Decline in Left Ventricular Early Systolic Function with Worsening Kidney Function in Children with Chronic Kidney Disease: Insights from the 4C and HOT-KID Studies

Haotian Gu, PhD, Karolis Azukaitis, PhD, Anke Doyon, MD, Sevcan Erdem, MD, Bruno Ranchin, MD, Jerome Harambat, PhD, Francesca Lugani, MD, Andrii Boguslavskyi, PhD, Janette Cansick, Eric Finlay, MSc, Rodney Gilbert, Larissa Kerecuk, Andrew Lunn, BM, Heather Maxwell, MD, Henry Morgan, MBChB, Mohan Shenoy, Rukshana Shroff, PhD, Pushpa Subramaniam, Jane Tizard, MBBS, Yincent Tse, MBChB, John Simpson, MD, Phil, Chowienczyk, BSc, Franz Schaefer, PhD, and Manish D. Sinha, PhD, for the 4C and HOT-KID studies, *London, Medway, Leeds, Southampton, Birmingham, Nottingham, Glasgow, Liverpool, Manchester, Bristol, and Newcastle Upon Tyne, United Kingdom; Vilnius, Lithuania; Heidelberg, Germany; Adana, Turkey; Lyon and Bordeaux, France; and Genova, Italy*

Introduction: Adults with childhood-onset chronic kidney disease (CKD) have an increased risk of cardiovascular disease. First-phase ejection fraction (EF1), a novel measure of early systolic function, may be a more sensitive marker of left ventricular dysfunction than other markers in children with CKD.

Objective: To examine whether EF1 is reduced in children with CKD.

Methods: Children from the 4C and HOT-KID studies were stratified according to estimated glomerular filtration rate (eGFR). The EF1 was calculated from the fraction of left ventricular (LV) volume ejected up to the time of peak aortic flow velocity.

Results: The EF1 was measured in children ages 10.9 ± 3.7 (mean ± SD) years, 312 with CKD and 63 healthy controls. The EF1 was lower, while overall ejection fraction was similar, in those with CKD compared with controls and decreased across stages of CKD (29.3% ± 3.7%, 23.5% ± 4.5%, 19.8% ± 4.0%, 18.5% ± 5.1%, and 16.7% ± 6.6% in controls, CKD 1, 2, 3, and ≥ 4, respectively, $P < .001$). The relationship of EF1 to eGFR persisted after adjustment for relevant confounders ($P < .001$). The effect size for association of measures of LV structure or function with eGFR (SD change per unit change in eGFR) was greater for EF1 ($\beta = 0.365$, $P < .001$) than for other measures: LV mass index ($\beta = -0.311$), relative wall thickness ($\beta = -0.223$), E/e' ($\beta = -0.147$), and e' ($\beta = 0.141$) after adjustment for confounders in children with CKD.

From the King's College London British Heart Foundation Centre, London, United Kingdom (H.G., A.B., P.C., M.D.S.); Clinic of Pediatrics, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania (K.A.); Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg University Hospital, Heidelberg, Germany (A.D., F.S.); Department of Pediatric Cardiology, Faculty of Medicine, Çukurova University, Adana, Turkey (S.E.); Pediatric Nephrology Unit, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Université de Lyon, Lyon, France (B.R.); Pediatric Nephrology Unit, Department of Pediatrics, Centre de Référence Maladies Rénales Rares, Bordeaux University Hospital, Bordeaux, France (J.H.); Division of Nephrology, Dialysis, Transplantation, IRCCS Istituto Giannina Gaslini, Genova, Italy (F.L.); Department of Paediatrics, Medway Maritime Hospital, Medway, United Kingdom (J.H.); Department of Paediatric Nephrology, Leeds General Infirmary, Leeds, United Kingdom (E.F.); Department of Paediatric Nephrology, Southampton General Hospital, Southampton, United Kingdom (R.G.); Department of Paediatric Nephrology, Birmingham Children's Hospital, Birmingham, United Kingdom (L.K.); Department of Paediatric Nephrology, Nottingham University Hospital NHS Trust, Nottingham, United Kingdom (A.L.); Department of Paediatric Nephrology, Royal Hospital for Children, Glasgow, United Kingdom (H.M.); Department of Paediatric Nephrology, Alder Hey Children's Hospital, Liverpool, United Kingdom (H.M.); Department of Paediatric Nephrology, Royal Manchester Children's Hospital, Manchester, United Kingdom (M.S.); Department of Paediatric Nephrology, UCL Great Ormond Street Hospital and Institute of Child Health, London, United Kingdom (R.S.); Department of Paediatrics, St Georges Hospital, Tooting, London, United Kingdom (P.S.); Department of Paediatric Nephrology, Bristol Royal Hospital for Children, Bristol, United Kingdom (J.T.); Department of Paediatric Nephrology, Great North Children's Hospital, Newcastle Upon Tyne, United Kingdom (Y.T.); and Departments of Congenital Heart Disease (J.S.), and Paediatric Nephrology, Evelina London Children's Hospital, London, United Kingdom (M.D.S.).

Drs. Schaefer and Sinha contributed equally to this work and should be considered joint senior authors.

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Reprint requests: Manish D. Sinha, PhD, Kings College London, Department of Paediatric Nephrology, Evelina London Children's Hospital, Guys & St. Thomas NHS Foundation Trust, 3rd Floor Beckett House, Westminster Bridge Road, London SE1 7EH, United Kingdom (E-mail: *manish.sinha@nhs.net*).

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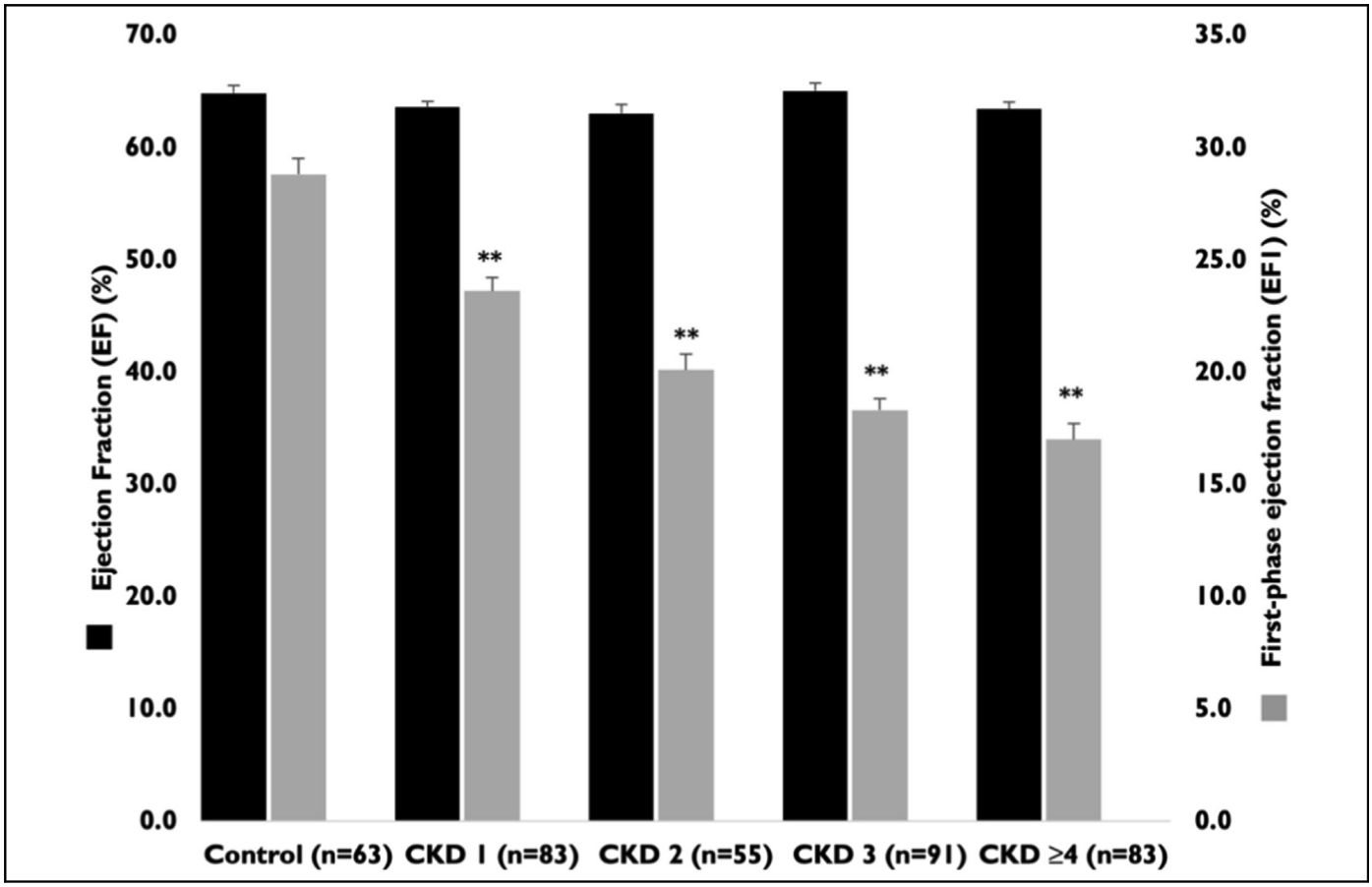
Conclusions: Children with CKD exhibit a marked and progressive decline in EF1 with falling eGFR. This suggests that EF1 is a more sensitive marker of LV dysfunction when compared to other structural or functional measures and that early LV systolic function is a key feature in the pathophysiology of cardiac dysfunction in CKD. (J Am Soc Echocardiogr 2023;■:■-■.)

Keywords: Early systolic function, First-phase ejection fraction, Chronic kidney disease



Central Illustration Ejection fraction (*black bars*) was preserved in all CKD groups compared to controls in the HOT-KID and 4C studies; EF1 (*gray bars*) was significantly reduced across CKD stages after adjustment for age, sex, height *Z* score, MAP, antihypertensive medication use, LVMi, EF, E/e', and S wave. $^{**}P < .001$ compared to control.

INTRODUCTION

Children with chronic kidney disease (CKD) exhibit greatly increased mortality and morbidity from cardiovascular disease (CVD) as they progress into adulthood compared to those without CKD.[1-3] This increase in CVD is likely to have its origins in childhood and to relate, at least in part, to left ventricular (LV) remodeling including LV hypertrophy and subclinical ventricular dysfunction.[2,4-7] Left ventricular systolic function as measured by conventional measures such as ejection fraction (EF) is usually preserved in children with CKD, but subclinical systolic dysfunction as measured by tissue Doppler,[7] midwall shortening,[8] myocardial strain[9] and diastolic dysfunction[10] are often present and associated with LV remodeling. First-phase EF (EF1), the EF up to the time of maximal LV rate of contraction, has previously been shown to be impaired and possibly associated with LV remodeling and diastolic dysfunction in adult and children with hypertension.[11,12] Other investigators have demonstrated that EF1 is afterload dependent in adults with aortic stenosis.[13,14]

The objective of this study was to evaluate early-phase systolic ventricular function as measured by EF1 and its relationship with LV geometry and diastolic function in a large cohort of children with mild to severe nondialysis CKD and with comparison to healthy children.

MATERIALS AND METHODS

Study Population

Children with CKD included participants of the HOT-KID study (the Hypertension Optimal Treatment in Children With Chronic Kidney Disease Study)[15] and of the 4C cohort (the Cardiovascular Comorbidity in Children With Chronic Kidney Disease Study).[16]

Abbreviations

4C = Cardiovascular Comorbidity in Children With Chronic Kidney Disease Study

ANOVA = Analysis of variance

BMI = Body mass index

BP = Blood pressure

CKD = Chronic kidney disease

CVD = Cardiovascular disease

EDV = End-diastolic volume

EDVi = End-diastolic volume index

EF = Ejection fraction

EF1 = First-phase ejection fraction

eGFR = Estimated glomerular filtration rate

ET = Ejection time

GLS = Global longitudinal strain

HOT-KID = Hypertension Optimal Treatment in Children With Chronic Kidney Disease Study

LAV = Left atrial volume

LAVi = Left atrial volume index

LV = Left ventricular

LVM = Left ventricular mass

LVMi = Left ventricular mass index

MAP = Mean arterial pressure

MWS = Myocardial wall stress

RWT = Relative wall thickness

TPAFV = Time of peak aortic flow velocity

HOT-KID Study. The HOT-KID study included a parallel-group, open-label, multicenter, randomized controlled trial that has recently been reported.[15] As part of the HOT-KID study, we also completed an observational study and report here the assessments at baseline for all participants including those in the randomized controlled trial and the observational study. Children between 2 and 15 years with CKD were recruited from 14 UK centers. Healthy children in the same age range were recruited as part of the HOT-KID study contemporaneously from siblings of patients or children of staff attending pediatric outpatient clinics at the Evelina London Children's Hospital. All participants underwent standardized measurement of office blood pressure (BP), echocardiography, and other study-related investigations including measurement of plasma creatinine, and details have been reported previously.[15] Office BP was measured by a trained staff member (physician or nurse). Patients were required to rest for at least 5 minutes in a seated position, systolic BP was initially confirmed by palpation, and then the BP was measured 3 times in quick succession using auscultation and aneroid sphygmomanometer with an appropriately sized cuff by inflating the cuff higher than systolic BP. Cuff size was selected by ensuring cuff bladder length and width according to standard guidelines. The HOT-KID study was approved by the UK National Research Ethics Committee (10/H0802/13), participating institutions, and relevant regulatory authorities.

4C Study. The 4C is an observational cohort study that includes children (ages 6-17 years) with CKD stages 3 to 5 not on kidney replacement therapy in 55 nephrology centers across 12 European countries. The protocol of the 4C study has been published previously.[16] All participants had BP measurements with a locally available oscillometric device validated for use in children and underwent echocardiography according to a standardized procedure.[16,17] The 4C study was approved by ethics committees and institutional review boards from each participating institution as detailed previously.[7]

Inclusion and Exclusion Criteria. Participants selected for this analysis include those not on kidney replacement therapy in whom suitable echocardiography images were available to measure EF1. Additional exclusion criteria were congenital heart disease, cardiac arrhythmias, and inability to obtain high-quality cardiovascular measurements (mainly because of movement artifact). Both studies were approved by research ethics committees, and written informed consent was obtained from parents and (where appropriate) children. In children with CKD, estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula [0.413 * (height/serum creatinine)] and CKD staged as per existing definitions.[18,19]

Echocardiography and EF1

Transthoracic echocardiographic studies were analyzed by one author (H.G.) who was blinded to the participants' kidney function, BP, and other characteristics. All echocardiographic views and measurements were performed using standard techniques according to American Society of Echocardiography.[20] Left ventricular mass was measured by two-dimensional directed M-mode echocardiography according to American Society of Echocardiography guidelines.[20] Left ventricular mass varies widely across the pediatric age range. Therefore, to allow standardization, it is expressed as LV mass (LVM) index (LVMi): LVM divided by height in meters raised to allometric power of 2.7 ($g/m^{2.7}$) as a measure that accounts for body size.[21] Left ventricular end-diastolic diameter, interventricular septal, and posterior wall thickness were measured from a parasternal long-axis view. Relative wall thickness (RWT) was measured to assess LV geometry.[22] End-diastolic volume (EDV), end-systolic volume, EF, and left atrial volume (LAV) were measured from two-dimensional apical views. Global longitudinal strain (GLS) was measured using a Tomtec 2D Cardiac Performance Analysis package (Tomtec, TTA2). End-diastolic volume and LAV were indexed to body surface area (EDVi and LAVi). Tissue Doppler imaging was obtained at the level of the lateral and septal mitral annulus for measurement of the e′ wave and s′ wave (average of lateral and septal values). The E/e′ ratio was used as a surrogate measure of LV filling pressure. Ejection time (ET) was defined as R wave to the end of systole.

First-Phase EF and Arterial Stiffness. First-phase EF was defined as the percentage change in LV volume from end diastole to the time of peak aortic flow velocity (TPAFV), a time that approximates the time of peak ventricular contraction in individual myocytes.[23] Time of peak aortic flow velocity was measured using the continuous-wave Doppler signal from an apical 5-chamber view. First-phase EF was calculated using the following equation: EF1 = (EDV − V1)/EDV%, where V1 is LV volume at TPAFV.[11] The frame for determining V1 was calculated by measuring the total number of frames from the R wave on electrocardiogram to end systole and multiplying this by the fraction of R wave to TPAFV and R wave to the end systole. Interobserver variability was assessed in 39 randomly selected subjects by measurements repeated by 2 observers (H.G. and A.B.) with the coefficient of variation defined as the SD of difference in measures expressed as a percentage of the mean measurement and displayed by a Bland-Altman plot. Arterial stiffness was estimated by the ratio of central pulse pressure/stroke volume index, an echocardiographic surrogate of arterial stiffening.[24]

Statistical Analysis

Subject characteristics are summarized as means ± SD. To examine the relationship between cardiovascular measures and eGFR,

HIGHLIGHTS

- Children with CKD have abnormal EF1, a novel marker of LV early systolic function.
- EF1 is a more sensitive measure compared to conventional indices such as EF and GLS.
- Abnormal EF1 is independent of TPAFV, conventional cardiac structure, and function.

children with CKD were divided into 4 groups according to CKD stages[19]: CKD 1 (eGFR >90 mL/min/1.73 m^2), CKD 2 (eGFR, 60-90 mL/min/1.73 m^2) CKD 3 (eGFR, 30-59 mL/min/1.73 m^2), and CKD ≥4 (including stage 4 and nondialysis stage 5 of CKD; eGFR < 30 mL/min/1.73 m^2). Given the age-related change in BP throughout childhood, BP measurements were presented both as mm Hg and as *Z* scores (the number of SDs above or below a population mean assigned a value of 0) using published reference values.[25] Height, weight, and body mass index (BMI) were also standardized to *Z* scores using the lambda-mu-sigma method.[26] Comparisons between different CKD stages were then made using analysis of variance (ANOVA) with and without adjustment for potentially confounding factors (age, gender, height *Z* score, mean arterial pressure [MAP], anti-hypertensive medications, LVMi, EF, E/e', and S wave). We additionally compared TPAFV and the ratio of TPAFV to ET between groups. Univariable and multivariable linear regression analyses were used to examine the relation between EF1, other cardiovascular measures, and eGFR in the total CKD population. Multivariable models were adjusted for confounders that were physiologically relevant and/or known to be associated with the outcome measures[27,28] and included age, sex, BMI, antihypertensive medications (yes/no), MAP, LVMi, RWT, EDVi, LAVi, EF, S wave, and E/e' ratio. Regression models were repeated using a backwards stepwise variable deselection to examine the sensitivity of the analysis to the inclusion of confounding covariates. To assess the relative strengths of association measures of cardiac function and structure with eGFR, regression coefficients were additionally calculated in units of SD per unit change in eGFR. Goodness of fit was expressed as the adjusted r^2. Effect size for the difference in EF1 between groups was evaluated using η^2 for ANOVA, which measures the difference between groups as a proportion of the variance.[29] A *P* value <.05 was considered statistically significant, and all tests were 2-tailed. Statistical analyses were performed using SPSS version 24.

RESULTS

Participant Characteristics

A total of 375 children were included from the HOT-KID study ($n = 256$) and the 4C study ($n = 119$). Characteristics of healthy children ($n = 63$) and children with CKD stratified according to stages of CKD (1, 2, 3, and ≥ 4) are shown in Table 1. Chronic kidney disease was secondary to congenital anomalies of the kidney and urinary tract in 195, glomerular disease in 32, and other causes in 85 including cystic kidney disease, tubulopathies, metabolic renal disease, and unknown etiology. Children with earlier stages of CKD were of comparable age to control children, and those with CKD stage ≥4 were older compared with controls (Table 1). There were more boys than girls in the CKD 3 and CKD ≥4 groups. There was no significant difference in height and weight *Z* scores between controls and CKD

Table 1 Subject characteristics in children with CKD in HOT-KID and 4C studies shown as mean (SD)

Measure	Control (n = 63)	CKD 1 (n = 83)	CKD 2 (n = 55)	CKD 3 (n = 91)	CKD ≥4 (n = 83)	*P* value (ANOVA)
Age, years	10.6 (3.4)	9.6 (3.6)	9.9 (3.6)	11.5 (3.8)	12.4 (3.7)*	<.001
Sex, male (%)	28 (44.4)	50 (60.2)	32 (58.1)	60 (65.9)*	61 (73.5)*	.008
Height *Z*-score	0.28 (1.0)	0.33 (1.2)	−0.23 (1.2)†	−0.70 (1.0)*	−1.09 (1.2)*	<.01
Weight *Z*-score	0.54 (1.1)	0.63 (1.3)	0.05 (1.2)†	−0.21 (1.1)*	−0.72 (1.2)*	<.001
BMI *Z*-score	0.5 (1.1)	0.6 (1.3)	0.05 (1.2)	0.29 (1.2)	−0.13 (1.1)	.166
Anti-HTN (%)	0	29 (34.9)	25 (45.5)	44 (48.4)	52 (62.7)	<.001
HR, bpm	81.4 (13.8)	81.0 (16.1)	79.8 (15.7)	77.5 (14.0)	77.5 (11.6)	.251
SBP, mm Hg	98.7 (12.3)	101.5 (11.9)	107.3 (10.4)*	104.9 (12.3)*	112.3 (12.9)*	<.001
SBP *Z*-score	−0.32 (0.9)	0.05 (0.9)†	0.54 (0.9)*	0.09 (1.0)	0.70 (1.2)*	<.001
DBP, mm Hg	56.1 (9.3)	58.2 (11.9)	63.0 (11.2)*	61.9 (11.5)*	65.6 (12.0)*	<.001
DBP *Z*-score	−0.46 (0.8)	−0.16 (1.1)	0.27 (1.0)*	0.11 (1.0)*	0.33 (1.1)*	<.001
MAP, mm Hg	70.3 (8.8)	72.7 (10.7)	77.8 (9.7)*	76.2 (10.8)*	81.2 (11.0)*	<.001
Hb, g/L	129.8 (8.1)	130.8 (11.3)	130.9 (12.9)	124.3 (18.4)	116.7 (13.9)*	<.001
Serum albumin, g/L	47.6 (2.1)	44.8 (3.7)*	43.5 (4.0)*	41.6 (4.5)*	39.9 (3.6)*	<.001
Phosphate, mmol/L	1.4 (0.2)	1.4 (0.2)	1.4 (0.2)	1.4 (0.2)	1.6 (0.3)*	<.001
Serum iPTH, ng/L	28.2 (7.6)	31.0 (22.2)	35.4 (32.0)	51.6 (116.8)	32.1 (56.2)	.393
eGFR, mL/min per 1.73 m^2	127.7 (24.8)	115.3 (20.2)†	76.7 (8.5)*	44.3 (10.0)*	18.8 (6.3)*	<.001

Anti-HTN, Anti-hypertensive treatment; *DBP*, diastolic BP; *Hb*, hemoglobin; *HR*, heart rate; *SBP*, systolic BP; *Z*, *Z* score (value expressed as number of SDs from mean of reference population).
*$P < .01$ compared to control.
†$P < .05$ compared to control.

1, but children in CKD groups 2, 3, and ≥ 4 were shorter, of lower weight, and with increased BP compared with controls. Twenty-nine (34.9%), 25 (45.5%), 44 (48.4%), and 52 (62.7%) children in CKD 1, CKD 2, CKD 3, and CKD ≥4, respectively, were taking antihypertensive medication ($P < .001$ between groups). Children in the 4C study had worse kidney function (with 40 in stage 3 and 79 in stage ≥4 of CKD) compared to children in the HOT-KID study (83, 55, 51, and 4 in CKD stages 1, 2, 3, and ≥4, respectively). Participant characteristics, LV geometry, and function for the 2 cohorts are shown in the online Supplementary Data (Supplemental Tables 1 and 2).

Left Ventricular Geometry and Function and Arterial Stiffness. Children with CKD (including those in stage 1 of CKD) had increased LVMi and had higher RWT compared to controls. Left atrial volume index was also higher in those with CKD 3 and CKD ≥4 compared to controls. End-diastolic volume index was higher in children with CKD ≥4 compared to controls (Table 2). Conventional measures of systolic function including EF, GLS, and S wave were similar across all 4 CKD groups when compared with controls. There was evidence of diastolic dysfunction with increased E/e′ ratio and reduced e′ in children with CKD compared to controls. First-phase EF was lower in children across all stages of CKD when compared with controls, with lower EF1 values observed in those with more advanced CKD (Table 2). Difference as measured by η^2 between EF1 in children with CKD and controls is shown in Table 2. This relationship persisted after adjustment for age, sex, height *Z* score, MAP, antihypertensive medication use, LVMi, EF, E/e′, and S wave ($P < .001$, Central Illustration). The TPAFV and TPAFV/ET were similar across all 4 CKD groups when compared to controls. There was no significant difference in arterial stiffness between children with CKD and controls. On interobserver variability analysis, the coefficient of variation for EF1 was 10.4% (Supplemental Figure 1).

Association of EF1 With eGFR in Children With CKD. On univariable linear regression analysis, EF1 was positively associated with hemoglobin, albumin, eGFR, EF, and TPAFV/ET and was negatively associated with SBP, MAP, LVMi, LAVi, and E/e′ (Table 3). In multivariable regression (with all covariates in Table 3 forced into the model), EF1 was positively associated with eGFR ($\beta = 0.384$, $P < .001$), EF ($\beta = 0.300$, $P < .001$), and TPAFV/ET ($\beta = 0.278$, $P < .001$; Table 4). After backward stepwise regression removing covariates that were not associated with EF1, the association of EF1 with eGFR ($\beta = 0.462$, $P < .001$) was stronger than that with EF ($\beta = 0.330$, $P < .001$; Table 4). When TPAFV/ET was treated as a dependent variable, there was no association between eGFR and TPAFV/ET ($\beta = -0.062$, $P = .273$) on univariable analysis.

When expressing regression coefficients as SD change per unit change in eGFR, EF1 was the only measure of systolic function associated with eGFR (EF [$\beta = -0.024$, $P = .655$], S wave [$\beta = -0.004$, $P = .949$], and GLS [$\beta = 0.036$, $P = .689$]). The effect size for association of EF1 with eGFR ($\beta = 0.365$, $P < .001$) was greater than for other measures of LV geometry and diastolic function: LVMi ($\beta = -0.311$, $P < .001$), RWT ($\beta = -0.223$, $P < .001$), E/e′ ($\beta = -0.147$, $P = .002$), and e′ ($\beta = 0.141$, $P = .005$) after adjustment for age, sex, MAP, and antihypertensive treatments in children with CKD (Figure 1).

DISCUSSION

We evaluated EF1, a novel measure of LV early systolic function, in a group of over 300 children across all stages of nondialysis CKD and compared it with that of healthy children. Our main finding is the marked reduction of early systolic function as measured by EF1 across all stages of CKD including those in the early stages of CKD. This contrasts with various other measures of LV function that have been

Table 2 LV geometry and function in children with CKD in HOT-KID and 4C studies shown as mean (SD)

Measure	Control (*n* = 63)	CKD 1 (*n* = 83)	CKD 2 (*n* = 55)	CKD 3 (*n* = 91)	CKD ≥4 (*n* = 83)	*P* value (ANOVA)
LVMi, g/m$^{2.7}$	27.9 (6.1)	30.0 (6.5)*	31.8 (10.8)*	32.4 (7.7)†	39.2 (9.7)†	<.001
RWT	0.32 (0.05)	0.35 (0.05)†	0.33 (0.06)	0.38 (0.10)†	0.45 (0.15)†	<.001
LAVi, mL/m^2	10.2 (3.0)	10.0 (3.0)	10.2 (3.3)	13.0 (4.8)†	16.9 (6.2)†	<.001
EDVi, mL/m^2	44.1 (9.5)	43.0 (9.6)	42.8 (8.0)	42.4 (9.5)	47.8 (10.3)*	.010
EF, %	64.8 (5.3)	63.6 (4.9)	63.0 (5.6)	65.0 (6.3)	63.4 (5.8)	.127
GLS, % (*n* = 215)	−18.0 (6.4)	−17.8 (3.1)	−17.4 (2.1)	−18.2 (3.0)	−17.7 (3.8)	.924
S wave, m/sec	8.8 (1.4)	8.7 (1.3)	8.4 (1.4)	8.8 (1.4)	9.4 (2.0)	.007
E/e’	6.1 (0.9)	6.6 (1.5)*	6.7 (1.3)†	6.8 (1.3)†	7.2 (1.6)†	.021
e’, m/sec	15.0 (2.0)	14.6 (2.0)*	14.7 (2.0)	14.3(2.0)†	13.9 (2.0)†	<.001
EF1, %	29.3 (3.7)	23.5 (4.5)†	19.8 (4.0)†	18.5 (5.1)†	16.7 (6.6)†	<.001
TPAFV, msec	114 (18)	109 (21)	109 (24)	116 (21)	115 (19)*	.081
TPAFV/ET	0.36 (0.05)	0.35 (0.05)	0.35 (0.06)	0.36 (0.05)	0.35 (0.05)	.394
Arterial stiffness, mm Hg/mL/m^2	1.16 (0.34)	1.21 (0.37)	1.23 (0.41)	1.20 (0.33)	1.18 (0.38)	.818

Effect size of EF1: ANOVA η^2 (mean 0.430; 95% CI, 0.352-0.488).
*$P < .05$ compared to control.
†$P < .01$ compared to control.

Table 3 Univariable linear regression analysis of relation between EF1, eGFR, and other measures in children with CKD in HOT-KID and 4C studies

Univariable	EF1	
	β	*P* value
Age	−0.100	.077
Sex	0.042	.455
BMI, kg/m^2	0.012	.865
Antihypertensive drugs	0.105	.065
Systolic BP, mm Hg	−0.127	.025
Diastolic BP, mm Hg	−0.111	.051
MAP, mm Hg	−0.127	.026
Hemoglobin, g/L	0.177	.003
Albumin, g/L	0.194	<.001
Phosphate, mmol/L	−0.064	.274
eGFR, mL/min per 1.73 m^2	0.405	<.001
LVMi, g/m$^{2.7}$	−0.164	.004
RWT	−0.043	.449
EDVi, mL/m^2	−0.109	.054
LAVi, mL/m^2	−0.174	.002
EF, %	0.212	<.001
S wave, cm/sec	−0.047	.408
E/e'	−0.127	.026
TPAFV/ET	0.201	<.001
Arterial stiffness, mm Hg/mL/m^2	−0.006	.912

Table 4 Multivariable linear regression analysis of relation between EF1, eGFR, and other measures in children with CKD in HOT-KID and 4C studies

Covariables	EF1 (r^2 = 0.296)	
	β	*P* value
Model 1 (enter)		
Age	−0.044	.575
Sex	−0.004	.939
BMI, kg/m^2	0.048	.435
Antihypertensive drugs	0.004	.941
MAP, mm Hg	−0.070	.262
Hemoglobin, g/L	0.068	.292
Albumin, g/L	0.061	.331
Phosphate, mmol/L	0.019	.743
eGFR, mL/min per 1.73 m^2	0.384	<.001
LVMi, g/m$^{2.7}$	−0.059	.374
RWT	0.140	.028
EDVi, mL/m^2	−0.103	.274
LAVi, mL/m^2	0.044	.528
EF, %	0.300	<.001
S wave, cm/sec	−0.005	.938
E/e'	−0.049	.421
TPAFV/ET	0.278	<.001
Arterial stiffness, mm Hg/mL/m^2	−0.100	.277
Model 2 (stepwise)	r^2 = 0.309	
eGFR, mL/min per 1.73 m^2	0.462	<.001
RWT	0.104	.065
EF, %	0.330	<.001
TPAFV/ET	0.262	<.001

shown to be abnormal in childhood CKD to date, in which the abnormalities have been reported to be subtle and/or to not appear until CKD is advanced. Furthermore, we report progressive reduction of EF1 with more advanced stages of CKD, with a strong positive association of EF1 with eGFR. This association is independent of other measures of cardiac structure and function and is stronger than that for LV geometry (LVMi and RWT), conventional measures of systolic (EF, GLS, and S wave), and diastolic function (E/e' and e').

Subclinical systolic dysfunction as measured by tissue Doppler,[7] midwall shortening,[5,7,8] and myocardial strain[9] has been shown previously. However, these were in relatively small samples of children with a wide range of eGFR (including those on dialysis and following kidney transplantation), and the strength of association of these measures with eGFR was much weaker than that observed for EF1 in the present study. In particular, these studies did not have data in children with early-stage CKD. The reduction of EF1 in children with early-stage CKD compared to healthy children (20%, 32%, and 37% in CKD 1, 2, and 3, respectively) was much more profound than that previously reported for midwall shortening, with a 5% difference between those with stage 2 and those with stage 4 of CKD.[8] The finding of reduced EF1 in children with early stages of CKD and progressive decline in later stages suggests that a reduction in EF1 is a key feature of the cardiac dysfunction in children with CKD and develops early, before change in conventional structural and functional measures.

To what extent the reduction in early systolic function could predispose to the development of more severe cardiac dysfunction and

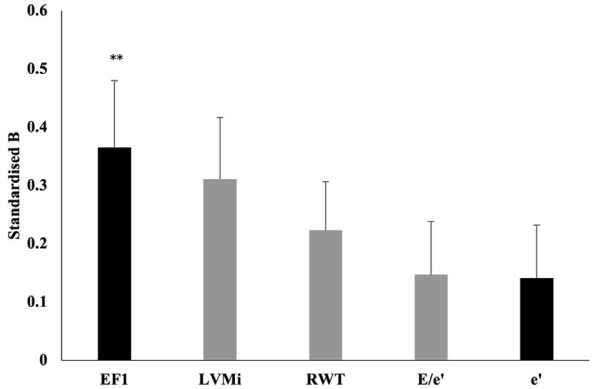


Figure 1 Standardized regression coefficients β of EF1 (β = 0.365, *P* < .001), LVMi (β = −0.311, *P* < .001), RWT (β = −0.223, *P* < .001), E/e' (β = −0.147, *P* = .002), and e' (β = 0.141, *P* = .005) with eGFR after adjustment for age, sex, MAP, and antihypertensive treatments in children with CKD in the HOT-KID and 4C studies. **P* < .05 compared to RWT, E/e' and e'. *Black bars*: positive β value; *gray bars*: negative β value.

clinical outcomes as children with CKD progress into adulthood can only be answered by longitudinal studies. However, the progressive reduction of EF1 with advancing CKD in children suggests it will be further reduced in adults with childhood-onset CKD and likely be similar to adults with other cardiac pathologies such as aortic stenosis and heart failure, in whom EF1 is highly predictive of clinical outcomes.[13,30,31] Thus, the hypothesis that a reduction in EF1 occurs early in childhood-onset CKD and drives major adverse cardiovascular events deserves testing.

The mechanism of reduction in EF1 remains to be determined, but children with CKD offer a unique opportunity to evaluate this in the absence of comorbidities usually seen in adults with CKD, in whom smoking, presence of diabetes mellitus, and hypertension remain significant confounders. A few studies have shown that aortic acceleration time is a simple Doppler measure of increased arterial load,[32,33] and similarly in patients with pulmonary hypertension, pulmonary artery acceleration time is a method used to measure right ventricular mechanical performance and pulmonary vascular load and compliance.[34,35] First-phase EF is the integral of flow from the start of ejection to TPAFV and therefore in part dependent on TPAFV. However, TPAFV did not differ between groups and therefore suggests that reduction of EF1 was not explained simply by timing of flow. In our study, a strong association of EF1 with eGFR remained even following adjustment for BP, LVMi, arterial stiffness, and TPAFV/ET, so it is unlikely that the observed reduction in EF1 occurs secondary to raised afterload or structural remodeling of the left ventricle. In patients with primary hypertension, a reduction in EF1 is associated with increased late systolic myocardial wall stress (MWS),[11] and an increase in late MWS is also observed in children with CKD when compared to those without CKD.[36] It is possible that an increase in MWS may also arise from an increase in preload and contribute to a reduction in EF1.[11,37] However, ventricular and atrial volumes were only modestly increased in children with CKD, and adjustment for these and E/e′ (a surrogate of filling pressure) did not affect the relationship of EF1 to eGFR.

It is known that myocardial fibrosis affects more than 90% of adult patients with CKD, which in turn leads to myocardial stiffness and diastolic dysfunction.[37] One previous study showed that children on dialysis had increased T2 relaxation time and increased T2 heterogeneity, which could be explained by the prevalence of myocardial fibrosis in this population.[9] Prolonged myocardial contraction into late systole through impaired shortening deactivation may preserve overall EF in children with CKD, but this may lead to the development of replacement myocardial fibrosis,[38] which has been shown to be associated with reduction of EF1 by previous studies in adults.[13,39] Myocardial fibrosis, however, is less likely to be applicable to most children in this study given that most participants had nondialysis and early stages of CKD. The most likely mechanism, therefore, is a reduction in the intrinsic contractile function of the myocardium. A possible explanation for this is that alterations in metabolism, particularly glucose metabolism, that are well recognized in CKD have an impact on the efficiency of myocardial contraction.[40]

Our study is subject to limitations. Its cross-sectional design limits inferences on causality. Children with CKD were not characterized according to proteinuria. However, associations of EF1 with CKD defined by eGFR were robust and persisted across all stages of CKD. Office BP was measured using different methods between the 2 studies, but a sensitivity analysis performed separately in the HOT-KID and 4C study cohorts revealed comparable results (data not shown). Ambulatory BP monitoring and central BP measurements would ideally be used in this type of analysis but were not available in most children. However, both are highly correlated with office BP, and, as adjustment for office BP made little difference to the strength of the relationship between EF1 and eGFR, it seems unlikely that these other BP measures would influence our findings. Ventricular volumes were obtained from two-dimensional echocardiography, with inherent limitations relating to the assumption of cardiac geometry. 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. Central pulse pressure/stroke volume index is an echocardiographic surrogate of arterial stiffness and has not been validated in children. The relationship between EF1 and the gold standard measure of arterial stiffness (pulse-wave velocity) should be explored in future studies.

Our observation of a marked impairment in LV early systolic function is novel, with a 20% reduction in EF1 in those with stage 1 CKD when compared with healthy peers, with a progressive reduction of early systolic function across advancing stages of CKD. First-phase EF as a simple but novel measure of early systolic function may be an important diagnostic marker and therapeutic target to prevent the development of CVD in adulthood.

REVIEW STATEMENT

Given his role as a *JASE* Associate Editor, John Simpson, MD, had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Thomas R. Kimball, MD.

CONFLICTS OF INTEREST

None.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2023.11.013.

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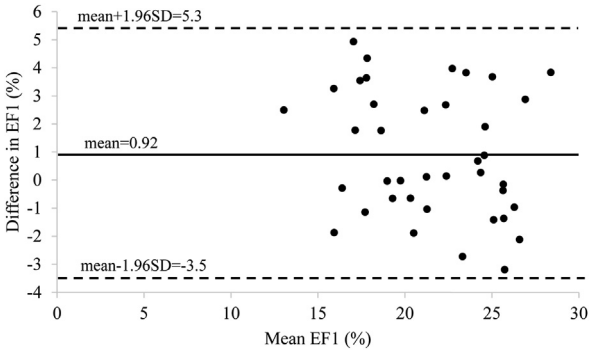
SUPPLEMENTAL DATA

Supplemental Table 1 Subject characteristics in children with CKD in HOT-KID and 4C studies shown as mean (SD)

Measure	HOT-KID (*n* = 193)	4C (*n* = 119)	*P* value
Age, years	9.9 (3.6)	12.6 (3.5)	<.001
Sex, male (%)	146 (57.0)	85 (71.4)	.008
Height *Z*-score	−0.10 (1.2)	−1.01 (1.1)	<.001
Weight *Z*-score	0.28 (1.2)	−0.65 (1.1)	<.001
BMI *Z*-score	0.43 (1.2)	0.16 (1.1)	.046
Anti-HTN (%)	78 (30.4)	72 (60.5)	<.001
HR, bpm	80.5 (15.1)	76.1 (12.6)	.007
SBP, mm Hg	103.1 (11.4)	111.7 (12.8)	<.001
SBP *Z*-score	−0.15 (0.9)	0.6 (1.2)	<.001
DBP, mm Hg	60.0 (11.9)	65.5 (11.3)	<.001
DBP *Z*-score	0.02 (1.1)	0.30 (1.0)	.022
MAP, mm Hg	74.4 (10.5)	80.9 (10.7)	<.001
Hb, g/L	129 (13)	119 (18)	<.001
Albumin, g/L	44.0 (4.0)	10.9 (3.0)	<.001
Phosphate, mM	1.4 (0.2)	1.5 (0.3)	<.001
eGFR, mL/min per 1.73m^2	84.9 (32.4)	25.1 (11.4)	<.001

Anti-HTN, Antihypertensive treatment; *DBP*, diastolic BP; *Hb*, hemoglobin; *HR*, heart rate; *SBP*, systolic BP; *Z*, *Z* score (value expressed as number of SDs from mean of reference population).



Supplemental Figure 1 Bland-Altman plot of interobserver analysis for EF1.

Supplemental Table 2 LV geometry and function in children with CKD in HOT-KID and 4C studies

Measure	HOT-KID (*n* = 193)	4C (*n* = 119)	*P* value
LVMi, g/m$^{2.7}$	31.0 (8.6)	37.4 (9.0)	<.001
RWT	0.34 (0.05)	0.45 (0.14)	<.001
LAVi, mL/m^2	10.3 (3.2)	16.6 (5.8)	<.001
EDVi, mL/m^2	42.9 (10.3)	46.2 (9.5)	.006
EF, %	63.3 (5.4)	64.6 (6.2)	.061
GLS, % (*n* = 215)	−17.8 (2.9)	—	—
S wave, cm/sec	8.5 (1.3)	9.4 (2.0)	<.001
E/e'	6.8 (1.4)	7.0 (1.5)	.30
e', cm/sec	16.3 (3.0)	17.0 (3.5)	.078
EF1, %	20.4 (5.2)	18.2 (6.4)	<.001
TPAFV/ET	0.36 (0.05)	0.35 (0.05)	.229
Arterial stiffness	1.18 (0.33)	1.20 (0.38)	.575