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CLINICAL/ORIGINAL PAPERS

Derivation of a size-independent variable for scaling of cardiac dimensions in a normal paediatric population

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Aims It is general practice to correct cardiac chamber size for body size by the process of scaling or normalization. Normalization is most commonly performed using simple linear or isometric correction; however, there is increasing evidence that this approach may be flawed. Likewise, there is little agreement concerning the appropriate scaling variable (measure of body size) for normalization. Therefore, we aimed to establish the optimal method for correcting the differences in body size in a large population of echocardiographically normal paediatric subjects.
Methods and results We compared the relative ability of standard size variables including height (HT), body weight (BW), body mass index (BMI), and body surface area (BSA), in both isometric and allometric models, to remove the effect of body size in 4109 consecutive echocardiographically normal subjects $<$18 years of age, using the left atrial dimension (LAD) as a reference standard. Simple linear normalization resulted in significant residual correlations ($r = -0.57$ to -0.92) of the indexed value with the body size variable, the correlations with weight (WT) and BSA actually increasing. In contrast, correction by the optimal allometric exponent (AE) removed the effects of the indexed variable (residual correlations -0.01 to 0.01), with BW and BSA best removing the effects of all the measures of body size.
Conclusion Conventional linear correction for body size is inaccurate in children and paradoxically increases the relationship of the indexed parameter with WT and BSA. Conversely, correction using the optimal AE removes the effect of that variable, with WT best correction for all measures of body size.

Cardiac chamber size and cardiac output increases with increasing body size during normal growth and development.[1,2] In order to define the range of normality, and separate changes due to normal growth from those caused by disease, it is generally necessary to correct observed values for difference in body size through the process of scaling or normalization. Initial studies performed to establish a range of normal among children assumed a linear or isometric relationship between the physiologically dependent variable and body size variable.[3,4] In this linear model, the relationship between the physiological variable (Y) and body variables (X) takes the form $Y = bX$, with the line of best fit passing through the origin. In this format the simple per ratio standard Y/X is assumed to be size independent. However, there is increasing evidence that this assumption is incorrect.[1,5]

Because the relationship of cardiac dimensions and body size follows a curvilinear relationship, an alternative approach to normalization of cardiac dimensions has been suggested.[2,6] This alternative approach to scaling is called allometric modelling and adjusts for the non-linear relationship between body size variables and physiological variables. The allometric model is of the general form $Y = aX^b$ where b is the scaling exponent and a is the scaling factor.

In two prior studies in adults we have shown [using the left atrial dimension (LAD) as an example] that linear scaling, rather than removing the effects of body size, actually increases the residual correlation between most scaling variables and LAD, and that allometric modelling using the simple measure of body weight (BW) almost completely removes the effects of body size. However, in children, other measures of body size such as height (HT) and body

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surface area (BSA) have been proposed as more appropriate scaling factors. In addition, while some authors have advocated allometric as opposed to isometric models, there are no data concerning the consistency of the allometric exponents (AE) and scaling factors between the adult and paediatric populations (specifically whether the same exponents can be used for different segments of the population). The purpose of this study therefore was to define the optimal scaling method (exponent and factor) in normal children, and also to compare these results with those obtained in both normal adults and predominantly obese adults.

Methods

Study design

The study sample was composed of 4109 consecutive children aged 1–17 years with normal echocardiographs performed from 1992 to 2005 in the Cardiac Ultrasound Laboratory, Massachusetts General Hospital. We only included individuals with complete data on age, gender, HT, and weight (WT). Subjects with implausible HT and WT data based upon extreme values deviating from age-specific normal ranges were excluded from analysis.[7] Height and WT were measured immediately prior to echocardiographic assessment.

Baseline measurements and echocardiographic assessment

Four body size variables were examined. These were WT, HT, body mass index (BMI), and BSA. BMI was defined as BW in kg divided by the square of the HT in meters, while BSA was calculated using the formula:[8] BSA (in m^2) $= 0.20247 \times$ (height in m)$^{0.725} \times$ (weight in kg)$^{0.425}$. Two-dimensional measurement of the LAD was made in the standard parasternal long-axis view from the anterior to posterior margins of the chamber along a line drawn perpendicular to the left ventricular long axis (which if extended would transect the aortic leaflets) using the innermost, bright edge reflection as the intercept. For the purpose of this analysis, an LA dimension of $\leq$38 mm was considered normal. All echocardiographic interpretations were made by Level 3 American Society of Echocardiography-certified cardiologists. This study was conducted in full compliance with all federal, state, and institutional guidelines pertaining to human research. LAD was chosen as a reference standard as it appears to be subject to the least inter- and intra-observer variability.

Statistical analysis

Per-ratio standard estimates of indexed LA size were calculated by taking the simple ratio of LA size to each body size parameter, e.g. LA/BSA. Allometric estimates of indexed LA size were obtained by first considering the equation $Y = aX^b$. To determine the appropriate AE by which each body size parameter (X) should be raised, a logarithmic transformation of this equation was used: Ln $Y =$ Ln $a + b$ Ln X. Ordinary least squares linear regression was then used to estimate the allometric scaling factor and scaling exponent. A multivariable allometric model with HT and WT, as opposed to the constant relationship in the BSA and BMI calculation, as independent predictors was also constructed. The allometric indexed LA size was then calculated as follows: observed Y/expected Y. This ratio for any individual represents the degree of deviation of LA size from that expected based on change in body size alone, such that values exceeding 1.0 reflect a disproportionately high LA size, and a value below 1.0 suggests the LA dimension is below than predicted. Pearson correlation coefficients were obtained for un-indexed and indexed LA size using both the per-ratio standard and allometric estimate against each body size parameter. The indexed LA size was then examined after stratification of the population based on gender and age (ranges 1–4.9, 5–12.9 and $\geq$13 years). The respective R^2 for each model was then compared to assess the proportion of variance in LA size explained by the isometric and allometric methods. Residual and regression diagnostic analyses were performed. Residuals were normally distributed and the assumption of constant variance appeared to be valid. Extreme leverage points were identified by studentized residuals exceeding a value of ± 2. Results did not differ when these influential points were excluded, e.g. the scaling exponents for BW with and without influential points ($n = 168$, 4% of data) were 0.252 and 0.255, respectively. Analysis was performed with SAS 9.0 statistical software (SAS Institute). A P-value <0.05 was considered significant.

Results

Subject characteristics

Patients had a mean age of 9.0 ± 5.2 years (range 1–17 years) (*Table 1*). Overall 44.0% of subjects were female. The mean BW was 36.0 ± 19.9 kg, with an average HT of 1.3 ± 0.3 meters. The mean BMI and BSA were 18.5 ± 3.3 kg/m^2 and 1.1 ± 0.5 m^2, respectively. The mean anterior to posterior LA dimensions was 25.7 ± 4.9 mm.

Correlation coefficients for the un-indexed and indexed left atrial size

As expected, we found strong correlations between measured LA size and all the body size variables ($r = 0.77$ WT; $r = 0.75$ HT; $r = 0.55$ BMI; $r = 0.77$ BSA; all $P < 0.001$) (Row 1: *Table 2*). This confirms that in general an increase in body size in children is associated with an increase in LA size. Although, the aim of normalization is to remove the effect of the body size variable on the cardiac dimension, normalization of left atrial size by simple linear methods, instead of removing the association, either increased the association between the body size variable and the cardiac dimension or failed to completely remove it (*Table 2*: rows 2–5). For example, dividing by BW increased the degree of correlation between BW and LAD from 0.76 to 0.87, while dividing by HT only decreased the association between HT and LAD from 0.75 to 0.63, leaving a strong residual relationship. Furthermore, simple linear correction had the effect of converting the relationship between all body size variables and cardiac dimensions from a positive to a negative, suggesting an over-correction. Also, simple linear scaling of LAD by one body size variable did not remove the effect of other measures of body size. For example, linear normalization using HT left strong residual

Table 1 Demographics and anthropometrics of the study population ($N = 4109$)

	Mean (SD)	Range
Age (years)	9.0 (5.2)	1–17
Body weight (kg)	36.0 (19.9)	8.2–91.4
Height (m)	1.3 (0.3)	0.7–1.9
BMI (kg/m^2)	18.5 (3.3)	10.7–33.0
BSA	1.1 (0.5)	0.4–2.1
LA size (mm)	25.7 (4.9)	10–38

Female gender: 44.0% ($n = 1809$).

Table 2 Indexing left atrial size: Pearson correlation coefficients

	LA size	Body weight	Height	BMI	BSA
LA size		0.77	0.75	0.55	0.77
LA size/BW	−0.58	−0.87	−0.92	−0.59	−0.91
LA size/HT	0.02	−0.50	−0.63	−0.12	−0.57
LA size/BMI	0.54	0.07	0.30	−0.39	0.17
LA size/BSA	−0.46	−0.83	−0.90	−0.48	−0.87
LA size/BW^2	−0.62	−0.77	−0.87	−0.48	−0.83
LA size/HT^2	−0.49	−0.77	−0.90	−0.33	−0.84
LA size/BMI^2	0.02	−0.37	−0.11	−0.78	−0.27
LA size/BSA^2	−0.61	−0.80	−0.91	−0.45	−0.86
LA size/$a BW^x$	0.62	−0.01	−0.01	−0.01	−0.01
LA size/$b HT^y$	0.66	0.10	0.01	0.25	0.06
LA size/$c BMI^z$	0.83	0.41	0.56	0.01	0.48
LA size/$d BSA^w$	0.63	0.02	−0.02	0.09	0.01
LA size/f	0.62	−0.01	−0.01	0.01	−0.01

$F = f(BW, HT) = g \times BW^s \times HT^t$.

Allometric scaling factors and exponents with 95% CI obtained from ordinary least squares linear regression (see Methods section): $a = 10.665 \pm 1.022$, $x = 0.252 \pm 0.006$; $b = 21.693 \pm 1.006$, $y = 0.591 \pm 0.016$; $c = 4.433 \pm 1.090$, $z = 0.600 \pm 0.030$; $d = 24.903 \pm 1.004$, $w = 0.348 \pm 0.010$; $g = 11.179 \pm 1.075$, $s = 0.235 \pm 0.026$, $t = 0.042 \pm 0.061$.

correlations between the LAD, WT, and BSA ($r = -0.50$ and $r = -0.57$, respectively). Raising the body size index to an arbitrary higher power (in this instance the second power) further increased the residual correlations with all of the scaling variables (*Table 2*: row 6–9).

In contrast, the LA size indexed using the optimal AE for each variable completely was more successful at removing the effect of the indexing body size variable on the LAD. For example, allometric indexing by BW using an exponent of 0.25 and a scaling factor of 10.67 decreased the residual correlation of BW with LAD from 0.77 to −0.01. While all scaling variables of the optimal AE successfully removed the effect of that variable, only scaling by BW and the optimal allometric combination of BW and HT removed the effect of all size variables (all residual correlations within ±0.01). While allometric correction for HT completely removed the residual correlation between the indexed LAD and HT, it did not completely remove the association between LAD indexed using HT and other body size variables (WT, $r = 0.10$; BMI, $r = 0.25$; and BSA $r = 0.06$).

Effect of gender on left atrial dimension

The mean LA size, using any of the allometrically derived models approached 1.0, suggesting a close relationship between the observed LA and expected LA size (*Table 3*). The mean LA size before correction for body size was greater in males than females, and this difference remained significant even after correction using any of the allometric models. However the actual differences in corrected means were small and unlikely to be clinically relevant (0.022 for BW, 0.019 for HT, 0.039 for BMI, and 0.022 for BSA). However, if required, gender-specific exponent and factors can be employed to eliminate these differences (*Table 4*).

The influence of age on the allometrically indexed left atrial dimension

To assess the influence of age on the allometrically-derived formula, we stratified our subjects into three age groups (*Table 5*). Increasing age among children did not appear to be associated with a trend towards an increase in corrected LA size. Apart from allometrically indexed BMI, there were no differences between the different age strata. Even among the BMI group, the maximal difference between groups was <2% and unlikely to be clinically significant.

The proportion of left atrial variance predicted by body size parameters using both the liner and allometric models

With regard to the relative ability of either method to explain the variability of LA size observed, the proportion of variance accounted for by the allometric model was similar to the simple linear model in this regard. In children, both WT and HT explained ∼60% of the variance in LAD, whereas BMI explained 30% (*Table 6*).

Discussion

In theory, for a scaling technique to correctly remove the effects of body size on a physiologic variable, the scaled variable should be independent of body size.[9] In this study of over 4000 echocardiographically normal children, we show that, as in adults: (i) conventional linear scaling using BW, HT, BSA, and BMI does not remove the association between these indices and the left atrial size and in some cases actually increased the association, albeit shifting the correlation from positive to negative, (ii) scaling using an allometric model successfully removed the influence of each body size parameter on the indexed cardiac dimension (for example, indexing using BW successfully removed the influence of BW on the indexed LA dimension), however, only allometric scaling using BW and the allometric combination of BW and HT completely removed the influence of the indexing body size parameter and all other body size parameters (i.e. indexing using BW removed the influence of BW as well as removed the influence of HT, BSA, and BMI) with BW being the most practical and the easiest to measure.

These data differ from our results in adults in which the correlations between LA size and body size are stronger in the child than in the adult [BW $r = 0.77$ vs.0.43, HT 0.75 vs. 0.20, BMI 0.55 vs. 0.39, and BSA 0.77 vs. 0.44 (JASE, 2008, in press)], consistent with the recognized exponential relationship between body size and chamber size over the full range of human growth and aging. Likewise the degree of variance explained by subject size is much greater in the child than in the adult. For example, HT accounts for only 4% of the variance in LA size in adults compared with 57% in children. The same relationship holds true for BW (21% vs. 60%) and BSA (19% vs. 59%), where the impact in children far exceeds than in adults. Despite these differences, the AE for BW was quite similar between the two populations (0.26 in adults vs. 0.25 in children). In contrast the exponents for HT-containing variables differed between the two groups (HT 0.43 vs. 0.59, BMI 0.27 vs. 0.60, and BSA 0.45 vs. 0.35, in adults and children, respectively). Thus in two separate cohorts, totalling almost 20 000 subjects,

Table 3 Indexed left atrial size by ordinary least squared (OLS) estimates of scaling factor and exponents, overall and by gender

	Mean ± SD	Range	Males (mean ± SD)	Females (mean ± SD)	*P*-value (male vs. females)
LA size/aBW^x	1.008 ± 0.121	0.436–1.490	1.018 ± 0.119	0.996 ± 0.123	<0.001
LA size/bHT^y	1.008 ± 0.126	0.410–1.530	1.016 ± 0.124	0.997 ± 0.129	<0.001
LA size/cBMI^z	1.012 ± 0.162	0.403–1.622	1.029 ± 0.167	0.990 ± 0.154	<0.001
LA size/dBSA^w	1.007 ± 0.122	0.425–1.492	1.017 ± 0.120	0.995 ± 0.124	<0.001
LA size/f	1.009 ± 0.121	0.434–1.485	1.018 ± 0.119	0.996 ± 0.123	<0.001

See *Table 2* footnote for scaling factors and exponents.

Table 4 Male and female specific scaling factors and exponents (males $N = 2300$; females $N = 1809$)

	Males scaling factor, AE	Females scaling factor, AE	Males indexed LA (mean ± SD)	Females indexed LA (mean ± SD)	*P*-value (male vs. female)
LA size/aBW^x	10.665, 0.255	10.740, 0.246	1.008 ± 0.118	1.009 ± 0.124	0.81
LA size/bHT^y	21.846, 0.596	21.499, 0.580	1.008 ± 0.123	1.008 ± 0.130	0.87
LA size/cBMI^z	4.586, 0.593	4.217, 0.609	1.015 ± 0.164	1.014 ± 0.158	0.83
LA size/dBSA^w	25.128, 0.351	24.582, 0.341	1.007 ± 0.119	1.009 ± 0.126	0.75
LA size/f	11.811, 0.219, 0.090	10.186, 0.265, −0.047	1.005 ± 0.118	1.009 ± 0.124	0.37

AE, allometric exponent.

including echocardiographically normal adults and children, and an additional cohort of almost 1500 predominantly obese females, we find virtually the same AE for BW (0.26, 0.25, and 0.25, respectively). Likewise, the BW exponent in the optimal allometric combination of BW and HT in each of the studies was similar (0.27, 0.24, and 0.23) emphasizing the stability of this measure. Our results are similar to those of George *et al.*,[10] who reported an AE of 0.29 for body mass in a group of 464 junior athletes. Several authors have discounted WT as a scaling variable for cardiac dimensions, based on the observed exponential relationship of WT and cardiac dimensions,[1,11,12] the fact that WT can change significantly in the same individual, and the different contributions of fat-free mass (FFM) and fat mass to body mass between individuals. This has generally been done without testing the ability of WT to remove the effects of body size using an allometric approach. Furthermore, the argument that WT can change in the same person does not negate the fact that cardiac dimensions can change proportionately.[13]

Although we find BW to be the simplest and most accurate method for removing the effects of body size, other authors have suggested HT and BSA as the appropriate scaling parameters in both children and adults.[2,14] Height has been advocated since it is constant, unlike the disease-related change in WT, is independent of obesity, and may be a surrogate for FFM (although the latter assumption has been challenged[11,15]). In a study on junior athletes, George *et al.*[10] also question the use of HT as a scaling variable because of the limited range of HT's in adults and the difference in slopes between the HT variable and cardiac dimensions in male and female athletes. Our data indicate that HT as a linear scaling variable is clearly inaccurate, since normalization by HT fails to remove the residual correlation with HT (−0.63) and the optimal AE for HT is 0.59 rather than 1. Even scaling by HT to the optimal AE failed to completely remove all of the effects of body size, although the residual correlations with WT containing parameters in children are smaller than those noted in adults.

Because of its recognized value in normalizing cardiac output for patient size, BSA has also been advocated as a scaling parameter for cardiac dimensions.[1,2,16] Gutgesell *et al.*[1] demonstrated that BSA to the first power failed to account for the curvilinear relationship between body size and linear cardiac chamber dimensions and that a more appropriate normalization was obtained using BSA to the 0.5 power. Unfortunately, in their study, based on normal values from the literature, the exponent was arbitrarily selected and residual correlations were not examined. Sluysmans and Colan[2] likewise found that indexing valve and vascular dimensions by BSA to the 0.5 power removed the residual correlation of the indexed variable with BSA. They also found that the average correlation between BSA (calculated using the Haycock formula) and each of their 19 valvular and vessel dimensions was better than that for WT (mean $r = 0.880$ for WT vs. 0.885 for BSA), however, the differences were minimal and they did not examine the ability of either variable to remove all of the effects of body size. In our study, all of the scaling variables to the optimal exponent successfully removed the effects of that variable, but BSA to the optimal exponent, while performing better than HT failed to correct body size as completely as WT alone. In addition, while the exponents for WT were similar in both adults and children, the exponent for BSA in our studies was smaller in children (0.35) than adults (0.45). These results are comparable with those

Table 5 Indexed left atrial size stratified by age

	Age 1–4.9 years, Mean ± SD ($n = 1102$)	Age 5–12.9 years, Mean ± SD ($n = 1655$)	Age ≥ 13 years, Mean ± SD ($n = 1352$)	*P*-value trend
LA size/ aBW^x	1.004 ± 0.127	1.016 ± 0.119	1.002 ± 0.119	0.52
LA size/ bHT^y	1.011 ± 0.129	0.998 ± 0.121	1.017 ± 0.130	0.18
LA size/ cBMI^z	0.873 ± 0.136	1.047 ± 0.141	1.082 ± 0.136	<0.001
LA size/ dBSA^w	1.009 ± 0.127	1.007 ± 0.119	1.005 ± 0.122	0.42
LA size/ f	1.006 ± 0.127	1.015 ± 0.119	1.003 ± 0.120	0.45

See *Table 2* footnote for scaling factor and exponent.

Table 6 Proportion of variance explained (R^2) from OLS allometric and isometric linear models

Body size prediction measure	Allometric model	Isometric model
BW	0.601	0.585
HT	0.569	0.565
BMI	0.275	0.306
BSA	0.595	0.592
BW and HT	0.601	0.595

previously reported by our group (BSA exponent = 0.38) in a study of 268 normal subjects, 73% of whom were children.[16] Our data in children is also similar to that of Henry *et al.*,[3] who found that regression equations based on WT and BSA provide almost identical corrections for body size with LAD relating to the cube root of BSA.

Although the scaling factors are omitted in most studies and the scaled values expressed in absolute terms (e.g. cm/m or cc/m^2), retaining the scaling factors results in an expected mean value of '1' and a standard deviation of ≈0.1. In this format the relative size of all chamber/vascular dimensions can be compared between populations and chambers obviating the need to remember different normal values for every chamber dimension. Although scaling factors, like exponents, will differ slightly when calculated for different populations, our results for adults and children are again quite similar for all parameters, except BMI (BW 10.52 vs. 10.66, HT 25.66 vs. 21.7, BMI 13.65 vs. 4.43, and BSA 24.63 vs. 24.9, for adults and children, respectively). As in adults the choice of a scaling variable depends on the question being asked. However, our data suggest that if the goal is to remove the effects of body size then WT is the simplest and most accurate choice for both adults and children.

All of the allometric models, except BMI, successfully removed the effects of age. This differs from the adult population where there is a small but significant age-related increase in LAD. This may be caused by age-related changes in LV relaxation in the adult. These changes are well recognized to accompany the normal aging process, and are not present in children.[17] Consistent with other studies, even after correction for body size, males were still significantly larger than females although the actual differences in the mean values were small.

Our study has several limitations which merit discussion. First, we used the formula of Du Bois and Du Bois to determine the BSA, consistent with our approach in other populations. Although widely used, this formula has been shown to increasingly underestimate BSA at values <0.7 m^2, [18] therefore an improved fit might have been obtained using other formulae for calculating BSA, such as the Haycock formula.[2,18] Second, selecting only echocardiographically normal patients (nine children with LA dimensions >38 mm were excluded) may also have eliminated very large subjects from the analysis. However, since most of our subjects had LA dimensions well below this level and the exponents and scaling factors we observed in this study were similar to those we observed in adults, we doubt this significantly affected our results. Third, a number of authors have suggested that FFM is the optimal indexing variable since fat mass has been found to be of minor importance in determining cardiac dimensions in adolescents and children.[19,20] Accurate measurement of FFM, however, is complex, and ideally requires the use of dual-energy X-ray absorptiometry (DEXA) which was beyond the scope of this large population study. Finally, our sample was hospital-based (but consisted of both inpatients and outpatients) and we did not have data on concomitant co-morbid conditions that may have impact on LA size. Therefore, it is possible that our findings may not be generalizable to other populations of healthy children. However, our restriction of the study population to those without echocardiographic evidence of structural heart disease minimizes the likelihood of inclusion of subjects unaccounted for cardiovascular disorders.

Our data, in a large population of echocardiographically normal children, confirms prior data indicating that the conventional assumption of linearity of cardiac chamber size and body size is flawed and the relationship between LA dimension and body size variables is more accurately expressed using an allometric model. We also demonstrate that, as in adults, WT accounts for the largest variance in LA dimensions and is the optimal body size variable to correct for difference in body size. The exponents and scaling factors for BW are similar in both adults and children and hence similar scaling parameters can be applied to both populations.

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