Aortic Root Diameter and Longitudinal Blood Pressure Tracking

Erik Ingelsson, Michael J. Pencina, Daniel Levy, Jayashri Aragam, Gary F. Mitchell, Emelia J. Benjamin, Ramachandran S. Vasan

Abstract—Proximal aortic diameter, including aortic root (AoR) diameter, has been inversely related to pulse pressure in cross-sectional studies. So, investigators have hypothesized that a smaller AoR diameter may increase the risk of developing hypertension. Prospective studies are lacking to test this hypothesis. We measured AoR diameter in 3195 Framingham Study participants (mean age: 49 years; 57% women; 8460 person-examinations) free from hypertension and previous cardiovascular disease who underwent routine echocardiography. We related AoR to hypertension incidence and blood pressure (BP) progression (increment of ≥1 category, as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). On follow-up (median: 4 years), 1267 individuals (15%; 661 women) developed hypertension, and 2978 participants experienced BP progression (35%; 1588 women). In logistic regression models adjusted for age, sex, and height, AoR was positively associated with hypertension incidence (odds ratio: 1.15; 95% CI: 1.08 to 1.23) and BP progression (odds ratio: 1.09; 95% CI: 1.04 to 1.14) on follow-up. However, adjustment for other factors known to influence BP tracking (baseline systolic and diastolic BP, smoking, diabetes, and weight) rendered these relations statistically nonsignificant (odds ratio: 1.03; 95% CI: 0.96 to 1.11 for hypertension incidence; odds ratio: 1.03; 95% CI: 0.97 to 1.08 for BP progression). In our large community-based sample of nonhypertensive individuals, AoR diameter was not associated with hypertension incidence or BP progression prospectively after adjustment for potential confounders. Our prospective study does not support the notion that a smaller AoR predisposes to hypertension. (Hypertension. 2008;52:473-477.)

Key Words: blood pressure • aorta • hypertension

High blood pressure (BP) is a major risk factor for cardiovascular disease (CVD), estimated to account for 7.1-million deaths per year worldwide.1 Globally, >60% of cerebrovascular disease and ~50% of coronary heart disease have been attributed to suboptimal BP.1 Recent guidelines have put emphasis on the importance of the prevention and reduction of the community burden of hypertension, given its public health importance and potential as a modifiable vascular risk factor.2 Therefore, it is important to elucidate the pathophysiological mechanisms underlying hypertension and to discover new approaches for identifying individuals prone to hypertension development.

Given the public health importance of hypertension, considerable attention has been focused recently on the complex relations of the aortic root (AoR) diameter and hypertension risk. On one hand, dilation of the AoR diameter has been noted in individuals with hypertension, although the prevalence of such dilation in recent studies is low.3 A larger AoR is recognized also as a cross-sectional correlate for the presence of cardiac and extracardiac target organ damage4,5 and a predictor of incident CVD longitudinally.6 The aforementioned studies would seem to suggest that a larger AoR is a marker of higher vascular risk. Yet, on the other hand, a parallel set of cross-sectional studies has repeatedly demonstrated an inverse association between AoR diameter and BP measurements, especially pulse pressure.3–10 These latter observations have generated the hypothesis that a smaller AoR may be a marker of higher BP and possibly of future hypertension risk.11,12 However, this hypothesis has been challenged,13 and there is an ongoing debate over whether the proximal aortic diameter, including that of the root, is implicated in the pathogenesis of hypertension.11,14,15

The availability of longitudinal BP measurements, as well as echocardiographic AoR dimensions, in the Framingham Heart Study provides a unique opportunity to test the hypothesis that AoR diameter predicts the development of hypertension. Thus, we investigated the associations of AoR dimensions and longitudinal BP tracking (including the inci-
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Figure. Number of participants included in the present study at the baseline examinations and number of participants with incident hypertension or BP progression at the follow-up examinations.

Methods

Study Sample

The selection criteria and design of the Framingham Offspring Study have been detailed previously. Approximately every 4 years, offspring cohort participants undergo routine medical history, physical examination including BP measurement, anthropology, and laboratory assessment of CVD risk factors in the heart study. At several examinations, participants also undergo routine transthoracic echocardiography using a standardized protocol (see below). Participants who underwent routine echocardiographic measurement of the AoR diameter at examination cycles 2 (1979–1983), 4 (1987–1991), 5 (1991–1995), or 6 (1995–1998) referred to as baseline examinations of the present investigation were eligible if they also attended the subsequent examination cycle (examinations 3, 5, 6, and 7, respectively; referred to as follow-up examinations) 4 years later (Figure). This sampling design was chosen to maximize the use of the wealth of echocardiographic and BP data to test our study hypothesis with adequate statistical power to discern modest associations. Thus, the same individual could contribute multiple observations to the present investigation if he or she experienced either hypertension or BP progression (35%; 1588 women). There was a conceivable that a smaller AoR diameter may be associated with very modest increments in BP on follow-up that may not be reflected by either the development of hypertension or BP progression, we also evaluated changes in systolic and diastolic BP and pulse pressure on follow-up in additional analyses.

Echocardiographic Methods

All of the study participants underwent routine transthoracic echocardiography using a standardized protocol. The echocardiographic equipment used for image acquisition varied across the 4 baseline examinations: Hoffrel 201 ultrasound receiver (and Aerotech transducer) at examination cycle 2; Hewlett Packard (model 77020AC) ultrasound machine at examinations 4 and 5; and a Sonos 1000 Hewlett-Packard machine at examination 6. The AoR diameter was measured from the M-mode tracings in accordance with the American Society of Echocardiography guidelines using a leading-edge-to-leading-edge measurement of the maximal distance between the anterior AoR wall and the posterior AoR wall at end diastole. The reproducibility of AoR measurements was systematically assessed at the sixth examination and was excellent.

Hypertension Development and BP Progression on Follow-Up

We examined the associations of baseline AoR diameter with the incidence of 2 BP outcomes on follow-up (median: 4 years): (1) incidence of hypertension, defined as a systolic BP ≥140 mm Hg, or diastolic BP ≥90 mm Hg, or use of antihypertensive medication; and (2) BP progression, defined as an increase in BP category on follow-up (according to the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). For this purpose, nonhypertensive participants were allocated to a BP category at baseline (systolic BP <120 mm Hg and diastolic BP <80 mm Hg; systolic BP 120 to 129 mm Hg or diastolic BP 80 to 84 mm Hg; or systolic BP 130 to 139 mm Hg or diastolic BP 85 to 89 mm Hg). An increase of BP category on follow-up in an individual was defined as an increment of ≥1 category or development of hypertension. Because it is conceivable that a smaller AoR diameter may be associated with very modest increments in BP on follow-up that may not be reflected by either the development of hypertension or BP progression, we also evaluated changes in systolic and diastolic BP and pulse pressure on follow-up in additional analyses.

Statistical Analyses

We used pooled repeated observations in multivariable logistic regression analyses to relate AoR diameter at baseline with hypertension incidence and BP progression on follow-up in models adjusted for age, sex, and height, as well as models adjusted for age, sex, height, weight, baseline systolic and diastolic BP, smoking, and diabetes. We examined effect modification by testing the statistical significance of the 2-way interaction term among age, sex, obesity, systolic BP (above versus below the median), and AoR diameter separately for the outcomes of hypertension incidence.

We performed additional analyses examining the relations of AoR diameter with longitudinal changes in systolic and diastolic BP and pulse pressure analyzed as continuous variables. General estimating equations were used to account for repeated observations on some individuals, and the algorithm described in Levy et al was used to adjust for antihypertensive treatment on follow-up. These models were adjusted for the covariates in the fully adjusted model. In secondary analyses, we examined associations of AoR diameter at baseline with hypertension incidence and BP progression on follow-up after additional adjustment for fractional shortening, stroke volume calculated using the Teicholz formula, total and high-density lipoprotein cholesterol, or mean arterial pressure, in separate models. Also, we performed analyses without adjustment for baseline BP. In further secondary analyses, we related AoR diameter at baseline with the following: incidence of isolated systolic hypertension; changes in systolic and diastolic BP after exclusion of individuals who were started on antihypertensive medication during follow-up; and incidence of BP outcomes over 8 years of follow-up (instead of 4 years).

We had statistical power of 80% to detect an odds ratio (OR) effect of 1.12 (per SD increment in AoR diameter) and 90% power for an OR of 1.14 (at an α of 0.05). All of the analyses were performed using SAS 9.1 (SAS Institute Inc), and a 2-sided P value of <0.05 was considered significant.

Results

The characteristics of our study sample are shown in Table 1. On follow-up (median: 4 years), 1267 individuals (15%; 661 women) developed hypertension, and 2978 participants experienced BP progression (35%; 1588 women). There was a positive and statistically significant association of AoR diameter with hypertension incidence on follow-up in analyses adjusted for age, sex, and height (Table 2, left). If adjusting
Table 1. Characteristics of the Study Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.7 (10.5)</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>56.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.1 (9.4)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.8 (15.7)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>117 (12)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74 (8)</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>43 (9)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>2.8</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>25.4</td>
</tr>
<tr>
<td>Aortic root diameter, cm</td>
<td>3.07 (0.38)</td>
</tr>
</tbody>
</table>

The study sample consisted of 8460 person-examinations of 3195 unique participants, because the same individual could contribute multiple observations if he or she attended >1 examination (and the corresponding follow-up examination).

Table 2. Relation of AoR Diameter to Incidence of Hypertension or BP Progression Over 4 Years of Follow-Up

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Hypertension Incidence</th>
<th>BP Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) Per SD of AoR Diameter</td>
<td>P</td>
</tr>
<tr>
<td>Age, sex, and height</td>
<td>1.15 (1.08 to 1.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, sex, height, systolic and diastolic BP, smoking, diabetes, and weight</td>
<td>1.03 (0.96 to 1.11)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Progression was defined as an increase in blood pressure category, as defined in the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
impact of AoR diameter on BP in our middle-aged sample may have already occurred. Studies of the relations of AoR and BP tracking in younger samples are needed to investigate this possibility.

The strengths of our study include the large community-based sample, the direct measurement of AoR diameter, and the longitudinal design, which allowed us to evaluate temporal relations of AoR diameter and BP. There were several limitations of our study. Our sample consisted of middle-aged, white individuals of European descent, limiting the generalizability of our findings to other age groups and ethnicities. Also, the variability of BP measurements could have introduced errors in the stratification of participants into BP categories. In addition, the change in BP in our sample was small, potentially limiting our power to detect a relation between change in diameter and change in BP. Aortic diameter was measured at the root at the level of the sinuses of Valsalva, which are geometrically complex, potentially limiting the precision of our diameter measurements. Also, M-mode AoR diameter measurements can be less accurate and may underestimate true AoR diameter (as measured from 2D images), which should also be considered as a limitation of the present study. The sinuses are also substantially larger than the adjacent tubular segment of aorta, just above the sinotubular junction. Because characteristic impedance of the aorta has a strong inverse relation to diameter (power of \(-2.5\)), it is sensitive to measurements of AoR diameter and the level of measurement. Thus, small discrepancies between AoR diameters at the level of the sinuses as compared with the tubular proximal aorta may be amplified, which may result in missing potentially important physiological effects of variations in aortic diameter measured at a slightly higher level above the root. Indeed, there is evidence to suggest that the proximal AoR diameter (as measured routinely) is less associated with BP than the ascending aortic diameter.

**Perspectives**

The present study fulfills an important gap in our understanding of the complex relations of AoR to BP. Prospectively, AoR diameter measured at the level of the sinuses of Valsalva was not associated with hypertension incidence or BP progression over time after adjustment for potential confounders in our young-to-middle-aged large community-based sample of individuals free of hypertension and previous CVD at baseline. Our study does not support a causal role for AoR diameter in the pathophysiology of hypertension development in this age group. As noted above, we measured aortic diameter at the root, and it is conceivable that proximal ascending aortic dimensions may play a more important role in influencing the propensity for future hypertension. Additional studies that measure ascending aortic dimensions at multiple points and also simultaneously assess proximal aortic compliance may help elucidate the relations of aortic properties (structure and function) to the development of an elevated pulse pressure and hypertension.

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**Disclosures**

G.F.M. is owner of Cardiovascular Engineering Inc, a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness. The remaining authors report no conflicts.

**References**


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