Left atrial strain by speckle-tracking: incremental role in diastolic assessment of pediatric patients with chronic kidney disease

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September 13, 2022

Abstract

Background: cardiovascular complications are the leading mortality cause among children with chronic kidney diseases (CKD), being responsible for up to 30% of deaths. Left ventricle (LV) diastolic dysfunction is common and has been linked to poor cardiovascular outcomes. Echocardiographic assessment of diastolic function in CKD children is usually limited to spectral and tissue Doppler imaging, known to be less reliable techniques in pediatrics. Two-dimensional Speckle tracking echocardiography (2DST) evaluation of LA strain has recently been confirmed as a robust measure of diastolic function, in different clinical scenarios. **Objectives:** to investigate LA strain role in diastolic function assessment of children at different stages of CKD, comparing it with standard echocardiographic parameters. **Methods:** From February 2019 to July 2022, 55 consecutive pediatric CKD patients without cardiovascular symptoms and 55 healthy volunteers were evaluated by standard and 2DST echocardiograms. Clinical data were collected from medical records by the attendant physician. **Results:** patients and controls had similar age [9.78 (0.89 – 17.54) years vs. 10.72 (1.03 – 18,44) years; $p = 0.41$] and gender (36M:19F vs. 34M:21F; $p = 0.84$). The median duration of the disease was 8.1 (0.83 - 17.5) years. There were 7 (12.8%) CKD stage I, 4 (7.3%) CKD stage II, 12 (21.8%) CKD stage III, 2 (3.6%) CKD stage IV and 30 (54.5%) CKD stage V patients. Standard echo reveled preserved ([?] 55%) LV EF in all of them. Although average E/e' was higher in CKD [6.99 (4.75 – 14.20) vs. 6.38 (3.88 – 11.11); $p = 0.009$], it was above normal limits in only one individual. Comparing CKD and controls, LA reservoir strain was lower (48.22 ± 10.62% vs. 58.52 ± 10.70%; $p < 0.0001$) and LA stiffness index was higher [0.14 (0.08 – 0.48) $\%^{-1}$ vs. 0.11 (0.06 – 0.23) $\%^{-1}$; $p < 0.0001$]. LV hypertrophy was associated with lower LA reservoir strain (42.05 ± 8.74% vs. 52.99 ± 9.52%; $p < 0.0001$), higher LA stiffness index [0.23 (0.11 – 0.48) $\%^{-1}$ vs. 0.13 (0.08 – 0.23) $\%^{-1}$; $p < 0.0001$) and filling index (2.39 ± 0.63 cm/s x $\%^{-1}$ vs. 1.74 ± 0.47 cm/s x $\%^{-1}$; $p = 0.0001$). Uncontrolled hypertension was associated with lower LA reservoir strain (41.9 ± 10.6% vs. 50.6 ± 9.7; $p = 0.005$). CKD stage showed negative correlation with LA reservoir strain ($r = -0.37$; $p = 0.006$) and conduit strain ($r = -0.28$; $p = 0.0035$), besides positive correlation with LA stiffness index ($r = 0.48$; $p = 0.0002$). E/e' showed inferior accuracy in differentiating CKD patients from controls (AUC = 0.64), when compared with LA reservoir strain (AUC = 0.75) and LA stiffness index (AUC = 0.73). LA reservoir strain showed the best accuracy in differentiating dialysis form non dialysis patients (AUC = 0.77). **Conclusions:** LA strain parameters, especially reservoir strain and stiffness index, showed better accuracy than conventional E/e' ratio concerning diastolic evaluation in pediatric CKD population. Since diastolic dysfunction bears strong prognostic value in CKD, incorporation of LA strain in routine echocardiographic evaluation of this particular pediatric population seems to be an appropriate strategy

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Objectives: to investigate LA strain role in diastolic function assessment of children at different stages of CKD, comparing it with standard echocardiographic parameters.

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Results: patients and controls had similar age [9.78 (0.89 – 17.54) years vs. 10.72 (1.03 – 18,44) years; p = 0.41] and gender (36M:19F vs. 34M:21F; p = 0.84). The median duration of the disease was 8.1 (0.83 - 17.5) years. There were 7 (12.8%) CKD stage I, 4 (7.3%) CKD stage II, 12 (21.8%) CKD stage III, 2 (3.6%) CKD stage IV and 30 (54.5%) CKD stage V patients. Standard echo reveled preserved ([?] 55%) LV EF in all of them. Although average E/e' was higher in CKD [6.99 (4.75 – 14.20) vs. 6.38 (3.88 – 11.11); p= 0.009], it was above normal limits in only one individual. Comparing CKD and controls, LA reservoir strain was lower (48.22 +- 10.62% vs. 58.52 +- 10.70%; p < 0.0001) and LA stiffness index was higher [0.14 (0.08 – 0.48) $\%^{-1}$ vs. 0.11 (0.06 – 0.23) $\%^{-1}$; p < 0.0001]. LV hypertrophy was associated with lower LA reservoir strain (42.05 +- 8.74% vs. 52.99 +- 9.52%; $p < 0.0001$), higher LA stiffness index [0.23 (0.11 – 0.48) $\%^{-1}$ vs. 0.13 (0.08 – 0.23) $\%^{-1}$; $p < 0.0001$) and filling index (2.39 +- 0.63 cm/s x $\%^{-1}$ vs. 1.74 +- 0.47 cm/s x $\%^{-1}$; p = 0.0001). Uncontrolled hypertension was associated with lower LA reservoir strain (41.9 +- 10.6% vs. 50.6 +- 9.7; $p = 0.005$). CKD stage showed negative correlation with LA reservoir strain (r = - 0.37; $p = 0.006$) and conduit strain (r = - 0.28; $p = 0.0035$), besides positive correlation with LA stiffness index (r = 0.48; p = 0.0002). E/e' showed inferior accuracy in differentiating CKD patients from controls (AUC = 0.64), when compared with LA reservoir strain (AUC = 0.75) and LA stiffness index (AUC = 0.73). LA reservoir strain showed the best accuracy in differentiating dialysis form non dialysis patients (AUC = 0.77).

Conclusions:

LA strain parameters, especially reservoir strain and stiffness index, showed better accuracy than conventional E/e' ratio concerning diastolic evaluation in pediatric CKD population. Since diastolic dysfunction bears strong prognostic value in CKD, incorporation of LA strain in routine echocardiographic evaluation of this particular pediatric population seems to be an appropriate strategy.

Keywords: pediatric chronic kidney disease, speckle-tracking echocardiography, left atrial reservoir strain, left atrial stiffness index**.**

1.Introduction

Cardiovascular complications are the leading mortality cause among children and adolescents with chronic kidney diseases (CKD), being responsible for up to 35% of deaths in this particular population[1] . These data are in sharp contrast to the general pediatric population, in which cardiovascular disease mortality is very low and accounts for $< 3\%$ of all deaths. In spite of renal substitutive therapy advances, mortality rates due to cardiovascular diseases in CKD pediatric patients are still a matter of concern[2] . Myocardium remodeling in CKD has traditionally been understood as a physiologic adaptation to reduce ventricular wall stress in response to volume overload and hypertension. However, there are several additional factors that contribute to left ventricle (LV) remodeling and diastolic dysfunction, such as uremic toxins, anemia, FGF23, high serum levels of phosphorus, hyperparathyroidism and fibrosis induced by oxidative stress, as well as by activation of the renin-angiotensin-aldosterone system[3] .

LV diastolic dysfunction is common in CKD patients, and has been linked to poor cardiovascular outcomes[4] . Nevertheless, most of the published literature on the assessment of diastolic function in CKD children has been limited to spectral and tissue Doppler imaging, known to be less reliable techniques in pediatrics. A recent study by Dragulescu *et al* demonstrated that diastolic parameters derived from adult studies are inadequate and not sufficiently discriminatory in childhood[5] . Moreover, the large range of normal pediatric reference values allows diagnosis of diastolic disfunction in only a small proportion of patients[6] .

Given its dynamic relationship with LV function, the left atrium (LA) reflects changes in LV filling pressures, making it a sensitive surrogate marker of diastolic dysfunction[7] . Two-dimensional Speckle tracking echocardiography (2DST) evaluation of LA strain has recently been confirmed as a robust measure of LA function, in different clinical scenarios[8] . The left atrium plays a critical role in maintaining LV filling by functioning as a reservoir for pulmonary venous flow during LV systole, a conduit for blood flow into the LV during early diastole and as a booster pump during late diastole[8] . Alterations in LA reservoir strain precedes changes in LA volumes, favoring its use to detect subclinical diastolic dysfunction[9] . LA stiffness index, calculated as ratio of E/e' to LA reservoir strain, was able to differentiate children with cardiomyopathy from healthy controls with good accuracy[10] . LA filling index, calculated as ratio of Mitral E to LA reservoir strain, showed better diagnostic performance to determine elevated LV filling pressure than E/e'[11] . Furthermore, a recent work demonstrated that LA reservoir strain was an independent predictor of cardiovascular death and adverse events in adult CKD patients[4] .

Based on these considerations, the present study aimed to investigate LA strain role in diastolic function assessment of children and adolescents at different stages of CKD, comparing it with standard echocardiographic parameters.

2.Methods

Study design and population

From February 2019 to July 2022, 55 CKD consecutive patients were recruited during their routine outpatients' visits to our Pediatric Nephrology Unit. None of them showed symptoms of heart failure (New York Heart Association class I) and congenital heart diseases had been ruled out by previous echocardiographic evaluations. Exclusion criteria included inadequate quality of image or refusal to participate in the study. The control group comprised 55 healthy volunteers from primary care clinics. The ethics committee of our institution approved this cross-sectional study, and written informed consent was obtained from all participants and their legal guardians. No patients nor controls have had documented SARS-Cov-2 infection by the time of the study.

Patients' medical records were carefully reviewed for demographic and clinical data by the attendant physician, by the time of the echocardiogram. Demographic data included age, gender, dry weight, height and body surface area (BSA), calculated by the Haycock formula[12] . Clinical data included: CKD etiology; presence, type and duration of dialysis; presence of hypertension; cardiovascular medications in use; hematocrit[13] , phosphorus[14] and parathyroid hormone levels[14] . According to recommendations of the task force, hypertension was defined when systolic and/or diastolic blood pressure was $>95^{\text{th}}$ percentile for the child's age, sex, and height[15] . CKD classification was based on glomerular filtration rate (GFR), estimated by Schwartz

formula: stage I (GRF > 90 ml/min/1.73 m^2); stage II (GFR between 60 and 89 ml/min/1.73 m^2); stage III (GFR between 30 and 59 ml/min/1.73 m^2); stage IV (GFR between 15 and 29 ml/min/1.73 m^2) and stage V (GFR < 15 ml/min/1.73 m^2) [16] .

Standard and 2DST echocardiograms were obtained by the same pediatric cardiologist, blinded to medical records. The examiner was, however, aware of the subjects as either patients or controls. Dialysis patients were evaluated between 4 to 6 hours after the last session.

Standard echocardiogram

Standard transthoracic echocardiography was performed according to the recommendations of the American Society of Echocardiography (ASE) and included M-mode, two-dimensional imaging, conventional, and tissue Doppler evaluation at the septal and lateral mitral annulus[17] . The equipment used was a Philips Affiniti 70 (Andover, MA 01810 USA), with multifrequency transducers (S 5-1 and S 8-3 MHz). Cardiac chamber dimensions were obtained using two-dimensional mode, and left ventricle ejection fraction (LV EF) was calculated by Simpson's method. LV mass (g) was estimated using Devereaux's formula according to the Penn convention and indexed for height (m) raised to an exponential power of 2.7[17] . LV mass index (LVMI) percentile was calculated for each patient, according to age-specific reference intervals proposed by Khoury *et al* . LV relative wall thickness (RWT) was calculated as the sum of septum and posterior wall thickness divided by LV diastolic diameter (normal value [?] 0.42). LV geometry was then classified as concentric remodeling (abnormal RWT and normal LVMI), concentric hypertrophy (abnormal RWT and LVMI) and eccentric LV hypertrophy (abnormal LVMI and normal RWT)[18] .

Evaluation of LV diastolic function included conventional as well as tissue Doppler-based measurements: mitral E and A velocities, E/A ratio, and E/e' ratio, with e' being the average of values obtained by tissue Doppler at the septal and lateral annulus. Left atrial volume was estimated using the biplane area-length method, and values were indexed to the BSA[17] .

2DST echocardiogram

LA-focused two-dimensional cine-loop recordings were obtained from apical four chamber view and digitally stored for offline speckle-tracking auto strain analysis by a dedicated software (Q Lab 15, Philips Medical Systems). The frame rate was set between 80 and 90 frames/s to ensure adequate speckle-tracking. Care was taken to obtain true apical images, avoiding foreshortening. In segments with insufficient tracking, manual readjustment of the endocardial border was applied to optimize tracking quality. The LA tracing for strain was terminated 0.5 cm above the atrioventricular junction, to avoid influence of mitral annular motion[19] . The onset of R-wave on the electrocardiographic trace was used as zero-reference point of the strain analysis. LA reservoir strain was defined as the peak systolic strain, just before mitral valve opening. This was followed by a plateau and a second late peak at the onset of the P-wave indicating the contractile strain. Conduit strain was calculated as the difference between reservoir and contractile strain[19] **(Figure 1).** LA stiffness index was calculated as ratio of E/e' to LA reservoir strain[10] and LA filling index as ratio of Mitral E to LA reservoir strain[11] .

To evaluate global longitudinal LV systolic deformation, two-dimensional cine-loop recordings of apical, four-, three-, and two-chamber views were acquired and digitally stored for analysis. A sector scan angle of 30 - 60° and frame rates of 80–90 Hz were chosen. The endocardial tracing was automatically generated by the computer algorithm (Q Lab 15, Philips Medical Systems) and manually adjusted when necessary. Global LV peak systolic global longitudinal strain was calculated, representing the average values of the 17 ventricular segments analyzed in the three views[20] .

Intra- and interobserver variability was tested, regarding 2DST measurements. The first examiner repeated the analysis of 20 CKD patients and 20 healthy controls randomly selected, 3 months after having acquired images. A second observer, unaware of previous results, also performed offline analysis of the same individuals.

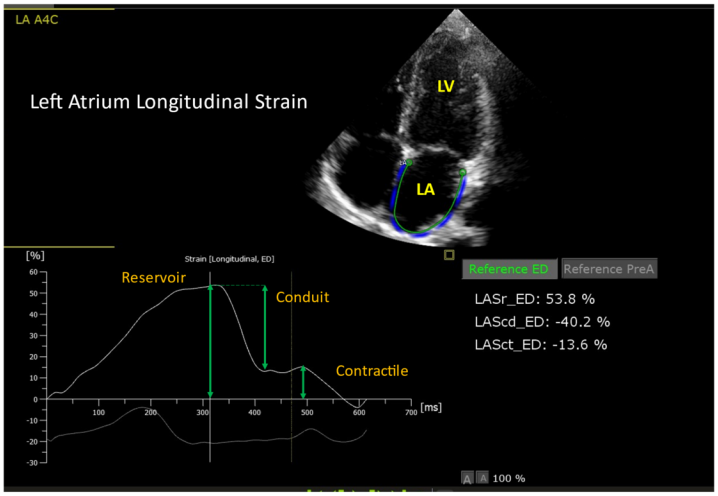

Figure 1. Left atrium longitudinal strain components. LA: left atrium; LV: left ventricle; LASr: reservoir strain; LAScd: conduit strain; LASct: contractile strain.

3.Statistical analysis

Statistical analyses were performed using R software with the R Studio integrated development environment (Version 4.1.0, RStudio, Inc).

Categorical data were reported as percentages and continuous data as mean ± standard deviation (sd) or median (range). Student's t test was used to assess normally distributed continuous data and Mann-Whitney test to assess non-normally distributed continuous data. Linear model was used to compare more than two groups of samples, for variables with normal distribution; Kruskal-Wallis was chosen for non-normally distributed variables. In both situations, multiple comparisons were conducted in the post hoc test applying Bonferroni procedure.

Chi-square test was chosen to compare categorical data. Spearman's correlation coefficient was used to investigate the relationships between 2DST and standard echocardiographic parameters.

The accuracy of E/e', LA reservoir strain, LA stiffness and filling index to identify CKD patients in the total study population, as well as dialysis patients in the CKD group, was analyzed by means of the area under the curve (AUC) of receiver operating characteristic (ROC) curves. The optimal cut-off value of parameter was determined by the Youden Index.

The level of significance was set at 5% ($p < 0.05$). Intra- and interobserver variability for strain measurements was assessed using intraclass correlation coefficient (ICC), with good correlation being defined as ICC > 0.8.

4.Results

Demographic and clinical data

CKD patients and controls had similar age [9.78 (0.89 – 17.54) years vs. 10.72 (1.03 – 18,44) years; $p = 0.41$] and gender distribution (36M:19F vs. 34M:21F; $p = 0.84$). Dry weight, height and body surface area were significantly lower among CKD patients, as expected in chronic diseases in childhood **(Table 1).**

The underlying causes of CKD were congenital anomalies of kidney and urinary tract (CAKUT) in 34 (61.8%), tubulopathies in 7 (12.7%), glomerulopathies in 6 (11%) and miscellanea in 8 (14.5%) patients. The median duration of the disease was 8.1 (0.83 - 17.5) years. There were 7 (12.8%) CKD stage I, 4 (7.3%) CKD stage II, 12 (21.8%) CKD stage III, 2 (3.6%) CKD stage IV and 30 (54.5%) CKD stage V patients.

19 (34.5%) patients did not had hypertension, 21 (38.2%) had controlled hypertension and 15 (27.3%) had uncontrolled hypertension. Antihypertensive drugs included amlodipine (25.5%), enalapril (14.5%), carvedilol (9%), losartan (7.3%), atenolol (3.6%), hydralazine (3.6%) and furosemide (3.6%). 68% of patients treating hypertension received a single agent, 16% two agents and 16% three agents. The median value of hematocrit was 35.6% (27.2% - 46.9%), of serum phosphorus 4.5mg/dl (2.4mg/dl - 7.2mg/dl) and of PTH 128pg/ml (13 pg/ml - 628 pg/ml). 26 (47.3%) CKD patients had anemia[13] , 20 (36.4%) had phosphorus levels above the expected threshold[14] and 33 (60%) showed PTH levels above target values[14] .

Among the 30 dialysis patients, 14(46.7%) were on hemodialysis and 16 (53.3%) on peritoneal dialysis. The average duration of dialysis was 2.25 ± 1.2 years in the hemodialysis group and 1.35 ± 1.09 years in the peritoneal dialysis group.

Standard echocardiogram: CKD patients vs. controls

LV ejection fraction was normal in all individuals (> 55%), although lower in patients than in controls. LV diameters and mass index was higher among CKD patients. Except for LA volume, all diastolic function parameters were different between the two groups. Even though average E/e' was higher in CKD patients, it was above normal limits in only one individual (E/e' = 14.2)[21] **(Table 1).** Among CKD patients, 14 (25.4%) showed normal ventricular geometry, 17 (30.9%) concentric remodeling, 18 (32.7%) concentric hypertrophy and 6 (11%) eccentric hypertrophy.

2DST echocardiogram: CKD patients vs. controls

Satisfactory images were obtained from all CKD patients and controls; no individuals were excluded from myocardial strain evaluation. Patients showed lower values of all LA strain components (reservoir, conduit and contraction), higher LA stiffness and filling index and lower LV peak systolic global longitudinal strain **(Table 1).**

Demographic dada	CKD (n=55)	Control (n=55)	*p*-value
Age (years)	9.5 ± 4.9	10.4 ± 5	0.3878
Gender (male)	36 (65.45%)	34 (61.81%)	0.8429
Dry Weight (kg)	25 (5 – 100)	43 (10 – 84)	**0.0009**
Height (m)	1.29 (0.66 – 1.85)	1.45 (0.74 – 1.84)	**0.0053**
BSA (m^2)	0.97 ± 0.42	1.25 ± 0.44	**0.0009**
Heart rate (bpm)	85 ± 14	90 ± 25	**0.1900**
Standard echocardiographic parameters			
RVDD (mm/m^2)	17.35 (10.7 – 43.43)	12.94 (1.7 – 23.28)	**<0.0001**
LVDD (mm/m^2)	37.14 (21.08 – 81.71)	32.04 (22.47 – 57.71)	**0.0059**
LVSD (mm/m^2)	22.91 (12.97 – 50.57)	18.94 (11.52 – 34.38)	**0.0002**
LV EF (%)	66.69 ± 5.92	72.05 ± 6.09	**<0.0001**
Septum (mm/m^2)	7.87 (4.55 – 19.33)	5.52 (3.48 – 11.25)	**<0.0001**
LV posterior wall (mm/m^2)	7.88 (4.58 – 17.33)	5.66 (4.05 – 9.43)	**<0.0001**
LV mass index ($g/m^{2,7}$)	41.74 (17.72 – 108.39)	32.57 (19.07 – 74.7)	**0.0010**
Frequency of individuals with LV mass index > P95	24 (43.63%)	0 (0%)	**<0.0001**
Relative wall thickness (RWT)	0.44 ± 0.08	0.36 ± 0.05	**<0.0001**
Frequency of individuals with RWT > 0.42	35 (63.63%)	0 (0%)	**<0.0001**
LA diameter (mm/m^2)	23.60 (12.09 – 58)	20.44 (11.59 – 37.29)	**0.0061**
LA volume (ml/m^2)	15.63 ± 05.08	16.19 ± 04.54	0.5385
Mitral E (cm/s)	92.79 ± 21.47	102.91± 17.41	**0.0077**
Mitral A (cm/s)	61.6 (27.6 – 142)	51.40 (33.8 – 93.6)	**0.0180**
Mitral E/A (cm/s)	1.57 ± 0.56	1.96 ± 0.51	**0.0003**
Tissue Doppler septal e' (cm/s)	10.7 ± 2.61	13.46 ± 2.2	**<0.0001**
Tissue Doppler lateral e' (cm/s)	14.2 (6.58 – 29.2)	18.8 (11.5 – 33.1)	**<0.0001**

Demographic dada	CKD (n=55)	Control (n=55)	*p*-value
E/e' (cm/s)	6.99 (4.75 – 14.2)	6.38 (3.88 – 11.11)	**0.0092**
2DST Echocardiographic parameters			
Left atrium longitudinal reservoir strain (%)	48.22 ± 10.62	58.52 ± 10.7	**<0.0001**
Left atrium longitudinal conduit strain (%)	37.26 ± 09.77	43.79 ± 10.13	**0.0008**
Left atrium longitudinal contractile strain (%)	11.8 (1.60 – 19.6)	14.30 (5.20 – 27.2)	**0.0009**
Left atrium stiffness index ($\%^{-1}$)	0.14 (0.08 – 0.48)	0.11 (0.06 – 0.23)	**<0.0001**
Left atrium filling index (cm/s x $\%^{-1}$)	2.02 ± 0.63	1.8 ± 0.39	**0.0335**
Left ventricle peak systolic global longitudinal strain (%)	19.4 (9 – 36.4)	21.9 (18.1 – 27.2)	**<0.0001**

Table 1. CKD patients vs. controls: demographic data, standard and 2DST echocardiographic parameters. RVDD: right ventricle diastolic diameter; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LV: left ventricle; LA: left atrium; P95: 95^{th} percentile; RWT: relative wall thickness; bold indicates p<0.05; continuous data are presented as mean ± standard-deviation or median (minimum – maximum) and categorial as frequency and percentage.

In the CKD group, LA reservoir strain correlated negatively with LV diastolic diameter (r = -0.28; p = 0.038), LV mass index (r = -0.48; p = 0.0002) and E/e' (r = -0.48; p = 0.0002). LA reservoir strain correlated positively with lateral e' (r = 0.46;p = 0.0004), septal e' (r = 0.34; p = 0.01) and average e' (r = 0.49; p = 0.0001). LA conduit strain correlated negatively with LV diastolic diameter (r = -0.34; p = 0.01), LV mass index (r = -0.42; p = 0.001), and E/e' (r = -0.30; p = 0.025). LA conduit strain correlated positively with lateral e' (r = 0.46;p = 0.0004), septal e' (r = 0.40; p = 0.0027) and average e' (r = 0.50; p = 0.0001). LA contractile strain correlated negatively with mitral E (r = -0.28; p = 0.037) and E/e' (r = -0.33; p = 0.014). LA stiffness index correlated negative with patients' height (r = 0.32; p = 0.018), lateral e' (r = -0.57; p< 0.0001), septal e' (r = -0.32; p = 0.018) and average e' (r = -0.56; p < 0.0001). La stiffness index correlated positively with LV diastolic diameter (r =0.35; p = 0.0088), LV mass index (r = 0.50; p = 0.0001), mitral E (r = 0.35; p = 0.0082), mitral A (r = 0.29; p = 0.034), and E/e' (r = 0.83; p < 0.0001). LA filling index correlated positively with LV mass index (r = 0.37; p = 0.006), mitral E (r = 0.70; p < 0.0001) and E/e' (r = 0.73;p < 0.0001).

2DST echocardiographic parameters according to CKD stage

CKD stage showed weak negative correlation with LA reservoir strain (r = - 0.37; p = 0.006) and conduit strain (r = - 0.28; p = 0.0035). A moderate positive correlation was detected between CKD stage and LA stiffness index (r = 0.48; p = 0.0002). LA contractile strain, LA filling index and LV peak systolic global longitudinal strain did not correlate with CKD stage.

2DST echocardiographic parameters according to LV mass index in CKD

Patients with LV with LV mass index > 95^{th} percentile (P95) showed lower values of LA reservoir and conduit strain, as well as higher stiffness and filling index. LA contractile strain and LV peak systolic global longitudinal strain were similar between groups **(Table 2).**

2DST echocardiogram	LV mass index [?] P95 (n=31)	LV mass index > P95 (n=24)
Left atrium longitudinal reservoir strain (%)	52.99 ± 9.52	42.05 ± 8.74
Left atrium longitudinal conduit strain (%)	41 ± 9.63	32.43 ± 7.74
Left atrium longitudinal contractile strain (%)	12.5 (4.2 – 19.6)	9.3 (1.6 – 16.2)
Left atrium stiffness index ($\%^{-1}$)	0.13 (0.08 – 0.23)	0.23 (0.11 – 0.48)
Left atrium filling index (cm/s x $\%^{-1}$)	1.74 ± 0.47	2.39 ± 0.63
Left ventricle peak systolic global longitudinal strain (%)	19.4 (15.2 – 36.4)	19.35 (9 – 27.5)

Table 2. 2DST echocardiogram: CKD patients with LV hypertrophy vs. CKD patients without LV hypertrophy. P95: 95thpercentile. Bold indicates p<0.05; continuous data are presented as mean ± standard-deviation or median (minimum – maximum).

2DST echocardiographic parameters according to LV geometry in CKD

CKD patients with concentric hypertrophy had lower LA reservoir strain, higher LA stiffness index and LA filling index than CKD patients with normal LV geometry or concentric remodeling. LA conduit strain was lower in CKD patients with concentric hypertrophy, compared to patients with normal LV geometry **(Table 3).**

2DST echocardiogram	LV geometry	LV geometry	LV geometry
	Normal (n=14)	Concentric remodeling (n=17)	Concentric remodelin
LA longitudinal reservoir strain (%)	**54.36 ± 8.6 a**	**51.86 ± 10.34 a**	**40.97 ± 9.53 b**
LA longitudinal conduit strain (%)	**41.89 ± 9.32 a**	**40.27 ± 10.1 ab**	**32.23 ± 8.59 b**
LA longitudinal contractile strain (%)	13.05 (4.2 – 19.6) a	12.2 (4.2 – 19.4) a	6.75 (1.6 – 16.2) a
LA stiffness index (%$^{-1}$)	**0.12 (0.08 – 0.23) a**	**0.13 (0.08 – 0.19) a**	**0.23 (0.11 – 0.48) b**
LA filling index (cm/s x %$^{-1}$)	**1.73 ± 0.49 a**	**1.74 ± 0.46 a**	**2.43 ± 0.59 b**
LV peak systolic longitudinal strain (%)	19.65 (17.1 – 36.4) a	19 (15.2 – 26.9) a	19.35 (9 – 27.5) a

Table 3. 2DST echocardiogram: LA and LV strain according to LV geometry. LV: left ventricle; LA left atrium. Bold indicates p<0.05; continuous data are presented as mean ± standard-deviation or median (minimum – maximum). Different lowercase letters indicate significant differences between groups at the 5% level.

2DST echocardiographic parameters according to blood pressure control in CKD

CKD patients with uncontrolled hypertension showed lower LA longitudinal reservoir and conduit strain. LV peak systolic global longitudinal strain was also reduced in the group with uncontrolled hypertension

(Table 4).

2DST echocardiogram	No hypertension/ controlled hypertension (n=40)	Uncontrolle
Left atrium longitudinal reservoir strain (%)	50.6 ± 9.7	41.9 ± 10.6
Left atrium longitudinal conduit strain (%)	38.30 (22.3 – 63.60)	32.00 (11.60
Left atrium longitudinal contractile strain (%)	12.10 (1.60 – 19.40)	10.00 (3.00
Left atrium stiffness index (%$^{-1}$)	0.14 (0.08 – 0.28)	0.15 (0.10 –
Left atrium filling index (cm/s x %$^{-1}$)	1.93 ± 0.57	2.27 ± 0.72
Left ventricle peak systolic global longitudinal strain (%)	19.85 (15.20 – 36.40)	18.80 (9.00

Table 4. 2DST echocardiogram: CKD patients with normal pressure/controlled hypertension vs. CKD patients with uncontrolled hypertension. Bold indicates p<0.05; continuous data are presented as mean ± standard-deviation or median (minimum – maximum).

Comparisons between non-dialysis and dialysis CKD patients

Non-dialysis and dialysis CKD patients were similar regarding age (10.6 ± 4.1years vs. 8.5 ± 5 years; $p = 0.11$) and gender distribution (13M:12F vs 23M:7F; $p = 0.10$). Dialysis patients had lower dry weight, height and body surface area.

Standard and 2DST echocardiographic parameters of non-dialysis and dialysis patients are presented in **Table 5.** LV diameters, LV mass index and E/e' were higher among dialysis patients, whereas LV ejection

fraction and LA volume were similar between groups. LA reservoir strain was lower and LA stiffness index were higher in the dialysis group.

Demographic data	Non-Dialysis (n=25)	Dialysis (n=30)	*p*-value
Age (years)	10.6 ± 4.1	8.5 ± 5	0.1100
Gender (male)	13 (52.00%)	23 (76.67%)	0.1029
Dry Weight (kg)	31.00 (14.50 – 100.00)	18.05 (05.00 – 73.00)	**0.0075**
Height (m)	01.04 (01.00 – 01.85)	01.11 (00.66 – 01.67)	**0.0026**
BSA (m^2)	01.12 ± 00.39	00.85 ± 00.41	**0.0046**
Heart rate (bpm)	100 ± 13	105 ± 14	**0.1800**
Standard echocardiographic parameters			
RVDD (mm/m^2)	14.89 (10.7 – 43.43)	20.48 (11.76 – 39.33)	**0.0007**
LVDD (mm/m^2)	32.73 (22.33 – 81.71)	46.48 (21.08 – 70)	**0.0070**
LVSD (mm/m^2)	20.47 (15.27 – 50.57)	27.76 (12.97 – 45.95)	**0.0043**
LV EF (%)	66.35 ± 6.48	66.97 ± 5.51	0.7082
Septum (mm/m^2)	7.19 (4.55 – 17.71)	9.03 (4.58 – 19.33)	**0.0016**
LV posterior wall (mm/m^2)	7.19 (4.6 – 17.14)	9.18 (4.58 – 17.33)	**0.0014**
LV mass index ($g/m^{2,7}$)	32.37 (17.72 – 54.1)	51.6 (21.58 – 108.39)	**<0.0001**
Frequency of individuals with LV mass index > P95	6 (24.00%)	18 (60.00%)	**0.0160**
RWT	0.43 (0.31 – 0.64)	0.46 (0.25 – 0.63)	0.2452
Frequency of individuals with RWT > 0.42	14 (56.00%)	21 (70.00%)	0.4276
LA diameter (mm/m^2)	22.55 (12.09 – 58)	25.77 (14.31 – 47.37)	0.0654
LA volume (ml/m^2)	16.18 (9.15 – 28.57)	13 (9.13 – 24)	0.1369
Mitral E (cm/s)	92.98 ±16.51	92.64 ± 25.16	0.9524
Mitral A (cm/s)	55.1 (27.6 – 102)	64.45 (36.9 – 142)	**0.0006**
Mitral E/A (cm/s)	1.87 ± 0.59	1.33 ± 0.41	**0.0003**
Tissue Doppler septal e' (cm/s)	11.99 ± 2.25	9.63 ± 2.42	**0.0004**
Tissue Doppler lateral e' (cm/s)	16.66 ± 3.61	13.11 ± 3.58	**0.0006**
E/e' (cm/s)	6.3 (4.75 – 9.54)	7.89 (5.47 – 14.2)	**0.0007**
2DST echocardiographic parameters			
Left atrium longitudinal reservoir strain (%)	52.24 ± 9.58	44.87 ± 10.42	**0.0086**
Left atrium longitudinal conduit strain (%)	40.0 2 ± 9.82	34.96 ± 9.26	0.0563
Left atrium longitudinal contractile strain (%)	12.2 (4.2 – 19.6)	9.8 (1.6 – 17.5)	0.1281
Left atrium stiffness index ($\%^{-1}$)	0.13 ± 0.05	0.2 ± 0.08	**0.0005**
Left atrium filling index (cm/s x $\%^{-1}$)	1.86 ± 0.55	2.15 ± 0.66	0.0766
Left ventricle peak systolic global longitudinal strain (%)	19.4 (16.1 – 26.9)	19.35 (9 – 36.4)	0.7738

Table 5. Non-dialysis vs. dialysis CKD patients: demographic data, standard and 2DST echocardiographic parameters. RVDD: right ventricle diastolic diameter; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LV: left ventricle; LA: left atrium; P95: 95^{th} percentile; RWT: relative wall thickness; Bold indicates p<0.05; continuous data are presented as mean ± standard-deviation or median (minimum – maximum).

Comparisons between patients on peritoneal dialysis and hemodialysis

LA strain parameters were not different comparing peritoneal and hemodialysis patients **(Table 6).**

Strain parameters	Peritoneal (n=14)	Hemodialysis (n=16)	P-value
Left ventricle peak systolic global longitudinal strain (%)	21.20±6.47	19.55±2.83	0.3894
Left atrium longitudinal reservoir strain (%)	41.36±10.41	47.94±9.72	0.0859
Left atrium longitudinal conduit strain (%)	31.63±9.24	37.88±8.52	0.0661

Strain parameters	Peritoneal (n=14)	Hemodialysis (n=16)	P-value
Left atrium longitudinal contractile strain (%)	8.40 (4.50 – 16.00)	12.15 (1.60 – 17.50)	0.9834
Left atrium stiffness index ($\%^{-1}$)	0.21 (0.11 – 0.48)	0.18 (0.10 – 0.28)	0.3816
Left atrium filling index (cm/s x $\%^{-1}$)	2.29 (1.25 – 2.95)	2.14 (0.88 – 3.33)	0.6100

Table 6. Peritoneal vs. hemodialysis: 2DST parameters.

Receiver operating characteristic (ROC) curves

The best identification accuracy of CKD patients was obtained with LA reservoir strain: AUC = 0.75 (0.66 – 0.84); optimal cut-off value of 52.3%; specificity of 72.73% and sensitivity of 74.55%**(Figure 2)** . Regarding accuracy in differentiating dialysis from non-dialysis CKD patients, the best parameter was LA stiffness index: AUC = 0.77 (0.65 – 0.90); optimal cut-off value of 0.15 $\%^{-1}$; specificity of 84% and sensitivity of 67% **(Figure 3).**

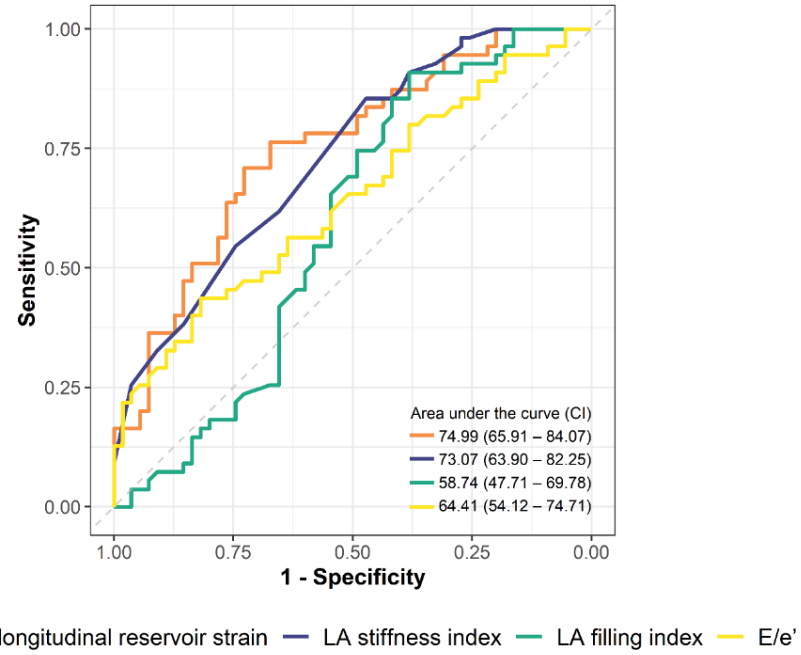

Figure 2. Receiver operating characteristic curve showing the accuracy of each diastolic function parameter in differentiating CKD patients from controls. LA: left atrium

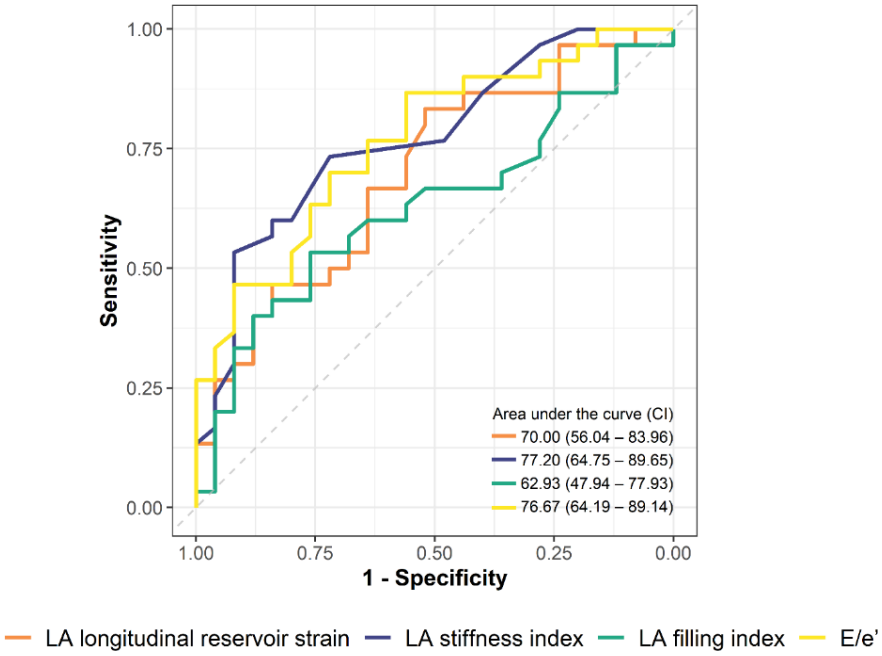

Figure 3. Receiver operating characteristic curve showing the accuracy of each diastolic function parameter in differentiating dialysis from non-dialysis CKD patients. LA: left atrium.

Intra and inter-observer variability

Adequate ICC (> 0.80) was obtained for all 2DST echocardiographic parameters for intra and inter-observer variability, except for LA contractile strain (ICC = 0.61 for inter-observer variability) **(Table 7).**

Parameters	Intra-observer test	Intra-observer test	Intra-observer test	I
	ICC (CI)	*p*-value	ICC (CI)	
Left atrium longitudinal reservoir strain (%)	0.99 (0.98 – 1.00)	**<0.0001**	0.83 (0.57 – 0.93)	0
Left atrium longitudinal conduit strain (%)	0.99 (0.98 – 1.00)	**<0.0001**	0.87 (0.67 – 0.95)	0
Left atrium longitudinal contractile strain (%)	0.92 (0.81 – 0.97)	**<0.0001**	0.61 (0.03 – 0.84)	0
Left ventricle peak systolic global longitudinal strain (%)	0.98 (0.94 – 0.99)	**<0.0001**	0.89 (0.74 – 0.96)	0

Table 7. Intra and inter-observer variability of 2DST echocardiographic parameters. ICC: intraclass correlation coefficient.

5.Discussion

The present study stands out for the detection of subclinical LA deformation impairment in pediatric CKD patients at different stages of the disease, with great feasibility and reproducibility. It was possible to demonstrate significant correlations between LA strain and standard echocardiographic diastolic parameters, as well as LA strain superior accuracy in differentiating CKD patients from healthy controls and dialysis from non-dialysis CKD patients.

Like our study, previous works using tissue Doppler imaging suggested impaired LV diastolic parameters early in the progression of pediatric CKD, with the worst values being recorded in patients undergoing maintenance dialysis [22] . Nevertheless, only one CKD patient in our study showed average E/e' greater than 14, one of the key noninvasive markers of diastolic dysfunction among patients with preserved ejection fraction, according to ASE guidelines[21] .

There is growing evidence that current algorithms for evaluation of diastolic dysfunction in adults are not as reliable in pediatric populations. In fact, in children with various types of cardiomyopathies, criteria for diastolic dysfunction were discrepant in a majority of patients and half of them exhibited E/e' values that were within the normal range for age[5] . Not surprisingly, E/e' showed inferior accuracy in differentiating our pediatric CKD patients from controls (AUC = 0.64), when compared to LA reservoir strain (AUC = 0.75) and LA stiffness index (AUC = 0.73). In line with the study of Morris *et al* , our data favors LA reservoir strain and LA stiffness index as additive diastolic parameters, which may improve the accuracy of E/e' ratio when applied in pediatric population[23] .

In spite of significant reduction of LA reservoir strain, LA volume index in our pediatric CKD and control group were alike. Indeed, LA reservoir strain alterations had been recently shown to precede LA volume increase, classically known as a hallmark of diastolic dysfunction [24] . Studies in adult CKD patients have depicted an inverse correlation between LA strain and mean wedge pressure obtained by catheterization, independently of LA volume[25] . Nakanishi *et al* hypothesized different underlying mechanisms that may be implicated in LA function impairment in CKD, with still normal LA volume: chronic inflammatory state, LA myocardium fibrosis induced by chronic renin–angiotensin–aldosterone activation, sympathetic stimulation and oxidative stress[26] .

There is scant published data regarding diastolic function of pediatric CKD patients through the different stages of the disease. In our study, CKD stage correlated negatively with LA reservoir strain and positively with LA stiffness index, suggesting that these novel parameters may reflect kidney disease progression and diastolic function deterioration, even in the absence of overt heart failure. Our findings are consistent with those of Gan *et al* . The authors demonstrated the prognostic value of LA reservoir strain as an independent predictor of progression of renal dysfunction in stage 3/4 adult CKD patients, without previous cardiac history and stable renal function [27] .

Although our CKD patient with and without LV mass index > 95$^{\text{th}}$ percentile showed similar LV systolic strain, LA strain impairment was significantly associated with LV hypertrophy. Moreover, CKD patients with concentric hypertrophy had lower LA reservoir strain, higher LA stiffness index and LA filling index than CKD patients with normal LV geometry or concentric remodeling. This information seems clinically relevant, since LV hypertrophy is the most important indicator of cardiovascular risk in CKD population and abnormal patterns of LV geometry adversely affect prognosis[28,29,30] .

Uncontrolled hypertension in our CKD patients was frequent (27.3%), and associated with lower LA reservoir strain and higher LA stiffness index. These findings may impact on future prognosis, since a recent study from Zhao *et al* demonstrated that LA stiffness index precedes LV hypertrophy, besides being independently correlated with individual target organ damage in adult patients with hypertension[31] .

Even though dialysis had been previously associated with subclinical systolic disfunction[32] , values of LV peak systolic global longitudinal strain were similar, comparing our non-dialysis and dialysis pediatric CKD patients. Conversely, LA reservoir strain and stiffness index were both impaired in our dialysis group, suggesting diastolic involvement may precede systolic compromise in children. Rapid fluid removal and intradialytic hypotension during hemodialysis, leading to myocardial ischemia and dysfunction (myocardial stunning), may contribute to LV diastolic impairment[2]. In a small cohort of pediatric CKD patients, Doan *et al* had also documented subclinical diastolic dysfunction by evaluating LA strain prior to, during and after hemodialysis sessions. The authors described significant reduction of LA strain in mid-dialysis, with return to baseline values post-dialysis[33] .

Finally, LA stiffness index showed the best accuracy in differentiating our dialysis from non-dialysis CKD patients, favoring it as a useful diastolic parameter in children under renal replacement therapy.

6.Study limitations

Possible limitations include the small number of patients enrolled and the single center character of the study, which may preclude generalizations of conclusions to larger populations.

Patients undergoing dialysis were examined closer to their clinically estimated dry weight, since we did not assed blood volume.

We did not include serum levels of pro-Brain Natriuretic Peptide (pro-BNP) or inflammation mediators in the present study, since they are not routinely ordered by the physicians at our outpatients' clinics. Those exams could have helped to detect subtle myocardial impairment associated with LA strain compromise.

Although hemodialysis is usually associated with greater cardiovascular compromise than peritoneal dialysis[2] , we did not find significant difference of LA strain parameters between these two types of renal replacement therapy, perhaps due to the small sample size in each group of patients.

7.Conclusion

LA strain parameters, especially reservoir strain and stiffness index, showed better accuracy than conventional E/e' ratio concerning diastolic evaluation in pediatric CKD population. Since diastolic dysfunction bears strong prognostic value in CKD, incorporation of LA strain in routine echocardiographic evaluation of this particular pediatric population seems to be an appropriate strategy.

Longitudinal assessment using these novel non-invasive indices may unfold the effects of CKD on long-term cardiovascular health throughout children development.

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