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PLASMA FGF23 IS ASSOCIATED WITH LEFT ATRIAL REMODELING IN CHILDREN ON HEMODIALYSIS

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Abstract

Background: FGF23 mediates cardiac fibrosis through the activation of pro-fibrotic factors in *in-vitro* models and is markedly elevated in kidney disease. Left atrial global longitudinal strain (LA GLS) derived by echocardiographic speckle-tracking measures the longitudinal shortening of the LA walls, quantifies atrial performance, and may enable detection of early LA remodeling in the setting of normal ventricular function. We hypothesized that LA GLS is abnormal in children on hemodialysis (HD) compared to healthy controls of comparable age/sex distribution and that, among HD patients, greater FGF23 levels are associated with abnormal LA GLS.

Methods: Clinical and echocardiographic data from 29 children receiving HD and 13 healthy controls were collected in a cross-sectional single center study. Plasma FGF23 concentrations were measured using ELISA. Primary outcome was LA GLS measured using 2D speckle-tracking strain analysis. Linear regression analysis was used to investigate predictors of LA GLS in HD.

Results: Median dialysis vintage was 1.5 (IQR 0.5–4.3) years. Median intact FGF23 levels were substantially higher in the HD vs control group (1206 [215, 4707] vs 51 [43, 66.5] pg/ml;

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Authors Contributions

Research idea and study design: SS, JHI, IBS, KLN; data acquisition: IBS, MRH, NRP, SS, KLN; data analysis/interpretation: NRP, JHI, SS, KLN; statistical analysis: SS, NRP; supervision or mentorship: IBS, JHI, KLN. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated, and resolved, including with documentation in the literature if appropriate.

Statements and Declarations-

Dr. Ix is principal investigator of an investigator-initiated research grant from Baxter International, serves as a data safety monitoring board member for Sanifit International, and has served on advisory boards for Alpha Young, AstraZeneca, Ardelyx Inc., and Jnana Inc. Dr. Salusky has served on advisory boards for Akebia, Inozyme and Ardelyx.

Remaining authors have declared no relevant conflicts of interest.

P=0.0001) as was LA GLS (39.9% SD 11.6 vs 32.8% SD 5.7; P=0.04). Among HD patients, higher FGF23 was associated with lower LA GLS (β per unit Ln-FGF23: −2.7; 95% CI slope −5.4, −0.1; P=0.04 after adjustment for age, body size, and HD vintage. FGF23 was not associated with LA phasic reservoir, conduit, or contractile strain.

Conclusions: In children on HD and preserved LVEF, greater FGF23 is associated with lower LA GLS (indicative of impaired atrial performance).

Keywords

FGF23; LA function; Children

Introduction

Dialysis patients exhibit disordered mineral bone metabolism which is characterized by high plasma concentrations of fibroblast growth factor (FGF23) concentrations, a bone-derived hormone that is increased early and progressively in both children[1] and adults[2] with chronic kidney disease (CKD). This is thought to be a result of increased bone production of FGF23 (2) and decreased degradation, but clearance by dialysis does not appear to contribute meaningfully to the circulating level (1). Elevation of FGF23 in HD patients is thought to be a result of several factors including residual renal function, dialysis vintage, phosphate clearance (4,5). Elevated concentrations of circulating FGF23 have been associated with poor clinical outcomes in different patient populations,[3, 4] including children with CKD [5]. Studies in animals and *in vitro* demonstrate that FGF23 may have direct pathogenic effects on the heart, causing left ventricular (LV) hypertrophy via an FGF receptor 4-dependent pathway[6] and mediating cardiac fibrosis through the activation of pro-fibrotic factors[7]. However, the association of plasma FGF23 concentrations with left atrial (LA) functional performance in children on HD remains unclear.

The LA plays a key role in modulating LV filling by acting as an elastic reservoir to store venous return during ventricular systole (or atrial diastole). During early- to mid-LV diastole, the LA acts as a passive conduit to enable the flow of blood from the pulmonary veins into the LV and further serves as a priming pump to boost LV filling during active atrial systole. Therefore, LA remodeling or myopathy--reflected as functional changes during phases of the cardiac cycle--may precede geometric and morphologic changes such as increased LA volume. Both poor atrial performance and LA remodeling have been associated with a predisposition to arrythmias,[8, 9] which was identified as the most common cardiac-related event in a study of 1454 incident pediatric dialysis patients[10]. Quantification of functional changes in the myocardium is made possible through use of strain parameters derived from 2-dimensional (2D) echocardiography.While LA strain has been examined in adults with CKD and preserved LVEF, the relationship between FGF23 and LA strain in pediatric CKD patients remains unexplored.

In children with kidney failure, cardiovascular disease is the leading cause of death[11] and young adults who develop kidney failure during childhood have a significantly diminished life expectancy even though they have neither diabetes nor symptomatic atherosclerosis at the time of CKD diagnosis to suggest as a direct cause of their CKD. Moreover,

children with kidney failure generally have preserved LV systolic function[12, 13]. Thus, identification of early markers of cardiac remodeling may provide new insights into biological pathways and offer opportunities for earlier prevention and treatment before cardiovascular disease is clinically manifest in a young and high-risk population.

Although echocardiographic-derived LA size or volume index has been used routinely in adult cardiovascular imaging laboratories to evaluate LA function, 2D-STE provides a more sensitive tool than conventional cardiac ultrasound methods for tracking cardiac tissue motion and deformation [14, 15]. Through provision of cardiac phasic analysis and by tracking “speckles” or acoustic signals relative to other speckles within the ultrasound image, 2D-STE provides insight into myocardial tissue function beyond depiction of myocardial geometric changes in size or volume as surrogates for cardiac function. Specifically, LA GLS measures the longitudinal shortening of the LA walls, quantifies global atrial performance, and may serve as an indicator of early remodeling in the setting of normal ventricular function[16, 17].

The goal of the present study were to: a) assess LA global longitudinal strain (GLS) using 2D speckle-tracking echocardiography (2D-STE) in children with kidney failure treated by hemodialysis (HD) and healthy controls; and b) to study the association of plasma FGF23 with LA performance parameters in children with kidney failure on HD. We hypothesize that LA GLS in children on HD is different from that observed in healthy controls, and that higher FGF23 concentration is associated with reduced LA GLS in children with kidney failure treated with hemodialysis,

Materials & Methods

Study Design and Setting

This study was approved by the local Institutional Review Board and all participants provided written informed consent. This cohort was previously described [18]. Briefly, the current study is a secondary analysis of participants who were enrolled in a larger single center cohort study of kidney disease. The patient population in the larger study consisted of children and adults receiving outpatient care for chronic kidney disease stage 2 through stage 5 (including those treated with dialysis) between 2009 and 2011. Inclusion criteria for the current analysis included pediatric kidney failure patients on HD as their first type of kidney replacement therapy and who had both intact FGF23 data as well as clinical echocardiographic studies (within 6 months of the blood draw for intact FGF23 assays). Exclusion criteria for the current analysis included poor echocardiographic image quality, arrhythmia, and congenital heart disease.

Thirteen healthy subjects, without any known disease, of comparable age and sex distribution, were recruited from the same center to serve as the control group. The choice of healthy controls was for comparison of cardiac function in a pediatric hemodialysis cohort relative to normal healthy cardiac function of control subjects of comparable age.

Clinical and Laboratory Evaluation

Demographic parameters (age, sex, height, weight) and clinical variables, including HD vintage, cause of kidney failure, hemoglobin, markers of iron status (ferritin, total iron binding capacity), inflammation (C-reactive protein) were collected. The formula for calculating body surface area (BSA) was (0.0061 X *height* + 0.0124 X *weight* – 0.0099) [19]. A single-thaw of frozen plasma samples collected at the beginning of the subjects' HD sessions and stored at –80°C was used to measured intact FGF23 in duplicate using a second-generation ELISA (Quidel, San Diego, CA) as previously described[3]. Intact FGF23 levels for the control group were similarly assayed. The mean intra- and inter-assay coefficients of variation were 2% and 3.5%, respectively; the lower limit of detection was 1.5 pg/ml. Other clinical variables were abstracted from the patient's clinical laboratory medical records.

Echocardiographic Assessment

All patients were imaged using commercially available echocardiographic systems (Terason t3000 Ultrasound, Burlington, MA, USA; Philip iE33 Ultrasound with S5–1 transducer, USA). Mean frame rate for all the study participants was 49.8 ± 10.3 Hz. 2D-STE was conducted using vendor-independent software (2D Cardiac Performance Analysis, TomTec Arena, Unterschleisseim, Germany). Apical 4-chamber echocardiographic images were used for all LA STE analyses (Figure 1). To generate LA strain and strain rate curves, the endocardial border of the LA was traced in a clockwise direction from the base of the anterior mitral valve leaflet to the lateral aspect of the mitral valve annulus. Left atrial appendage, pulmonary veins, and the aorta were excluded from LA tracings. LA reservoir, conduit, and contractile strain and strain rates were derived from the average strain and strain rate curves. Reservoir strain was defined as the maximum or peak strain value on the average LA strain curve. To obtain contractile strain, the timing of LA contractile phase was identified from the P-wave on the respective EKG or, when the EKG signal was noisy, from the LA mechanical function of the respective 2D image. Conduit strain was defined as the difference between reservoir and contractile strain. LA reservoir strain rate (SRs) was defined as the maximum or peak strain rate value on the average strain rate curve. LA conduit strain rate (SRe) was obtained from the first negative peak of the average strain rate curve. If no primary negative peak was identifiable, SRe was obtained from the timepoint between the T-wave and P-wave. When using LA mechanical function to obtain the contractile strain or strain rate values, the respective peak conduit strain rate was defined as the time point between maximal LA filling (end of reservoir phase) and the initiation of the LA contractile phase. LA contractile strain rate (SRa) was derived from the second negative peak on the average strain rate curve. If no secondary negative peak was identifiable, SRa was collected from the timepoint corresponding to the peak of the p-wave on the respective EKG. If no p-wave was identifiable, the timing for the LA contractile phase was identified using LA mechanical function.

Statistical Analysis

We examined continuous variables graphically and summarized baseline characteristics. Data are tabulated as mean ± standard deviation (SD) or median and IQR (interquartile

range). Comparisons were made using ANOVA (analysis of variance) or ANOVA on ranks, as appropriate. Categorical variables were examined by frequency distribution, recorded as proportions, and compared with the chi-square test. We evaluated the unadjusted correlation between LA GLS and phasic strain parameters with intact FGF23 tertiles using Spearman correlation coefficients. We used multivariate linear regression to evaluate factors associated with change in LA GLS. Our covariates of interest included HD status, natural log transformed intact FGF23 concentrations, HD vintage, age, body surface area (BSA), and sex. We used complete case analysis approach to handle missing data. Importantly, none of the covariates included in the final regression models were missing. Statistical analyses were performed with STATA Version 17 (StataCorp LLC, College Station, Texas). Two-sided P-values <0.05 were considered statistically significant.

Results

Clinical and echocardiographic characteristics of kidney failure patients treated by HD and healthy controls are detailed in Table 1. The mean (±SD) age of HD patients was 16.6 (± 3.8) years, and nine of the 29 patients were female. Causes of kidney failure were congenital anomalies of the kidney and urinary tract (CAKUT), glomerulonephritis or focal segmental glomerulosclerosis. None had diabetes, or essential hypertension, as is characteristic of cardiovascular disease in pediatric kidney failure. None of the subjects had LV hypertrophy, or reduced LV ejection fraction (LVEF). Median dialysis vintage was 1.5 (IQR 0.5, 4.3) years, and the median intact FGF23 concentration was 1206 (IQR 215, 4707) pg/ml, which is comparable to values observed in HD cohorts [20]. Median time elapsed between blood draw and the 2D speckle-tracking echocardiographic study was 86 days (IQR 25, 146). Mean heart rate was 78.5 (±18.5) bpm, and mean LVEF was 60.5 (± 5.3) %. The mean (±SD) age of healthy controls was 15.2 (± 5.4) years, and three of the 13 control subjects were female. All healthy controls had no known kidney disease and the median intact FGF23 concentration was 51 (IQR 43, 66.5) pg/ml. Mean heart rate was 71.2 (±12.5) bpm, and all had preserved LVEF (>60%).

Left Atrial GLS Measurements in kidney failure and Control Subjects

Illustrative LA strain and strain rate curves for a kidney failure and a healthy subject are shown in Figure 1. Mean LA GLS in the HD group was significantly greater than healthy controls (39.9 ± 11.6 vs 32.8 ± 5.7%; P=0.04). The association remained unchanged when adjusted for age and BSA (Table 2).

Correlations and Associations of Left Atrial Strain Measurements with Intact FGF23 in kidney failure

Among the 29 children on HD, we found the correlation between intact FGF23 tertiles and LA GLS was inverse and of moderate strength (r= −0.36; P=0.04; Figure 2). As detailed in the methods section, LA reservoir, conduit, and contractile strain and strain rates were derived from the average strain and strain rate curves (Figure 1). We also found correlation between higher concentrations of intact FGF23 with lower LA contractile strain (r= −0.39; P=0.03). In contrast, higher concentrations of intact FGF23 were not significantly correlated with LA reservoir strain (r= −0.29; P= 0.12) and LA conduit strain (r= −0.17; P= 0.35).

In the univariate model, higher natural log transformed intact FGF23 was significantly associated with lower LA GLS (β: −2.38; 95% CI for slope −4.44 to −0.33; P=0.02). Higher HD vintage was associated with lower LA GLS (β: −2.68; 95% CI for slope −5.080 to -0.282; P=0.03). In the multivariate model, the relationship between intact FGF23 and LA GLS remained significant and was essentially unaltered after adjusting for age, BSA, and HD vintage (β: -2.77; 95% CI for slope −5.47 to −0.07; P=0.04; Table 3), whereas HD vintage was no longer significantly associated with LA GLS once intact FGF23 was taken into account. Intact FGF23 was not significantly associated with LA phasic reservoir, conduit, or contractile strain.

Discussion

This study has two main findings. Compared to healthy controls, we found that children on HD have altered LA GLS. Second, among the children with kidney failure treated with HD who had no LV hypertrophy and preserved systolic function, we found that higher concentrations of intact FGF23 are associated with lower LA GLS. These findings suggest children on HD may have impaired atrial performance which correlated strongly with intact FGF23 levels.

The LA is an underrecognized contributor to LV function. It is vital in maintaining hemodynamic function by contributing 30% of the LV stroke volume. Moreover, the LA facilitates LV filling throughout the cardiac cycle and is directly exposed to LV pressure during ventricular diastole (when the mitral valve is open). Therefore, LA function is closely tied to and influenced by LV filling[21]. In prior studies, LA remodeling and ultimately dysfunction, has been associated with adverse clinical outcomes,[22–24] further emphasizing the importance of its early identification. This is particularly true in the setting of heart failure with preserved ejection fraction which is highlighted by LA dysfunction [25, 26]. LA remodeling may occur as a pathophysiological response to insults including inflammation and stretching of the atria, leading to atrial myopathy. Increased collagen turnover and atrial fibrosis have been described in rodent models of atrial remodeling[27, 28]. In addition, LA remodeling is also associated with impaired calcium uptake by cardiac myocytes leading to slow and incomplete relaxation[29].

The role of LA strain in patients on HD and preserved LVEF has been examined in a few studies utilizing 2D-STE (Supplementary Table 1) but limitations exist. Most of the studies were conducted in adults with co-existing cardiovascular risk factors or disease. In separate studies comparing adult kidney failure patients with healthy controls, LA phasic strain parameters (reservoir, conduit, contractile), [30, 31] and LA GLS measurements were lower than among their respective healthy control groups and the degree of impairment in LA function preceded the development of left atrium dilatation[32,33]. Although associations between LA GLS, LA contractile function with LA volumes, B-type natriuretic peptide and blood volume removal in kidney failure has been examined, [34, 35, 36] the relationship of LA strain with FGF23 concentrations remains unexplored.

In the current study, we demonstrate mean LA GLS to be higher in children on HD when compared to healthy controls with similar age/gender distribution. However, LA

GLS has an inverse relationship with intact iFGF23, such that in the highest tertile group of intact iFGF23, LA GLS was lower. We speculate that the early augmentation of LA GLS in kidney failure (relative to those found in healthy controls) is compensatory to factors leading to LA remodeling which are ultimately beyond adaptive responses. One such mechanism leading to atrial remodeling may be FGF23-induced atrial fibrosis. FGF23 is a phosphaturic hormone produced mainly by osteocytes. As kidney function declines, FGF23 rises early and counteracts phosphate accumulation. Elevated FGF23 levels have been shown to independently associated with cardiovascular disease and mortality in CKD and kidney failure populations[3–5]. Further, animal and *in vitro* models demonstrate that FGF23 has direct pathogenic effects on the heart, causing LV hypertrophy via an FGF receptor 4-dependent pathway [6]. Through the activation of pro-fibrotic factor β-catenin, which participates in transforming growth factor (TGF-β1) signaling, FGF23 promotes myocardial fibrosis by indirectly affecting the expression of collagen, fibronectin, and proteoglycans[7, 37]. Moreover, FGF23 administration to cardiomyocytes *in vitro* has been shown to result in abnormalities of intracellular calcium handling, [38] this may manifest as abnormalities in myocyte tissue motion and deformation, which are potentially trackable by non-invasive 2D-STE, as demonstrated in our pilot study of children on HD.

Patel et al evaluated the associations of intact FGF23 with measures of LA and LV mechanical function assessed by cardiac magnetic resonance in 2276 participants with preserved kidney function (mean eGFR 79.6 ± 14.9 ml/min/1.73m^2) from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. They found that intact FGF23 was associated with reduced LA total emptying fraction at 10 years follow-up[39]. They did not find an association between intact FGF23 and LA longitudinal strain in these patients with preserved kidney function. Our findings expand upon these findings in important ways. We provide a unique cross-sectional evaluation of the associations between intact FGF23 and LA function through indices of 2D-STE among a pediatric group of kidney failure patients, who are free of traditional cardiovascular risk factors. This allows for understanding of alterations in LA function associated with very high levels of intact FGF23 without the confounding effects of established cardiovascular risk factors. We demonstrate changes in LA function that are known to precede the development of morphological changes in LA. Finally, the independent associations of intact FGF23 with reduced LA GLS in our study are mechanistically supported, as FGF23 is known to promote cardiac fibrosis and influence intracellular calcium handling in *in vitro* models. These findings need to be verified in a larger population. We speculate LA GLS may serve a sensitive imaging biomarker for early detection of atrial remodeling in children with kidney failure, preserved LVEF and this will need to be verified in larger studies.

This study has several strengths. We utilized a pediatric population, a cohort free of prevalent cardiovascular risk factors in contrast to adults. All patients had no comorbid conditions, underwent uncomplicated dialysis treatment sessions, and relatively short dialysis vintage. The intact or biologically active form of FGF23 was measured in the current study, as opposed to the C-terminal fragment. We also utilized 2D-STE, which is a sensitive technique to quantify microstructural changes in the myocardium and has been studied in detail[16, 17].

This study also has important limitations. The study had limited power due to the small number of patients. Nonetheless, the strong associations observed here provided statistically significant findings that are unlikely related to chance. The study was limited to a single-center pediatric outpatient HD unit. This cross-sectional study design precludes evaluation of temporal directions of associations. In the absence of longitudinal data, we are unable to draw a true cause-effect relationship. Our inclusion criteria allowed for elapsed time of six-months between blood draw for FGF23 and ECHO studies. As our study group included kidney failure patients on HD, these findings cannot be generalized to kidney failure patients on peritoneal dialysis. The data used in this study were collected within the context of a larger clinical study with different aims. Therefore, we do not have data on volume overload (such as pro-BNP levels) or their hydration status (IVC diameter). Klotho protein, which is a co-receptor for FGF23 was also not measured in this group. WE CANNOT SXCLUDE POSSIBILITY OF LA STRETCHING OR CHANGES IN VOLUMES STATUS IN THIS COHORT AS WE ARE LIMITED BY CLINICAL PROTOCOL OF ECHO USED IN THIS PPULATION.

Volume status was not directly assessed in our patients, and we do not have data on their dry weight. Therefore, the influence of volume changes on the study could not be assessed. However, LA GLS is thought to be a less load dependent measure of LA function.

In conclusion, we found that children on HD relative to healthy controls, have altered LA GLS. Importantly, among children with kidney failure treated by HD and preserved LVEF, greater intact FGF23 concentrations were found to be independently associated with lower LA GLS (indicative of impaired atrial performance). Future studies should determine if LA GLS may serve as a sensitive imaging biomarker for identification of atrial remodeling in children with kidney failure and preserved LVEF who may be at risk for downstream adverse cardiovascular events. Additional studies are needed to evaluate if modifications in FGF23 levels may alter LA remodeling or delay the onset of LA myopathy in children with kidney failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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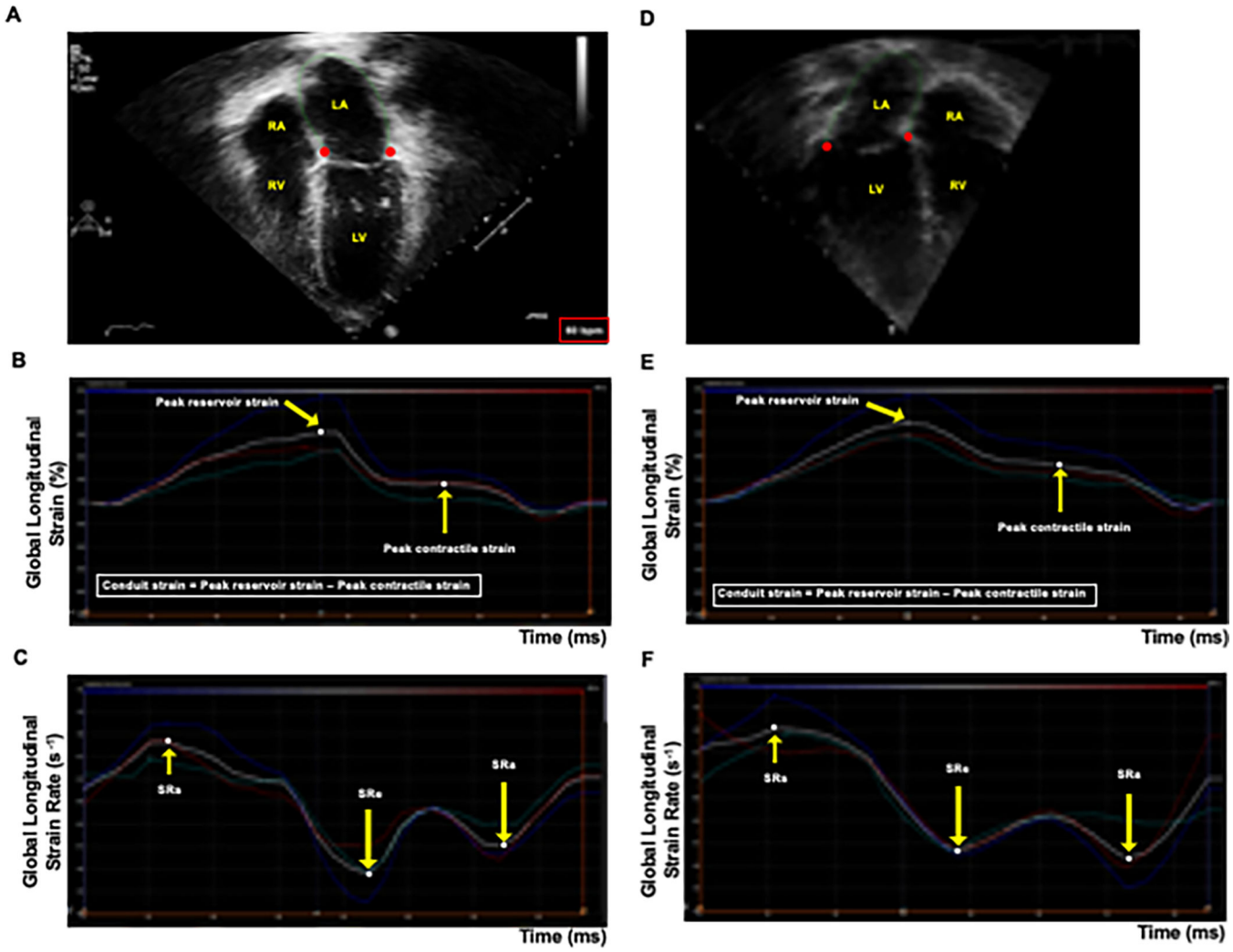

Figure 1:

Left atrial (LA) 2D speckle-tracking echocardiography tracing of the apical 4-chamber view in a 17-year-old kidney failure patient with preserved LVEF (A-C) and a 16-year-old healthy subject (D-F) for comparison. LA strain (B, E) and strain rate (C, F) curves were generated after LA endocardial borders were defined, and appropriate tracking was manually confirmed. The multi-colored curves represent individual segments of the LA wall. The white curve represents the average strain or strain rate of all segments in the LA. Phasic LA strain and strain rates were collected from the average strain or strain rate curves at the identified points (yellow arrows). RA, right atrium; RV, right ventricle; LV, left ventricle; SRs, reservoir strain rate; SRe, conduit strain rate; SRa, contractile strain rate.

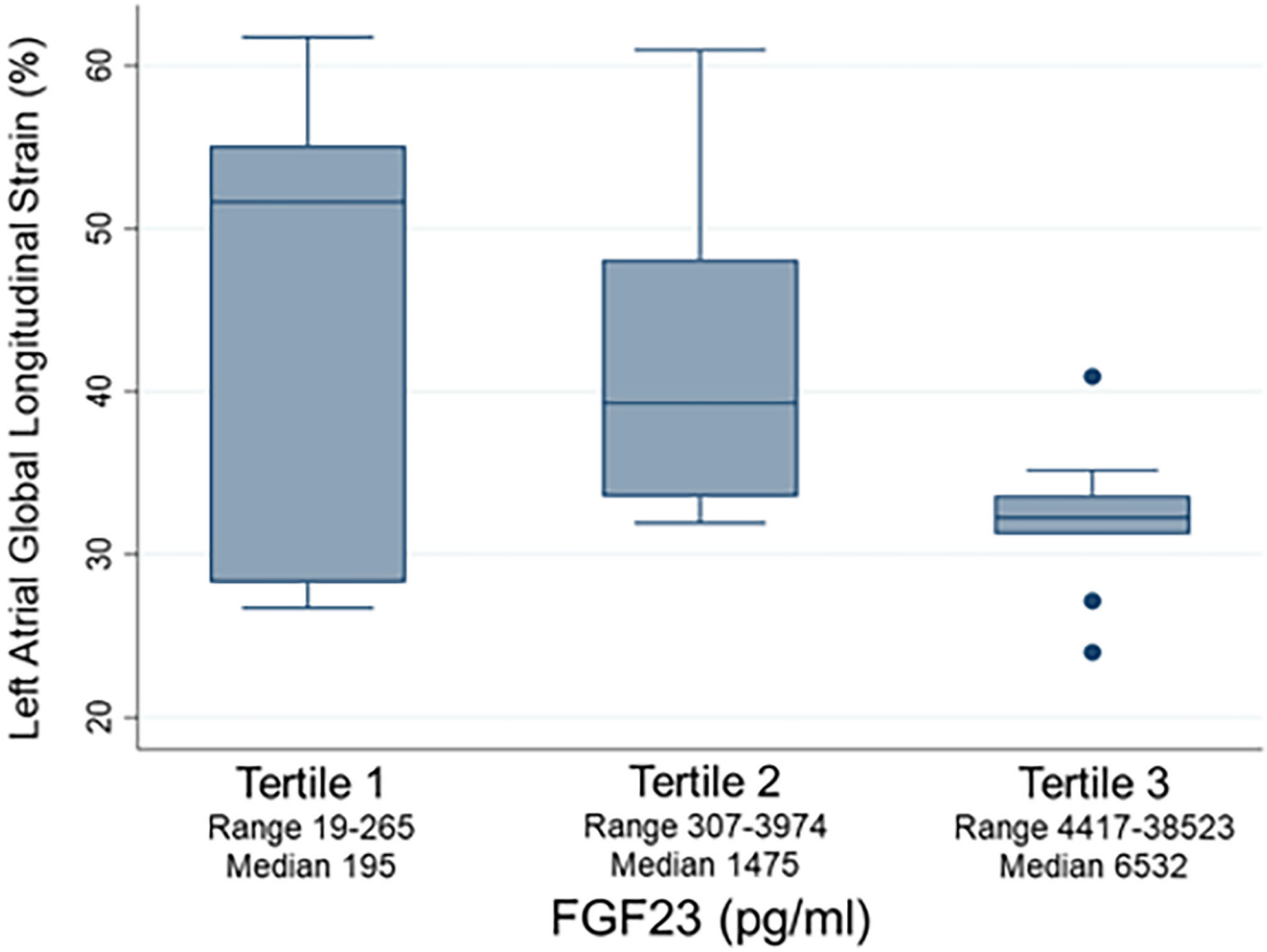

Figure 2:

Box plots show the relationship of intact FGF23 tertiles with left atrial global longitudinal strain (LA GLS) in 29 children on hemodialysis and preserved left ventricular function. Higher intact FGF23 was associated with lower LA GLS ($r = -0.36$; $P < 0.04$). FGF23, Fibroblast growth factor 23

Table 1:

Clinical and Echocardiographic Characteristics of Children on Hemodialysis and Healthy Controls

Variable	Hemodialysis	Controls
Number of Participants	29	13
Clinical Characteristics		
Age, year	16.6 ± 3.8[a]	15.2 ± 5.4[a]
Female Sex	9 (31)[a]	3 (23)[a]
Height, cm	159.0 [135.5, 166.5]	170.2 [148.4, 177.8]
Weight, kg	52.8 [34, 65.5]	58.8 [42.6, 82.6]
Body Surface Area, m^2	1.5 ± 0.2[a]	1.5 ± 0.3[a]
HD Vintage, year	1.5 [0.5, 4.3]	–
Laboratory Indices		
Hemoglobin, g/dl	11.9 ± 1.9	–
Transferrin Saturation, %	28 [22, 35]	–
Ferritin, ng/ml	449 [242.5, 680.5]*	–
C-reactive protein, mg/L	2.65 [0.7, 7.2]**	–
Creatinine, mg/dl	–	0.78 ± 0.2
Intact FGF23, pg/ml	1206 [215, 4707][b]	51 [43, 66.5][b]
Left Atrial Echocardiographic Parameters		
Left Atrial End Systolic Volume, ml	13.6 ± 7.2[a]	18.7 ± 11.7[a]
Left Atrial End Diastolic Volume, ml	44.6 ± 19.3[a]	47.4 ± 24[a]
Left Atrial Ejection Fraction, %	70.1 ± 7.5[b]	62.4 ± 8.4[b]
Left Atrial Global Longitudinal Strain, %	39.9 ± 11.6[b]	32.8 ± 5.7[b]
Left Atrial Reservoir Strain, %	39.8 ± 11.1[b]	32.5 ± 6.4b
Left Atrial Conduit Strain, %	30.8 ± 8.1[a]	32.1 ± 9.8[a]
Left Atrial Contractile strain, %	9.0 ± 6.3[a]	11.3 ± 6.7[a]
Left Atrial Reservoir Strain Rate, %	1.4 ± 0.4[a]	1.5 ± 0.4[a]
Left Atrial Conduit Strain Rate, %	−1.3 ± 0.5[a]	−1.5 ± 0.5[a]
Left Atrial Contractile Strain Rate, %	−0.9 ± 0.6[a]	−0.8 ± 0.5[a]

Values for continuous variables given as mean ± SD or median [IQR]; for categorical variables, as count (percentage)

*1 missing value

**>1 missing value; Abbreviations: Cm, centimeter; FGF23, Fibroblast growth factor 23; HD, Hemodialysis; IQR, Interquartile range; Kg, Kilogram

[a]denotes P>0.5 between groups

[b]denotes P<0.5 between groups.

Table 2:

Association between Hemodialysis and Left Atrial Global Longitudinal Strain

Left Atrial Global Longitudinal Strain				
Variable	**Univariate Analysis**		**Multivariate Analysis**	
	β (95% CI)	*P-value*	*β (95% CI)*	*P-value*
HD vs Controls	7.04 (0.15, 13.93)	0.04	7.30 (0.10, 14.50)	0.04
Age	−0.02 (−0.79, 0.74)	0.94	−0.48 (−1.15, 0.79)	0.71
BSA	−0.64 (−11.70, 10.41)	0.90	0.72 (−13.14, 14.59)	0.91

β reflects % change in LA GLS per 1 standard deviation higher of each variable

Abbreviations: BSA, Body surface area; HD, Hemodialysis

Table 3:

Association between Intact FGF23 with Left Atrial Global Longitudinal and Phasic Strain among Children on Hemodialysis

Left Atrial Global Longitudinal Strain				
Variable	**Univariate Analysis**		**Multivariate Analysis**	
	β (95% CI)	*P-value*	*β (95% CI)*	*P-value*
Age	−0.13 (−1.31, 1.04)	0.81	0.39 (−1.23, 2.02)	0.62
BSA	2.66 (−13.19, 18.52)	0.73	4.34 (−19.755, 28.45)	0.71
Intact FGF23 *	−2.38 (−4.44, −0.33)	0.02	−2.77 (−5.47, −0.07)	0.04
HD vintage	−2.68 (−5.08, −0.28)	0.03	−1.62 (−4.55, 1.29)	0.26
Left Atrial Reservoir Strain				
Age	0.00 (−1.13, 1.12)	0.99	0.29 (−1.46, 2.06)	0.72
BSA	2.33 (−12.89, 17.57)	0.75	4.87 (−21.15, 30.90)	0.70
Intact FGF23 *	−1.43 (−3.53, 0.66)	0.17	−1.98 (−4.89, 0.93)	0.17
HD vintage	−1.35 (−3.81, 1.10)	0.26	−0.49 (−3.65, 2.66)	0.75
Left Atrial Conduit Strain				
Age	0.27 (−0.53, 1.09)	0.49	0.14 (−1.12, 1.41)	0.81
BSA	6.79 (−3.91, 17.50)	0.20	8.23 (−10.50, 26.98)	0.37
Intact FGF23 *	−0.42 (−1.99, 1.13)	0.57	−1.06 (−3.16. 1.03)	0.30
HD vintage	−1.11 (−2.88, 0.64)	0.20	−0.31 (−2.58, 1.96)	0.78
Left Atrial Contractile Strain				
Age	−0.28 (−0.91, 0.34)	0.36	0.15 (−0.83, 1.15)	0.74
BSA	−4.45 (−12.88, 3.98)	0.28	−3.36 (−18.09, 11.37)	0.64
Intact FGF23 *	−1.006 (−2.16, 0.15)	0.08	−0.91 (−2.56, 0.73)	0.26
HD vintage	−0.238 (−1.65, 1.18)	0.73	−0.18 (−1.96, 1.60)	0.83

* Intact FGF23 is natural log transformed

β reflects % change in LA GLS per 1SD higher of each variable

Abbreviations: BSA, Body surface area; FGF23, Fibroblast growth factor 23; HD, Hemodialysis