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New reference values for echocardiographic dimensions of healthy Dutch children

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KEYWORDS
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Children

Abstract *Aim:* To renew the echocardiographic reference values of heart dimensions in healthy children.
Methods and results: Group 1 consisted of 587 children, of which 361 boys and 226 girls, age from birth to 18 years, body weight over 2500 g, who visited the Pediatric Cardiology outclinic during the period January 2000 till March 2004. All included children were diagnosed as normal, or as having innocent heart murmur. The second group was taken from an earlier study and comprised 160 children (77 boys and 83 girls). The echocardiographic measures were taken from conventional M-mode recording of the left ventricle (LV) parasternal long axis view. End diastolic septal (IVS) and LV posterior wall thickness (LVPW) and end diastolic as well as end systolic LV intracavity dimensions were retrospectively analyzed. The regression lines from all measured sizes are significantly different from those collected in the early eighties. Especially the thickness of the IVS is smaller. The regression lines are independent of gender.
Conclusions: New reference values have been found which should replace the presently used ones. There is no difference between boys and girls. Why the muscular wall thicknesses are thinner than found 20 years ago needs to be further explored.
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Introduction

Echocardiography is the most widely used method in pediatric cardiology to diagnose congenital heart disease. This imaging modality has an excellent temporal and spatial resolution. Therefore, the dimensions of the various anatomical structures, as well as of many malformations can be assessed. To interpret quantitative echocardiographic data, cardiac dimensions have to be compared with normal values. The reference range of values of each cardiac dimension has to be assessed from a population of normal hearts.

Reference ranges were established in the early eighties by measuring cardiac dimensions of healthy Dutch children and adults by M-mode echocardiography.[1] Body weight and gender appeared to be significant determinants for all cardiac dimensions. Length appeared not a significant determinant when weight was accounted for.[1,2] For this reason, body surface area (BSA) is not expected to be a better determinant than weight alone. In contrast to these findings, a study using cross-sectional echocardiography showed that for all cardiac dimensions the best correlation was present with BSA and no gender difference was found.[3] A more recently published study also concludes that BSA correlates best with cardiac structure, again without a gender difference.[4] Also, in a very large population of European children and infants no difference in heart dimension of boys and girls was found.[5] Normal values of echocardiographic dimensions in newborn infants were expressed in relation to body weight, for all other subjects, the data were expressed in relation to BSA.

The length of Dutch children has increased[6]; this is a normal trend in modern society. A recent phenomenon in the Netherlands is an increase in body mass index (BMI), which is commonly used as an index for obesitas.[7,8] Effects of these changes on the size of the heart are unknown. To date, more precise measurement of cardiac dimensions is available because echocardiographic technology has evolved. Hence, biological and technological changes induce the question whether it would be time to renew reference values for cardiac dimensions of healthy infants and children. Appropriate reference ranges are essential for identifying quantitative abnormalities.

The purpose of this study is to examine whether the average echocardiographic dimensions have changed in healthy infants and children. If cardiac dimensions appear to be different nowadays as compared to the past, new reference ranges have to be established and used in the routine echocardiographic diagnosis.

Methods

Subjects

The study population consisted of two groups of a total of 747 infants and children, of whom 438 boys and 309 girls, mean age 5.3 years (range: one day to 18 years) and mean body weight 21.1 kg (range: 2.5–90 kg). Study group 1 consisted of 587 infants and children (361 boys and 226 girls) who were retrospectively analyzed. They were selected from the echocardiographic database of the University Children's Heart Center of Nijmegen, the Netherlands. Infants and children had been referred to the Children's Heart Center between January 2000 and March 2004 to exclude comorbidity of the heart, or for cardiological consultancy in case of functional heart murmur. Subjects were included if the diagnosis was either normal heart or innocent cardiac murmur. If a subject had more than one echocardiographic examination, the data of the first examination were used for analysis. Subjects were excluded if body weight was 2500 g or less, which is considered as low birth weight (WHO), and if left ventricular fractional shortening (FS), which is described below, was lower than 25%, which defines insufficient shortening of the left ventricle.

Study group 2 contained the echocardiographic data from 160 healthy children (77 boys and 83 girls) who participated in a recent, prospective study on normal ranges of conventional echocardiographic dimensions as well as of myocardial velocities estimated by using tissue Doppler imaging.[9] In this study group 2, cardiac dimensions of healthy subjects were measured in the same equipment settings and according to the same protocol as the data of study group 1. However, a single experienced pediatric cardiologist measured cardiac dimensions. Twelve cardiologists and technicians performed the cardiac examinations of study group 1. For this reason, a comparison was made between data of the two study groups, before considering a merging of the data.

Echocardiographic measurements

Echocardiographic dimensions of study group 1 were measured with a ''System Five'' model echocardiographic scanner (GE/Vingmed, Horten,

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Norway) and the ''Powervision'' scanner (Model SSA-380A software version 2.5 0ER000, Toshiba, Nasu, Japan), whereas, echocardiographic dimensions of study group 2 were measured with the ''Powervision'' only. Depth calibration of both systems was checked by using a tissue-mimicking phantom (ATS, Inc., Bridgeport, CT) and a standardized quality assurance protocol.[10] All echocardiographic examinations were performed at the Children's Heart Center of the Radboud University Medical Center of Nijmegen, The Netherlands. The echocardiographic measures were taken from M-mode recordings, selected in left ventricle parasternal long axis view B-mode images, and measured according to the ''leading-edge'' method.[11] The following four echocardiographic dimensions were measured (cf., Fig. 1): thickness of interventricular septum at end diastole (IVS) and of left ventricular posterior wall at end diastole (LVPW), left ventricular inner dimension at end diastole (LVID ED) and at end systole (LVID ES). End diastole (ED) is defined as the beginning of the Q-wave on the ECG. End systolic (ES) LV-dimension is measured as the smallest LV-dimension during the time interval between the time at peak septal motion and peak anterior movement of the LVPW. Left ventricular fractional shortening (FS) was calculated from the left ventricular dimensions. The definition of FS is as follows: (LVID (ED) − LVID (ES))/LVID (ED) × 100 [%]. Left ventricle FS appeared to be independent of body weight ($R^2 = 0.01$). The mean FS was 35.2% (sd = 6.5) and equal for all categories of body weight ($p = 0.64$).

Statistical analysis

Comparing new data with current reference ranges

The echocardiographic data were log transformed prior to the statistical analysis. The data were then plotted versus the natural logarithm of body weight together with the current reference percentiles. This logarithmic transformation yielded a linear relation between echocardiographic dimensions and body weight. The intercept, slope and residual standard deviation of the current reference values are presented in Table 1.[12] These values were dependent on gender, thus comparing data to the current reference values was done separately for boys and girls. The percentages of the retrospective data (study group 1) below the current P_5, P_{50} and above the P_{95} were calculated with their respective 95% confidence interval.

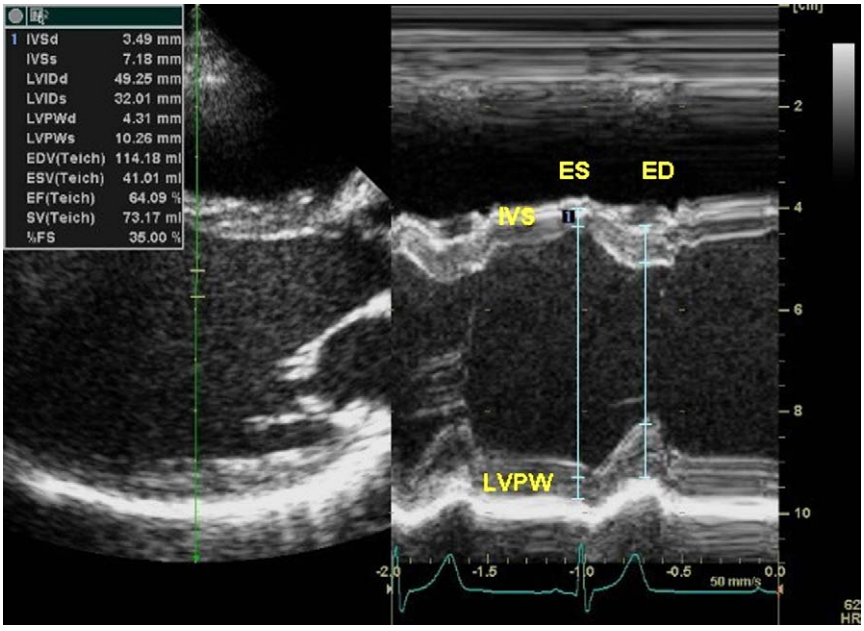


Figure 1 Echocardiographic measurement. Left: B-mode long axis view, M-mode line indicated in B-mode (drawn line) Right: M-mode from indicated line, ECG is displayed in bottom trace. End diastolic (ED) LV inner dimension is defined at the beginning of the Q-wave on the ECG. End systolic (ES) LV inner dimension is measured as the smallest LV-dimension during the time interval between the time at peak systolic septal motion and peak anterior movement of the LVPW. IVS = Interventricular septum, LVID = left ventricle inner dimension, LVPW = left ventricle posterior wall.

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Table 1 Intercept, slope and standard deviation of residuals (sd) of regression equation after logarithmic transformation of data for *current* reference ranges of interventricular septum (IVS), left ventricle posterior wall (LVPW), left ventricle inner dimension (LVID) at end diastole (ED) and at end systole (ES) for boys and girls[12]

	Boys			Girls		
	Intercept	Slope	Sd residuals	Intercept	Slope	Sd residuals
IVS (ED)	0.618	0.394	0.167	0.636	0.372	0.172
LVPW (ED)	0.577	0.365	0.155	0.615	0.337	0.149
LVID (ED)	2.739	0.293	0.072	2.673	0.302	0.083
LVID (ES)	2.313	0.283	0.106	2.260	0.294	0.105

Retrospective study group (group 1)

To assess the new relation between cardiac dimensions and gender, age and body weight of infants and children, a multiple linear regression technique was used on logarithmically transformed data. Regression equations were obtained for the cardiac dimensions: IVS, LVPW, LVID (ED) and LVID (ES) of the retrospective study group (group 1).

Also, a logarithmic transformation of the determinants body weight and age was performed. The first model contained all the determinants (body weight, age, gender) and the interaction variables with gender. From this full model a simple model was derived. The best predicting model was chosen by the determinants that turned out to be significant ($p < 0.05$) and by the proportion of variance that could be explained by the regression (R^2).

The residuals of the best predicting model were further analyzed. To test for differences in scatter between boys and girls and between several categories of body weight, the standard deviations of the residuals were compared. This was done with Levene's test for homogeneity of variances. The relevance of differences was checked. Four categories of body weight with equal width on a logarithmic scale were made.

The regression equation of the best predicting model was used to produce nomograms of the 5th, 50th and 95th percentile limits for all cardiac dimensions. The 50th percentile was given by the regression equation. To calculate the 5th and 95th percentile a term $\pm 1.645 \times$ standard deviation of the residuals was added to the regression equation. This term is valid for a Gaussian probability density function with equal variance in the various body weight categories.

Prospective group (group 2)

The cardiac dimensions of the prospective data (group 2) were plotted within the reference values obtained for the retrospective data (group 1). To compare data of only one observer versus those of different observers, the scatter, i.e., the standard deviation of the residuals of the prospective data was compared with the standard deviation of the residuals of the retrospective data.

Results

The percentages of cardiac dimensions under the current P_5 and P_{50} and above the current P_{95} are presented separately for boys and girls. The results for boys are given in Table 2, for girls in Table 3. All cardiac dimensions show more than 5% of the data under the current P_5 varying from 15.9% for LVPW of girls up to 52.6% for IVS of boys. Although the median LVPW is close to the current P_{50} both the percentage below the P_5 and above the P_{95} are greater than 5%. Thicknesses of IVS and LVPW are smaller in the whole range of body weight, whereas, for LVID (ED) and LVID (ES) the dimensions are smaller especially for the lowest category

Table 2 Percentages with 95% confidence interval of cardiac dimensions, which are under the current P_5, under the current P_{50} and above the current P_{95} for *boys* ($N = 361$)

	% Under current P_5	% Under current P_{50}	% Above current P_{95}
IVS (ED)	52.6 (46.1–58.9)	88.6 (84.6–92.6)	1.1 (0.3–2.8)
LVPW (ED)	18.8 (13.9–23.7)	57.9 (51.7–64.1)	6.1 (3.1–9.1)
LVID (ED)	24.1 (18.7–29.5)	62.1 (56.0–68.2)	5.3 (2.5–8.1)
LVID (ES)	17.2 (12.5–22.0)	60.1 (54.0–66.3)	3.3 (1.1–5.6)

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Table 3 Percentages with 95% confidence interval of cardiac dimensions, which are under the current P_5, under the current P_{50} and above the current P_{95} for *girls* ($N = 226$)

	% Under current P_5	% Under current P_{50}	% Above current P_{95}
IVS (ED)	39.4 (33.2–45.7)	82.7 (77.9–87.5)	2.7 (0.7–4.7)
LVPW (ED)	15.9 (11.3–20.5)	51.8 (45.5–58.1)	12.0 (7.9–16.1)
LVID (ED)	18.1 (13.3–23.0)	58.4 (52.2–64.6)	4.9 (2.2–7.6)
LVID (ES)	18.6 (13.7–23.5)	58.9 (52.7–65.1)	2.7 (0.7–4.7)

of body weight. This is clearly shown in Fig. 2 (for boys) and Fig. 3 (for girls) where both the heart dimensions and body weight are plotted on a natural logarithmic scale. It may be noted in these figures that the percentages as given in Tables 2 and 3 are different for different weight categories. This phenomenon will have a consequence for the slope of the linear regression line of the new data.

For the cardiac dimensions IVS, LVPW, LVID (ED) and LVID (ES) body weight is a significant determinant ($p < 0.0001$), with an R^2 of 0.55, 0.60, 0.88 and 0.81, respectively. Except for IVS, if body weight and age are analyzed simultaneously, both determinants turn out to be significant. However, just a very small increase in R^2 is seen when comparing R^2 of body weight alone and R^2 of body weight and age together.

For one cardiac dimension, LVID (ED), gender is a significant determinant ($p = 0.014$), but adding gender to the model does not increase R^2. Only for LVID (ED) gender could influence the relation between body weight and LVID (ED) (p-value for interaction = 0.07), however no increase in R^2 is seen. The other cardiac dimensions, IVS, LVPW and LVID (ES), show no gender difference ($p > 0.30$) and no interaction between gender and body weight ($p > 0.15$). Analysis of residuals demonstrates that spread of data around the regression line is practically identical for boys and girls. Exceptionally, residuals of LVPW of girls show

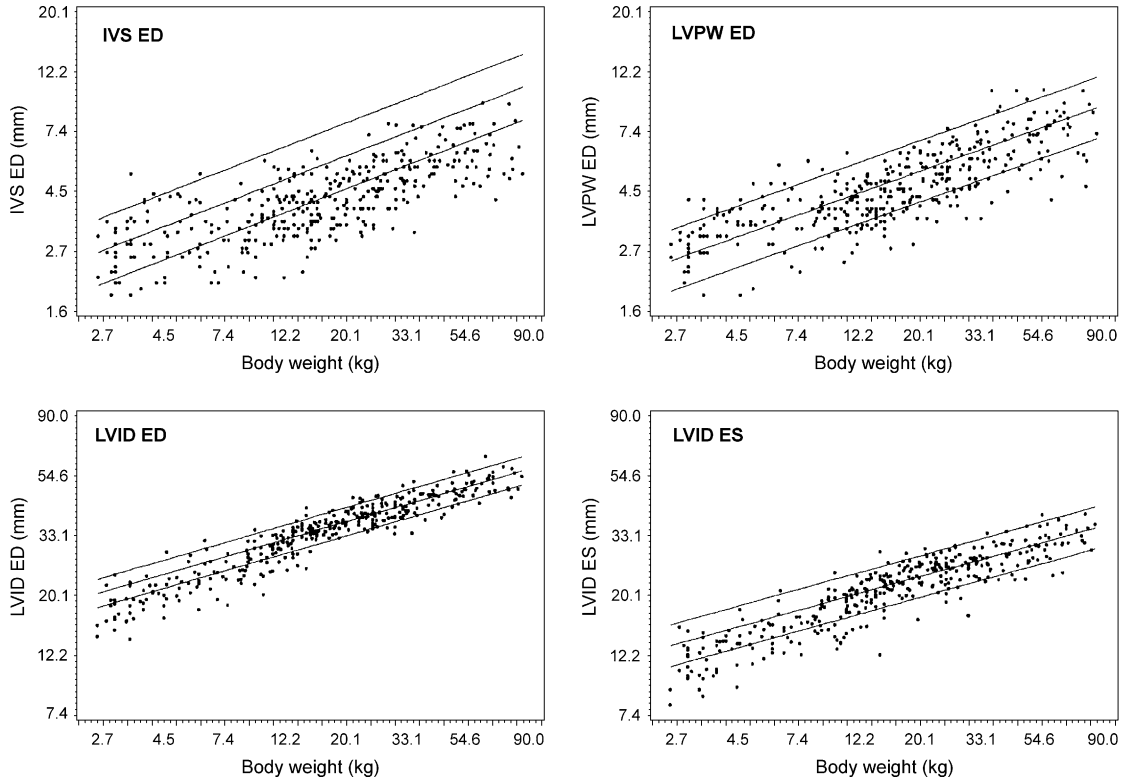


Figure 2 Current reference ranges (solid lines) and cardiac dimensions for *boys* (dots) plotted against body weight on a double logarithmic scale. IVS = Interventricular septum and LVPW = left ventricle posterior wall both at end diastole, LVID (ED) = left ventricle inner dimension at end diastole, LVID (ES) = left ventricle inner dimension at end systole.

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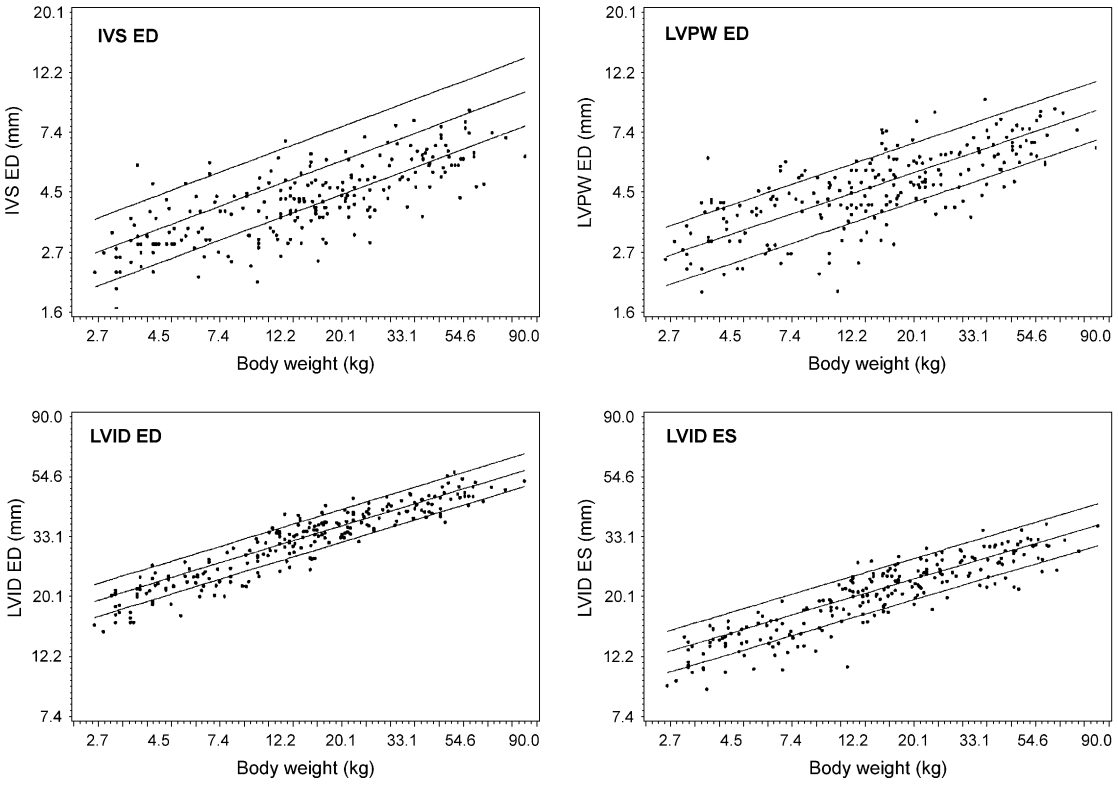


Figure 3 Current reference ranges (solid lines) and cardiac dimensions for *girls* (dots) plotted against body weight on a double logarithmic scale. IVS = Interventricular septum, LVPW = left ventricle posterior wall both at end diastole, LVID (ED) = left ventricle inner dimension at end diastole, LVID (ES) = left ventricle posterior wall at end systole.

a higher standard deviation than residuals of LVPW of boys ($p = 0.045$). This was not consistent in different categories of body weight. For two cardiac dimensions, IVS and LVID (ED), the standard deviation of residuals is higher for the lowest category of body weight ($p = 0.050$, and $p = 0.009$, respectively).

The intercept, slope and standard deviation of residuals of the logarithmic regression lines, yielding the new reference ranges, are given in Table 4. The P_{50} of a particular body weight can be calculated by the following formula: $P_{50} = e^{\text{intercept}} \times (\text{body weight})^{\text{slope}}$. Comparing the intercept and slope of the current and the new reference ranges, it is seen that IVS and LVPW show a different pattern than LVID (ED) and LVID (ES). The new parameters of IVS and LVPW show a higher intercept and a lower slope compared with the current parameters, whereas, the new regressions of LVID (ED) and LVID (ES) show a lower intercept and higher slope compared with the current parameters. The standard deviations of all the echocardiographic dimensions are higher now compared to the past. Fig. 4 shows the new nomograms, together with the data points of study group 1 (boys and girls mixed).

Table 4 Study group 1, intercept, slope and standard deviation (sd) of residuals of regression equation for *new* reference ranges of interventricular septum (IVS), left ventricle posterior wall (LVPW), left ventricle inner dimension (LVID) at end diastole (ED) and at end systole (ES)

	Intercept	Slope	Sd residuals
IVS (ED)	0.665	0.277	0.213
LVPW (ED)	0.704	0.298	0.211
LVID (ED)	2.551	0.341	0.108
LVID (ES)	2.123	0.332	0.138

Comparing cardiac dimensions of two study groups

Fig. 5 shows the data of the prospective study (study group 2) with the new reference ranges for IVS, LVPW, LVID (ED) and LVID (ES) obtained from study group 1. The echocardiographic measurements of the two study groups are comparable. However, it may be seen that LVPW data of study group 1 are generally smaller than the P_{50}, whereas LVID (ED) are showing a lower regression

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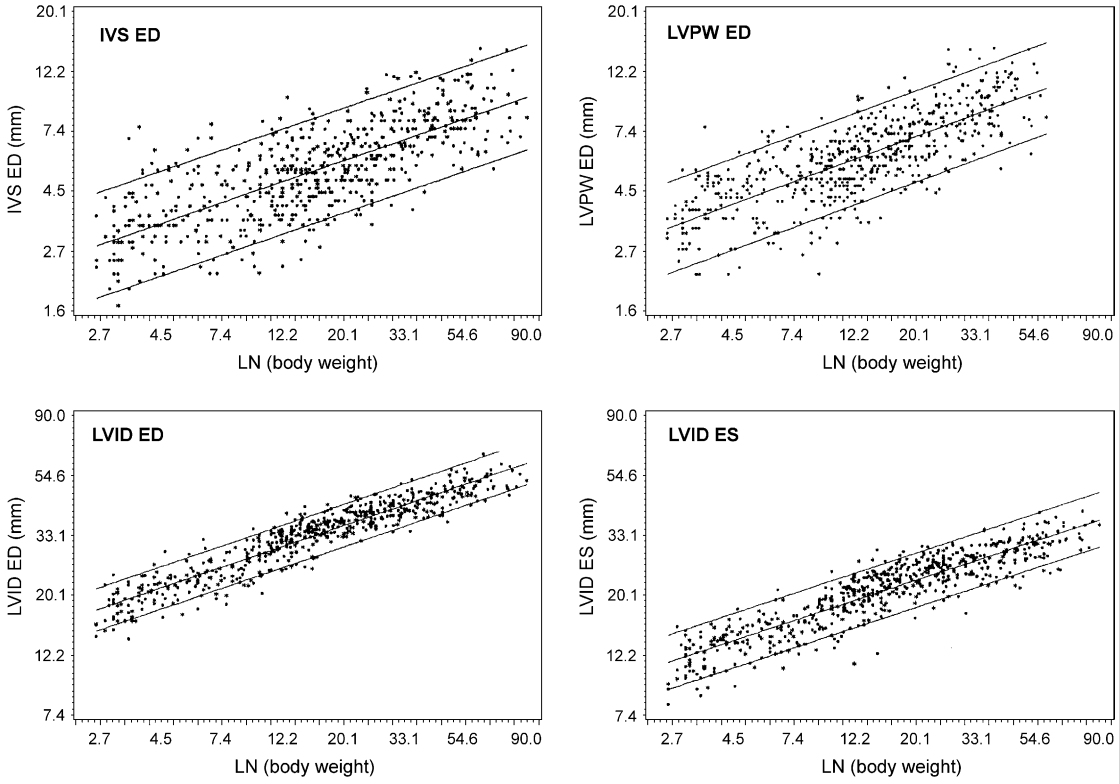


Figure 4 New nomograms of interventricular septum (IVS), left ventricle posterior wall (LVPW), left ventricle inner dimension at end diastole (LVID ED) and at end systole (LVID ES). Dots: boys, stars: girls.

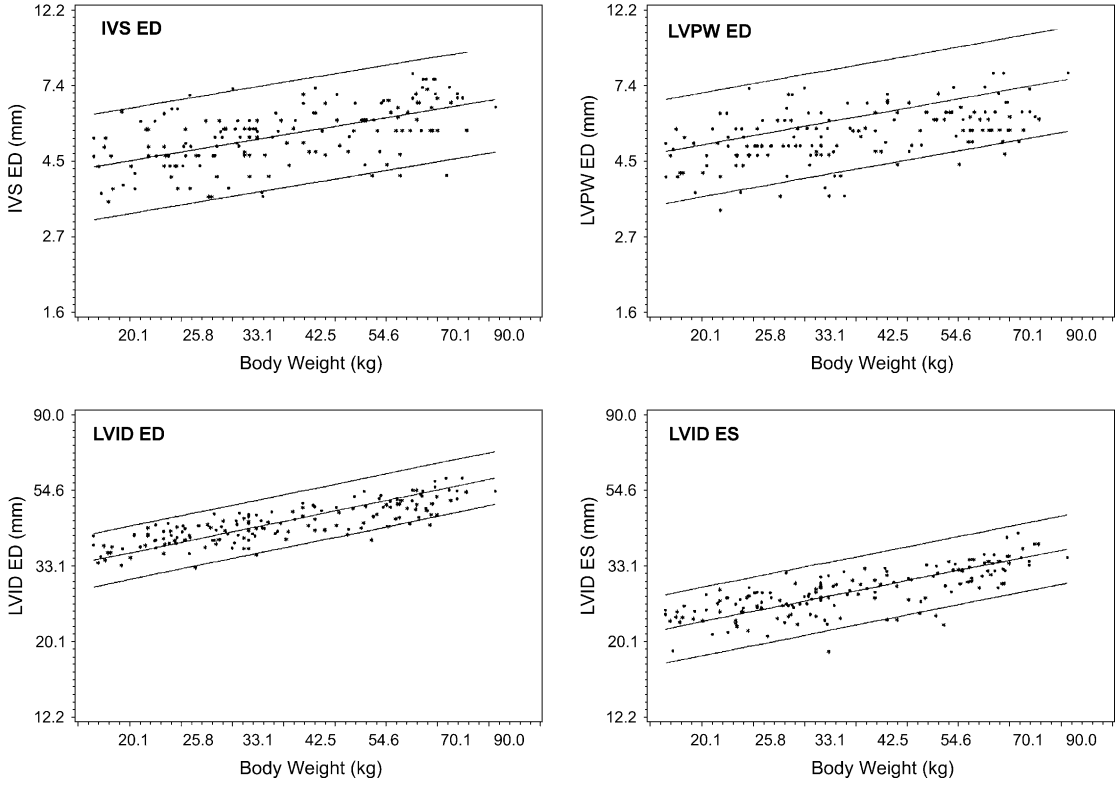


Figure 5 New reference ranges (solid lines) and cardiac dimensions of study group 2 (dots) plotted against body weight. IVS = Interventricular septum, LVPW = left ventricle posterior wall, LVID (ED) = left ventricle inner dimension at end diastole, LVID (ES) = left ventricle posterior wall at end systole.

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slope. It is clearly seen that the data of the prospective study group with a single observer show less spread of data compared with the retrospective study group with several observers. For this reason, the two groups were not merged in the analyses.

Discussion

Appropriate reference ranges are essential for identifying abnormalities of the heart quantitatively. The aim of this study was to examine whether the average echocardiographic dimensions have changed in healthy infants and children during the past 20 years. It appeared that heart dimensions on average are smaller and the slope of regression lines is different nowadays. Especially the normal values for IVS have decreased considerably. Values were related exclusively to body weight. New reference ranges could be established and no gender difference was found.

Today, higher temporal and spatial resolutions of echocardiographic scanners provide more accurate measurement of cardiac structures. In addition, cardiac anatomy is displayed more clearly and in particular heart structures can be identified more easily. For instance, the trabeculae of the right ventricle walls are generally well visible and can be avoided while measuring IVS thickness. This might at least partly explain why smaller cardiac dimensions are measured, as compared with 20 years ago. On the other hand, if the trabeculae would be more easily detectable with modern equipment, avoiding them in the thickness measurement would mean thinner IVS, as well as LVPW, and at the same time larger LV cavity dimensions. The latter is not observed in our data (cf., Figs. 2 and 3) and this speaks against the assumption of a significant instrument involvement in the results.

Another consideration is whether changes in reference values should be related to the development of echocardiographic technology or whether cardiac structures have also changed in size themselves. In literature it has become evident that Dutch children become taller[6] and that they gain weight.[7,8] The effects of these changes on the size of the heart were beyond the scope of this study and need to be further explored. Furthermore, children's life style is less active than two decades ago (Report RIVM, National Institute of Public Health and the Environment of The Netherlands, and Report Municipal Health Service Nijmegen, The Netherlands, August 2004) and sedentary children are known to have thinner heart muscle walls than active children.[13] Additional research will be necessary to identify effects of physical activity on cardiac structures at young age.

The current reference ranges were obtained separately for boys and girls. Gender used to be a significant determinant for all cardiac dimensions in Dutch children.[1] In our study, gender appeared only a significant determinant for LVID (ED). If gender would be an important determinant, it would have been significant for all cardiac dimensions, since the expectation has to be that a larger heart needs thicker walls because of Laplace's law. So, if boys would have larger LV-dimensions, it should be expected that the walls are thicker as well, which was not observed in the present study. Therefore, it was chosen to establish new reference ranges of cardiac dimensions independent of gender. This is in accordance with the results of other studies.[3–5] A reason, which could explain the absence of gender difference found in our study, might be that any small gender difference would be hidden within the range of interobserver variability.[14] In the study, which showed gender differences,[1] the number of observers who performed the echocardiographic examinations was not mentioned. It is not clear why the influence of gender has changed in Dutch children.

The standard deviation of the residuals was dependent of body weight for two cardiac dimensions. IVS and LVID (ED) showed higher standard deviations of residuals with lower body weight (cf., Fig. 4). However, differences in standard deviations for each category of body weight were small and no consistency was found between cardiac dimensions. For these reasons, we have chosen to use the mean standard deviation of the residuals to calculate the 5th and 95th percentiles for all cardiac dimensions. The standard deviation of the residuals is higher now compared to the past. The number of observers who performed the echocardiographic examinations might explain this. Again, no conclusions can be drawn because the number of observers of the previous study of reference ranges of Dutch children[1] is not known. In a study of normal values, echocardiographic dimensions were expressed in relation to body weight for newborns.[5] Their echocardiographic dimensions up to 4 kg of body weight to their data are comparable to ours. Especially standard deviations are quite similar for all echocardiographic dimensions. LVID (ED) and LVID (ES) are also comparable for mean values, whereas the IVS and LVPW found in the present study are slightly lower.

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The new regression parameters of IVS and LVPW show a higher intercept and a lower slope as compared with the current parameters, whereas the new parameters of LVID (ED) and LVID (ES) show a lower intercept and higher slope compared with the current parameters. This implies that the growth rate of thicknesses of IVS and of LVPW has decreased and the growth of LVID (ED) and LVID (ES) has therefore relatively increased.

Fractional shortening was found to be independent of body weight. The derived parameter FS is used as a diagnostic threshold value. An FS below 25% is generally considered as insufficient shortening of the ventricle, this is used for everybody, independent of body weight. According to the new data, a cut-off point of FS of 25% caused an exclusion of 6% of the data.

Subjects were selected from the echocardiographic database of the Children's Heart Center and subjects were included if the result of the echocardiographic examination was either normal heart or innocent cardiac murmur. Subjects displaying an FS lower than 25% were excluded as well. This criterion is internationally accepted. The data of the prospective study of healthy children fit well in the new reference ranges. This confirms the correctness of the use of the retrospective study group to establish reference ranges for cardiac dimensions of healthy children. In addition, the echocardiographic examinations must also be representative. It is seen that the single cardiologist who performed the prospective study group produced a smaller spread of data compared with the data obtained with a group of several cardiologists involved in the retrospective study. Nevertheless, reference ranges cannot be based exclusively on the data of the prospective study, because in clinical setting echocardiographic examinations are always performed by a group of cardiologists and technicians. In the prospective study group the measured thicknesses of the LVPW are smaller, but still within the range of normal values, as compared with those measured in the retrospective study group. If the data of the prospective study would be included for the reference ranges, one single cardiologist would be represented abundantly, because the prospective study group consisted of 160 subjects. Therefore, new reference ranges were made of the retrospective study group without using the data of the prospective study group.

In conclusion, cardiac dimensions measured by echocardiography are smaller nowadays compared with 20 years ago and growth rates have changed. Hence, new reference ranges were established. Values are expressed in relation to body weight and are independent of gender. Why cardiac dimensions are smaller needs to be further explored.

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