Elevated Ejection-Phase Myocardial Wall Stress in Children With Chronic Kidney Disease

Haotian Gu, Manish D. Sinha, Ye Li, John Simpson, Phil J. Chowienczyk

Abstract—Myocardial wall stress (MWS) is thought to be the mechanical stimulus to ventricular hypertrophy. The objective of this study was to examine whether MWS is elevated in children with chronic kidney disease (CKD) who are at high risk of developing adverse cardiovascular events related to left ventricular (LV) hypertrophy. MWS, a function of left ventricular pressure, myocardial wall volume, and cavity volume, was obtained using carotid tonometry to estimate ventricular pressure and 2-dimensional transthoracic echocardiographic wall-tracking to obtain LV cavity and wall volumes. Ninety-two children (50 boys) aged 11.2±3.2 (mean±SD) years, including healthy controls (n=16), and those with CKD disease divided into 3 groups according to estimated glomerular filtration rate (mL/min per 1.73 m²) >90 (CKD 1, n=26), 60 to 90 (CKD 2, n=23), and <60 (CKD≥3, n=27) were studied. There was no significant difference in age, height, weight, central or peripheral blood pressure, LV mass, or mass index in the 4 study groups. By contrast, peak, mean, and end-systolic MWS were higher in children with CKD and increased across stages of CKD (peak MWS, 338.8±18.5 and 397.5±14.3 s/cm² in controls and CKD≥3, respectively; P=0.01). Higher systolic MWS was explained by a form of LV dysfunction whereby dynamic values of the ratio of wall volume/cavity size during systole were lower in children with CKD than in those without (P=0.001). Children with CKD exhibit blood pressure–independent LV dysfunction which results in increased systolic MWS and which may predispose to LV hypertrophy in later life. (Hypertension. 2015;66:823-829. DOI: 10.1161/HYPERTENSIONAHA.115.05704.) ● Online Data Supplement

Key Words: blood pressure ■ echocardiography ■ hypertension ■ hypertrophy, left ventricular ■ renal insufficiency, chronic

Children with chronic kidney disease (CKD) exhibit greatly increased mortality and morbidity from cardiovascular disease as they progress into adulthood compared with those without CKD.1–3 This increase in cardiovascular disease is likely to have its origins in childhood and to relate, at least in part, to ventricular remodeling, including left ventricular hypertrophy (LVH).2,4–6 Myocardial wall stress (MWS) is a crucial factor linked to myocardial hypertrophy: systolic wall stress patterns are thought to influence hypertrophic responses and interstitial fibrosis by stretch activation of the extracellular matrix.7–9 In adults, MWS has a major impact on LV geometry and structure,8,10 and adults with even mild renal dysfunction exhibit LV remodeling.11,12 We thus hypothesized that MWS may be elevated in children with CKD who have not yet developed LVH.

MWS has previously been estimated using brachial blood pressure (BP) and LV dimensions measured by M-mode echocardiography. More recently, time-varying wall stress has been studied by measurement of time-varying load (central aortic BP as an estimate of LV pressure during systole) and the continuous assessment of LV geometry using cross-sectional echocardiography and feature-tracking to track LV cavity volume and wall volume.13–15 However, time-varying wall stress has not previously been studied in children (with or without CKD). The objective of this study was to evaluate ejection-phase MWS and its relationship with LV geometry and arterial load in children with mild to moderate CKD without LVH and healthy control children.

Materials and Methods

Study Population

Children with CKD were recruited from those participating in a prospective observational study investigating the relationship of target organ damage with peripheral and central BP in children at the Evelina London Children’s Hospital, United Kingdom. Children and their parents were consecutively approached by a clinician with whom they were familiar in an outpatient setting; healthy children were recruited contemporaneously from the local community and included children of medical staff. None of the children with CKD were undergoing dialysis or had received kidney transplantation. Additional exclusion criterion included congenital heart disease, cardiac arrhythmias, and inability to obtain high-quality cardiovascular measurements (mainly because of movement artifact). A target sample size of 80 was set as justified in the statistics section, and 92 children were recruited into the study. The institutional ethics committee approved the study.

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and written informed consent was obtained from parents and (where appropriate) children in the study. Anthropometric, clinical, and laboratory data were collected on the day of the research investigations. Healthy children underwent all examinations except for venesection. In children with CKD, estimated glomerular filtration rate (eGFR) was calculated because a relative reduction in stress in late systole may protect the myocardium against the deleterious effects of systolic load.11

**Time-Varying MWS**

We used carotid applanation tonometry to estimate LV pressure and echocardiography with wall-tracking to obtain wall and cavity volume over time during systole. MWS was obtained from LV pressure (estimated from carotid tonometry) and myocardial dimensions using the Arts formula26 to obtain time-resolved systolic MWS as previously described by Chirinos et al14 (see online-only Data Supplement for full details). The difference between peak MWS and end-systolic MWS was calculated because a relative reduction in stress in late systole may protect the myocardium against the deleterious effects of systolic load.13

**Peripheral BP, Central BP, and Aortic Input Impedance**

Peripheral brachial BP was measured by a trained observer using aneroid sphygmomanometer according to British Hypertension Society guidelines. The mean of 3 values of peripheral systolic BP (SBP) and diastolic BP (DBP) were used for analysis. Given the age-related change in BP throughout childhood, all peripheral BP measurements were also analyzed as z scores (the number of SD above or below a population mean assigned a value of 0) using published criteria.21 Carotid and radial arterial pressure waveforms were obtained by a high-fidelity micromanometer and processed by the SphygmoCor device (Figure 1) as described in the online-only Data Supplement. We have recently verified that central aortic SBP can be derived from the carotid waveform (from wall-tracking of the carotid artery) in children.22

**Echocardiography**

A transthoracic echocardiographic study was obtained using the Philips IE33 ultrasound system (Philips Healthcare, Andover) and analyzed by one author (H.G.) while blinded to CKD stage and BP values. Time-resolved cavity volume and myocardial wall volume and global longitudinal strain (GLS) and radial strain (GRS) were measured using a Tomtec analysis package (2-dimensional [2D] cardiac performance analysis, Tomtec, Munich, Germany) from a 2D apical 4-Chamber view as described in the online-only Data Supplement.

**Statistical Analysis**

The target sample size of 80 with ≥20 children in each CKD group as defined below was set to give 80% power ($P<0.05$) to detect a >1 SD difference between MWS in CKD and control children and a relationship between MWS and GFR accounting for >15% of the variance in MWS. Subject characteristics are summarized as mean±SD and results as mean±SEM. To examine the relationship between cardiovascular measures and GFR, children with CKD were divided into 3 approximately equal groups according to recognized CKD stages23: CKD 1, eGFR>90 mL/min per 1.73 m²; CKD 2, eGFR: 60 to 90 mL/min per 1.73 m²; and CKD≥3, eGFR<60 mL/min per 1.73 m². Comparisons between these groups were then made using ANOVA with adjustment for confounding factors. Multiple regression analysis was also used to examine the relationship between cardiovascular measures and eGFR, treating eGFR as a continuous variable. Multivariate models were adjusted for confounders that were physiologically relevant or known to be associated with the outcome measures14,17 and included: age, body mass index, sex, mean arterial pressure, LV end-diastolic volume (EDV), and antihypertensive medications. Goodness of fit was expressed as the adjusted $r^2$. A $P$ value $<0.05$ was considered statistically significant, and all tests were 2-tailed. Statistical analyses were performed using SPSS (SPSS Inc, Chicago, IL, version 21).

**Results**

**Subject Characteristics**

Characteristics of healthy control children and children with CKD divided into 3 groups according to stages of CKD (CKD 1, 2, and ≥3) are shown in Table 1. CKD was secondary to congenital anomalies of the kidney and urinary tract in 52 of 76, glomerular disease in 7 of 76, tubulointerstitial disease in 5 of 76, and renovascular disease in 4 of 76. The remainder (8/76) had CKD of unknown pathogenesis.18 There was no significant difference in age, height, weight, and heart rate between the control and the 3 CKD groups (Table 1). In children with CKD, 2 of 26 (8%), 11 of 23 (48%), and 14 of 27 (52%) children in groups CKD 1, CKD 2, and CKD≥3, respectively, were taking antihypertensive medication ($P<0.001$ between groups).

**Peripheral BP, Central BP, and Aortic Input Impedance**

Only 3 children had elevated SBP, and none had elevated DBP on the day of investigations. There was no significant difference in SBP, DBP, SBP z score, DBP z score, mean arterial pressure, or peripheral pulse pressure among control and the 3 CKD groups (Table 2). Central BP was also similar in all groups with no significant difference in central aortic SBP or central pulse pressure between groups (Table 2). There was no significant difference in the phase or modulus of aortic input impedance between control subjects and the 3 CKD groups (Figure S2 in the online-only Data Supplement).

**LV Geometry, Mass, Ejection Fraction, and Indices of Strain**

There was no significant difference in EDV, LV mass (LVM), LVM index, relative wall thickness, or LVM/EDV ratio between control subjects and the 3 CKD groups. Average LVM z score was $<0$ in children with CKD, indicating that LVM was not greater than that in the reference population from which z scores have been derived (Table 2). LVH was only found in 1 subject with CKD when using age-specific reference intervals for normal children.23

In children with CKD, LVM ($P=0.682$), LVM index ($P=0.283$), relative wall thickness ($P=0.998$), and LVM/
EDV ($P=0.729$) were not significantly related to GFR with or without adjustment for confounders. LVM was positively associated with SBP (standardized $\beta=0.247, P=0.007$). LVM index ($\beta=0.241, P=0.035$) and LVM/EDV ($\beta=0.312, P=0.006$) were positively associated with SBP $z$ score in all patients.

There was no significant difference in end-systolic volume, ejection fraction (Table 2), GLS, and GRS between control and 3 CKD groups. However, there was a trend to a reduction in strain values in CKD compared with control groups (Table 2). End-diastolic myocardial wall volume/cavity volume ratio was not significantly different between

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control (n=16)</th>
<th>CKD 1 (n=26)</th>
<th>CKD 2 (n=23)</th>
<th>CKD≥3 (n=27)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>104±10</td>
<td>101±18</td>
<td>108±14</td>
<td>99±12</td>
<td>0.154</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>59±11</td>
<td>52±10</td>
<td>61±13</td>
<td>55±15</td>
<td>0.058</td>
</tr>
<tr>
<td>LVM $z$ score*</td>
<td>−0.49±0.82</td>
<td>−0.30±1.27</td>
<td>0.12±1.12</td>
<td>−0.46±0.96</td>
<td>0.252</td>
</tr>
<tr>
<td>DBP $z$ score*</td>
<td>−0.28±0.94</td>
<td>−0.86±0.81</td>
<td>−0.08±1.12</td>
<td>−0.51±1.32</td>
<td>0.085</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>74±8</td>
<td>69±10</td>
<td>78±13</td>
<td>70±14</td>
<td>0.068</td>
</tr>
<tr>
<td>cPP, mm Hg</td>
<td>46±11</td>
<td>49±15</td>
<td>46±10</td>
<td>44±12</td>
<td>0.462</td>
</tr>
<tr>
<td>cSBP, mm Hg</td>
<td>89±8</td>
<td>85±13</td>
<td>93±15</td>
<td>85±13</td>
<td>0.103</td>
</tr>
<tr>
<td>LVM, g</td>
<td>89.0±38.2</td>
<td>81.7±31.5</td>
<td>94.7±30.9</td>
<td>86.3±33.1</td>
<td>0.582</td>
</tr>
<tr>
<td>LVMi, g/m$^{2.7}$</td>
<td>31.2±8.0</td>
<td>30.6±6.4</td>
<td>31.4±7.0</td>
<td>33.3±7.2</td>
<td>0.550</td>
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<tr>
<td>RWT</td>
<td>0.36±0.069</td>
<td>0.34±0.061</td>
<td>0.34±0.048</td>
<td>0.33±0.059</td>
<td>0.398</td>
</tr>
<tr>
<td>LVM/EDV, g/mL</td>
<td>1.33±0.26</td>
<td>1.21±0.38</td>
<td>1.21±0.23</td>
<td>1.21±0.22</td>
<td>0.482</td>
</tr>
<tr>
<td>LVM $z$ score*</td>
<td>−0.96±1.23</td>
<td>−1.10±1.17</td>
<td>−0.85±1.23</td>
<td>−0.67±1.19</td>
<td>0.750</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>67.5±6.1</td>
<td>70.5±5.0</td>
<td>79.2±5.0</td>
<td>72.1±5.3</td>
<td>0.501</td>
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<tr>
<td>ESV, mL</td>
<td>29.7±10.4</td>
<td>32.1±12.2</td>
<td>35.9±10.5</td>
<td>33.2±12.5</td>
<td>0.456</td>
</tr>
<tr>
<td>GLS, %</td>
<td>−19.5±0.8</td>
<td>−19.2±0.6</td>
<td>−18.9±0.5</td>
<td>−18.5±0.8</td>
<td>0.806</td>
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<td>GRS, %</td>
<td>23.3±2.1</td>
<td>22.3±1.5</td>
<td>22.2±1.7</td>
<td>21.7±1.6</td>
<td>0.946</td>
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<tr>
<td>EF, %</td>
<td>55.8±5.8</td>
<td>54.1±5.5</td>
<td>54.5±5.1</td>
<td>53.1±8.2</td>
<td>0.598</td>
</tr>
<tr>
<td>E/E'</td>
<td>5.44±0.27</td>
<td>5.41±0.23</td>
<td>5.60±0.30</td>
<td>5.84±0.22</td>
<td>0.591</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>84.7±2.2</td>
<td>80.4±2.6</td>
<td>80.4±2.8</td>
<td>82.2±3.0</td>
<td>0.725</td>
</tr>
<tr>
<td>SV, mL</td>
<td>37.8±15.2</td>
<td>38.4±15.0</td>
<td>43.4±15.1</td>
<td>38.1±15.5</td>
<td>0.562</td>
</tr>
</tbody>
</table>

**BP** indicates blood pressure; CKD, chronic kidney disease; cPP, central pulse pressure; cSBP, central SBP; DBP, diastolic blood pressure; E/E', ratio of mitral valve Doppler early flow (E wave Velocity) and tissue Doppler mitral annulus movement (E' wave velocity); EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; GRS, global radial strain; HR, heart rate; LV, left ventricle; LVM, LV mass; LVMi, LVM index; MAP, mean arterial pressure; RWT, relative wall thickness; SBP, systolic blood pressure; and SV, stroke volume.

*Calculated as the number of SD above a reference population to account for confounding effects of age and sex; see text for details.
groups (P=0.173), whereas this ratio at the time of peak stress (P=0.001) and end-systole (P<0.001) was lower in children with CKD than in controls (Figure 2).

Myocardial Wall Stress

Peak, mean, and end-systolic MWS were greater in children with CKD than in controls and increased with severity of CKD stage (Figure 3). In children with CKD≥3, with the lowest eGFR, peak MWS was 396.3±13.5 kdynes/cm² compared with 336.5±17.5 kdynes/cm² in control children (P=0.01). Mean MWS in children with CKD≥3 was 328.8±10.6 kdynes/cm² compared with 273.3±13.8 kdynes/cm² in control children (P=0.003), and end-systolic MWS in children with CKD≥3 was 250.0±8.8 kdynes/cm² compared with 202.4±11.5 kdynes/cm² in control children (P=0.002). The difference between peak, mean, and end-systolic MWS in the 3 CKD groups and controls persisted irrespective of adjustment for confounders, including age, body mass index, and mean arterial pressure (Figure 3). Mean ejection-phase time-varying wall stress for each of the CKD and control groups is shown in Figure 4.

In children with CKD, peak MWS (β=−0.253, P=0.028), mean MWS (β=−0.276, P=0.016), and end-systolic MWS (β=−0.241, P=0.036) were all negatively associated with eGFR as a continuous measure. This relationship persisted after adjustment for any or all of the following confounders: age, body mass index, sex, mean arterial pressure, LVM, LVEDV, and antihypertensive medications (Table S1; β=−0.280, P=0.011; β=−0.262, P=0.01; and β=−0.183, P=0.047 for peak, mean, and end-systolic MWS, respectively). The reduction from peak to end-systolic MWS was not significantly different (P=0.546) between control (132.6±13.5 kdynes/cm²) and CKD 1 (127.6±9.8 kdynes/cm²), 2 (143.7±14.5 kdynes/cm²), or ≥3 (147.1±8.0 kdynes/cm²) groups.

Discussion

High cardiovascular morbidity in adults with CKD is closely linked to LV remodeling. LVH, in particular, is prevalent in these subjects and predicts cardiovascular morbidity. In those with onset of CKD in childhood, it is likely that LV remodeling is initiated in childhood. The first major finding of this study is that in our cohort of children with CKD in whom BP was well controlled and aortic input impedance was similar to that in controls, LVM as indexed for height was not greater than in our control group and the prevalence of LVH was not significantly greater than that in the general population or in our control group of healthy children without CKD. One explanation for this could be that hypertension is the sole determinant of LV remodeling. Other studies, however, suggest that, especially in children and adults with later stages of CKD, LVH is not explained simply by the level of BP. It should also be noted that different methods of indexing LVM influence the prevalence of LVH in children with CKD. MWS represents the load per unit cross-sectional area within individual myocytes and as such is thought to be the primary mechanical stimulus to LV remodeling. To our knowledge, this is the first study to have examined time-varying ejection-phase MWS in a pediatric population. Both peak and mean ejection-phase MWS were significantly higher in children with CKD than in controls. Furthermore, MWS demonstrated a graded increase with stage of CKD and was inversely related to eGFR. Although the reduction in late systolic stress relative to peak stress was preserved, the absolute value of late systolic stress was significantly related to CKD stage and eGFR. This elevation of MWS is likely to contribute to LV remodeling and LVH as CKD progresses and hence to cardiovascular disease morbidity in young adults. Our findings differ from an earlier study in which end-systolic wall stress was estimated by a less direct method (M-mode echocardiography derived velocity of circumferential fiber shortening) and found to be lower in children with CKD than in healthy controls. However, these children had more severe CKD than those in the present study with many on dialysis and they had a greater prevalence of LVH, which would tend to normalize MWS. The only other study in which MWS has
been measured in children with CKD is the ESCAPE study. In the ESCAPE study, children with CKD had greater renal impairment than children in the present study. They also had greater LV mass and reduced systolic function than controls. End-systolic MWS estimated from brachial SBP was higher than in control subjects and was not fully explained by increased BP. Thus, despite a tendency to increased wall thickness and LV mass that would tend to normalize MWS, MWS was elevated. This is consistent with the hypothesis that MWS initiates hypertrophic remodeling in CKD.

Mechanism of Increased MWS in Children With CKD

Elevated MWS may result from either increased central pressure during systole or altered LV geometry. In this study, peripheral and central BPs were similar in children with and without CKD and across the stages of CKD. It should be noted that in children, peak central aortic systolic pressure usually occurs at the time of peak stress. Therefore, differences in MWS were not explained simply by higher BP. The usual measure of LV geometry, ratio of LVM/EDV was not different in children with and without CKD, nor across stages of CKD. However, the ratio of LV wall volume/cavity volume at peak stress and throughout systole (but not in diastole) was significantly lower in children with CKD than in those without CKD and demonstrated a graded relationship with stage of CKD accounting for the observed relation between MWS and CKD. The change in LV wall volume and cavity volume over systole is determined by strain of the ventricle, and although neither GLS nor GRS (or ejection fraction) was different between children with CKD and control children, there was a tendency to lower values of strain in children with CKD compared with control children consistent with lower end-systolic LV wall volume to cavity volume in the CKD group compared with the control group. It may be this ratio is a more sensitive measure of early LV dysfunction in children with CKD than individual measures of strain. Thus, our study suggests that, in children with CKD, a BP independent form of LV dysfunction results in increased systolic wall stress which may predispose to LVH later in childhood or in early adulthood. Contributory factors could include those that have previously been implicated as associated with LVH in children with CKD, such as anemia and ponderosity. Alternatively, other factors, such as alteration in sodium and fluid balance, predisposing to volume overload could be implicated.

Optimum Level of Clinical BP to Normalize MWS

In adults with CKD, current guidelines recommend stringent BP targets equivalent to the 50th and 75th percentile in the general population. Recently, the European Society of Hypertension recommended maintaining BP below the 75th percentile for children with CKD. Our findings of a higher wall stress in CKD groups with BP similar to a control group and across the stages of CKD; the findings are, therefore, unlikely to have arisen by chance.

Central aortic systolic pressure was measured noninvasively and, although we have recently validated a similar method in children, there is inevitably some error in a noninvasive estimation of central systolic pressure. However, errors in estimation of central pressure are unlikely to have confounded our finding of increased wall stress because this resulted from a lower ratio of wall volume/cavity volume rather than an increase in pressure in children with CKD. Our measures of ventricular volumes were obtained from a single plane across the ventricle and would be affected by asymmetrical ventricular geometry and suboptimal 2D image resolution. However, all of the subjects in this study had normal LV systolic function with no regional wall motion abnormalities and normal cardiac anatomy, and subjects with poor acoustic window were excluded from the final analysis. Our measures of pressure waveforms and ventricular volumes were not taken simultaneously, but heart rate was closely monitored to minimize the impact of beat-to-beat variations. The cross-sectional nature of this study limits conclusions on causality and interventional trials will be required to test whether additional BP reduction confers benefit in children with CKD.

Perspectives

MWS is the mechanical stimulus to myocardial hypertrophy. It is determined by left ventricular pressure and dimensions and can be estimated using carotid tonometry and

[Image 50x116 to 277x286]
echocardiography. LVH is thought to contribute to increased cardiovascular morbidity and mortality in CKD. Our finding of elevated MWS in children with CKD independent of raised BP and before development of LVH suggests that MWS may play an important role in LVH in children with CKD even when BP is apparently well controlled. Children with CKD may benefit from more aggressive reduction of BP to offset greater intrinsic MWS.

Conclusions

Left ventricular mass may be within normal limits in children with CKD but there is evidence of a complex blood pressure–independent LV dysfunction which results in increased systolic wall stress and which may predispose to LVH in later life.

Acknowledgments

We acknowledge Miss Laura Milne’s help in performing arterial tonometry in some subjects.

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Disclosures

P.J. Chowienczyk has an interest in Centron Diagnostics.


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**Novelty and Significance**

**What Is New?**

- This is the first study to show that myocardial wall stress is elevated, independent of blood pressure, in children with chronic kidney disease and gives insight into the remodeling associated with adverse cardiac outcomes in these children.

**What Is Relevant?**

- Our finding of elevated myocardial wall stress in children with chronic kidney disease independent of raised blood pressure and before development of left ventricular hypertrophy suggests that myocardial wall stress may play an important role in left ventricular hypertrophy in children with chronic kidney disease even when blood pressure is apparently well controlled.

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**Summary**

Left ventricular mass may be within normal limits in children with chronic kidney disease, but there is evidence of a complex blood pressure-independent left ventricular dysfunction that results in increased systolic wall stress and which may predispose to left ventricular hypertrophy in later life.
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Methods and Data Supplement

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Methods
Peripheral, central blood pressure and aortic input impedance

Carotid and radial arterial pressure waveforms were obtained by a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX) and processed by the Sphygmocor device (Atcor medical, Australia) from the right radial and right carotid artery. Radial waveforms meeting the inbuilt quality control criteria of the Sphygmocor device were averaged and calibrated from peripheral brachial measures of SBP and DBP, from which mean arterial pressure (MAP) was calculated by integrating the radial waveform. The carotid pressure waveform was then calibrated from MAP and peripheral DBP (which unlike SBP are equal at aortic and peripheral sites). Previous studies in adults have shown that because of its close proximity to the aorta, the carotid waveform can be used as a surrogate of the central aortic pressure waveform and left ventricular pressure during systole and we have recently verified that central aortic SBP (cSBP) can be derived from the carotid waveform (from wall-tracking of the carotid artery) in children. The carotid waveform thus calibrated was used to identify the first (P1) and second (P2) shoulders of the central pressure waveform and end systolic pressure (ESP) (Figure 1). In children, cSBP usually occurs synchronously with P1, at the time of peak systolic MWS (Figure 1), whereas in older adults it occurs at P2. Aortic input impedance was calculated from the carotid pressure and aortic flow by in house software developed in Matlab (MathWorks Inc, Natick, MA).

Echocardiography

All echocardiographic views and measurements were performed using the Philips IE33 ultrasound system (Philips Healthcare, Andover, USA) according to the American Society of Echocardiography (ASE) guidelines. Frequency and frame rate were optimized to allow adequate penetration for endocardial border definition. Left ventricular mass (LVM) was measured by two-dimensional directed M-mode echocardiography (for which normal ranges for LVM and LVM index (LVMI) in children are available) according to ASE recommendations. LVM was indexed by height raised to a power of 2.7 as g/m$^2.77$ and also expressed as a z-score. Relative wall thickness (RWT) was calculated as the mean thickness of the septal and posterior walls divided by LV end-diastolic diameter. Times of aortic valve opening (AVO) and closure (AVC) were measured from aortic valve spectral Doppler. Ejection duration was then defined from the beginning of AVO to AVC and ejection volume was the volume ejected from the LV between AVO and AVC.

Global longitudinal / radial (transverse) strain and Time-resolved cavity volume / myocardial wall volume

Time-resolved cavity volume and myocardial wall volume were measured using a Tomtec analysis package (2D cardiac performance analysis, Tomtec, Munich, Germany) from a 2D apical 4-Chamber view with optimized gain and depth using both endocardial and epicardial definition. The endocardium was initially defined by placing at least 6 points along it; the width of interest was then adjusted to accommodate myocardial thickness in each frame. Both the endocardial and epicardial border were then tracked automatically throughout the whole cardiac cycle (Figure S1). Auto-tracking was reviewed and edited frame by frame to ensure accurate tracking. Global longitudinal and radial
strain, reflecting the relative changes in shortening or thickening between points of tissue along the border, were derived from speckle tracking analysis.\textsuperscript{10} End-diastolic volume (EDV) and end-systolic volume (ESV) were derived from the LV volume curve in the same view. The reproducibility of this wall tracking for EDV, and ESV were evaluated from measurements on 12 subjects, aged 13.0±3.6 years repeated on two separate occasions separated by approximately 3 months by the same observer and by two independent observers on the same occasion. The between-visit coefficient of variation (CV, equal to the SD as a percentage of the mean) was 2.0% and 3.1% for ED and ES cavity volumes respectively. Inter-observer CVs were 3.0% for ED and ES cavity volumes respectively.

**Time-varying ejection-phase myocardial wall stress**

Time-varying ejection-phase MWS (Figure S1) was computed from LV pressure estimated from carotid tonometry and from myocardial wall and cavity volumes by in-house software written in Matlab (MathWorks, Natick, MA) from the Arts formula:

\[
MWS = \frac{P}{\frac{1}{3} \ln(1 + \frac{V_w}{V_{lv}})}
\]

Where \( P = \) LV pressure, \( \ln = \) natural logarithm, \( V_w = \) myocardial wall volume, \( V_{lv} = \) LV cavity volume; \( V_w = V_{epi} - V_{lv} \), where \( V_{epi} = \) epicardial wall volume.

The mean ejection-phase time-varying wall stress for each of the CKD and control groups was regenerated from 4 specified time points (end-diastole, P1, P2 and end-systole). To analyze instantaneous changes in LV geometry, the myocardial wall volume to LV cavity volume \( (V_w/V_{lv}) \) relationship at end-diastole, time of peak stress and end-systole was calculated.
Reference


5. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18:1440-1463.


Table S1. Multiple linear regression analysis of relation between MWS and eGFR (n=76)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Peak MWS ((\text{Adjusted } r^2=0.330))</th>
<th>Mean MWS ((\text{Adjusted } r^2=0.429))</th>
<th>End-systolic MWS ((\text{Adjusted } r^2=0.525))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\beta)</td>
<td>(P) Value</td>
<td>(\beta)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.700</td>
<td>(&lt;0.001)</td>
<td>-0.625</td>
</tr>
<tr>
<td>Sex</td>
<td>0.125</td>
<td>0.230</td>
<td>0.143</td>
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<tr>
<td>BMI (kg/m2)</td>
<td>0.093</td>
<td>0.486</td>
<td>0.01</td>
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<tr>
<td>MAP (mmHg)</td>
<td>0.318</td>
<td>0.003</td>
<td>0.502</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td>-0.281</td>
<td>0.012</td>
<td>-0.263</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>0.518</td>
<td>0.003</td>
<td>0.481</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>0.050</td>
<td>0.632</td>
<td>0.083</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>-0.032</td>
<td>0.788</td>
<td>-0.023</td>
</tr>
</tbody>
</table>

MWS: myocardial wall stress; BMI: body mass index; MAP: mean arterial pressure; eGFR: estimated glomerular filtration rate; EDV: end-diastolic volume; HR: heart rate; bpm: beats per minute.
Figure S1. (a): 2D Echo automated wall tracking on apical 4-chamber view using Tom Tec imaging software. The outer green line tracks epicardium from which LV epicardial volume is derived and the inner green line tracks endocardium from which LV cavity volume is derived; myocardial wall volume is the difference between LV epicardial wall volume and cavity volume. (b): LV cavity volume tracked over one cardiac cycle (red line).
Figure S2. a) Average modulus and b) phase of aortic input impedance in control and CKD groups. CKD 1 (square dotted line), CKD 2 (round dotted line) and CKD≥3 (solid line) healthy control children (dashed line). Neither modulus nor phase are significantly different between groups.