Defining Left Ventricular Hypertrophy in Children on Peritoneal Dialysis

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Summary

Background and objectives Left ventricular hypertrophy (LVH) is an important end point of dialysis-associated cardiovascular disease. The objective of this study was to evaluate the effect of different pediatric reference systems on the estimated prevalence of LVH in children on chronic peritoneal dialysis (CPD).

Design, setting, participants, & measurements Echocardiographic studies in 507 pediatric CPD patients from neonatal age to 19 years were collected in 55 pediatric dialysis units around the globe. We compared the prevalence of LVH on the basis of the traditional cutoff of left ventricular mass (LVM) index (>38.5 $g/m^{2.7}$) with three novel definitions of LVH that were recently established in healthy pediatric cohorts.

Results Application of the new reference systems eliminated the apparently increased prevalence of LVH in young children obtained by the traditional fixed LVM index cutoff currently still recommended by consensus guidelines. However, substantial differences of LVM distribution between the new reference charts resulted in a marked discrepancy in estimated LVH prevalence ranging between 27.4% and 51.7%.

Conclusions Although our understanding of the anthropometric determinants of heart size during childhood is improving, more consistent normative echocardiographic data from large populations of healthy children are required for cardiovascular diagnostics and research.

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Introduction

Notwithstanding the excessive long-term cardiovascular morbidity and mortality associated with childhood-onset chronic kidney disease (CKD) (1,2), the number of children dying from cardiovascular disease is small. Hence, cardiovascular research in pediatric CKD must focus on intermediate end points. Left ventricular hypertrophy (LVH) is one of the most consistent predictors of mortality in adults with CKD (3). The reported prevalence of LVH in children with CKD ranges from 17% to >80%, dependent mainly on the stage of disease (2,4–10).

However, the definition of LVH is a matter of ongoing controversy. When assessing left ventricular mass (LVM), age, gender, body size, and composition must be considered because metabolic demand and perfusion vary with stature and gender, determining the physiologic adaptation of heart size. The most commonly used method to express LVM in adults is an allometric index normalizing LVM to statural height raised to the power of 2.7 (the left ventricular mass index [LVMI]) (11). In adults, LVH is usually defined by an LVMI >51 $g/m^{2.7}$, a cutoff associated with increased cardiovascular morbidity and mortality (12). In children, cardiovascular outcome studies are lacking because of the low incidence of cardiovascular events. Therefore, the definition of LVH is based by convention upon the distribution of LVMI in the general pediatric population. Until recently, LVH in children used to be defined by the fixed LVMI partition value of 38.6 $g/m^{2.7}$, which defines the 95th percentile of LVMI distribution in healthy children and adolescents from 6 to 17 years of age (13). The age-independency of the LVMI has recently been questioned for infants and young children (14,15), and the use of height-specific percentile charts or SD scores (SDS) for LVMI has been advocated to establish the diagnosis of LVH in children (14,15).

The International Pediatric PD Network (IPPN) is a global consortium collecting detailed prospective information from a large cohort of children undergoing CPD. In most centers data collection includes echocardiographic measurements. Hence, the IPPN

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database provides a unique opportunity to reassess and compare the effect of different indexation methods and reference systems on the calculated prevalence of LVH.

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 peritoneal dialysis (PD) treatment modalities and medications are submitted every 6 months. Puberty status is assessed every 6 months by the Tanner scale.

In addition, the results of echocardiographic investigations and 24-hour ambulatory BP monitoring (ABPM) are recorded. In the echocardiography input section of the registry, left ventricular end-diastolic diameter (LVEDD), posterior wall thickness (PWT), and diastolic interventricular septal thickness (IVST) are reported. The echocardiographic input section is an optional field in the registry and it is completed whenever a patient has an echocardiographic assessment within 3 months from the 6-month clinical update.

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

Definitions and Statistics

LVM was calculated according to the formula by Devereux: $LVM\ (g) = 0.8\ \{1.04\ [(LVEDD + PWT + IVST)^3 - (LVEDD)^3] + 0.6\}$ (16).

The following definitions of LVH were compared: (*1*) LVMI exceeding 38.6 $g/m^{2.7}$ (13), (*2*) LVMI exceeding the 95th percentile for gender and chronological age according to Khoury *et al.* (15), (*3*) substituting chronological age by height age (*i.e.*, the age of a child of the same height growing at the 50th height percentile), and (*4*) LVM exceeding the 95th percentile (*i.e.*, LVM SDS > 1.645) according to the lambda-mu-sigma (LMS) reference charts provided by Foster *et al.* (14). Associations were assessed by Spearman correlation analysis and linear regression analysis. A P value of 0.05 was considered significant. Data were analyzed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Five-hundred seven children and adolescents (54% boys, aged 3 months to 19 years) from 55 centers for whom at least one echocardiography was reported to the IPPN between April 2007 and February 2010 were analyzed. Of the patients, 24% were treated in Latin American, 17% in North American, 12% in Turkish, 30% in other European, and 17% in Asian centers. Thirty-seven were infants <1 year (7.3%), 66 (13%) were children 1 to 2 years of age, 55 (11%) were 3 to 5 years old, 75 (15%) were 6 to 9 years old, 150 (29%) were 10 to 14 years old, 97 (19%) were 15 to 18 years old, and 27 (5%) were young adults older than 18 years of age. The median (interquartile range) cumulative time on dialysis at the time of study was 1.7 (1.93) years, the median height SDS was −2.08 (2.13), and the median body mass index (BMI) SDS was 0.21 (1.53).

Effect of Reference System on Diagnosis of LVH

Indexing LVM to height to the allometric power of 2.7 resulted in an inverse correlation with height in children shorter than 130 cm (Figure 1).

Figure 2, upper panel shows the increasing difference between chronological age and height age (*i.e.*, the age at which a given height corresponds to the 50th height percentile) as a result of growth failure in the children under study. Figure 2, lower panel illustrates the effect of referring to height age *versus* chronological age on LVMI percentile assignment.

The use of the height-specific LMS reference tables of Foster *et al.* yielded a widely scattered distribution of LVM SDS (mean ± SD: 0.27 ± 2.33) with 21% of measurements ranking below the 5th LVM percentile (Figure 3, upper panel). When referring to the Khoury tables, modified by substituting chronological age by height age, the fraction of measurements in the low normal range did not differ from expected (7% of measurements below the 10th percentile) (Figure 3, lower panel).

The overall LVH prevalence was 64.9% when using the traditional fixed LVMI criterion, 51.7% according to the 95th percentile of the Khoury reference charts based on age and gender, 48.1% when using height age with the same charts, and 27.4% using the 95th percentile of LVM for height according to the Foster tables. As expected, the prevalence of LVH calculated with the different reference

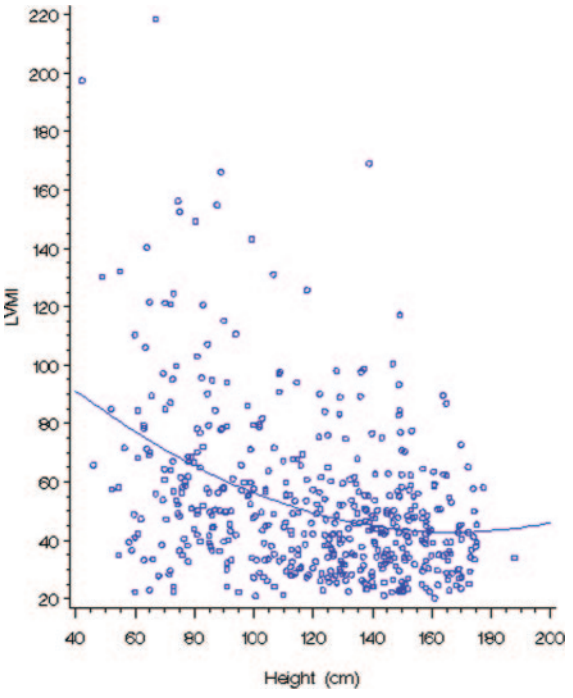


Figure 1. | Inverse correlation of left ventricular mass index (LVMI) with body height in 507 children on chronic peritoneal dialysis (CPD).

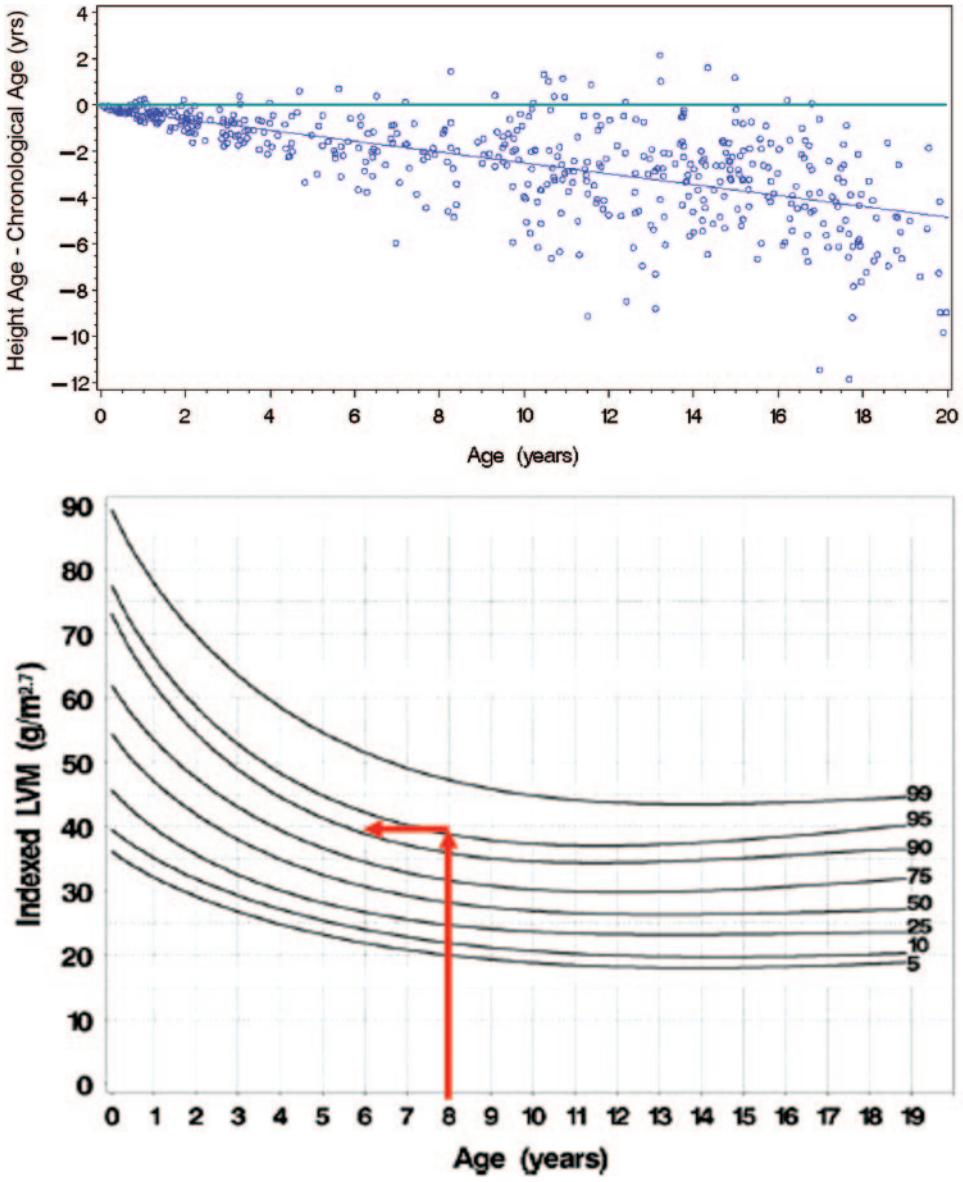


Figure 2. | Upper panel: Deviation of height age from chronological age in 507 children on CPD. Lower panel: Effect of reference to height age rather than chronological age on LVMI percentile assignment. At the age of 8 years, the mean height age in the CPD population is 6 years. As a consequence, an 8-year-old child with average growth retardation and LVMI at the 95th percentile for age will be ranked in the 90th LVMI percentile when referring to height age.

systems markedly differed with age (Figure 4). The fixed LVMI criterion yielded a much higher apparent LVH prevalence during the first 5 years of life than the age- or height-adjusted LVMI reference systems. When using the Khoury charts with chronological age, LVH prevalence was significantly higher in growth-retarded children (height SDS < -2) than in children of normal height (55.7 *versus* 47.3%, $P < 0.05$). This difference was attenuated when relating LVMI to height age (49.5% *versus* 46.5%, $P = 0.48$).

Discussion

In this study we utilized the largest series of echocardiographies collated in dialyzed children to date to examine the effect of using different reference systems on the apparent prevalence of LVH in this population.

Current consensus guidelines recommend indexing LVM to height to the power of 2.7 in pediatric subjects (13). These guidelines are based on studies performed in the early 1990s, when obesity was still less prevalent and different echocardiographic equipment and techniques were utilized.

In analogy to the findings of Foster *et al.* and Khoury *et al.* in healthy children (14,15), we observed a significant inverse relationship of this LVMI with body size in children shorter than 130 cm. Although we cannot rule out the possibility of more marked LVH in young as compared with older children on dialysis, it is most likely that the

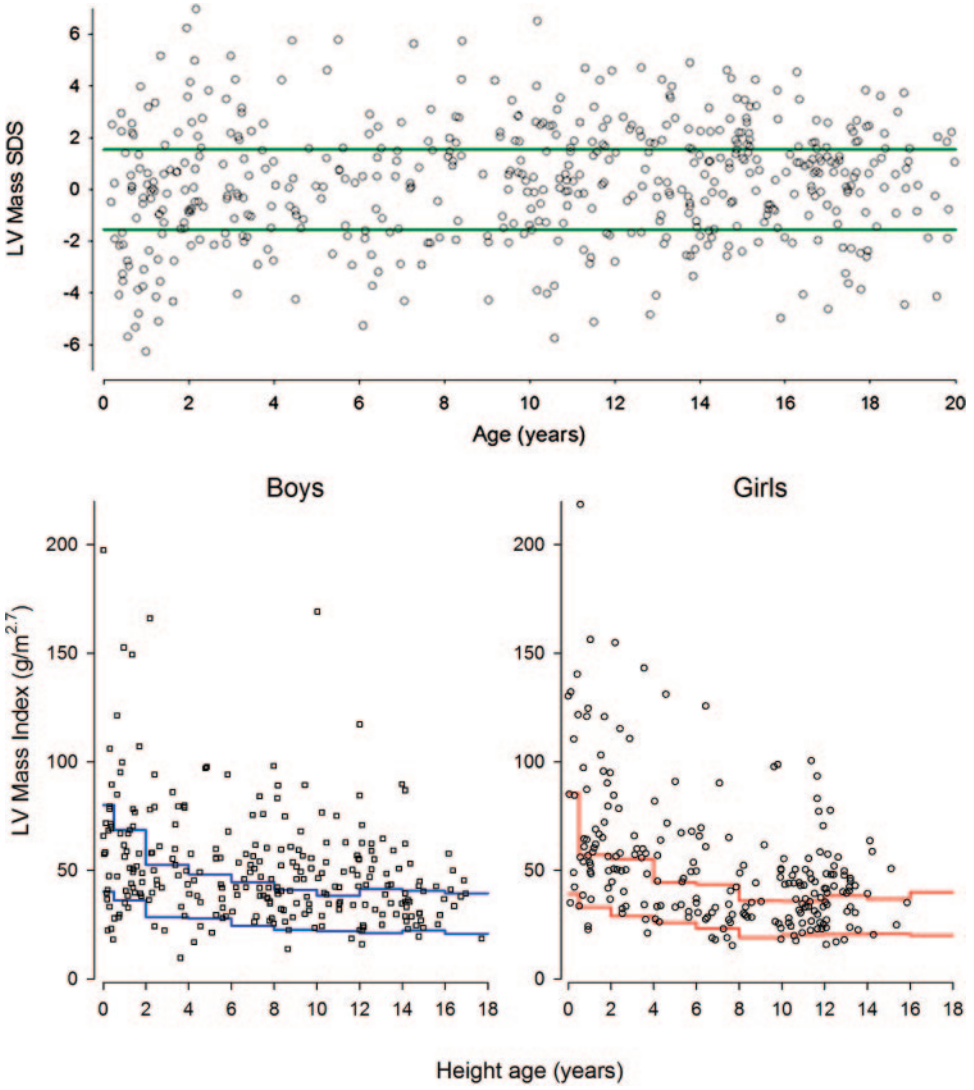


Figure 3. | **Upper panel: Distribution of left ventricular mass (LVM) SD score (SDS) using the lambda-mu-sigma (LMS) reference tables of Foster** *et al.* Lines indicate the 5th and 95th percentiles (14). Lower panels: Distribution of LVMI for height age relative to the reference range of Khoury *et al.* Lines indicate the 10th and 95th percentiles (15).

height exponent of 2.7 does not adequately reflect the biologic relationship between heart size and body size in small children with CKD as in healthy children. The reason for the incomplete age normalization might be given by the fact that the inadequate normalization achieved by indexing to height to the power of 2.7 in very small individuals was apparently ignored in the original publication, which encompassed 241 adults and 444 infants, children, and adolescents (11). LVM is likely to scale best to lean body mass (17,18), of which height, even if used with allometric correction factors, is a rather imperfect surrogate. Whereas a precise assessment of lean body mass requires elaborate technologies such as densitometry or isotope dilution studies, allometric equations utilizing height and weight allow for estimation of lean body mass. One approximation is body surface area, which is closely correlated with basal metabolic rate and incorporates the product of height to the power of 0.73 and weight to the power of 0.43. Recently, an allometric pediatric estimation equation for lean body mass utilizing slightly modified allometric exponents to weight and height has been proposed (19). However, the approach to normalize LVM to anthropometric estimates of lean body mass is inherently limited by the predictive power of allometric equations based on height and weight. The body weight component in the equation may introduce bias related to variable inclusion of obese subjects in the reference and study cohorts. In diseased populations such as children with CKD, additional inaccuracies may occur because of simultaneous malnutrition and fluid retention, which may result in normal weight for height despite reduced lean body mass. It would be of interest to utilize more direct measures of lean body mass such as multifrequency bioimpedance and other emerging noninvasive technologies.

While awaiting further fundamental research in pediatric echocardiography, current studies in diseased populations have to utilize the existing body of reference information (Table 1). Here, we applied four reference systems

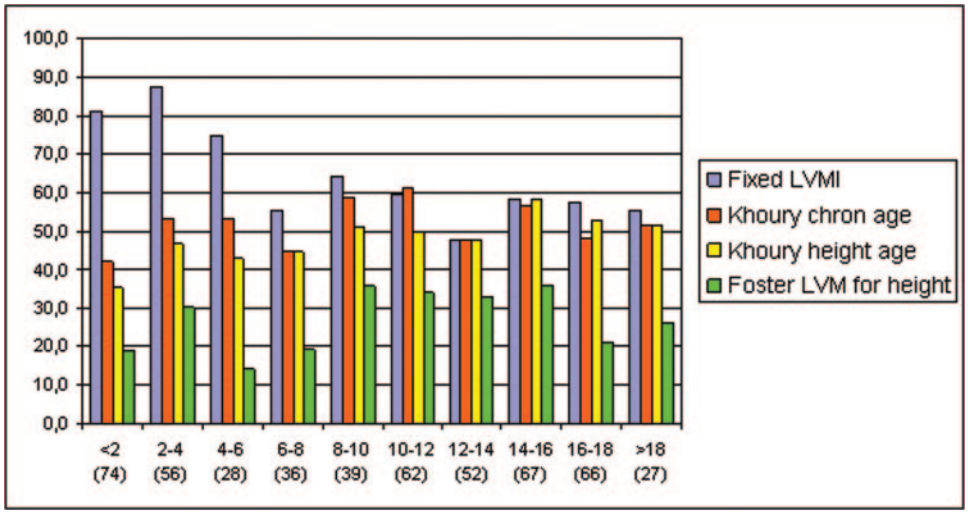


Figure 4. | Age-related prevalence of left ventricular hypertrophy (LVH) in 507 children on CPD using different reference systems. LVH criteria were fixed LVMI > 38.6 g/m$^{2.7}$ (11), 95th LVMI percentile for chronological age according to Khoury *et al.* (15), 95th LVMI Khoury percentile using height age for reference, and 95th percentile of LVM for height according to Foster *et al.* (14).

to our study cohort and compared the results with respect to the calculated prevalence of LVM abnormalities in children on dialysis.

The most widely used definition of LVH is an LVMI exceeding 38.6 g/m$^{2.7}$, which corresponds to the 95th percentile of LVM distribution in a study of 192 healthy children aged 6 to 17 years living in Cincinnati, Ohio, in the early 1990s (20). Major advances in echocardiographic methodology and changes in anthropometric indices at the population level have occurred since then, creating a need for updated reference standards.

Recently, Foster *et al.* studied 440 healthy children and 239 children at risk of LVH (14). This single-center study was carefully standardized and a single cardiologist performed all measurements. All participants were normotensive at the time of the study and 1 year later. The authors utilized the LMS method to provide height-specific coefficients describing the distribution of LVM in the reference population and allowing quantitation of an individual's value by standardized SDS. Being particularly advantageous for parameters with non-Gaussian distribution, this approach is the current method of choice in cardiovascular auxology, applied, for instance, to express BMI, ABPM, and carotid intima-media thickness (21–23).

Khoury *et al.* recently published reference percentile tables for LVM and LVMI (g/m$^{2.7}$) obtained in 2273 healthy children, the largest reference population collected to date (15). Details regarding the standardization of echocardiographic and anthropometric measurements were not given. The authors chose to categorize by gender and age (0 to 6 months, 6 to 18 months, and thereafter at 2-year intervals). The relatively broad age categories could introduce errors, mainly in the youngest, smallest children, among whom even a small difference in age may translate into a big difference in height and consequently in normal LVMI. Moreover, the reference to chronological age in the Khoury charts creates a problem of applicability in populations in which the normal relations among age, height, and sexual maturation are disturbed, as is the case in children with CKD. An approximative solution to this problem is the use of height age instead of chronological age, assuming that the body composition, cardiac mass, and cardiac output of a growth-retarded child should match that of a child with the same height who is at the 50th percentile for age. Although one could speculate whether the lean mass of a very short, but fully sexually mature, adolescent should be appropriate for pubertal stage rather than matching that of a late prepubertal child of the same height, this consideration is largely irrelevant for LVMI, which attains constant values in the second decade of life. Hence, we propose to use height age when referencing a growth-retarded population to the Khoury tables. In this analysis, we compared the effects of referencing to chronological and height age, respectively. Although the overall difference in LVH prevalence was small, referencing to height age eliminated the apparent effect of growth retardation on LVH prevalence that was observed when referencing to chronological age.

Applied to our cohort, the Khoury and the Foster reference tables efficiently corrected the overestimation of LVH by the fixed LVMI criterion in young children, resulting in prevalence estimates independent of or even slightly increasing with age. However, the two reference systems yielded markedly different LVH prevalence figures. Whereas the 95th LVMI percentile of Khoury *et al.* approaches the previously established constant LVH criterion of 38.6 g/m$^{2.7}$ in school children and adolescents, the Foster charts show a much higher cutoff level and lower prevalence of LVH. The LVM SDS distribution plot further showed a large fraction of patients with apparent abnormally small heart size with the Foster charts that was not evident from the LVMI distribution within the Khoury charts. This suggests that the mu coefficients (distribution median) may have been overestimated and the sigma coefficients (distribution width) may have been underestimated in the relatively small validation cohort in the Foster study.

Table 1. Echocardiographic reference studies in healthy children

	De Simone *et al.* 1992 (11)	Daniels *et al.* 1995 (20)	Foster *et al.* 2008 (14)	Khoury *et al.* 2009 (15)
Purpose of study	To determine most appropriate method to normalize LVM for body size	To determine most appropriate method to normalize LVM for body size; to determine cutoff points (90th and 95th percentile) defining LVH	To compare traditional LVM indexation (LVMI = LVM/height$^{2.7}$) to novel method expressing LVM relative to body size (centile curves for height)	To determine normal values of LVMI (LVM/height$^{2.7}$) for children and adolescents (centile curves for age)
Population studied	n = 444 Age range: 4 months to 23 years Percent male: 51 BMI > 95th percentile: 4.5%	n = 192 Age range: 6 to 17 years Percent male: 52 BMI <30 kg/m^2	n = 440 Age range: 0 to 21 years Percent male: 57.7 BMI < 95th percentile for age Median BMI: 59th percentile No systemic disease Normal heart morphology	n = 2273 Age range: 0 to 18 years Percent male: 55.7 BMI < 85th percentile Median BMI: 45th percentile No systemic disease Normal heart morphology
Echocardiographic standardization	M-mode echo according to ASE guidelines Tracking recorded on strip chart paper and interpreted by two independent investigators	M-mode echo according to ASE guidelines	Echo according to ASE guidelines recorded and read by single pediatric cardiologist Dimensions calculated by mean of three measurements; chamber borders digitized manually; diameters calculated from digitized borders; alternatively electronic calipers used to calculate heart dimensions at end-diastole	M-mode echo according to ASE guidelines Heart dimensions measured by edge to leading edge technique
Statistical and scaling method	LVM calculation: Devereux formula Linear regression analysis; allometric scaling with fixed cutoff	LVM calculation: Devereux formula Log-log linear regression; allometric scaling with fixed cutoff	LVM calculation: Devereux formula LVM for height centiles calculated by LMS method	LVM calculation: Devereux formula Allometric scaling with age-specific cutoff; percentile curves for LVMI defined as LVM/height$^{2.7}$

Table 1. (Continued)

	De Simone *et al.* 1992 (11)	Daniels *et al.* 1995 (20)	Foster *et al.* 2008 (14)	Khoury *et al.* 2009 (15)
Results	LVM/height$^{2.7}$ had least residual relationship with height	LVM/height$^{2.97}$ best correlated with LV mass/LBM; 95th percentile for LVMI defined as LVM/height^{3}: 33.6; for height$^{2.7}$: 38.6	LVMI inversely correlated with height; LVM for height centile curves superior to LVMI for normalizing LVM in children	LVMI-for-age centile curves superior to LVMI in normalizing LVM in children
Strengths of study		Direct measurement of LBM (DEXA)	Careful standardization of echocardiographic measurements; LVM scaling on a continuous scale; LMS method used to provide height-specific coefficients	Large sample size
Limitations of study	Data obtained in early 1990s	Data obtained in early 1990s; small sample size; no infants studied	Relatively small sample size; nonstandard echocardiographic technique	Categorization by broad age intervals; limited applicability in children with abnormal height for age

LVM, left ventricular mass; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; BMI, body mass index; ASE, American Society of Echocardiography; LV, left ventricle; LBM, lean body mass; DEXA, dual-energy x-ray absorptiometry; LMS, lambda-mu-sigma.

The differences in LVM distribution between the two recent reference cohorts might in part be explained by differences in body composition: Mean BMI was around the 58th percentile in the Foster study, whereas it was around the 45th percentile in the study of Khoury *et al.* These differences might reflect systematic differences in lean body mass that were not sufficiently accounted for by referencing to age or height. Furthermore, it is important to recognize the potential effect of methodological differences between the two studies. In the echocardiographic studies for the Foster paper, the wall and septum borders were hand-digitized using custom software, and thicknesses and diameters were calculated from the digitized borders as continuous variables throughout the cardiac cycle. End-diastole was defined as the time of maximum left ventricular dimension. The end-diastolic dimensions and wall thicknesses were calculated as the average of three successive cardiac cycles (14,24). Because this methodology of image analysis is not widely used, it may be the main reason for the difference in LVM estimates between the Foster and the Khoury papers.

Hence, the Foster and the Khoury studies represent significant advances in pediatric echocardiography, and both have drawbacks. The strength of the Khoury study is its very large cohort size and its partial concordance with previous reference data.

In subjects taller than 130 cm, the 95th LVMI percentile of Khoury approaches 38 $g/m^{2.7}$, the widely used—albeit not end point–validated—cutoff to define LVH in previous pediatric studies. The reference to age categorized at relatively broad intervals instead of a measure of body size is an important limitation of the Khoury tables that may be partially overcome by referencing to height age.

The weakness of the Foster reference group is its relatively small sample size and the fact that the measurement techniques used are not the same as those that are broadly applied in clinical practice.

On the other hand, the scaling of LVM to body size on a continuous scale is a clear advantage of the Foster study, as is the expression of LVM for height by standardized SDS. The latter allows using individual values from children of all ages for parametric statistical analysis in cross-sectional and longitudinal studies, a clear advantage over the traditional dichotomous LVH classification. With respect to the definition of LVH, the 97th percentile of the Foster reference data at the upper end of the height distribution corresponds with the LVMI cutoff of 51 $g/m^{2.7}$, which has been linked with adverse outcomes in adults (25).

In this study we validated existing definitions of LVH in a global registry-based population of children on CPD. The lack of standardization of echocardiographic technique and anthropometric measurements is an obvious limitation inherent to the data. Potential bias might also emerge from the application of reference systems validated in healthy children in case the underlying the relationship between LVM and body size differs fundamentally in children with ESRD. This general possibility is difficult to exclude and applies to any echocardiographic study in diseased pediatric populations.

In conclusion, recent advances in pediatric echocardiography allow a fresh look at abnormalities of cardiac adaptation in health and disease. However, further efforts will be required to develop optimal normalization techniques to express LVM and other morphologic and functional measures across the pediatric age range.

APPENDIX

The following principal investigators are contributing to the IPPN registry:

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Disclosures

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

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