Left Ventricular Geometry in Children with Mild to Moderate Chronic Renal Insufficiency

Maria Chiara Matteucci,* Elke Wühl,† Stefano Picca,* Antonio Mastrostefano,* Gabriele Rinelli,* Carmela Romano,‡ Gianfranco Rizzoni,* Otto Mehls,† Giovanni de Simone,‡ Franz Schaefer;† and ESCAPE Trial Group

**Division of Pediatric Nephrology, Bambino Gesú Hospital, Rome, Italy; †Division of Pediatric Nephrology, University Hospital of Pediatric and Adolescent Medicine, Heidelberg, Germany; and ‡Department of Clinical and Experimental Medicine, Federico II University Hospital, Naples, Italy*

Left ventricular hypertrophy (LVH) is the most important independent marker of cardiovascular risk in adults with chronic kidney disease. Cardiovascular morbidity seems increased even in children with chronic renal insufficiency (CRI), but the age and stage of CRI when cardiac alterations become manifest are unknown. For assessing the prevalence and factors associated with abnormal LV geometry in children with CRI, echocardiograms, ambulatory BP monitoring, and biochemical profiles were obtained in 156 children aged 3 to 18 yr with stages 2 through 4 chronic kidney disease (GFR 49 ± 19 ml/min per 1.73 m^2) and compared with echocardiograms obtained in 133 healthy children of comparable age and gender. LV mass was indexed to height$^{2.7}$. Concentric LV remodeling was observed in 10.2%, concentric LVH in 12.1%, and eccentric LVH in 21% of patients. LVH was more common in boys (43.3 *versus* 19.4%; $P < 0.005$). Probability of LVH independently increased with male gender (odds ratio [OR] 2.62; $P < 0.05$) and standardized body mass index (OR 1.56; $P = 0.01$). Low hemoglobin, low GFR, young age, and high body mass index were independent correlates of LV mass index ($0.005 < P < 0.05$). LV concentricity (relative wall thickness) was positively associated with serum albumin ($P < 0.05$). Probability of abnormal LV geometry increased with C-reactive protein >10 mg/dl (OR 26; $P < 0.001$). In conclusion, substantial cardiac remodeling of both concentric and eccentric type is present at young age and early stages of CRI in children. Prevalence of LVH is related to male gender, anemia, and ponderosity but not to BP. Additional effects of volume status and inflammation on cardiac geometry are also evident.

J Am Soc Nephrol 17: 218–226, 2006. doi: 10.1681/ASN.2005030276

ESRD is associated with an excessive cardiovascular morbidity and mortality, which, in contrast to the general population, is not a function of patient age but rather driven by disease-related factors, resulting in severe cardiovascular damage in any period of life (1). Hence, annual cardiovascular mortality rates are elevated several hundredfold in young adults with longstanding, childhood-onset chronic renal failure (2,3). Even in the pediatric age range, where cardiovascular mortality is extremely low, 25% of deaths in ESRD are attributable to cardiovascular disease (4). In adults, cardiovascular disease usually begins before ESRD, and patients with chronic renal insufficiency (CRI) are more likely to die of cardiovascular complications than to develop ESRD (5,6).

Left ventricular (LV) hypertrophy (LVH) is the most common and identifiable cardiac alteration in ESRD, affecting up to 75% of dialysis patients (1,7–9). LVH is the most important indicator of cardiovascular risk both in the general population (10) and in adult patients with ESRD (11,12). In dialysis patients, LVH is closely correlated with hypertension and volume overload (13), resulting in both concentric and eccentric changes in LV geometry. Less information is available in patients with mild to moderate CRI (1,6,14). LVH seems to develop early in the course of renal failure and to correlate to some degree with GFR, hemoglobin, and BP (14).

In adult patients with CRI, the assessment of the impact of renal failure on LV geometry is inevitably confounded by concomitant frequent presence of coronary heart disease and/or diabetic microvascular disease. The absence of these potential confounders makes pediatric CRI populations uniquely suited to study the association between renal failure and LV geometry. Because of the low incidence of CRI among children, published information on prevalence and severity of abnormalities of LV geometry in children is restricted to relatively small, selected groups of patients (15,16). The ongoing Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRI in PEdiatric Patients (ESCAPE) trial is evaluating progression of renal failure in children who have mild to moderate CRI and are undergoing angiotensin-converting enzyme (ACE) inhibition and intensified antihypertensive therapy (17). A substudy

Received March 14, 2005. Accepted September 28, 2005.

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

Address correspondence to: Dr. Franz Schaefer, Pediatric Nephrology Division, University Hospital for Pediatric and Adolescent Medicine, University of Heidelberg, Im Neuenheimer Feld 151, 69120 Heidelberg, Germany. Phone: 49-6221-563-2396; Fax: 49-6221-56-4203; E-mail: franz.schaefer@med.uni-heidelberg.de

ISSN: 1046-6673/1701-0218

of the ESCAPE trial has been conceived to assess the effects of antihypertensive treatment on echocardiographic LV geometry. This study examines prevalence, severity, and correlates of abnormal LV geometry at baseline.

Materials and Methods

Patients and Control Subjects

Concomitant echocardiograms and 24-h ambulatory BP monitoring (ABPM) profiles were obtained in 156 children who were treated for CRI in 20 pediatric nephrology units in seven European countries (see Appendix). Children were studied as part of the screening procedure for the ongoing ESCAPE trial (17). The study protocol, including echocardiographic examinations, ABPM, and biochemical assessments, was designed in adherence to the declaration of Helsinki and approved by local Ethical Committees. Written informed consent was given from all parents, and informed consent or assent from the patients was given as appropriate. A group of 133 normotensive children who were of comparable age (15% aged 3 to 5 yr, 22% 6 to 8 yr, 23% 9 to 11 yr, 23% 12 to 14 yr, and 18% 15 to 18 yr) and gender distribution and studied in Naples, Italy, including a previously studied school population (18) and additional healthy volunteers, formed the normal reference population for this study.

Echocardiography

Echocardiograms initially were obtained in 179 children, according to local procedures, in the absence of standardization of acquisition method. Videotapes were shipped to the reading center for quality check and off-line reading. Quality of two-dimensional echocardiograms for measurements of LV dimensions was considered sufficient in 156 children. All echocardiograms were coded locally and in the reading center for cross-check of identity and compared with a historical reference group with comparable age and gender distribution. Echocardiograms were examined off-line, and the frames of interest were acquired digitally in a workstation that was equipped with digital overlay and a frame grabber. Measurements of interventricular septum, posterior wall, and internal dimension in systole and diastole were performed on two to five cardiac cycles, according to the American Society of Echocardiography recommendations (19), using digital calipers on M-mode stop-frames, from perfectly oriented short-axis or long-axis parasternal view, whenever this was possible. When M-mode was considered suboptimal, measurements were taken using two-dimensional parasternal long-axis view (20). All echocardiograms were measured by an expert sonographer who placed the electronic calipers on the interfaces. This first reading was double checked by a second, senior reader. The few disagreements were resolved by joint examination of the stop-frame and, when needed, by magnification of the region of interest to identify the interface better. LV mass (LVM) therefore was obtained according to a necropsy validated formula (21), the reliability of which has been determined in test–retest analyses (22). For accounting for differences in body size, LV end-diastolic diameter (LVEDD) was normalized for height. LVM was normalized for height in meters raised to the allometric power 2.7, which linearizes the relation between LVM and height (23), and expressed in $g/m^{2.7}$ (LVMI). LVH was defined as an LVMI greater than the 95th percentile of the healthy control subjects (38 $g/m^{2.7}$) for both boys and girls. In addition, the prevalence of LVH was defined using a previously reported pediatric partition value that was based on an allometric exponent of 3 rather than 2.7 (*i.e.*, 33.6 g/m^3) (24).

Relative wall thickness (RWT), a measure of concentricity, was calculated as the average thickness of the posterior and septal wall divided by LV diastolic diameter. A value of 0.375 (95th percentile of control subjects) was used as the cutoff to define concentricity (25). Concentric remodeling was defined as elevated RWT with normal LVMI. No significant valve regurgitation was detected, and stroke volume could be calculated by linear measures of LV dimensions (26) and cardiac output obtained by stroke volume× heart rate.

BP Monitoring

ABPM was performed with a Spacelabs 90207 automatic cuff-oscillometric device (Issaquah, WA). The cuff size was adjusted to the upper arm circumference. ABPM measurements were performed according to a standardized protocol (17). ABPM measurements were performed every 15 min during the daytime and every 20 to 30 min at night. All ABPM profiles were analyzed centrally. ABPM profiles were divided into daytime (8:00 a.m. to 8:00 p.m.) and nighttime periods (12:00 a.m. to 6:00 a.m.). Mean values of 24-h mean, systolic, and diastolic BP were calculated and compared with published reference data from healthy children (27). In addition to ABPM, office BP measurements were obtained at the time of the echocardiography after sitting for 5 min in a relaxed position, using auscultatory or oscillometric techniques.

Laboratory Assessments

A full biochemical profile was locally obtained in each center using standard laboratory techniques. In addition, serum and urinary sodium, creatinine (modified Jaffé method), C-reactive protein (CRP; ultrasensitive assay), intact parathyroid hormone (Nichols immunoradiometric assay), and urinary protein (Coomassie method) were measured centrally. GFR was estimated from serum creatinine and height using the pediatric equations of Schwartz *et al.* (28).

Statistical Analyses

ABPM data were analyzed using the Spacelabs ABPM Report Management System. ABPM SD scores (SDS) were calculated using German reference data (27). Swiss reference data were used to calculate height SDS (29), and German reference data were used to calculate BMI SDS (30).

All results are expressed as means ± SD. Statistical analysis was performed using SAS version 8.2 (SAS, Cary, NC) and SPSS 12 (SPSS Inc., Chicago, IL). All variables were assessed for Gaussian distribution by Shapiro-Wilk testing, and nonnormally distributed parameters such as LVMI, CRP, and parathyroid hormone were log-transformed for parametric testing. Between-group differences in continuous variables were assessed for significance by t test in case of two groups and by ANOVA followed by Student Newman-Keuls multiple comparison testing in case of more than two groups. Spearman correlation coefficients were calculated for univariate analysis of associations among echocardiographic, anthropometric, and biochemical variables. Multiple stepwise linear regression analysis was performed to assess potential independent predictors of logLVMI, RWT, and LVEDD, controlling for the presence or absence of antihypertensive treatment. All anthropometric, biochemical, and BP-related parameters that showed significant or near-significant univariate correlations with logLVMI, RWT, or LVEDD were offered for selection to the model, and the default $P < 0.15$ for entry to and $P > 0.10$ for exclusion from the model were applied. χ^2 or Fisher exact test was used to investigate differences in proportions of categorical variables. Logistic regression analysis was performed to identify independent effectors of categorical variables such as LVH and concentricity.

Results

Patient Characteristics

The baseline clinical characteristics of the patients and control subjects are given in Tables 1 and 2. The underlying renal

Table 1. Anthropometric and blood pressure characteristics of patients and control subjects[a]

	CRI	Controls
N	156	133
% male	43	57
Age at examination (yr)	11.2 ± 4	10.4 ± 3.8
Duration of CRI (yr)	6.3 ± 4.4	—
Height (cm)	139 ± 23	142 ± 23
Height SDS	−0.81 ± 1.38[b]	0.15 ± 1.15
BMI (kg/m^2)	18.0 ± 3.7	18.3 ± 3.1
BMI SDS	0.05 ± 1.24[b]	0.39 ± 1.06
CKD class 2/3/4 (%)	34/45/21	—
Casual systolic BP (mmHg)	117 ± 14[b]	107 ± 9
Casual diastolic BP (mmHg)	72 ± 13[b]	63 ± 9
24 h MAP SDS	1.17 ± 1.75	NA
Daytime MAP SDS	0.88 ± 1.62	NA
Nighttime MAP SDS	1.34 ± 1.92	NA
Heart rate	83 ± 15	81 ± 15
24-h heart rate SDS	0.03 ± 1.03	NA

[a]Values are mean ± SD. CRI, chronic renal insufficiency; SDS, SD score; BMI, body mass index; CKD, chronic kidney disease; MAP, mean arterial pressure; NA, not applicable.
[b]$P < 0.001$.

diseases were glomerulopathies in 12.9%, renal hypo/dysplasia in 63%, and other congenital or hereditary disease in 18.1%. Patients were comparable to control group for age and gender but slightly shorter and lighter (Table 1). Eighty-seven patients did not receive any antihypertensive medication, 52 were on ACE inhibitor monotherapy, and 18 received additional antihypertensive drugs. Casual BP was elevated by 1 SD and 24-h BP was elevated by 1.2 SD relative to the reference populations. The time-integrated standardized values of mean arterial pressure and heart rate were positively correlated with each other ($r = 0.22$, $P < 0.01$). None of the casual or 24-h BP parameters was associated with any of the anthropometric indices.

Table 2. Biochemical characteristics of study population[a]

Characteristic	Mean ± SD
Blood hemoglobin (g/dl)	12.1 ± 1.6
Serum bicarbonate (mmol/L)	22.6 ± 3.1
Serum triglycerides (mg/dl)	126 ± 64
Serum cholesterol (mg/dl)	187 ± 41
Serum albumin (g/L)	42.6 ± 5.1
Serum CRP (mg/L)	2.1 ± 5.8
Serum PTH (pmol/L)	9.0 ± 9.8
Serum calcium (mmol/L)	2.37 ± 0.14
Serum phosphate (mmol/L)	1.48 ± 0.26
Serum Ca × P (mmol^2/L^2)	3.52 ± 0.64
GFR (ml/min per 1.73 m^2)	49 ± 19
Urine protein/creatinine ratio (g/g)	1.1 ± 1.3
Fractional sodium excretion (%)	2.6 ± 3.6

[a]CRP, C-reactive protein; PTH, parathyroid hormone.

LV Geometry

Table 3 shows that patients with CRI presented with larger left ventricles, greater LVM, and greater relative wall thickness than healthy control subjects. An abnormal LV geometry was found in 43.3% of the patients, with 22.3% of all patients showing concentric LV geometry (*i.e.*, hypertrophy or remodeling) and 21% exhibiting eccentric LVH. The prevalence of LVH was slightly higher using the previously reported cutoff value normalizing LVM to height^3 (40 *versus* 33% for height$^{2.7}$; $P < 0.01$); however, no significant difference was found for LVH distribution or LV geometry between the two approaches. Among the patients with LVH, eccentric geometry was present in 63.5%. The distribution of LV geometry was independent of the presence of arterial hypertension and did not differ between patients who were not taking any antihypertensive medication or who were taking ACE inhibitor monotherapy and other antihypertensive medication. The nature of the underlying renal disease was unrelated to the distribution of LV geometry.

Predictors of LV Geometry: Univariate Analysis

Although mean LVMI or RWT did not differ significantly between genders, LVH was more frequent in boys (43.3%) than in girls (19.4%; $P < 0.005$; Figure 1). The prevalence of LVH was higher in boys who were younger than 9 yr (67.9%) than in older boys (32.2%; $P < 0.005$).

LVMI was positively correlated with BMI SDS ($r = 0.27$, $P < 0.001$) and negatively with age ($r = -0.22$, $P < 0.01$) and height SDS ($r = -0.18$, $P < 0.05$). These relations were absent in the control group. LVMI was also inversely associated with GFR ($r = -0.22$, $P < 0.01$) and hemoglobin ($r = -0.17$, $P < 0.05$) and positively with serum triglycerides ($r = 0.21$, $P < 0.05$) and phosphate ($r = 0.17$, $P < 0.05$).

In contrast, LVMI was not correlated with casual BP or with any of the ABPM BP characteristics. Even in the 87 patients who were not receiving any antihypertensive medication, no correlation between LVMI and BP was found, despite a wide range of LVMI (18 to 101; mean 36.2 ± 12.9 g/m$^{2.7}$) and 24-h mean arterial pressure (−1.45 to 6.48; mean 1.1 ± 1.4 SDS). Patients with chronic kidney disease (CKD) stage 4 had significantly higher mean LVMI (41 ± 14.5 g/m$^{2.7}$) than patients with CKD stage 3 (36 ± 12.1 g/m$^{2.7}$; $P < 0.05$) or stage 2 (33 ± 9.1 g/m$^{2.7}$; $P < 0.05$; Figure 2).

LV concentric geometry was significantly more common in patients who were younger than 12 yr (30.7%) than in adolescents who were older than 12 yr (8.7%). LV concentric remodeling or hypertrophy was observed in five (83%) of six patients with CRP ≥10 mg/dl but in only 19.1% of patients with lower or negative CRP levels ($P < 0.005$). RWT was positively correlated with serum albumin levels ($r = 0.20$, $P = 0.01$). RWT was significantly lower in the 41 patients with serum albumin <40 g/L (0.302 ± 0.056) than in normoalbuminemic patients (0.334 ± 0.052; $P < 0.01$). Moreover, RWT was weakly associated with standardized daytime heart rate ($r = 0.16$, $P < 0.05$) but not with BP, age, GFR, or hemoglobin. The distribution of

Table 3. Echocardiographic findings in 156 pediatric patients with CRI and 133 healthy control subjects[a]

Finding	CRI	Controls	*P*
LV end-diastolic diameter indexed for height (cm/m)	3.03 ± 0.35	2.91 ± 0.29	0.004
LVMI ($g/m^{2.7}$)	35.9 ± 12.1	26.5 ± 6.2	0.0001
RWT	0.34 ± 0.05	0.30 ± 0.06	0.0001
LV geometry			
normal LV geometry (%)	56.7	97.5	0.001
eccentric LVH (%)	21.0	2.5	0.001
concentric LVH (%)	12.1	0	0.001
concentric remodeling (%)	10.2	0	0.001

[a]LV, left ventricular; LVMI, LV mass index; RWT, relative wall thickness; LVH, LV hypertrophy.

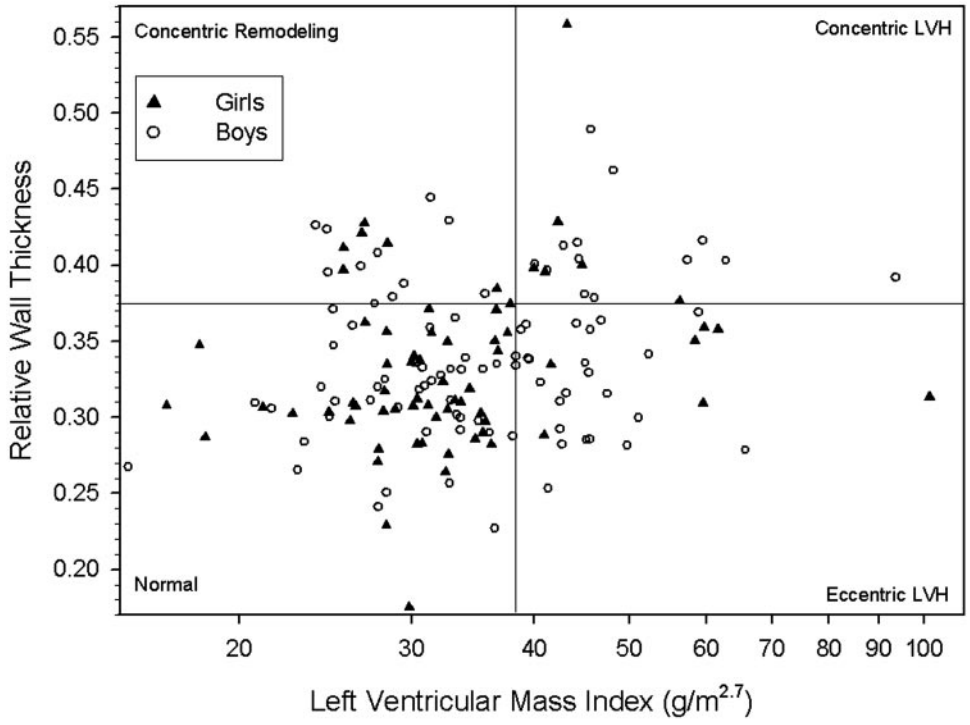

Figure 1. Distribution of left ventricular mass index (LVMI) and relative wall thickness (RWT) in 156 children with chronic renal insufficiency (CRI). Reference lines indicate 95th percentiles of LVMI and RWT in healthy control populations (18).

LV geometry did not differ between patients who were not taking antihypertensive medication or who were receiving ACE inhibitor monotherapy and other antihypertensive medication.

LVEDD, a rough measure of preload, was inversely correlated with age ($r = -0.34$, $P < 0.0001$), hemoglobin ($r = -0.24$, $P < 0.005$), GFR ($r = -0.17$, $P < 0.05$), serum bicarbonate ($r = -0.14$, $P < 0.01$), and serum albumin ($r = -0.18$, $P < 0.05$) and positively correlated with BMI SDS ($r = 0.19$, $P < 0.01$) and proteinuria ($r = 0.26$, $P < 0.005$).

Predictors of LV Geometry: Multivariate Analysis

Among the multiple factors that correlated with individual echocardiographic parameters in the univariate analysis, high LVMI was independently correlated to younger age, high BMI, low hemoglobin, and low GFR (Table 4). LV concentric geometry was positively related to albumin, and larger LV chamber was positively related to younger age, high BMI, and low hemoglobin.

The probability of LVH was independently increased by BMI SDS (odds ratio [OR] 1.56; 95% confidence interval [CI] 1.1 to 2.2; $P = 0.01$) and male gender (OR 2.62; 95% CI 1.06 to 6.5; $P < 0.05$). The probability of eccentric LVH was increased in boys (OR 4.38; 95% CI 1.38 to 13.9; $P = 0.01$), whereas the likelihood of concentric LV geometry markedly increased with CRP >10 mg/dl (OR 26; 95% CI 1.8 to 385; $P < 0.001$), with an additional minor contribution of BMI SDS (OR 1.48; 95% CI 1.01 to 2.18; $P < 0.05$).

Discussion

To establish the prevalence of LV geometric abnormalities in children with mild to moderate CRI, several methodologic

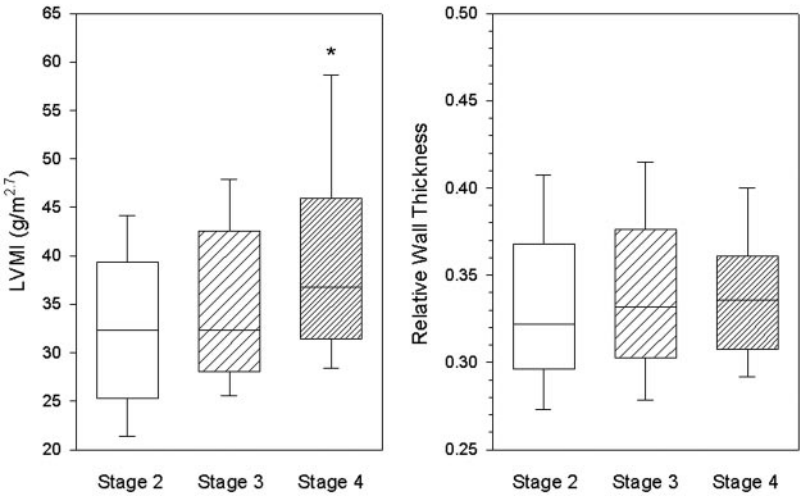

Figure 2. Distribution of LVMI and RWT according to chronic kidney disease stage. Central line indicates median, lower and upper box borders the 25th and 75th, and extension borders the 10th and 90th distribution percentiles. *Significant difference to stage 2 and stage 3 ($P < 0.05$).

Table 4. Independent predictors of LV geometry in pediatric patients with CRI[a]

Dependent Variable	Predictor	β	P	R^2
Log LVMI	Hemoglobin	−0.221	0.0003	0.107
	BMI SDS	0.173	0.005	0.059
	Age	−0.209	0.04	0.031
	GFR	−0.194	0.04	0.030
				Cum: 0.227
RWT	Albumin	0.225	0.04	0.045
	BMI SDS	0.173	0.09	0.027
	Phosphate	0.171	0.10	0.027
				Cum: 0.099
LVEDD	Age	−0.274	<0.0001	0.119
	Hemoglobin	−0.137	0.005	0.054
	BMI SDS	0.137	0.05	0.024
				Cum: 0.197

[a]Results of stepwise linear regression analysis. LVEDD, LV end-diastolic diameter.

issues had to be solved. Because of the low incidence of CRI in children, a multicenter study was required to collect a sufficiently sized pediatric sample of predialysis CRI. Because stringent standardization of echocardiographic acquisitions was not possible in this setting, off-line reading of videotaped examinations was performed using very strict criteria and two experienced observers. Furthermore, an appropriate definition of LVH in children had to be made. The reported frequencies of LVH in hypertensive children vary greatly, as a result, in part, of the use of differences in LVM normalization and in the criteria used to define pediatric LVH (20–23,31). We accounted for the physiologic allometric changes of LVM during childhood by indexing LVM to height$^{2.7}$, according to most recent recommendations (23,24). This approach was adopted recently in several pediatric populations (24,32), and recent findings in adults have demonstrated that this method of normalization is superior to other standardization techniques in predicting cardiovascular disease (33).

Prevalence of Abnormal LV Geometry in Children with CRI

Our study reports on the largest population sample of children with CRI in whom LV geometry has been assessed. One third of the 156 patients studied presented with LVH. This figure is similar to the rate of LVH observed in adults with mild to moderate CRI (1,14), whereas previous pediatric studies reported somewhat lower prevalences (15,16). The slight differences to earlier pediatric surveys may be due mainly to methodologic differences regarding population size, LVM standardization, and the choice of reference cutoff values (15,34). The methodologic issues briefly highlighted above also may explain in part the apparent differences in the distribution of LV geometry observed in this population in comparison with earlier

work (15,34). In the two previous pediatric single-center studies that assessed LV geometry, concentric LVH appeared more frequent in predialytic CRI (15,34), whereas eccentricity was more common in children who were on dialysis (34). Applying for the first time an RWT cutoff value established in healthy children (25), we observed concentric LV geometry in 50% of all children with abnormal LV morphology in this large population with mainly mild to moderate CRI, whereas two thirds of patients in whom LVM was increased showed the eccentric type of LVH. These results are more consistent with findings in adults with CRI, in whom eccentric geometry was observed in 42 to 65% of patients with established LVH (14,35). Whereas in adult CRI populations associated coronary heart disease is a major confounder affecting the severity and geometry of LVH, our findings provide unequivocal evidence that LV remodeling of both eccentric and concentric types occurs early in the course of CRI even in the young.

Hemodynamic Mechanisms Related to Abnormal LV Geometry in Children with CRI

The left ventricle principally adapts to increased afterload by concentric and to increased preload by eccentric remodeling (36). In advanced and end-stage renal failure, hypertension and volume overload are in fact the major contributors to concentric and eccentric remodeling, respectively. In the population studied here, detailed analysis of BP characteristics by ABPM did not demonstrate any relationship with LVM. In this cross-sectional study, it cannot be excluded that early antihypertensive treatment masked an underlying association of BP and concentric LV geometry by preventing or reversing concentric LVH. However, also in the large subgroup of untreated patients, no relationship between BP and LVM or concentricity was apparent, despite a wide range of BP. Hence, our data suggest a minor role of hypertension in the pathogenesis of LVH in early CRI. In line with this notion, in previous studies, consistent correlations of LVM and BP were limited to patients with ESRD (7,9).

The high proportion of patients with eccentric LVH was unexpected. Fluid overload is generally believed to be a feature of ESRD and was even more surprising in a pediatric CRI population with predominating hypo/dysplastic renal disorders, where salt and water loss is common. Nevertheless, the clear increase in LV diastolic dimension, accentuated in young and anemic children, indicates significant volume overload even in mild to moderate CRI. A relationship between preload and eccentricity was also indirectly suggested by the positive association between serum albumin and RWT, the marker of LV concentricity: Low serum albumin levels, likely indicating an increased circulating volume, were associated with a lower RWT. An overactivation of the renin-angiotensin-aldosterone system as reported in various progressive nephropathies might provide a plausible explanation for an early increase in circulating volume in this population (37).

Nonhemodynamic Mechanisms Related to Abnormal LV Geometry in Children with CRI

Male gender was independently associated with a more than four-fold risk for LVH. This finding is in keeping with previous observations in animals as well as pediatric and adult patients showing an increased LV growth in male individuals who were exposed to increased cardiac pre- or afterload (9,38,39). It is interesting that in our study, the association was strongest in prepubertal children, in whom gender-specific gonadal steroid production is not yet established. It is tempting to speculate about genes that regulate the activity of myocardial remodeling located on a sex chromosome. A possible candidate may be the angiotensin type II receptor gene, which resides on the X chromosome, exists in polymorphic variants resulting in different protein expression levels, and exerts mainly antiproliferative, proapoptotic actions on cardiomyocytes (40,41).

Relative body mass was a major predictor of LVM and geometry. The probability of LV concentric geometry increased by 48%, and the risk for LVH increased by 56% per unit of standardized BMI. Although obesity is known to be associated with concentric LV geometry and LVH in children and adults (31,42,43), BMI is also a strong determinant of LVM within the normal range of body weight and in the absence of hypertension when LVM is normalized for height$^{2.7}$ (24,32). The common relationship between BP parameters and anthropometric indices was not manifest in this study. The presence of few obese patients and few patients with low normal BP probably concealed this physiologic relationship in the CKD population studied here.

Renal anemia is a serious complication of CRI with a potential major impact on LV remodeling. Changes in hemoglobin levels parallel LV growth in longitudinal observational studies in adult patients with CRI (1,14,44). In our population, hemoglobin was an independent negative correlate of both LVMI and LV chamber dimension, suggesting that anemia is associated with increasing circulating volume and preload. However, only a minor part of the variation in LVM was explained by anemia, and hemoglobin levels did not predict the geometry of cardiac remodeling. Hence, renal anemia seems to contribute moderately to the high prevalence of LVH in children with stages 2 to 4 CKD.

Recent evidence suggests that CRI can directly influence LV growth and function through nonhemodynamic-mediated stimuli such as chronic inflammation and hyperparathyroidism (45,46). In this study, elevations (>10 mg/dl) of serum CRP, the most sensitive marker of tissue inflammation, was associated with concentric LV geometry. In adult CRI and dialysis populations, CRP is elevated in a large proportion of patients, correlates with LVH, and is a strong predictor of cardiovascular morbidity and mortality (47,48). Both in malnourished and obese patients with CRI, low-grade inflammation is found in the presence of an accelerated, calcifying arteriopathy (3,46,49), a process that results in increased arterial stiffness and an LV pressure overload (50,51). Arterial stiffness and calcification are in fact closely associated with LVH in hemodialysis patients (52). Our findings suggest that a link between inflammation and LVH may already be operating even in pediatric CRI. Whereas vascular disease is commonly considered irrelevant in this age group, we recently observed arterial thickening and increased arterial stiffness even in children with mild to moderate CRI (53). However, it should be emphasized that although

the association of CRP with concentricity was highly significant, only a small absolute number of patients in this young, mildly uremic population presented with elevated CRP, and CRP was subthreshold in 80% of all patients with manifest concentric changes in cardiac geometry.

In conclusion, LV geometric abnormalities are present in a high proportion of children with mild to moderate chronic renal failure. Concentric and eccentric LV geometry are represented, likely as a result of an interaction between hemodynamic and nonhemodynamic factors. Male gender, a high BMI, anemia, fluid overload, and low-grade inflammation participate in the variation of LVM and geometry, whereas arterial hypertension seems to be less important.

Appendix

Participants of the ESCAPE Trial Group: A. Anarat (Adana*), A. Bakkaloglu, F. Ozaltin (Ankara*), A. Peco-Antic (Belgrade*), U. Querfeld, J. Gellermann (Berlin*), P. Sallay (Budapest), D. Drozdz (Cracow*), K.-E. Bonzel, A.-M. Wingen (Essen), A. Zurowska, I. Balasz (Gdansk), F. Perfumo, A. Canepa (Genoa), D.E. Müller-Wiefel, K. Zepf (Hamburg), G. Offner, B. Enke (Hannover*), O. Mehls, F. Schaefer, E. Wühl, C. Hadtstein (Heidelberg*), U. Berg, G. Celsi (Huddinge), S. Emre, A. Sirin, I. Bilge (Istanbul*), S. Çaliskan (Istanbul-Cerrahpasa*), S. Mir, E. Serdaroglu (Izmir), C. Greiner, H. Eichstädt (Leipzig), K. Hohbach-Hohenfellner (Mainz*), N. Jeck, G. Klaus (Marburg*), A. Appiani, G. Ardissino, S. Testa (Milano*), G. Montini (Padova*), P. Niaudet, M. Charbit (Paris*), J. Dusek (Prague), A. Caldas-Afonso, A. Texeira (Porto), S. Picca, M.C. Matteucci (Rome*), M. Wigger (Rostock*), M. Fischbach, J. Terzic (Strasbourg), J. Fydryk, T. Urasinski (Szczecin*), R. Coppo, L. Peruzzi (Torino*), A. Jankauskiene (Vilnius), M. Litwin, M. Abuauba, R. Grenda (Warszawa*), K. Arbeiter (Vienna), T.J. Neuhaus (Zurich*).

*These centers contributed patients to the echocardiography study.

Acknowledgments

Support for this study was obtained from the European Commission (5th Framework Programme, QLG1-CT-2002-00908), the Boehringer Ingelheim Stiftung, the Baxter Extramural Grant Program, and Aventis Pharma.

References

1. Parfrey PS, Foley RN: The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol* 10: 1606–1615, 1999
2. Groothoff JW, Gruppen MP, Offringa M, Hutten J, Lilien MR, Van De Kar NJ, Wolff ED, Davin JC, Heymans HS: Mortality and cause of death of end-stage renal disease in children: A Dutch cohort study. *Kidney Int* 61: 621–629, 2002
3. Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, Mehls O, Schaefer F: Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation* 106: 100–105, 2002
4. Parekh RS, Caroll CE, Wolfe RA, Port FK: Cardiovascular mortality in children and young adults with end-stage kidney disease. *J Pediatr* 141: 191–197, 2002
5. London GM: Cardiovascular disease in chronic renal failure: Pathophysiologic aspects. *Semin Dial* 16: 85–94, 2003
6. Wheeler DC, Townend JN, Landray MJ: Cardiovascular risk factors in predialysis patients: Baseline data from the Chronic Renal Impairment in Birmingham (CRIB) study. *Kidney Int Suppl* 63[Suppl 84]: S201–S203, 2003
7. Mitsnefes MM, Daniels SR, Schwartz SM, Meyer RA, Khoury P, Strife CF: Severe left ventricular hypertrophy in pediatric dialysis: Prevalence and predictors. *Pediatr Nephrol* 14: 898–902, 2000
8. Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, Klag MJ: Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: The CHOICE Study. *J Am Soc Nephrol* 13: 1918–1927, 2002
9. Gruppen MP, Groothoff JW, Prins M, van der Wouw P, Offringa M, Bos WJ, Davin JC, Heymans HS: Cardiac disease in young adult patients with end-stage renal disease since childhood: A Dutch cohort study. *Kidney Int* 63: 1058–1065, 2003
10. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 322: 1561–1566, 1990
11. Silberberg JS, Barre PE, Prichard SS, Sniderman AD: Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int* 36: 286–290, 1989
12. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Ciacone G, Stancanelli B, Catalioto A, Malatino LS: Left ventricular mass monitoring in the follow-up of dialysis patients: Prognostic value of left ventricular hypertrophy progression. *Kidney Int* 65: 1492–1498, 2004
13. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE: Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 47: 186–192, 1995
14. Levin A, Singer J, Thompson CR, Ross H, Lewis M: Prevalent left ventricular hypertrophy in the predialysis population: Identifying opportunities for intervention. *Am J Kidney Dis* 27: 347–354, 1996
15. 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* 50: 998–1006, 1996
16. 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* 107: 864–868, 2003
17. Wuhl E, Mehls O, Schaefer F; ESCAPE trial group: Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure. *Kidney Int* 66: 768–776, 2004
18. de Simone G, Mureddu G, Greco R, Scalfi L, Del Puente AE, Franzese A, Contaldo F, Devereux RB: Relations of left ventricular geometry and function to body composition in children with high casual blood pressure. *Hypertension* 30: 377–382, 1997
19. Sahn DJ, DeMaria A, Kisslo J, Weyman A: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 58: 1072–1083, 1978
20. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux RB, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, Silverman NH, Tajik AJ: Recommendations for quantitation of the left ventricle by two-dimensional

echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 2: 358–367, 1989
21. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N: Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 57: 450–458, 1986
22. de Simone G, Muiesan ML, Ganau A, Longhini C, Verdeccia P, Palmieri V, Agabiti-Rosei E, Mancia G: Reliability and limitations of echocardiographic measurement of left ventricular mass for risk stratification and follow-up in single patients: The RES trial. Working Group on Heart and Hypertension of the Italian Society of Hypertension. Reliability of M-mode Echocardiographic Studies. *J Hypertens* 17: 1955–1963, 1999
23. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH: Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 20: 1251–1260, 1992
24. Daniels SR, Kimball TR, Morrison JA, Khoury P, Meyer RA: Indexing left ventricular mass to account for differences in body size in children and adolescents without cardiovascular disease. *Am J Cardiol* 76: 699–701, 1995
25. de Simone G, Daniels SR, Kimball TR, Roman MJ, Romano C, Chinali M, Galdeirsi M, Devereux RB: Evaluation of concentric left ventricular geometry in humans: Evidence for age-related systematic underestimation. *Hypertension* 45: 64–68, 2005
26. Teichholz LE, Kreulen T, Herman MV, Gorlin R: Problems in echocardiographic volume determinations: Echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 37: 7–11, 1976
27. Wühl E, Witte K, Soergel M, Mehls O, Schaefer F: Distribution of 24-h ambulatory blood pressure in children: Normalized reference values and role of body dimensions. German Working Group on Pediatric Hypertension. *J Hypertens* 20: 1995–2007, 2002
28. Schwartz GJ, Brion LP, Spitzer A: The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children and adolescents. *Pediatr Clin North Am* 34: 571–590: 571–590, 1987
29. Prader A, Largo RH, Molinari L, Issler C: Physical growth in Swiss children from birth to 20 years of age. *Helv Paediatr Acta* 52: S1–S125, 1989
30. Schaefer F, Georgi M, Wuhl E, Scharer K: Body mass index and percentage fat mass in healthy German schoolchildren and adolescents. *Int J Obes Relat Metab Disord* 22: 461–469, 1998
31. Hanevold C, Waller J, Daniels S, Portman R, Sorof JM: International Pediatric Hypertension Association: The effects of obesity, gender, and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: A collaborative study of the International Pediatric Hypertension Association. *Pediatrics* 113: 328–333, 2004
32. Urbina EM, Gidding SS, Bao W, Pickoff AS, Berdusis K, Berenson GS: Effect of body size, ponderosity, and blood pressure on left ventricular growth in children and young adults in the Bogalusa Heart Study. *Circulation* 91: 2400–2406, 1995
33. de Simone G, Kizer J, Chinali M, Roman MJ, Bella JN, Best LG, Lee ET, Devereux RB: Normalization for body size and population attributable risk of left ventricular hypertrophy: The Strong Heart Study. *Am J Hypertens* 18: 191–196, 2005
34. Mitsnefes MM, Kimball TR, Border WL, Witt SA, Glascock BJ, Khoury PR, Daniels SR: Impaired left ventricular diastolic function in children with chronic renal failure. *Kidney Int* 65: 1461–1466, 2004
35. Tucker B, Fabbian F, Giles M, Thuraisingham RC, Raine AE, Baker LR: Left ventricular hypertrophy and ambulatory blood pressure monitoring in chronic renal failure. *Nephrol Dial Transplant* 12: 724–728, 1997
36. Grossman W, Jones D, McLaurin LP: Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest* 56: 56–64, 1975
37. Schaefer F, Mehls O: Hypertension in chronic kidney disease. In: *Pediatric Hypertension*, edited by Portman RJ, Sorof JM, Ingelfinger JR, Totowa, NJ, Humana Press, 2004, pp 371–387
38. Gardner JD, Brower GL, Janicki JS: Gender differences in cardiac remodeling secondary to chronic volume overload. *J Card Fail* 8: 101–107, 2002
39. Weinberg EO, Mirotsou M, Gannon J, Dzau VL, Lee RT, Pratt RE: Sex dependence and temporal dependence of the left ventricular genomic response to pressure overload. *Physiol Genomics* 12: 113–127, 2003
40. Alfakih K, Maqbool A, Sivananthan M, Walters K, Bainbridge G, Ridgway J, Balmforth AJ, Hall AS: Left ventricle mass index and the common, functional, x-linked angiotensin II type-2 receptor gene polymorphism (−1332 G/A) in patients with systemic hypertension. *Hypertension* 43: 1189–1194, 2004
41. van Kesteren CA, can Heugten HA, Lamers JM, Saxena PR, Schalekamp MA, Danser AH: Angiotensin II-mediated growth and antigrowth effects in cultured neonatal rat cardiac myocytes and fibroblasts. *J Mol Cell Cardiol* 29: 2147–2157, 2005
42. Li X, Li S, Ulusoy E, Chen W, Srinivasan SR, Berenson GS: Childhood adiposity as a predictor of cardiac mass in adulthood: The Bogalusa Heart Study. *Circulation* 110: 3488–3492, 2004
43. Fox E, Taylor H, Andrew M, Han H, Mohamed E, Garrison R, Skelton T: Body mass index and blood pressure influences on left ventricular mass and geometry in African Americans: The Atherosclerotic Risk In Communities (ARIC) Study. *Hypertension* 44: 55–60, 2004
44. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, Burgess E, Jindal K, Barrett B, Singer J, Djurdjev O: Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 34: 125–134, 1999
45. Amann K, Wiest G, Klaus G, Ritz E, Mall G: A role of parathyroid hormone for the activation of cardiac fibroblasts in uremia. *J Am Soc Nephrol* 4: 1814–1819, 1994
46. Pecoits-Filho R, Lindholm B, Stenvinkel P: The malnutrition, inflammation and atherosclerosis (MIA) syndrome—The heart of the matter. *Nephrol Dial Transplant* 17[Suppl 18]: 28–31, 2002
47. Wang AY, Wang M, Woo J, Lam CW, Lui SF, Li PK, Sanderson JE: Inflammation, residual kidney function, and cardiac hypertrophy are interrelated and combine adversely to enhance mortality and cardiovascular death risk

of peritoneal dialysis patients. *J Am Soc Nephrol* 15: 2186–2194, 2004
48. Oberg BP, McMenamin E, Lucas FL, McMonagle E, Morrow J, Ikizler TA, Himmelfarb J: Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. *Kidney Int* 17: 229–232, 2004
49. Beddhu S: The body mass index paradox and an obesity, inflammation, and atherosclerosis syndrome in chronic kidney disease. *Semin Dial* 17: 229–232, 2004
50. Olsen MH, Hjerkinn E, Wachtell K, Hoieggen A, Bella JN, Nesbitt SD, Fossum E, Kjeldsen SE, Julius S, Ibsen H: Are left ventricular mass, geometry and function related to vascular changes and/or insulin resistance in long-standing hypertension? ICARUS: A LIFE substudy. *J Hum Hypertens* 17: 305–311, 2003
51. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM: Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 38: 938–942, 2001
52. Nitta K, Akiba T, Uchida K, Otsubo S, Otsubo Y, Takei T, Ogawa T, Yumura W, Kabaya T, Nihei H: Left ventricular hypertrophy is associated with arterial stiffness and vascular calcification in hemodialysis patients. *Hypertens Res* 27: 47–52, 2004
53. Litwin M, Wühl E, Jourdan C, Trelewicz J, Niemirska A, Fahr K, Jobs K, Grenda R, Wawer ZT, Rajszys P, Troger J, Schaefer F: Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. *J Am Soc Nephrol* 16: 1494–1500, 2005