Arterial Stiffness and Risk of Coronary Heart Disease and Stroke
The Rotterdam Study

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Background—Arterial stiffness has been associated with the risk of cardiovascular disease in selected groups of patients. We evaluated whether arterial stiffness is a predictor of coronary heart disease and stroke in a population-based study among apparently healthy subjects.

Methods and Results—The present study included 2835 subjects participating in the third examination phase of the Rotterdam Study. Arterial stiffness was measured as aortic pulse wave velocity and carotid distensibility. Cox proportional hazards regression analysis was performed to compute hazard ratios. During follow-up, 101 subjects developed coronary heart disease (mean follow-up period, 4.1 years), and 63 subjects developed a stroke (mean follow-up period, 3.2 years). The risk of cardiovascular disease increased with increasing aortic pulse wave velocity index. Hazard ratios and corresponding 95% CIs of coronary heart disease for subjects in the second and third tertiles of the aortic pulse wave velocity index compared with subjects in the reference category were 1.72 (0.91 to 3.24) and 2.45 (1.29 to 4.66), respectively, after adjustment for age, gender, mean arterial pressure, and heart rate. Corresponding estimates for stroke were 1.22 (0.55 to 2.70) and 2.28 (1.05 to 4.96). Estimates decreased only slightly after adjustment for cardiovascular risk factors, carotid intima-media thickness, the ankle-arm index, and pulse pressure. The aortic pulse wave velocity index provided additional predictive value above cardiovascular risk factors, measures of atherosclerosis, and pulse pressure. Carotid distensibility as measured in this study was not independently associated with cardiovascular disease.

Conclusions—Aortic pulse wave velocity is an independent predictor of coronary heart disease and stroke in apparently healthy subjects. (Circulation. 2006;113:657-663.)

Key Words: aging ■ arterial stiffness ■ coronary heart disease ■ epidemiology

Aging is associated with structural and functional changes of the vessel wall, which result in decreased vascular distensibility and elevated arterial stiffness. As a consequence of arterial stiffness, systolic blood pressure increases, causing a rise in left ventricular workload and subsequent hypertrophy, and diastolic blood pressure decreases, leading to an impaired coronary perfusion. Arterial stiffness can be evaluated by measuring pulse wave velocity (PWV) between 2 sites in the arterial tree, with a higher PWV indicating stiffer arteries. Alternatively, the relative change in lumen diameter during the cardiac cycle adjusted for the driving pulse pressure provides a measure of arterial distensibility. Several studies have shown that aortic PWV and carotid distensibility are predictors of cardiovascular events in patients with hypertension and end-stage renal disease. Only 2 studies investigated the association of arterial stiffness and incident cardiovascular events in the general population. In one study, an association was found between carotid stiffness and cardiovascular events. However, this study was conducted in men only, included a small number of events, and found an association with cardiovascular events for only 1 of the

Received April 12, 2005; revision received October 27, 2005; accepted October 31, 2005.
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Circulation is available at http://www.circulationaha.org DOI: 10.1161/CIRCULATIONAHA.105.555235

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examined indicators of carotid stiffness. A second study showed an association between aortic PWV and cardiovascular disease in well-functioning older adults; however, the association with coronary heart disease was weak after adjustment for all potential confounders. The present study investigates whether aortic PWV and carotid distensibility are predictors of incident coronary heart disease and stroke in a large population of apparently healthy subjects.

Methods

Study Population

This study was conducted within the framework of the Rotterdam Study, an ongoing prospective, population-based cohort study comprising 7983 men and women aged ≥55 years and living in Ommoord, a suburb of Rotterdam, the Netherlands. The rationale and design of the Rotterdam Study have been described elsewhere. The overall aim of the study is to investigate the incidence and determinants of chronic disabling diseases. Baseline data were collected during 1990–1993. The third examination phase took place during 1997–1999. During this phase, measurements of cardiovascular risk factors, atherosclerosis, and arterial stiffness were conducted. Subjects in nursing homes did not visit the research center and were not invited for these measurements. The Medical Ethics Committee of Erasmus Medical Center approved the study, and written consent was obtained from all participants.

Measures of Arterial Stiffness

PWV Index

Carotid-femoral PWV index, a measure of aortic stiffness, was calculated with the subjects in supine position. PWV index was assessed with an automatic device (Complior Artech Medical) that measures the time delay between the rapid upstroke of the feet of simultaneously recorded pulse waves in the carotid and the femoral arteries. The distance between the recording sites in the carotid and the femoral arteries (the carotid artery and the groin) was measured with a tape over the surface of the body. PWV index was calculated as the ratio between the distance and the foot-to-foot time delay and was expressed in meters per second.

Carotid Distensibility

Common carotid distensibility was assessed with the subjects in supine position, with the head tilted slightly to the contralateral side for the measurement in the common carotid artery. The vessel wall motion of the right common carotid artery was measured by means of a duplex scanner (ATL Ultrasound) connected to a vessel wall movement detector system. The details of this technique have been described elsewhere. After 5 minutes of rest, a region at 1.5 cm proximal to the origin of the bulb of the carotid artery was identified with the use of B-mode ultrasound. The displacement of the arterial walls was obtained by processing the radiofrequency signals originating from 2 selected sample volumes positioned over the anterior and posterior walls. The end-diastolic diameter (D), the absolute stroke change in diameter during systole (ΔD), and the relative stroke change in diameter (ΔD/D) were computed as the mean of 4 cardiac cycles of 3 successive recordings. The cross-sectional arterial wall distensibility coefficient was calculated according to the following equation: distensibility coefficient = 2ΔD/D × pulse pressure (10⁻³/kPa). In a reproducibility study performed among 47 subjects, the intraclass correlation coefficient was 0.80 for both the PWV index and the carotid distensibility coefficient.

Cardiovascular Risk Factors

Information on cardiovascular risk factors was collected during the third follow-up examination. Data on drug use and smoking habits were obtained during the home interview. Smoking was classified as never, former, or current smoking. Systolic (first Korotkoff phase) and diastolic (fifth Korotkoff phase) blood pressures were measured twice on the right arm with a random-zero sphygmomanometer, after the participant had been seated for at least 5 minutes. The mean of the 2 blood pressure values was used in the analyses. Pulse pressure was defined as the difference between systolic and diastolic blood pressure. Mean arterial pressure was calculated as diastolic blood pressure plus one third pulse pressure. Body mass index (weight [kg]/height [m]²) was calculated. Serum total cholesterol and HDL cholesterol values were determined by an automated enzymatic procedure (Boehringer Mannheim System). Diabetes mellitus was defined as the use of blood glucose-lowering medication and/or a fasting serum glucose level ≥ 7.0 mmol/L. History of myocardial infarction and stroke was defined as described previously.

Measurement of Atherosclerosis

Ultrasonography of both carotid arteries was performed with a 7.5-MHz linear-array transducer and a duplex scanner (ATL Ultrasound). Common carotid intima-media thickness (IMT) was determined as previously described. The maximum common carotid IMT was determined as the average of the maximum IMT of near wall and far wall measurements over a length of 1 cm, and the average of left and right maximum common carotid IMT was computed. The ankle-arm index (AAI) is the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm. According to the protocol of the Rotterdam Study, the AAI was measured at both legs. For the present analyses, we used the lowest measure obtained. Subjects with an unmeasurable ankle pressure, which was considered to be due to atherosclerosis, were assigned an AAI of 0.

Incident Cardiovascular Events and All-Cause Mortality

Subjects participating in the Rotterdam Study are monitored continuously for the occurrence of cardiovascular events through automated linkage with the files from general practitioners in the study district. When a cardiovascular event was reported, the research assistants collected additional information from medical records of the general practitioner and, in addition, obtained information from the hospital discharge records or nursing home records including letters from medical specialists. For the diagnosis of cardiac events,

| TABLE 1. Baseline Characteristics of the Study Population (n=2835) |
|------------------------------|-----------------|
| Characteristics             | Mean±SD or %    |
| Age, y                       | 71.7±6.7        |
| Men, %                       | 39.2            |
| Systolic blood pressure, mm Hg | 143±21         |
| Diastolic blood pressure, mm Hg | 75±10          |
| Mean arterial pressure, mm Hg | 106±12         |
| Pulse pressure, mm Hg        | 67±17           |
| Heart rate, bpm              | 73±11           |
| Body mass index, kg/m²       | 26.6±3.8        |
| Total cholesterol, mmol/L    | 5.8±0.9         |
| HDL cholesterol, mmol/L      | 1.4±0.4         |
| Current smoker, %            | 15.5            |
| Diabetes mellitus, %         | 7.1             |
| Use of antihypertensive medication, % | 20.9 |
| IMT, mm                      | 0.86±0.14       |
| AAI                          | 1.11±0.16       |
| PWV index, m/s               | 13.3±2.9        |
| Distensibility coefficient, 10⁻³/kPa* | 10.6±4.4     |

*Measures of the distensibility coefficient were available for 2265 subjects.
2 research physicians independently coded all reported events. In case of disagreement, a decision was made by a medical expert in the field. In case of stroke, events were coded by 2 research physicians and an experienced neurologist. Codes were assigned according to the International Classification of Diseases, 10th Revision (ICD-10). Coronary heart disease was defined as the occurrence of a fatal or nonfatal myocardial infarction (ICD-10 code I21), a percutaneous transluminal coronary angioplasty, a coronary artery bypass graft, other forms of acute (I24) or chronic ischemic heart disease (I25), sudden cardiac death (I46 and R96), and death due to ventricular fibrillation (I49) and congestive heart failure (I50). ICD-10 codes used for coding stroke were I61, I63, and I64. Information on vital status was acquired at regular intervals from the municipal authorities of Rotterdam. Follow-up for coronary heart disease and all-cause mortality was complete until January 1, 2003. Follow-up for stroke was complete until January 1, 2002. Follow-up for all-cause mortality was complete until July 1, 2004. Differences in duration of follow-up periods are due to logistic reasons.

Population for Analysis
A total of 4024 subjects visited the research center during the third phase of the Rotterdam Study. PWV index was measured in 3550 subjects, and the carotid distensibility coefficient was measured in 3098 subjects. Missing information on PWV index and the carotid distensibility coefficient was due almost entirely to logistic reasons. Of the 3550 subjects with a measurement of PWV index, 69 subjects (1.9%) were excluded from the analyses because of poor quality of the PWV index recordings, leaving 3481 subjects. We excluded subjects who developed both CHD and stroke during follow-up.

Data on cardiovascular risk factors, IMT, AAI, and pulse pressure were available for >95% of subjects.

Statistical Analysis
For subjects with missing data on clinical characteristics measured on a continuous scale, we imputed the population mean. For dichotomous variables, missing variable indicators were used. Mean values with SD and percentages were calculated for continuous and noncontinuous baseline variables, respectively. After the proportionality assumption was assessed, Cox proportional hazards regression analysis, adjusted for age and gender, was performed to estimate hazard ratios with corresponding 95% CIs for coronary heart disease, stroke, and all-cause mortality associated with tertiles of PWV index and the carotid distensibility coefficient. Cutoff points for gender-specific tertiles of PWV index were 12.3 and 14.6 m/s for the second and third tertiles in men; corresponding cutoff points in women were 11.9 and 14.2 m/s. Cutoff points for tertiles of the carotid distensibility coefficient were $8.8 \times 10^{-3}/kPa$ and $12.7 \times 10^{-3}/kPa$ for the second and third tertiles in men; corresponding cutoff points in women were $7.8 \times 10^{-3}/kPa$ and $11.3 \times 10^{-3}/kPa$. Reference categories were subjects in the first tertile of PWV index and subjects in the last tertile of the carotid distensibility coefficient. Analyses were additionally adjusted for mean arterial pressure and heart rate and subsequently also for body mass index, total cholesterol, HDL cholesterol, diabetes mellitus, smoking status, use of antihypertensive medication, carotid IMT, AAI, and pulse pressure. In the test for trend analysis, we replaced tertiles of PWV index and distensibility coefficient with their corresponding continuous values. We tested the interaction of stiffness measures with age and gender by entering interaction terms in the Cox regression models. The Kaplan-Meier method was used to estimate survival curves of cardiovascular events.

### Table 2. Hazard Ratios of Cardiovascular Disease, Coronary Heart Disease, Stroke, and All-Cause Mortality Associated With Tertiles of PWV Index

<table>
<thead>
<tr>
<th>PWV Index</th>
<th>HR (95% CI)</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD cases/subjects</td>
<td>Tertile 1</td>
<td>26/945</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2</td>
<td>45/945</td>
<td>1.50 (0.92–2.44)</td>
<td>1.39 (0.84–2.29)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3</td>
<td>85/945</td>
<td>2.40 (1.51–3.83)</td>
<td>2.02 (1.22–3.34)</td>
</tr>
<tr>
<td>CHD cases/subjects</td>
<td>Tertile 1</td>
<td>15/945</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2</td>
<td>32/945</td>
<td>1.71 (0.92–3.19)</td>
<td>1.72 (0.91–3.24)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3</td>
<td>54/945</td>
<td>2.44 (1.33–4.45)</td>
<td>2.45 (1.29–4.66)</td>
</tr>
<tr>
<td>Stroke cases/subjects</td>
<td>Tertile 1</td>
<td>12/945</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2</td>
<td>16/945</td>
<td>1.24 (0.57–2.70)</td>
<td>1.22 (0.55–2.70)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3</td>
<td>35/945</td>
<td>2.34 (1.13–4.82)</td>
<td>2.28 (1.05–4.96)</td>
</tr>
<tr>
<td>All-cause mortality cases/subjects</td>
<td>Tertile 1</td>
<td>65/945</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2</td>
<td>127/945</td>
<td>1.38 (0.99–1.92)</td>
<td>1.29 (0.90–1.85)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3</td>
<td>160/945</td>
<td>1.48 (1.07–2.06)</td>
<td>1.43 (1.06–2.00)</td>
</tr>
</tbody>
</table>

Model 1 is adjusted for age and gender; model 2, model 1 plus mean arterial pressure and heart rate; model 3, model 2 plus body mass index, total cholesterol, HDL cholesterol, diabetes mellitus, smoking status, use of antihypertensive medication, carotid IMT, AAI, and pulse pressure. CVD indicates cardiovascular disease (coronary heart disease [CHD] and stroke combined); HR, hazard ratio. The number of CVD cases is not equal to the sum of CHD and stroke cases because of subjects who developed both CHD and stroke during follow-up.
Table 3 presents the baseline characteristics of the study population. A total of 101 subjects developed coronary heart disease (mean follow-up period, 4.1±0.8 years), 63 subjects developed a stroke (mean follow-up period, 3.2±1.1 years), and 352 subjects died (mean follow-up period, 5.4±1.1 years). The risk of coronary heart disease increased with increasing PWV index up to an age- and gender-adjusted hazard ratio of 2.44 (95% CI, 1.33 to 4.45) for subjects with the highest PWV index compared with the reference group (P for trend=0.02) (Table 2). Estimates remained statistically significant after additional adjustment for cardiovascular risk factors, carotid IMT, AAI, and pulse pressure. Compared with the reference category, the age- and gender-adjusted hazard ratio of stroke in the upper tertile of PWV index was 2.34 (1.13 to 4.82) (P for trend=0.03). In multivariable adjusted models, the estimates were slightly lower. In addition, the hazard ratio for all-cause mortality was increased, at 1.48 (1.07 to 2.06), in the third tertile of PWV index compared with the reference category (P for trend=0.06), although the strength of the association was attenuated after full adjustment. Table 3 shows the hazard ratios of the different outcomes associated with the carotid distensibility coefficient. In age- and gender-adjusted models, the risks of coronary heart disease and stroke increased with decreasing distensibility coefficient, albeit not significantly, but relations markedly decreased after further adjustments. No significant interactions were found of age and gender with aortic PWV index. Higher PWV index was positively associated with cardiovascular disease, and risks seemed proportional over follow-up time (Figure; P=0.001 for the log-rank statistic). The area under the ROC curve (Table 4) was 0.70 for the model on the basis of age, gender, cardiovascular risk factors, carotid IMT, AAI, and pulse pressure. When PWV index was added to this model, the discriminatory power improved to 0.72 (P=0.04).

Discussion
In this prospective, population-based study, aortic PWV was found to be a strong and independent predictor of coronary heart disease and stroke. Aortic PWV had additive predictive value for risk of cardiovascular disease above the known cardiovascular risk factors, measures of atherosclerosis, and...
pulse pressure. Associations of carotid distensibility with coronary heart disease and stroke were less consistent.

A previous study found that aortic PWV has been found to predict incident cardiovascular disease in well-functioning older adults.\textsuperscript{10} In this study PWV was relatively strongly associated with incident stroke, but the association with coronary heart disease was weak after adjustment for all potential confounders. In the present study we found a strong and graded association between PWV index and coronary heart disease and stroke, as well as after adjustment for confounders. After multivariable adjustment, risk estimates for stroke were reduced slightly; however, the association lost statistical significance, probably because of the limited number of events. Advantages of the present study are the comprehensive adjustment for measures of atherosclerosis,

\begin{table}[h]
\centering
\caption{Prognostic Value of Different Sets of Cardiovascular Risk Markers}
\begin{tabular}{ll}
\hline
 & Area Under the ROC Curve (95\% CI), Cardiovascular Disease \\
\hline
Model 1 & \textit{Age, gender, and risk factors} 0.69 (0.65–0.73) \\
Model 2 & \textit{Age, gender, risk factors, IMT, and AAI} 0.70 (0.67–0.74) \\
Model 3 & \textit{Age, gender, risk factors, IMT, AAI, and PP} 0.70 (0.66–0.74) \\
Model 4 & \textit{Age, gender, risk factors, IMT, AAI, PP, and PWV index} 0.72 (0.68–0.75)* \\
\hline
\end{tabular}
\end{table}

PP indicates pulse pressure. Cardiovascular disease is coronary heart disease and stroke combined. Risk factors include mean arterial pressure, heart rate, body mass index, total cholesterol, HDL cholesterol, diabetes mellitus, smoking status, and use of antihypertensive medication.

*Model 4 is statistically different from model 3 ($P=0.04$).

the examination of the additive predictive value of PWV index beyond pulse pressure, and the inclusion of both PWV index and carotid distensibility.

We found that carotid distensibility was not independently associated with risk of cardiovascular disease and mortality. Although age- and gender-adjusted hazard ratios for the distensibility coefficient were increased, the risk estimates were attenuated after further adjustment for mean arterial pressure and heart rate. To interpret our findings, several methodological aspects of the measures of stiffness need to be discussed. First, using the distance between the carotid and the femoral arteries leads to an overestimation of the real distance traveled by the pulse wave, resulting in higher mean values of aortic PWV. Second, the use of a tape measure over the surface of the body may lead to an overestimation of the distance traveled by the pulse wave, and therefore we adjusted for body mass index. Third, in computing the carotid distensibility coefficient, we used the brachial pulse pressure rather than the carotid pulse pressure. Information on comparisons between carotid and brachial pulse pressures indicates that the difference between these pressures is 8 mm Hg in a presumed healthy population and 2.6 mm Hg in patients with severe coronary artery disease.\textsuperscript{22} These findings indicate that using brachial artery pulse pressure instead of carotid artery pulse pressure may have led to an underestimation of the distensibility, which is different in subjects with and without cardiovascular disease. This may lead to an underestimation of the association with disease. It has been suggested to derive carotid artery pulse pressure with the use of brachial artery pulse pressure.\textsuperscript{23} However, to perform this procedure, brachial mean pressure should be measured directly, whereas in our study this was computed from blood pressure components by the Korotkoff sound method. Therefore, we cannot exclude the possibility that other methods for assessing carotid distensibility show an association with cardiovascular disease.
Several mechanisms may explain the association between aortic stiffness and coronary heart disease. Arterial stiffening may lead to early pulse wave reflection causing an increase of central systolic blood pressure, a decrease of diastolic blood pressure, and a consequent increase of pulse pressure. The elevation of systolic blood pressure increases myocardial oxygen demand, reduces ejection fraction, and increases ventricular load, thereby inducing left ventricular hypertrophy. Moreover, because myocardial blood supply depends largely on pressure throughout diastole and the duration of diastole, the contemporary decrease of diastolic blood pressure can compromise coronary perfusion, resulting in subendocardial ischemia. A raised pulse pressure due to increased vascular stiffness may induce arterial remodeling, increasing wall thickness, and the development of plaques. Additionally, stiffer arteries may contribute to rupture and ulceration of atherosclerotic plaques, especially when an inhomogeneity in stiffness in and around the plaque is present; this is likely to result in increased shear stress and subsequent rupture. Finally, it has been shown that pulse pressure, which is a consequence of arterial stiffness, is independently associated with arterial plaque ulceration, supporting the hypothesis that cyclical hemodynamic forces are important determinants of plaque rupture. Some of these mechanisms may also explain the association between aortic stiffness and stroke. The association between pulse pressure and the risk of stroke has been described previously. Furthermore, aortic stiffness may be a proxy for stiffness in other vessels. Arterial stiffness is caused by structural changes, including fibrosis, medial smooth muscle necrosis, breaks in elastin fibers, calcifications, and diffusion of macromolecules into the arterial wall, which have also been described at the site of the cerebral vasculature. Finally, thromboembolism subsequent to plaque rupture may increase the risk of stroke.

The predictive value of several cardiovascular risk factors decreases with age because of selective survival and the influence of comorbidity on risk factors levels. In contrast, vascular stiffness increases steadily with age and can be considered a cumulative measure of previous exposures. Elevated pulse pressure, the pulsatile component of blood pressure, is an expression of arterial stiffness, which can be derived easily from blood pressure measurements, and has been associated with incident cardiovascular disease. Nevertheless, adding PWV index to models containing cardiovascular risk factors, measures of atherosclerosis, and pulse pressure improved the predictive value for cardiovascular events, demonstrating its additive value in cardiovascular risk stratification.

Some remaining methodological issues need to be discussed. First, information on measures of stiffness was not available for all subjects who visited the research center. However, missing information was primarily due to logistic reasons, which is likely to be random and thus will not have biased our results. Second, subjects may have started antihypertensive treatment after the baseline examination, which may have affected arterial stiffness and underestimated the risk estimates. Finally, because our study was performed in a population of predominantly elderly white subjects, the generalizability of our data to younger individuals or other ethnicities remains uncertain.

In conclusion, we found that aortic PWV is a strong predictor of coronary heart disease and stroke in a large population-based study. Aortic PWV improved the prediction of cardiovascular disease when added to known risk factors, measures of atherosclerosis, and pulse pressure.

Disclosures

Dr Reneman reports having served as a consultant for PIE Medical. The remaining authors report no conflicts of interest.

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**CLINICAL PERSPECTIVE**

The predictive value of conventional cardiovascular risk factors decreases with age because of selective survival and the influence of comorbidity on risk factor levels. In contrast, vascular stiffness increases steadily with age and can be considered a cumulative measure of previous exposures. Elevated pulse pressure is an indicator of arterial stiffness and can be derived easily from blood pressure measurements. Arterial stiffness can be measured more directly by noninvasive assessment of the velocity of the arterial wave propagation between 2 arterial points or by assessment of the vascular distensibility at a given site of the arterial tree. In a prospective, population-based study, we found that increased aortic pulse wave velocity predicted coronary heart disease and stroke in apparently healthy subjects. Moreover, aortic stiffness provided additional predictive value above cardiovascular risk factors, measures of atherosclerosis, and pulse pressure. Associations of carotid distensibility, as measured in this study, with coronary heart disease and stroke were less consistent. Our results show that arterial stiffness should no longer be considered an innocent expression of vascular aging but is a marker of cardiovascular risk. Future studies should investigate the role of aortic pulse wave velocity in cardiovascular risk stratification.
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*Circulation*. 2006;113:657-663
doi: 10.1161/CIRCULATIONAHA.105.555235
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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