Research Article

Cardiac Abnormalities in Children with Autosomal Recessive Polycystic Kidney Disease

Marcello Chinali^a Laura Lucchetti^b Agnese Ricotta^a Claudia Esposito^a
Carolina D'Anna^a Gabriele Rinelli^a Francesco Emma^b Laura Massella^b

^aDivision of Pediatric Cardiology, Department of Pediatric Cardiology and Cardiac Surgery, Bambino Gesù Children's Hospital – IRCCS, Rome, Italy; ^bNephrology and Dialysis Unit, Department of Pediatric Subspecialties, Bambino Gesù Children's Hospital – IRCCS, Rome, Italy

Keywords

Autosomal recessive polycystic kidney disease · Echocardiography · Pediatrics · Strain · Function

Abstract

Background: No previous study has defined the prevalence of cardiac geometric and mechanical function abnormalities through the analysis of advanced echocardiographic parameters in children with autosomal recessive polycystic kidney disease (ARPKD). **Aim:** The purpose of this study was to evaluate cardiac geometry and function through advanced echocardiography in a well-characterized sample of pediatric patients with ARPKD. **Methods:** Standard echocardiograms were obtained in 27 children with ARPKD (0–18 years) and in 88 healthy children of similar age, gender distribution, and body build. Left ventricular (LV) hypertrophy was defined as LV mass $>45\text{g}/(\text{m}^{2.16} + 0.09)$ and cardiac remodeling was defined by age-adjusted relative wall thickness (RWT). Systolic function was assessed by ejection fraction, midwall fractional shortening (mFS), and global longitudinal (GLS) and circumferential strain (GCS). **Results:** Patients with ARPKD exhibited a higher LV mass index as compared to controls, and a more concentric LV geometry (both $p < 0.001$). Accordingly, the prevalence of abnormal LV geometry was significantly higher in ARPKD (33 vs. 0%; $p < 0.005$). No differences could be observed in the two groups for ejection fraction or GLS (both $p = \text{n.s.}$), while a significantly lower mFS ($p < 0.05$) as well as GCS ($p < 0.001$) could be observed. In the analysis of covariance, both LV mass index and RWT remained significantly higher in the ARPKD group, while mFS and GCS remained significantly lower (all $p < 0.05$). The prevalence of sub-clinical systolic dysfunction was significantly higher in patients with ARPKD as compared with

Marcello Chinali, MD, PhD
Pediatric Cardiology Unit, Department of Pediatric Cardiology and Cardiac Surgery
Bambino Gesù Children's Hospital – IRCCS, Piazza Sant'Onofrio 4
IT-00165 Rome (Italy)
E-Mail marcello.chinali@opbg.net

control subjects (33 vs. 0%; $p < 0.001$). **Conclusions:** Children with ARPKD show significantly impaired cardiac phenotype, characterized by high rates of LV abnormal geometry paired with systolic mechanical dysfunction.

© 2019 S. Karger AG, Basel

Introduction

Autosomal recessive polycystic kidney disease (ARPKD) is a rare congenital hepato-renal fibrocystic disease with an incidence between 1:10,000 and 1:40,000 live births [1]. In most cases, the disease is caused by mutations in the *PKHD1* gene, encoding fibrocystin, also termed polyductin [2]. Recently, mutations in the *DZIP1L* gene have been found to be responsible of the disease in a minority of subjects [3]. ARPKD is often suspected in late pregnancy or at birth and is characterized in severe neonatal forms by oligohydramnios, enlarged kidneys, and various degrees of pulmonary hypoplasia. Fetal demise or death in the first year of life has been reported in 23–30% of patients. With improvements in neonatal respiratory support and renal replacement therapies, the long-term survival of these infants has significantly improved. From a renal standpoint, data show renal survival rates of 86% at 5 years, 71% at 10 years, and 42% at age 15 years [1]. In a minority of cases, the phenotype is less severe and symptoms do not develop until adolescence or adulthood. Renal symptoms are characterized by kidney enlargement in small children, hypertension, and varying degrees of renal dysfunction. Hypertension is the most common and earlier finding. Accordingly, more than 90% of patients receive antihypertensive treatment within the first year of life [4].

Abnormal left ventricular (LV) geometry and function are common in children with chronic kidney disease (CKD) and hypertension. We have previously reported that in children with CKD the presence of concentric geometry (both remodeling and hypertrophy) is associated with subclinical abnormalities of systolic mechanic function secondary to significant increased cardiac workload, despite normal ejection fraction [5, 6]. When the heart is exposed to increased workload (e.g., hypertension, renal failure), LV hypertrophic remodeling is stimulated to compensate for increased stress and to preserve function. However, hypertrophic remodeling is associated with worse outcome, even after accounting for other risk factors. Data in CKD children from our group and others have shown that subtle systolic dysfunction might be present in patients with LV hypertrophy before impairment is identified through the analysis of LV ejection fraction [7]. Furthermore, previous evidence from rat models of ARPKD have shown a significant temporal relation between cyst development, hypertension, and LV hypertrophy [8]. To date, no study has yet analyzed the presence and the degree of geometrical and function abnormalities in children with ARPKD by advanced analysis of cardiac mechanics by echocardiography.

Accordingly, the aim of this study was to investigate the prevalence of cardiac performance abnormalities in ARPKD children with normal ejection fraction using advanced indices of cardiac systolic function. The ultimate goal is to identify ARPKD children at higher risk of future cardiovascular events.

Methods

Study Population

The inclusion criteria for the present study were: (a) age between 0 and 18 years; (b) a definite diagnosis of ARPKD, based on family history and clinical signs and/or genetic analysis; (c) available complete echocardiographic examination, as described below, and (d) normal ejection fraction. Creatinine clearance was calculated by the formula described by Gao et al. [9]. A normal renal function was defined by a creatinine

clearance value >90 mL/min [10]. Hypertension was defined as any values above 95th percentile accordingly to the European Society of Cardiology Consensus Recommendation [11] for children >1 year of age, and by normative data provided by Dionne et al. [12] when age <1 year. A group of 88 children of similar age, gender distribution, and body build, who were referred for examination to evaluate innocent murmurs and/or chest pain, and shown by echocardiography to have normal hearts, comprised the control population of the study. The study was approved by the local IRB and performed following the principles outlined in the Declaration of Helsinki. Informed consent was waived, due to the retrospective nature of the analysis.

Echocardiography

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 (C.D., M.C.). 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.

The parameters measured in our study included LV diameters and wall thicknesses to obtain LV mass (LVM). LVM was calculated according to the Devereux formula [13] and analyzed as both unindexed as well as indexed to the allometric power of height ($m^{2.16} + 0.09$) [14]. To define LV hypertrophy, age-specific partition values were applied as previously reported by our group [14]. For the identification of concentricity of LV remodeling, myocardial thickness (wall + septum) was divided by the LV minor axis (diameter) to generate a relative wall thickness (RWT). As we have previously shown, although the relation between wall thickness and LV chamber radius is mostly linear, a significant influence is caused by age during body growth. Thus, especially in children, concentric LV geometry might be severely underestimated [15]. Accordingly, to offset the confounding effect of age, RWT was normalized to a mean age of 10 years [15] with a value of 0.38 used as the cutoff to define concentric LV geometry [15]. LV systolic function was determined by LV ejection fraction from volumes calculated by the biplane Simpson's rule, and by analysis of midwall fractional shortening (mFS) as previously reported [16]. Strain analysis was used to obtain global longitudinal (GLS) and circumferential strain (GCS) of the left ventricle on three consecutive beats [17].

In more details, when adequate echocardiographic examinations were available (defined as images with good quality and a frame rate >40 frames/s), images were exported and analyzed centrally offline using Philips QLAB Cardiac Analysis v.10.7 (Philips Inc., Andover, The Netherlands) for the semi-automatic analysis of strain curves. Endocardial surfaces were semi-automatically traced from the 4-chamber, 3-chamber, and 2-chamber apical views for GLS and from the parasternal short axis at mid-ventricular level for GCS. Feature tracking of the myocardium was 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 was traced manually from a single frame of the digital loop providing the clearest still-frame endocardial border definition. Accuracy of border tracking was visually confirmed by viewing the cardiac cycle with only border information displayed. If necessary, individual regions of the border were adjusted until the border was correctly tracked for each frame. Cardiac strain was derived from myocardial deformation and displayed in a six-segment model for each view. Peak systolic strain values were recorded, representing orthogonal deformation of the cardiac muscle during contraction. Accordingly, as in systole the myocardium reduces its wall length in both the longitudinal and the circumferential plane, a more negative value of longitudinal and/or circumferential strains represent a better cardiac contraction [17]. Subclinical cardiac systolic dysfunction was defined by the presence of either age-specific reduced midwall shortening [7] and/or presence of age-specific reduced strain of either the longitudinal or the circumferential vector [18].

Statistical Analysis

Data are presented as the mean $\pm$ SD for normally distributed variables and/or as the median $\pm$ IQR for non-normally distributed variables. Statistical analysis was performed by SPSS Statistics for Windows software, version 21.0 (released 2012; IBM Corp., Armonk, NY, USA). Comparison between groups of patients was carried out by *t* tests for normally distributed continuous variables and Mann-Whitney U test for non-normally distributed continuous variables, while the χ^2 test was used to compare categorical variables. When necessary, comparison between groups was performed using analysis of covariance to reduce the effect of

Table 1. Patient characteristics

	ARPKD (<i>n</i> = 27)	Controls (<i>n</i> = 88)	<i>p</i> value
Mean age at echocardiogram, years	3.8±4.5	3.8±5.1	n.s.
Echocardiogram performed at age <1 year	12 (44)	36 (40)	n.s.
Weight, kg	14.2±12.4	12.9±2.6	n.s.
Height, cm	87±40	86.2±42.1	n.s.
Creatinine clearance ≥90 mL/min	10 (37)	88 (100)	<0.05
Creatinine clearance <90 mL/min	17 (63)	0	–
Creatinine clearance <30 mL/min	3 (11)	0	–
Hypertensive patients	19 (74)	0	–
On anti-HTN treatment	17/19 (85)	0	–
Hypertensive treatment			
Treated with ACE-I	10 (58.8)	–	–
On 1 anti-HTN drug	6 (35.3)	–	–
On 2 anti-HTN drugs	6 (35.3)	–	–
On 3 anti-HTN drugs	5 (29.4)	–	–

Values are presented as the mean ± SD or *n* (%). HTN, hypertension; ACE-I, angiotensin-converting enzyme inhibitor; n.s., not significant.

confounding variables (age, heart rate, and blood pressure 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 geometric abnormality). To account for significant confounders, multiple regression analysis was performed when appropriate, with model tolerance >0.70. A *p* value <0.05 was considered statistically significant.

Results

Twenty-seven patients (37% boys) with ARPKD from 25 families and 88 healthy children of similar age and gender distribution were included in the study. Molecular analysis was performed in 19/27 subjects; a mutation in *PKHD1* was identified in 16/19 patients, and results are pending in the other 3 patients. At the time of echocardiogram, the mean age of ARPKD patients was 3.8 years with a range from 0 to 17.6 (median 4.61). In 12 (44%) patients, echocardiogram was performed before 1 year of age. Overall, 17/27 (63%) had a creatinine clearance <90 mL/min. Of these, 3 patients had stage IV CKD (i.e., creatinine clearance <30 mL/min) and 5 patients were on peritoneal dialysis. Hypertension was present in 74% of ARPKD patients. Of these, 85% were receiving pharmacological treatment. Prescribed anti-hypertensive medications included angiotensin-converting enzyme inhibitors (ACE-I; enalapril in most cases), Ca²⁺-channel blockers, and β-blockers. Creatinine clearance was normal in all controls; none had hypertension or required treatment. The data are summarized in Table 1.

Cardiac Geometry

Echocardiographic geometric parameters for the two groups are detailed in Table 2. As shown, patients with ARPKD exhibited a higher LVM index as compared to controls (38.7 ± 12.0 vs. 28.9 ± 4.3). In addition, a more concentric LV geometry (RWT = 0.35 ± 0.1 vs. 0.27 ± 0.03; both *p* < 0.001) was observed in ARPKD patients. Accordingly, the prevalence of LV hypertrophy was significantly higher in ARPKD (*n* = 4 or 15 vs. 0%; *p* < 0.005). When analyzing the different adaptational geometric pattern in the ARPKD cohort, we found that 9/27 patients

Table 2. Echocardiographic geometric features of the study population

	ARPKD (<i>n</i> = 27)	Controls (<i>n</i> = 88)	<i>p</i> value
LVIDD/height, cm/m	3.5±0.5	2.9±0.5	<0.01
RWT	0.35±0.1	0.27±0.03	<0.01
LVM, g	36.5±29	37±23	n.s.
LVM index (g/[m ^{2.16} + 0.09])	38.7±12	28.9±4.3	<0.001
Normal LV geometry	18 (67)	88 (100)	<0.01
Abnormal LV geometry	9 (33)	0	<0.01
Concentric LV remodeling	5 (18.5)	0	–
Concentric LV hypertrophy	2 (7.4)	0	–
Eccentric LV hypertrophy	2 (7.4)	0	–

Data are presented as the mean ± SD or *n* (%). LV, left ventricular; LVIDD, LV internal dimension diastole; RWT, relative wall thickness; LVM, LV mass; n.s., not significant.

Table 3. Multivariate correlates of cardiac geometry and function

a Multivariate regression for LVM index (adjusted for age, gender, and heart rate)

	SE	Beta	<i>t</i>	Tolerance	<i>p</i> value
SBP Z-score	1.18	0.56	3.66	0.97	0.001
GFR	1.30	0.28	1.31	0.85	0.204
EF	0.38	–0.13	–0.75	0.73	0.462

b Multivariate regression for mFS (adjusted for age, gender, and heart rate)

	SE	Beta	<i>t</i>	Tolerance	<i>p</i> value
SBP Z-score	0.56	1.33	0.52	0.71	0.600
GFR	0.52	0.42	2.00	0.74	0.037
LVMi	0.77	–0.41	1.54	0.74	0.136

c Multivariate regression for GCS (adjusted for age, gender, and heart rate)

	SE	Beta	<i>t</i>	Tolerance	<i>p</i> value
SBP Z-score	0.95	0.16	0.51	0.73	0.619
GFR	0.29	0.34	1.35	0.81	0.195
LVMi	0.13	0.21	–0.62	0.71	0.547

(33%) had abnormal LV geometry. Of these, 5 patients showed a concentric LV remodeling without hypertrophy, two had concentric LVH, and two eccentric LVH. After covariance analysis adjusting for age, systolic blood pressure and both LVM index and RWT retained statistical significance.

In multiple linear regression analysis, after adjustment for differences in age, gender, and heart rate, LVMi was independently associated with higher systolic blood pressure ($R = 0.566$, $p = 0.001$; model tolerance >0.7), as shown in Table 3a. No significant association was observed with diastolic blood pressure or eGFR. Similarly, no correlation was observed between RWT

Table 4. Echocardiographic functional features

	ARPKD (<i>n</i> = 27)	Controls (<i>n</i> = 88)	<i>p</i> value
Ejection fraction, %	68.4±5.5	68.1±5.9	n.s.
mFS, %	19.0±3.5	21.6±2.1	<0.05
Longitudinal strain, %	−24.9±2.0	−24.1±2.3	n.s.
Circumferential strain, %	−21.5±3.3	−23.6±4.0	<0.05
Prevalent systolic dysfunction, %	33	0	<0.001

Fig. 1. At similar values of ejection fraction, ARPKD children (x) show significantly impaired cardiac mechanics as compared to normal controls (●).

and eGFR. Among patients with abnormal LV geometry no significant difference was described between those treated with ACE-I and those not under treatment. Moreover, no significant correlation was found between treatment with ACE-I, LVM index, and/or RWT.

Cardiac Function

As shown in Table 4, there were no significant differences between the two groups in ejection fraction and GLS, while a significantly lower mFS (19.1 ± 3.5 vs. $22.2 \pm 2.1\%$; $p < 0.05$) and less negative GCS (-21.5 ± 3.3 vs. $-23.6 \pm 4.0\%$; $p < 0.05$) were observed. The prevalence of subclinical systolic dysfunction was significantly higher in patients with ARPKD compared to control subjects (33 vs. 0%; $p < 0.001$), indicating cardiac function impairment with preserved ejection fraction. As shown in Figure 1, mFS was lower in children with ARPKD compared to healthy control subjects at any given value of ejection fraction ($p < 0.001$). Moreover, in contrast to the LVM index, no correlation was found between measures of systolic function and either systolic or diastolic blood pressure (Tables 3b, c). Conversely, mFS was positively correlated to eGFR ($p < 0.05$). We observed a mild positive correlation between treatment with ACE-I and mFS; however, given the small study sample, this correlation was not statistically significant.

Discussion

Our study shows high prevalence of geometrical cardiac abnormalities and subclinical systolic dysfunction in children with ARPKD. Abnormal cardiac geometry was associated with impaired midwall mechanics and circumferential LV strain. By multivariate analysis,

systolic hypertension correlated positively with LVM, regardless of antihypertensive therapy, while preservation of cardiac systolic mechanics was associated with higher eGFR, but not with lower blood pressure.

Previous studies have reported on the prevalence of abnormal LV geometry, including LVH, in children with various degrees of chronic kidney failure. Concentric LVH is usually more frequent in pre-dialysis children due to increased afterload, while patients undergoing dialysis often develop eccentric LVH secondary to high cardiac pre-load. Geometrical abnormalities are secondary to hemodynamic (i.e., blood pressure and volume) and non-hemodynamic factors (i.e., male gender, anemia, body mass index, and potentially other unidentified factors) [5, 19, 20].

Studies from the late 90s suggested that in CKD children LVH is associated with normal or even supernormal ejection fraction, reflecting an adaptive mechanism aiming at increasing cardiac output and blood pressure in order to maintain renal perfusion and to compensate for higher metabolic requirements [21]. In contrast, in 2003 Mitsnefes et al. [19] described changes in systolic function during physical activity in children undergoing dialysis. Results of that pioneer study showed that children undergoing dialysis have a reduced LV response during stress despite normal LV performance at rest, suggesting higher long-term risk of heart failure in this population.

Later, in 2007, we analyzed LV shortening at the midwall level in 130 children with mild to moderate chronic kidney failure. We found a significant reduction in mFS, despite normal ejection fraction, suggesting that in many children with CKD, the LV contractile force is decreased despite a normal ejection fraction, mainly as a consequence of abnormal cardiac geometry [7]. Furthermore, in 2015 another study performed by our group showed that reduced parameters of cardiac mechanics were evident in several CKD children with normal ejection fraction even in the absence of overt LVH [6], suggesting that subclinical systolic dysfunction in children with CKD is common, also in the absence of overt geometric abnormalities [7]. These results have strong clinical relevance as both midwall dysfunction and reduced LV strain are validated markers of unfavorable cardiovascular prognosis in adults. Specifically, midwall dysfunction is a validated independent risk factor for cardiovascular disease in hypertensive patients with abnormal LV geometry and preserved ejection fraction [22], while reduced strain has been shown to independently predict cardiovascular events in CKD adults [23, 24].

In the present study, we analyzed myocardial geometry and function, including advanced echocardiography parameters, in pediatric patients with ARPKD that did not have overt cardiac dysfunction. To our knowledge, only the recent report by Dell et al. [25] has investigated the prevalence of LVH in ARPKD patients, although advanced analysis of cardiac mechanics was not performed [25]. In that study, children with ARPKD were compared to children with kidney hypoplasia/dysplasia and to children with obstructive nephropathy. No differences were observed in the prevalence of LVH in these three groups of patients. On average, however, children with ARPKD needed a higher number of antihypertensive drugs to control blood pressure [25].

In the present study, we observed a high prevalence of cardiac geometry abnormalities in ARPKD children, which was characterized by higher LVM and/or RWT. Specifically, we observed significant subclinical systolic abnormalities (i.e., without impairment of the ejection fraction), which were characterized by low mFS and decreased circumferential strain parameters, but intact longitudinal strain. The evidence of normal longitudinal strain is in contrast with observations from adult patients with hypertension, in whom selective impairment of the longitudinal strain component is the prominent abnormality [26, 27]. However, this finding is consistent with our previous observations in children with CKD secondary to other causes, in whom we equally observed impaired mFS and reduced circumferential strain but normal longitudinal strain [6, 7]. This suggests that our finding identifies a population with a

different mechanic and geometric adaptation phenotype compared to adults with hypertension. To our knowledge, no associations between specific mutations of PKHD1 and cardiac abnormalities have been described to date.

Similar to previous reports in other CKDs, cardiac dysfunction in ARPKD appears to be primarily caused by volume and/or pressure overload. In both conditions, blood pressure is increased, leading to cardiac hypertrophy, myocardial fibrosis, and subclinical dysfunction [7]. Myocardial fibrosis and increased LVM have been shown to be associated with symptomatic diastolic and/or systolic dysfunction [28–31]. Accordingly, cardiac death in the CKD population is less frequently caused by atherosclerosis-related cardiac ischemia, and more to functional LV abnormalities, severe electrolyte imbalances, hypertensive crises, or volume overload [32].

These observations may suggest the intriguing hypothesis that cardiac hypertrophy might also be a consequence of myocardial contraction impairment in ARPKD, and not only a compensatory response to increased workload. In fact, it could be speculated that reduced circumferential strain in the absence of LVH may be the consequence of systolic dysfunction caused by intrinsic structural abnormalities of the cardiac muscle, in addition to changes in cardiac geometry (also suggested by the lack of correlation between mFS and blood pressure). However, the hypothesis that systolic dysfunction might precede both hypertension and renal failure in ARPKD children cannot be adequately supported by the data reported in our present report. A larger population, as well as analysis of additional biochemical parameters that were not included in our study (e.g., FGF-23 levels, details of calcium-phosphorus metabolism, as well as serum galectin, BNP, TnI, etc.), should be analyzed in future studies in order to support our speculation.

The present study has additional significant limitations, including its retrospective nature. The age of patients at echocardiographic examination varied considerably. Therefore, differences in cardiac muscle exposure to high blood pressures and to uremic toxins may have influenced heart geometry and function in ways that could not be fully appraised by multivariate analysis. Also, analysis of cardiac strain was limited to the left ventricle. In fact, analysis of right ventricular systolic function was not a pre-specified aim of the data acquisition and thus no analysis of ventricular interdependence could be performed. Also, only a very preliminary analysis on the effect of ACE inhibitors (the most prescribed medication in our study sample) and cardiac parameters could be performed and no thorough analysis on the effect of medications on cardiac geometry and function was possible. Eventually, the small study sample may potentially affect the result of our correlation analysis, thus preventing it from supporting a more traditional explanation for the reported strain abnormalities (i.e., caused by increased afterload and chronic pressure overload).

In conclusion, our study provides novel insights into the cardiac disease of children with ARPKD. A significant proportion of these patients has geometrical abnormalities and alterations in systolic mechanics, which cannot be identified by the analysis of traditional echocardiographic parameters.

Statement of Ethics

The study was approved by the local IRB and performed following the principles outlined in the Declaration of Helsinki. Informed consent was waived, due to the retrospective nature of the analysis.

Disclosure Statement

The authors declare that there are no conflicts of interest related to the present report.

References

- 1 Büsscher R, Büsscher AK, Weber S, Mohr J, Hegen B, Vester U, et al. Clinical manifestations of autosomal recessive polycystic kidney disease (ARPKD): kidney-related and non-kidney-related phenotypes. *Pediatr Nephrol*. 2014 Oct;29(10):1915–25.
- 2 Bergmann C, Senderek J, Windelen E, Küpper F, Middeldorf I, Schneider F, et al.; APN (Arbeitsgemeinschaft für Pädiatrische Nephrologie). Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). *Kidney Int*. 2005 Mar;67(3):829–48.
- 3 Lu H, Geleano MCR, Ott E, Kaeslin G, Kausalya PJ, Kramer C, et al. Mutations in DZIP1L, which encodes a ciliary-transition-zone protein, cause autosomal recessive polycystic kidney disease. *Nat Genet*. 2017;49(7):1025–34.
- 4 Sweeney WE, Avner ED. Polycystic kidney disease, autosomal recessive. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, et al. editors. Source GeneReviews® [Internet]. Seattle: University of Washington; 2001 Jul 19. p. 1993–2018. [updated 2016 Sep 15].
- 5 Matteucci MC, Wühl E, Picca S, Mastrostefano A, Rinelli G, Romano C, et al.; ESCAPE Trial Group. Left ventricular geometry in children with mild to moderate chronic renal insufficiency. *J Am Soc Nephrol*. 2006 Jan;17(1):218–26.
- 6 Chinali M, Matteucci MC, Franceschini A, Doyon A, Pongiglione G, Rinelli G, et al. Advanced Parameters of Cardiac Mechanics in Children with CKD: The 4C Study. *Clin J Am Soc Nephrol*. 2015 Aug;10(8):1357–63.
- 7 Chinali M, de Simone G, Matteucci MC, Picca S, Mastrostefano A, Anarat A, et al.; ESCAPE Trial Group. Reduced systolic myocardial function in children with chronic renal insufficiency. *J Am Soc Nephrol*. 2007 Feb;18(2):593–8.
- 8 Phillips JK, Hopwood D, Loxley RA, Ghatara K, Coombes JD, Tan YS, et al. Temporal relationship between renal cyst development, hypertension and cardiac hypertrophy in a new rat model of autosomal recessive polycystic kidney disease. *Kidney Blood Press Res*. 2007;30(3):129–44.
- 9 Gao A, Cachat F, Faouzi M, Bardy D, Mosig D, Meyrat BJ, et al. Comparison of the glomerular filtration rate in children by the new revised Schwartz formula and a new generalized formula. *Kidney Int*. 2013 Mar;83(3):524–30.
- 10 Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. *Pediatrics*. 2003 May;111(5 Pt 1):1072–80.
- 11 Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens*. 2016 Oct;34(10):1887–920.
- 12 Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management and outcome. *Pediatr Nephrol*. 2012 Jan;27(1):17–32.
- 13 Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986 Feb;57(6):450–8.
- 14 Chinali M, Emma F, Esposito C, Rinelli G, Franceschini A, Doyon A, et al. Left ventricular mass indexing in infants, children, and adolescents: a simplified approach for the identification of left ventricular hypertrophy in clinical practice. *J Pediatr*. 2016 Mar;170:193–8.
- 15 de Simone G, Daniels SR, Kimball TR, Roman MJ, Romano C, Chinali M, et al. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. *Hypertension*. 2005 Jan;45(1):64–8.
- 16 de Simone G, Devereux RB, Ganau A, Hahn RT, Saba PS, Mureddu GF, et al. Estimation of left ventricular chamber and stroke volume by limited M-mode echocardiography and validation by two-dimensional and Doppler echocardiography. *Am J Cardiol*. 1996 Oct;78(7):801–7.
- 17 Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. *J Am Coll Cardiol*. 2006 Feb;47(4):789–93.
- 18 Levy PT, Machefsky A, Sanchez AA, Patel MD, Rogal S, Fowler S, et al. Reference Ranges of Left Ventricular Strain Measures by Two-Dimensional Speckle-Tracking Echocardiography in Children: A Systematic Review and Meta-Analysis. *J Am Soc Echocardiogr*. 2016 Mar;29(3):209–225.e6.
- 19 Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Left ventricular mass and systolic performance in pediatric patients with chronic renal failure. *Circulation*. 2003 Feb;107(6):864–8.
- 20 Johnstone LM, Jones CL, Grigg LE, Wilkinson JL, Walker RG, Powell HR. Left ventricular abnormalities in children, adolescents and young adults with renal disease. *Kidney Int*. 1996 Sep;50(3):998–1006.
- 21 Colan SD, Sanders SP, Ingelfinger JR, Harmon W. Left ventricular mechanics and contractile state in children and young adults with end-stage renal disease: effect of dialysis and renal transplantation. *J Am Coll Cardiol*. 1987 Nov;10(5):1085–94.
- 22 de Simone G, Devereux RB, Koren MJ, Mensah GA, Casale PN, Laragh JH. Midwall left ventricular mechanics. An independent predictor of cardiovascular risk in arterial hypertension. *Circulation*. 1996 Jan;93(2):259–65.
- 23 Sulemane S, Panoulas VF, Bratsas A, Grapsa J, Brown EA, Nihoyannopoulos P. Subclinical markers of cardiovascular disease predict adverse outcomes in chronic kidney disease patients with normal left ventricular ejection fraction. *Int J Cardiovasc Imaging*. 2017 May;33(5):687–98.

- 24 Krishnasamy R, Isbel NM, Hawley CM, Pascoe EM, Burrage M, Leano R, et al. Left Ventricular Global Longitudinal Strain (GLS) Is a Superior Predictor of All-Cause and Cardiovascular Mortality When Compared to Ejection Fraction in Advanced Chronic Kidney Disease. [PLoS One](#). 2015 May;10(5):e0127044.
- 25 Dell KM, Matheson M, Hartung EA, Warady BA, Furth SL, Muñoz A, et al.; Chronic Kidney Disease in Children (CKiD) Study. Kidney disease progression in autosomal recessive polycystic kidney disease. [J Pediatr](#). 2016 Apr;171:196–201.e1.
- 26 Narayanan A, Aurigemma GP, Chinali M, Hill JC, Meyer TE, Tighe DA. Cardiac mechanics in mild hypertensive heart disease: a speckle-strain imaging study. [Circ Cardiovasc Imaging](#). 2009 Sep;2(5):382–90.
- 27 Sengupta SP, Caracciolo G, Thompson C, Abe H, Sengupta PP. Early impairment of left ventricular function in patients with systemic hypertension: new insights with 2-dimensional speckle tracking echocardiography. [Indian Heart J](#). 2013 Jan-Feb;65(1):48–52.
- 28 Salvetti M, Muiesan ML, Paini A, Monteduro C, Bonzi B, Galbassini G, et al. Myocardial ultrasound tissue characterization in patients with chronic renal failure. [J Am Soc Nephrol](#). 2007 Jun;18(6):1953–8.
- 29 Schärer K, Schmidt KG, Soergel M. Cardiac function and structure in patients with chronic renal failure. [Pediatr Nephrol](#). 1999 Nov;13(9):951–65.
- 30 Grandi AM, Imperiale D, Santillo R, Barlocco E, Bertolini A, Guasti L, et al. Aldosterone antagonist improves diastolic function in essential hypertension. [Hypertension](#). 2002 Nov;40(5):647–52.
- 31 Kuwahara F, Kai H, Tokuda K, Kai M, Takeshita A, Egashira K, et al. Transforming growth factor-beta function blocking prevents myocardial fibrosis and diastolic dysfunction in pressure-overloaded rats. [Circulation](#). 2002 Jul;106(1):130–5.
- 32 Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. [J Am Soc Nephrol](#). 2004 May;15(5):1307–15.