Morphological, Hemodynamic, and Clinical Independent Risk Factors for Anterior Communicating Artery Aneurysms

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Background and Purpose—The pathogenesis of cerebral aneurysms still raises some controversies. The aim of this study was to identify morphological, hemodynamic, and clinical independent risk factors for anterior communicating artery (ACoA) aneurysm development.

Methods—Computed tomography angiography and transcranial color-coded sonography were performed in 77 patients with a nonbleeding ACoA aneurysm and in 73 controls. Symmetry of A1 segments of the anterior cerebral arteries, angles between A1 and A2 segments, tortuosity, diameter, mean velocity ($V_m$), pulsatility index, and volume flow rate in both A1 segments were determined. Moreover, all study participants completed a survey on their medical history. Multivariate backward stepwise logistic regression analysis was performed to identify independent risk factors for ACoA aneurysm development.

Results—Smoking, hypertension, asymmetry of A1 segments, the angle between A1 and A2 segments, A1 segment diameter, $V_m$, pulsatility index, and volume flow rate turned out to be associated with the occurrence of ACoA aneurysms on univariate analysis. Multivariate analysis identified smoking (odds ratio, 2.036; 95% confidence interval, 1.277–3.245), asymmetry of A1 segments >40% (odds ratio, 2.524; 95% confidence interval, 1.275–4.996), pulsatility index (odds ratio, 0.04; 95% confidence interval, 0.000–0.124), and the angle between A1 and A2 segments $\leq 100^\circ$ (odds ratio, 4.665; 95% confidence interval, 2.247–9.687) as independent strong risk factors for ACoA aneurysm development.

Conclusions—The risk of ACoA aneurysm formation is determined by several independent clinical, morphological, and hemodynamic factors. The strongest independent risk factors include smoking, asymmetry of A1 segments >40%, low blood flow pulsatility, and the angle between A1 and A2 segments $\leq 100^\circ$. (Stroke. 2014;45:2906-2911.)

Key Words: anterior cerebral artery ■ hemodynamics ■ intracranial aneurysm ■ multidetector computed tomography ■ risk factors ■ ultrasonography, doppler, transcranial
autosomal dominant polycystic kidney disease, (5) other severe systemic disorders, for example, advanced neoplastic disease, advanced heart failure, or multiorgan failure, (6) hemodynamically significant extracranial carotid stenosis, (7) history of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage, and (8) family history of cerebral aneurysm.

Eventually, a total of 150 patients satisfying the above-mentioned criteria were enrolled between October 2007 and November 2013; among them 77 individuals with ACoA aneurysms (35 men and 42 women) and 73 controls (29 men and 44 women). Both patients and controls were referred for CTA after the conventional CT, to exclude the presence of an ACoA aneurysm, to undergo medical check-up of the brain for minor symptoms, such as headache or vertigo, or for screening without obvious medical indications. After obtaining written informed consent, all the participants completed a survey on their age, sex, body height and weight (for body mass index calculation), cigarette smoking status, and comorbidities (hypertension, diabetes mellitus, heart disease, and hypercholesterolemia). The presence of the latter was further confirmed based on medical documentation analysis. Hypertension was considered if the patient was taking antihypertensive medications or had a history of unstable and untreated hypertension with systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg. Hypercholesterolemia was considered when the patient was treated with antihyperlipidemic agents or had a total cholesterol level of ≥220 mg/dL. A heart disease was considered if the patient had a history of myocardial infarction, coronary heart disease, or valvular heart disease. Diabetes mellitus was considered if the patient was taking antidiabetic agents or insulin injections. Based on a data on cigarette smoking, the patients were classified as current regular smokers, former regular smokers, and nonsmokers.

CTA Protocol

The CTA examination was performed with a 64-channel multidetector CT scanner (LightSpeed VCT; GE Healthcare, Pittsburgh, PA) with intravenous bolus administration of a nonionic contrast medium (Iomeron 400, Bracco, Italy). The scanning parameters were as follows: collimation 39.38×0.625 mm, spiral pitch 0.984, tube voltage 120 kV, tube amperage 450 mA, 0.4-s rotation time, and slice thickness 0.625 mm. A total quantity of 60 mL of contrast material, followed by 30 mL of saline solution, were injected into the antecubital vein at a 5 mL/s rate with a power injection platform (Medrad Stellant D Dual Syringe CT Injection System, Bayer Healthcare, Germany). CT scanning was triggered using a Smart Prep protocol, with the region of interest placed on a data on cigarette smoking, the patients were classified as current regular smokers, former regular smokers, and nonsmokers.

![CTA Protocol Diagram](http://stroke.ahajournals.org/content/116/12/2907/F1)

**Figure 1.** Three-dimensional model of the anterior communicating artery (ACoA) complex after a graphic removal of the aneurysm obtained in Mimics v.16 based on DICOM files from computed tomography angiography. The center line (red line) was automatically fit to the model. Points A and B correspond to the largest curvatures of A1 and A2 segments, respectively. Point C is the connection point of center lines of A1 and A2 segments and determines the ACoA issuing and the vertex of A1 to A2 angle. Arms of A1 to A2 angle are drawn through the points of the largest curvatures of A1 (point B) and A2 (point A) segments. L A1 and L A2 indicate left A1 and A2 segments of the anterior cerebral artery (ACA), respectively, and R A1 and R A2, right A1 and A2 segments of the ACA, respectively.

was exported to 3-matic application, where angles between A1 and A2 segments were calculated. Arms of the angle were drawn through the points of the largest A1 and A2 curvatures, localized nearest to the ACoA, and the vertex of the angle was placed in the point of connection of A1 and A2 segments’ centerlines (Figure 1). In the case of aplasia of the A1 segment, these measurements were applied only to the larger (dominant) A1 segment. All morphological measurements were performed by the same author (P.L.).

Protocol of Transcranial Color-Coded Sonography

After enrollment, all the patients were subjected to transcranial color-coded sonography with a Vivid 3 Pro (GE Healthcare, Pittsburgh, PA) equipped with a multifrequency transcranial probe (1.5–3.6 MHz), according to the previously described standards.7 All transcranial color-coded sonography examinations were performed by the same examiner (W.K.). The angle-corrected mean blood flow velocity ($V_{\text{mean}}$) was measured for both A1 segments of the ACA. The pulsatility index (PI) for each vessel was calculated as $\text{PI} = V_{\text{mean}}/V_{\text{p}}$, where $V_{\text{p}}$ is the peak systolic velocity and $V_{\text{mean}}$ end-diastolic velocity. Each transcranial color-coded sonography examination was performed with the sample volume being placed within the color flow image of the examined artery, as closely as possible to the distal end of the A1 segment (Figure 2). The volume flow rate (VFR) was calculated based on the formula: $\text{VFR} = V_{\text{mean}} \cdot S \cdot \text{FVF}$. Both the author (W.K.) who performed the transcranial color-coded sonography examination and calculated hemodynamic parameters and the researcher (P.L.) who performed morphological calculations were blinded to the results.

**Ethics**

The institutional review board (The Medical University of Silesia, Sosnowiec, Poland) approved the examination protocol for patients enrolled in this study.
Normal distribution of continuous variables was tested and homogeneity of their variance was verified with the Levine test. Statistical characteristics of the continuous variables were presented as arithmetic means and their SDs or medians and interquartile ranges. The Student t test and Mann–Whitney U test were used for intergroup comparisons. The distributions of qualitative parameters in the studied groups were compared with the χ² test or the Fisher exact test. Relationships between pairs of variables were determined on the basis of the values of the Spearman coefficients of rank correlation (R).

All demographic (age, sex) variables, body height and weight, smoking, patient’s medical history, and morphological and hemodynamic variables were assessed as potential risk factors for ACoA aneurysm development. The univariate analysis was first conducted to determine which variables were associated with the occurrence of an ACoA aneurysm. Correlations between the parameters that were identified as significant on univariate analysis were examined using the Pearson correlation test. The variables that differed between the ACoA patients and the controls with univariate P value <0.10 were included in multivariate backward stepwise logistic regression analysis to identify independent risk factors for the presence or absence of an ACoA aneurysm (dichotomous outcome). Risk factors with P value <0.05 were considered statistically significant. Statistical calculations and analyses were performed with Statistica 10.0 (StatSoft, Tulsa, OK) software.

Results

Clinical and morphological characteristics of patients with ACoA aneurysms and the controls are presented in Table 1. In the group of 33 patients (43%) diagnosed with an ACoA aneurysm and hypoplasia of one of A1 segments (VAC >40%), all ACoA aneurysms were localized on the dominant A1 segment. This group consisted of 9 patients with aplasia of one of the A1 segments. Among 32 patients (41%) with asymmetrical A1 segments (VAC >10% and ≤40%) and 12 individuals (16%) with normoplastic A1 segments (VAC ≤10%), there were 1 and 6 persons, respectively, with an ACoA aneurysm on the side of the smaller (nondominant) A1 segment. Only 1 patient in the control group presented with aplasia of one of A1 segments.

Morphological and hemodynamic parameters of patients with an aneurysm and the controls are presented in Table 2. In the case of patients with ACoA aneurysm, the results of morphological and hemodynamic measurements of A1 segments were presented both for the side associated with the aneurysm and for the contralateral side. In the control group, the results of morphological measurements and hemodynamic findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACoA Group (n=77)</th>
<th>Control Group (n=73)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>42 (55)</td>
<td>44 (60)</td>
<td>0.478*</td>
</tr>
<tr>
<td>Age, y</td>
<td>57 (49–64)</td>
<td>50 (38–61)</td>
<td>0.122†</td>
</tr>
<tr>
<td>Smoking</td>
<td>48 (62)</td>
<td>28 (38)</td>
<td>&lt;0.01‡</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47 (61)</td>
<td>30 (41)</td>
<td>&lt;0.05§</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>49 (64)</td>
<td>36 (49)</td>
<td>0.137‡</td>
</tr>
<tr>
<td>Heart disease</td>
<td>6 (8)</td>
<td>6 (8)</td>
<td>0.923*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (6)</td>
<td>3 (4)</td>
<td>0.719‡</td>
</tr>
<tr>
<td>BMI</td>
<td>26.3 (22.7–29.1)</td>
<td>25.7 (22.5–28.4)</td>
<td>0.371†</td>
</tr>
<tr>
<td>Site of aneurysm, left</td>
<td>46 (60)</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Symmetry of A1 segments, %</td>
<td>32.6 (16.8–60.2)</td>
<td>11.5 (6.2–28.9)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Symmetry of A1 segments, %</td>
<td>…</td>
<td>…</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>≤10</td>
<td>12 (16)</td>
<td>33 (45)</td>
<td>…</td>
</tr>
<tr>
<td>&gt;10 to ≤40</td>
<td>32 (41)</td>
<td>31 (43)</td>
<td>…</td>
</tr>
<tr>
<td>&gt;40</td>
<td>33 (43)</td>
<td>9 (12)</td>
<td>…</td>
</tr>
</tbody>
</table>

Values expressed as number (%) or median (interquartile range). ACoA indicates anterior communicating artery; and BMI, body mass index. *χ² test; †Mann–Whitney U test; ‡Fisher exact test; and §Spearman rank correlation test.
Table 2. Morphological and Hemodynamic Characteristics of the A1 Segments of the Anterior Cerebral Artery in 77 Patients With ACoA Aneurysms and 73 Patients From the Control Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACoA Group</th>
<th>Control Group</th>
<th>P Value*</th>
<th>P Value†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1–A2 angle, degree</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm Side</td>
<td>97.0 (89.6–119.7)</td>
<td>112.9 (101.1–133.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonaneurysm Side</td>
<td>128.7 (113.0–143.6)</td>
<td>129.5 (113.2–142.1)</td>
<td>&lt;0.001§</td>
<td>&lt;0.001§</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>A1 tortuosity</td>
<td>0.95 (0.92–0.97)</td>
<td>0.88 (0.83–0.93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1 diameter, mm</td>
<td>2.64±0.65</td>
<td>1.72±0.53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vₐ, cm/s</td>
<td>60.4±14.1</td>
<td>44.0±14.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>0.81 (0.72–0.87)</td>
<td>0.85 (0.77–0.99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VFR, cm³/s</td>
<td>2.95 (1.86–4.51)</td>
<td>1.00 (0.55–1.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VFR in A1 segment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm Side</td>
<td>2.29 (1.41–3.08)</td>
<td>1.22 (0.68–2.06)</td>
<td>&lt;0.001§</td>
<td>&lt;0.01§</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Nonaneurysm Side</td>
<td>0.88 (0.75–0.99)</td>
<td>0.86 (0.79–0.98)</td>
<td>&lt;0.01§</td>
<td>0.01§</td>
<td>0.01§</td>
</tr>
</tbody>
</table>

Values expressed as mean±SD or median (interquartile range). ACoA indicates anterior communicating artery; PI, pulsatility index in the A1 segment; Vₐ, mean velocity in the A1 segment; and VFR, volume flow rate in the A1 segment.

†Aneurysm side vs nonaneurysm side; ‡aneurysm side vs dominant A1 segment; §aneurysm side vs nondominant A1 segment; Mann–Whitney U test; †Student t test; ‡Student t test with independent estimation of the variance.

Discussion

Hypertension and cigarette smoking are well-known modifiable risk factors for aneurysm formation.10,11 Hashimoto et al12 showed that increased blood flow because of experimentally induced arterial hypertension results in the formation of cerebral aneurysms on pathways of collateral circulation. Hemodynamic stress results in degradation of the internal elastic lamina followed by thinning of the media because of the decrease of medial smooth muscle cells.3 Cigarette smoke induces endothelial inflammatory response and proinflammatory phenotypic modulation of vascular smooth muscle cells and subsequent aneurysm formation.12 Vlak et al11 demonstrated that the joint risk of current smoking and hypertension for the aneurysm development was higher than the sum of the separate risks.

Hemodynamic forces, particularly high wall shear stress (WSS), play a crucial role in initiating cerebral aneurysm formation.4,5,12,13 Alfano et al14 showed a significant association between a vessel bifurcation where aneurysms are frequent (ie, the ACoA complex, middle cerebral artery bifurcations, and ICA/posterior communicating artery junction) and high WSS. Studies on glass models revealed that the magnitude of hemodynamic stress increases proportionally to the bifurcation angle and asymmetry of the branch diameter.14 Ingebrigtsen et al11 analyzed 107 bifurcations of the middle cerebral artery, distal ICA, and the basilar artery, reconstructed based on 3D digital subtraction angiography and demonstrated that branch angles in the bifurcations with aneurysm were significantly larger than those without. The angles turned out to be the only independent predictors for the occurrence of an aneurysm on logistic regression analysis.15 Bor et al16 compared the original CTA/magnetic resonance angiography images of bifurcations of A1 segment–ACoA, ICA–posterior communicating artery, distal ICA, and basilar artery of 26 patients who developed an aneurysm and 78 controls. They found that aneurysms were significantly more frequent in hypoplastic branches and bifurcations with sharper angles between parent artery and its derivatives.16 Kasuya et al17 used 3D CTA to analyze the angles between A1 and A2 segments of the ACoAs in 42 patients after subarachnoid hemorrhage from a ruptured ACoA aneurysm. They found significant association between smaller A1 to A2 angle (larger ACoA–A2) and prevalence of an aneurysm.17 Also, our findings suggest that the vessel bifurcation angle may be a predictor of cerebral aneurysm formation. We found that the angle between A1 and A2 segments were classified as those related to the larger A1 segment and the smaller A1 segment.

Univariate and Multivariate Analyses

The first step was to identify the factors being associated with either the presence or the absence of an ACoA aneurysm on univariate analysis. The analysis included demographic variables of the study and control groups, as well as morphological and hemodynamic variables: for the A1 segment on the side of an aneurysm in the group of patients with ACoA aneurysms and for the dominant A1 segment in the controls. The choice of the dominant A1 segment side in the control group was dictated by the intention of matching the controls to the study group in terms of morphology of the A1 segment. In the group of patients with ACoA aneurysm, all except 7 aneurysms were located on the side of the dominant A1 segment. Smoking, hypertension, asymmetry of A1 segments, the angle between A1 and A2 segments, A1 segment diameter, Vₐ, mean velocity in the A1 segment; and VFR, volume flow rate in the A1 segment were documented between A1 segment diameter and VFR, as well as between A1 and A2 segments, A1 segment diameter, Vₐ, PI, and VFR in A1 segment turned out to be significantly associated with the presence of ACoA aneurysms on univariate analysis (Table 3).

Correlations between the factors that proved to be significant on the univariate analysis were examined using the Pearson correlation test. Strong significant correlations were documented between A1 segment diameter and VFR, as well as between Vₐ and PI. Therefore, only VFR and PI were included in the multivariate backward stepwise logistic regression analysis. The remaining parameters used in the multivariate model and the characteristics of the latter are presented in Table 4. Smoking (odds ratio, 2.036; 95% confidence interval, 1.109–3.763), hypertension (odds ratio, 1.277–2.345), asymmetry of A1 segments >40% (odds ratio, 2.524; 95% confidence interval, 1.275–4.996), PI (odds ratio, 0.004; 95% confidence interval, 0.000–0.124), and the angle between A1 and A2 segments ≤100° (odds ratio, 4.665; 95% confidence interval, 2.247–9.687) turned out to be the strongest independent risk factors for ACoA aneurysm development.
atastic formation. We showed that low PI is associated with a high risk of the aneurysm development. In their computational fluid dynamics analysis, Le et al found that high WSS values in the neck region of a saccular aneurysm correlated strongly with low pulsatility inflow waveform. For the low PI, the WSS temporal variation could locally exhibit high frequency oscillations and large temporal gradients, leading to the endothelial cell damage and aneurysm formation.

The PI value is determined by several factors, namely blood flow in the investigated vessel, the peripheral resistance, elasticity of the vessel wall, and the caliber of the vessel. Hypoplastic vessels are characterized by high PI. We showed that low PI is an independent risk factor for aneurysm development (Table 4). Pulsatility effect of the blood flow waveform is thought to play an important role in the development and rupture of an aneurysm. Holzschuh et al found that PI in intracranial arteries of a patient with the Ehlers-Danlos syndrome and an middle cerebral artery aneurysm was lower than the PI of the reference group. They hypothesized that low PI is associated with a high risk of the aneurysm development. In their computational fluid dynamics analysis, Le et al found that high WSS values in the neck region of a saccular aneurysm correlated strongly with low pulsatility inflow waveform. For the low PI, the WSS temporal variation could locally exhibit high frequency oscillations and large temporal gradients, leading to the endothelial cell damage and aneurysm formation. The PI value is determined by several factors, namely blood flow in the investigated vessel, the peripheral resistance, elasticity of the vessel wall, and the caliber of the vessel. Hypoplastic vessels are characterized by high PI. We showed that low PI is an independent risk factor for aneurysm development (Table 4).

Aneurysms are frequently associated with asymmetrical A1 segments of the ACAs. Ujjie et al conducted a study on the glass model of the ACAs and showed that an increase in blood flow or diameter of one of the A1 segments of ACA results in a significant increase in hemodynamic stress at the junction of the A1 segment and ACoA. This suggests that the geometry of the ACoA complex may significantly modulate both the magnitude and the distribution of hemodynamic load at the junction of the A1 segment and ACoA.

Xu et al used the 3D numeric simulation model of the ACoA complex to demonstrate that WSS in the region of the dominant A1–ACoA increased proportionally to a decrease in the diameter of the nondominant A1 segment. According to high-flow theories, high WSS acts directly on the vascular endothelium leading to weakening of the vessel wall and aneurysm formation. We showed that V_m, VFR, diameter of the A1 segment, and asymmetry of A1 segments are significantly associated with the presence of an ACoA aneurysm (Table 3). Hypoplasia or aplasia of one of the A1 segments turned out to be the strongest independent risk factor for ACoA aneurysm occurrence (Table 4).
of indications for CTA did not include any of the risk factors for aneurysm formation analyzed in our study (eg, hypercholesterolemia). This likely prevented over-representation of individuals with these risk factors in our sample. One potential limitation may be associated with the fact that small aneurysms cannot be detected on conventional CT that was the only examination conducted in some of the prequalified patients. Therefore, it cannot be excluded that some individuals with the small aneurysms remained unidentified and thus were not enrolled. A further limitation stems from the fact that the study group consisted of patients with already diagnosed ACoA aneurysm. Therefore, hemodynamic parameters at the moment of aneurysm initiation could be slightly different than those determined at the time of enrollment to the study. Moreover, the presence of an aneurysm could influence the morphology of the ACoA complex. However, this last limitation seems to be at least as significant as ACoA aneurysms of our patients were relatively small (4.7±2.3 mm; range, 2.0–11.0 mm). Another potential limitation pertains to the fact that rheological and humoral parameters were not included in our analysis.

Apart from the standardized protocol and binding the researchers with regard to patient assignment, also relatively large size and homogeneity of the group of subjects with ACoA aneurysms, sufficient for the purpose of multivariate risk analysis, should be considered as a strength of our study. Moreover, it should be noted that the compared groups did not differ significantly in terms of statistical characteristics of age and sex, that is, established confounders of cerebral hemodynamic studies. Although this was not a consequence of our purposeful actions, but rather a result of simultaneous selection of patients and controls originating from the same catchment area, it undoubtedly improved reliability of the hereby presented findings. Finally, the prospective manner of collecting clinical and imaging data enabled us to avoid another potential selection bias, namely exclusion of patients in whom aneurysms were treated by embolization or clipping.

In conclusion, our study constitutes a starting point for further analyses of associations among WSS, the established risk factor for aneurysm formation, and the hereby discussed hemodynamic and morphological factors.

Acknowledgments

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Disclosures

None.

References

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