Clinical relevance of anterior cerebral artery asymmetry in aneurysmal subarachnoid hemorrhage

Ramazan Jabbarli, MD,1,2 Matthias Reinhard, MD,3,4 Roland Roelz, MD,1 Klaus Kaier, PhD,5 Astrid Weyerbrock, MD,1 Christian Taschner, MD,6 Christian Scheiwe, MD,7 and Mukesch Shah, MD1

Departments of 1Neurosurgery, 2Neurology and Neurophysiology, and 3Neuroradiology; 4Institute for Medical Biometry and Medical Informatics, University Medical Center Freiburg; 5Department of Neurosurgery, University Hospital Essen; and 6Department of Neurology and Clinical Neurophysiology, Klinikum Esslingen, Germany

OBJECTIVE An asymmetry of the A1 segments (A1SA) of the anterior cerebral arteries (ACAs) is an assumed risk factor for the development of anterior communicating artery aneurysms (ACoAAs). It is unknown whether A1SA is also clinically relevant after aneurysm rupture. The authors of this study investigated the impact of A1SA on the clinical course and outcome of patients with aneurysmal subarachnoid hemorrhage (SAH).

METHODS The authors retrospectively analyzed data on consecutive SAH patients treated at their institution between January 2005 and December 2012. The occurrence and severity of cerebral infarctions in the ACA territories were evaluated on follow-up CT scans up to 6 weeks after SAH. Moreover, the risk for an unfavorable outcome (defined as > 3 points on the modified Rankin Scale) at 6 months after SAH was assessed.

RESULTS A total of 594 patients were included in the final analysis. An A1SA was identified on digital subtraction angiography studies from 127 patients (21.4%) and was strongly associated with ACoAA (p < 0.0001, OR 13.7). An A1SA independently correlated with the occurrence of ACA infarction in patients with ACoAA (p = 0.047) and in those without an ACoAA (p = 0.015). Among patients undergoing ACoAA coiling, A1SA was independently associated with the severity of ACA infarction (p = 0.023) and unfavorable functional outcome (p = 0.045, OR = 2.4).

CONCLUSIONS An A1SA is a common anatomical variation in SAH patients and is strongly associated with ACoAA. Moreover, the presence of A1SA independently increases the likelihood of ACA infarction. In SAH patients undergoing ACoAA coiling, A1SA carries the risk for severe ACA infarction and thus an unfavorable outcome.

Clinical trial registration no.: DRKS00005486 (http://www.drks.de/)
https://thejns.org/doi/abs/10.3171/2016.9.JNS161706

KEY WORDS A1 asymmetry; hypoplasia; aplasia; subarachnoid hemorrhage; anterior communicating artery; cerebral infarct; functional outcome; vascular disorders

It has been pointed out that anomalies in the circle of Willis are frequently associated with intracranial aneurysms.17,18 In particular, A1SA has been assumed to play a significant role in the formation of aneurysms of the anterior communicating artery (ACoA).1,18,19 In the literature, the incidence of A1SA among carriers of ACoA aneurysms (ACoAAs) ranges between 41% and 85%.1,15,27 Experimentally, ACoAAs can be produced in hypertensive...
rats by unilateral ligation of the common carotid artery, supporting a causative relationship between increased flow and aneurysm formation.2

Along with its developmental role, A1SA is also considered a risk factor for the rupture of ACoAAs, but only in relatively small series with contradictory results.19,21–23 In addition, impaired collateral blood flow through the circle of Willis, including the A1SA, is a recognized risk factor for ischemic stroke4 and incomplete endovascular aneurysm occlusion.2 However, data about the impact of A1SA on the clinical course and outcome of patients with aneurysmal subarachnoid hemorrhage (SAH) are still missing.

To evaluate the clinical impact of A1SA in SAH patients, particularly with regard to the formation, rupture, and treatment success of ACoAAs, we analyzed a large series of SAH patients from a single center.

Methods

Patient Population

We retrospectively analyzed an institutional SAH database containing data on all consecutive patients with ruptured aneurysms treated between January 2005 and December 2012 at the University Medical Center Freiburg, Germany. Inclusion criteria for this study were 1) hospital admission within 72 hours after the bleeding event, 2) digital subtraction angiography (DSA) studies obtained at admission, and 3) treatment of the ruptured aneurysm by means of coiling or clipping.

The study was approved by the institutional review board and performed within the clinical trial registered in the German Clinical Trials Register (Deutsches Register Klinischer Studien, unique identifier DRKS00005486, http://www.drks.de/).

Management of SAH

All patients were initially admitted to our neurocritical intensive care unit. After identification of the ruptured aneurysm on DSA, treatment allocation to coiling or clipping was made upon interdisciplinary assessment by the officiating neurosurgeon and neuroradiologist. Acute hydrocephalus was treated with external ventricular drainage (EVD). All patients underwent at least 1 posttreatment CT scan, and additional CT scans were obtained upon clinical indications. Transcranial Doppler (TCD) ultrasonography was performed daily during the first 3 weeks after SAH, in which absolute mean flow velocities > 160 cm/sec were deemed suspicious for clinically relevant vasospasm. The different aspects of SAH management at our institution have already been elaborated on in our previous publications.15–14

Data Management

The data were collected from a retrospective SAH database constructed based on the hospital’s electronic medical records. The following demographic, clinical, and radiological parameters at admission were recorded: patient age and sex, initial clinical grade according to Hunt and Hess (HH), severity of SAH according to the original Fisher scale, characteristics (size and location) of identified intracranial aneurysm(s), and treatment modality.

All DSA reports were reviewed with regard to documentation of the A1SA, as originally interpreted by neuroradiologists. In addition, the reported complications during aneurysm coiling were recorded.

The development of new cerebral infarctions was evaluated on the follow-up CT up to 6 weeks after SAH by the first author (R.J.). Hypodensities resulting from EVD, the surgical approach, and/or intracerebral hematoma were not considered infarctions. Identifed infarct patterns were classified according to the main arterial territories,24 with subsequent selection of the cases with ACA infarction. Along with the incidence of ACA infarction, the severity of cerebral infarction in the ACA territories was assessed using an arbitrary scoring system based on the maximum infarct burden (Fig. 1): 1) each ACA territory was assigned an infarct score depending on the infarcted portion of the vascular territory (1, 2, and 3 points for 1%–10%, 11%–50%, and > 50%, respectively); and 2) the summary infarct score was calculated from the score values for both ACA territories.

The new scale for assessing the severity of cerebral infarction in the ACA territories has been internally validated using an intraclass correlation coefficient (ICC). This test showed excellent interrater agreement (ICC = 0.820) for measuring the severity of ACA infarction.

The timing of the occurrence of ACA infarction was recorded as the interval between the ictus and the follow-up CT scan on which the infarct was first documented.

Functional outcome was evaluated using the modified Rankin Scale (mRS) score on the medical reports from the outpatient care visits routinely performed at 6 months after SAH. Accordingly, patients with an mRS score > 3 were considered to have an unfavorable outcome.

Statistical Analysis

Correlations between A1SA and ACoAA (their presence, rupture status, and intraprocedural complications) were analyzed in a univariate manner using chi-square or Fisher exact tests, as appropriate. Differences between continuous variables were analyzed using the Student t-test for normally distributed data and the Mann-Whitney U-test for non-normally distributed data.

Study end points (unfavorable outcome, occurrence and severity of ACA infarction) were evaluated using multivariable binary logistic or linear regression analyses, as appropriate. Along with A1SA, the following potential confounders were included in the multivariate analysis: demographic parameters of the patients (age and sex), clinical (HH grade) and radiological (Fisher grade) severity of SAH, treatment modality, and occurrence of cerebral vasospasm (on TCD ultrasonography). Patient age was assessed in a dichotomized manner. According to the correlation with functional outcome in the receiver operating characteristic curve, the cutoff for age was set at 50 years.

Data analysis was performed using PRISM (version 5.0, GraphPad Software Inc.) and SPSS (version 21, IBM Corp.) statistical software. Differences with a p value < 0.05 were considered statistically significant.
Results

Patient Population

A total of 594 SAH patients were included in the final analysis. The mean age of the cohort was 55.2 years (range 21–94 years). The male/female ratio was 1:1.7. Three hundred seventy-four patients (63%) underwent aneurysm coiling. At 6 months after SAH, 226 patients (38%) had an unfavorable outcome and the mortality rate was 17% (101 patients).

A1SA and ACoAA: Incidences and Associations

An A1SA was identified on 127 admission DSA studies (21.4%), mostly with a left dominant A1 segment (85 [67%] of 127 angiograms). The patients with A1SA were older (mean age 57.8 vs 54.6 years, p = 0.0277) and less likely to be female (53.5% vs 65.5%, p = 0.0169).

Aneurysms of the ACoA were found in 238 patients, and most (227 lesions) were ruptured. Regardless of the rupture status, the ACoAAs had an identical mean sack size of 6.7 mm (p = 0.9793). Of 236 treated ACoAAs, 175 (74.2%) were treated with endovascular coiling.

There was a strong correlation between A1SA and the presence of an ACoAA on admission DSA studies (Fig. 2). One hundred seven patients with A1SA presented with (ruptured or unruptured) ACoAA, yielding a 13.72-fold higher probability of ACoAA with A1SA in the investigated cohort (p < 0.0001). Subanalysis among the ACoAA carriers identified a significant association between A1SA and a ruptured status of the ACoAA (OR 7.82, 95% CI 0.97–62.77, p = 0.025). However, the presence of an A1SA had no impact on the size of the ACoAA (p = 0.7355).

Role of A1SA in the Risk of ACA Infarction and Unfavorable Outcome After SAH

In 158 SAH patients, at least 1 new cerebral infarction in the ACA territories was identified on follow-up CT scans. The mean severity of ACA infarction averaged 3.7 points (range 1–6 points; Fig. 1). The mean timing of ACA infarction was 164.9 and 205.5 hours in the A1SA and non-A1SA cohorts, respectively. However, the difference between the two did not reach statistical significance (p = 0.3772). Subanalysis according to treatment modality did not change the significance level.

Among the cases with ACA infarction(s) and A1SA (52 cases), cerebral infarction was present on the hypoplastic side in 41 cases (78.8%) and on the side with the dominant A1 segment in 39 cases (75%; p = 0.8164).

Cerebral Infarction in the ACA Territories

The presence of A1SA was an independent risk factor for the development of ACA infarction. This finding was observed both in the group of SAH patients with ACoAA (adjusted odds ratio [aOR] 1.89, 95% CI 1.01–3.53, p = 0.047) and in the non-ACoAA cohort (aOR 3.33, 95% CI 1.27–8.72, p = 0.015; Table 1).

Severity of ACA Infarction

An A1SA narrowly missed a significant correlation with the severity of infarction in the ACoAA cohort (p = 0.057) and was not a significant factor for the severity of ACA infarction in the non-ACoAA cohort (p = 0.705; Supplementary Table S1). A subgroup analysis within the ACoAA cohort showed that A1SA independently predicted the severity of ACA infarction in patients undergoing ACoAA coiling (p = 0.023; Table 2). In contrast, A1SA had no impact on the severity of ACA infarction for the patients who underwent microsurgical clipping of ACoAAs (p = 0.829).

Clinical Outcome

An A1SA was a significant predictor of an unfavorable outcome in the multivariate analysis performed among SAH individuals with coiled ACoAAs (p = 0.045; Table 3). For the clipped ACoAA cohort (p = 0.098) as well as
the non-ACoAA cohort (p = 0.968; Supplementary Table S2), A1SA had no independent predictive value for functional outcome after SAH.

In line with the coiling-related associations between A1SA and the above-mentioned treatment end points, the presence of A1SA strongly correlated with the risk of intra-procedural complications during ACoAA coiling (OR 2.39, 95% CI 1.1–5.2, p = 0.029; basic clinical characteristics of SAH patients with coiled ACoAAs are presented in Supplementary Table S3).

Discussion

In this large retrospective series of SAH patients, we identified A1SA as an independent risk factor for the development of cerebral infarction in the ACA territories. In addition, the patients with an A1SA undergoing ACoAA coiling have an increased risk for intra-procedural complications, severe ACA infarction, and thus an unfavorable outcome after SAH.

A1SA: Rare Angiographic Finding?

The circle of Willis is not symmetric in up to 54.8% of the population. An A1SA representing a dominant ACA with a hypoplastic or absent contralateral ACA is the most frequent anatomical variation. However, there is great variability in the reported frequency of A1SA, which can be found in 1%–21% of the healthy population, as derived from angiograms and autopsy reports.

An A1SA was very commonly identified (21.4%) in our study. This circumstance may have several reasons. First, the diagnostic accuracy of angiographic studies has been considered to be superior to traditional cadaver series. Second, a relatively high frequency of A1SA in our series can be explained by the specific cohort of aneurysm carriers. The association between variations in the circle of Willis and development of intracranial aneurysms has already been suggested.

A1SA: Clinically “Harmless” Anatomical Variation?

Numerous angiographic and cadaver studies describe the coincidence of A1SA and ACoAAs. This correlation may indicate a causative role for A1SA in the formation of ACoAA resulting from an asymmetrical local inflow with chronic hemodynamic stress on the walls of the ACoA. Experimental research confirms this hypothesis—ACoAA can be produced in hypertensive rats by unilateral ligation of the common carotid artery.

The hemodynamic stress related to anatomical variations in the circle of Willis may contribute not only to aneurysm formation, but also to their growth and rupture. However, many of these conclusions are based on relatively small series with partially discrepant results. Our large angiographic study of SAH patients unambiguously confirms the association between A1SA and a ruptured status of identified ACoAAs. Nevertheless, there was no association between A1SA and the size of ACoAAs.

In particular, A1SA carriers show an increased risk of aneurysm recurrence following coil embolization. In support of the clinical importance of A1SA for the endovascular treatment of ACoAAs, we showed a higher risk of intra-procedural complications during ACoAA coiling in SAH patients with A1SA.

In summary, A1SA seems to play a crucial role in the formation, further progression, and rupture of ACoAAs, as well as represents an important risk factor during coil embolization.
embolization. Therefore, the presence of A1SA in SAH patients with ACoAA may argue in favor of microsurgical clipping in the cases in which the ACoAA is considered to be eligible for surgery.

**A1SA in SAH Patients: The Phantom Menace**

An A1SA may also play an important role in cerebral hemodynamic complications regardless of the ACoAA. Anatomical variations in the circle of Willis have been shown to be associated with the risk of ischemic stroke\(^7\) and intraoperative ischemic complications.\(^{17}\) In particular, a clinical study of 280 acute ischemic stroke patients\(^4\) identified A1SA as a risk factor contributing to ischemic stroke, especially strokes in arteries penetrating the striatal area. Moreover, A1SA is regarded as a predisposing factor in hemispheric low-flow infarcts in carotid occlusive disease.\(^{4,9,16}\) The increased risk for ischemic complications in patients with A1SA may occur because of impaired collateral circulation.\(^4\) Therefore, these individuals may be less resistant to disturbances of cerebral perfusion that are common during the acute phase of SAH due to early brain injury, pathological intracranial pressure, and cerebral vasospasm. Nevertheless, there are no data on the clinical value of A1SA for SAH patients to date.

In this study, we identified A1SA as an important and independent risk factor for the development of cerebral infarction in the ACA territory. Probably because of the additional impact of the treatment-related complications, SAH individuals with A1SA and ACoAA clipping showed more frequent and severe ACA infarction and unfavorable functional outcomes. In summary, severe ACA infarction was one of the confounders but not the only reason for an unfavorable outcome in SAH patients with A1SA and ACoAA coiling. Considerable morbidity and mortality after SAH is generally acknowledged to be multifactorial in nature.\(^{13}\)

Therefore, SAH patients with A1SA on admission DSA, and especially those with disturbed consciousness, may be considered for intensive surveillance of the cerebral perfusion in the ACA territory by means of additional diagnostic tools such as perfusion CT imaging (at predefined time intervals), continuous electrophysiological monitoring, microdialysis, or near-infrared spectroscopy.

**Study Limitations**

The most important limitations of this study arise from its retrospective design. The diagnosis of A1SA was made on the original interpretations of the radiological reports written by different institutional neuroradiologists over the 7-year study period. However, the reported rate of A1SA and its associations with ACoAAs are in line with recent angiographic reports.\(^{17,19,21}\) The left-sided A1 dominance in our patients with A1SA is similarly noted in previous reports.\(^{3,17,21}\) Another important drawback regarding A1SA is that our analysis did not allow for evaluation of the impact of the degree of A1SA on the functional and radiological outcome of SAH. The development of cerebral infarction was judged on follow-up CT scans, which may have led to the underestimation of 1) small ischemic lesions, which are better visualized on MRI; 2) asymptomatic

---

**TABLE 1. Multivariable logistic regression analysis of the predictors of ACA infarction**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACoAA Cohort</th>
<th>p Value</th>
<th>Non-ACoAA Cohort</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1SA</td>
<td>1.89 (1.01–3.53)</td>
<td>0.047</td>
<td>3.33 (1.27–8.72)</td>
<td>0.015</td>
</tr>
<tr>
<td>Age, &gt;50 yrs old</td>
<td>0.98 (0.5–1.96)</td>
<td>0.964</td>
<td>1.62 (0.88–3.01)</td>
<td>0.124</td>
</tr>
<tr>
<td>Sex, female</td>
<td>1.33 (0.69–2.56)</td>
<td>0.388</td>
<td>1.03 (0.56–1.88)</td>
<td>0.931</td>
</tr>
<tr>
<td>HH, per-grade increase</td>
<td>1.53 (1.13–2.07)</td>
<td>0.007</td>
<td>1.72 (1.3–2.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fisher, per-grade increase</td>
<td>10.18 (2.25–46.03)</td>
<td>0.003</td>
<td>1.33 (0.48–3.69)</td>
<td>0.590</td>
</tr>
<tr>
<td>Treatment modality, coiling</td>
<td>2.4 (1.2–4.82)</td>
<td>0.014</td>
<td>1.18 (0.65–2.13)</td>
<td>0.591</td>
</tr>
<tr>
<td>Vasospasm on TCD</td>
<td>1.21 (0.58–2.49)</td>
<td>0.613</td>
<td>1.23 (0.65–2.33)</td>
<td>0.534</td>
</tr>
</tbody>
</table>

Boldface type indicates statistical significance.

**TABLE 2. Multivariate linear regression analysis for predictors of the severity of ACA infarction in the ACoAA cohort**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACoAA Clipping</th>
<th>p Value</th>
<th>ACoAA Clipping</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1SA</td>
<td>0.71 (0.1 to 1.33)</td>
<td>0.023</td>
<td>−0.13 (1.3 to 1.04)</td>
<td>0.829</td>
</tr>
<tr>
<td>Age, &gt;50 yrs old</td>
<td>−0.2 (−0.88 to 0.49)</td>
<td>0.574</td>
<td>−0.47 (−1.68 to 0.73)</td>
<td>0.444</td>
</tr>
<tr>
<td>Sex, female</td>
<td>0.09 (−0.56 to 0.74)</td>
<td>0.783</td>
<td>0.27 (−0.9 to 1.43)</td>
<td>0.655</td>
</tr>
<tr>
<td>HH, per-grade increase</td>
<td>0.47 (0.16 to 0.78)</td>
<td>0.003</td>
<td>0.13 (−0.43 to 0.69)</td>
<td>0.646</td>
</tr>
<tr>
<td>Fisher, per-grade increase</td>
<td>0.85 (−0.09 to 1.79)</td>
<td>0.076</td>
<td>1.06 (−0.39 to 2.51)</td>
<td>0.154</td>
</tr>
<tr>
<td>Vasospasm on TCD</td>
<td>1.12 (0.45 to 1.8)</td>
<td>0.001</td>
<td>0.31 (−1.01 to 1.63)</td>
<td>0.643</td>
</tr>
</tbody>
</table>

RC = regression coefficient. Boldface type indicates statistical significance.
atric cerebral infarctions since the CT scans were obtained if clinically indicated; 3) severity of ACA infarction in individuals with a shorter survival; and 4) the true timing of ACA infarctions since the presented data fully depend on the time and frequency of the follow-up CT scans with certain diagnostic delays. Nevertheless, our data represent the first evidence about the clinical impact of AISA after SAH in a large series.

Conclusions

Among patients with aneurysmal SAH, AISA is a very common anatomical variation strongly associated with the development and rupture of ACoA. In addition, AISA is a pivotal risk factor for ACA infarction. In particular, SAH patients with AISA who undergo ACoAA coiling have an exceptionally high risk for severe ACA infarction and thus an unfavorable outcome.

References

26. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van...

Disclosures
Dr. Reinhard has served on an advisory board for Daiichi Sankyo Inc. and has received speaker honoraria from Bayer Healthcare and Boehringer Ingelheim.

Author Contributions
Conception and design: Jabbarli, Reinhard. Acquisition of data: Jabbarli. Analysis and interpretation of data: Jabbarli, Reinhard, Taschner, Shah. Drafting the article: Jabbarli, Roelz, Weyerbrock, Scheiwe, Shah. Critically revising the article: all authors. Reviewed submitted version of manuscript: Jabbarli, Roelz, Kaier, Weyerbrock, Taschner, Scheiwe, Shah. Approved the final version of the manuscript on behalf of all authors: Jabbarli. Statistical analysis: Jabbarli, Kaier.

Supplemental Information
Online-Only Content
Supplemental material is available with the online version of the article.

Correspondence
Ramazan Jabbarli, Department of Neurosurgery, University Medical Center Freiburg, Freiburg/Breisgau D-79106, Germany. email: ramazan@jabbarli.com.