Aortic Stiffness Predicts Functional Outcome in Patients After Ischemic Stroke

Dariusz Gąsecki, MD, PhD; Agnieszka Rojek, MD, PhD; Mariusz Kwarciany, MD; Marlena Kubach; Pierre Boutouyrie, MD, PhD; Walenty Nyka, MD, PhD; Stephane Laurent, MD, PhD; Krzysztof Narkiewicz, MD, PhD

Background and Purpose—Increased aortic stiffness (measured by carotid–femoral pulse wave velocity) and central augmentation index have been shown to independently predict cardiovascular events, including stroke. We studied whether pulse wave velocity and central augmentation index predict functional outcome after ischemic stroke.

Methods—In a prospective study, we enrolled 99 patients with acute ischemic stroke (age 63.7±12.4 years, admission National Institutes of Health Stroke Scale score 6.6±6.6, mean±SD). Carotid–femoral pulse wave velocity and central augmentation index (SphygmoCor) were measured 1 week after stroke onset. Functional outcome was evaluated 90 days after stroke using the modified Rankin Scale with modified Rankin Scale score of 0 to 1 considered an excellent outcome.

Results—In univariate analysis, low carotid–femoral pulse wave velocity (P=0.000001) and low central augmentation index (P=0.028) were significantly associated with excellent stroke outcome. Age, severity of stroke, presence of previous stroke, diabetes, heart rate, and peripheral pressures also predicted stroke functional outcome. In multivariate analysis, the predictive value of carotid–femoral pulse wave velocity (<9.4 m/s) remained significant (OR, 0.21; 95% CI, 0.06–0.79; P=0.02) after adjustment for age, National Institutes of Health Stroke Scale score on admission, and presence of previous stroke. By contrast, central augmentation index had no significant predictive value after adjustment.

Conclusions—This study indicates that aortic stiffness is an independent predictor of functional outcome in patients with acute ischemic stroke. (Stroke. 2012;43:543-544.)

Key Words: arterial stiffness ■ augmentation index ■ pulse wave velocity ■ stroke

Aortic stiffness, directly measured by carotid–femoral pulse wave velocity (CF-PWV), and wave reflections, estimated by central augmentation index (cAIx), have been shown to be independent predictors of cardiovascular morbidity and mortality.1 Recent studies suggest an association between CF-PWV and both cerebral large artery disease2 and white matter lesions.3 White matter lesions are predictive of clinical outcome after acute ischemic stroke.4 Because aortic stiffness and wave reflections integrate the ill effects of age and major risk factors, and further directly influence cardiovascular outcome, we investigated whether CF-PWV and cAIx predict stroke functional outcome.

Materials and Methods

We prospectively recruited 99 adult patients with acute ischemic stroke (baseline characteristics; Table 1) at the Department of Neurology, Medical University of Gdanśk, from October 2008 to February 2010. Patients’ inclusion and exclusion criteria are provided in the online Supplement (http://stroke.ahajournals.org). The study was approved by the Ethics Committee of Medical University of Gdanśk. Informed consent was obtained from all patients.

At Day 7 (±2) after stroke onset, demographic, clinical, and radiological data were recorded, and hemodynamic variables, including CF-PWV and cAIx, were measured by applanation tonometry (SphygmoCor, Atcor, Australia) as described previously.5,6 cAIx were assessed in all 99 patients and CF-PWV in 86 of them (Online Supplement). Excellent outcome was defined as a modified Rankin Scale ≤1 at Day 90 after stroke.

Binary and multivariate logistic regression models of patients with excellent outcome versus the remaining study cohort were performed with CF-PWV and cAIx as independent variables (online Supplement).

Results

In univariate analysis, CF-PWV, cAIx, age, National Institutes of Health Stroke Scale score, presence of previous stroke, diabetes, heart rate, and peripheral pressures significantly predicted stroke functional outcome (online supplement). Inspection of the receiver operating characteristic curve showed that the predictive value of CF-PWV increased sharply beyond a threshold value of 9.4 m/s (specificity of
stroke severity, which are the traditional commonly accepted predictors of stroke outcome. A clear threshold appeared for CF-PWV, with patients having CF-PWV values <9.4 m/s being 5 times more likely to achieve functional recovery at 90 days after stroke, than those with elevated aortic stiffness, after adjustment for clinically important covariates.

In multivariate analysis, cAIx had no predictive value for stroke outcome. cAIx may lose its predictive value once stroke has occurred because it is highly sensitive to vasomotor tone and may be far too variable during this period. By contrast, CF-PWV likely represents the integrated effects over time of various risk factors on the arterial wall, both at the systemic and cerebrovascular levels. Previous longitudinal studies demonstrated that increased aortic pulse wave velocity was associated with elevated risk of stroke in the general population and of fatal stroke in patients with hypertension. The present study suggests that aortic stiffness is related to functional recovery after stroke. The mechanisms underlying this relationship are not clear. Increased aortic stiffness might be implicated directly or more likely reflect other processes affecting brain repair. Pulse wave velocity cannot be measured accurately in patients with arrhythmia, an important cause of stroke, and consequently our conclusions are limited to patients in sinus rhythm.

We conclude that aortic stiffness, measured by CF-PWV, predicts long-term stroke functional outcome independent of well-accepted clinical factors. Our study included a relatively small number of patients. If confirmed by larger studies, aortic stiffness measurement might constitute an important clinical tool for risk stratification of patients with ischemic stroke.

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Disclosures
None.

References

Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted CF-PWV (≥ 9.4 m/s)</td>
<td>0.095 (0.032–0.279)</td>
<td>0.00002</td>
</tr>
<tr>
<td>Model 2</td>
<td>R² = 0.34</td>
<td></td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>0.59 (0.36–0.98)</td>
<td>0.044</td>
</tr>
<tr>
<td>CF-PWV (≥9.4 m/s)</td>
<td>0.18 (0.05–0.62)</td>
<td>0.006</td>
</tr>
<tr>
<td>Model 3</td>
<td>R² = 0.39</td>
<td></td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>0.60 (0.34–1.03)</td>
<td>0.067</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.18 (0.05–0.67)</td>
<td>0.010</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>0.18 (0.03–0.97)</td>
<td>0.049</td>
</tr>
<tr>
<td>CF-PWV (≥9.4 m/s)</td>
<td>0.21 (0.06–0.79)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

CF-PWV indicates carotid–femoral pulse wave velocity; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval.
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SUPPLEMENTAL MATERIAL
**Supplemental methods**

We prospectively recruited adult patients with acute ischemic stroke (≤24 hours from onset). The study received ethical committee approval on November 16, 2007 (approval reference number NKEB/430/2007). The patients were recruited between October 2008 and February 2010.

Inclusion criteria were: (1) well-defined time of onset of stroke symptoms, and (2) absence of cerebral hemorrhage or other non-vascular lesion. Exclusion criteria were: pre-stroke disability (modified Rankin Scale score >0) or dementia. Patients were included regardless of stroke subtype and severity. Tonometric applanation might be applied only in patients in sinus rhythm. Consequently, patients with arrhythmias, including atrial fibrillation and atrial flutter, were not eligible for the study.

Statistical analyses were performed by NCSS 2000 software (Hintze JL, Kaysville, Utah) and S-Plus software (Lucent, Technologies, Corporate, Murray Hill, New Jersey).

**Supplemental results**

**Baseline characteristics**

The mean age of patients was 63.7 years (range 30 to 87 years) and 26% were women. There were 15 (15%) patients with recurrent ischemic stroke. The mean NIHSS upon admission was 6.6, median 4 (IQR 2 to 8.5), range 0 to 39.

Outcome evaluation of the stroke population after 90 days showed a mortality rate of 3% (n=3). The functional outcome assessment revealed a mean mRS of 1.7, median 1 (IQR 1 to 2) in the whole stroke population, and 53 patients (53%) had an excellent functional outcome defined as mRS 0 or 1.

Pressure wave analysis and derived cAIX were assessed in all 99 patients. Eight patients with significant carotid plaque or carotid thrombus were excluded from measurement.
of carotid-femoral pulse wave velocity requiring compression of the carotid artery. Furthermore, we were not able to obtain stable CF-PWV measurement in 5 patients due to lack of cooperation. Consequently, carotid-femoral pulse wave velocity (CF-PWV) was assessed in 86 (86%) patients, including 49 (92%) of 53 subjects with excellent outcome and 37 (80%) of 46 subjects with poor outcome.

**Aortic PWV and cAIx and functional outcome of stroke patients within 90 days**

Univariate analysis showed that several factors (clinical, arterial, hemodynamic) had predictive value for 90-day stroke outcome. CF-PWV was one of the strongest of the non-clinical factors (Supplemental Table).
**Supplemental Table.** Univariate analysis of the determinants of the more severe stroke outcome

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$R^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS 1</td>
<td>0.255</td>
<td>0.000001</td>
</tr>
<tr>
<td>CF-PWV (&gt;9.4 m/s)</td>
<td>0.249</td>
<td>0.000001</td>
</tr>
<tr>
<td>Age</td>
<td>0.133</td>
<td>0.0002</td>
</tr>
<tr>
<td>CF-PWV</td>
<td>0.122</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of previous stroke</td>
<td>0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>HR</td>
<td>0.058</td>
<td>0.016</td>
</tr>
<tr>
<td>Brachial PP</td>
<td>0.058</td>
<td>0.016</td>
</tr>
<tr>
<td>cAIx@HR75</td>
<td>0.049</td>
<td>0.028</td>
</tr>
<tr>
<td>Brachial SBP</td>
<td>0.038</td>
<td>0.054</td>
</tr>
<tr>
<td>DM</td>
<td>0.035</td>
<td>0.06</td>
</tr>
<tr>
<td>Brachial MBP</td>
<td>0.028</td>
<td>0.10</td>
</tr>
</tbody>
</table>

NIHSS 1 indicates National Institutes of Health stroke scale on admission; CF-PWV, carotid-femoral pulse wave velocity; AIX@HR75, normalized augmentation index; HR, heart rate; PP, pulse pressure; SBP, systolic BP; MBP, mean BP; DM, diabetes mellitus.