Determinants of Aortic Root Dilatation and Reference Values Among Young Adults Over a 20-Year Period

Coronary Artery Risk Development in Young Adults Study

Gisela Teixido-Tura, Andre L.C. Almeida, Eui-Young Choi, Ola Gjesdal, David R. Jacobs, Jr, Harry C. Dietz, Kiang Liu, Stephen Sidney, Cora E. Lewis, David Garcia-Dorado, Artur Evangelista, Samuel Gidding, João A.C. Lima

***Abstract*—**Aortic size increases with age, but factors related to such dilatation in healthy young adult population have not been studied. We aim to evaluate changes in aortic dimensions and its principal correlates among young adults over a 20-year time period. Reference values for aortic dimensions in young adults by echocardiography are also provided. Healthy Coronary Artery Risk Development in Young Adults (CARDIA) study participants aged 23 to 35 years in 1990–1991 (n=3051) were included after excluding 18 individuals with significant valvular dysfunction. Aortic root diameter (ARD) by M-mode echocardiography at year-5 (43.7% men; age, 30.2±3.6 years) and year-25 CARDIA exams was obtained. Univariable and multivariable analyses were performed to assess associations of ARD with clinical data at years-5 and -25. ARD from year-5 was used to establish reference values of ARD in healthy young adults. ARD at year-25 was greater in men (33.3±3.7 versus 28.7±3.4 mm; P<0.001) and in whites (30.9±4.3 versus 30.5±4.1 mm; P=0.006). On multivariable analysis, ARD at year-25 was positively correlated with male sex, white ethnicity, age, height, weight, 20-year gain in weight, active smoking at baseline, and 20-year increase in diastolic, systolic, and mean arterial pressure. A figure showing the estimated 95th percentile of ARD by age and body surface area stratified by race and sex is provided. This study demonstrates that smoking, blood pressure, and increase in body weight are the main modifiable correlates of aortic root dilation during young adulthood. Our study also provides reference values for ARD in young adults. **(*Hypertension*. 2015;66:23-29. DOI: 10.1161/HYPERTENSIONAHA.115.05156.)** • **Online Data Supplement**

Key Words: aorta ■ aortic diseases ■ aortic aneurysm ■ echocardiography

Aortic dilatation in mid to advanced adulthood has been related to cardiovascular risk factors and cardiovascular events,[1–3] and it may begin early in young adulthood and be a marker for accelerated vascular aging. Furthermore, the study of aortic dilatation and its major determinants is crucial in the diagnosis and follow-up of several inherited aortic diseases (eg, Marfan syndrome and bicuspid aortic valve). However, the determinants of aortic root dilatation in young adults have not been previously described in a large generally healthy population.

Echocardiography is the most used technique in the clinical evaluation of aortic root dilatation because of its availability, low cost, and accuracy. Even though recent studies have defined equations and nomograms for aortic dimensions by 2-dimensional (2D) echocardiography in children[4] and over broad ranges of age,[5] data focused on young adults are limited. Reference values for aortic dimensions are crucial in the follow-up of young patients with aortic conditions and may become central to preventive cardiology efforts. Definition of aortic enlargement requires the use of nomograms, normalization by age and body size, or the calculation of z scores.[6] Those methods account for age and body size as these factors are direct determinants of aortic dimensions.[2,7]

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a population-based study involving 4 communities in the United States. CARDIA has followed 5115 black and white men and women aged 18 to 30 years recruited in 1985 for 25 years. Echocardiography was performed in 1990–1991 (year-5) and 2010–2011 (year-25) allowing for accurate measurements of aortic size which can

Received January 7, 2015; first decision January 19, 2015; revision accepted April 6, 2015.

From the Department of Medicine and Medical Genetics, Johns Hopkins University, Baltimore, MD (G.T.-T., A.L.C.A., E.-Y.C., O.G., H.C.D., J.A.C.L.); Department of Cardiology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain (G.T.-T., D.G.-D., A.E.); Department of Epidemiology, University of Minnesota, Minneapolis (D.R.J.); Department of Preventive Medicine, Northwestern University, Chicago, IL (K.L.); Kaiser Permanente, Division of Research, Oakland, CA (S.S.); Division of Preventive Medicine, University of Alabama, Birmingham (C.E.L.); and Division of Cardiology, Nemours Cardiac Center, A. I. DuPont Hospital for Children, Wilmington, DE (S.G.).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.115.05156/-/DC1.

Correspondence to Gisela Teixido-Tura, Department of Cardiology, Hospital Universitari Vall d'Hebron, Passeig Vall d'Hebron, 119-129, Barcelona 08035, Spain. E-mail gteixido@vhebron.net

be correlated with diverse risk factors and phenotypic observations. CARDIA is therefore ideal for the study of vascular structure and function in early adulthood and its alterations secondary to exposure to a large number of environmental risk factors. In this study, we aim to investigate the main determinants of aortic dilatation through 20 years of follow-up and to establish reference values for aortic root diameters (ARDs) by M-mode echocardiography in young adults.

Methods

Study Sample

The overall study design of CARDIA has been described in detail elsewhere.[8] In summary, CARDIA was initiated by the National Heart, Lung, and Blood Institute (NHLBI) as a large cohort of young adults to longitudinally investigate lifestyle and other variables that influence the evolution of coronary risk factors. The CARDIA cohort initially comprised 5115 participants who were aged 18 to 30 years at the time of enrollment (1985–1986), 5 years before the first echocardiography examination. CARDIA includes approximately equal numbers of participants from 4 geographically diverse urban field centers (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) and similar proportions of black and white, men and women.

A total of 3069 subjects from the CARDIA study, who underwent echocardiography both at the year-5 (aged 23–35 years in 1990–1991) and at year-25 examination, constitute the study sample for this investigation. Subjects were excluded if they fulfilled any of the following criteria at any of the 2 studies, in hierarchical order: aortic regurgitation or stenosis more than mild (n=9), aortic bicuspid valve (n=8), or aortic valve prosthesis (n=1). Then, a total of 3051 subjects were included. Compared with the overall CARDIA population, subjects were older in the present subcohort (25.2±3.6 versus 24.9±3.7 years; $P<0.001$) but with a mean difference of only 0.3 years. Sex distribution was not different (56.3% versus 54.3% in the subcohort versus the overall cohort, respectively; $P=0.09$). However, the included subcohort showed a higher proportion of white (55.0% versus 48.5% in the overall cohort; $P<0.001$).

Methods of Measurement and Definitions

A total of 3051 subjects with echocardiography at year-5 and year-25 were included. At year-5, all studies were performed with an Acuson 128 cardiovascular system, and at year-25, studies were performed with a Toshiba Artida ultrasound system. M-mode studies were obtained with 2D echocardiography guidance on the parasternal long-axis view. Aortic root size, both at baseline and at year-25, was measured from the M-mode tracings in accordance with the American Society of Echocardiography (ASE) guidelines using the leading edge-to-leading edge approach at end-diastole (Figure 1).[9] Aortic root measurement variability in the CARDIA study has been previously published.[10] In summary, aortic root M-mode measurements had an intraclass correlation coefficient of 0.81 and coefficients of variations (intra and intersonographer) <6%.

Body height and weight measurements were obtained at the index examination and used to calculate body surface area (BSA) by the Du Bois formula[11] and body mass index. Blood pressure was measured at each examination; 3 blood pressure measurements were obtained, and the second and third readings were averaged for analysis. Pulse pressure (PP) was calculated as systolic blood pressure (SBP) minus diastolic pressure and mean arterial pressure (MAP) as diastolic blood pressure (DBP) plus one third of the PP.

Physical activity was assessed with the CARDIA Physical Activity History Questionnaire,[12] an interviewer-administered self-report of frequency of participation in each of 13 categories of sports and exercise during the previous 12 months. Afterward, the exercise score was computed taking into account the frequency and intensity of activity and expressed in exercise units (EU).

Statistical Analysis

Demographic, anthropometric, and clinical characteristics at each examination were summarized with percentage or mean and SD as appropriate.

Main determinants of ARD at year-25 were determined by analyzing univariate associations between demographic and clinical data at years-5 and -25 and ARD at year-25. Change in aortic root diameter was calculated as ARD at year-25 minus ARD at year-5. Multivariable analyses were used to define the main determinants of ARD at year-25 by introducing demographic and clinical covariates at year-5, such as age, sex, race, weight, height, treatment for hypertension, diabetes mellitus, smoking status, physical activity, and total cholesterol

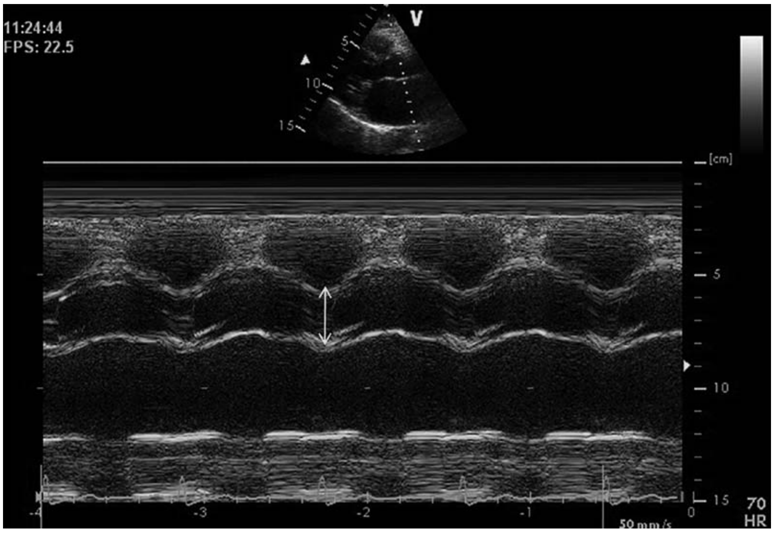

Figure 1. Echocardiographic aortic root measurements using the leading edge-to-leading edge approach at end-diastole.

levels and 20-year change of weight, cholesterol levels, and physical activity. Each blood pressure measurement (systolic, diastolic, PP, and MAP) and their 20-year change were separately introduced in a model with the rest of the covariates. Afterwards, to evaluate the steady and pulsatile components of blood pressure, PP, MAP, and 20-year change of both measurements were introduced simultaneously in the same model with ARD at year-25 as dependent variable. Multicollinearity was then evaluated by calculation of the variance inflation factor. Change in aortic root diameter through the 20-year period of this study was evaluated by introducing year-5 ARD as a covariate in the model.

Reference values for ARD in young adults were defined using data from year-5. Number of cases for age intervals (5 years) and BSA intervals (0.1 m^2) were analyzed to ensure proper representation of the entire spectrum. Mean unadjusted ARD by M-mode was calculated for men and women, black and white separately. Because demographic and anthropometric variables have been previously described to account for most of the variation observed in aortic dimensions,[2] only these variables were considered as covariates to obtain a simple model with more clinical applicability. Six multiple linear regression models were evaluated; 1 model included age, sex, and race. Four models added each of the body size parameters separately (height, weight, BSA, and body mass index) and a sixth model included height and weight simultaneously. The most explanatory model (higher R^2 value) was selected. The β-coefficients for each covariate from the selected model were used to calculate the predicted mean ARD from a designated set of values for each of the covariates. This predicted mean and the SE of the estimate (SEE) were then used to calculate the 95th percentile (predicted mean by the model±1.64·SEE).

Results

Clinical and demographic characteristics at year-5 (1990–1991) and year-25 (2010–2011) are shown in Table 1. Mean ARD at year-25 was greater than at year-5 (30.7±4.2 mm versus 27.8±3.8 mm; P<0.001). ARD at year-25 was greater in men than in women (33.3±3.7 versus 28.7±3.4 mm; P<0.001) and greater in whites than in blacks (30.9±4.3 versus 30.5±4.1 mm; P<0.01). However, no statistically significant differences were observed between blacks and whites stratified by sex (black men 33.1±3.5 versus white men 33.4±3.8 mm, P=0.070; black women 28.8±3.5 versus white women 28.7±3.3 mm, P=0.377). Mean 20-year change in ARD was 3.0±3.6 mm.

ARD at year-25 was significantly correlated with baseline (year-5) age, weight, height, BSA, body mass index, blood pressure, total cholesterol levels, and physical activity in univariate analyses (Table 2). Height and BSA were the anthropometric variables most linearly correlated with aortic root dimension at year-25. Importantly, current smokers at year-5 had higher ARD at year-25 (31.1±4.2 versus 30.6±4.2 mm; P<0.01). However, individuals under treatment for hypertension at year-5 (n=44) had no significant differences in ARD at year-25 compared with patients without treatment at year-5 (P=0.838). Twenty-year change in aortic root was weakly correlated with age, weight, height, and BSA, and with 20-year change in weight, SBP, DBP, and MAP (Table 3).

Table 1. Clinical Characteristics

Clinical or Demographic Variables	Year-5 3051	Year-25 3051	*P* Value (Paired Test)
Age, y	30.2±3.6	50.2±3.6	N/A
Male sex (%)	1334 (43.7)		N/A
Race (% black)	1373 (45.0)		N/A
Weight, kg	75.7±17.9	87.4±21.9	<0.001
Height, cm	170.3±9.5	170.4±9.5	0.329
Body surface area, m^2	1.86±0.23	1.98±0.25	<0.001
Body mass index, kg/m^2	26.1±5.7	30.1±7.2	<0.001
Systolic blood pressure, mm Hg	107.2±11.2	119.5±16.0	<0.001
Diastolic blood pressure, mm Hg	68.8±9.8	74.7±11.1	<0.001
Pulse pressure, mm Hg	38.4±8.2	44.8±9.0	<0.001
Mean arterial pressure, mm Hg	81.6±9.5	89.6±12.2	<0.001
Hypertension (%)	241 (7.9)	986 (32.3)	<0.001
Treatment for hypertension (%)	44 (1.4)	810 (26.5)	<0.001
Total cholesterol, mg/dL	178.6±33.3	192.7±36.9	<0.001
Diabetes mellitus (%)	51 (1.7)	317 (10.4)	<0.001
Current cigarette smoker (%)	778 (25.5)	483 (15.8)	<0.001
Physical activity, exercise units*	378.6±291.9	337.7±274.2	<0.001
M-mode aortic root, mm	27.8±3.8	30.7±4.2	<0.001

N/A indicates not applicable.

*Exercise score expressed in exercise units (EU) representing the frequency and intensity of exercise over the past year. For reference, 300 EU roughly approximates 5 sessions of 1260 kJ (300 kcal) of energy expenditure weekly.

In multivariable analyses, age, male sex, white ethnicity, height, weight, and baseline active smoking, as well as changes in weight, were significantly associated with larger aortic diameter at year-25 (Table 4). Models including SBP, DBP, MAP, and PP separately are shown in Table 4. SBP, DBP, and MAP were significantly associated with ARD at year-25. Also importantly, PP was negatively associated with ARD at year-25.

When introducing baseline ARD at each model, it was, as expected, positively associated with ARD at year-25, but age lost its association to ARD at year-25. Similar results were found for the rest of covariables (Table S1 in the online-only Data Supplement).

A multivariable model including simultaneously PP and MAP was used to evaluate the pulsatile and nonpulsatile components of blood pressure (Table S2). In this, ARD at year-25 was positively correlated with MAP and 20-year change in MAP and negatively correlated with PP and 20-year change in PP.

Although treatment for hypertension at year-5 was not related to ARD at year-25, further analyses were performed to confirm this result using the same model as in Table 4, treatment for hypertension was introduced with 4 categories: individuals that never received treatment (no treatment at year-5 or at year-25, n=2215), treatment only at year-5 (n=9), treatment only at year-25 (n=775), or treatment at both years-5 and -25 (n=35). When analyzed, these categories were also not significantly related to ARD at year-25. Moreover, the rest of the model remained similar.

Table 2. Unadjusted Analyses for Aortic Root Diameter at Year-25 and Continuous Variables at Baseline (Year-5)

	Clinical Variable	Pearson Correlation Coefficient With ARD at Year-25
Variable at baseline (year-5)	Age	0.051*
	Weight	0.383†
	Height	0.492†
	Body surface area	0.488†
	Body mass index	0.166†
	Systolic blood pressure	0.200†
	Diastolic blood pressure	0.196†
	Pulse pressure	0.037†
	Mean arterial pressure	0.213†
	Total cholesterol	0.083†
	Physical activity	0.145†
	ARD	0.592†
20-y change‡	Weight	0.023
	Systolic blood pressure	0.002
	Diastolic blood pressure	–0.014
	Pulse pressure	0.019
	Mean arterial pressure	–0.009
	Total cholesterol	–0.105†
	Physical activity	–0.052§

ARD indicates aortic root diameter.
*$P<0.05$.
†$P<0.001$.
‡Year-25 minus year-5 value.
§$P<0.01$.

Reference values for ARD were originated from year-5 measurements. Mean ARD at year-5 used to estimate reference values (n=3051; mean, 27.8±3.8 mm) was similar to the overall CARDIA year-5 cohort (n=4210; mean, 27.9±3.9 mm). Appropriate representation of all age groups (5 years), as well as of different BSA strata (0.1 m^2), was confirmed: all groups had >5% of all individuals except for the BSA≤1.5 m^2 that included a 3.5% of the total sample, but comprised 108 individuals. Mean unadjusted ARD by M-mode were 29.7±3.4 mm (black men), 30.1±3.7 mm (white men), 26.1±3.2 mm (black women), and 26.1±3.0 mm (white women).

Multivariable linear models for ARD, including demographic and anthropometric covariates, were evaluated to define reference values using ARD at year-5. The model with highest R^2 was the one including BSA (R^2=0.320; $P<0.001$); this was similar to the one including both height and weight (R^2=0.319; $P<0.001$). The model with BSA was selected because of simplicity and also included age, sex, and race: ARD (mm)=15.042+0.079×years+2.612 (if male sex)–0.407 (if black)+5.035×BSA (m^2), SEE=3.14. Interaction between sex and race was not significant (P=0.618). To calculate the predicted 95th percentile for ARD, a designated set of values was introduced in the model to obtain the predicted mean subsequently used to calculate the 95th percentile. Age was introduced by 5-year interval and BSA by 0.1-m^2 interval. These values are graphically presented in Figure 2.

Table 3. Unadjusted Analyses for CAR and Continuous Variables at Baseline (Year-5)

	Clinical Variable	Pearson Correlation Coefficient With CAR
Variable at baseline (year-5)	Age	–0.042*
	Weight	0.044*
	Height	0.095†
	Body surface area	0.071†
	Body mass index	0.002
	Systolic blood pressure	0.012
	Diastolic blood pressure	0.032
	Pulse pressure	–0.022
	Mean arterial pressure	0.027
	Total cholesterol	–0.005
	Physical activity	0.022
20-y change‡	Weight	0.064†
	Systolic blood pressure	0.077†
	Diastolic blood pressure	0.075†
	Pulse pressure	0.027
	Mean arterial pressure	0.081†
	Total cholesterol	0.004
	Physical activity	–0.023

CAR indicates change in aortic root diameter.
*$P<0.05$.
†$P<0.001$.
‡Year-25 minus year-5 value.

Discussion

Our study provides longitudinal data on clinical correlates of aortic root size and dilatation through a 20-year period of early adulthood, being age, sex, ethnicity, and body size, the main determinants of aortic root dimensions and dilatation. Importantly, active smoking at early adulthood was positively correlated with aortic size and dilatation 20 years later. Furthermore, components of blood pressure had different roles in relation to aortic dimensions: studied separately, DBP, MAP, and 20-year change in SBP were positively related to aortic dimensions, whereas baseline PP was negatively correlated with aortic dimensions and dilatation 20 years later.

Alterations of aortic material properties, in parallel with alterations of the vasculature in general, have been conclusively related to adverse cardiac remodeling and cardiovascular outcomes.[13–15] Aortic structural and functional alterations that occur in mid and late adulthood and their clinical correlates have been the object of extensive investigation.[2,7,16] However, data focused in early adulthood are scarce. In this period of adulthood, vascular changes are incipient but may be more informative toward the overall understanding of vascular aging and also more malleable to intervention.

In this regard, prior investigation has clearly demonstrated that elastin, the constitutional element that affords distensibility to the aortic structure, has a half-life of 40 years, and, most importantly it is not synthesized during mid-to-late adulthood.[17,18] Fatigue and fracture of elastin because of repeated cycles of deformation is thought to be the mechanism of elastin degradation.[19] In this regard, recent MRI studies showing

Table 4. Multivariable Analysis Comparing Contributions of Blood Pressure Parameters With Aortic Root Diameter at Year-25 (mm)

Clinical Variable	Model 1 (SBP) R^2=0.361 P<0.001 β Coefficient	Model 2 (DBP) R^2=0.365 P<0.001 β Coefficient	Model 3 (PP) R^2=0.361 P<0.001 β Coefficient	Model 4 (MAP) R^2=0.363 P<0.001 β Coefficient
SBP at year-5, 10 mm Hg	0.023	…	…	…
Delta SBP, 10 mm Hg	0.197*	…	…	…
DBP at year-5, 10 mm Hg	…	0.419*	…	…
Delta DBP, 10 mm Hg	…	0.364*	…	…
PP at year-5, 10 mm Hg	…	…	−0.328†	…
Delta PP, 10 mm Hg	…	…	0.019	…
MAP at year-5, 10 mm Hg	…	…	…	0.276†
Delta MAP, 10 mm Hg	…	…	…	0.311*
Age, 10 y	0.412‡	0.456‡	0.408‡	0.446‡
Sex, being male	3.125*	3.000*	3.202*	3.028*
Race, being black	−0.510*	−0.602*	−0.398†	−0.583*
Height at year-5, 10 cm	0.590*	0.622*	0.561*	0.611*
Weight at year-5, 10 kg	0.535*	0.479*	0.546*	0.498*
Delta weight, 10 kg	0.137†	0.105‡	0.163†	0.117‡
Diabetes mellitus at year-5	0.119	0.197	0.107	0.166
Total cholesterol at year-5, 10 mg/dL	−0.022	−0.003	−0.019	−0.028
Delta cholesterol, 10 mg/dL	−0.015	−0.002	−0.001	−0.019
Current cigarette smoker at year-5	0.378†	0.371†	0.463†	0.363‡
Treatment for HBP at year-5	−0.333	−0.665	−0.329	−0.574
Physical activity at year-5, 100 EU§	0.014	0.018	0.025	0.015
Delta physical activity, 100 EU§	0.002	0.005	0.003	0.003

Delta: year-25 value minus year-5 value. DBP indicates diastolic blood pressure; HBP, high blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; and PP, pulse pressure.

*P<0.001.

†P<0.01.

‡P<0.05.

§Exercise score expressed in exercise units (EU) representing the frequency and intensity of exercise over the past year. For reference, 300 EU roughly approximates 5 sessions of 1260 kJ (300 kcal) of energy expenditure weekly.

marked decrease in aortic deformation before the fifth decade have provided important understanding on the time course of changes in aortic structure and function in early adulthood.[20]

Our results are in line with a previous cross-sectional study from Palmieri et al,[21] which showed that hypertensives with suboptimal blood pressure control have larger aortic root dimensions than normotensives or hypertensives with optimal blood pressure. However, the longitudinal design of our study emphasizes the importance of progressive increase in BP with age on aortic root enlargement.

The simultaneous analysis of MAP and PP is meaningful because it provides information on the steady-flow versus pulsatile components of arterial pressure and circulatory function related to small artery (steady-flow) and large artery (pulsatile) contribution. In our study, MAP was positively correlated with aortic root size and dilatation. Conversely, PP was negatively associated with aortic root size and dilatation This last finding seems counterintuitive at first, but may be explained by the decline in PP seen in several previous observational studies between ages 20 and 40,[22] the age period during which baseline ARD measurements were obtained in our study. Moreover, studies of populations in mid-to-late adulthood have found similar results with SBP and PP being negatively associated with aortic dimensions.[2,14,16,23,24]

Similar to previous studies,[2] in our study, male sex was associated with greater aortic dimensions and dilatation, and white ethnicity related to greater aortic dimensions than black. Although no differences were observed between blacks and whites stratified by sex, this might be explained by the differences in weight between sex–race groups (data not shown), which is confirmed in the multivariable analysis where white ethnicity is associated with higher ARD adjusted by body size. Interestingly, our data suggest a positive correlation of active smoking at baseline with aortic root dimensions and dilatation through this 20-year period of follow-up. To the best of our knowledge, this last finding has not been previously described in a longitudinal study and it is notably important in the follow-up of aortic conditions.

Reference values of aortic root dimensions by M-mode echocardiography depending on age and BSA in young adulthood stratified by sex and race are provided in this study with the aim to guide physicians and other healthcare providers on what can be expected to be the normal aortic root dimensions in early adulthood.

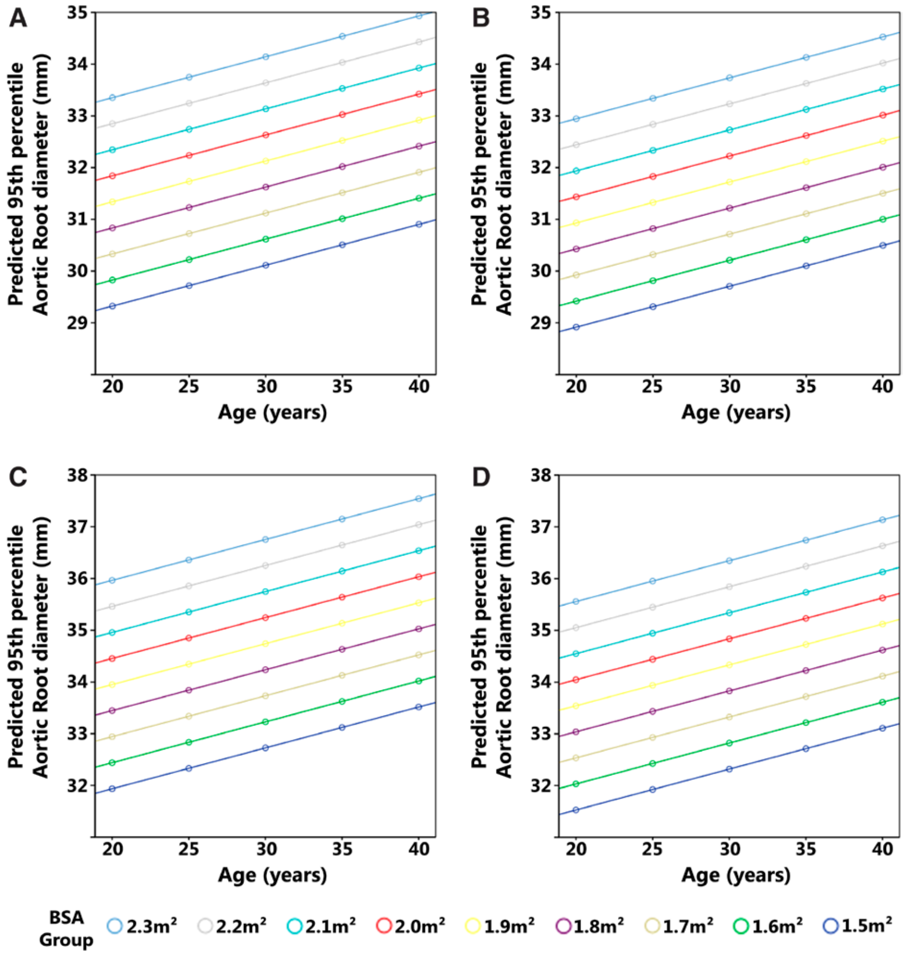

Figure 2. 95th percentiles of predicted aortic root diameter (ARD) by age, stratified by race and sex. This chart is designed for practical use: to evaluate ARD for a particular patient, use body surface area (BSA) to choose the line that defines the upper limit of normal from the appropriate race–sex group. **A**, White females; (**B**) black females; (**C**) white males; and (**D**) black males.

Our study has some limitations. First, M-mode echocardiography was used for both year-5 and year-25 studies. Although currently bidimensional echocardiography is recommended to determine aortic dimensions,[9] this approach was not used 20 years ago. However, M-mode and bidimensional echocardiography are well correlated with a systematic underestimation of 2 mm by M-mode in comparison with bidimensional measurements.[6] Second, although a higher proportion of white subjects was observed in the included subcohort respect to the overall CARDIA participants (55.0% versus 48.5% in the overall cohort; $P<0.001$), black and white ethnicities are well represented in our study, and ethnicity has been introduced as a covariable in the analysis. Third, despite that the multivariable models used in our analysis only explain ≈40% of the variation of ARD at year-25, the significant predictors analyzed still represent the mean change in the response for 1 unit of change. Last, despite the associations found between smoking, blood pressure, and body weight gain and ARD, the real effect of the intervention on these factors to avoid aortic root dilatation cannot be elucidated from this study.

Perspectives

In summary, this study based on the 20-year longitudinal follow-up of CARDIA participants demonstrates that smoking, blood pressure, and body weight gain are the main modifiable determinants of aortic root dilation through young adulthood. Our study also provides reference values for ARDs in this age group.

Sources of Funding

The Coronary Artery Risk Development in Young Adults Study (CARDIA) is supported by contracts HHSN268201300025C, HHSN268201300026C, HHSN268201300027C, HHSN268201300028C, HHSN268201300029C, and HHSN268200900041C from the National Heart, Lung, and Blood Institute (NHLBI), the Intramural Research Program of the National Institute on Aging (NIA), and an intra-agency agreement between NIA and NHLBI (AG0005).

Disclosures

None.

References

1. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121:505–511. doi: 10.1161/CIRCULATIONAHA.109.886655.
2. Lam CS, Xanthakis V, Sullivan LM, Lieb W, Aragam J, Redfield MM, Mitchell GF, Benjamin EJ, Vasan RS. Aortic root remodeling over the adult life course: longitudinal data from the Framingham Heart Study. *Circulation*. 2010;122:884–890. doi: 10.1161/CIRCULATIONAHA.110.937839.
3. Farrar DJ, Bond MG, Riley WA, Sawyer JK. Anatomic correlates of aortic pulse wave velocity and carotid artery elasticity during

atherosclerosis progression and regression in monkeys. *Circulation*. 1991;83:1754–1763.
4. Gautier M, Detaint D, Fermanian C, Aegerter P, Delorme G, Arnoult F, Milleron O, Raoux F, Stheneur C, Boileau C, Vahanian A, Jondeau G. Nomograms for aortic root diameters in children using two-dimensional echocardiography. *Am J Cardiol*. 2010;105:888–894. doi: 10.1016/j.amjcard.2009.11.040.
5. Devereux RB, de Simone G, Arnett DK, Best LG, Boerwinkle E, Howard BV, Kitzman D, Lee ET, Mosley TH Jr, Weder A, Roman MJ. Normal limits in relation to age, body size and gender of two-dimensional echocardiographic aortic root dimensions in persons ≥15 years of age. *Am J Cardiol*. 2012;110:1189–1194. doi: 10.1016/j.amjcard.2012.05.063.
6. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol*. 1989;64:507–512.
7. Biaggi P, Matthews F, Braun J, Rousson V, Kaufmann PA, Jenni R. Gender, age, and body surface area are the major determinants of ascending aorta dimensions in subjects with apparently normal echocardiograms. *J Am Soc Echocardiogr*. 2009;22:720–725. doi: 10.1016/j.echo.2009.03.012.
8. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41:1105–1116.
9. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006;7:79–108. doi: 10.1016/j.euje.2005.12.014.
10. Armstrong AC, Ricketts EP, Cox C, Adler P, Arynchyn A, Liu K, Stengel E, Sidney S, Lewis CE, Schreiner PJ, Shikany JM, Keck K, Merlo J, Gidding SS, Lima JA. Quality control and reproducibility in M-Mode, two-dimensional, and speckle tracking echocardiography acquisition and analysis: the CARDIA study, year 25 examination experience [published online ahead of print November 9, 2014]. *Echocardiography*. doi: 10.1111/echo.12832. http://onlinelibrary.wiley.com/doi/10.1111/echo.12832/abstract;jsessionid=1B13BCF583DFA5BD38D985351CF62289.f03t01. Accessed April 22, 2015.
11. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition*. 1989; 5: 303–311; discussion 312–3.
12. Sidney S, Jacobs DR Jr, Haskell WL, Armstrong MA, Dimicco A, Oberman A, Savage PJ, Slattery ML, Sternfeld B, Van Horn L. Comparison of two methods of assessing physical activity in the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Epidemiol*. 1991;133:1231–1245.
13. Cuspidi C, Meani S, Fusi V, Valerio C, Sala C, Zanchetti A. Prevalence and correlates of aortic root dilatation in patients with essential hypertension: relationship with cardiac and extracardiac target organ damage. *J Hypertens*. 2006;24:573–580. doi: 10.1097/01.hjh.0000209992.48928.1f.
14. Bella JN, Wachtell K, Boman K, Palmieri V, Papademetriou V, Gerdts E, Aalto T, Olsen MH, Olofsson M, Dahlöf B, Roman MJ, Devereux RB. Relation of left ventricular geometry and function to aortic root dilatation in patients with systemic hypertension and left ventricular hypertrophy (the LIFE study). *Am J Cardiol*. 2002;89:337–341.
15. Gardin JM, Arnold AM, Polak J, Jackson S, Smith V, Gottdiener J. Usefulness of aortic root dimension in persons ≥65 years of age in predicting heart failure, stroke, cardiovascular mortality, all-cause mortality and acute myocardial infarction (from the Cardiovascular Health Study). *Am J Cardiol*. 2006;97:270–275. doi: 10.1016/j.amjcard.2005.08.039.
16. Vasan RS, Larson MG, Levy D. Determinants of echocardiographic aortic root size. The Framingham Heart Study. *Circulation*. 1995;91:734–740.
17. O'Rourke MF. Arterial aging: pathophysiological principles. *Vasc Med*. 2007;12:329–341. doi: 10.1177/1358863X07083392.
18. O'Rourke MF, Safar ME, Dzau V. The Cardiovascular Continuum extended: aging effects on the aorta and microvasculature. *Vasc Med*. 2010;15:461–468. doi: 10.1177/1358863X10382946.
19. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation*. 2003;107:139–146.
20. Redheuil A, Yu WC, Wu CO, Mousseaux E, de Cesare A, Yan R, Kachenoura N, Bluemke D, Lima JA. Reduced ascending aortic strain and distensibility: earliest manifestations of vascular aging in humans. *Hypertension*. 2010;55:319–326. doi: 10.1161/HYPERTENSIONAHA.109.141275.
21. Palmieri V, Bella JN, Arnett DK, Roman MJ, Oberman A, Kitzman DW, Hopkins PN, Paranicas M, Rao DC, Devereux RB. Aortic root dilatation at sinuses of valsalva and aortic regurgitation in hypertensive and normotensive subjects: the Hypertension Genetic Epidemiology Network study. *Hypertension*. 2001;37:1229–1235.
22. Nichols W, O'Rourke M, Vlachopoulos C. Interpretation of blood pressure in epidemiological studies and clinical trials. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. 6th ed. London: Hodder Arnold; 2011:469–484.
23. Mitchell GF, Lacourcière Y, Ouellet JP, Izzo JL Jr, Neutel J, Kerwin LJ, Block AJ, Pfeffer MA. Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. *Circulation*. 2003;108:1592–1598. doi: 10.1161/01.CIR.0000093435.04334.1F.
24. Dart AM, Kingwell BA, Gatzka CD, et al. Smaller aortic dimensions do not fully account for the greater pulse pressure in elderly female hypertensives. *Hypertension*. 2008;51:1129–1134. doi: 10.1161/HYPERTENSIONAHA.107.106310.

Novelty and Significance

What Is New?

- This population-based study is the first to provide 20-year longitudinal data on clinical correlates of aortic root size and dilatation through early adulthood. Age, male sex, white ethnicity, body size, weight gain, blood pressure, and smoking were the main determinants of aortic root dimensions and dilatation.

What Is Relevant?

- Components of blood pressure had different roles in relation to aortic dimensions: diastolic blood pressure, mean arterial pressure, and 20-year change in systolic blood pressure were positively related to aortic dimensions, whereas baseline pulse pressure was negatively correlated with aortic dimensions and dilatation 20 years later.

Summary

This study based on the 20-year longitudinal follow-up of CARDIA participants demonstrates that smoking, blood pressure, and body weight gain are the main modifiable determinants of aortic root dilation through young adulthood. Our study also provides reference values for aortic root diameters in this age group.