Advanced Parameters of Cardiac Mechanics in Children with CKD: The 4C Study

Marcello Chinali,* Maria Chiara Matteucci,† Alessio Franceschini,* Anke Doyon,‡ Giacomo Pongiglione,§ Gabriele Rinelli,* and Franz Schaefer*

Abstract

Background and objectives New parameters of cardiac mechanics provide additional insights on cardiac dysfunction in adult patients with CKD. The aim of this study was to identify prevalence of subclinical abnormalities in cardiac function through the analysis of novel indices of cardiac mechanics in a large population of children with CKD.

Design, setting, participants, & measurements Between 2009 and 2011, the prospective observational Cardiovascular Comorbidity in Children with CKD Study enrolled patients with CKD ages 6–17 years old with eGFR=10–45 ml/min per 1.73 m² in 14 European countries. Cardiac morphology and function were assessed through echocardiography. The analysis presented encompasses global radial, longitudinal, and circumferential strains as well as time to peak analysis. Data were compared with 61 healthy children with comparable age and sex.

Results Data on 272 patients with CKD with complete echocardiographic assessment are reported (age =12.8 ± 3.5 years old; 65% boys). Patients with CKD showed mildly higher office BP values and higher prevalence of left ventricular hypertrophy, but no differences were observed among groups in left ventricular ejection fraction. Strain analysis showed significantly lower global radial strain (29.6% ± 13.3% versus 35.5% ± 8.9%) and circumferential strain components (−21.8% ± 4.8% versus −28.2% ± 5.0%; both P<0.05) in patients with CKD without significant differences observed in longitudinal strain (−15.9% ± 3.4% versus −16.2% ± 3.7%). Lower values of global radial strain were associated with lower circumferential endocardial-to-epicardial gradient (r=0.51; P<0.01). This association remained significant after adjusting for BP, eGFR, and presence of left ventricular hypertrophy. Eventually, patients with CKD also showed higher delay in time to peak cardiac contraction (58 ± 28 versus 37 ± 18 milliseconds; P<0.05).

Conclusions A significant proportion of children with CKD show impaired systolic mechanics. Impaired systolic function is characterized by lower radial strain, transmural circumferential gradient, and mild cardiac dysynchrony. This study suggests that analysis of cardiac strain is feasible in a large multicenter study in children with CKD and provides additional information on cardiac pathophysiology of this high-risk population.


Introduction

Abnormal left ventricular (LV) geometry and function are common in CKD. These structural abnormalities include LV hypertrophy, LV dilatation, and impaired systolic function, and each is strongly linked to a poor cardiovascular prognosis (1–6). Although heart failure and sudden cardiac death are common in CKD, the appropriate management of myocardial disease is not fully understood (7–10).

When the heart is subject to increased workload (e.g., hypertension or renal failure), LV hypertrophic remodeling is stimulated to compensate for increased stress and preserve function. However, paradoxically, this hypertrophic remodeling is associated with worse outcome, even accounting for other risk factors (11–14). Accordingly, data from several groups have proven that, in adults, subtle systolic dysfunction might be present in patients with LV hypertrophy before impairment is identified through the analysis of LV ejection fraction (15,16). The ability to identify early markers of LV dysfunction in CKD represents one of the main applications of echocardiography in preventing overt cardiac diseases of this high-risk pediatric population. One fascinating aspect of LV remodeling in CKD is that prevalence of LV concentric hypertrophy is remarkably high, despite the substantial volume overload, and associated with functional consequences.

We have previously reported in the Effect of Strict Blood Pressure Control and Angiotensin-Converting Enzyme Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients Trial that, in the presence of concentric geometry (both remodeling and hypertrophy), subclinical abnormalities of systolic mechanic...
function are, indeed, present, despite normal ejection fraction (17). The mechanic abnormalities underlining this impairment are not yet well understood. In addition, it has been shown in small studies that, in adult and pediatric patients with end stage CKD, abnormal LV systolic deformation (through the analysis of Doppler measurement of tissue velocities, strain, and strain rate) precedes changes in more traditional indices of myocardial function, including ejection fraction. However, to date, no studies are available in large samples of pediatric patients with CKD using newer indices of systolic function.

Studies performed in adults with hypertension with speckle tracking technology have suggested that abnormalities in systolic performance in hypertensive LV hypertrophy can be identified, despite normal ejection fraction (18–20). Subclinical abnormalities of LV myocardial deformation in adults with early stage CKD have also been reported (21) as well as abnormal longitudinal systolic deformation in asymptomatic individuals with early CKD without clinical evidence of heart disease. Recently, a cross-sectional comparison of conventional and speckle tracking parameters was performed between controls and patients with different stages of CKD by Panoulas et al. (22). Adult patients with CKD were followed up for major adverse cardiovascular events, and impaired global longitudinal strain was observed in almost one quarter of patients with CKD and associated with a reduced major adverse cardiovascular events–free survival at 12-month follow-up. Accordingly, the aim of this analysis was to identify abnormality in cardiac performance through the analysis of advanced indices of cardiac systolic function, despite a normal ejection fraction, with the ultimate aim of improving the identification of children with CKD at higher risk of future cardiovascular events.

Because no widely accepted normal pediatric reference values for two-dimensional strain are available in the literature, data were compared with a reference group of 61 healthy children of similar age and sex distribution equally recruited from each participating center, referred for examination to evaluate innocent murmurs and/or chest pain, and shown by echocardiography to have normal hearts.

**Echocardiography Methods**

All patients and controls underwent a complete transthoracic echocardiographic examination with commercially available machines. Examinations were stored and analyzed in a central echocardiographic reading center by two independent readers unaware of the clinical data. Two-dimensional images were obtained for the analysis of LV volumes on three consecutive beats from apical 4- and 2-chamber views. Wall thickness and chamber dimensions were obtained from the two-dimensional parasternal long axis or M-mode short axis at the midventricular level, when perfect alignment of the left ventricle was possible, on three consecutive beats.

Parameters measured in our study included LV diameters and wall thicknesses to obtain LVM. LVM was calculated according to the Devereux formula. LVM was analyzed as both unindexed as well as indexed to the allometric power of 2.7. To define LV hypertrophy, age-specific partition values were applied as previously reported by Khoury et al. (24). For evaluation of the concentricity of LV geometry, myocardial thickness (wall+septum) was divided by LV minor axis (diameter) to generate a relative wall thickness (RWT) normalized to a mean age of 10 years old. A value of 0.38 was used as the cutoff to define concentric LV geometry (25).

LV systolic function was determined by LV ejection fraction from volumes estimated by the Teicholozz formula and linear measures of LV minor axis at the midwall level (midwall shortening) as previously reported (17).

Strain analysis was used to obtain radial (Re), circumferential (Ce), and longitudinal (Le) strains of the left ventricle on three consecutive beats from the apical 4-chamber window (Le) or the parasternal short-axis view (Re and Ce).

In detail, when adequate echocardiographic examinations were available (defined as images with good image quality and frame rate >40 frames per second), images were exported and analyzed centrally offline using Tomtec 2D-CPA for the semiautomatic analysis of strain curves. Preliminary findings from our group show that Tomtec 2D-CPA permits analysis of Digital Imaging and Communications in Medicine images acquired with machines from different vendors, offsetting differences. Endocardial surfaces were manually traced from the 4-chamber apical views for longitudinal strain and the parasternal short axis for the analysis of radial and circumferential strains (at both endocardial and epicardial levels).

Feature tracking of the myocardium is achieved through the combination of echocardiographic tracking of speckle signals, mitral annulus motion, tissue-blood border detection, and periodicity of the cardiac cycle using R-R intervals.

After definition of the cardiac cycle, the endocardium of the left ventricle is traced manually from a single frame of
the digital loop that provides the clearest still-frame endocardial border definition. Endocardial tracing begins at the edge of the atrioventricular valve annulus, extends to the apex of the ventricle without incorporation of the papillary muscle complex, and returns basally to the other edge of the atrioventricular valve annulus, providing both the border and annuli position information necessary for the feature-tracking component of the algorithm. To improve the tracking results, the algorithm applies a sequence of intermediate passages to accurately follow myocardial motion. Accuracy of border tracking is visually confirmed by viewing the cardiac cycle with only border information displayed (i.e., with velocity vectors removed). If necessary, individual regions of the border are adjusted until the border is correctly tracked for each frame. Cardiac strain calculated myocardial deformation from the velocity vector information and displayed it in a six-segment model. Averaged segmental peak strain and time to peak values were calculated to obtain global radial, longitudinal, and circumferential strains and systolic synchrony.

The software provides peak and time to peak systolic strain values for three orthogonal planes (radial, circumferential, and longitudinal), representing orthogonal deformation of the cardiac muscle during contraction. Accordingly, such as in systole, the myocardium reduces its wall length in both the circumferential and longitudinal planes, and more negative values of circumferential and longitudinal strains represent a better cardiac contraction. In contrast, as the myocardium increases its wall length in the radial strain, a more functional left ventricle will show a more positive value in radial strain.

**BP Monitoring**

Office BP measurements were obtained using the oscillometric technique at the time of the echocardiography after sitting for 5 minutes in a relaxed position.

All patients received 24-hour ambulatory BP monitoring (ABPM). All centers were equipped with ABPM devices (Spacelab ABPM Device 90207–Q2; Spacelabs Medical, Issaquah, WA). Standard operating procedures for ABPM had been placed on the study website for continuous reference by participating centers. The ABPM SD score was calculated using German reference data, as previously reported (3).

### Statistical Analyses

Data are presented as means ± SD. Statistical analysis was performed by SPSS software, version 21.0 (SPSS Inc., Chicago, IL). Comparison between the two groups of patients was carried out with *t* tests for continuous variables and chi-squared tests for categorical variables. When necessary, comparison between groups was performed using analysis of covariance to reduce the effect of confounding variables (age, sex, heart rate, and BP when appropriate). Correlation between variables was evaluated through linear regression analysis (for continuous variables) and logistic regression in the presence of dichotomous variables (e.g., presence/absence of LV hypertrophy). To account for significant confounders, multiple regression analysis was performed. A *P* value <0.05 was considered statistically significant.

### Results

**Clinical Characteristics**

Complete analysis of cardiac strain was feasible in 272 patients with CKD (84% of the total study sample). Major reasons for exclusion were lack of sufficient cardiac beats recorded (less than three) and/or poor image quality. No differences were observed regarding age and sex distribution, 24-hour BP, heart rate, hemoglobin, GFR, and prevalence of medications between this group and the remaining patients in whom analysis of cardiac strain was not available.

Clinical data of the study population are shown in Table 1. Renal hypodysplasia/dysplasia was the underlying kidney disorder in 74%, acquired glomerulopathies were the underlying kidney disorder in 4.6%, and hereditary or other kidney diseases were the underlying kidney disorder in the remaining patients; 5% of the patients had no antihypertensive medication at baseline, whereas 14.2% were on antihypertensive monotherapy (all angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), and 80.4% were on two or more antihypertensive drugs.

Whereas no differences were observed between patients and controls with respect to age (12.8 ± 3.5 versus 11.5 ± 5.7), sex distribution (65% versus 66% boys), and body mass index, office systolic (114 ± 15 versus 107 ± 9)

<table>
<thead>
<tr>
<th>Variables</th>
<th>CKD (<em>n</em>=272)</th>
<th>Controls (<em>n</em>=61)</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>12.8±3.5</td>
<td>11.5±5.7</td>
<td>0.26</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.5±3.6</td>
<td>17.8±3.2</td>
<td>0.46</td>
</tr>
<tr>
<td>Casual systolic BP (mmHg)</td>
<td>114±15*</td>
<td>107±9*</td>
<td>0.02</td>
</tr>
<tr>
<td>Casual diastolic BP (mmHg)</td>
<td>69±13*</td>
<td>63±9*</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82±15</td>
<td>80±18</td>
<td>0.36</td>
</tr>
<tr>
<td>24-h Systolic BP SD score</td>
<td>0.83±1.5</td>
<td>NA</td>
<td>—</td>
</tr>
<tr>
<td>24-h Diastolic BP SD score</td>
<td>0.57±1.2</td>
<td>NA</td>
<td>—</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>30.5±16.5</td>
<td>NA</td>
<td>—</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.5±1.6</td>
<td>NA</td>
<td>—</td>
</tr>
</tbody>
</table>

**Antihypertensive treatment**

- No. of drugs (*n*) | 3±1.8 | 0 | — |
- RAS (%) | 61.4 | 0 | — |
- Non-RAS (%) | 38.6 | 0 | — |

*Values are means±SD. BMI, body mass index; BP, blood pressure; RAS, renin-angiotensin system antagonist.*
cause of a significant difference in transmural circumferential gradient among the two groups (−9.1 ± 4.0 versus −15.6 ± 6.2; P < 0.01). In univariate analysis, lower radial strain was strongly related to the decrease in circumferential systolic transmural gradient, suggesting a significant impairment in cardiac contractile physiology among children with CKD (Figure 1). Eventually, children with CKD showed a mild, although significantly higher, difference in segmental time to systolic peak, suggesting some degree of cardiac dyssynchrony in systolic contraction (58 ± 28 versus 37 ± 18 milliseconds; P < 0.05).

In univariate analysis, we also found that, in children with CKD, significant correlates of radial strain were higher 24-hour systolic BP SDs (r = 0.21; P = 0.01), LVM (r = −0.15; P = 0.04), and RWT (r = −0.34; P = 0.02), whereas lower circumferential transmural gradient was mainly related to lower eGFR (r = 0.16; P = 0.04) and higher RWT (r = −0.28; P = 0.03). In multivariate analysis (analysis of covariance), as shown in Table 4, after adjusting for differences among groups in sex and heart rate, we found that correlates of lower radial strain were lower circumferential transmural gradient and higher RWT. No independent effect was found for LVM index, hemoglobin level, eGFR, use of either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker medications, LV ejection fraction, and systolic or diastolic BP SDs.

Discussion

Our study shows a high prevalence of subclinical systolic dysfunction in children with CKD characterized by lower...

### Table 2. Comparison of cardiac geometry and traditional systolic functional indices controlling for age and sex

<table>
<thead>
<tr>
<th>Variables</th>
<th>CKD (n=272)</th>
<th>Controls (n=61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDD (cm)</td>
<td>4.2 ± 0.5</td>
<td>4.0 ± 0.8</td>
<td>0.52</td>
</tr>
<tr>
<td>RWT</td>
<td>0.49 ± 0.07</td>
<td>0.34 ± 0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>44 ± 15</td>
<td>35 ± 8</td>
<td>0.01</td>
</tr>
<tr>
<td>LV hypertrophy (%)</td>
<td>55</td>
<td>7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Concentric geometry (%)</td>
<td>65</td>
<td>0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>67 ± 14</td>
<td>67 ± 12</td>
<td>0.87</td>
</tr>
<tr>
<td>MWS (%)</td>
<td>16.2 ± 3.7</td>
<td>18.3 ± 4.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are means ± SD. LVIDD, left ventricular internal diameter in diastole; RWT, relative wall thickness; LV, left ventricular; MWS, midwall fractional shortening.

### Table 3. Left ventricular systolic strain parameters controlling for age and sex

<table>
<thead>
<tr>
<th>Variables</th>
<th>CKD (n=272)</th>
<th>Controls (n=61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal strain (%)</td>
<td>−15.9 ± 3.4</td>
<td>−16.2 ± 3.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Radial strain (%)</td>
<td>29.6 ± 13.3</td>
<td>35.5 ± 8.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Epicircumferential strain (%)</td>
<td>−12.3 ± 3.4</td>
<td>−13.6 ± 4.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Endocircumferential strain (%)</td>
<td>−21.8 ± 4.8</td>
<td>−28.2 ± 5.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Transmural circumferential strain (%)</td>
<td>−9.1 ± 4.0</td>
<td>−15.6 ± 6.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Overall difference in time to peak (ms)</td>
<td>58 ± 28</td>
<td>37 ± 18</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are means ± SD.
radial and circumferential LV strain paired with a mild cardiac systolic dyssynchrony. To our knowledge, this is the first study describing myocardial function by strain echocardiography in a large pediatric CKD population without overt cardiac dysfunction. In fact, despite a high prevalence of abnormalities in cardiac geometry, all patients with CKD showed a normal ejection fraction (ejection fraction >56%). Compared with the reference population, children with CKD showed lower values of circumferential and radial strains (with no significant effect in the longitudinal component), showing a high prevalence of subclinical systolic dysfunction.

The major factors leading to myocardial disease in CKD include volume overload, anemia, and pressure overload. This results in cardiac hypertrophy paired to myocardial fibrosis and subclinical dysfunction (26). In children with CKD, vascular disease rarely progresses to overt clinical manifestations. However, changes in LV muscle mass and fibrosis can cause symptomatic diastolic and/or systolic dysfunction (2, 27, 28). In fact, cardiac death in this population is rarely caused by atherosclerosis or arteriosclerosis but rather, LV functional abnormalities, severe electrolyte imbalance, hypertensive crisis, or volume overload. A comprehensive study pointed to cardiovascular-related diseases as the main cause of death (overall 41%1) in a cohort of patients with early-onset ESRD (0–14 years of age) (29). The list of etiologies included cerebrovascular events, congestive heart failure, cardiac arrest, and dissection of the aorta—all of them, at least in part, are consequences of hypertension, electrolyte anomalies, and volume overload rather than secondary to vascular or myocardial disease per se.

We observed significant differences in cardiac systolic function, despite normal ejection fraction, which was characterized by a high prevalence of LV hypertrophy (mainly

![Figure 1. Mechanical dysfunction in CKD children. Correlation between radial strain and the circumferential epicardial-to-endocardial strain gradient (r = –0.51; P < 0.001).](image)

Table 4. Correlates of global radial left ventricular systolic strain in children with CKD (n=272) controlling for sex

<table>
<thead>
<tr>
<th>Variables</th>
<th>%</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>0.151</td>
<td>–0.22 to +0.41</td>
<td>0.06</td>
</tr>
<tr>
<td>24-h Systolic BP (SD score)</td>
<td>–0.069</td>
<td>–0.12 to +0.09</td>
<td>0.33</td>
</tr>
<tr>
<td>24-h Diastolic BP (SD score)</td>
<td>–0.010</td>
<td>–0.03 to +0.02</td>
<td>0.86</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>0.109</td>
<td>–0.31 to +0.48</td>
<td>0.45</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>–0.071</td>
<td>–0.22 to +0.16</td>
<td>0.69</td>
</tr>
<tr>
<td>Body mass index (SDs)</td>
<td>–0.052</td>
<td>–0.12 to +0.21</td>
<td>0.71</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.121</td>
<td>–0.04 to +0.26</td>
<td>0.08</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>–0.173</td>
<td>–0.06 to –0.31</td>
<td>0.04</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m²)</td>
<td>–0.120</td>
<td>–0.42 to +0.14</td>
<td>0.12</td>
</tr>
<tr>
<td>Therapy (use of ARB/ACEi)</td>
<td>0.168</td>
<td>–0.25 to +0.36</td>
<td>0.08</td>
</tr>
<tr>
<td>Circumferential epi–endo gradient (Δ%)</td>
<td>–0.510</td>
<td>–0.25 to –1.03</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

BP, blood pressure; SDs, standard deviations; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
of the concentric type) paired with lower radial strain and circumferential strain parameters with no significant differences in longitudinal strain. This finding is in remarkable contrast to previous observations in adult patients with hypertension, in whom a selective impairment of the longitudinal strain component was observed as the major abnormality of cardiac strain without remarkable differences in either radial or circumferential components (30). However, we believe that the population comprising this study differs somewhat from those previously reported. In the 4C Study, a significant fraction of patients presents with concentric geometry (either with or without hypertrophy). Accordingly, these patients present impaired midwall shortening, which is pathophysiologically related to measures of circumferential systolic mechanic function rather than longitudinal mechanics. This is also supported by the significant association between circumferential strain and RWT (Table 3). Thus, we believe that our finding correctly identifies a population with a different mechanic and geometric adaptation phenotype compared with a population with hypertension that is more similar to what was previously reported in teenagers with hypertrophic cardiomyopathy (31).

Moreover, in our study, a strong association between lower radial strain and circumferential transmural gradient was found, even after controlling for differences in LVM and ejection fraction. This mechanic relationship supports the hypothesis that the higher cardiac wall thickness (as shown by the high rate of concentric LV hypertrophy) does not represent a compensatory effect but rather, a secondary response to significant impairment in myocardial contraction. In fact, the presence of a lower transmural circumferential gradient in children with CKD—despite the significant higher cardiac wall thickness—is particularly intriguing, because it supports the hypothesis that this dysfunction not only occurs secondary to alterations of cardiac geometry (i.e., hypertrophy) but potentially reflects intrinsic structural abnormalities of the heart muscle in children with CKD. This hypothesis is also supported by previous findings in adult patients with CKD, in whom a higher cardiac muscular mass was related to a significant higher cardiac fibrotic content compared with patients with hypertension with similarly high LVM (32, 33).

Our study provides novel insights into cardiac function in children with predialysis CKD and suggests a peculiar mechanism of cardiac adaptation characterized by higher LV wall thickness and lower transmural circumferential function leading to impaired radial systolic function.

In conclusion, a significant proportion of children with CKD has abnormal cardiac geometry paired with lower indices of systolic mechanics, which are not identifiable when limiting the analysis to traditional echocardiographic parameters. Additional studies are needed to assess whether these abnormalities are predictive of cardiovascular events and/or need for dialysis treatment.

Acknowledgments

The authors acknowledge support from a Research Programme of the European Renal Association–European Dialysis and Transplant Association Grant, a KRH Foundation for Preventive Medicine Grant, and German Federal Ministry of Education and Research Grant 01EO0802.

Disclosures

None.

References


**Received:** November 2, 2014 **Accepted:** April 13, 2015

Published online ahead of print. Publication date available at www.cjasn.org.