Cross-Sectional and 4-Year Longitudinal Associations Between Brachial Pulse Pressure and Common Carotid Intima-Media Thickness in a General Population

The EVA Study

Mahmoud Zureik, MD, PhD; Pierre-Jean Touboul, MD; Claire Bonithon-Kopp, MD, PhD; Dominique Courbon, BS; Claudine Berr, MD, PhD; Chantal Leroux, MD; Pierre Ducimetière, PhD

Background and Purpose—The cross-sectional and 4-year longitudinal associations between brachial pulse pressure (PP) and ultrasound measurements of common carotid intima-media thickness (CCA-IMT) were assessed.

Methods—A population of 957 volunteers aged 59 to 71 years was recruited from the electoral rolls of the city of Nantes (western France) and reexamined 4 years later. Longitudinal changes in PP and CCA-IMT were computed as the difference between 4-year follow-up and baseline values.

Results—Baseline CCA-IMT and PP were positively associated in both age- and sex-adjusted analysis (partial correlation coefficient 0.20, P<0.001) and in multivariate analysis adjusted for traditional cardiovascular risk factors and mean blood pressure (partial correlation coefficient 0.18, P<0.001). In longitudinal analysis, baseline PP was associated with the change in 4-year CCA-IMT (partial correlation coefficient 0.11, P<0.001), and baseline CCA-IMT was a predictor of the 4-year change in PP (partial correlation coefficient 0.10, 0.001<P<0.01). No association between mean blood pressure and CCA-IMT was observed once PP was taken into account, in either cross-sectional or longitudinal analyses (partial correlation coefficients ranged from 0.00 to 0.03). Similar patterns of results were observed in hypertensive, nonhypertensive, and antihypertensive-treated and -nontreated subjects.

Conclusions—This longitudinal study of a large population of relatively aged subjects suggests that elevated levels of PP are associated with the progression of CCA-IMT, and increased CCA-IMT is associated with PP widening. The nature of these relationships and whether atherosclerosis progression over time is involved or not in these associations merit further investigations.

Key Words: aged ■ blood pressure ■ carotid arteries ■ ultrasonography

Arterial blood pressure may be divided into 2 components: a steady component (mean blood pressure [MBP]), which is the pressure that may be present in the aorta and its major arteries during a given cycle when cardiac output is nonpulsatile, and a pulsatile component (pulse pressure [PP], the difference between systolic [SBP] and diastolic [DBP] blood pressures), which is the oscillation around mean arterial blood pressure.1 A large PP may occur owing to 3 principal factors: an increase in the velocity of ventricular ejection and/or stroke volume, a reduction in the viscoelastic properties of the arterial wall, and a modification in the timing of reflected waves.2

Recently, it has been reported that a large, brachial PP was independently associated with morbidity and mortality from cardiovascular and coronary heart diseases (CHD) in both hypertensive and general populations.3,4 The specific underlying mechanisms are not well known. Several cross-sectional epidemiological studies have shown positive but moderate associations between brachial PP and ultrasound measurements of common carotid intima-media thickness (CCA-IMT),5–8 an early marker of atherosclerosis and/or vascular remodeling.8–10 However, cross-sectional results do not allow determination of the direction and time-dependent relationships. In fact, it is not clear whether a large PP is related to subsequent arterial thickening or whether the CCA-IMT increase is related to a subsequent PP widening. Longitudinal studies are thus necessary to confirm and extend the cross-sectional findings and indicate the possible direction of the relationships. The magnitude of the observed longitudinal associations is expected to be attenuated due to the cumulative effects of known intraindividual variability and error measurements of both casual blood pressure and ultrasound carotid values11–13 when changes over time in these parameters are used in the statistical analysis. In
observational studies, a large number of subjects is thus needed to assess the longitudinal associations between brachial PP and ultrasound measurements of the CCA-IMT. The Étude du Vieillissement Artériel (EVA) study, a longitudinal population study of 957 subjects aged 59 to 71 years, provides an opportunity to address this question.

Subjects and Methods
Details of the EVA Study have been reported previously. In brief, the EVA Study is a longitudinal study on cognitive and vascular aging. The initial study population was composed of volunteers aged 59 to 71 years who were recruited from the electoral rolls of the city of Nantes (western France). During the baseline visit, which took place between June 1991 and July 1993, high-resolution ultrasound examinations of the carotid arteries were performed in 1384 of the 1389 subjects recruited. Participants were reexamined after 2 and 4 years, and this report will focus on the B-mode ultrasound carotid measurements at the baseline and third examinations, approximately 4 years apart. The study protocol was approved by the Comité d’Éthique du Centre Hospitalier Universitaire de Kremlin-Bicêtre, and written, informed consent was obtained from all participants.

Ultrasoundography
Ultrasound examinations at baseline and at 4-year follow-up were performed using the Aloka SSD-650, with a transducer frequency of 7.5 MHz. This system provides an axial resolution of 0.30 mm. Acquisition, processing, and storage of B-mode images were computer assisted with software especially designed for longitudinal studies (EUREQUA, TSI).

Details of the protocol have been described elsewhere. All measurements were made at the time of examination, which involved scanning of the CCAs, the carotid bifurcations, and the origin (first 2 cm) of the internal carotid arteries. For all arterial segments, optimal longitudinal and transverse images were stored on an optical disk. The IMT was measured on the far wall of the middle and distal CCA as the distance between the lumen-intima interface and the media-adventitia interface by using an automated edge-detection algorithm. One transverse and 2 longitudinal measurements of the IMT were completed on both the right and left CCAs, and the mean of the right and left longitudinal CCA-IMT measurements was used in the analysis. All measurements of CCA-IMT were made at a site free of any discrete plaques. The occurrence of plaques was defined as localized echo structures encroaching into the vessel lumen for which the distance between the media-adventitia interface and the internal side of the lesion was ≥1 mm.

Reproducibility of the scanning and reading procedures have been reported elsewhere. A rereading study was made on random subsamples of images of CCAs (n=81). The mean absolute difference and correlation coefficient between repeated readings of CCA-IMTs were, respectively, 0.06 mm and 0.82. In a previous work from our group, it was shown that the intersonographer and intraarterial variabilities (expressed as absolute differences and correlation coefficients) obtained by using the repositioning function of the EUREQUA software, were, respectively, 0.07 mm with a correlation coefficient = 0.71 and 0.06 mm with a correlation coefficient = 0.77.

Ultrasound examinations at baseline and at 4-year follow-up were performed by the same 4 sonographers. At the 4-year follow-up examination, the sonographers were unaware of the baseline CCA-IMT. Both examinations were performed by the same sonographer for 80% of subjects. The correlation coefficient between the baseline and 4-year follow-up CCA-IMT measurements was 0.60 (P<0.001). It was 0.61 (P<0.001) when the same sonographer performed both examinations and 0.57 (P<0.001) when ultrasound measurements were obtained by different sonographers.

Blood Pressure Measurements
Sitting brachial blood pressure was measured at each examination, by trained research assistants, on the right arm. Two independent measurements of SBP and DBP were made before the B-mode ultrasound examination with a digital electronic tensiometer (SP9 Spengler) after a 10-minute rest, and the average value was used in the analysis. MBP and PP were calculated by using the following formula: \( MBP = \frac{1}{3} (2SBP + DBP) \) and PP = SBP − DBP. For each examination, subjects with an SBP ≥160 mm Hg or a DBP ≥95 mm Hg or who were using antihypertensive drugs were considered as hypertensives.

Medical History and Standard Biological Procedures
Similar medical information was obtained at each examination by a standardized questionnaire, which provided information about demographic background, occupation, medical history, drug use, and personal habits such as cigarette consumption. A self-reported personal history of myocardial infarction or angina pectoris (personal history of CHD) was also recorded. The body mass index was computed as weight (in kilograms) divided by the square of height (in meters). Serum total cholesterol and fasting plasma glucose were measured at both examinations by the same biological procedures described elsewhere.

Data Analysis
Standard procedures from the Statistical Analysis System (SAS) were used for univariate and multivariate analyses. Longitudinal changes in blood pressure measurements and CCA-IMT were computed as the difference between 4-year follow-up and baseline values. In cross-sectional and longitudinal analyses, the associations between blood pressure measurements and CCA-IMT were assessed by Pearson correlation coefficients, after adjustment for sex and age. Multivariate cross-sectional and longitudinal correlations were also adjusted for baseline body mass index, fasting glucose, total cholesterol, smoking habits, and personal history of CHD. Multiple linear regression models were also used in the analysis.

For longitudinal associations between blood pressure measurements and CCA-IMT, 2 strategies were used. The first was to correlate baseline values of PP and MBP with the subsequent 4-year change in CCA-IMT. The second was to correlate baseline CCA-IMT with the subsequent 4-year changes in PP and MBP. For each longitudinal variable (4-year change in CCA-IMT, PP, or MBP), adjustment for the corresponding baseline value, in the longitudinal analysis, was systematically performed.

Subjects who were examined during the training period (between June and December 1991) were considered to have unreliable initial ultrasound examinations on the basis of interreader reproducibility studies, and their data were systematically excluded from statistical analysis (n=235). Of the 1149 subjects with reliable ultrasound measurements, 957 (83%) underwent the 4-year follow-up B-mode ultrasound examination. At baseline, there were no significant differences between subjects who participated and those who did not participate in the 4-year follow-up survey for sex (59.6% versus 58.7% of women, P=0.85), age (65.2±3.0 versus 64.8±3.0 years, P=0.17), MBP (96.6±12.1 versus 97.9±12.3 mm Hg, P=0.19), PP (52.7±13.4 versus 53.6±13.5 mm Hg, P=0.45), and CCA-IMT (0.66±0.11 versus 0.67±0.13 mm, P=0.32).

Results
The mean age (±SD) at baseline of the 957 subjects was 65.2 years (±3.0 years). Two hundred ninety-nine subjects (31.2%) were considered hypertensive, and 59 (6.2%) reported a personal history of CHD at baseline. Five hundred sixty-three subjects (58.9%) were never-smokers, 311 (32.4%) were ex-smokers, and 83 (8.7%) were current smokers. Baseline values and changes in characteristics of the participants are shown in Table 1. During the 4-year follow-
TABLE 1. Baseline Values and Changes in Characteristics of the 957 Subjects During the 4-Year Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>4-Year Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.2 ± 3.0</td>
<td>4.0 ± 0.3 †</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5 ± 3.2</td>
<td>0.3 ± 1.5 †</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.2 ± 0.9</td>
<td>−0.3 ± 0.9 †</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.7 ± 1.0</td>
<td>0.1 ± 1.1 ±</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>136.8 ± 18.4</td>
<td>5.0 ± 17.6 †</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>80.9 ± 11.1</td>
<td>−1.0 ± 10.0 *</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>55.9 ± 13.6</td>
<td>6.0 ± 14.3 †</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>99.5 ± 12.4</td>
<td>1.0 ± 11.2 ±</td>
</tr>
<tr>
<td>CCA-IMT, mm</td>
<td>0.68 ± 0.12</td>
<td>0.05 ± 0.11 *</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

*P < 0.05, †P < 0.01 for 4-year change, calculated by Student’s paired t test. Longitudinal changes were computed as the differences between the 4-year follow-up and the baseline values.

Cross-Sectional Correlations (Baseline Data)

In the analysis adjusted for age and sex (Table 2), CCA-IMT was positively associated with PP and MBP (partial correlation coefficients were, respectively, 0.20 and 0.12, P < 0.001 for each). Further adjustment for baseline total cholesterol, plasma glucose, body mass index, smoking habits, and personal history of CHD yielded similar results for PP, but the association between MBP and CCA-IMT became weaker (Table 2). When PP and MBP were simultaneously introduced in the multivariate model, MBP was no longer related to CCA-IMT. In contrast, PP remained significantly associated with CCA-IMT, independently of MBP and the other risk factors (Table 2). In multiple linear regression analysis, the predicted CCA-IMT increase for a 15-mm Hg increase in PP (±1SD) was 0.03 mm (95% confidence interval, 0.01 to 0.04). Similar patterns of results were observed for men and women, although the associations were stronger in men (Table 2).

Four-Year Longitudinal Correlations

Associations of Baseline Blood Pressure Measurements With 4-Year Change in CCA-IMT

Baseline PP and MBP were positively and significantly associated with the 4-year change in CCA-IMT, both in analysis adjusted for sex, age, and baseline CCA-IMT and in full multivariate analysis (Table 3). However, as in the cross-sectional analysis, when baseline PP and MBP were

TABLE 2. Cross-Sectional (Baseline) Correlations Between Blood Pressure Measurements and CCA-IMT

<table>
<thead>
<tr>
<th>Baseline vs. CCA-IMT</th>
<th>Age- and Sex-Adjusted Pearson Correlation (Model 1)</th>
<th>Partial Pearson Correlation* (Model 2)</th>
<th>Partial Pearson Correlation† (Model 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 957)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>0.20 §</td>
<td>0.20 §</td>
<td>0.18 §</td>
</tr>
<tr>
<td>MBP</td>
<td>0.12 §</td>
<td>0.09 ‡</td>
<td>0.00</td>
</tr>
<tr>
<td>Men (n = 395)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>0.27 §</td>
<td>0.24 §</td>
<td>0.21 §</td>
</tr>
<tr>
<td>MBP</td>
<td>0.16 ‡</td>
<td>0.11 ‡</td>
<td>0.01</td>
</tr>
<tr>
<td>Women (n = 562)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>0.14 §</td>
<td>0.15 §</td>
<td>0.13 §</td>
</tr>
<tr>
<td>MBP</td>
<td>0.09 ‡</td>
<td>0.05</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Adjusted for sex (when applicable), age, smoking habits, total cholesterol, plasma glucose, and body mass index.
†Adjusted for the same variables as in the previous model, plus MBP for PP and PP for MBP.
‡P < 0.05, §P < 0.001.
used together in the model, only baseline PP was a significant predictor of the 4-year change in CCA-IMT (Table 3). The estimated 4-year CCA-IMT change increments for a 15-mm Hg increase in baseline PP were 0.02 mm (95% confidence interval, 0.01 to 0.03).

**Associations of Baseline CCA-IMT With the 4-Year Change in Blood Pressure Measurements**

Baseline CCA-IMT was not associated with the 4-year change in MBP (Table 4). In contrast, a positive association of baseline CCA-IMT with the 4-year PP change was observed. Full multivariate analysis did not alter this result (Table 4). When further adjustment for the 4-year MBP change was performed, the PP change over time remained independently associated with baseline CCA-IMT (Table 4). The estimated 4-year PP change increment for a 0.15-mm increase in baseline CCA-IMT (±1SD) was 1.85 mm Hg (95% confidence interval, 0.48 to 3.22).

For the associations of 4-year changes in PP and MBP with the 4-year change in CCA-IMT, there were, though statistically significant, weak associations (correlation coefficients were, respectively, 0.07 and 0.07, *P<0.05* for each). When 4-year changes in PP and MBP were used together in the model, only the PP change was a significant predictor of the 4-year change in CCA-IMT. The partial correlation coefficients were, respectively, 0.06 (*P<0.05*) and 0.03 (not significant).

All analyses were repeated separately in hypertensive and nonhypertensive subjects at baseline. Similar patterns of results were observed (data not shown). Furthermore, in treated hypertensive subjects at baseline (n=245), the partial cross-sectional correlation between CCA-IMT and PP was 0.16 (*P<0.01*). In these subjects, baseline CCA-IMT was associated with the change in PP (partial correlation coefficient=0.12, *P=0.051*), and baseline PP was related to the change in CCA-IMT (partial correlation coefficient=0.14, *P<0.05*). When all analyses were repeated in the whole population after adjustment for antihypertensive treatment at baseline (yes/no), very similar results to those reported in Tables 2 through 4 were observed.

**Discussion**

In this 4-year longitudinal study performed in a large population of relatively aged subjects, we found that PP was associated with the change over time in CCA-IMT and that CCA-IMT was associated with the change over time in PP. These associations were independent of MBP and other traditional cardiovascular risk factors and were observed both in hypertensive and nonhypertensive subjects as well as in antihypertensive-treated and -nontreated subjects.

The consistent lack of association between MBP and CCA-IMT, after adjustment for PP, both in cross-sectional and longitudinal analyses, is noteworthy. These results suggest that in the elderly, the relationship of MBP with IMT is far less important than that of PP.

The magnitude of the association between brachial PP and carotid IMT in our cross-sectional analysis was very close to that observed in the other cross-sectional studies. A wide PP in elderly subjects could be considered a result of an increase in arterial stiffness in large conduit arteries (alterations in the viscoelastic properties of the arterial wall). Few studies have reported the relationships between carotid wall thickness and more specific markers of arterial stiffness. In the Atherosclerosis Risk in Communities (ARIC) Study, an increase in CCA-IMT was associated with a stiffer arterial wall, as assessed by a change in arterial diameter of the CCAs occurring during the cardiac cycle. However, this association was limited to subjects with the thickest carotid arteries (>90th percentile of IMT). Another cross-sectional study has shown a decrease in carotid distensibility (an increase in arterial stiffness) associated with an increase in CCA-IMT in hypertensive subjects compared with controls.

Our longitudinal results extend the findings of cross-sectional studies and suggest that elevated levels of PP at baseline are associated with progression of CCA-IMT, and an increased CCA-IMT at baseline is associated with PP widening.

Both arterial hypertrophy and atherosclerosis could be involved in this cycle. Blood pressure, particularly SBP and PP, could increase wall stress that strains the elements within the wall, leading to both intimal and, to a larger extent, medial thickening. The increase in IMT is due to an increase in both smooth muscle mass and extracellular collagen content. Changes in the ratio of collagen to elastin have been known to structurally affect the elastic behavior of the arterial wall. This could, in turn, result in an increase in arterial stiffness and thus, a subsequent increase in PP. The potential effects of atherosclerosis in the observed cycle are another explanation. A large PP might promote the process of atherosclerosis. Thickening of the intima-media at the CCA is generally considered to be an early marker of generalized atherosclerosis because of its association with the main cardiovascular risk factors, the presence of other localiza-
tions of atherosclerosis,\textsuperscript{10,20} and an increased risk of CHD and stroke.\textsuperscript{21,22} A cross-sectional association of PP with carotid atherosclerotic plaques has been previously reported.\textsuperscript{23,24} Furthermore, mental stress–induced PP change has recently been shown to be associated with the development of early carotid atherosclerosis in healthy postmenopausal women.\textsuperscript{25} Isolated systolic hypertension, a disorder more frequently observed in the elderly and in which a high SBP and PP are the major characteristics, is associated with carotid atherosclerosis.\textsuperscript{26,27}

Atherosclerotic changes in the arterial wall (including smooth muscle cell proliferation; deposition of lipid; and accumulation of collagen, elastin, and proteoglycans without compensatory development of scar collagen\textsuperscript{,7,28,29}) could, in turn, lead to a loss of elasticity, an increase in arterial stiffness, and thus, a subsequent increase in PP. In animal studies, a direct relationship has been observed between regression (or progression) of atherosclerosis and an increase (or a decrease) in aortic arterial distensibility.\textsuperscript{30} In humans, progression of radiographically diagnosed atherosclerosis of the abdominal aorta was accompanied by a decrease in DBP in an epidemiological study of 855 women aged 45 to 64 years at baseline who were followed up for 9 years, suggesting that a decline in DBP could indicate vessel wall stiffening resulting from atherosclerosis progression.\textsuperscript{31}

The average annual rate of progression of CCA-IMT observed in the EVA Study (\(\approx 0.01 \text{ mm/y} \)) is comparable to the cross-sectional estimates of the progression rate of carotid IMT observed in aged populations (estimates of \(\approx 0.008 \text{ to } 0.01 \text{ mm/y} \) in both sexes).\textsuperscript{10,32} Few longitudinal data on the rate of progression of carotid IMT in general populations are available. In the ARIC Study,\textsuperscript{33} the progression rate of CCA-IMT in the participants aged 45 to 64 years was similar (0.035 mm over 3 years) to ours and much slower than the rate observed in the Finnish KIHD study (0.12 mm over 2 years).\textsuperscript{34} PP increased over time and MBP remained unchanged (Table 1). SBP increases more with age than does DBP.\textsuperscript{19} In the elderly, DBP even tends to fall, so there is a progressive widening of PP while MBP remains relatively unchanged or rises only modestly.\textsuperscript{19} In the present study, a widening PP over time was mainly due to an SBP increase and, to a lesser extent, to a DBP decrease (Table 1). A larger part of the associations observed could thus be explained by SBP rather than DBP. In fact, if we regress cross-sectional CCA-IMT values on both SBP and DBP measurements, the contribution of each (after taking into account the other) is statistically significant but of opposite sign, indicating that a combination of these parameters as PP is a better predictor than is SBP alone.

**Study Limitations**

Our population consisted of elderly volunteers who agreed to undergo 4-year follow-up examinations. The potential effects, on the observed associations, of selective survival as well as self-selection biases leading to an underrepresentation of diseased persons (eg, the prevalence of CHD at baseline was relatively low) cannot be ruled out.

Blood pressure was measured at the level of the brachial artery. MBP remains fairly constant throughout the length of the arterial tree, but PP is higher in the peripheral than in the central arteries.\textsuperscript{35} However, the PP gradient along the entire arterial tree tends to disappear with age, due to a greater increase in PP with age in the aortic and central arteries than in the peripheral arteries.\textsuperscript{35} Thus, the indirectly measured brachial PP in this study could reasonably be an acceptable approximation of the PP in central arteries. This method has been commonly used in other published research.\textsuperscript{4,7,28}

The strength of the relationships (measured either by correlation coefficients or regression slopes) was relatively weak, although cross-sectional results were comparable to those reported in other studies. The known intraindividual variability and error measurements of casual blood pressure and ultrasound carotid values\textsuperscript{11–13,16} very likely lead to an underestimation of the true magnitude of their associations, especially when longitudinal change values are involved.

In conclusion, this longitudinal study suggests that CCA-IMT is associated with a subsequent change in PP, and PP is associated with a subsequent change in CCA-IMT in a general population of relatively aged subjects. Whether atherosclerosis progression over time is involved or not in these associations merits further investigations.

**Acknowledgments**

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