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ORIGINAL ARTICLE

Left ventricular mass and systolic function in children with chronic kidney disease—comparing echocardiography with cardiac magnetic resonance imaging

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Abstract
Background Increased left ventricular mass (LVM) is an important risk marker of uremic cardiovascular disease. Calculation of LVM by echocardiography (Echo) relies on geometric assumptions and in adults on hemodialysis overestimates LVM compared to cardiac magnetic resonance (CMR). We compare both techniques in children with chronic kidney disease (CKD).
Methods Concurrent Echo and CMR was performed in 25 children with CKD (14 after kidney transplantation) aged 8–17 years.
Results Compared to normal children, CMR-LVM was increased (standard deviation score (SDS) 0.39±0.8 (p=0.03)), stroke volume and cardiac output decreased (SDS −1.76±1.1, p=0.002 and −1.11±2.0, p=0.001). CMR-LVM index but not Echo-LVMI correlated to future glomerular filtration rate (GFR) decline (r=−0.52, p=0.01). Mean Echo-LVM was higher than CMR-LVM (117±40 vs. 89±29 g, p<0.0001), with wide limits of agreement (−6.2 to 62.8 g). The Echo-CMR LVM difference increased with higher Echo-LVMI (r=0.77, p<0.0001). Agreement of classifying left ventricular hypertrophy was poor with Cohen's kappa of 0.08. Mean Echo and CMR-ejection fraction differed by 1.42 % with wide limits of agreement (−12.6 to 15.4 %).
Conclusions Echo overestimates LVM compared to CMR, especially at higher LVM. Despite this, CMR confirms increased LVM in children with CKD. Only CMR-LVMI but not Echo-LVMI correlated to future GFR decline.

Keywords Left ventricular hypertrophy · Ejection fraction · Echocardiography · CMR · Chronic renal failure · Adolescents

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Introduction

Cardiovascular mortality is the leading cause of death in adult patients with chronic kidney disease and end-stage renal failure. Left ventricular mass (LVM) is an established risk marker for prediction of mortality. Children with chronic kidney disease (CKD) also show features of beginning cardiovascular disease such as left ventricular hypertrophy (LVH) [1, 2], alterations of systolic [3] and diastolic function [4, 5], increased intima media thickness [6, 7], and stiffening of the aorta and peripheral vessels [8], even though other risk factors such as diabetes or smoking are normally absent. Despite the very low cardiovascular mortality in this age group, early detection of

cardiovascular abnormalities is still important in evaluating the risk of and potentially prevent future cardiovascular disease.

Echocardiography (Echo) offers a well-established and non-invasive technique for cardiac examination. LVM can be estimated by the American Society of Echocardiography (ASE) formula, which is validated by autopsy in adults [9]. LVM-index (LVMI) to body height to the power of 2.7 is preferred over normalization to body surface area (BSA) as the latter underestimates LVH in overweight patients [10]. LVMI cut-offs are also suitable for children over the age of 9 years, however, in younger patients LVMI is still height-dependent. For children, normal values for LVM and LVMI are available by Khoury [11], which for older children are quite similar to the 95th percentile of LVMI found by the group of de Simone [2, 12].

Several problems remain though: the ASE formula has not been validated in children and because it uses squares of several measurements, it is easily distorted by measurement errors. Additionally, it is less suitable for patients with altered geometry, which may sometimes be the case in fluid-overloaded patients. Application of different echo reference values can result in large differences in the number of children classified to have LVH and thus raises doubt whether this method is reliable in children with chronic kidney disease [12, 13].

Cardiac magnetic resonance imaging (CMR) offers an alternative for measuring LVM, which is not dependent on normal cardiac geometry, as heart contours are individually traced. CMR has higher inter-reader and inter-study reproducibility for measuring LVM than echocardiography [14, 15]. Echo and CMR are both predictive of mortality but no head-to-head comparison has been performed in any patient group [16]. Two studies have employed CMR in children with CKD and have been able to partially reproduce echocardiographic findings [17, 18]. However, when compared to CMR, echocardiography substantially overestimates LVM in adult hemodialysis patients [19, 20], but this has not been examined in children. Therefore, the aim of this study was to assess the agreement of Echo and CMR in quantifying both left ventricular mass and functional parameters in children with chronic kidney disease.

Patients and methods

Patients

Children and adolescents with chronic kidney disease stage 3 or higher (i.e., with an estimated glomerular filtration rate (GFR) below 60 ml/min*1.73 m^2) and/or who had undergone renal transplantation were eligible for the study. The presence of structural anomalies of the heart, cardiac valves or great vessels, cardiomyopathies, a pacemaker, or other metallic foreign bodies were exclusion criteria.

Imaging techniques

Cardiac magnetic resonance scans without contrast medium were performed on a 1.5-Tesla scanner (TIM-Symphony, Siemens, Erlangen, Germany). For the measurement of LVM ECG-gated steady-state free precession (SSFP) cine images were taken of at least ten contiguous slices along the short axis of the heart (parallel to the plane of the atrioventricular valves) [21] using the following parameters: Echo time 1.25 ms, repetition time 3 ms, field of view 270 mm, slice thickness 8 mm, temporal resolution 24.8 ms, spatial resolution 1.5–2 mm. End-diastolic epi- and endocardial contours of the left ventricle were traced manually on each slice and a software (Argus, Siemens) used to calculate the end-diastolic left ventricular muscle volume (not including the papillary muscles) by multiplication of the cross-sectional area by the distance between slices. Further multiplication of the muscle volume by the specific muscle weight yields ventricular mass [22]. Stroke volume (SV) was measured as the difference between the end-systolic and end-diastolic volume (ESV and EDV), and the ejection fraction (EF) calculated as stroke volume/end-diastolic volume.

On the same day, 2D-guided M-Mode echocardiography was performed according to the standards of the American Society of Echocardiography [23] by an experienced examiner on a Vivid 7 Dimension cardiovascular ultrasound system (GE Healthcare, Milwaukee, WI, USA). Electronic calipers were used to measure left ventricular end-diastolic diameter, diastolic posterior wall thickness and interventricular septal thickness in order to calculate left ventricular mass according to the American Society of Echocardiography (ASE) formula by Devereux [9]. EF was also calculated based on M-mode measurements. For quality control, a number of examinations were checked by a second examiner.

Clinical measurements

Clinical examination, anthropometric measurements, and clinic blood pressure were usually taken on the same day as the imaging procedures. The following blood parameters were also measured: serum creatinine, cystatin C, bound urea nitrogen, standard blood count and electrolytes, parathyroid hormone, 25-OH-vitamin D, N-terminal pro brain natriuretic peptide (pro BNP), renin, and aldosterone (in supine position). Spot urines were used to quantify proteinuria as total protein/creatinine ratio. Ambulatory 24-h blood pressure measurements (ABPM) were taken every 15 min during the day and every 30 min during the night using Spacelabs 9,0207 monitors (Spacelabs Healthcare, Snoqualmie, WA, USA).

Data on kidney function, blood pressure control, and medication over 6 months preceding the study day were taken from clinical records. From the time of study, serum creatinine, BUN, and body height were recorded prospectively until start of renal replacement therapy (n=3) or transfer to adult unit (n=8). Two patients were lost to follow-up and one excluded due to rapid loss of transplant function due to noncompliance. The remaining 22 patients were followed up for 36.3±9.8 months (range, 12–49 months).

Normal values

For Echos, LVH was classified as LVMI>95th percentile for age according to the largest available reference population presented by Khoury et al. [11]. Incidentally, use of these age- and height-dependent percentiles resulted in identical patients being classified as having LVH as the use of the age- and height-independent cut-off found by the group of de Simone [2, 12] (where LVMI above 38.6 g/m$^{2.7}$ is considered hypertrophic). In addition, a relative wall thickness (RWT=posterior wall thickness/left ventricular end diastolic diameter) greater than 0.375 was used to distinguish concentric from eccentric hypertrophy and concentric remodeling from normal cardiac structure [24].

For normal ranges of cardiac mass on CMR using SSFP, normal populations have been examined by Buechel et al. [25], Robbers-Visser et al. [26], as well as Sarikouch et al. [27]. The latter two have been pooled by Kawel-Boehm [28] and are used here, as they represent the largest cohort and use an identical technique (e.g., papillary muscles not included in volumes). We define LVH as LVM/BSA above the 95th percentile (mean+1.65 × standard deviation).

ABPM standard deviation scores of blood pressure were calculated using normal values by Wühl et al. [29], while a large up-to-date German reference study (KIGGS) was used for normal values of clinic blood pressure and anthropometric measurements [30, 31].

Statistics

Before the start of the study, a power analysis estimated that a sample of about 15 children would be large enough to detect significant differences of LVMI from the norm. Group comparisons were made using the Chi-square test for categorical variables and Student's t test for continuous variables. The Bland–Altman method [32] was used to compare CMR and Echo measurements. To compare classification of LVH, Cohen's kappa was used [33], where a value of 0 signifies that the agreement between two methods is only as good as chance and 1 that they agree perfectly (negative values are possible and indicate agreement worse than expected by chance). Values below 0.2 are generally regarded as poor agreement and only above 0.61 as good or above 0.81 as very good [34]. Correlations are quantified by giving Pearson's correlation coefficient. Throughout, p values less than 0.05 were considered significant. Statistical analyses were performed using SAS V9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Twenty-eight patients consented to take part in the study. Two patients (a 13-year-old female and a 17-year-old male) withdrew due to unexpected claustrophobia in the scanner. One CMR study was not analyzable due to data storage problems. Of the remaining 25 children, 11 were males (44 %), 11 had chronic kidney disease (44 %), and 14 had received a renal transplant (56 %); none were on dialysis. Further patient characteristics are shown in Table 1. CKD was due to renal dysplasia or agenesis (with or without urinary tract malformations) in nine patients, congenital or acquired glomerulopathy in nine, nephronophthisis in four, and other causes in three patients. Small proteinuria (protein/creatinine ratio 0.2–1 g/g in spot urine) was present in six patients and large proteinuria (protein/creatinine ratio>1 g/g) in five children, none of whom were nephrotic.

Mean blood pressure was mildly elevated (see Table 1), however this was only possible with antihypertensive medication in 21 patients (85 %) (four patients received one agent, ten received two agents, and seven received three or more antihypertensive medications). The most commonly used drugs were ACE inhibitors (n=14), amlodipine (n=13), metoprolol (n=11), angiotensin receptor blocker (n=6), and diuretics (n=3). Uncontrolled systolic hypertension was revealed by ABPM in four patients, while none had diastolic hypertension on ABPM. Three of these four had normal clinic blood pressure, while seven children had white coat hypertension.

Renal anemia was treated with iron supplements in eight patients and with additional erythropoiesis-stimulating agents in five. Overt anemia (hemoglobin below 11 g/l) was present in five patients.

Echocardiography

Findings on standard echocardiography are shown in Table 2. Left ventricular hypertrophy was present in eight children (32 %), with exact agreement between the classification according to normal values by Khoury [11] and Matteuci [2]. Hypertrophy was concentric in seven and eccentric in one child (28 % and 4 %), while 12 of 17 without hypertrophy had concentric remodeling (48 % overall). LVM for BSA was above the 95th percentile in seven children (of whom six also

Table 1 Patient characteristics

	Mean	SD	Minimum	Maximum
Age (years)	13.72	2.85	8.3	17.7
Height (cm)	154.3	16.8	124	185
Weight (kg)	47.8	15.2	25.3	75.2
Body surface area* (m^2)	1.43	0.3	0.96	1.92
Height SDS	−0.79	1.02	−2.68	1.65
BMI SDS	−0.19	0.8	−1.67	1.39
Systolic/diastolic BP (mmHg)	122/70	11/9	98/55	144/90
Systolic/diastolic BP SDS	0.97/0.57	0.9/1.2	−0.4/–1.3	3.1/3.35
Systolic/diastolic 24 h BP (mmHg)	116/68	8.1/5	101/56	129/76
Systolic/diastolic 24 h BP SDS	0.47/0.08	1.1/1.0	−0.9/–2.3	2.4/1.4
Creatinine (μmol/l)	151	95	69	473
Cystatin C (mg/l)	1.7	0.7	0.8	3.6
eGFR (creatinine**) (ml/min/1.73 m^2)	62	26	14	113
eGFR (cystatin C***) (ml/min/1.73 m^2)	60	24	21	116
Hemoglobin (g/dl)	12.4	1.6	8.4	14.4

SD standard deviation, *SDS* standard deviation score, *BP* blood pressure, *BMI* body mass index, *eGFR* estimated glomerular filtration rate

*DuBois formula

**Schwartz formula [35]

***formula according to Filler [36]

had an increased LVMI, but one was normal according to Khoury [11]).

CMR

Left ventricular dimensions and functional parameters measured on CMR are shown in Table 3. CMR-LVM was increased significantly (i.e., SDS significantly above 0, see Table 3), while EDV, SV, and cardiac index were decreased from normal. However, LV hypertrophy was present in

Table 2 Echocardiographic measurements, left ventricular dimensions, and systolic function in 25 children with chronic kidney disease and/or after renal transplantation

	Mean	SD	Minimum	Maximum
Measurements of cardiac dimensions				
LVEDD (mm)	41.6	5.0	33	51
LVPWT (mm)	8.92	2.06	6	15
IVST (mm)	8.72	2.30	5	13
Calculated cardiac dimensions				
LVM (g)	117.0	39.7	62	207
LVMI ($g/m^{2.7}$)	35.6	7.3	23	48
LVM/BSA (g/m^2)	81.0	17.6	56	113
RWT	0.43	0.09	0.30	0.69
Parameters of systolic function				
EF (%)	64.7	6.6	52	75
FS (%)	36.4	8.1	26	68

LVEDD left ventricular end diastolic diameter, *LVPWT* left ventricular posterior wall thickness, *IVST* interventricular septal thickness, *LVM* left ventricular mass, *LVMI* LVM index, *RWT* relative wall thickness, *EF* ejection fraction, *FS* endocardial fractional shortening, *SD* standard deviation

Table 3 Measurements and SDS scores of cardiac dimensions and systolic function on cardiac magnetic resonance in 25 children with chronic kidney disease and/or after renal transplantation

	Mean	SD	Minimum	Maximum	*p* value
Measurements of cardiac dimensions					
LVM (g)	88.7	29.0	47	154	
LVM_{BSA} (g/m^2)	61.1	10.6	43	84	
LV EDV (ml)	103	31.9	50	181	
LV ESV (ml)	38.7	16.4	16	85	
Parameters of systolic function					
EF (%)	63.3	8.4	39.8	75.2	
SV (ml)	64.8	20.2	34.2	122.4	
CI ($l/min/m^2$)	3.32	0.9	1.69	5.33	
SDS values according to Kawel-Boehm					
LVM	0.39	0.8	−1.1	1.9	0.032
LVEDV	−0.53	1.0	−2.5	1.6	0.015
LVESV	−0.03	1.3	−2.0	3.7	ns
EF	−0.25	1.6	−5.2	2.0	ns
SV	−0.76	1.1	−3.1	1.4	0.002
CI	−1.11	2.0	−3.6	1.0	0.001

LVM left ventricular mass, *BSA* body surface area, *LVEDV* left ventricular end diastolic volume, *LVESV* left ventricular end systolic volume, *EF* ejection fraction, *CI* cardiac index (cardiac output/BSA), *SV* stroke volume. *SD* standard deviation, *SDS* SD score

only two children (8 %) according reference values from Kawel-Boehm [28].

CMR-LVMI and CMR-LVM$_{BSA}$ were both correlated to annualized GFR decline after the examination, i.e., future kidney function (see Fig. 1, r=−0.52, p=0.01, and r=−0.49, p=0.02). This was not true for Echo-LVMI or Echo-LVM$_{BSA}$ (and only marginally for CMR-LVM SDS, r=−0.40, p=0.06). CMR and Echo-LVM were not correlated to present kidney function or to the slope of GFR decline prior to examination.

Increased CMR-LVM SDS was negatively correlated to aldosterone/renin ratio (r=−0.63, p=0.02), which was not true for Echo-LVM-indices. Serum electrolytes, pH, PTH, vitamin D, and various markers of anemia correlated neither with CMR- nor Echo-LVM measures. Lean children had higher cardiac output per BSA (cardiac index), with a correlation of CMR-CI SDS to body mass index (BMI) SDS of r=−0.52 (p=0.007).

Agreement of left ventricular mass (LVM)

As is evident from Tables 2 and 3, absolute values of LVM differed widely between the two groups with mean CMR-LVM of 88.7±29.0 vs. mean echo-LVM of 117.0±39.7 (p<0.0001). Even though the correlation between both measurements was high at r=0.91 (p<0.00), this is an imprecise measure of agreement, and Fig. 2 shows that the regression line is not parallel to the line of equivalence. The regression equation was Echo-LVM=6.1+CMR-LVM* 1.25 with r^2= 0.84 (p of slope<0.001, p of intercept 0.58).

The Bland–Altman plot (see Fig. 3) shows a mean difference between Echo- and CMR-LVM of 28.26±17.6 g. Thus, the limits of agreement (mean±1.96 × SD) were −6.2 to 62.8 g. The visual impression of the Bland–Altman plot suggests greater scatter at higher LVM measurements. This was confirmed by a significant correlation of the LVM difference to Echo-LVMI (r=0.77, p<0.0001) but not CMR-LVMI (r= 0.33, p=0.11). The LVM measurement difference did not correlate to body dimensions, renal function, blood pressure, or anemia nor did it differ between males and females, pre- and post-transplantation or with stage of CKD.

However, the Echo-CMR difference of LVM was significantly higher in eight children treated for anemia with iron supplements or erythropoiesis stimulating agents (40.3±18.5

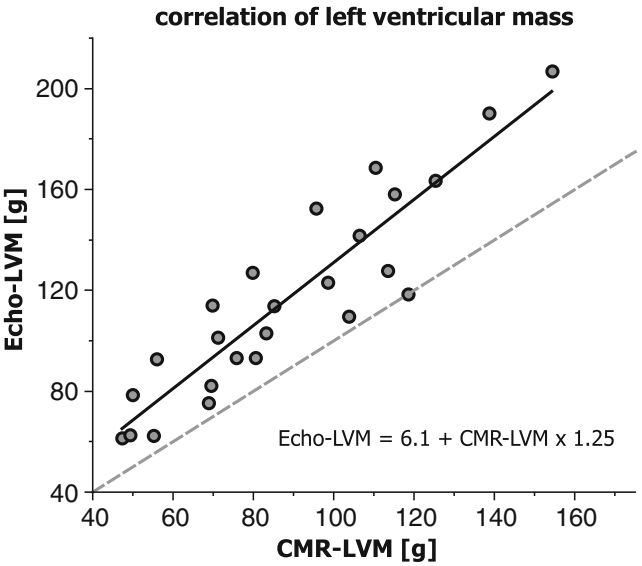

Fig. 2 Correlation of left ventricular mass (LVM) on echocardiography (Echo) and on cardiac magnetic resonance (CMR). *Dotted line*=line of equivalence. *Solid line*=regression line

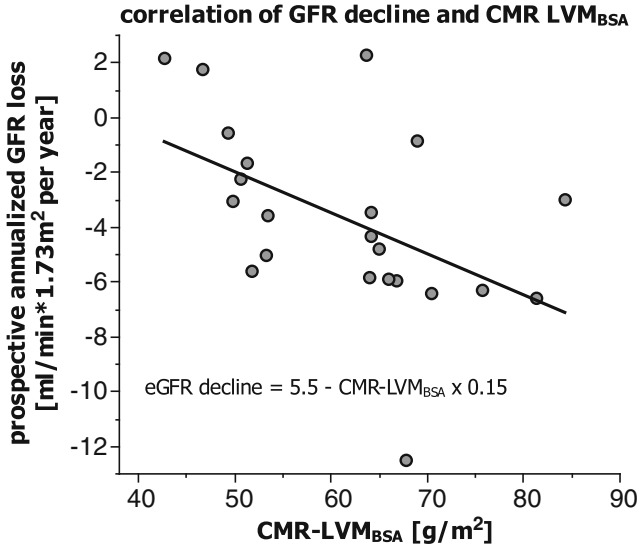

Fig. 1 Correlation of prospective annualized loss of estimated glomerular filtration rate (eGFR) with left ventricular mass (LVM) normalized to body surface area (BSA) measured by cardiac magnetic resonance (CMR). *Solid line*=regression line

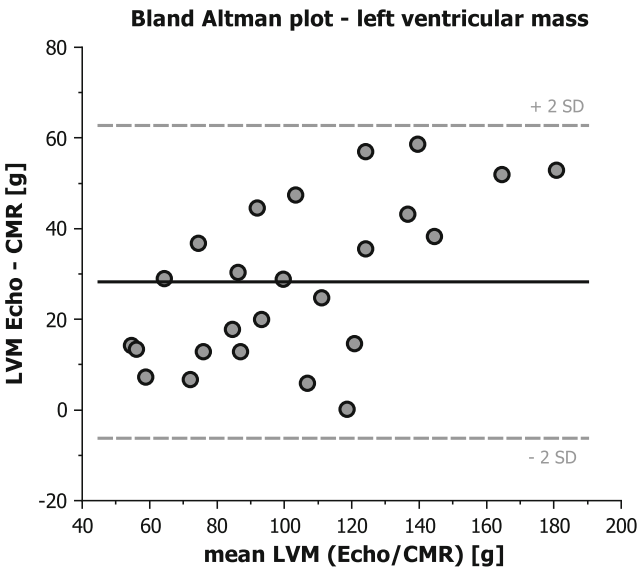

Fig. 3 Bland–Altman plot of the difference vs. the mean of left ventricular mass (LVM) measured by echocardiography (Echo) and cardiac magnetic resonance (CMR)

vs. 22.6±14.5 g in 17 untreated patients, p=0.016) and correlated to the dose of iron given (r=0.42, p=0.036). There was no correlation to other markers of anemia such as hemoglobin, erythrocyte count, or mean corpuscular volume.

Agreement of detecting left ventricular hypertrophy (LVH)

The number of children with Echo-LVMI above the 95th percentile was much higher (n=8), than those with CMR-LVM_{BSA} above the 95th percentile (n=2) (see Table 4a). Even though there was a stepwise increase of mean CMR-LVM SDS from those with normal echocardiography (n=5, 0.03±0.8), to concentric remodeling (n=12, 0.33±0.86), to concentric hypertrophy (n=7, 0.64±0.94) and to eccentric hypertrophy (n=1, 1.13), this did not reach statistical significance on ANOVA testing. Also, one of the two patients with CMR-LVH had a normal echocardiogram, however this patient's CMR-LVM_{BSA} was only on the 96th percentile (SDS 1.76). Thus, the agreement between the two methods was only poor with a Cohen's kappa of 0.08 (95 % CL −0.23 to 0.40). Presuming CMR to be the gold standard, echo had a poor specificity of 69.6 % (CI 47–87 %) and poor sensitivity of 50 % (95 % CI 1.3–98.7 %). Only the negative predictive value was good with 94.12 % (95 % CI 71.3–99.9 %), while the positive predictive value was expectedly low at 12.5 % (95 % CI 0.3–52.7 %).

To assess whether this disagreement was only due to the different indexing methods that are routinely used for Echo-LVM (to height to the power of 2.7) and CMR-LVM (to BSA), we calculated the incidence of Echo-LVH defined as Echo-LVM_{BSA} above the 95th percentile (see Table 4b). However, this only resulted in marginal improvement, with one less patient having Echo-LVH, resulting in a slightly better, but still poor Cohen's kappa of 0.11 (95 % CI −0.24 to 0.46). Accordingly, there was a slight increase of specificity (73.9 %) and positive predictive value (14.3 %), with identical sensitivity and negative predictive value.

Figure 4 shows the individual differences between Echo-LVMI percentile groups and CMR-LVM_{BSA} SDS score. Even though the Echo-LVMI percentiles were higher generally speaking, this was by no means true for all patients and there was considerable scatter.

Table 4 Agreement of left ventricular hypertrophy (LVH) found on cardiac magnetic resonance (CMR) and echocardiography (Echo)

		CMR-LVM_{BSA}		
		>95th percentile	Normal	Total
(a) Using standard indexing methods				
Echo-LVMI	>95th percentile	1	7	8
	Normal	1	16	17
	Total	2	23	25
(b) Using indexing to body surface area (BSA) for both methods				
Echo-LVM_{BSA}	>95th percentile	1	6	7
	Normal	1	17	18
	Total	2	23	25

LVMI left ventricular mass index

Agreement of ejection fraction (EF)

Even though mean ejection fraction measured by echocardiography and CMR was similar (64.7±6.6 vs. 63.3±8, p=ns), correlation was worse than for LVM (r=0.57, p=0.003, see Fig. 5). The regression equation was Echo-EF= 36.3+CMR-EF * 0.45 (p=0.0003 for intercept. p= 0.003 for slope). The Bland–Altman plot shows a mean difference of 1.42 percentage points (limits of agreement: −12.6 to 15.4), with greater scatter at ejection fractions below 60 % (see Fig. 6).

Thus, the agreement of detecting a reduced ejection fraction (below 55 %) was poor with a Cohen's kappa of 0.17 (95 % CI −0.31–0.65); see Table 5. Assuming CMR to be the gold standard, echo had a good specificity of 90.5 % and negative predictive value of 86.4 %, but a very poor sensitivity of 25 % and positive predictive value of only 33 %.

As for LVM, the Echo-CMR difference of EF was significantly higher in children treated for anemia (ΔEF 5.71± 6.8 % vs. −0.61±6.5 %, p=0.036) and correlated to the dose of iron given (r=0.61, p=0.0013), but not to other markers of anemia.

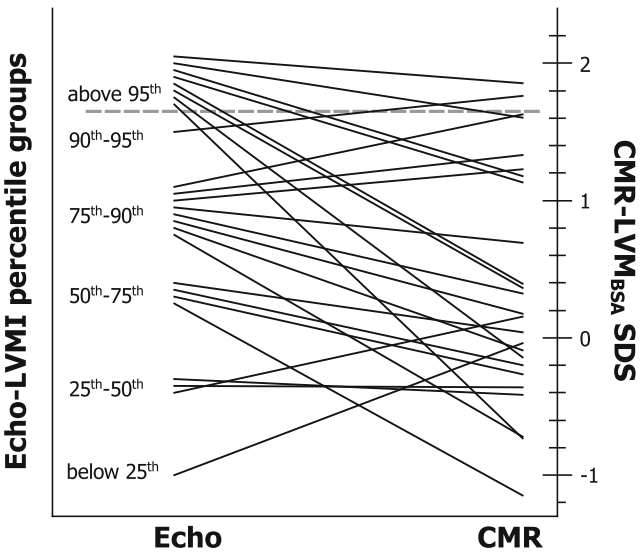

Fig. 4 Agreement of echocardiographic left ventricular mass index (Echo-LVMI) percentiles according to Khoury [11] with CMR-LVM_{BSA} standard deviation score (SDS) according to Kawel-Boehm [28]. *CMR* cardiac magnetic resonance, *LVM* left ventricular mass

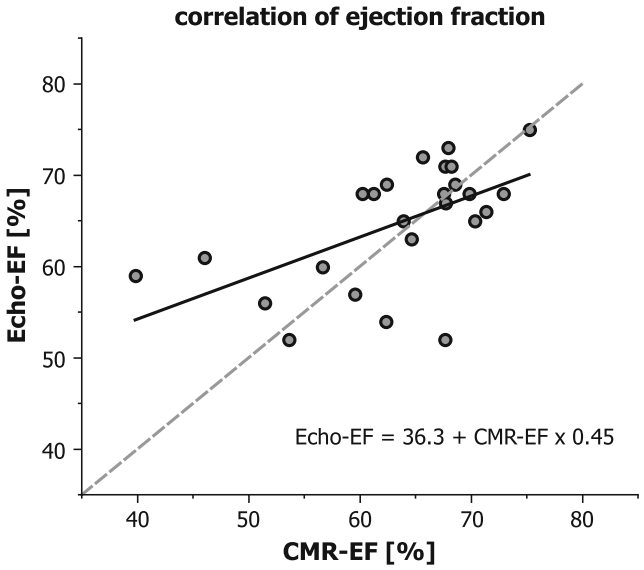

Fig. 5 Correlation of ejection fraction (EF) on echocardiography (Echo) and on cardiac magnetic resonance (CMR). *Dotted line*=line of equivalence. *Solid line*=regression line

Comparison of patients pre- and post-kidney transplant (KTx)

Patients with KTx had higher estimated GFR than those without (74±23 vs. 47±21 ml/min*1.73 m^2, p=0.005), but the two groups did not differ significantly with respect to age, gender, anthropometric measurements, anemia, ambulatory blood pressure or frequency, and intensity of antihypertensive treatment. The Echo-MRI differences in LVM, nLVM, and EF tended to be larger in patients with KTx, but these differences were not significant. Cohen's kappa for agreement of LVH

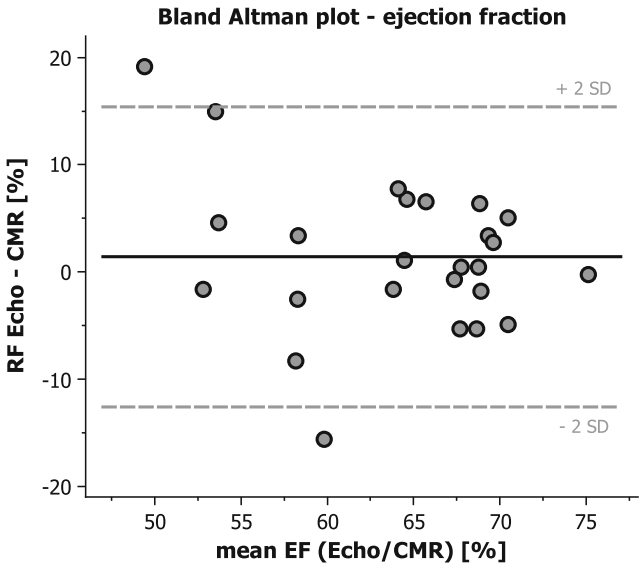

Fig. 6 Bland–Altman plot of the difference vs. the mean of ejection fraction (EF) measured by echocardiography (Echo) and cardiac magnetic resonance (CMR)

Table 5 Measurement of ejection fraction (EF) with echocardiography (Echo-) and cardiac magnetic resonance (CMR)

		CMR-EF		
		<55 %	>55 %	Total
Echo-EF	<55 %	1	2	3
	>55 %	3	19	22
	Total	4	21	25

classification was also worse in the KTx group, but 95 % confidence intervals overlap widely (0.12 (−0.37 to 0.1) vs. 0.42 (−0.17 to 1)).

Discussion

With the improving prognosis of children with chronic kidney disease, increasing numbers of survivors are affected by severe cardiovascular disease starting in early adulthood [37]; thus, measuring left ventricular mass as a surrogate marker of cardiovascular disease is becoming clinically increasingly relevant in trying to prevent these changes. Echocardiography has been the standard technique for many years, but cardiac magnetic resonance offers an alternative which is promising, especially with regard to reliably measuring left ventricular volume independent of geometric assumptions, which may not hold for volume overloaded patients. Echo has been shown to overestimate CMR-LVM in adults with reduced renal function [19, 20] and hypertension [38, 39], but evidence is less clear in children [40]. While CMR is generally accepted as superior in quantifying LVM, the lack of validation with autopsy studies means it is not yet a solid gold standard. The aim of this study was to compare how well Echo and CMR agree in children with CKD and whether one method showed better correlation to renal parameters than the other.

On echocardiography, we find an incidence of left ventricular hypertrophy of 32 %, which is similar to previous studies, but with a higher proportion of concentric vs. eccentric changes compared to previous reports [1, 2, 41, 42]. However, adult CMR studies have suggested that dialysis patients have a unique kind of LVH, which is neither clearly concentric nor eccentric [43], which may be the cause of varying classification. The incidence of LVH was much lower on CMR with only 8 %. However, CMR-LVM SDS was still significantly increased from normal, confirming early cardiac changes found in previous studies [17, 18]. Importantly, CMR-LVM and CMR-LVM_{BSA} were able to predict GFR decline, which has not been found in any other pediatric echocardiographic studies. This relationship is plausible, as it has also been described in adult CKD patients [44]. As part of the cardiorenal syndrome, a small but significant influence of LVM on renal

outcome is also found in studies in adult hypertensives [45, 46].

The comparison of LVM measurements by Echo and CMR showed a systematic difference between the two methods, where Echo-LVM was markedly higher than CMR-LVM, with an increasing difference at higher mean LVMs (see Figs. 2 and 3). As the difference did not correlate to body dimensions or CMR-LVM, but only to Echo-LVM, it can be postulated that it is due to a systematic error of the echo formula. Other authors have also found Echo-LVM to overestimate CMR-LVM, especially with reduced renal function [19, 20]. Indeed, the correlation of Echo-CMR-LVM difference to mean LVM found by Jakubovic et al. appears very similar to that in our study [20]. Absolute Echo-LVM differences only appear smaller in our study due to the smaller heart sizes in children. We also find that Echo-CMR agreement of both LVM and EF was worse for patients treated for anemia, which may also relate to larger intravascular volume and consequently altered ventricular geometry in this group. To resolve this discrepancy, necropsy validated studies of CMR and Echo in patients with distorted geometry would be desirable.

On the other hand, comparing absolute LVM may justifiably be criticized as comparing "apples with oranges" as differences are inconsequential if application of correct reference values yields comparable results. We therefore also compared the classification of left ventricular hypertrophy using accepted standards (95th percentile cut-offs of LVMI for echo and LVM_{BSA} for CMR), which still resulted in only poor agreement between the two methods with Cohen's kappa indicating agreement not significantly better than expected by chance. Applying identical indexing methods (i.e., 95th percentile of LVM_{BSA} for both methods) this could only be marginally improved (see Table 4a and b). Indexing LVM to BSA seems to underestimate the prevalence of hypertrophy especially in overweight patients [47], but while indexing to height 2.7 is more predictive of mortality in adult hemodialysis patients than indexing to BSA [48], it is still a matter of debate which method is superior in the general population [49, 50]. In addition to the ongoing debate about the best way to index LVM [51], this matter is complicated further by the pediatric need for age-adjusted reference values (see supplementary table for an overview of available normal values). It is therefore unsurprising that the Echo-CMR agreement of assigning LVH is even poorer in our children than in adult CKD and hypertensive cohorts [20, 52].

With regard to cardiac function, CMR revealed a significant reduction of stroke volume, cardiac index, and end-diastolic volume in our cohort of CKD children, while ejection fraction was preserved. In a similar population a previous CMR study also found normal EF. [18] Other functional cardiac studies on CKD children have employed various Echo techniques finding reduced fractional shortening and reduced EF, but both increased or decreased contractility [1, 3, 42, 53]. However, our comparison of Echo- and CMR-EF shows that agreement between both methods is far from optimal and especially poor in the clinically most relevant spectrum of EF below 60 % (see Figs. 5 and 6), even though it was slightly better than in children with aortic insufficiency [54]. Thus there was only a poor Cohen's kappa of 0.17 for detecting reduced EF below 55 %. Measurement of other functional indices on Echo, such as cardiac output is difficult, as the estimation of stroke volume requires the velocity time integral of flow at left ventricular outflow tract. One functional study employing Echo and exercise testing found increased CO and SV in children with CKD and LVH compared to those with CKD without LVH, however there was no comparison to normal children [55]. We too find a positive correlation of CMR-LVM_{BSA} to SV_{BSA} (r=0.44, p=0.03), but not to CO, however the overall SV and CO are decreased.

A CMR study in adult dialysis patients found decreased EF and increased EDV in adult dialysis patients, while EF was normal and EDV decreased in our pediatric non-dialysis population, which probably reflects more advanced stages of uremic cardiomyopathy in adults together with larger volume fluctuations under hemodialysis [43]. Other Echo studies in pediatric CKD have also found predominantly diastolic changes [56, 57], suggesting that impaired diastolic relaxation precedes systolic changes in uremic cardiomyopathy.

The current evidence does not justify the degradation of echocardiography, as it remains not only much easier and cheaper in clinical practice but also has the larger evidence base for outcome data so far. New developments such as 3D echocardiography show better correlation of LVM to CMR than 2D Echo even in children and may be suitable alternatives for clinical trials [58–60]. On the other hand, CMR is becoming increasingly available, protocols to measure LVM are relatively short (<30 min) and do not require contrast medium and mass calculations are reproducible and less laborious with semi-automated tracing of ventricular outlines.

In summary, we find that Echo significantly overestimates LVM compared to CMR in children with CKD, which is consistent with previous findings from adults. The discrepancy between both methods is not easily removed by application of reference values, partly because a number of different reference populations and methods of indexing exist. The fact that CMR-LVM shows better prediction of GFR decline here suggests that it is worth further investigating the prognostic value of CMR vs. echocardiography.

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Ethical approval The study confirmed to the declaration of Helsinki, was approved by the ethics committee of the University of Freiburg and registered in the German registry of clinical trials (Deutsches Register Klinische Studien, trial no. DRKS00003295).

Informed consent Prior written informed consent was obtained from all parents (and adolescents where appropriate).

Conflict of interest The authors declare no conflict of interest.

Glossary

BSA	Body surface area
CMR(−)	Cardiac magnetic resonance/measured by CMR
Echo(−)	Echocardiography/ echocardiographicaly measured
EF	Ejection fraction
LVM	Left ventricular mass
LVH	Left ventricular hypertrophy
LVMI	LVM indexed to height in $m^{2.7}$
LVM_{BSA}	LVM normalized to body surface area
ABPM	24-hour ambulatory blood pressure measurement
CKD	Chronic kidney disease
CI	Confidence interval

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