Original Research

Aortic Root Dilatation in Hypertensive Patients with Left Ventricular Hypertrophy–Application of A New Multivariate Predictive Model. The Life Study

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Abstract

Background: Available nomograms to predict aortic root (AoR) diameter for body surface area have limitations. The purpose of this study was to evaluate the use of a new multivariate predictive model to identify AoR dilatation in hypertensive patients with left ventricular hypertrophy. **Methods**: 943 of 961 patients in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) echocardiographic sub-study had the necessary baseline characteristics and echocardiographic 2D measurements of AoR size to be included. **Results**: Predicted AoR (Sinus of Valsalva) diameter was $1.519 + (age [years] \times 0.010) + (height [cm] \times 0.010) - (gender [1 = M, 2 = F] \times 0.247)$, and a measured AoR diameter exceeding the 97.5-percentile of this estimate was considered dilated. Measured AoR diameter was larger in men than in women (3.75 vs. 3.48 cm, $p < 0.001$) and AoR diameter predicted by the model was larger than predicted by nomogram (3.52 vs. 3.28 cm, $p < 0.001$). Using the multivariate model to identify patients with AoR dilatation, the prevalence was 13.7% in men and 12.3% in women ($p = 0.537$). There was consensus of AoR phenotype (normal/dilated) between model and nomogram in 92.8% of the patients. In multivariate logistic regression, AoR dilatation by model definition was predicted by presence of aortic regurgitation (OR 2.67, $p < 0.001$) and SD increase in age (OR 0.75, $p = 0.023$), pulse pressure (OR 0.64, $p < 0.001$), left ventricular mass index (OR 1.36, $p = 0.08$) and stroke volume (OR 1.45, $p = 0.002$), but not by body weight. **Conclusions**: Using the proposed model the prevalence of AoR dilatation was equal in men and women and the model seems to address the effects of gender, age and body size on AoR size. **Clinical Trial Registration**: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00338260.

Keywords: aortic root diameter; blood pressure; hypertension; left ventricular hypertrophy

1. Introduction

Being the immediate receiver of the total cardiac output the aortic root (AoR) is important when studying pathological changes in the heart and equally important is the heart when evaluating pathology in the proximal aorta. AoR dilatation is an important pathophysiological mechanism behind aortic regurgitation (AR) in patients with Marfan syndrome [1,2], bicuspid aortic valve [3,4] and in severe, pure AR in patients with no valvular abnormality [5,6]. With increasing AoR diameter the degree of cusp overlap is reduced leading to AR. AoR dilatation is also associated with serious conditions such as aortic dissection [7]. AoR diameter is frequently evaluated by echocardiography in patients with valvular heart disease, aortic aneurisms or manifest heart failure.

Early necropsy [8] and cross sectional studies [9] showed AoR dimensions to be related to body size, gender and age, and hence nomograms based on body surface area (BSA) and age intervals have been widely used and adopted in guidelines [10–12]. These nomograms have several limitations including no consideration of gender differences, broad age-intervals and indexation by BSA to adjust for differences in body size. This latter is compromised by overweight (increasing BSA makes larger diameters fall into the normal range) and has previously been described as mathematically incorrect [13,14]. In addition, reference values indexed to height are warranted by various researchers, e.g., in a recent recommendation paper from the European Association of Echocardiography [11]. To counter the limitations of existing nomograms Devereux *et al.* [15] developed a multivariate predictive model based on measurements of AoR size in 1207 healthy individuals. Patients

with hypertension and left ventricular hypertrophy are of particular interest in this context. The present study was a sub-study of the LIFE study [16,17], an investigation of 9193 hypertensive patients with left ventricular hypertrophy. This study had an echocardiographic sub-study comprising 961 patients with echocardiographic variables to access the aortic root diameter. The aim of this study was to validate further this new multivariable model by determining the prevalence and predictors of AoR dilatation in hypertensive patients with left ventricular hypertrophy (LVH). Furthermore, we compared the results obtained using this new model to those obtained using the existing nomograms in our study population.

2. Methods

2.1 Study Population

N = 961 patients with essential stage II–III hypertension and ECG-LVH were enrolled from the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) echocardiographic sub-study (representing 11% of the total LIFE study population). The LIFE Study was a randomized, prospective, double-blinded, parallel group study designed to compare the effects of losartan and atenolol regarding cardiovascular morbidity and mortality. Eligible patients were men and women age 55 to 80 with baseline blood pressure 160–200/95–115 mmHg and LVH by sex-adjusted Cornell voltage-duration criteria ($\geq$2440 mm $\times$ msec) and/or Sokolow-Lyon voltage criteria (SV1 + RV5/RV6 >38 mm) [16]. Exclusion criteria were known aortic stenosis (aortic pressure gradient >20 mmHg), symptomatic heart failure or LV ejection fraction <40%. Baseline characteristics of the LIFE study population have been described elsewhere [17]. Blood pressure was measured by arm-cuff sphygmomanometer subsequent to echocardiographic examination. Fasting blood samples were obtained. Obesity was considered present if body mass index (BMI) was above 30 kg/m^2 [18].

2.2 Echocardiographic Measurements

Ethical committees for all participating centers in the LIFE echocardiographic sub-study approved the protocol for the sub-study and all participating patients in the echo sub-study signed written informed consent. Echocardiograms were obtained at baseline and annually thereafter during the 5-year study period. Echocardiographic procedures for this study were performed using commercially available echocardiographs with M-mode, 2-dimensional and color-flow Doppler capabilities. All techniques were based on procedures employed in previous studies [19–22] and have been described in detail elsewhere [23, 24]. Standardized examinations included two-dimensional guided M-mode echocardiograms as well as selected two-dimensional and Doppler recordings. AoR diameter was evaluated at the level of the Sinus of Valsalva using two-dimensional measurements of the maximal distance be-

tween the leading edges of the anterior and posterior aortic root walls in end-diastole. The Sinus of Valsalva was used because it fits with other similar studies, and it is also recommended to use by the American Society of Echocardiography (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3462295/). Aortic regurgitation was assessed using color flow Doppler recordings from parasternal and apical windows [25]. Measures of LV internal dimension and wall thickness were performed at end-diastole and end-systole following recommendations of American Society of Echocardiography [26]. All echocardiographic recordings were sent to the Echocardiographic Reading Center at New York Hospital - Cornell Medical Center (New York, NY, USA) for standardized and blinded interpretation by experienced technician and physician readers. LVH was defined as left ventricular mass index $\geq$116 g/m^2 for men and $\geq$104 g/m^2 for women and further divided in eccentric and concentric hypertrophy according to relative wall thickness by a partition value of 0.42 [10].

2.2.1 Calculation of Derived Variables

The predicted AoR diameter at the Sinus of Valsalva for age, sex and height was calculated using a multi-variate regression model recently developed by Devereux *et al.* [15] based on measurements of 1207 healthy adults: AoR$_M$ [cm] = 1.519 + (age [years] $\times$ 0.010) + (height [cm] $\times$ 0.010) – (gender [1 = M, 2 = F] $\times$ 0.247), SEE = 0.215 cm. Aortic dilatation was defined as a measured AoR diameter exceeding the 97.5th percentile (+1.96 $\times$ SEE) of the confidence interval of the predicted diameter. To compare the multivariate predictive model to the existing nomograms, the predicted AoR diameter was also calculated using the equation behind these nomograms (for adults 40 years of age and older): AoR$_N$ [cm] = 1.92 + 0.74 $\times$ BSA [m^2]. (SEE = 0.37) [9]. BSA was calculated using the Du Bois formula [27].

2.3 Statistical Analysis

Data management and analysis were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The study population was divided into 2 groups by the presence or absence of AoR dilatation as described above. In the following, continuous variables are expressed as mean $\pm$ standard deviation and categorical variables as percentages. Between group differences were determined by Student's *t*-test for continuous variables and by Chi-square test for categorical variables. We calculated Pearson correlations coefficients between the predicted models and the measured AoR. When more than two groups were compared we used analysis of variance. To adjust for confounding factors analysis of covariance was used. Predictors of AoR dilatation were identified by logistic regression using the enter method with binary and continuous predictor variables. For all tests, a *p*-value less than 0.05 was considered statistically significant.

Table 1. Descriptive baseline data of the 943 LIFE Study participants.

	N = 943
Male sex (%)	58.7
Age (years)	65.9 ± 7.0
Body surface area (m^2)	1.89 ± 0.19
Body mass index (kg/m^2)	27.3 ± 4.4
Systolic blood pressure (mmHg)	174 ± 21
Diastolic blood pressure (mmHg)	95 ± 12
Pulse pressure (mmHg)	78 ± 19
Mean blood pressure (mmHg)	122 ± 13
Pulse rate (beats/min)	72 ± 11
Serum cholesterol (mmoL/L)	6.0 ± 1.1
Serum creatinine (μmoL/L)	90 ± 22
Serum glucose (mmoL/L)	6.0 ± 2.4
Diabetes mellitus (%)	11.2
Smoking (%)	20.2
Previous stroke (%)	7.8
Previous myocardial infarction (%)	5.5

3. Results

Descriptive data of the entire LIFE Study population have been reported elsewhere [16,17]. Of the 961 patients included in the LIFE echocardiographic sub-study, 945 patients had the necessary baseline 2D measurements of the AoR to be included in the present study. Baseline anthropometric measures for two patients were missing, and they were therefore excluded. N = 943 patients met the inclusion criteria (58.7% men) and their characteristics are presented in Table 1. Mean age was 65.9 ± 7.0 years, body surface area (BSA) was 1.89 ± 0.19 m^2 and body mass index (BMI) was 27.3 ± 4.4 kg/m^2. Resting blood pressure in the population was 174 ± 21/95 ± 12 mmHg. The prevalence of diabetes mellitus was 11.2% and 20.2% of the patients were current smokers. Among the 943 patients, 708 patients (75%) had a record of previous antihypertensive treatment prior to enrollment in the LIFE study. In the study population 8 patients (all men) had bicuspid aortic valves and none had unicuspid aortic valves. Descriptive data of the excluded 16 patients were not different from those included (data not shown).

The distributions of measured AoR dimensions in the study population of 943 patients are presented in Fig. 1. The mean AoR diameter (at the level of Sinus of Valsalva) was 3.60 ± 0.37 cm (range 2.50 to 5.00 cm). Men had larger AoR diameters than women (3.75 ± 0.33 vs. 3.48 ± 0.32 cm, $p < 0.001$) and this difference remained significant after adjusting for differences in body size (data not shown). No difference in AoR size was detected between diabetic and non-diabetic patients (3.61 ± 0.40 vs. 3.60 ± 0.37 cm, $p = 0.884$), between obese and non-obese patients (3.56 ± 0.39 vs. 3.61 ± 0.37 cm, $p = 0.08$), or between patients previously on antihypertensive treatment vs. those untreated

(3.59 ± 0.38 vs. 3.63 ± 0.34 cm, $p = 0.132$).

Using the new multivariate predictive model including height, age and gender, the mean predicted AoR diameter was 3.52 ± 0.20 cm vs. 3.28 ± 0.14 cm using the existing nomogram for BSA ($p < 0.001$). The mean difference between the two prediction methods was 0.24 ± 0.17 cm. These data are presented in the Bland-Altman plot comparing the two prediction methods (Fig. 2). Stratified by gender, the mean AoR diameter predicted by the new multivariate model compared to the existing nomograms was larger for both men (3.68 ± 0.09 vs. 3.34 ± 0.12 cm, $p < 0.001$) and women (3.31 ± 0.09 vs. 3.20 ± 0.12 cm, $p < 0.001$).

Using the new multivariate predictive model to identify patients with AoR dilatation the overall prevalence was 13.1% (124 of 943 patients) and there was no difference between genders (13.7% in men, 12.3% in women, $p = 0.537$). Using the existing nomograms the prevalence of AoR dilatation was 11.7% (110 of 943 patients) with a significantly higher prevalence among men (15.9% vs. 5.7%, $p < 0.001$).

Overall there was a consensus of AoR phenotype between nomogram and model in 875 of the 943 patients (92.8%, Table 2). Regarding gender there was disagreement concerning AoR dilatation in 28 women (7.2%) of which 27 women had AoR dilatation only by model definition and one woman had AoR root dilatation only by nomogram definition. In men, disagreement existed for 40 patients (7.2%) of which 14 had AoR dilatation only by model definition and 26 had AoR dilatation only by nomogram definition.

The two predicted variables (predicted ad modum Devereux and predicted ad modum Roman) were moderately correlated (R = 0.60, $p < 0.001$). The measured aortic root diameter was moderately correlated to the multivariate model prediction (predicted ad modum Devereux, R = 0.50, $p < 0.001$) and more weakly correlated to the nomogram prediction (predicted ad modum Roman, R = 0.41, $p < 0.001$).

Patients with AoR dilatation identified by the new multivariate predictive model were, in univariate analyses, younger (64.2 ± 7.2 vs. 66.2 ± 6.9 years, $p = 0.004$), had higher body weight (81.0 ± 14.2 vs. 78.0 ± 13.8 kg, $p = 0.026$), higher BMI (28.2 ± 4.9 vs. 27.1 ± 4.3 kg/m^2, $p = 0.010$), lower systolic blood pressure (169 ± 20 vs. 174 ± 21 mmHg, $p = 0.017$), higher diastolic blood pressure (97 ± 12 vs. 95 ± 12 mmHg, $p = 0.037$) and lower pulse pressure (72 ± 18 vs. 79 ± 19 mmHg, $p < 0.001$) (Table 3). When dividing pulse pressure into quartiles, there was a significant higher prevalence of AoR dilation for lower quartiles of pulse pressure (Fig. 3). In the group of patients with dilated aortic roots, fewer patients had a record of previous myocardial infarction (1.6 vs. 6.1%, $p = 0.036$). When comparing patients with normal and dilated aortic roots, men with dilated aortic roots were younger (63.3 ± 7.3 vs. 66.0 ± 6.8 years, $p = 0.001$), had lower systolic blood pressure (168 ± 19 vs. 173 ± 21 mmHg, $p = 0.048$), lower pulse
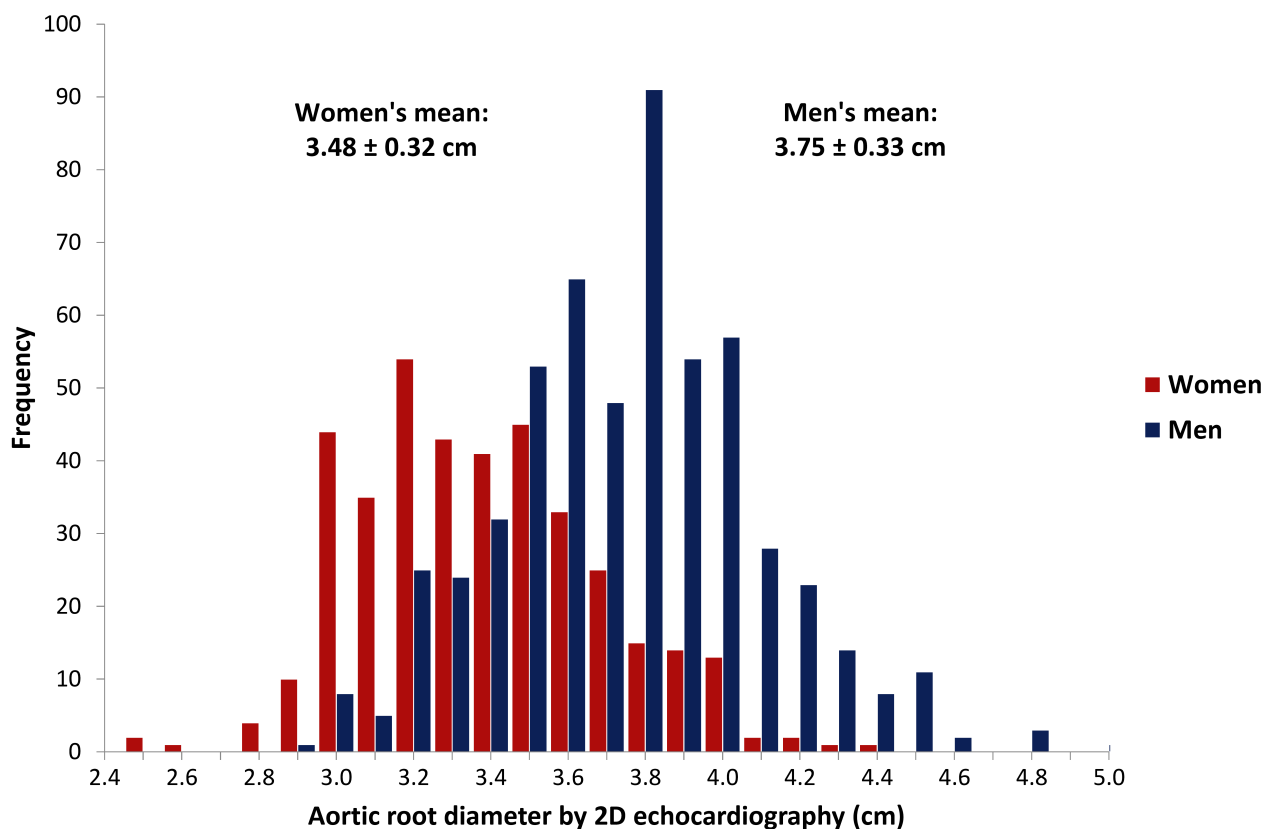
Fig. 1. Aortic root diameter at the Sinus of Valsalva measured by 2D echocardiography. The distributions of measured AoR dimensions in the study population of 943 patients are presented in men and women. Men had larger AoR diameters than women (3.75 ± 0.33 vs. 3.48 ± 0.32 cm, $p < 0.001$) and this difference remained significant after adjusting for body size.

pressure (70 ± 16 vs. 77 ± 18 mmHg, $p = 0.001$) and lower prevalence of self-reported previous myocardial infarction (1.3 vs. 7.1%, $p = 0.041$) than men with normal aortic roots. Women with dilated aortic roots had higher BMI (29.5 ± 5.9 vs. 27.8 ± 5.2 kg/m^2, $p = 0.035$) and lower pulse pressure (76 ± 20 vs. 82 ± 19 mmHg, $p = 0.022$) compared to women with normal aortic roots.

Using nomogram definition, AoR dilatation was associated with male gender (80 vs. 56%, $p < 0.001$), lower BMI (25.9 ± 3.3 vs. 27.5 ± 4.5 kg/m^2, $p < 0.001$), lower fasting serum cholesterol (5.7 ± 1.1 vs. 6.0 ± 1.1 mmoL/L, $p = 0.032$) and higher prevalence of smokers (28.2 vs. 19.1%, $p = 0.026$, Table 4).

Using either definition of AoR dilatation (multivariate predictive model or nomogram), patients with dilated AoR's had higher LV mass, LV mass index, stroke volume, stroke volume/pulse pressure ratio and cardiac output (Table 4). Using the multivariate model the difference was greater between patients with dilated and normal AoR and the p-values were lower than using nomogram definition. With the new model patients with AoR dilatation had higher left ventricular mass indexed by height$^{2.7}$ and lower total peripheral resistance. The prevalence of LVH was higher among patients with AoR dilatation using either definition.

Eccentric hypertrophy was the most frequent type of abnormal left ventricular geometry (Table 4).

The prevalence of aortic regurgitation (AR) in the present study population was 16.0% with no difference between genders (15.6 in men vs. 16.4% in women, $p = 0.774$). The prevalence of mild (1+) AR was 12.5% and moderate/severe ($\leq 2+$) AR was seen in 3.5% of the patients. Using the new multivariate predictive model, the prevalence of AR was 29.5% among patients with dilated aortic roots (18.8% mild and 10.7% moderate/severe AR) and 13.9% in patients with normal aortic roots (11.5% mild and 2.4% moderate/severe AR, all $p < 0.001$).

Factors associated with AoR dilatation in our population (by multivariate predictive model definition) were used as predictor variables (Table 5). In a multivariate logistic regression model with age, weight, history of myocardial infarction, pulse pressure, left ventricular mass index, stroke volume and aortic regurgitation, AoR dilatation was predicted by age (OR 0.75 per SD increase, $p = 0.023$), pulse pressure (OR 0.64 per SD increase, $p < 0.001$), left ventricular mass index (OR 1.36 per SD increase, $p = 0.008$), stroke volume (OR 1.45 per SD increase, $p = 0.002$) and aortic regurgitation (OR 2.67, $p < 0.001$).
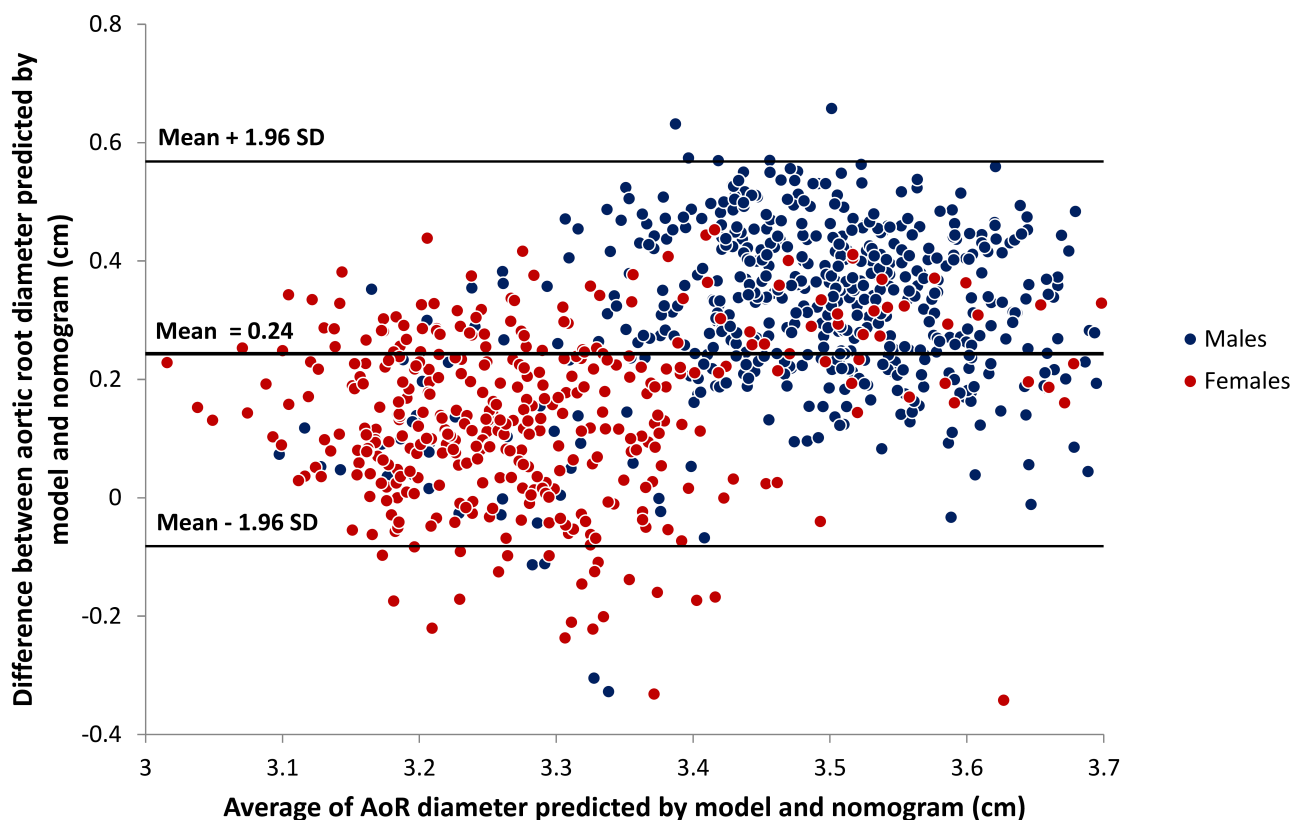
Fig. 2. Bland-Altman plot comparing AoR diameter predicted by model and by nomogram. Using the new multivariate predictive model including height, age and gender, the mean predicted AoR diameter was 3.52 ± 0.20 cm vs. 3.28 ± 0.14 cm using the existing nomogram for BSA ($p < 0.001$). The mean difference between the two prediction methods was 0.24 ± 0.17 cm. Stratified by gender, the mean AoR diameter predicted by the new multivariate model compared to the existing nomograms was larger for both men (3.68 ± 0.09 vs. 3.34 ± 0.12 cm, $p < 0.001$) and for women (3.31 ± 0.09 vs. 3.20 ± 0.12 cm, $p < 0.001$).

4. Discussion

This is the first study to evaluate the use of a multivariate model to predict normal aortic root size and identify aortic root dilatation in patients with hypertension and LVH. Our study shows three new observations using the proposed multivariate predictive model for gender, age and height. First, the overall prevalence of AoR dilatation in this specific population of hypertensive patients with LVH was 13%, which is higher than seen in previous reports. Second, in contrast previous studies [28–31], we report AoR dilatation to be equally prevalent in men and women. Finally, our study complements previous studies by the multivariate logistic regression analysis showing left ventricular mass index, stroke volume, pulse pressure and presence of aortic regurgitation to be predictors of AoR dilatation.

AoR dilatation is associated with aortic regurgitation [1–6] and risk for serious events such as aortic dissection [7]. Available nomograms to predict normal AoR diameter for body size are based on modest-sized reference populations and lack consideration of gender effects and direct continuous relationship with age. The new multivariate predictive model was derived from echocardiographic assess-

ment of 1207 normal individuals ≥15 years of age [15]. Previous studies that investigated the association between AoR dilatation and cardiovascular morbidity and mortality have relied on various definitions of AoR dilatation. Several investigators have used the available nomograms by Roman *et al*. [19,29], while others have used partition values based on the 97th or 98th percentile of specific reference populations [28,30–32] (e.g., AoR diameter >3.7 cm in females and >3.9 cm in males). In some studies partition values were indexed by body size (AoR diameter >2.0 cm/m^2) [7,33].

Evidently the prevalence of AoR dilatation in a studied population reflects the definition used and the purpose of this study was to evaluate the use of a more dynamic definition than the available nomograms and cutoff values. Interestingly, in our population the mean AoR diameter predicted by the multivariate model was higher than that predicted by the nomogram and this was true overall, in men and in women. Because the standard error of the estimate was lower with the multivariate model (0.22 cm vs. 0.37 cm), the average upper normal limit of normal AoR diameter was lower with this model, leading to an overall higher prevalence of AoR dilatation (13.1 vs. 11.7%). Consensus

Table 2. Consensus of aortic root phenotype between nomogram for BSA and multivariate model for age, sex and height.

AoR dilatation by nomogram [BSA]	No	Yes	No	Yes	Total	Consensus
AoR dilatation by model [age, sex, height]	No	No	Yes	Yes		
Women	340 (87.4)	1 (0.3)	27 (6.9)	21 (5.4)	389 (100)	361 (92.8)
Men	452 (81.6)	26 (4.7)	14 (2.5)	62 (11.2)	554 (100)	514 (92.8)
All patients	792 (84.0)	27 (2.9)	41 (4.3)	83 (8.8)	943 (100)	875 (92.8)

Legend: BSA, body surface area; AoR, aortic root diameter.
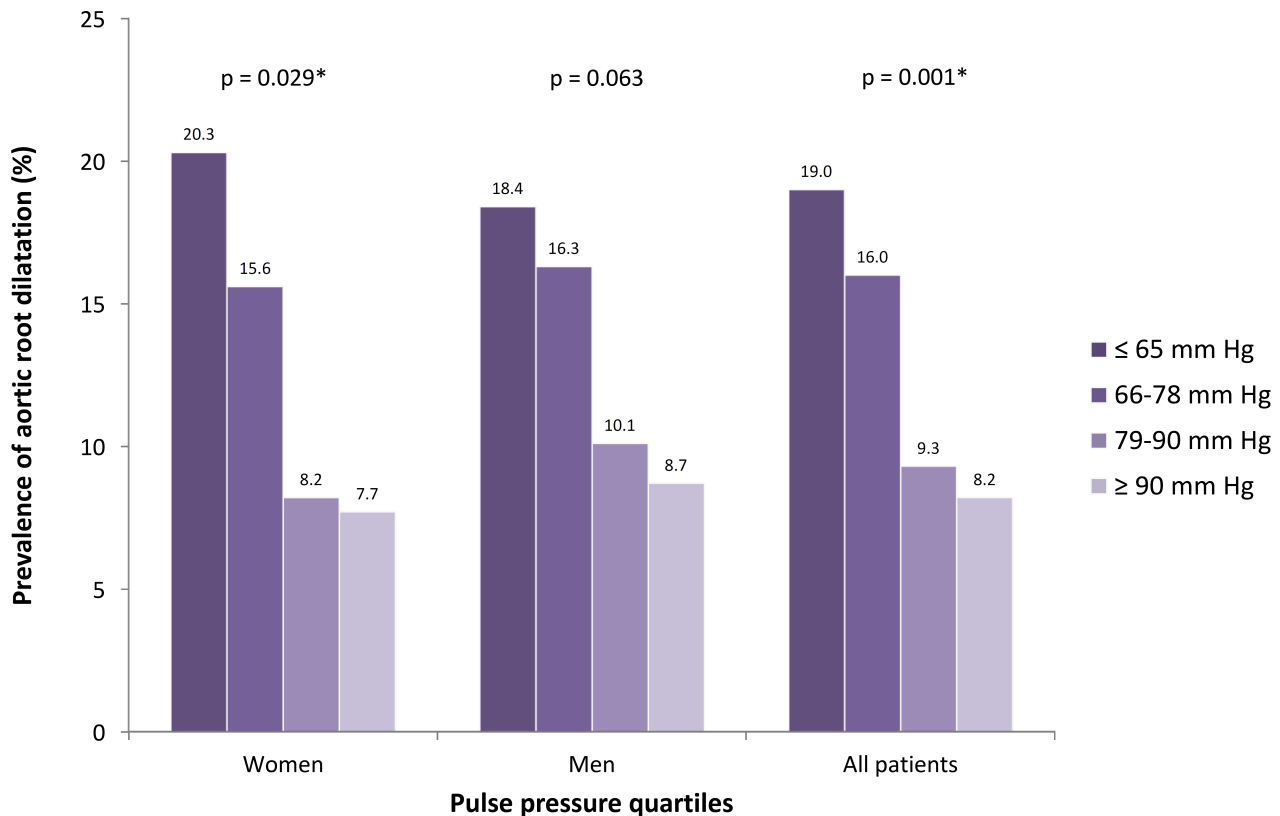
Fig. 3. Prevalence of aortic root dilatation for pulse pressure quartiles. When dividing pulse pressure into quartiles, there was a significant (*) higher prevalence of AoR dilation for lower quartiles of pulse pressure in both women and in all patients.

between the new multivariate model and the existing nomogram concerning the presence or absence of AoR dilatation was 92.8%.

The prevalence of AoR dilatation observed in our population is slightly higher than that found by Cipolli *et al.* [30] (10.5%) in comparable population of 438 patients with hypertension and LVH and by Cuspidi *et al.* [28] (11.8%) in a population of 2229 hypertensive patients referred to echocardiographic assessment of hypertension-related cardiac damage. The prevalence in our study is approximately twice that previously observed by Cuspidi *et al.* [28] (6.1%) in a population of 3366 patients with uncomplicated hypertension [31] and by Palmieri *et al.* [29] (4.6%) in 2096 hypertensive and 361 normotensive patients. The higher prevalence in our study may reflect that our patients are older and have more hypertension-related target organ dam-

age and that hypertension mediated target organ damage may also be found in the central vasculature.

The multivariate model identified more women and fewer men with dilated aortic roots, leading to an equal prevalence of AoR dilatation in men (13.7%) and women (12.3%). It is a matter of discussion whether AoR dilatation should be as much as 2–4 times more common in men than women as observed in previous studies using various definitions of normal AoR size [28–31]. However, gender is a prime determinant of AoR diameter independent of age and body size, emphasizing the need of differentiated normal values. In our population the difference in mean AoR diameter was 0.37 cm with men having larger diameters compared to women and this difference remained significant after controlling for age and height (data not shown). From our data, the multivariate model seems to address the

Table 3. Clinical characteristics, blood tests, cardiovascular risk factors and blood pressures of patients with aortic root dilatation defined by the new multivariate predictive model for height, sex and age and by nomogram for BSA.

	MODEL (height, sex, age)			NOMOGRAM (BSA)		
	Normal	Dilatation	*p*	Normal	Dilatation	*p*
	N = 819 (86.9%)	N = 124 (13.1%)		N = 833 (88.3%)	N = 110 (11.7%)	
Clinical characteristics:						
Men (%)	58	61	0.537	56	80	<0.001
Age (years)	66.2 ± 6.9	64.2 ± 7.2	0.004	65.8 ± 6.9	66.3 ± 7.6	0.480
Height (cm)	170 ± 9	170 ± 9	0.945	169 ± 10	171 ± 8	0.072
Weight (kg)	78 ± 14	81 ± 14	0.026	79 ± 14	76 ± 11	0.032
Body surface area (m^2)	1.89 ± 0.19	1.92 ± 0.18	0.107	1.89 ± 0.19	1.88 ± 0.16	0.409
Body mass index (kg/m^2)	27.1 ± 4.3	28.2 ± 4.9	0.010	27.5 ± 4.5	25.9 ± 3.3	<0.001
Blood tests:						
Serum cholesterol (mmoL/L)	6.0 ± 1.1	5.8 ± 1.0	0.083	6.0 ± 1.1	5.7 ± 1.1	0.032
Serum creatinine (μmoL/L)	91 ± 22	90 ± 22	0.713	90 ± 23	92 ± 21	0.324
Serum glucose (mmoL/L)	6.0 ± 2.4	5.9 ± 2.1	0.586	6.0 ± 2.3	6.0 ± 2.7	0.572
Cardiovascular disease risk factors:						
Diabetes mellitus (%)	11.7	8.1	0.230	11.3	10.9	0.907
Smoking (%)	19.2	26.6	0.055	19.1	28.2	0.026
Previous stroke (%)	7.9	7.3	0.792	7.6	10.0	0.372
Previous myocardial infarction (%)	6.1	1.6	0.041	5.8	3.6	0.359
Blood pressures and pulse:						
Systolic blood pressure (mmHg)	174 ± 21	169 ± 20	0.017	174 ± 21	172 ± 19	0.304
Diastolic blood pressure (mmHg)	95 ± 12	97 ± 12	0.037	95 ± 12	96 ± 11	0.438
Pulse pressure (mmHg)	79 ± 19	72 ± 18	<0.001	79 ± 19	75 ± 18	0.100
Mean blood pressure (mmHg)	121 ± 13	121 ± 12	0.997	121 ± 13	121 ± 11	0.938
Pulse rate (beats/min)	72 ± 11	73 ± 11	0.488	72 ± 11	72 ± 11	0.939

Legend: BSA, body surface area.

issue of significant gender differences in AoR size by identification of equal prevalence among men and women.

In both men and women we detected a higher brachial pulse pressure in patients with AoR dilatation compared to patients with normal aortic roots on basis of both lower systolic blood pressure and a higher diastolic blood pressure. This finding confirms what has been found in the Framingham cohort [34,35]. The relationship between AoR dimensions and systemic blood pressure has been investigated in numerous studies yielding conflicting results. Some studies find AoR size to be associated with both higher systolic and diastolic blood pressure [36], while others report association only to higher diastolic blood pressure [28,29,37]. The apparent relationship between AoR size and blood pressure has led to the notion that smaller AoR size predisposes to hypertension, but longitudinal studies on AoR dilatation and incidence of new onset hypertension have failed to show a causal relationship [38]. Intuitively it seems reasonable that a high distending pressure (both in systole and diastole) leads to dilatation of the AoR by pure mechanical force. On the other hand, a stiff and calcified arterial system with a non-dilated AoR leads to a higher systolic blood pressure, lower diastolic blood pressure and conse-

quently a higher pulse pressure. Hypertension is known to increase wall stress and promote atherosclerotic changes in the vessel wall and the explanation to the chicken-and-egg dilemma of AoR dilatation and hypertension [14] might be that patients susceptible to atherosclerotic changes have a diminished age-dependent dilatation and compliance of the AoR whereas less susceptible patients dilate and retain a low pulse pressure. The idea of AoR dilatation being a non-atherosclerotic process is in line with previous studies showing risk factors of atherosclerosis to account for less than 2% of the variability in aortic dimensions [39] and this study finding no association with diabetes or smoking. Furthermore, pulse pressure was associated with cardiovascular morbidity and mortality and in our population we detected a lower prevalence of previous myocardial infarction in patients with AoR dilatation.

5. Limitations

There are some limitations to the present study. The existing nomograms, the proposed multivariate model and our echocardiographic measurements all concentrate on the diameter at a single level of the AoR (Sinus of Valsalva),

Table 4. Echocardiographic characteristics of patients with aortic root dilatation defined by the new multivariate predictive model for height, sex and age and by the nomogram for BSA.

	MODEL (height, gender, age)			NOMOGRAM (BSA)		
	Normal	Dilatation	p	Normal	Dilatation	p
	N = 819 (86.9%)	N = 124 (13.1%)		N = 833 (88.3%)	N = 110 (11.7%)	
Aortic root diameter (cm)	3.52 ± 0.31	4.14 ± 0.27	<0.001	3.52 ± 0.31	4.20 ± 0.23	<0.001
Left ventricular mass (g)	231.3 ± 55.2	252.3 ± 61.2	<0.001	232.1 ± 56.1	248.8 ± 57.6	0.005
Left ventricular mass/BSA (g/m^2)	122.3 ± 25.1	131.6 ± 28	<0.001	122.3 ± 25.4	132.7 ± 26.6	0.000
Left ventricular mass/height$^{2.7}$ (g/m$^{2.7}$)	55.6 ± 12.6	60.6 ± 13	<0.001	56.0 ± 12.9	58.3 ± 11.3	0.076
Stroke volume (mL)	81 ± 17	86 ± 17	0.004	81 ± 17	86 ± 15	0.005
Stroke volume/pulse pressure (mL/mmHg)	1.09 ± 0,4	1.27 ± 0,41	<0.001	1.10 ± 0.41	1.21 ± 0.38	0.012
Cardiac output (L/min)	5.1 ± 1.3	5.7 ± 1.3	<0.001	5.2 ± 1.3	5.5 ± 1.4	0.035
Total peripheral resistance (dyn·sec·cm^{-5})	3763 ± 1081	3429 ± 763	0.003	3743 ± 1061	3547 ± 961	0.089
Aortic regurgitation (%)	13.9	29.5	<0.001	14	30.6	<0.001
- moderate/severe (%)	2.4	10.7	<0.001	2.6	10.2	<0.001
Left ventricular hypertrophy (%)	68.9	79.7	0.015	69.1	79.8	0.021
- eccentric (%)	42.8	50.4	0.114	43.1	49.5	0.200
- concentric (%)	26.1	29.3	0.460	26.0	30.3	0.346

Legend: BSA, body surface area.

Table 5. Univariate and multivariate predictors of aortic root dilatation by logistic regression.

	Univariate			Multivariate		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Age (per SD increase)	0.75	0.62–0.92	0.004	0.75	0.59–0.96	0.023
Weight (per SD increase)	1.23	1.02–1.47	0.027	0.94	0.74–1.2	0.616
History of myocardial infarction	0.25	0.06–1.05	0.058	0.30	0.07–1.32	0.110
Pulse pressure (per SD increase)	0.66	0.54–0.81	<0.001	0.64	0.51–0.82	<0.001
Left ventricular mass index (per SD increase)	1.38	1.16–1.64	<0.001	1.36	1.08–1.7	0.008
Stroke volume (per SD increase)	1.54	1.27–1.87	<0.001	1.45	1.15–1.84	0.002
Aortic regurgitation	2.59	1.64–4.1	<0.001	2.67	1.58–4.52	<0.001

Legend: SD, standard deviation; CI, confidence interval.

which prevents us from correlating our findings to the entire AoR. Furthermore, this study investigated patients enrolled in a randomized clinical trial, which might have excluded patients with more severe cardiovascular disease. The external validity of our findings might not extend beyond comparable patients with hypertension and LV hypertrophy. Finally, this is a descriptive study in nature and to address the question of prognostic value of AoR dilatation a prospective trial with a long observation period is needed using the proposed model to define AoR dilatation.

AoR dilatation was associated with higher LV mass, LV hypertrophy (in particular eccentric hypertrophy) and stroke volume as well as aortic regurgitation. In our hypertensive population patients with aortic root dilatation might constitute a subgroup of patients with increased volume load in addition to the pressure load of hypertension.

6. Conclusions

The clinical implication of this study is that we now have a more precise tool to predict AoR size and thereby identify patients with AoR dilatation. This is important for the clinician in echocardiographic assessment of a patient and for researchers designing future studies to investigate the implications of AoR dilatation. Compared to available nomograms for identification of aortic root dilatation, the multivariate predictive model integrating gender and age in addition to body size might identify aortic root dilatation more correctly and seems to identify a more homogenous group of patients. Furthermore, using the proposed multivariate model aortic root dilatation is equally common in men and women with a prevalence of 13% in our population of hypertensive patients with left ventricular hypertrophy.

Author contributions

SEK, SJ and RBD were involved in the study's conceptualization and methodology. AL, CNB, EG, ACL, SEK, SJ, PMO, KW and RBD were involved in the data collection. AL, CNB, PMO, KW and RBD were in involved in the statistical analysis. AL, KW and RBD were involved in the writing of the first draft. AL, CNB, EG, ACL, SEK, SJ, PMO, KW and RBD were involved in the review and editing of the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical committees for all participating clinical centers approved the LIFE Study. The study was performed in accordance with the Declaration of Helsinki. The protocol was written and the study was chaired by an academic steering committee, and it was overseen by an independent data and safety monitoring board. Ethical committees for all participating centers in the LIFE echocardiographic sub-study similarly approved the investigator written protocol for the sub-study and all participating patients in the echo sub-study signed written informed consent.

Conflict of interest

Sverre E. Kjeldsen has received lecture honoraria within the past 3 years from Getz Pharma, Merck Healthcare KGaA, Sanofi-Aventis and Vector-Intas. The other authors declare that they have no conflicts of interest.

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