Genetic Influences on Aortic Root Size in American Indians
The Strong Heart Study


Abstract—Aortic root dilatation is a major pathophysiological mechanism for aortic regurgitation and predisposes the aortic root to dissection or rupture. However, only a small proportion of the variance of aortic root size can be explained by its known clinical and demographic correlates. The present study was undertaken to determine the heritability of echocardiographically derived aortic root diameter in the American Indian participants in the second Strong Heart Study examination. Echocardiograms were analyzed in 1373 SHS participants who had ≥1 family member in the cohort. Heritability calculations were performed by using variance component analysis as implemented in SOLAR, a computer analysis program. In a polygenic model, the variables entered and identified as covariates of larger aortic root diameter were older age, male sex, and center (P < 0.001), which accounted for 35% of the overall variability of aortic root diameter. After simultaneous adjustment was made for these significant covariates, the proportion of phenotypic variance due to additive genetic contribution or residual heritability (h²) was 0.51 (SE = 0.08, P < 0.001). Additionally, simultaneous adjustment for height, weight, and systolic and diastolic BPs yielded slightly lower residual h² of aortic root diameter (h² = 0.44; SE = 0.08, P < 0.001), which accounted for 26% of the overall variance of aortic root size. Because center effects were identified as significant covariates in the analyses, h² analyses were performed separately in Arizona, Oklahoma, and North/South Dakota centers, which confirmed that a significant proportion of the phenotypic variance of aortic root diameter is due to additive genetic contribution. Heredity explains a substantial proportion of the variability of aortic root size that is not accounted for by age, sex, body size, and blood pressure. Echocardiographic screening of family members with aortic root dilatation may identify other individuals predisposed to aortic dissection or rupture. (Arterioscler Thromb Vasc Biol. 2002;22:········.)

Key Words: genetics ■ epidemiology ■ echocardiography ■ aorta

Aortic root dilatation is a major pathophysiological mechanism for aortic regurgitation in a variety of disorders and is found in as much as 30% of patients with severe pure aortic regurgitation in whom no valvular abnormality is apparent.¹ Enlargement of the aortic root has also been associated with the occurrence of aortic dissection and/or rupture, which accounts for 1% to 2% of deaths in industrialized countries.² Three major underlying pathologies, ie, abnormalities in aortic tissue associated with aortic dilatation, are summarized as cystic medial necrosis and are variable in severity.⁴,⁵ The aortic root diameter is strongly related to age, to body size,⁶ and, less strongly, to blood pressure (BP).⁷,⁸ However, only a small proportion of the variance of aortic root size can be explained by all of its known clinical and demographic variables.⁹ The present study was undertaken to determine the heritability of echocardiographically derived aortic root diameter in the American Indian participants in the second Strong Heart Study (SHS) examination.

Methods
The SHS is a population-based cohort study of cardiovascular risk factors and prevalent and incident cardiovascular disease in 13 American Indian tribes in Arizona, Oklahoma, and North and South Dakota, as previously described.¹⁰–¹³ The cohort included tribal members aged 45 to 74 years recruited from defined sampling frames of eligible individuals (overall participation rate 61%) for the first SHS examination between July 1989 and January 1992. A total of 3637 SHS cohort members (89% of those alive) attended the second SHS examination from August 1993 to December 1995. The examination included medical history, ECG, measurement of brachial and ankle BP, a 2-hour 75-g glucose tolerance test, and determination of fasting glucose, glycosylated hemoglobin, insulin, lipid, and lipoprotein levels. Anthropometric measurements were performed, and body mass index and waist/hip ratio were
measured. Family history questionnaires were used to identify the parents and full or half siblings of the SHS participants. For the present study, all SHS participants with identified biological relatives in the cohort on the family history questionnaires were included in the analyses.

Echocardiographic Techniques and Measurements
As previously described, studies were performed by using phased-array echocardiographs with M-mode, 2D, pulsed, continuous, and color-flow Doppler capabilities. The correct orientation of the planes for imaging and Doppler recordings was verified by using standard procedures. Measurements were made by using a computerized review station equipped with a digitizing tablet and monitor screen overlay for calibration and performance of each needed measurement. The aortic root diameter was measured at the sinuses of Valsalva; the parasternal long-axis view maximized these dimensions. We have previously assessed the reliability of echocardiographic left ventricular structure and function. Analysis of reliability of aortic root measurements in the same study yielded an intraclass correlation coefficient (p value) of 0.79 (P<0.001). Measurements of the ascending thoracic aorta, aortic arch, and descending thoracic aorta were not part of the SHS echocardiographic protocol.

Bicuspid aortic valve or valve calcification were determined by visualization of the valve in long- and short-axis views. Aortic regurgitation was identified on the basis of the extent of diastolic turbulent flow, indicated by a variance signal in the left ventricle, as previously described in detail. Heritability calculations were performed by using a general pedigree variance-component method in which the phenotypic covariance among relatives was used to simultaneously estimate the proportion of variance in the trait due to the additive effects of genes (ie, the additive genetic heritability [h²]) and the effects of a variety of measured covariates. The quantitative phenotype for individual i, yᵢ, can be written as a simple linear function as follows:

\[ yᵢ = \mu + \sum \beta_j x_j + g_i + e_i \]

where \( \mu \) is the mean of the trait, \( \beta \) is the regression coefficient of the covariate \( j \), \( x_j \) is the value of the covariate \( j \) in the individual \( i \), and \( g_i \) and \( e_i \) represent the random deviations from \( \mu \) for the individual \( i \) values that are attributable to additive genetic and unmeasured environmental effects, respectively. The effects of \( g_i \) and \( e_i \) are assumed to be uncorrelated with one another and are normally distributed with mean 0 and variances \( \sigma_g \) and \( \sigma_e \). The likelihood of the phenotypes of the family members is assumed to follow a multivariate normal distribution, although such an assumption can be violated without a substantial effect on its conclusions; and the phenotypic covariance matrix is modeled as a function of the coefficient of relationship between individuals and the additive genetic and environmental variances. Once the expected mean and the covariance matrix of each pedigree are defined, the likelihood of a pedigree is evaluated by using the multivariate normal density function and summed over all pedigrees. The general variance component method is implemented in the computer analysis program SOLAR, which uses the computer programs FISHER and SEARCH for likelihood optimization in quantitative trait analysis. By use of the variance component model, probability values for the \( h^2 \)'s were obtained by likelihood ratio tests, for which the likelihood of a model in which the \( h^2 \) is estimated is compared with the likelihood of the model in which the \( h^2 \) is constrained to 0. Twice the difference in these logarithmic likelihoods is asymptotically distributed as a 1/2:1/2 mixture of a \( \chi^2 \) variable with 1 df and a point mass at 0.

One potential limitation of adjusting the phenotype under study for all its known covariates is that genes that influence covariates may parallel those that influence the trait, thereby attenuating its residual \( h^2 \). Thus, 2 covariate adjustment strategies were used: the first model simultaneously adjusted for age, sex, and center; the second model additionally simultaneously adjusted for height, weight, and systolic and diastolic BPs. To estimate the proportions of the total variance of aortic root dimensions associated with clinical covariates and with the additive effects of genes, the percentage of variance due to conventional covariates was estimated as the multiple \( R^2 \times 100 \), and the percentage of residual variance associated with the additive genetic contribution was estimated as the following product: \( h^2 \times 100 \) (percentage of variance attributed to clinical covariates).

Clinical and echocardiographic data are presented as mean±SD for continuous variables and as proportions for categorical variables. Data management and analysis were performed by using SPSS 9.0 (SPSS Inc) software. Genetic and pedigree data management was performed by using the PEDSYS data management system (Southwest Foundation for Biomedical Research). Center effects were assessed by using dummy variables for Arizona and North/South Dakota residence. A 2-tailed value of \( P<0.05 \) indicated statistical significance in all analyses.

Results
Clinical Characteristics of SHS Participants
Of the 3502 SHS participants who underwent echocardiography in the second examination, 1373 participants had biological relatives participating in the study and, thus, could be included in the \( h^2 \) analyses, whereas 2129 participants could not be placed in pedigrees. The 1373 related individuals, from 445 families, formed 1305 relative pairs, mostly siblings (1077 pairs) as well as parents, half-siblings, grandparents, aunts, uncles, nieces, and nephews in multigenerational families. There were no significant differences in the demographic characteristics of the SHS participants who were included in the \( h^2 \) analyses compared with those of the remaining participants in the second SHS examination who were not in the analyzed families (Table 1). Similarly, there

### Table 1. Clinical Characteristics of SHS Participants in Families

<table>
<thead>
<tr>
<th></th>
<th>SHS Participants in Families</th>
<th>SHS Participants Not in Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Male</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Age, y</td>
<td>56±8.0</td>
<td>56.0±8.0</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164.7±9.0</td>
<td>164.0±9.1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.0±6.1</td>
<td>31.0±8.0</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.91±0.21</td>
<td>1.90±0.22</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129.6±19.9</td>
<td>130.3±20.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>74.8±9.7</td>
<td>75.0±10.5</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>54.9±17.0</td>
<td>55.2±17.5</td>
</tr>
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were no statistical differences in the mean aortic root diameter (3.5 ± 0.4 versus 3.4 ± 0.4 cm, P = NS) of the 1373 participants in the present h² analysis and the remaining 2129 SHS participants who underwent echocardiography.

**Prevalence of Conditions Associated With Aortic Root Dilatation**

The prevalence of aortic regurgitation did not differ statistically between the SHS participants in the present h² analysis (9.5%) and the remaining SHS participants with echocardiograms (10.5%, χ² = 2.4, P = NS). Similarly, the prevalence of at least mild aortic stenosis in SHS participants in the present h² analysis (1.0%) and in the remaining SHS participants with echocardiograms did not differ statistically (0.6%, χ² = 2.1, P = NS). There were 5 participants in the analyzed families who had bicuspid aortic valve compared with 4 in the remaining 2129 SHS participants.

**Heritability of Aortic Root Size**

In a polygenic model, the variables entered and identified as covariates of larger aortic root diameter were older age, male sex, and center (P < 0.001), which accounted for 35% of the overall variability of aortic root diameter. After simultaneous adjustment was made for these significant covariates, the proportion of phenotypic variance due to additive genetic contribution or residual h² was 0.51 (SE = 0.08, P < 0.001). After an additional simultaneous adjustment was made for height, weight, and systolic and diastolic BPs, the residual h² of aortic root diameter was reduced to 0.44 (SE = 0.08, P < 0.001), which accounted for 26% of the overall variance of aortic root size.

Because center effects were identified as significant covariates in the analyses, h² analyses were performed separately in the 3 SHS centers. Table 2 summarizes the substantial residual h² of aortic root diameter of the analyzed families from each SHS center after an initial simultaneous adjustment was made for age and sex and then an additional simultaneous adjustment was made for age, sex, height, weight, and systolic and diastolic BPs.

**Discussion**

To our knowledge, the present study is the first to assess the heritability of aortic root size in a large population-based sample. Our study indicates that a substantial proportion of the total phenotypic variance of aortic root diameter (26%) is due to the additive effects of genes, after simultaneous adjustment for age, sex, height, weight, and systolic and diastolic BPs. Our study also indicates that genetic influences on aortic root size are robust among the 3 study centers. Studies in twins have provided initial evidence that heredity influences aortic root size. In a study of 53 monozygotic and dizygotic twin pairs, Bielen et al. found that biological inheritance was responsible for 68% (P < 0.001) of the phenotypic variance of aortic diameter, after adjustment was made for body weight. However, because twins share environmental factors to a unique degree, h² estimates that include this shared environmental component in twins are almost always higher than estimates derived from other relatives.

Previous studies of genetic effects on aortic size have focused on the genetic causes of abdominal aneurysms. Tilson and Seashore were among the first to report a relatively high familial incidence of abdominal aortic aneurysms, and subsequently, several other groups have confirmed that abdominal aortic aneurysms are familial. Familial forms of ascending aortic aneurysms have also been reported, suggesting that a genetic defect may be the cause of some ascending aortic aneurysms. Milewicz et al. demonstrated that mutations in the FBN-1 gene, which encodes for fibrillin-1, a protein found in elastic fiber–associated microfibrils, occur in patients with thoracic aortic aneurysms with no evidence of Marfan’s syndrome. However, recent research suggests that familial aortic aneurysms may be genetically heterogeneous. Further studies are needed to identify genetic loci influencing aortic size in population-based samples.

The Framingham Heart Study has found that age, height, weight, and sex were the principal determinants of aortic root dimensions. The impact of BP on aortic root dimensions, independent of age and body size, remains controversial. We have previously demonstrated that aortic diameters increase with increasing quartiles of diastolic and systolic BPs, particularly at the supraortic ridge and ascending aorta but not at the sinuses of Valsalva. In multivariate analysis, BP remained an independent determinant of distal aortic diameters after body size and age were considered. More recently, we have found a lack of association between BP and aortic root measurements at the sinuses of Valsalva in a population-based sample of hypertensive adults and in a clinical cohort of hypertensive adults with ECG-determined left ventricular hypertrophy. In the SHS, older age, male sex, body size, and BP were found to be significant covariates of aortic root diameter and contributed to 40% of the overall variability of aortic root diameter at the level of the sinuses of Valsalva. Furthermore, the present study indicates that an additional 26% of the overall variability of aortic root size is due to additive genetic effects. Of note, there was minimal attenuation of the residual of aortic root size after full covariate adjustment, suggesting that genetic markers affecting body size and BP are distinct from those influencing aortic root size. Our findings of substantial residual h² of echocardiographic variables between the SHS participants in the present h² analysis and the remaining 2129 SHS participants who underwent echocardiography.
graphically determined aortic root diameter suggest that echocardiographic screening of family members with aortic dilatation may identify additional family members predisposed to aortic dissection or rupture.

A long-term goal of the present study is to detect and map new polymorphic genes that influence variation in aortic root size and thereby contribute to the development of asymptomatic subclinical aortic dilatation and, subsequently, to aortic regurgitation, dissection, or rupture. The first necessary step in this process is to determine that there is substantial heritability of aortic size that is independent of known confounding variables in members of the general population. The SHS is particularly suited for this purpose because its population-based cohort is unlikely to have a sufficient number of individuals with uncommon mendelian disorders such as Marfan’s syndrome (with a population prevalence of 1:5000 to 1:10,000) included in the present analyses to contribute impossibly to the evidence that we have obtained of strong genetic influences to aortic root size. However, it is possible that unmeasured environmental factors are potentially inflating our heritability estimates in this population-based sample. Therefore, other population-based studies on genetic factors influencing aortic size need to be performed. Studies that seek to identify specific genetic markers that determine aortic root size are currently being undertaken in the SHS, which may lead to improvement in diagnostic and therapeutic strategies in the prevention of aortic root dilatation and its complications.

In conclusion, heredity explains a substantial proportion of the variability of aortic root size that is not accounted for by age, sex, body size, and BP. Echocardiographic screening of family members with aortic root dilatation may identify other individuals predisposed to aortic dissection or rupture.

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References


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