Original Article

Impact and pitfalls of scaling of left ventricular and atrial structure in population-based studies

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Background: Several allometric methods for indexing cardiac structures to body size have been proposed but the optimal way for normalization of cardiac structures is still controversial. We aimed to estimate the allometric exponents that best describe the relationships between cardiac dimensions and body size, propose normative values, and analyze how the different scaling metrics influence the prevalence of left ventricular hypertrophy (LVH) and chambers enlargement as well as predictive models for cardiovascular outcome in the community.

Methods: We measured left ventricular end-diastolic dimension, end-diastolic volume, left ventricular mass, and left atrial volume in randomly recruited population cohorts ($n = 1509$; 52.8% women; mean age, 47.8 years).

Results: In a healthy subgroup ($n = 656$), the allometric exponents that described the relationships between left ventricular end-diastolic dimension and body size were 1, 0.5, and 0.33 for body height, body surface area (BSA), and estimated lean body mass, respectively. With regard to left ventricular end-diastolic volume, left ventricular mass, and left atrial volume the allometric exponents for body height were 2.9, 2.7, and 2.0, respectively; for BSA, they ranged from 1.7 to 1.8; for estimated lean body mass all exponents were around 1. These exponents were used to appropriately scale the cardiac dimensions to body size and derived sex-specific cut-off limits for different indexed cardiac dimensions. The hazard ratios of cardiovascular outcome were highest for LVH defined by left ventricular mass/height$^{2.7}$.

Conclusion: Our study resulted in a proposal for thresholds for various indexed cardiac dimensions. Left ventricular mass indexed to height was sensitive in detection of LVH associated with obesity and slightly better predicted outcome.

Keywords: allometric, body size, cardiac dimensions, echocardiography, normal values

Abbreviations: eLBM, estimated lean body mass; EPOGH, European Project on Genes in Hypertension; FLEMENGHO, Flemish Study on Environment, Genes and Health Outcomes; LAE, left atrial enlargement; LAV, left atrial volume; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVH, left ventricular hypertrophy; LVM, left ventricular mass; SD, standard deviation

INTRODUCTION

Scaling of cardiac dimensions is important because it normalizes these measures for differences in body size and, therefore, influences early detection of cardiac chamber enlargement and potentially treatment thresholds. Theoretically, an appropriate scaling method yields body size independent cardiac metrics in a healthy population, that is, there is no residual correlation between the indexed dimension and the scaling parameter.

Although indexing of various cardiac dimensions is routinely performed in the imaging laboratory [1], there is still some controversy on the best scaling method [2,3]. First, ratiometric indexing to BSA that is usually performed, may not be always appropriate, for instance, for linear dimension, such as left ventricular end-diastolic diameter (LVEDD). Second, previous studies have already addressed issue of left ventricular mass (LVM) indexing [4–9], but appropriate scaling and normative values of LVEDD, left ventricular end-diastolic volume (LVEDV), and left atrial volume (LAV) are not as well established [10]. Third,

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although women and men have different body composition, in practice, we still use the same thresholds for definition of left heart enlargement. Finally, it remains unclear whether indexing to lean body mass (LBM) which is theoretically more physiological would yield better prediction of outcome than indexing to BSA or height in allometry.

In the present population study, we sought to define the appropriate scaling methods that yield body size-independent metrics for LVEDD, LVEDV, LVM, and LAV in healthy patients and to propose sex-specific normative values for the indexed cardiac parameters. We used different measures of body size including BSA, height, and estimated LBM as well as both ratiometric and allometric modeling. Moreover, because of the important role of left ventricular hypertrophy (LVH) and left atrial enlargement (LAE) as predictors of cardiovascular outcome in the general population, we explored how different scaling metrics influence the prevalence and prognostic values of LVH and LAE in the community.

METHODS

Study participants

The Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO) and European Project on Genes in Hypertension (EPOGH) studies received ethical approval. From August 1985 until December 2005, we randomly recruited a family-based population sample (FLEMENGHO cohort) from a geographically defined area in northern Belgium as described elsewhere [11]. EPOGH recruited participants from 1999 until 2001. The EPOGH investigators applied the same protocol, as used in FLEMENGHO. The initial response rate at enrolment was 75.0% [12]. All patients provided informed consent in writing.

The FLEMENGHO and EPOGH participants remained in follow-up. Five centers opted to perform echocardiographic phenotyping and to assess cardiac structure. Our current study population includes 1530 patients, who were examined from June 2005 until September 2009. We excluded 21 patients from analysis, because of atrial fibrillation ($n=12$), a pacemaker ($n=2$), or because LVM could not be reliably determined ($n=7$). Thus, the current analysis included 1509 participants: 818 FLEMENGHO participants (Noorderkempen, Belgium) and 691 EPOGH patients from Gdańsk ($n=141$) and Kraków ($n=244$), Poland, Mirano, Italy ($n=127$), and Novosibirsk, Russian Federation ($n=179$).

Echocardiography

In each center, one experienced physician did the ultrasound examination, using a Vivid 7 Pro (GE Vingmed, Horten, Norway), interfaced with a 2.5- to 3.5-MHz phased-array probe, according to a standardized protocol described in detail in previous publications [13]. A complete echocardiographic protocol is provided in the Data Supplement, http://links.lww.com/HJH/A606. Briefly, the observer obtained images, along the parasternal long and short axes and from the apical 4-, 2-chamber and long-axis views. All recordings included at least five cardiac cycles and were digitally stored for off-line analysis. One experienced observer (T.K.) analyzed the digitally stored images, using the EchoPac software, version 4.0.4 (GE Vingmed), averaging three cardiac cycles. End-diastolic left ventricular dimensions were used to calculate LVM by an anatomically validated formula [14]. LAV was calculated using the prolate-ellipsoid method [1,14] and was reliably determined in 1355 patients.

Other measurements

A complete description of other measurements, selection of healthy reference group and assessment and definition of outcome is provided in the Data Supplement, http://links.lww.com/HJH/A606. BMI was weight in kilograms divided by the square of height in meters. Lean body mass (eLBM) was estimated using the validated Hume's formula [15] and was (height (cm) $\times$ 0.2668 + weight (kg) $\times$ 0.4066 − 19.19) in men and (height (cm) $\times$ 0.4720 + weight (kg) $\times$ 0.2518 − 48.32) in women. BSA was weight $(kg)^{0.425}$ $\times$ height $(cm)^{0.725}$ $\times$ 0.007184.

Statistical methods

For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute, Cary, North Carolina, USA). We compared means and proportions by means of a large sample z-test and the McNemar test, respectively. To obtain allometric exponents in the healthy reference group, we first log transformed cardiac and body size variables, and then used ordinary linear models to regress log-transformed cardiac parameters on body size. We also estimated allometric exponents using nonlinear regression as implemented in the PROC NLIN procedure of the SAS software. We used the healthy reference group to define normative data for indexed cardiac dimensions. To obtain 95% confidence intervals of the 95 percentiles of the indexed cardiac variables, we computed the bootstrap distribution of the thresholds by randomly resampling the study population 1000 times with replacement, using the PROC SURVEYSELECT procedure. Statistical agreement for classification of presence/absence of LVH or LAE defined by different indexation methods was assessed with the kappa (κ) statistics. The frailty Cox regression model was also applied to calculate adjusted hazard ratios in the LVH or LAE groups using participants with normal cardiac structural parameters as the reference group.

RESULTS

Characteristics of participants

Of the 1509 participants included, 797 (52.8%) were women, and 635 (42.1%) were hypertensive patients of whom 380 (25.2%) were on antihypertensive drug therapy. Mean age (±SD) was 47.8 ± 15.8 years. Table 1 lists the clinical and echocardiographic characteristics of the participants by sex in the entire study population and in the reference group. As expected, men had higher body height and weight, eLBM, and BSA than women (Table 1). The echocardiographic measurements reflecting cardiac dimensions and volumes were greater in men than in women (Table 1).

TABLE 1. Characteristics of participants

Characteristic	Entire population		Healthy reference group	
	Men ($n=712$)	Women ($n=797$)	Men ($n=307$)	Women ($n=349$)
Anthropometrics				
Age (years)	47.1 ± 16.3	48.4 ± 15.4	38.8 ± 14.4	38.6 ± 12.2
Height (cm)	175.5 ± 7.21	162.9 ± 6.63‡	176.9 ± 6.96	164.6 ± 6.20‡
Weight (kg)	82.4 ± 13.1	69.9 ± 14.2‡	76.4 ± 9.84	62.0 ± 8.37‡
Estimated lean body mass (kg)	61.1 ± 6.27	46.2 ± 5.28‡	59.1 ± 5.14	45.0 ± 4.17‡
BSA (m^2)	1.98 ± 0.16	1.75 ± 0.17‡	1.93 ± 0.14	1.68 ± 0.12‡
BMI (kg/m^2)	26.8 ± 4.07	26.4 ± 5.19	24.4 ± 2.81	23.0 ± 2.95‡
SBP (mmHg)	131.9 ± 16.0	127.8 ± 20.1‡	122.0 ± 8.97	114.7 ± 10.2‡
DBP (mmHg)	81.6 ± 10.4	78.9 ± 11.0‡	76.1 ± 7.69	73.2 ± 7.46‡
Questionnaire data				
Current smoking, *n* (%)	170 (23.9)	151 (19.0)*	92 (30.0)	80 (22.9)*
Drinking alcohol, *n* (%)	376 (52.8)	138 (17.3)‡	176 (57.3)	65 (18.8)‡
Hypertensive, *n* (%)	320 (44.9)	315 (39.5)*	...	...
Treated for hypertension, *n* (%)	168 (23.6)	212 (26.6)	...	...
Diabetes, *n* (%)	34 (4.78)	22 (2.76)*	...	...
Echocardiography				
Left ventricular end-diastolic diameter (cm)	5.26 ± 0.44	4.82 ± 0.39‡	5.20 ± 0.38	4.74 ± 0.35†
Interventricular septum (cm)	1.02 ± 0.16	0.91 ± 0.15‡	0.96 ± 0.13	0.82 ± 0.10‡
Posterior wall (cm)	0.95 ± 0.13	0.84 ± 0.13‡	0.89 ± 0.11	0.77 ± 0.09‡
Relative wall thickness	0.38 ± 0.06	0.36 ± 0.06‡	0.36 ± 0.05	0.34 ± 0.04‡
Left ventricular mass (g)	196.8 ± 47.1	146.1 ± 38.6‡	176.2 ± 35.1	124.4 ± 24.7‡
Left ventricular end-diastolic volume (ml)	111.0 ± 24.7	81.6 ± 17.0‡	108.7 ± 23.6	78.8 ± 15.1‡
Ejection fraction (%)	61.9 ± 6.62	64.2 ± 6.31‡	62.0 ± 5.72	63.6 ± 5.95‡
Left atrial volume (ml)	46.9 ± 14.8	37.3 ± 11.3‡	40.8 ± 9.69	30.7 ± 6.89‡

Values are mean (±SD), or number of patients (%). *P* values are for the differences between men and women.
*$P \leq 0.05$.
‡$P \leq 0.001$.

Relationship between cardiac size and body composition in healthy participants

Table 2 shows power exponents for the relationships between cardiac dimensions and body size variables derived from the healthy reference group. In our study, the allometric exponents that described the relationships between linear cardiac structure, such as LVEDD and body size were 0.97, 0.55, and 0.33 for height, BSA, and eLBM, respectively (Table 2). Allometric exponents derived for LVEDV, LVM, and LAV in relation to body height were 2.90, 2.65, and 2.04, respectively (Table 2). LVEDV and LVM were related to BSA raised to approximately a power of 1.8, whereas for the relationships between LAV and BSA, the allometric exponent was 1.7. Three-dimensional cardiac variables were related to eLBM to approximately a power of 1 (Table 2). We used the derived exponents to appropriately scale the cardiac dimensions to body size measures in our population (Table 3). Because indexing cardiac dimensions to BSA via the ratiometric approach (i.e., raised to power of 1) is commonly used in clinic, we included in our analysis scaling of cardiac dimensions to BSA. Although Fig. 1 shows that ratiometric scaling of LVEDD and LVM to BSA did not eliminate the influence of body size as compared with appropriate allometric scaling to height and eLBM.

Normal values of indexed cardiac dimensions in the healthy reference group

Table 4 shows the 95 sex-specific percentiles for the cardiac dimensions in all healthy patients selected from the entire study population. We rounded these 95 sex-specific percentiles cardiac dimensions to the closest integer value. All of these rounded thresholds fell within the 95% confidence boundaries for the 95 sex-specific percentiles of the cardiac structural variables in the reference group (Table 4). Supplemental Figures S1–S4, http://links.lww.com/HJH/A606 show the age-specific percentiles of the indexed LVEDD, LVEDV, LVM, and LAV in healthy men and women.

Prevalence of left ventricular hypertrophy and left atrial enlargement and the association with cardiovascular risk factors

We applied the derived sex-specific criteria of indexed LVM, LAV, LVEDD, and LVEDV to estimate the prevalence of cardiac dimensions enlargements in our population. Figure 2 shows the prevalence of LVH and LAE in the entire study population and by BMI category. The prevalences of LVH and LAE defined by different indexation methods were significantly different ($P < 0.001$) with exception of prevalence LVH/BSA and LVH/eLBM ($P = 0.58$). As expected in overweight ($n = 600$) and obese ($n = 319$) participants, indexation of LVM and LAV to height in allometry detected higher LVH and LAE prevalences than other indexation methods ($P < 0.0001$). Figure 3 shows the prevalence of LVEDD and LVEDV enlargements in the entire study population and by BMI category. We also observed that in overweight and obese participants, indexation of LVEDD and LVEDV to height detected higher prevalence of left ventricular dimensions enlargements than other indexation methods ($P < 0.0001$).

TABLE 2. Allometric exponents for the relationships between cardiac dimensions and body size variables in the healthy reference group

	Allometric exponent (±SD)					
	Height		BSA		eLBM	
Parameter	Calculated	Rounded	Calculated	Rounded	Calculated	Rounded
Left ventricular end-diastolic diameter						
Model 1	0.97 ± 0.054	1.0	0.55 ± 0.026	0.50	0.33 ± 0.016	0.33
Model 2	0.90 ± 0.054		0.55 ± 0.026		0.33 ± 0.016	
Left ventricular end-diastolic volume						
Model 1	2.90 ± 0.16	2.9	1.82 ± 0.074	1.8	1.10 ± 0.043	1.0
Model 2	2.93 ± 0.16		1.81 ± 0.076		1.15 ± 0.047	
LV mass						
Model 1	2.65 ± 0.17	2.7	1.85 ± 0.072	1.8	1.14 ± 0.044	1.0
Model 2	2.61 ± 0.17		1.81 ± 0.072		1.16 ± 0.046	
Relative wall thickness						
Model 1	-0.035 ± 0.099	NA	0.14 ± 0.052	NA	0.11 ± 0.032	NA
Model 2	-0.031 ± 0.099		0.14 ± 0.052		0.11 ± 0.032	
Left atrial volume						
Model 1	2.04 ± 0.20	2.0	1.69 ± 0.086	1.7	0.99 ± 0.055	1.0
Model 2	2.06 ± 0.20		1.66 ± 0.088		1.01 ± 0.056	

The calculated allometric exponents are derived from ordinary linear models after log-transformation of cardiac dimensions and body size (Model 1) and from nonlinear regression models (Model 2). The rounded values were obtained by rounding the calculated allometric exponents and were applied to index cardiac dimensions. The relationship between relative wall thickness and body size measurement was not significant and, therefore, this cardiac dimension should not be indexed.
eLBM, estimated lean body mass; NA, not applicable.

Overall, there was a good agreement between indexation of cardiac dimensions to BSA and eLBM in identifying patients with LVH or LAE or LVEDV enlargements (Supplemental Table S1, http://links.lww.com/HJH/A606). Moreover, we found 95% of agreement ($\kappa = 0.86$; $P = 0.58$) between LVM/height$^{2.7}$ and LVM/height$^{1.7}$ in identifying patients with LVH (Supplemental Table S1, http://links.lww.com/HJH/A606).

Table 5 shows the adjusted odds of having LVH or LAE in the entire cohort. Higher age and hypertension were significantly associated with increased risk of LVH and LAE defined by any indexation method. Except for the LVM/BSA$^{1.8}$, all indexation estimated a higher risk of LVH in women than in men (Table 5) when we applied sex-specific cut-offs. Moreover, indexing LVM to BSA, BSA$^{1.8}$, and LBM related to a lower risk of LVH in overweight and obese patients as compare with height-based indexes.

Outcome analysis

In the FLEMENGHO cohort, the median follow-up was 4.8 years (fifth to 95th percentile, 3.0—5.4). Sixty-three participants experienced a fatal or nonfatal cardiovascular endpoint including 45 patients who had a cardiac event. Table 6 shows the multivariable-adjusted hazard ratios

TABLE 3. Indexed echocardiographic structural characteristics of participants

	Entire population			Healthy reference group		
Indexed parameter	Men ($n = 712$)	Women ($n = 797$)	P	Men ($n = 307$)	Women ($n = 349$)	P
Left ventricular end-diastolic diameter						
BSA (cm/m^2)	2.67 ± 0.25	2.77 ± 0.26	<0.0001	2.70 ± 0.22	2.84 ± 0.20	<0.0001
BSA (cm/(m^2)$^{0.5}$)	3.74 ± 0.29	3.65 ± 0.27	<0.0001	3.74 ± 0.25	3.67 ± 0.23	<0.0001
eLBM (cm/10 kg$^{0.33}$)	2.90 ± 0.22	2.91 ± 0.22	0.10	2.89 ± 0.19	2.89 ± 0.19	0.84
Height (cm/m)	3.00 ± 0.26	2.96 ± 0.25	0.006	2.94 ± 0.21	2.88 ± 0.21	0.001
Left ventricular end-diastolic volume						
BSA (ml/m^2)	56.0 ± 11.2	46.8 ± 8.38	<0.0001	56.1 ± 10.9	46.8 ± 7.75	<0.0001
BSA (ml/(m^2)$^{1.8}$)	32.5 ± 6.68	30.2 ± 5.65	<0.0001	33.2 ± 6.47	31.0 ± 5.14	<0.0001
eLBM (ml/10 kg)	18.2 ± 3.61	17.7 ± 3.28	0.025	18.4 ± 3.54	17.5 ± 3.00	0.001
Height (ml/m$^{2.9}$)	21.7 ± 4.87	19.8 ± 4.25	<0.0001	20.8 ± 4.36	18.6 ± 3.60	<0.0001
Left ventricular mass						
BSA (g/m^2)	99.3 ± 21.8	83.4 ± 19.2	<0.0001	91.2 ± 16.4	74.2 ± 13.3	<0.0001
BSA (g/(m^2)$^{1.8}$)	57.7 ± 13.0	53.6 ± 12.4	<0.0001	54.0 ± 10.1	49.2 ± 8.94	<0.0001
eLBM (g/10 kg)	32.2 ± 7.01	31.7 ± 7.85	0.20	29.8 ± 5.35	27.8 ± 5.33	<0.0001
Height (g/m$^{2.7}$)	43.4 ± 11.4	39.5 ± 11.6	<0.0001	37.9 ± 8.08	32.6 ± 7.11	<0.0001
Height (g/m$^{1.7}$)	75.9 ± 18.9	64.0 ± 17.7	<0.0001	66.9 ± 13.5	53.5 ± 11.0	<0.0001
Left atrial volume						
BSA (ml/m^2)	23.6 ± 6.95	21.3 ± 5.72	<0.0001	21.0 ± 4.64	18.3 ± 3.69	<0.0001
BSA (ml/(m^2)$^{1.7}$)	14.6 ± 4.31	14.2 ± 3.83	0.37	13.3 ± 2.95	12.8 ± 2.55	0.05
eLBM (ml/10 kg)	7.63 ± 2.22	8.11 ± 2.31	0.004	6.88 ± 1.51	6.85 ± 1.47	0.97
Height (ml/m$^{2.0}$)	15.3 ± 5.10	14.2 ± 4.48	<0.0001	13.1 ± 3.21	11.4 ± 2.64	<0.0001

Values are mean (±SD). P values are for the differences between men and women.
eLBM, estimated lean body mass.

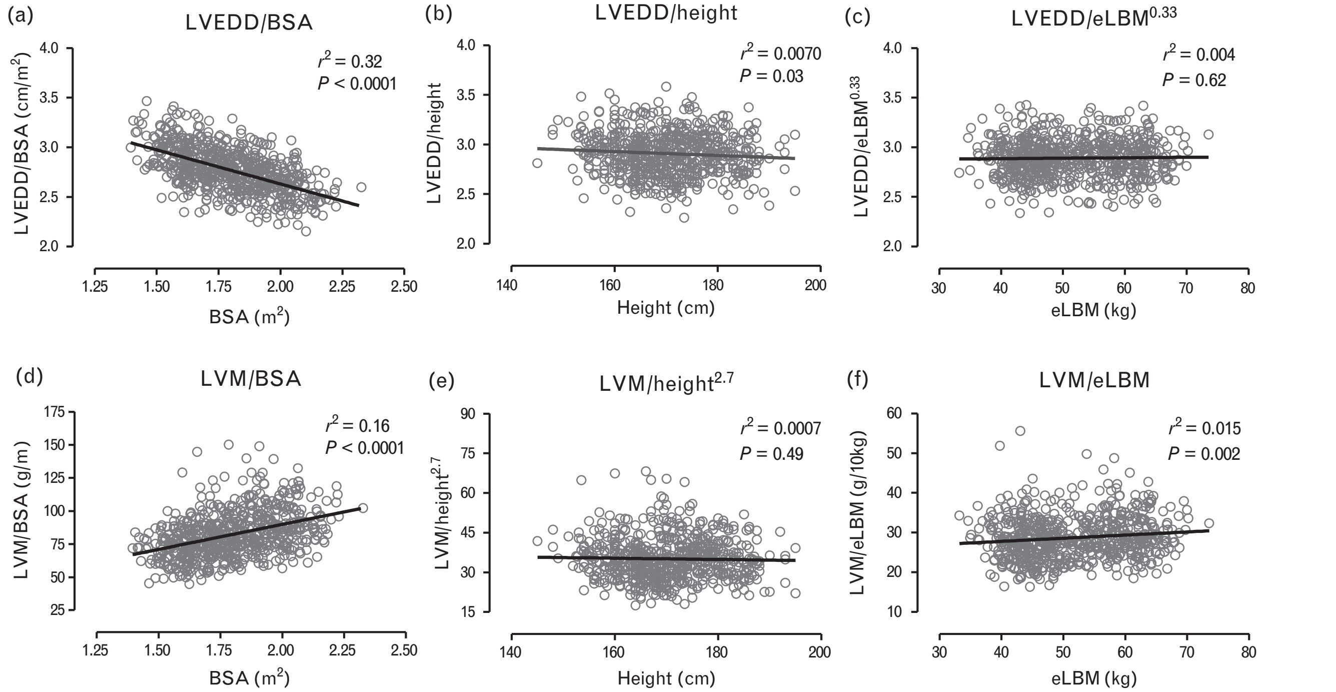

FIGURE 1 Scatter plot of indexed left ventricular end-diastolic dimension (panels a, b, and c) and left ventricular hypertrophy (panels d, e, and f) against their scaling parameters in 656 patients from the healthy reference group.

expressing the risk in LVH or LAE compared with normal cardiac structure. LVH classified by normalization to any of scaling indexes significantly predicted all cardiovascular events (Table 6). Although the hazard ratios of all cardiovascular events were highest for LVH defined by LVM/height$^{2.7}$ (Table 6). Supplemental Table S2, http://links.lww.com/HJH/A606, shows the multivariable-adjusted hazard ratios associated with every SD change in unindexed and indexed LVM and LAV analyzed as continuous variables.

DISCUSSION

Our study highlights the strengths and limitations of the different methods of indexing left cardiac dimensions in the general population. The key findings can be summarized as

TABLE 4. The 95th percentiles for the indexed echocardiographic parameters in the reference groups

	Men ($n = 307$)			Women ($n = 349$)		
Indexed parameter	95th percentile	95% CI for the percentiles	Rounded limits	95th percentile	95% CI for the percentiles	Rounded limits
Left ventricular end-diastolic diameter						
BSA (cm/m^2)	3.06	3.04–3.11	3.10	3.19	3.12–3.23	3.20
BSA$^{0.5}$ (cm/(m^2)$^{0.5}$)	4.16	4.11–4.23	4.20	4.06	4.00–4.11	4.10
eLBM$^{0.33}$ (cm/10 kg$^{0.33}$)	3.21	3.16–3.27	3.20	3.22	3.17–3.28	3.20
Height (cm/m)	3.29	3.22–3.34	3.30	3.26	3.21–3.32	3.25
Left ventricular end-diastolic volume						
BSA (ml/m^2)	74.6	72.2–78.2	75	60.5	59.3–61.9	60
BSA$^{1.8}$ (ml/(m^2)$^{1.8}$)	44.6	43.4–45.8	45	39.7	38.4–41.3	40
eLBM (ml/10 kg)	24.5	23.7–25.5	25	22.9	22.0–23.6	23
Height$^{2.9}$ (ml/m$^{2.9}$)	28.0	27.3–28.9	28	24.8	23.3–26.1	25
Left ventricular mass						
BSA (g/m^2)	120.5	116.7–123.2	120	96.3	92.5–100.1	95
BSA$^{1.8}$ (g/m^2)$^{1.8}$	71.5	68.3–75.4	70	63.7	62.1–64.9	64
eLBM (g/10 kg)	39.2	37.8–40.5	39	36.9	35.6–38.1	37
Height$^{2.7}$ (g/m$^{2.7}$)	51.8	49.9–53.5	52	45.4	43.8–46.5	45
Height$^{1.7}$ (g/m$^{1.7}$)	89.7	86.7–93.2	90	72.5	70.0–75.3	73
Left atrial volume						
BSA (ml/m^2)	28.9	28.1–29.7	29	24.8	24.2–27.5	25
BSA$^{1.7}$ (ml/m^2)$^{1.7}$	18.5	18.0–19.2	19	17.5	17.0–18.6	18
eLBM (ml/10 kg)	9.44	9.15–9.71	9.5	9.40	9.16–10.5	9.5
Height$^{2.0}$ (ml/m$^{2.0}$)	18.5	17.9–19.5	19	16.5	15.5–17.7	17

BSA, body surface area; eLBM, estimated lean body mass.

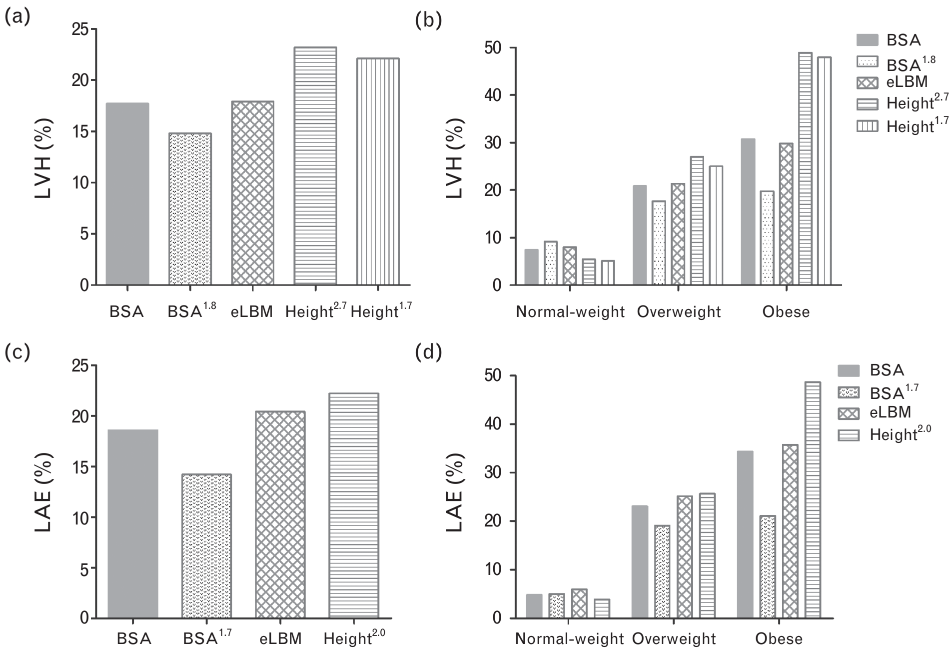

FIGURE 2 Crude prevalence of left ventricular hypertrophy and left atrial enlargement based in internal partition values for different indexation of left ventricular hypertrophy and left atrial enlargement in the entire study population (panels a and c) and by BMI category (panels b and d).

follows: body size indexation of cardiac parameters often follows the principle of geometric similarity, i.e. the cardiac dimension being scaled shares similar dimension with the scaling parameter raised to the appropriate power; sex-specific thresholds for most of the indexed cardiac parameters should be used to define left heart enlargement; allometric exponents for BSA derived in the healthy population may not be optimal when applied to the general population; and LVM indexed to height in allometry was more sensitive in detection of LVH associated with obesity and slightly better predicted cardiovascular outcome.

By definition, an optimal scaling parameter for cardiac dimensions should provide body size independent indexes [2,3]. The indexed cardiac parameter often shares

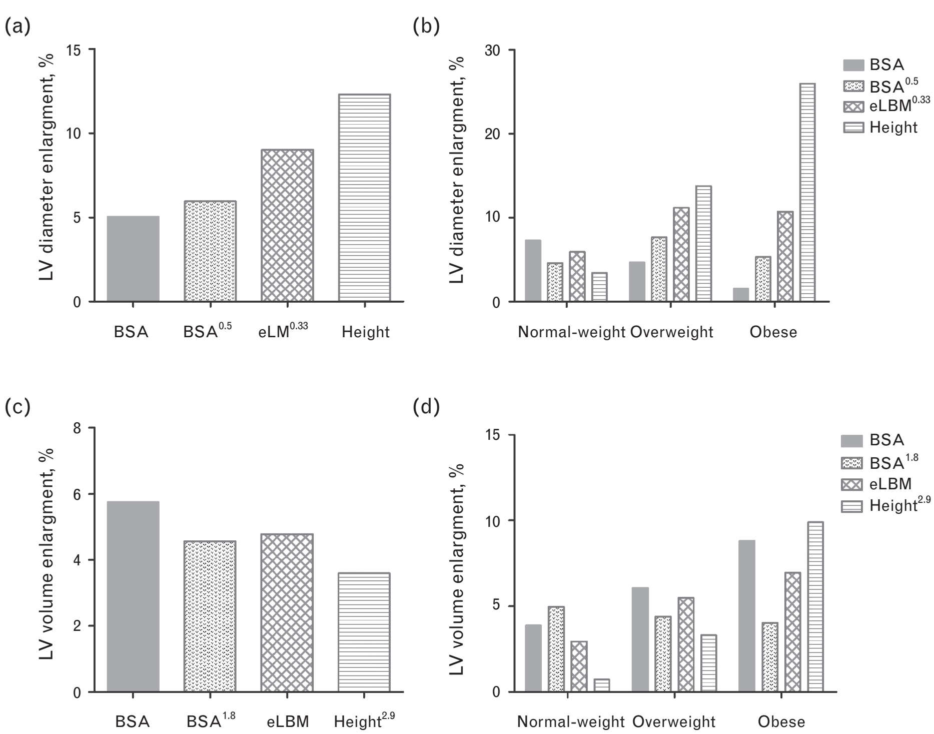

FIGURE 3 Crude prevalence of left ventricular end-diastolic diameter and volume enlargements based in internal partition values for different indexation of left ventricular end-diastolic dimension and left ventricular end-diastolic volume in the entire study population (panels a and c) and by BMI category (panels b and d).

TABLE 5. Adjusted odds ratios for having LVH or LAE in all subjects

Explanatory variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Left ventricular hypertrophy	BSA		$BSA^{1.8}$		eLBM		$Height^{2.7}$	
N, cases/noncases	267/1242		223/1286		270/1239		350/1159	
Age (+10 years)	1.68 (1.48–1.89)	<0.0001	1.91 (1.66–2.18)	<0.0001	1.76 (1.55–2.00)	<0.0001	2.02 (1.77–2.32)	<0.0001
Female	1.51 (1.11–2.05)	0.008	1.03 (0.76–1.41)	0.84	1.56 (1.15–2.12)	0.005	1.80 (1.33–2.43)	0.0001
Hypertension (1 vs. 0)	2.02 (1.43–2.87)	<0.0001	2.36 (1.63–3.41)	<0.0001	2.09 (1.47–2.96)	<0.0001	1.82 (1.31–2.53)	0.0004
Overweight	2.01 (1.34–3.01)	0.02	1.16 (0.77–1.67)	0.64	1.86 (1.25–2.76)	0.05	4.60 (2.94–7.21)	<0.0001
Obesity	3.03 (1.96–4.67)	<0.0001	1.11 (0.71–1.72)	0.84	2.62 (1.70–4.04)	0.0002	12.3 (7.63–19.7)	<0.0001
Left atrial enlargement[a]	BSA		$BSA^{1.7}$		eLBM		$Height^{2.0}$	
N, cases/ noncases	252/1103		192/1163		273/1082		303/1052	
Age (+10 years)	1.79 (1.63–2.16)	<0.0001	2.12 (1.81–2.48)	<0.0001	1.97 (1.79–2.37)	<0.0001	1.97 (1.79–2.37)	<0.0001
Female	1.64 (1.19–2.25)	0.002	1.22 (0.86–1.72)	0.26	1.38 (1.01–1.88)	0.04	1.35 (0.99–1.84)	0.06
Hypertension (1 vs. 0)	2.31 (1.61–3.30)	<0.0001	2.14 (1.43–3.21)	0.0002	2.37 (1.67–3.36)	<0.0001	2.17 (1.54–3.05)	<0.0001
Overweight	3.99 (2.47–6.43)	0.005	2.74 (1.68–4.45)	0.005	3.45 (2.20–5.39)	0.01	5.98 (3.57–10.0)	0.03
Obesity	6.18 (3.73–10.2)	<0.0001	2.71 (1.60–4.61)	0.014	5.13 (3.18–8.28)	<0.0001	16.8 (9.76–28.8)	<0.0001

Odd ratios (95% confidence interval) are for the risk associated with 10 years increase in age or with female sex, hypertension, overweight, and obesity. eLBM, estimated lean body mass.
[a]LAV was measured in 1355 patients.

comparable dimensions with its scaling parameters [16]. For example, the scaling exponents that describe the relationships of LVEDD (one-dimensional) with height (one-dimensional), BSA (two-dimensional), and eLBM (three-dimensional) are expected to be 1, 0.5, and 0.33, respectively [16]. In our study, we obtained exactly these allometric coefficients for LVEDD. Commonly used in the clinical practice scaling method to normalize LVEDD to BSA via the ratiometric approach might overadjust this cardiac dimension for the influence of body size especially in the obese patients and, therefore, as we demonstrated in our study, may underdiagnose increase in LV diastolic dimension in these patients [2]. We also observed that eLBM to the power of one emerged as appropriate scaling parameter for LVEDV, LVM, and LAV respecting the concordance of dimensions (all three-dimensional parameters). In our study, the derived allometric exponents for BSA and height were also close to values predicted by the geometric similarity and in line with previously published studies [5,9].

Epidemiology is highly regarded in evidence-based medicine for determining optimal thresholds for clinical practice. In the healthy participants, enrolled in this study, the 95th percentiles were considered as the higher limits of normality for the left heart dimensions. These preliminary threshold values for the population do not account for age. Although in absolute terms, the effect of age on cardiac dimensions is relatively small (Supplemental Figures S1–S4, http://links.lww.com/HJH/A606). To our knowledge, our

TABLE 6. Adjusted hazard ratios associated with LVH or LAE versus normal at baseline

		Fatal and nonfatal events					
		All cardiovascular			Cardiac		
Group	Total *N*	*N* of events	HR (95% CI)	*P*	*N* of events	HR (95% CI)	*P*
Left ventricular hypertrophy							
Normal	649	33	Referent		26	Referent	
LVH by BSA	149	30	2.15 (1.25–3.68)	0.0057	19	1.87 (0.98–3.55)	0.058
Normal	670	36	Referent		28	Referent	
LVH by $BSA^{1.8}$	128	27	1.72 (0.98–3.00)	0.059	17	1.45 (0.74–2.81)	0.28
Normal	646	33	Referent		26	Referent	
LVH by eLBM	152	30	1.95 (1.13–3.37)	0.016	19	1.64 (0.86–3.15)	0.13
Normal	603	28	Referent		21	Referent	
LVH by $height^{2.7}$	195	35	2.29 (1.25–4.17)	0.0070	24	2.37 (1.18–4.77)	0.015
Normal	618	32	Referent		24	Referent	
LVH by $height^{1.7}$	180	31	2.10 (1.18–3.72)	0.011	21	2.17 (1.10–4.29)	0.026
Left atrial enlargement[a]							
Normal	626	39	Referent		22	Referent	
LAE by BSA	157	22	1.18 (0.65–2.11)	0.59	18	1.74 (0.87–3.48)	0.12
Normal	655	42	Referent		29	Referent	
LAE by $BSA^{1.7}$	128	19	0.96 (0.53–1.73)	0.89	14	1.22 (0.61–2.46)	0.57
Normal	609	37	Referent		25	Referent	
LAE by eLBM	174	24	1.03 (0.58–1.83)	0.92	18	1.38 (0.70–2.71)	0.35
Normal	594	36	Referent		24	Referent	
LAE by $height^{2.0}$	189	25	1.07 (0.60–1.93)	0.81	19	1.61 (0.80–3.24)	0.18

Hazard ratios (HR) express the risk in each group of left ventricular hypertrophy or left atrial enlargement at baseline compared with the risk in the subjects with normal structural cardiac parameters at baseline. All hazard ratios were adjusted for sex, age, BMI, SBP, and current smoking. eLBM, estimated lean body mass; LAE, left atrial enlargement; LVH, left ventricular hypertrophy.
[a]LAV was measured in 783 patients.

TABLE 7. Summary of appropriate allometric exponents and upper reference limits for echocardiographic parameters indexed to height and eLBM

Parameter	Allometric exponent	Unit	Upper limit	
			Men	Women
Left ventricular end-diastolic diameter				
Height	1.0	cm/m	3.30	3.25
eLBM	0.33	cm/10 $kg^{0.33}$	3.20	3.20
Left ventricular end-diastolic volume				
Height	2.9	$ml/m^{2.9}$	28	25
eLBM	1.0	ml/10 kg	25	23
Left ventricular mass				
Height	2.7	$g/m^{2.7}$	52	45
eLBM	1.0	g/10 kg	39	37
Left atrial volume				
Height	2.0	$ml/m^{2.0}$	19	17
eLBM	1.0	ml/10 kg	9.5	9.5

eLBM, estimated lean body mass.

study was the first to provide normal values of various indexed cardiac dimensions, such as LVEDD, LVEDV, and LAV and highlight the importance of using sex-specific thresholds to detect cardiac dimension enlargement. Our sex-specific thresholds for LVM indexed to different body size variables are similar to the cut-offs reported from previous studies on LVM normal values in the general population [7,17]. Table 7 summarizes information on appropriate allometric exponents and upper reference limits for echocardiographic parameters indexed to height and eLBM as derived in our study. Further studies with large sample size are warranted to ensure internal and external validation of allometric indexes and optimal thresholds for left heart size and volumes.

The different scaling indexes derived from the healthy population might perform differently in distinguishing physiological from pathological cardiac remodeling. This may be explained by the fact that some indexing parameters are not truly body size independent and the scaling parameters relate differently to obesity or body composition. For instance, in previously published studies in athletes, physiological adaptation of LVM or LV volumes were closely associated with eLBM [17]. Therefore, indexing of LVM and LV volumes to eLBM might better identify the pathological increase in LVM that is disproportional to LBM [18]. Although this might be relevant only in morbidly obese patients. In our population, there were only a small number of patients with morbid obesity ($n=14$), and, therefore, indexing cardiac dimensions to BSA or eLBM yielded a comparable prevalence of LVH or chambers' enlargements. We also demonstrated that allometric indexation of LVM to BSA, significantly underestimated the prevalence of LVH and LAE in the obese patients, and may lead to erroneous conclusions in epidemiological studies. In contrast, indexing of LVM and LAV to height in allometry may be sensitive in detecting LVH and LAE particularly in overweight and obese patients compared with other methods, which are confounded by body weight. In contrast to Chirinos *et al.* [9] we found a very good agreement between LVM/$height^{2.7}$ and LVM/$height^{1.7}$ in identifying patients with LVH.

Our outcome analyses provide some additional insights of the value of the different indexing metric. We observed that LVH defined by LVM/$height^{2.7}$ and LVM/$height^{1.7}$ demonstrated highest predictive ability for all cardiovascular events (HRs 2.29 and 2.10, respectively). These findings are consistent with the study of Chirinos *et al.* [9]. In their study, the authors also showed that the risks of all cardiovascular events were significantly elevated in participants with LVH defined by LVM/$height^{2.7}$ (HR 1.73, $P<0.001$) and by LVM/$height^{1.7}$ (HR 1.53, $P=0.01$).

Our study has to be interpreted within the context of its potential limitations and strengths. First, the echocardiographic variables are prone to measurement error. In the present study, one experienced observer in each center recorded all echocardiographic images using a common highly standardized imaging protocol [13]. All digitally stored images were centrally postprocessed by one observer (T.K.). Second, because in our study, we included only white European populations, the generalizability of findings to other ethnicities is limited. Third, the derived exponents in our study were in line with previously published allometric analyses reported from theoretical models. This observation might be considered as a validation of our current results. Fourth, because of the small number of cardiovascular events collected only in the FLEMENGHO cohort, our study might be underpowered to determine which indexing method is best to predict outcome. Although our conclusions with regard to LVM were in line the findings of previous publications in general population [9]. On the other hand, we could not rule out that the associations between LAV and outcome that failed to reach statistical significance were because of a type II error.

In conclusion, our current study resulted in the proposal for diagnostic thresholds for various indexed cardiac dimensions, based on a healthy subgroup recruited via random sampling of the population in four European countries. LVM indexed to height has the advantage of being more sensitive in detection of LVH associated with obesity and slightly better for prediction of outcome.

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Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluation

Reviewer 1

This comprehensive echocardiographic study presents normal values and proposes threshold values for some cardiac dimension measures (left ventricular end-diastolic dimensions and volumes, left ventricular mass, and left atrial volume), and how they are best indexed for body size. This information is useful in order to improve risk prediction. Important study limitations are that the results are derived from white European populations and may not be relevant for other people. Finally, the association presented on cardiovascular outcome is based on rather few events.