Cardiac Geometry in Children Receiving Chronic Peritoneal Dialysis: Findings from the International Pediatric Peritoneal Dialysis Network (IPPN) Registry

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Summary

Background and objectives Left ventricular hypertrophy (LVH) is an independent risk factor and an intermediate end point of dialysis-associated cardiovascular comorbidity. We utilized a global pediatric registry to assess the prevalence, incidence, and predictors of LVH as well as its evolution in the longitudinal follow-up in dialyzed children.

Design, setting, participants, & measurements Cross-sectional echocardiographic, clinical, and biochemical data were evaluated in 507 children on peritoneal dialysis (PD), and longitudinal data were evaluated in 128 patients. The 95th percentile of LV mass index relative to height age was used to define LVH.

Results The overall LVH prevalence was 48.1%. In the prospective analysis, the incidence of LVH developing *de novo* in patients with normal baseline LV mass was 29%, and the incidence of regression from LVH to normal LV mass 40% per year on PD. Transformation to and regression from concentric LV geometry occurred in 36% and 28% of the patients, respectively. Hypertension, high body mass index, use of continuous ambulatory peritoneal dialysis, renal disease other than hypo/dysplasia, and hyperparathyroidism were identified as independent predictors of LVH. The use of renin-angiotensin system (RAS) antagonists and high total fluid output (sum of urine and ultrafiltration) were protective from concentric geometry. The risk of LVH at 1 year was increased by higher systolic BP standard deviation score and reduced in children with renal hypo/dysplasia.

Conclusions Using height-adjusted left ventricular mass index reference data, LVH is highly prevalent but less common than previously diagnosed in children on PD. Renal hypo/dysplasia is protective from LVH, likely because of lower BP and polyuria. Hypertension, fluid overload, and hyperparathyroidism are modifiable determinants of LVH.

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Introduction

Cardiovascular disease is an increasingly recognized issue in children with end stage renal disease (1–3). The reported incidence of cardiovascular deaths among dialyzed children in the United States has increased within the past 14 years from 17.7 to 23.4 deaths/1000 patient-years (4). The excessive incidence of dialysis-associated cardiovascular disease results from an accumulation of conventional and uremia-related risk factors (5–7). Left ventricular hypertrophy (LVH) is both an independent risk factor and an intermediate end point of cardiovascular morbidity in patients with chronic kidney disease (CKD) (2,8). Previous studies reported LVH prevalence rates ranging from 30% in mild to moderate CKD (9) to 73% in dialyzed children (7,10,11). Both pressure-related concentric and volume-related eccentric LVH appear to be common in children with CKD (7,10,11). However, pediatric studies face the difficulty of accounting for the physiologic changes in cardiac geometry that occur during growth. The commonly used diagnostic criterion for LVH is an allometric index normalizing LV mass to statural height raised to the power of 2.7 (LVMI), which, however, is not independent of body size at young age (12). Age- and gender-specific percentile charts for LVMI have only recently become available (13). Another level of complexity is added by the variable degree of growth retardation observed in children with end-stage renal disease, which invalidates referencing to age-matched healthy children with normal height. Matching for height age rather than chronological age provides an approximative solution to this problem.

The International Pediatric Peritoneal Dialysis Net-

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work (IPPN) collects detailed prospective clinical and echocardiographic information from a large cohort of children on chronic peritoneal dialysis (PD). We aimed to assess the prevalence, incidence, and risk factors of LVH in this cohort by using the Khoury reference charts adjusted to height age.

Materials and Methods

Data Collection

Data input to the IPPN registry is performed exclusively via an Internet-based web platform (www.pedpd.org). Data pertaining to basic patient characteristics are recorded at entry. Somatometric, clinical, and biochemical findings as well as data on PD treatment modalities and medications are submitted every 6 months. In addition, the results of echocardiographic investigations and 24-hour ambulatory BP monitoring (ABPM) are recorded.

In the echocardiogram input section of the registry, left ventricular end-diastolic diameter (LVEDD), posterior wall thickness (PWT), and diastolic interventricular septal thickness (IVST), as well as height and office BP at the time of the echocardiographic study, are reported. The echocardiographic data are evaluated according to the guidelines of the American Society of Echocardiography (14). The echocardiographic examinations analyzed in this study were usually scheduled close to the clinic visit (mean time lag, 2 ± 3 months; NS difference from 0) and ABPM studies (mean time lag: −1 ± 3 months, NS difference from 0).

Data protection is ensured by pseudonymized data input. The data are automatically checked for plausibility and completeness. The registry protocol was approved by the ethical committees/institutional review boards as required at each participating center. Written parental consent and, whenever appropriate, patient assent was obtained.

Definitions and Statistics

LV mass was calculated according to the formula by Devereux: LV mass (g) = 0.8 * (1.04 ((LVEDD + PWT + IVST)^3 − (LVEDD)^3) + 0.6) (15). LV mass was indexed for the power of its allometric or growth relation with height (height in $m^{2.7}$) (12). For the definition of LVH, LVMI exceeding the 95th percentile for gender and age in normal children and adolescents provided by Khoury *et al.* (13) was used but substituting chronological age by height age, *i.e.*, the age of a child of the same height growing at the 50th height percentile. Relative wall thickness was defined as RWT = PWT + IVST/LVEDD. RWT was normalized using the formula RWTa = RWT − 0.005 * (age-10) as proposed by de Simone *et al.* (16), but using height age rather than chronological age to account for growth retardation. The 95th percentile of the normalized RWT was used as cutoff value defining concentric geometry (16).

BP values were the averages of two consecutive office measurements 5 minutes apart and were recorded at the first data entry and each 6-month update. Office hypertension was defined by office BP (BP exceeding the 95th percentile of systolic and/or diastolic casual BP for age, height, and gender (17). ABPM data were recorded in patients taller than 120 cm. The diagnosis of hypertension by ABPM was made when 24-hour time-integrated mean arterial pressure exceeded the 95th percentile (18). BP data were also expressed as standard deviation scores (SDSs) indexed to gender and height (18). In the longitudinal part of the study, time-integrated patient-specific mean values were calculated for each variable according to individual observation times.

The data were checked for normal distribution by the Kolmogorov-Smirnoff test. Differences in group means (log-transformed in case of non-Gaussian distribution) were assessed by *t* test, Wilcoxon signed-rank test, or ANOVA followed by the Student-Newman-Keuls test. Differences in proportions were assessed using the chi-squared test. Associations were assessed by Spearman correlation analysis and univariate and multivariate logistic regression analyses. A sequential strategy was applied to identify multivariate predictors of LVH, concentric LVH, and persistent/*de novo* LVH. In a first step, an exploratory univariate logistic regression analysis was performed, expressing some factors alteratively as continuous or dichotomous variables. The following set of parameters was examined: age, PD duration, gender, height SDS, body mass index (BMI) SDS, obesity (BMI >95th percentile), malnutrition (BMI <5th percentile), systolic and diastolic BP SDS, controlled/uncontrolled/any hypertension, automated PD *versus* other PD modalities, hemoglobin, significant anemia (hemoglobin, <10 g/dl), serum bicarbonate, metabolic acidosis (serum bicarbonate, <20 mmol/L), parathyroid hormone (PTH), hyperparathyroidism this must be (>200 pg/ml), hyperphosphatemia oligoanuria (using 100, 300, or 500 ml/m^2 per day as arbitrary cutoffs), daily ultrafiltration, total daily fluid output (urine + ultrafiltration), total PD fluid turnover, underlying renal disease (congenital anomalies of the kidneys and urinary tract [CAKUT] *versus* others, glomerulopathies *versus* others), use of renin-angiotensin system (RAS) antagonists, calcium-channel blockers, beta blockers, and diuretics. In the second step, those variables that showed significant or near significant association ($P < 0.10$) by univariate analysis were utilized for multivariate model building.

To account for potential time dependence of effect sizes, the logistic regression analysis of the longitudinal study was adjusted for the time interval between the echocardiographic examinations (WEIGHT statement in PROC LOGISTIC of SAS software). The significance criteria to enter and retain variables during the stepwise multiple logistic regression procedure were 0.10 and 0.05, respectively. The data were analyzed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient and Treatment Characteristics

507 children and adolescents (54% boys, aged 3 months to 19 years) from 55 centers around the globe in whom at least one echocardiogram was reported to the IPPN between April 2007 and February 2010 were analyzed. The underlying kidney disorders included CAKUT (renal hypo/dysplasia with or without obstruction or reflux) in 45%, glomerulopathies in 24.4%, hemolytic uremic syndrome in 5.7%, nephropathy related to systemic diseases in 5.5%, polycystic kidney disease in 5.1%, tubulointerstitial/metabolic disorders in 3.0%, nephronophthisis in 2.8%, postischemic renal disease in 2.4%, and other/unknown in

6.1% of the patients. 24% of patients were treated in Latin American, 17% in North American, 12% in Turkish, 30% in other European, and 17% in Asian centers. The ethnic background was Caucasian in 55%, East Asian in 20%, Hispanic in 17%, African or African American in 3%, and unspecified in 5%. For 371 patients, PD was the first mode of renal replacement therapy; 80 patients had been transferred from hemodialysis (HD); and 54 had returned to dialysis after kidney transplant failure. There was no difference in LVH prevalence between patients transferred from HD or transplanted and those who had no previous HD or transplant history. Further demographic, biochemical, and PD-related information is provided in Table 1.

Office systolic BP was elevated in 162 (32%), and diastolic BP in 146 (29%) patients. Hypertension was present in 134 patients (26.4%) with and in 68 patients (13.4%) without antihypertensive medication. In addition, 152 patients (30%) receiving antihypertensive treatment had office normotension (controlled hypertension), and 153 patients (30.2%) were normotensive without medication. Medications included RAS antagonists in 37%, calcium-channel blockers in 34%, beta blockers in 17%, and diuretics in 10% of the patients. These were administered either as monotherapy (26%) or in combination (30%).

128 patients underwent a second echocardiographic examination after a median of 12 (range, 6 to 18) months. The baseline clinical and biochemical characteristics of this longitudinal cohort did not differ from those of the cross-sectional sample (Table 1).

Prevalence and Incidence of Abnormal LV Geometry

The prevalence of LVH and the distribution of LV geometry is given in Table 1 both for the cross-sectional and the longitudinal sample. LVH was present in 48% of all patients (32% concentric and 16% eccentric LVH), and concentric remodeling was present in 27% of all patients. Although the overall prevalence of LVH and concentricity did not change significantly during follow-up, dynamic changes in LV mass and geometry occurred in a large proportion of subjects (Figure 1). Among the 70

Table 1. Baseline clinical, and biochemical characteristics of 507 pediatric CPD patients undergoing echocardiography at study entry and of a subgroup of 128 children with follow-up echocardiogram

	Cross-sectional Sample (n = 507)	Longitudinal Cohort (n = 128)
Age (years)	9.8 ± 5.9	9.6 ± 5.8
Male patients (%)	54%	52%
Height SDS	−2.2 ± 1.7	−2.3 ± 1.8
BMI SDS	0.11 ± 1.3	0.07 ± 1.42
Office systolic blood pressure SDS	0.99 ± 1.41	0.84 ± 1.39
Office diastolic blood pressure SDS	0.94 ± 1.22	0.75 ± 1.13
24-h mean arterial pressure SDS	1.29 ± 2.56[a]	0.54 ± 2.07[b]
Residual urine output (L/m^2/24 h)	0.50 (1.09)	0.52 (1.05)
PD duration (years)	2.2 ± 2.0	2.5 ± 1.7
PD modality (CAPD/NIPD/CCPD/IPD) (%)	17/36/45/2	18/39/42/1
Total fluid turnover (L/m^2/day)	6.69 ± 1.59	6.6 ± 3.3
PD fluid dextrose concentration (%)	1.89 ± 0.55	1.81 ± 0.50
Average ultrafiltration (L/m^2/24 h)	0.60 ± 0.55	0.57 ± 0.36
Hemoglobin (g/dl)	11.2 ± 1.7	11.3 ± 1.7
Serum albumin (g/L)	37.4 ± 6.2	37.8 ± 6.2
Serum inorganic phosphorus (mg/dl)	5.51 ± 1.58	5.51 ± 1.25
Serum PTH (pg/ml)	201 (401)	173 (331)
Dialytic Kt/V urea	2.25 ± 2.21[c]	2.02 ± 0.83[d]
Renal Kt/V urea	1.03 ± 1.31[c]	1.14 ± 1.37[d]
Total Kt/V urea	3.09 ± 2.36[c]	2.97 ± 1.34[d]
Left ventricular mass index (g/m$^{2.7}$)	51.8 ± 29.2	49.9 ± 26.1
Relative wall thickness (%)	0.42 ± 0.15	0.43 ± 0.15
Adjusted relative wall thickness (%)	0.43 ± 0.16	0.44 ± 0.16
Left ventricular geometry		
normal	125 (25%)	34 (27%)
concentric remodeling	138 (27%)	36 (28%)
concentric LVH	165 (32%)	42 (33%)
eccentric LVH	79 (16%)	16 (12%)

The data are given as means ± SD, median (interquartile range) or percentage as appropriate. None of the listed variables differed significantly between the longitudinal subgroup and the total cohort. CPD, chronic peritoneal dialysis; PD, peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; NIPD, nightly intermittent peritoneal dialysis; CCPD, continuous cyclic peritoneal dialysis; IPD, intermittent peritoneal dialysis; PTH, parathyroid hormone; LVH, left ventricular hypertrophy.
[a]Available in 71 patients.
[b]Available in 20 patients.
[c]Available in 213 patients.
[d]Available in 58 patients.

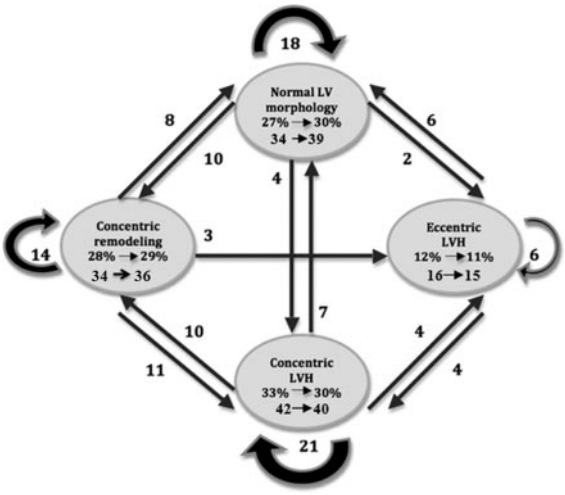

Figure 1. | Evolution of left ventricular geometry in 128 chronic peritoneal dialysis patients with follow-up echocardiogram after 12 ± 4 months. The percentage figures indicate prevalence rates at first and second examination. Straight arrows indicate the numbers of patients changing between categories from first to second examination. Curved arrows indicate the numbers of the patients remaining in the same geometric category. LV, left ventricle; LVH, left ventricle hypertrophy.

patients in the longitudinal study without LVH at first observation, 20 developed LVH (15 concentric and five eccentric). Of the 58 subjects with prevalent LVH, 23 regressed to either concentric remodeling ($n = 10$) or normal LV morphology ($n = 13$) (Figure 1). These figures translate into a 29% incidence of *de novo* LVH and a 40% incidence of LVH regression per year on dialysis. Concentric transformation of LV geometry developed in 18 patients (10 remodeling and eight LVH) or 36%, and reversion from concentric geometry developed in 22 patients (28%).

Univariate and Multivariate Associations with LVH

The factors associated with LVH in the cross-sectional analysis are summarized in Table 2. Patients with underlying CAKUT were significantly less likely to present with LVH than patients with other nephropathies (55% *versus* 41%, $P < 0.005$). Children with BMI exceeding the 85th percentile showed a higher prevalence of LVH than lighter subjects (69% *versus* 49% $P < 0.01$), with a positive correlation between BMI SDS and LVMI ($r = 0.18$, $P < 0.0001$). The use of automated PD modalities was associated with a trend toward lower prevalence of LVH when compared with the use of continuous ambulatory peritoneal dialysis (CAPD) (46% *versus* 58%, $P = 0.06$). Hypertension increased the risk of LVH. In addition, LVH was associated with oligoanuria (daily urine output <0.5 L/m^2 BSA), anemia (hemoglobin <10 g/dl), hyperphosphatemia (>5.5 mg/dl for adolescents and >6 mg/dl for children 1 to 12 years of age) (19), and hyperparathyroidism as best defined by PTH >200 pg/ml.

Logistic regression analysis was performed to identify independent predictors of LVH, including age, gender, dialysis vintage, dialysis modalities, underlying renal disease, residual renal function, BP/hypertension, BMI SDS/obesity/malnutrition, anemia, hyperparathyroidism, and hyperphosphatemia. Systolic hypertension, high BMI SDS, hyperparathyroidism, and lower urine output emerged as independent risk factors for the presence of LVH (Table 2).

Factors Associated with Concentric LV Geometry

Patients with concentric geometry were slightly younger (9.1 ± 6.0 *versus* 10.6 ± 5.7 years, $P < 0.01$) and had a higher standardized 24-hour mean arterial pressure (1.95 ± 2.65 *versus* 0.75 ± 2.37 SDS, $P < 0.05$), although office BP did not differ significantly. Daily urine (0.61 ± 0.66 *versus* 0.75 ± 0.77 L/m^2, $P < 0.05$) and total fluid output (urine output + ultrafiltration volume; 1.21 ± 0.60 *versus* 1.39 ± 0.93 L/m^2, $P < 0.05$), as well as serum albumin (36.6 ± 6.6 *versus* 38.2 ± 5.7 g/L, $P < 0.01$), were

Table 2. Univariate and multivariate logistic regression analyses of factors associated with LVH in 507 children

	Univariate		Multivariate (full model)		Multivariate (stepwise selection)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Systolic hypertension	2.01 (1.38 to 2.94)	<0.01	1.68 (1.0 to 2.81)	0.05	1.93 (1.25 to 2.98)	<0.01
BMI >95th percentile	2.06 (1.23 to 3.46)	<0.01	2.49 (1.35 to 4.62)	<0.01	2.27 (1.25 to 4.12)	<0.01
Hyperparathyroidism (PTH >200 pg/ml)	1.65 (1.16 to 2.34)	<0.01	1.80 (1.19 to 2.72)	<0.01	1.87 (1.25 to 2.78)	<0.01
Age (years)	1.04 (1.01 to 1.07)	0.01	1.04 (1.00 to 1.08)	0.06	1.05 (1.01 to 1.09)	<0.01
Urine output (L/m^2/day)	0.67 (0.51 to 0.89)	<0.01	0.96 (0.93 to 1.00)	0.03	0.96 (0.93 to 0.99)	<0.01
CAKUT	0.58 (0.41 to 0.82)	<0.01	0.85 (0.54 to 1.32)	0.05	—	—
Hyperphosphatemia	1.67 (1.17 to 2.37)	<0.01	1.30 (0.82 to 2.07)	0.26	—	—
Diastolic hypertension	1.57 (1.07 to 2.31)	0.02	1.22 (0.71 to 2.12)	0.47	—	—
Anemia (hemoglobin <10 g/dl)	1.55 (1.03 to 2.31)	0.03	1.13 (0.71 to 1.81)	0.60	—	—
Automated PD	0.64 (0.40 to 1.01)	0.06	0.61 (0.37 to 1.02)	0.06	—	—
Male gender	0.73 (0.51 to 1.04)	0.08	1.41 (0.94 to 2.13)	0.10	—	—

The numbers are odds ratios and 95% confidence intervals. LVH, left ventricular hypertrophy; OR, odds ratio; CI, confidence interval; BMI, bodymass index; PTH, parathyroid hormone; CAKUT, congenital anomalies of the kidneys and urinary tract; PD, peritoneal dialysis.

Table 3. Features of patients with persistence of or progression to LVH among 128 children followed longitudinally

	Normal LV mass maintained/achieved	Persistent/*de novo* LVH
n	73	55
Age (years)	9.5 ± 5.9	9.7 ± 5.6
Dialysis vintage (years)	2.5 ± 1.8	2.6 ± 1.6
CAKUT	66%	40%[b]
Deviation from estimated dry weight (%)	1.3 ± 1.6	2.6 ± 1.6[c]
Mean daily urine output (ml/m^2)	0.75 ± 0.79	0.44 ± 0.61[d]
Mean daily ultrafiltration (ml/m^2)	0.56 ± 0.38	0.71 ± 0.34[d]
Hypertension (controlled or uncontrolled)[a]	57%	77%[c]
Mean systolic blood pressure (mmHg)	104 ± 15	111 ± 15[c]
SDS	0.52 ± 1.21	1.25 ± 1.22[b]
Mean diastolic blood pressure (mmHg)	63 ± 12	67 ± 12[d]
SDS	0.59 ± 0.92	0.94 ± 1.06[d]
Mean hemoglobin (g/dl)	11.2 ± 1.1	10.8 ± 1.0[d]
Mean serum albumin (g/L)	38.7 ± 5.5	36.6 ± 5.3[d]

LVH, left ventricular hypertrophy; CAKUT, congenital anomalies of the kidneys and urinary tract; SDS, standard deviation score.
[a]Uncontrolled hypertension, elevated blood pressure irrespective of antihypertensive treatment; controlled hypertension, normotensive blood pressure while on antihypertensive medication.
[b]$P < 0.005$.
[c]$P < 0.01$.
[d]$P < 0.05$.

lower in children with concentric LV geometry. Also, concentric LV geometry tended to be less common in patients using RAS antagonists (46% *versus* 55%, $P = 0.03$).

Whereas multivariate regression analysis did not identify any independent predictors of concentric geometry, the likelihood of presenting with concentric as opposed to eccentric LVH was lower with the use of RAS antagonists (odds ratio [OR], 0.51; 95% confidence interval [CI], 0.28 to 0.92; $P = 0.02$) and, at borderline significance, by a high fluid output (OR, 0.63; 95% CI, 0.37 to 1.06; $P = 0.08$).

Predictors of Longitudinal Change in LV Morphology

The factors associated with the evolution of LV mass on dialysis are indicated in Table 3, where time-averaged measures in children who maintained or achieved normal LV morphology during follow-up are compared with those who showed persistent or *de novo* LVH. The latter group was characterized by a lower prevalence of CAKUT, lower urine output incompletely compensated by higher ultrafiltration volume, higher BP, and lower hemoglobin and albumin levels. Systolic BP SDS was highest in patients with LVH (persistent LVH or progressed to LVH), lowest in children with persistently normal LV morphology, and intermediate in those regressing from LVH during follow-up (Figure 2). The risk of persistent or *de novo* LVH was independently associated with systolic hypertension (OR, 1.51; 95% CI, 1.09 to 2.07; $P = 0.01$ *versus* normotension) and obesity (OR, 3.95; 95% CI, 1.03 to 15.23; $P = 0.04$ *versus* normal weight), whereas children with CAKUT had a significantly lower risk of persistent or *de novo* LVH (OR, 0.36; 95% CI, 0.16 to 0.79; $P = 0.04$ *versus* other diagnoses) (Table 4).

Discussion

In this study, we utilized the largest cohort of dialyzed children to investigate the prevalence and evolution of LVH and to perform a comprehensive risk factor analysis of risk factors for abnormal LV geometry in pediatric CPD patients. Using the Khoury LVMI reference charts relative to height age, the overall prevalence of LVH was 48% in our study, which is substantially lower than previously reported. Previous pediatric LVH prevalence estimates using a fixed LVMI cutoff were 68% to 73% in the PD (7,11,20) and 82 to 85% in the HD populations (20,21).

In the prospective part of our analysis, we observed a high incidence of progression to but also regression from LVH despite little net change in overall prevalence rates. Hence, our findings indicate a remarkable plasticity of

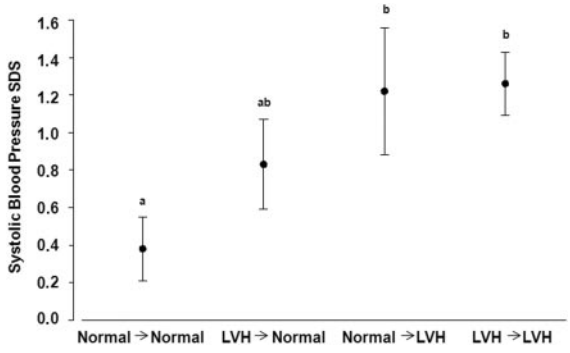

Figure 2. | Average systolic BP standard deviation score (SDS) during follow-up in 50 children without left ventricular hypertrophy (LVH), 23 children regressing from LVH to normal left ventricular (LV) mass index, 20 children progressing to LVH, and 35 children with persistent LVH during prospective echocardiographic monitoring. BP is expressed as SDS to account for patient age, height, and gender. The bars are the means ± SEMs. Superscript letters denote significance of between-group differences; groups sharing the same letter do not differ significantly at $P < 0.05$.

Table 4. Multivariate logistic regression analysis of factors associated with persistent/*de novo* LVH in 128 children followed longitudinally

	Multivariate (Full Model)		Multivariate (Stepwise Selection)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
BMI >95th percentile	4.51 (1.07 to 18.9)	0.04	3.95 (1.03 to 15.23)	0.04
Systolic hypertension	1.70 (1.0 to 2.90)	0.05	1.51 (1.09 to 2.07)	0.01
CAKUT	0.32 (0.13 to 0.84)	0.04	0.36 (0.16 to 0.79)	0.04
Hyperparathyroidism (PTH >200 pg/ml)	1.35 (0.53 to 3.44)	0.53	—	—
Age (years)	1.04 (0.94 to 1.14)	0.44	—	—
Automated PD	0.69 (0.29 to 0.95)	0.51	—	—
Urine output (L/m^2/day)	0.79 (0.53 to 2.07)	0.31	—	—
Diastolic hypertension	0.73 (0.37 to 1.43)	0.35	—	—
Anemia (hemoglobin <10 g/dl)	1.41 (0.51 to 3.89)	0.51	—	—
Hyperphosphatemia	0.63 (0.23 to 1.68)	0.35	—	—
Male gender	1.47 (0.62 to 3.47)	0.51	—	—

LVH, left ventricular hypertrophy; OR, odds ratio; CI, confidence interval; CAKUT, congenital anomalies of the kidneys and urinary tract; PTH, parathyroid hormone; PD, peritoneal dialysis.

children's hearts in response to changing hemodynamic conditions.

The most important determinant of LVH prevalence, incidence, and persistence was BP. Office hypertension was present in 39% of the children in this global cohort, not dissimilar from the 53% prevalence reported by the North American Pediatric Renal Trials and Collaborative Studies registry (22). The risk of LVH was more than doubled in children with systolic hypertension; during follow-up, systolic office BP was 7 mm higher in children who developed or retained LVH than in children who regressed to or maintained normal LV morphology. Surprisingly, the association of BP with concentric LV geometry was less conspicuous and significance was limited to 24-hour BP results. The relationship of LV concentricity with BP may have been partially concealed by the common use of RAS antagonists, the use of which was associated with a reduced rate of concentric LVH. RAS antagonists may attenuate myocardial remodeling in a partially BP-independent manner by antagonizing the effects of locally formed angiotensin II, resulting in reduced myocyte hypertrophy, fibroblast proliferation, matrix formation, and myocardial fibrosis (23–25). Volume status was the second most important parameter affecting the risk of LVH in dialyzed children.

Apart from direct associations of LVH with residual diuresis and estimated fluid excess, several parameters indirectly linked to volume status were closely correlated with LVH. These included the diagnosis of CAKUT, disorders characterized by increased salt and water losses. Also, patients undergoing automated PD, which has a higher fluid removal capacity than CAPD, appeared partially protected. Wang *et al.* (6) demonstrated that residual renal function is an important independent predictor of LVMI and also one of the main determinants of mortality in adult PD patients. Moreover, a rapid decline in residual renal function has been suggested as a powerful prognostic factor in adults on long-term PD (26). In children on PD, loss of residual renal function also predicted diastolic dysfunction (7).

In addition to the effects of pressure and volume, several nonhemodynamic factors affect LV mass in CKD. We identified a high BMI as a powerful independent risk factor for LVH. This association has also been demonstrated in community-based studies (27,28). BMI is a strong determinant of LV mass even within the normal range of body weight and in the absence of hypertension (27). This effect may relate primarily to the relationship between BMI and lean body mass. In nonobese populations such as the patients studied here, lean body mass contributes more to BMI than fat mass (29). LV mass and cardiac output is physiologically adapted to metabolic activity, which in turn is a function of lean body mass (12,30,31). The observed independent association of LVH with BMI SDS is likely to reflect this physiologic association, which is incompletely accounted for by the normalization of LV mass to height.

Furthermore, we observed a link between abnormalities of mineral metabolism and LVH, as described previously (32,33). PTH exerts trophic effects on cardiac myocytes and stimulates cardiac fibroblasts and intramyocardial arterial wall thickening, resulting in LVH and myocardial fibrosis (34,35). These effects are clinically relevant as evident from the well documented BP independent association of PTH with LVH in primary and secondary hyperparathyroidism (32,33,36). The most distinctive PTH cutoff level, independently predicting a 73% increase of LVH risk, was 200 ng/ml, suggesting that the cardiotrophic actions of PTH are operative even at moderate degrees of hyperparathyroidism. This interpretation is supported by recent findings from a population-based study in Norway, which found sharp increases in the prevalence of LVH and diastolic dysfunction when PTH levels exceeded the normal range (37,38).

We are aware of the limitations of this global cohort study on the basis of a voluntary registry collaboration. Although data collection was strictly prospective, it was not possible to standardize the echocardiographic, BP, and laboratory technologies throughout 55 centers. This methodological variability may have limited the sensitivity of identifying correlates of LV mass. Also, it was not possible to obtain more refined

measures of fluid status and vascular morphology and function that would have allowed a more elaborate analysis and comprehensive insight into the mechanisms of dialysis-associated cardiovascular comorbidity. Notwithstanding these restrictions, our study represents significant progress in our understanding of LVH in children on PD. The use of percentile- and height-age-based LVMI referencing in a large, heterogeneous cohort of pediatric PD patients provides the most reliable estimates of LVH prevalence to date in this population. Showing consistent associations across any methodological and geographic variation, hypertension, fluid overload, and secondary hyperparathyroidism appear to be the most important determinants of LVH in dialyzed children. Notably, all of these factors are potentially modifiable by therapeutic efforts.

APPENDIX

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Franz Schaefer is a Consultant for Amgen, Genzyme, Mitsubishi Pharmaceuticals, Otsuka, and Takeda. Bradley A. Warady is a Consultant for Amgen, Abbott, and Genzyme and has received speakers' honoraria from Genentech.

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