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## **Allometric versus Ratiometric Normalization of Left Ventricular Stroke Volume by Doppler-echocardiography for Outcome Prediction in Severe Aortic Stenosis with Preserved Ejection Fraction**

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

## STRUCTURED ABSTRACT

**Background:** Appropriate normalization methods to scale Doppler-derived stroke volume (SV) to body size in patients with aortic stenosis (AS) are poorly defined and reference values are lacking. We aim to establish reference values of normalized SV in adults, and to compare the prognostic value of SV normalized by different methods in AS patients.

**Methods:** In 2781 normotensive, non-obese adults without cardiovascular disease we defined normal relationships between SV and body size by nonlinear regression. Reference SV values were calculated by quantile regression. We subsequently analyzed by Cox analysis the prognostic performance of ratiometric and allometric normalized SV in 1450 patients with severe AS and preserved LVEF under medical and surgical management.

**Results:** Unlike ratiometric normalization, allometric indexation eliminated the residual relationships between normalized SV and body size. The allometric exponents that adequately described the SV-height (H) and SV-body surface area (BSA) relationships were 1.32, and respectively 0.88. In males, low-flow (LF) reference values were:  $<28\text{ml/m}^2$ ,  $<30\text{ml/m}$ ,  $<30\text{ml}/(\text{m}^2)^{0.88}$ , and, respectively,  $<26\text{ ml}/\text{m}^{1.32}$ , and in females  $<27\text{ml/m}^2$ ,  $<28\text{ml/m}$ ,  $<29\text{ml}/(\text{m}^2)^{0.88}$ , and, respectively,  $<24\text{ ml}/\text{m}^{1.32}$ . In patients with severe AS,  $\text{SV}/\text{H}^{1.32}$  was most consistently associated with mortality and showed better prognostic performance than other normalized SV parameters (adjusted hazard ratios: 1.86 for  $\text{SV}/\text{H}^{1.32}$ , 1.72 for SV/H, 1.64 for SV/BSA, and 1.61 for  $\text{SV}/\text{BSA}^{0.88}$ ). Compared to H-normalization, BSA-normalization markedly overestimated the frequency of LF (3% vs. 9%).

**Conclusions:** We provide normative reference values and appropriate normalization methods for SV by Doppler-echocardiography. In severe AS,  $\text{SV}/\text{H}^{1.32}$  seems the most appropriate indexation method, especially in obese individuals.

## INTRODUCTION

In aortic stenosis (AS) with preserved ( $\geq 50\%$ ) left ventricular ejection fraction (LVEF), low-flow (LF) is defined [1,2] by a stroke volume (SV) normalized to body surface area (BSA)  $< 35 \text{ ml/m}^2$ . This cut-off, although arbitrarily established<sup>3</sup> has been found predictive of poor outcome in severe AS [3-5], and in mild-to-moderate AS [6]. While some studies showed a graded inverse relation between SV index and mortality [7], recent data in a wide spectrum of patients with severe AS and preserved LVEF suggest that the LF cut-off should be lowered below  $30 \text{ ml/m}^2$ . [8]

SV is routinely measured using Doppler-echocardiography at the aortic annulus. This measurement is recommended by guidelines [9] and is well correlated with invasive calculations. [10,11] However, few studies have reported reference values for Doppler-derived SV in healthy individuals. [12-14] As most cardiovascular parameters, SV is usually normalized to BSA by ratiometric indexation. This approach might not be optimal because in humans, the relationships between organ functions and body size are nonlinear. [15-17] In the presence of nonlinear relationships, the appropriate power of the allometric relation between the physiological measurement and body size is needed. [15-18] With this approach, the variable of interest is divided by a body size variable raised to a scalar exponent. [17] Data on allometric normalization of SV to body size in normal adults are scarce [16] and the prognostic value of different SV normalization methods in patients with AS has never been compared.

The objectives of this study are fourfold: 1) to establish the allometric exponents that drive the relationship between SV and body size in a large healthy adult population; 2) to provide normative reference values of normalized SV in adults; 3) to analyze the relationship

between normalized SV and obesity; and 4) to quantify and compare the prognostic value of SV normalized by different methods in patients with severe AS.

## **METHODS**

### **Study population**

We merged data from the Asklepios study [19] and from the Amiens-Lille cohort [8] both of which included adults free of overt cardiovascular disease. The Asklepios study recruited between October 2002 and October 2004 a cohort of 2524 apparently healthy, community-dwelling male and female volunteers aged 35-55 years, sampled from the twinned Belgian communities of Erpe-Mere and Nieuwerkerken, as previously described. [19] The Amiens-Lille cohort included 1991 consecutive individuals  $\geq 18$  years of age with normal echocardiograms identified from the echocardiography databases of the two institutions. [8] These individuals had normal blood pressure, no personal history of cardiovascular disease, and no major concomitant illnesses. To provide reference standards for normal body size - SV relationships, we selected a reference sample of 2781 normotensive non-obese (body mass index: 18 to 30 kg/m<sup>2</sup>) adults free of cardiovascular disease at baseline.

The effect of normalized SV on the risk of death during follow-up was assessed in 1450 patients with severe AS (defined as aortic valve area [AVA]  $< 1\text{cm}^2$  and/or AVA normalized to body surface area [BSA]  $< 0.6\text{cm}^2/\text{m}^2$ ) and preserved LVEF. [8] These patients were prospectively enrolled between 2000 and 2015 in two tertiary centres in France (Amiens, and Lille) and followed in the outpatient clinics of the two centres or in public hospitals or private practices by referring cardiologists working together with the tertiary centres. Information on follow-up was obtained by direct patient interview or by repeated follow-up letters and questionnaires to physicians, patients and (if necessary) next of kin.

Clinical decisions regarding medical management and indications for surgery were made in accordance with guideline recommendations [20].

We obtained institutional review board authorizations prior to conducting the study. The study was conducted in accordance with institutional policies, national legislation, and the revised Helsinki declaration.

### **Echocardiography**

All patients underwent a comprehensive Doppler-echocardiography study, using commercially available ultrasound systems. SV was calculated by multiplying the LV outflow tract area with the LV outflow tract time-velocity integral [21]. The LV outflow tract diameter was measured in zoomed parasternal long-axis views in early systole at the level of aortic cusp insertion. [8] The LV outflow tract time-velocity integral was recorded from the apical 5-chamber view, with the sample volume positioned proximal to the aortic valve [21]. Aortic flow was recorded using continuous-wave Doppler, systematically in several acoustic windows. The highest aortic velocity was used to calculate aortic time-velocity integral and mean pressure gradient. AVA was calculated by using the continuity equation. LVEF and volumes were measured by the Simpson biplane method. LV internal diameters and wall thickness were measured at end-diastole and end-systole in the 2-dimensional parasternal long axis view.

### **Statistical analysis**

Continuous variables are expressed as mean  $\pm$  standard deviation for normally distributed data or median [25th, 75th percentiles] otherwise. Categorical variables are expressed as number of subjects and proportion. Measures of body size included height (H) and BSA estimated with the Gehan method [22]. Body mass index (BMI) was calculated as the individual's body weight divided by the square of H. SV was assessed to establish whether it met Tanner's special circumstance. Tanner's special circumstance is met when the

coefficient of variation for the body size variable (BSA or H) divided by the coefficient of variation of SV is equal to the Pearson's correlation between the two variables [23]. The relationship of SV with body size measurements (BSA and H) was characterized in the reference sample using bivariate and multivariate regression analysis. Allometric relations between SV and body size were tested in the reference sample using the allometric equation:  $y = ax^b + \varepsilon$ , where  $x$  is a measure of body size (BSA or H),  $a$  and  $b$  are parameters, and  $\varepsilon$  is a random additive error term. Parameters  $a$  and  $b$  were first estimated by ordinary least squares analysis after logarithmic transformation to a linear model. Subsequently, we determined the viability of a common  $b$  exponent for both sexes across the age range by entering two interaction terms: sex/body size and sex/age/body size. If the interaction terms are not significant ( $p$  value  $>0.05$ ), the presence of a common  $b$  exponent applicable to both genders across the age range is confirmed. [24-25] Definitive estimation of allometric powers was performed using non-linear regression. Distribution of residuals and the assumption of homoscedasticity were tested by the Shapiro-Wilk normality test, the Breusch-Pagan/Cook-Weisberg test, and by visual inspection. Bivariate linear regression was applied to study the residual correlation between normalized SV by ratiometric and allometric approach and body size parameters. Normative values for normalized SV were calculated in the reference sample using quantile regression. Fifth percentiles of normalized SV were considered as lower-normal limits and for each normalized SV parameter, LF was defined by values  $<5^{\text{th}}$  percentile (LF-BSA, LF-BSA<sup>0.88</sup>, LF-H, and LF-H<sup>1.32</sup>). Comparison of normalized SV between non-obese, normotensive subjects and subjects with BMI  $\geq 30$  kg/m<sup>2</sup> was performed using analysis of covariance, adjusting for age and sex differences between the groups. Finally, the independence of the power ratio (allometrically scaled SV) and independent variables was confirmed in the cohort of patients with severe AS.

Ratiometric and allometric normalized SV were further tested for mortality prediction in patients with severe AS. Time-to-event variable was time from inception of the study to death or end of study, irrespective if aortic valve replacement was performed or not. Univariate and multivariable analyses of mortality were performed using Cox proportional hazards models. Covariates of potential prognostic impact were entered in the model on an epidemiological basis (age, sex, comorbidity index, symptoms, history of hypertension, coronary artery disease, atrial fibrillation, LVEF, peak aortic jet velocity, AVA, and BMI). The effect of aortic valve replacement on outcome was analyzed as a time-dependent covariate using the entire follow-up. The proportional hazards assumption was confirmed using statistics and graphs based on the Schoenfeld residuals. For continuous variables, the assumption of linearity was assessed by plotting residuals against independent variables. We tested the homogeneity of the association of normalized SV and mortality in obese and non-obese patients entering first-order interaction terms between BMI >30 kg/m<sup>2</sup> and each normalized SV parameter.

The overall performance of the multivariable models was assessed using the Akaike's Information Criterion. The predictive accuracy of the models was investigated by estimating Uno's C statistics (a type of C statistic measure for censored survival data) for models with and without SV parameters [26]. The integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) were determined to further describe the added utility of each normalized SV parameter when added to the model [27]. In the absence of verified risk categories in AS, we used the continuous NRI method which does not require prior definition of strata risk and considers the change in the estimation prediction as continuous variable. C statistics, NRI, and IDI were computed at median follow-up using the R software. A significance level of 0.05 was assumed for all tests. All p-values are results of two-tailed



tests. Data were analyzed with SPSS (v 18.0; IBM Corp, Armonk, NY, USA), and the R software (The R Foundation for Statistical Computing).

## RESULTS

Table 1 summarizes the characteristics of subjects in the reference sample according to sex. Characteristics of obese apparently healthy individuals are presented in the Supplemental table 1.

### *Normalized SV in normal adults*

#### *Relation of SV to BSA and H*

Table 2 and Figure 1 show the relation of SV to BSA and H in the reference sample. The results of Tanner's exceptional circumstance equation in the reference sample are presented in the Supplemental table 2. The allometric exponent for BSA was 0.88 (0.79-0.97). The test for heteroscedasticity showed that the residual errors from the model were randomly distributed ( $p=0.69$ ). The Shapiro-Wilk test confirmed the normality of the residuals distribution ( $p=0.11$ ) and visual inspection of residual plots showed no apparent systematic variations (Figure 1). The allometric exponent for H was 1.32 (1.14-1.51). Breusch-Pagan/Cook-Weisberg test p value was 0.74. The normality of residual distribution was confirmed by the Shapiro-Wilk test ( $p=0.15$ ), and by visual inspection (Figure 1). Ratiometric indexation (SV/BSA and SV/H) resulted in significant residual correlation with BSA and, respectively H, while residual correlation was not observed after allometric normalization (Table 2).

#### *Normalized SV reference values*

Age showed a weak inverse correlation with SV ( $R=-0.10$ ,  $p=0.03$ ). On multivariate regression, age and sex were independently associated with SV ( $R^2$  of the model 0.19). The inclusion of body size variables improved the overall variance in SV explained by the model ( $R^2$  0.29-0.30 for ratiometric models and  $R^2$  0.30-0.41 for allometric models).

Distributions of SV normalized by different methods in reference subjects are summarized in Table 2. LF reference values in males were:  $<28\text{ml}/\text{m}^2$ ,  $<30\text{ml}/\text{m}$ ,  $<30\text{ml}/(\text{m}^2)^{0.88}$ , and, respectively,  $<26\text{ ml}/\text{m}^{1.32}$ . In females, LF reference values were:  $<27\text{ml}/\text{m}^2$ ,  $<28\text{ml}/\text{m}$ ,  $<29\text{ml}/(\text{m}^2)^{0.88}$ , and, respectively,  $<24\text{ ml}/\text{m}^{1.32}$  (Table 2).

#### *Relation of SV to obesity*

Comparisons of non-indexed and normalized SV between the reference sample and obese subjects ( $\text{BMI} \geq 30\text{kg}/\text{m}^2$ ,  $n=962$ ) without cardiovascular disease are presented in Supplemental Table 3. Compared to subjects in the reference sample, obese subjects had greater non indexed SV and SV normalized to H, and lower SV normalized to BSA. The frequency of LF-BSA in obese subjects was about two times greater than in reference subjects.

#### *Normalized SV as mortality predictor in severe AS*

The baseline characteristics of the 1450 patients with severe AS are presented in Supplemental Table 4. Ratiometric SV normalization in patients with AS resulted in significant residual correlation with body size ( $R=0.10$  for BSA,  $p<0.001$ ;  $R=0.13$  for H,  $p<0.001$ ), while allometric SV normalization showed no residual correlation with body size ( $R=-0.004$  for BSA;  $p=0.54$ ;  $R=-0.006$  for H;  $p=0.35$ ).

Compared to non-obese AS patients, obese AS patients had greater non indexed SV and SV normalized to H, and smaller SV normalized to BSA. The frequency of LF in obese vs. non obese patients was 9% vs. 5% for LF-BSA and 2.9% vs. 4.8% for LF-H<sup>1.32</sup> (Supplemental Table 5).

Median (25th, 75th percentile) overall follow-up was 38(17-69) months. Ninety three percent of patients were followed up to 2 years or death (7% of patients were censored at 2 years). Follow-up was complete up to death or to the end of the study in 1295 patients (89%). The total number of deaths recorded during follow-up was 440. Aortic valve replacement was

performed during follow-up in 1072 patients (74%) by surgical (90.5%) or percutaneous (9.5%) techniques. Table 3 shows the hazard ratios (HR) associated with LF as predictor of all-cause mortality. On multivariable analysis, LF was independently predictive of mortality. The association between LF and mortality was consistent in obese and non-obese patients with no interaction between LF and BMI >30 kg/m<sup>2</sup> (all p values for interaction >0.20). LF-H<sup>1.32</sup> showed the strongest independent association with mortality (Table 3 and Supplemental figure 1). We conducted analyses to evaluate the added value for mortality prediction of introducing each normalized SV parameter (SV/BSA, SV/H, SV/BSA<sup>0.88</sup>, and SV/H<sup>1.32</sup>) as covariate in a multivariable Cox proportional hazard model. The Akaike Information Criterion was lowest for the model including SV/H<sup>1.32</sup> indicating best model fit. The effects on the C-statistics when adding normalized SV parameters to the basic model were overall modest, better for SV/H<sup>1.32</sup>. Reclassification favoured SV/H<sup>1.32</sup> over SV/BSA, SV/H, and SV/BSA<sup>0.88</sup> (Table 3).

## **DISCUSSION**

The present analysis of a large adult population without cardiovascular disease reports on the metrics of physiological relations of left ventricular SV measured by Doppler echocardiography to measures of body size and provides normative reference values for normalized Doppler-derived SV in adults. First, we demonstrate that indexing SV to appropriate allometric powers eliminates the residual relationship between normalized SV and body size. Furthermore, we show that obese individuals have higher absolute SV than non-obese individuals and, unlike normalization to H, BSA normalization reverses this difference resulting in marked overestimation of LF prevalence. Finally, we test the ability of normalized SV parameters for mortality prediction in patients with severe AS under medical and surgical management. The prognostic impact of LF is powerful because on multivariable analysis, LF is associated with about 60-90% increase in the risk of mortality during follow-

up. Among the 4 indexation methods, SV normalized to  $H^{1.32}$  has better predictive capacity in terms of reclassification and discrimination. These results suggest that that the cut-off used to define LF in AS should be lowered below 30 ml/m<sup>2</sup> and that SV normalization to  $H^{1.32}$  might be preferred over the current ratiometric normalization to BSA.

In clinical practice, SV is assessed by Doppler-echocardiography at the level of the LV outflow tract. However, published reference values in normal individuals are scarce [12-14]. Our study shows that lower reference values for Doppler-derived SV normalized to BSA are <28ml/m<sup>2</sup> in men and <27 ml/m<sup>2</sup> in women. Recently, the EchoNORMAL collaboration [28] reported lower reference values for SV/BSA  $\leq 20$  ml/m<sup>2</sup> in European subjects based on the biplane Simpson's method which generally underestimates SV due to the frequent foreshortening of the left ventricular cavity [29]. The above lower reference values and previous published prognostic data [8] in patients with severe AS strongly support the need of modifying the current 35ml/m<sup>2</sup> LF cut-off [1,2] in patients with AS and preserved LVEF.

Ratiometric BSA normalization is currently used to correct observed SV for differences in body size. However, this approach does not take into account the fact that the relations between body size and cardiac structural and functional parameters are often nonlinear [15,17,18,24]. In contrast, the allometric method has been reported to be superior from a theoretical and statistical standpoint to other normalization methods [15,18,24]. Furthermore, fat-free body mass is the ideal SV normalization variable [30] but its measurement in routine practice is difficult. Therefore H has been increasingly supported as the most appropriate fat-free body mass surrogate given the link between skeletal length and a genetically programmed amount of muscle mass [17,31]. The value of allometric indexation has been demonstrated for LV mass (normalization for  $H^{2.7}$ ) [32]. Data on allometric normalization of SV to body size in normal adults are scarce [16]. De Simone et al reported that in a group of 393 normal-weight, normotensive adults, SV assessed by M-mode

echocardiography was related by allometric relations to BSA (power 1.19) and H (power 2.04) [16]. In our reference sample of non-obese apparently healthy normotensive adults, the allometric exponents that adequately described the SV-BSA and SV-H relationships were slightly lower (0.88, and respectively 1.32) probably due to the different method used for SV assessment. Unlike ratiometric normalization, allometric indexation eliminated the residual relationships between normalized SV parameters and body size in the reference sample and in patients with AS.

The best SV normalization method in obese individuals is subject of debate. In normal-weight subjects, the normalization method does not affect the detection of SV alterations, while in a population with a large prevalence of obesity, BSA- or weight-normalization might reduce or even reverse SV differences between obese and non-obese subjects. The landmark study by de Simone shows that in overweight adults, observed SV was 17% greater than predicted for ideal BSA, and that the difference was approximated by normalization of SV for height to age-specific allometric powers [16]. We show that obese healthy subjects have greater observed SV compared to non-obese individuals and that this difference persists after normalization to height (allometric or ratiometric), but is reversed by BSA-normalization. It has been speculated that in patients with AS, obesity might lead to an underestimation of SV normalized to BSA, and, thus to misclassification of patients with normal-flow into the LF group [33]. We show that in AS patients SV normalization to BSA doubles the frequency of LF compared to non-obese patients, while normalization to height results in similar LF frequency in obese and non-obese patients (3% to 5%). These findings support the use of SV normalized to H instead of BSA for diagnosing patients with paradoxical LF low-gradient AS, especially in populations with a large prevalence of obesity [34]. SV normalization to BSA in obese individuals should be added to the list of errors (underestimation of LV outflow tract diameter, fast echo-Doppler examination without

interrogation of the right parasternal window, uncontrolled hypertension) leading to a false diagnosis of the LF/low-gradient pattern and might in part explain the heterogeneous published prevalence of LF/low-gradient AS with preserved LVEF (between 3% and 35%). Moreover, AVA indexation to BSA overestimates the severity of the valvular obstacle in obese individuals and from a prognostic point of view, AVA normalization to H seems more appropriate [35].

Current guidelines recommend the 35 ml/m<sup>2</sup> cut-off to define LF in severe AS with preserved LVEF [1,2]. We recently suggested that the cut-off for LF in AS should be lowered below 30 ml/m<sup>2</sup> [8]. We observed that LF defined as SV normalized to BSA <30 ml/m<sup>2</sup> was associated with more than 50% increase of the mortality risk during follow-up, while above this value mortality was not affected by further flow stratification. The present study supports and extends these findings. Lower reference values for SV/BSA in adults are <30ml/m<sup>2</sup>. Furthermore, from a prognostic point of view, LF as defined in this study strongly impacts outcome irrespective of the normalization method with similar magnitude in obese and non-obese patients. On reclassification analysis, however, allometric normalization to H showed stronger association with mortality.

### ***Limitations***

Our study has several limitations which merit discussion. Our article provides allometric powers derived from a large sample of white adults. Future studies should address the validity of these allometric powers in other populations, in particular among subjects from different ethnic groups. Fat-free body mass is considered as the optimal indexing variable, however accurate measurement of this parameter is complex and ideally requires the use of dual-energy X-ray absorptiometry which was beyond the scope of this population study. We included overweight individuals in the reference sample because we aimed to compare SV normalization in obese versus non obese individuals. Exclusion of overweight individuals

from the reference sample would result in greater SV and LF differences between reference and obese individuals and higher allometric exponents. However, when analyses were rerun after excluding overweight individuals from the reference sample, allometric exponents were only slightly higher (0.90 for BSA and 1.34 for H). Information on follow-up of patients with AS was retrospectively obtained. We acknowledge that Doppler-derived SV values are lower compared to SV assessed by magnetic resonance imaging. However, the Doppler-derived SV measurement, despite its limitations, is part of any routine echocardiographic examination and, in patients with AS, is systematically used to calculate the AVA by quantitative Doppler-echocardiography.

## **CONCLUSIONS**

Based on a large population of apparently healthy normotensive non-obese adults, we provide normative reference values for normalized Doppler-derived SV in adults. Unlike ratiometric normalization, indexing SV to appropriate allometric powers (1.32 for H, and 0.88 for BSA) eliminates the residual relationship between normalized SV and body size. In patients with AS, SV normalization to H should be preferred over BSA normalization as the latter results in marked overestimation of LF prevalence in obese patients. Our results suggest that the cut-off used to define LF in AS should be  $<28 \text{ ml/m}^2$  in men and  $<27 \text{ ml/m}^2$  in women and that SV normalization to  $H^{1.32}$  (LF cut-off  $<26 \text{ ml/m}^{1.32}$  in men and  $<24 \text{ ml/m}^{1.32}$  in women) might be preferred over the current ratiometric normalization to BSA especially in obese patients.

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## **FIGURE LEGEND**

**Figure 1:** Scatter plots of relations between SV and body size in the reference sample

**A.** Relation between SV and BSA: Scatter plot of SV against BSA (A1); Scatter plot of residuals vs. predicted values after linear regression SV-BSA (A2); normality of the data set and residual analysis of the natural log-transformed data sets after regression analyses to derive the allometric BSA exponent (A3 and A4)

**B:** Relation between SV and H: Scatter plot of SV against H (B1); Scatter plot of residuals vs. predicted values after linear regression SV-H (B2); normality of the data set and residual analysis of the natural log-transformed data sets after regression analyses to derive the allometric H exponent (B3 and B4).

**Table 1:** Descriptive characteristics of the subjects in the reference sample of apparently healthy normotensive non-obese adults

	<b>Overall (n=2781)</b>	<b>Men (n=1342)</b>	<b>Female (n=1439)</b>	<b>p value</b>
Age (years)	52.9±14.8	51.7±13.9	53.2±15.6	0.27
Height (m)	1.68±0.09	1.75±0.07	1.63±0.06	<0.001
Weight (kg)	70.2±11.8	77.4±10.0	63.5±9.0	<0.001
Body surface area (m <sup>2</sup> )	1.79±0.19	1.93±0.15	1.68±0.13	<0.001
Body mass index (kg/m <sup>2</sup> )	24.5±2.9	25.3±2.6	23.9±2.9	<0.001
Overweight (BMI 25 to 30 kg/m <sup>2</sup> ; n %)	1262 (45%)	658 (49%)	604 (42%)	0.001
LVOT diameter (cm)	2.1±0.2	2.2±0.2	1.9±0.2	<0.001
LVOT time-velocity integral (cm)	20.9±3.8	20.4±3.8	21.4±3.7	<0.001
Stroke volume (ml)	70.9±17.0	82.6±21.6	64.1±14.4	<0.001
LV end-diastolic volume (ml)	101.5±29.1	117.9±28.1	86.5±20.7	<0.001
LV end-systolic volume (ml)	41.9±16.9	49.7±17.0	34.8±13.4	<0.001
LV ejection fraction (%)	60.3±8.6	59.6±8.3	61.1±8.8	<0.001

**Legend:** LV – left ventricular, LVOT – left ventricular outflow tract. P values are from t-tests.

**Table 2:****Upper panel:** Relation of stroke volume to body surface area and height in the reference sample before and after indexation**Lower panel:** Normalized stroke volume percentiles in the reference sample of apparently healthy normotensive non-obese adults

Body size variable	Association non-indexed SV		p for interaction sex*body size variable ‡	p for interaction age*sex*body size variable ‡	Allometric exponent	Residual association ratiometric indexation †		Residual association allometric indexation †	
	R	p				R	p	R	p
	Body surface area	0.46				<0.001	0.30	0.10	0.88 (0.79-0.97)
Height	0.40	<0.001	0.28	0.25	1.32 (1.14-1.51)	0.13	<0.001	-0.002	0.78

  

SV normalization	Sex	Percentiles							p for sex difference
		5	10	25	50	75	90	95	
		SV/BSA	Male	28	30	35	40	45	
	Female	27	29	33	38	43	48	53	
SV/H	Male	30	33	38	44	50	57	61	<0.01
	Female	28	30	34	39	44	50	54	
SV/BSA <sup>0.88</sup>	Male	30	33	37	43	49	56	60	<0.01
	Female	29	31	35	40	46	51	56	
SV/H <sup>1.32</sup>	Male	26	28	32	36	42	48	51	<0.01
	Female	24	26	29	33	38	43	46	

**Legend:** R – Pearson correlation coefficient, SV – left ventricular stroke volume by Doppler echocardiography.

† correlation between SV normalized for the body size variable and the first power of the corresponding body size variable

‡ interaction term from log-log models



**Table 3:**

**A.** Multivariable Cox analyses assessing the impact of stroke volume normalization on mortality in severe aortic stenosis with preserved left ventricular ejection fraction  
**B.** Discrimination and reclassification associated with different SV normalizations

A. Outcome impact of SV normalization	Mortality			
	HR (95% CI)	p		
<b>Model 1: adjusted for age and sex</b>				
LF-BSA	1.94 (1.43 – 2.64)	<0.001		
LF-H	2.21 (1.61 – 3.05)	<0.001		
LF-BSA <sup>0.88</sup>	1.95 (1.44 – 2.66)	<0.001		
LF-H <sup>1.32</sup>	2.36 (1.70 – 3.29)	<0.001		
<b>Model 2: model 1 plus clinical variables *</b>				
LF-BSA	1.84 (1.35 – 2.51)	<0.001		
LF-H	2.17 (1.57 – 2.99)	<0.001		
LF-BSA <sup>0.88</sup>	1.85 (1.36 – 2.53)	<0.001		
LF-H <sup>1.32</sup>	2.27 (1.63 – 3.18)	<0.001		
<b>Model 3: model 2 plus echocardiographic variables †</b>				
LF-BSA	1.56 (1.12 – 2.19)	0.009		
LF-H	1.93 (1.36 – 2.74)	<0.001		
LF-BSA <sup>0.88</sup>	1.58 (1.14 – 2.21)	0.008		
LF-H <sup>1.32</sup>	2.02 (1.41 – 2.91)	<0.001		
<b>Model 4: model 3 plus aortic valve replacement</b>				
LF-BSA	1.52 (1.09 – 2.05)	0.006		
LF-H	1.73 (1.22 – 2.46)	0.002		
LF-BSA <sup>0.88</sup>	1.56 (1.12 – 2.18)	0.009		
LF-H <sup>1.32</sup>	1.80 (1.25 – 2.59)	0.001		
<b>Model 5: model 4 plus body mass index</b>				
LF-BSA	1.64 (1.17 – 2.29)	0.004		
LF-H	1.72 (1.21 – 2.45)	0.003		
LF-BSA <sup>0.88</sup>	1.61 (1.15 – 2.27)	0.006		
LF-H <sup>1.32</sup>	1.86 (1.29 – 2.65)	0.002		
<b>B. Discrimination and reclassification‡</b>				
<b>Multivariable model§</b>	AIC	C statistic	NRI	IDI
Multivariable model§	1560	0.75 (0.71, 0.79)	reference	reference
Multivariable model§ with SV/BSA	1531	0.76 (0.73, 0.79)	0.08 (0.02, 0.16), p=0.03	0.04 (0.01-0.08), p<0.001
Multivariable model§ with SV/H	1551	0.77 (0.75, 0.81)	0.18 (0.07, 0.25), p=0.007	0.05 (0.02-0.08), p<0.001
Multivariable model§ with SV/BSA <sup>0.88</sup>	1547	0.76 (0.74, 0.79)	0.11 (0.05, 0.18), p=0.009	0.01 (0.008-0.03), p<0.001
Multivariable model§ with SV/H <sup>1.32</sup>	1522	0.79 (0.77, 0.83)	0.22 (0.11, 0.29), p=0.002	0.08 (0.05-0.14), p<0.001

**Legend:** AIC - Akaike Information Criterion, BSA – body surface area, CI – confidence interval, H – height, HR – hazard ratio, IDI – integrated discrimination improvement, LF- low-flow, NRI – net reclassification improvement, SV – stroke volume

Aortic valve replacement is treated as a time-dependent covariate using the entire follow-up. For each index, LF is defined as <5<sup>th</sup> percentile of reference subjects with normal echocardiograms (see Table 3)

\* Clinical variables are: history of hypertension, coronary artery disease, symptoms, Charlson comorbidity index, and atrial fibrillation.

† Echocardiographic variables are: peak aortic jet velocity, aortic valve area and left ventricular ejection fraction.

‡ Results of discrimination and reclassification analyses are for median follow-up and 95% confidence intervals are presented.

§ Multivariable model is adjusted for age, gender, body mass index, history of hypertension, coronary artery disease, symptoms, Charlson comorbidity index, atrial fibrillation, peak aortic jet velocity, aortic valve area, and left ventricular ejection fraction.

SV/BSA, SV/H,  $SV/BSA^{0.88}$ , and  $SV/H^{1.32}$  are used in the models as continuous variables.

