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-
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 $\geq 140$ mm Hg, or diastolic BP $\geq 90$ 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 $\geq 1$ 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 $\alpha$ 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...
for a set of standard CVD risk factors, the association was attenuated altogether. None of the interaction terms evaluated reached statistical significance (P>0.1 for all), suggesting that the association of AoR diameter with incident hypertension was not modified by age, sex, level of systolic BP, or obesity.

Similarly, there was a highly significant association between AoR diameter and BP progression on follow-up in age-, sex-, and height-adjusted analyses (Table 2, right). Again, when adjusting for additional CVD risk factors, the association was attenuated altogether.

In additional analyses, AoR diameter was not related to longitudinal changes in systolic (mean change: 3.0 mm Hg; SD: 11.9 mm Hg), diastolic BP (mean change: 0.6 mm Hg; SD: 7.9 mm Hg), or pulse pressure (mean change: 2.4 mm Hg; SD: 10.0 mm Hg) evaluated as continuous outcomes (P=0.36, 0.64, and 0.40, respectively).

In secondary analyses, there was a borderline significant association of AoR with hypertension incidence in models that did not adjust for baseline BP (OR: 1.07; 95% CI: 0.99 to 1.14; P=0.052). In addition, in analyses based on 8 years of follow-up (instead of 4 years), there was a statistically significant positive association of AoR diameter with BP progression (OR: 1.11; 95% CI: 1.04 to 1.18; P=0.003) and a borderline significant positive association with hypertension incidence (OR: 1.08; 95% CI: 0.99 to 1.18; P=0.09). All of the other secondary analyses (with additional adjustment for fractional shortening, stroke volume, total and high-density lipoprotein cholesterol, or mean arterial pressure; associations of AoR diameter with isolated systolic hypertension incidence and changes in systolic and diastolic BP after exclusion of individuals who were started on antihypertensive medication during follow-up) were statistically nonsignificant (P>0.1 for all).

### Discussion

Previous studies have established the cross-sectional associations between AoR diameter and different BP measures in individuals from the general population,6,7,10 in hypertensive subjects,3–5 and in individuals with Marfan syndrome.9 Several of these studies have found stronger positive associations of AoR diameter with diastolic BP6,10 or pulse pressure4,7 than with systolic BP. Consistently, they have shown direct relations of AoR diameter with diastolic BP6,10 and inverse relations with pulse pressure.4,7,10 In some of these studies, the relations were adjusted for height and weight,5–7,10 which, together with age and sex, have been shown to explain the major part of the interindividual variation in AoR diameter.10 The inverse relation of AoR diameter with pulse pressure was confirmed in a recent study in hypertensive subjects.23 In that cross-sectional study, elevated pulse pressure was mainly attributable to decreased AoR diameter, measured above the sinotubular ridge, and increased wall stiffness. The authors speculated that interindividual differences in AoR diameter, in addition to age-related tissue alterations in the aortic wall, may contribute to the pathogenesis of increased pulse pressure and isolated systolic hypertension. However, this hypothesis is controversial and has been debated much over the past few years.11,13,14 It has been suggested that only a prospective study could clarify the potential role (if any) of a smaller AoR in the development of hypertension.15 To our knowledge, there are no previous studies examining the longitudinal relation between AoR diameter and BP.

In our large, community-based sample of men and women free from hypertension and previous CVD at baseline, AoR diameter was related positively with incident hypertension and progression of BP on follow-up in minimally adjusted analyses but not after additional adjustment for standard CVD risk factors. There was a borderline statistically significant positive association of AoR with hypertension incidence in multivariable models that did not adjust for baseline BP and a positive association of AoR diameter with BP progression in analyses based on 8 years of follow-up. However, in both cases the OR were slightly above 1, indicating an association in the direction opposite to the hypothesis we tested, ie, that a smaller AoR predisposes to the development of hypertension. It should be noted that it is conceivable that AoR diameter influences BP earlier in the life course, and any

### 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 decent, 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 precisions 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),24 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.25

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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