (133 - 172)	147 (130 - 163)	156 (132 - 180)	153 (134 - 171)	0.200
Diastolic BP (mmHg)	79 (71 - 89)	78 (72 - 89)	80 (70 - 92)	79 (69 - 89)	0.737
Total of anti-hypertensive drugs (n)	3 ± 2	3 ± 2	4 ± 2	4 ± 1	< 0.001
Charlson comorbidity score	6 (5 - 8)	6 (5 - 7)	7 (5 - 8)	7 (5 - 9)	0.001
Body mass index (Kg/m ²)	29.2 ± 5.6	26.7 ± 5.2	30.1 ± 5.7	30.3 ± 5.7	< 0.001
Malnutrition inflammation score	5 (3 - 8)	5 (3 - 8)	4 (2 - 7)	5 (3 - 8)	0.524
Intra cellular water (L) ¹	22 (17 - 26)	20 (16 - 25)	22 (18 - 27)	23 (19 - 27)	< 0.001
Extra cellular water (L) ¹	20 (17 - 23)	18 (15 - 20)	20 (18 - 23)	21 (18 - 24)	< 0.001

¹Data regarding extracellular water were available in 275 patients (95 vs. 81 vs. 89).

Table 2. Laboratorial and cardiac assessments of the 288 CKD stages 3 - 5 patients, overall and according to the left atrium diameter.

	All Patients (n = 288)	Low LAD (n = 98)	Middle LAD (n = 94)	High LAD (n = 96)	P for trend
Laboratorial parameters					
Glomerular filtration rate (ml/min/1.73m ²)	23 (14 - 35)	22 (14 - 36)	22 (15 - 32)	23 (14 - 35)	0.733
24h Urinary albumin excretion (g)	0.76 (0.13 - 2.34)	0.53 (0.13 - 1.59)	1.32 (0.34 - 3.20)	0.55 (0.79 - 2.16)	0.787
Plasma sodium (mmol/L)	139.1 ± 3.3	139.1 ± 3.4	138.9 ± 3.4	139.2 ± 3.1	0.835
Total Cholesterol (mg/dL)	173 (147 - 226)	189 (159 - 233)	176 (136 - 229)	164 (144 - 212)	0.017
Triglycerides (mg/dL)	150 (111 - 208)	170 (121 - 228)	150 (104 - 206)	138 (98 - 183)	0.008
Albumin (g/dL)	3.8 (3.5 - 4.2)	3.9 (3.6 - 4.3)	3.8 (3.5 - 4.1)	3.8 (3.4 - 4.2)	0.146
C-reactive protein (mg/L)	3.7 (1.3 - 8.2)	2.3 (0.1 - 6.0)	4.2 (1.4 - 8.2)	5.5 (1.6 - 11.0)	0.002
Cardiac Troponin-T (ng/mL)	0.02 (0.01 - 0.05)	0.02 (0.01 - 0.04)	0.02 (0.01 - 0.05)	0.03 (0.01 - 0.07)	0.016
Brain natriuretic peptide (pg/mL)	76 (29 - 182)	35 (19 - 78)	72 (29 - 163)	148 (79 - 397)	< 0.001
Echocardiography, tomography and scintigraphy parameters					
Left atrium diameter (cm)	42 (38 - 46)	37 (35 - 39)	42 (42 - 43)	48 (46 - 51)	-----
Left ventricular mass index (g/Lt ^{2.7})	72 (59 - 89)	59 (47 - 72)	70 (64 - 85)	86 (72 - 98)	< 0.001
Left ventricular geometry patterns (n, %)					
Normal	30 (10%)	23 (24%)	6 (6%)	1 (1%)	
Concentric remodeling	3 (1%)	3 (3%)	0 (0%)	0 (0%)	
Eccentric hypertrophy	137 (48%)	35 (36%)	45 (48%)	57 (59%)	< 0.001
Concentric hypertrophy	118 (41%)	37 (38%)	43 (46%)	38 (40%)	
Left ventricular ejection fraction (%)	64 (56 - 68)	65 (63 - 69)	64 (59 - 68)	60 (42 - 65)	< 0.001
Diastolic dysfunction (n, %) ¹	220 (87%)	75 (77%)	78 (93%)	67 (94%)	< 0.001
Coronary artery calcium score (Agatston) ²	148 (02 - 546)	09 (00 - 250)	179 (05 - 276)	255 (21 - 1045)	< 0.001
Myocardial ischemia (n, %) ³	51 (23%)	8 (11%)	20 (27%)	23 (32%)	0.002

¹Data regarding diastolic function were available in 253 patients (98 vs. 84 vs. 71).

²Data regarding coronary artery calcium score were available in 264 patients (89 vs. 85 vs. 90).

³Data regarding myocardial ischemia were available in 218 patients (74 vs. 73 vs. 71).

Table 3. Factors associated left atrium diameter in a backward linear regression analysis in patients with CKD stages 3 - 5¹⁻³

Covariates	Unstandardized coefficient	95% Confidence interval	P
Intercept	-----	-----	< 0.001
Male sex	0.156	0.058 - 0.253	0.002
Ischemic heart disease	0.159	0.056 - 0.261	0.003
Logarithm transformed brain natriuretic peptide (pg/mL)	0.076	0.038 - 0.113	< 0.001
Logarithm transformed left ventricular mass index (g/height ^{2.7})	0.638	0.480 - 0.796	< 0.001
Extracellular water (L)	0.026	0.016 - 0.037	< 0.001

¹ Due to missing values, the final complete-cases analysis included 275 individuals.

² Excluded variables: Age, peripheral vascular disease, total of antihypertensive drugs, body mass index, glomerular filtration rate, total cholesterol, C-reactive protein, cardiac troponin-T, left ventricular geometry, left ventricular ejection fraction, diastolic dysfunction, coronary artery calcium score, and myocardial ischemia.

³ The adjusted R² for the model was 0.57.

Table 4. Etiological Cox model representing hazard ratios (95% confidence intervals) for all-cause mortality (n=77) and cardiovascular events (n=62) as a function of an increased left atrial diameter in 288 CKD stages 3 - 5 patients¹.

All-cause mortality		
Model	Variables	LAD (per 1-SD of increase)
1	Crude model	1.53 (1.23 - 1.89)
2	1 + age and sex	1.57 (1.26 - 1.95)
3	2 + glomerular filtration rate	1.54 (1.24 - 1.91)
4	3 + Charlson comorbidity index and malnutrition inflammation score	1.55 (1.24 - 1.92)
5	4 + left ventricular mass index and left ventricular ejection fraction	1.31 (1.01 - 1.70)
6	5 + extracellular water	1.09 (0.80 - 1.47)
Cardiovascular events		
Model	Variables	LAD (per 1-SD of increase)
1	Crude model	1.68 (1.32 - 2.14)
2	1 + age and sex	1.68 (1.31 - 2.15)
3	2 + glomerular filtration rate	1.67 (1.30 - 2.13)
4	3 + Charlson comorbidity index	1.66 (1.29 - 2.12)
5	4 + left ventricular mass index and left ventricular ejection fraction	1.35 (1.01 - 1.81)
6	5 + extracellular water	1.02 (0.96 - 1.08)

¹ Due to missing values, number of events computed after the inclusion of extracellular water was 72 for all-cause mortality and 55 for cardiovascular events.

Conclusion

In patients with nondialysed CKD stages 3 to 5, LAD associates with the risk of mortality and cardiovascular events independent of systemic measures of left ventricular mass and function, but not of fluid overload. These results support previous suggestions that clinical trials are warranted to establish the role of assessment of left atrial volume as a potential valuable tool to aid in patient risk stratification and decision on medical therapy to follow.