Aortic Stiffness Is an Independent Predictor of Fatal Stroke in Essential Hypertension

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Background and Purpose—Pulse pressure is a stronger predictor of cardiovascular events than systolic or diastolic blood pressure in large cohorts of French and North American patients. However, its influence on stroke is controversial. Large-artery stiffness is the main determinant of pulse pressure. The influence of arterial stiffness on the occurrence of stroke has never been demonstrated. Our aim was to establish the relationship between aortic stiffness and stroke death in hypertensive patients.

Methods—We included, in a longitudinal study, 1715 essential hypertensive patients who had a measurement of arterial stiffness at entry (ie, between 1980 and 2001) and no overt cardiovascular disease or symptoms. Mean follow-up was 7.9 years. At entry, aortic stiffness was assessed from the carotid-femoral pulse wave velocity. A Cox proportional hazard regression model was used to estimate the relative risk (RR) of stroke and coronary deaths.

Results—Mean ± SD age at entry was 51 ± 13 years. Twenty-five fatal strokes and 35 fatal coronary events occurred. Pulse wave velocity significantly predicted the occurrence of stroke death in the whole population. There was a RR increase of 1.72 (95% CI, 1.48 to 1.96; \( P<0.0001 \)) for each SD increase in pulse wave velocity (4 m/s). The predictive value of pulse wave velocity remained significant (RR=1.39 [95% CI, 1.08 to 1.72]; \( P=0.02 \)) after full adjustment for classic cardiovascular risk factors, including age, cholesterol, diabetes, smoking, mean blood pressure, and pulse pressure. In this population, pulse pressure significantly predicted stroke in univariate analysis, with a RR increase of 1.33 (95% CI, 1.16 to 1.51) for each 10 mm Hg of pulse pressure (\( P<0.0001 \)) but not after adjustment for age (RR=1.19 [95% CI, 0.96 to 1.47]; \( P=0.10 \)).

Conclusions—This study provides the first evidence, in a longitudinal study, that aortic stiffness is an independent predictor of fatal stroke in patients with essential hypertension. (Stroke. 2003;34:1203-1206.)

Key Words: arteries ■ elasticity ■ hypertension ■ pulse ■ stroke

Aging and environmental and genetic factors are responsible for structural and functional changes of the arterial wall, leading to decreased elasticity and increased stiffness.\(^1\)\(^-\)\(^3\) Increased arterial stiffness is responsible for an inadequate increase in systolic blood pressure (SBP) and a relative decrease in diastolic blood pressure (DBP), thus increasing pulse pressure (PP) at any given value of mean blood pressure (MBP).\(^1\) Several findings suggest that increased arterial stiffness may be predictive of cerebrovascular events through an increase in central PP. Indeed, brachial PP is associated with carotid artery disease, including intima-media thickness and plaque area.\(^4\)\(^-\)\(^6\) PP is a major determinant of small-artery disease, particularly wall hypertrophy of cerebral arterioles in stroke-prone spontaneously hypertensive rats.\(^7\) PP is associated with the prevalence and severity of cerebral white matter lesions in the population of the Atherosclerosis Risk in Communities (ARIC) study.\(^8\) Although PP has been associated with stroke in some longitudinal studies,\(^9\)-\(^11\) its predictive value remains controversial.\(^12\)\(^-\)\(^14\) One possibility is that brachial PP, measured in these studies, may not reflect aortic PP, which influences the extracerebral and intracerebral circulation. In addition, measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of cerebral vasculature. For these reasons, we hypothesized that arterial stiffness would be a significant predictor of stroke, independently of classic atherosclerosis risk factors, and a better independent predictor than PP.

Arterial stiffness can be assessed noninvasively by measurement of pulse wave velocity (PWV), a simple and reproducible method.\(^1\)\(^,\(^1\)\(^5\)\(^,\(^1\)\(^6\)\) PWV measured along the aortic and aortoiliac pathway is the most clinically relevant since the aorta and its first branches are responsible for most of the pathophysiological effects of arterial stiffness. In previous longitudinal studies, our group\(^17\)\(^,\(^1\)\(^8\) and others\(^19\)\(^,\(^2\)\(^0\) directly demonstrated that arterial stiffness was an independent predictor of all-cause and cardiovascular mortality in hypertensive patients,\(^17\) in patients with end-stage renal disease,\(^19\) and

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in elderly people. We also showed the independent predictive value of PWV for primary coronary heart disease events. In hypertensive patients, arterial stiffness, which is increased in response to the higher distending pressure, may expose those patients to a higher risk of stroke. However, to our knowledge, the predictive value of aortic stiffness for stroke has never been established in patients with essential hypertension.

Thus, the aims of the present study were (1) to establish the relationship between aortic stiffness, measured through PWV, and stroke death in hypertensive patients and (2) to show that PWV retains its predictive value independently of classic cardiovascular risk factors.

Subjects and Methods

Study Design

The cohort included 1715 consecutive patients with no overt cardiovascular disease or symptoms who attended the outpatient hypertension clinic of Hôpital Broussais (then Hôpital Pompidou) between April 1980 and December 2001 and had a determination of arterial stiffness at entry with PWV. Among them, 614 were treated with at least 1 antihypertensive drug at the time of the PWV measurement. The others were referred for clinical and biological investigation before treatment. Demographic data with details of cardiovascular risk factors were collected on the day when PWV was measured. None of these patients were referred for typical symptoms of stroke, coronary heart disease, or cardiovascular disease other than hypertension. Diabetes was indicated by abnormal fasting plasma glucose levels or the current use of insulin or an oral hypoglycemic agent. Hypercholesterolemia was indicated by abnormal fasting plasma cholesterol levels or the current use of a cholesterol-lowering agent. Smoking status was defined as current use. The study was approved by the Ethics Committee of Hôpital Pompidou.

Blood pressure was measured as previously published. PWV, a classic index of arterial stiffness, was measured along the descending thoraco-abdominal aorta by the foot-to-foot velocity method, as previously published and validated. Briefly, waveforms were obtained transcutaneously over the common carotid artery and the right femoral artery, and the time delay was measured between the feet of the 2 waveforms. The distance (D) covered by the waves was assimilated to the distance measured between the 2 recording sites. PWV was calculated as PWV = D/2t (seconds). Annual mean values of PWV did not change over the study period, ruling out any major time or population recruitment effect on the obtained values.

Stroke Mortality

The follow-up period ended on December 31, 2001 (mean follow-up, 7.9 years). Deceased subjects were identified from the French mortality records provided by the Institut National de la Statistique et des Etudes Economiques, as previously published. A member of the cohort was considered to have died when he had the last contact. To overcome the possibility that some people born abroad were lost to follow-up because of emigration, the censoring date for these patients was set as the last visit to our institution, free of cardiovascular event.
hypercholesterolemia, diabetes, smoking). Under these conditions, 1 SD of PWV was associated with a 39% increase in risk (RR = 1.39 [95% CI, 1.08 to 1.72]; P = 0.02), independently of age and smoking (Table 3). No other cardiovascular risk factor remained significantly included in the model (Table 3). In this population, PP significantly predicted stroke in univariate analysis, with a RR increase of 1.33 (95% CI, 1.16 to 1.51) for each 10 mm Hg of pulse pressure (P < 0.0001). However, PP had no independent predictive value for stroke after adjustment for age (RR = 1.19 [95% CI, 0.96 to 1.47]; P = 0.10). Including SBP and DBP in the model, instead of MBP and PP, did not change the results.

PWV was significantly higher in patients treated with antihypertensive drugs at baseline than in untreated patients (12.70 ± 4.23 versus 12.19 ± 3.83 m/s; P = 0.01). However, this difference was only marginal (4%) and did not affect the relationship between PWV and stroke death. Indeed, when antihypertensive treatment at original screening (yes/no) was included in a multivariate model, in addition to the aforementioned classic cardiovascular risk factors (Table 3), the RR for an increase in PWV of 4 m/s was 1.44 (95% CI, 1.12 to 1.76; P = 0.01) for stroke death, a value similar to that of Table 3, which was obtained without taking into account the administration of antihypertensive drugs.

Discussion

The main result of the present longitudinal study is that in a population of essential hypertensive patients, with no overt cardiovascular disease or symptoms at baseline, arterial stiffness, measured through PWV, predicted the occurrence of fatal stroke beyond the prediction provided by classic risk factors.

Several mechanisms may explain our finding of an association between increased PWV and stroke. First, arterial stiffness may favor the occurrence of cerebrovascular events through an increase in central PP. A growing body of in vitro studies shows that cyclic stretching exerts a greater influence than static load on phenotype and growth of vascular smooth muscle cells.26–28 Thus, the amplitude of PP may influence arterial remodeling at the site of both the extracranial and intracranial arteries, increasing the carotid wall thickness and the development of plaques,4–6 the likelihood of plaque rupture,29 and the prevalence and severity of cerebral white matter lesions.9 In patients of the Rotterdam Study, atherosclerosis, indicated by increased common carotid intima-media thickness and plaques, was related to cerebral white matter lesions.30 Second, the measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of cerebral vasculature. Indeed, aortic stiffening accompanying age and cardiovascular risk factors is caused by various phenomena, including fibrosis, medial smooth muscle necrosis, breaks in elastin fibers, calcifications, and diffusion of macromolecules within the arterial wall, which have also been described at the site of the cerebral vasculature.1,31,32 Third, coronary heart disease and heart failure, which are favored by high PP and arterial stiffness,18,33 are also risk factors for stroke.

The international guidelines for the management of hypertension34 suggested that it would be useful to demonstrate whether arterial stiffness has any independent prognostic relevance for mortality. The present study clearly shows that arterial stiffness may help in the evaluation of the individual risk of stroke death in hypertensive patients regularly attending the outpatient clinic of a university hospital. Because the population group was only mildly hypertensive at original screening, with the minority on antihypertensive treatment at that time, one might reasonably speculate that results may apply to the population as a whole. The independent predictive value of aortic stiffness can be quantified in the study population. In univariate models (Table 2), the increased stroke risk due to a 4-m/s increase in PWV (RR = 1.68) is equivalent to that of 7 years of aging.

The present findings also suggest that, to better prevent the occurrence of fatal stroke, antihypertensive treatment should preferably target drugs able to intrinsically reduce aortic stiffness, ie, drugs that have demonstrated their efficacy in reducing PWV independently of the reduction in MBP.3,35 Various pharmacological approaches have been recommended for obtaining a pressure-independent reduction in arterial stiffness, Including blockade of the renin-angiotensin aldosterone system, smooth muscle cell relaxation by nitric oxide donors or related molecules, targeting of molecular events leading to arterial stiffening (such as advanced-glycation end-products), or interference with collagen metabolism. However, large clinical trials remain to be performed to demonstrate that the prevention of stroke by these molecules is associated with the reduction in arterial stiffness, independently of blood pressure reduction.

The present study concerned a slightly different population from our previously published cohort,17,18 since additional patients were

### Table 2. Relative Risk of Stroke Death According to PWV and Cardiovascular Risk Factors: Univariate Analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Relative Risk</th>
<th>Lower 95% CI</th>
<th>Higher 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV (4 m/s)</td>
<td>1.72</td>
<td>1.48</td>
<td>1.96</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>2.00</td>
<td>1.60</td>
<td>2.60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PP (10 mm Hg)</td>
<td>1.33</td>
<td>1.16</td>
<td>1.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP (10 mm Hg)</td>
<td>1.20</td>
<td>1.06</td>
<td>1.34</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; PWV, pulse wave velocity; PP, pulse pressure; SBP, systolic blood pressure.

### Table 3. Relative Risk of Stroke Death According to PWV or Pulse Pressure, and Other CV Risk Factors: Multivariate Models

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model including PWV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>χ² = 39.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWV (4 m/s)</td>
<td>1.39</td>
<td>1.08–1.72</td>
<td>0.022</td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>1.80</td>
<td>1.37–2.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>3.34</td>
<td>1.06–10.50</td>
<td>0.03</td>
</tr>
<tr>
<td>Model including pulse pressure</td>
<td>χ² = 30.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP (10 mm Hg)</td>
<td>1.19</td>
<td>0.96–1.47</td>
<td>0.10</td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>2.39</td>
<td>1.54–3.71</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; PWV, pulse wave velocity; PP, pulse pressure; SBP, systolic blood pressure.
included during the period 1996–2001. In addition, previously included patients7,18 had a longer follow-up.

We focused on the risk of stroke death, which is less subject to misclassification than nonfatal strokes. Thus, the present study did not assess nonfatal strokes. In addition, we included all fatal strokes because of the difficulty of distinguishing, from our records, ischemic stroke from hemorrhagic stroke. Finally, because we sought to determine the stroke risk in a population of asymptomatic hypertensives, we excluded patients without medical follow-up and those who had cardiovascular disease at baseline.

Because one third of the patients were already being treated for hypertension at baseline, the predictive value of PWV, observed in the whole population, might not apply to this subgroup. However, in a multivariable Cox model including previous antihypertensive treatment (yes/no) among other classic risk factors (see Results), an increased PWV remained significantly and independently associated with an increased risk of stroke. The present study was not designed to examine interactions between ongoing antihypertensive treatments and PWV. Indeed, no follow-up of antihypertensive treatment was available in our population.

We conclude that aortic stiffness was significantly associated with the risk of stroke death in patients with essential hypertension. Measurement of aortic stiffness retains its predictive power even after classic cardiovascular risk factors have been considered.

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