Vertebral Artery Hypoplasia
Frequency and Effect on Cerebellar Blood Flow Characteristics

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Background and Purpose—Vertebral artery hypoplasia (VAH) is supposed to be a risk factor for posterior circulation ischemia (PCI), particularly in the territory of the posterior inferior cerebellar artery (PICA). The aim of our study was to determine whether VAH impedes perfusion in the dependent PICA territory even in the absence of manifest PCI.

Methods—VA diameter was retrospectively measured in 934 consecutive patients who underwent whole-brain multimodal computed tomography because of suspected stroke. VAH was defined by a diameter of ≤2 mm and an asymmetry ratio of ≤1:1.7 of both VAs. We performed blinded computed tomography perfusion reading in patients with VAH without PCI (MRI-confirmed) and in control patients (ratio 1:2) with normal VAs. Four different perfusion maps were evaluated for a relative hypoperfusion in the PICA territory.

Results—VAH was found in 146 of 934 patients (15.6%). It was more frequent on the right side (66.1%). Of 146 patients, 59 without PCI qualified for computed tomography perfusion analysis. Depending on the perfusion map, ≤42.4% (25/59) of patients with VAH, but only 7.6% (9/118) without VAH, showed an ipsilateral PICA hypoperfusion (P<0.001). Sensitivities in patients with VAH were as follows: time to drain 42.4% (25/59)>mean transit time 39.0% (23/59)>cerebral blood flow 25.4% (15/59). Cerebral blood volume was never affected.

Conclusions—VAH is a frequent vascular variant that can lead to a relative regional hypoperfusion in the PICA territory. Additional research should clarify the pathophysiological role of VAH in PCI. (Stroke. 2014;45:1363-1368.)

Key Words: brain infarction, posterior circulation • brain ischemia • perfusion imaging • risk factors • stroke

The vertebral arteries (VAs), which originate from the subclavian arteries and unite to form the basilar artery after branching into the posterior inferior cerebellar arteries, are the primary blood supply for infratentorial brain structures, such as mesencephalon, cerebellum, pons, and medulla oblongata. Congenital variations in the arrangement and size of the VAs are common, and VA hypoplasia (VAH) has frequently been recognized among healthy individuals without symptoms of vertebrobasilar insufficiency.1,4

Still, the reported VAH prevalence in the literature is highly incongruent and ranges between 1.9 and ≤26.5%. This discrepancy is in part related to the fact that there is no consensus on a standard definition of VAH. Despite its presumably high prevalence, relatively little is known about the clinical relevance of VAH. The absence of symptoms resulting from a possible vertebrobasilar insufficiency among individuals with VAH is consistent with the long-prevailing opinion that VAH is a harmless anatomic variant.1–3 It is only in the past years that VAH has been paid increasing attention mainly because of accumulating evidence, suggesting that it constitutes a risk factor for vertebrobasilar stroke, especially infarcts of the posterior inferior cerebellar artery (PICA) and lateral medullary infarcts.4,5

Functional studies using Doppler flowmetry have shown that VAH may lead to a decrease of the ipsilateral net vertebral flow volume in healthy subjects, and it has been speculated that this might lead to a regional tissue hypoperfusion potentially constituting a hidden disease.5,6 However, to date, it remains elusive whether VAH indeed leads to a relevant regional impairment in tissue perfusion. In the past years, computed tomography (CT) perfusion (CTP) has been increasingly used to assess the cerebral perfusion in the setting of acute stroke. Recently introduced whole-brain CT perfusion (WB-CTP) allows for an assessment of the infratentorial perfusion, albeit large studies on the diagnostic accuracy of WB-CTP have not yet been published.

The aim of this retrospective study was to characterize the occurrence and hemodynamic effect of VAH in the dependent PICA territory in the absence of posterior circulation ischemia (PCI). To achieve this, we sought to (1) determine the frequency of VAH as assessed by CT angiography (CTA) and (2) characterize the effect of VAH on blood perfusion of the PICA territory using WB-CTP.

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Methods

Study Population
From April 2009 to July 2012, 934 consecutive patients, who were admitted to our institution because of suspected stroke and who underwent emergency multimodal stroke CT, were screened for VAH frequency. The study was designed as a retrospective single-center study at a university hospital. The institutional review board approved the retrospective study and waived requirement for informed consent.

CT Examination Protocol and Image Processing
Multimodal stroke CT included nonenhanced CT to rule out intracerebral hemorrhage, supra-aortic CTA, and WB-CTP. We performed nonenhanced CT, WB-CTP, and CTA on a 128-slice dual source CT scanner with 0.6-mm collimation (SOMATOM Definition Flash; Siemens Healthcare, Erlangen, Germany).

CT Angiography
For CTA, 50 mL of highly iodinated contrast agent was administered intravenously, followed by a saline chaser of 40 mL, both with a flow rate of 5 mL/s. CTA was performed from the aortic arch to the vertex with 10-mm and an increment of 3 mm were acquired continuously >48 s. Tube voltage and current were set to 80 kV and 200 mAs, respectively. CTDIvol was 276.21 mGy.

Whole-Brain CT Perfusion
For CTP, 35-mL contrast agent was administered intravenously, followed by a saline chaser of 40 mL, both with a flow rate of 5 mL/s. WB-CTP was performed with extended scan coverage of 100 mm in the z axis using the toggling-table technique. Thirty-one axial slices with a thickness of 10 mm and an increment of 3 mm were acquired continuously >48 s. Tube voltage and current were set to 80 kV and 200 mAs, respectively. CTDIvol was 276.21 mGy.

For all data sets, perfusion analysis was performed with the vendor given Syngo VPCT Neuro software using a semiautomated deconvolution algorithm (Auto Stroke MTT) as described before.30 A set of 31 color-coded slices was reconstructed for each perfusion parameter. For further evaluation, only the default window settings were used.

Analysis of VAH Frequency Using CTA
First, CTA images of all patients were evaluated with respect to the VAs. VAH was defined by a V4 diameter of ≤2.0 mm4,5,7,13 and a concomitant diameter asymmetry ratio of ≤1:1.7 in all of the 4 vertebral segments (V1–V4).4,5,7,13 V1 was measured at its origin from the subclavian artery, V2 caudally of the second cervical vertebra. The V3 segment was measured at its midlevel, and measurements of the V4 segments were performed 10 mm cranial to the entrance of the VA into the foramen magnum.

The same window settings were used for all CTA studies. Diameter was measured using dedicated open-source imaging software (OsiriX 64-bit). Measurements were performed on corresponding segmental height levels of both VAs. Multiplanar reformats served for the identification of VA orientation to ensure true cross-sectional measurements.

Screening for Hypoperfusion in the PICA Territory Using WB-CTP
In a second step, all patients with confirmed VAH were screened with respect to the eligibility for WB-CTP reading to assess the effect of VAH on regional perfusion in the PICA territory. We excluded patients with VAH and poor image quality, incomplete data sets, or missing follow-up MRI.

Other pathology or vascular variant that could alter posterior circulation (significant stenosis of the posterior circulation (>50% diameter), occlusion of the vertebral or the basilar artery, occlusion of the carotid artery, intracranial hemorrhage with the risk of vasospasm, missing VA, or PICA), posterior circulation infarction as confirmed by follow-up MRI.

The study was designed as a case control study with a ratio of cases:controls of 1:2 to prevent a biased reading.15 Patients who met the same inclusion and exclusion criteria but who had no VAH were chosen as controls (non-VAH cohort).

Two experienced CT-readers (1 radiologist of 5 years and 1 neuroradiologist of 7 years experience) independently evaluated multimodal CT images. CTA and CTP were assessed in different sessions. Readers were blinded to clinical data and, while assessing CTP, to CTA. In case of disagreement, a consensus was reached in a respective separate session. Inter- and intrareader agreement was not determined. For CTP reading, all 4 CTP maps were displayed simultaneously. Readers visually assessed the presence of regional hypoperfusion in the PICA territory for each perfusion parameter data set (low cerebral blood flow [CBF], low cerebral blood volume, delayed time to drain [TTD], and delayed mean transit time [MTT]). For the definition of the PICA territory, we used the most common definition of the territory, which comprises the inferior and Occipital surface of the cerebellum.15,16

We avoided using rigid quantitative thresholds for the definition of infarct core and hypoperfused area because postprocessing methods vary widely among manufacturers,17 and thresholds for penumbra and infarct core are not operationally defined and universally accepted.18 Moreover, the chosen approach allowed for individual comparison with the perfusion of the contralateral PICA territory. This proved to be beneficial as absolute perfusion values vary among individuals.19,20 A regional hypoperfusion was only considered substantial if it was present in ≥2 adjacent slices.

Statistical Analysis
Normal distribution was tested with the Kolmogorov–Smirnov test. Student t test for unpaired samples and paired samples, and Pearson χ² test were applied to test differences (α=95%) between patients and controls in vessel diameter and general characteristics. If another test is not explicitly mentioned, the Student t test for unpaired samples was applied. Two-sided P values of <0.05 were considered to indicate statistical significance. Statistical analysis was performed using standard statistical software SPSS (SPSS version 21; SPSS Inc, Chicago, IL).

Results

Prevalence of VAH
In 934 screened patients with suspected stroke, VAH was detected in 146 (15.6%) subjects. To study CTP further, 87 patients were excluded according to our exclusion criteria: 9 had poor image quality (motion artifacts, 5; poor bolus timing, 3; metal artifacts, 1), 16 had incomplete perfusion maps, 18 had an insufficient cerebellar CTP coverage, 10 had no follow-up imaging, 11 had VA pathology or a hemodynamically relevant vascular variant, 8 had intracranial hemorrhage, and 15 had a posterior circulation stroke. In total, 59 patients with VAH and 118 patients without VAH were enrolled to study CTP further, as shown in Figure 1.

General Characteristics of the VAH and the Non-VAH Patient Cohort
As shown in Table 1, there were no significant differences with respect to age (65.8±15.5 versus 65.8±18.1), sex (male individuals 61.0% versus 51.7%) and the National Institute
of Health Stroke Scale (2.9±3.9 versus 4.4±5.7) between the VAH and the non-VAH cohort.

CT Characteristics of the VAH and the Non-VAH Cohort

Among all 59 patients with VAH enrolled to analyze the perfusion of the PICA territory, VAH was found more frequently on the right side (66.1% right-sided VAH). In the non-VAH cohort, the nondominant VA was also located more frequently on the right side (66.1% right-sided VAH). In the VAH cohort, relative PICA hypoperfusion was present in the CBF, the TTD, and the MTT map. Among these maps, TTD was most sensitive and showed the perfusion reduction in 42.4% (25/59), whereas MTT was positive in 39.0% (23/59), and CBF in 25.4% of all patients with VAH (15/59). No perfusion alterations were detected in the cerebral blood volume map. Figure 2A and 2B shows 2 examples of a relative PICA hypoperfusion relating to an ipsilateral VAH. TTD, MTT, and CBF show a unilateral hypoperfusion in the PICA territory of the corresponding side.

Discussion

This retrospective study shows that VAH, defined by a vessel diameter of ≤2.0 mm in the V4 segment and a concomitant diameter asymmetry of ≤1:1.7 in the course of the VA (V1–V4) has a fairly high frequency among patients with suspected stroke. It often leads to a relative hypoperfusion in the dependent PICA territory without causing a subsequent infarction. TTD and MTT were the most sensitive CTP maps to reflect the perfusion impairment, followed by CBF. Cerebral blood volume did not show a perfusion alteration. To our knowledge, this is the first CTP study on the hemodynamic effect of VAH on the cerebellar perfusion.

By screening >900 patients, we could demonstrate that, with a prevalence of 15.6%, VAH is a frequent vascular variation. To date, the published prevalence of VAH varies substantially. This may result from measurement differences (autopsy studies, time of flight, contrast-enhanced MR angiography, CTA, and duplex ultrasonography), varying sample size, and the characteristics of the screened cohort (healthy subjects and patients with stroke). However, probably the most important

Table 1. General Characteristics of the VAH* and the Non-VAH Cohort

<table>
<thead>
<tr>
<th></th>
<th>VAH</th>
<th>Non-VAH</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>59</td>
<td>118</td>
<td>...</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>65.8±15.5</td>
<td>65.8±18.1</td>
<td>0.995†</td>
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<tr>
<td>% men</td>
<td>61.0</td>
<td>51.7</td>
<td>0.240‡</td>
</tr>
<tr>
<td>NIHSS, mean±SD</td>
<td>2.9±3.9</td>
<td>4.4±5.7</td>
<td>0.352†</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; and VAH, vertebral artery hypoplasia.

*Defined by an asymmetry ratio of ≤1:1.7 and a diameter of ≤2 mm in V1 to V4.
†Student t test for unpaired samples.
‡Pearson r test.
point is that no consensus exists on how to define VAsH. To date, diameters between 2 and 3 mm,\(^1,5\) as well as an asymmetry ratio threshold >1:1.7,\(^2,5,20\) have been used to describe VAsH. The prevalence reported in our study is still consistent with the rates recently published by others. In a CT study of patients with stroke (definition of VAsH: diameter <2 mm using CTA and contrast-enhanced MR-angiography), a prevalence of 10.8\(^%\)\(^13\) was found; another study using the same definition stated a prevalence of 11.51\(^%\).\(^7\) A large ultrasound study of 725 patients with cerebral infarction found a VAsH prevalence of 7.4\(^%\) (definition: diameter of VAs ≤2.5 mm and diameter discrepancy of <1:1.7).\(^5\) A VAsH frequency of 35.2\(^%\) was reported within a cohort of 529 patients with stroke and of 26.5\(^%\) within a cohort of healthy individuals (definition: diameter ≤2 mm as determined by time of flight MR angiography).\(^4\) Altogether, the VAsH frequency observed in our study is consistent with previous reports and depends on the approach and definitions applied for its diagnosis.

We found that VAsH was more frequent on the right side, which is consistent with previous reports.\(^4,5,7,13\) It has been proposed that relates to the fact that the left subclavian artery,
from which the VA derives, directly arises from the aortic arch. Thus, it is supposed to undergo higher shear stress during development, potentially leading to a blood supply that is dominated by the left VA.16

Until now, the hemodynamic consequences of V AH have been mostly studied using duplex ultrasonography. Using varying definitions of V AH (diameter of $\leq 2.5$ mm$^2$, $\leq 2.2$ mm$^2$, and $\leq 2$ mm$^2$), the net flow volume in the ipsilateral VA in healthy subjects is substantially reduced when compared with individuals with a normally sized VA. The ipsilateral flow resistance was significantly increased in patients with V AH.7 Furthermore, it could be shown that the contralateral VA shows a compensatory increase in flow volume.7 Flow volume insufficiency of the VA (as defined by a net flow volume of $<100$ mL/min) occurred significantly more often in individuals with V AH than in those without V AH.7

Our results reflect and extend these observations because we could show that V AH may also lead to a relevant hemodynamic disturbance in the dependent brain tissue as determined by CTP. A relative hypoperfusion of the PICA territory could be detected in the TTD map of 42.4% of all screened patients. TTD is a novel deconvolution-based parameter describing the time of contrast medium washout.11,22 It is very sensitive to all kinds of hemodynamic disturbances, and first experiences showed TTD to be well suited to assess the extent of hemodynamic disturbances with high image quality.17,18 In line with these results, it was more sensitive than the conventionally used MTT and CBF map, which showed a reduced PICA perfusion in 39% and 25.4%, respectively. It is important to note that we could detect a regional hypoperfusion in the PICA territory in patients devoid of subsequent infarction. CTP studies show that there is a high rate of intracerebral perfusion deficits that occur without subsequent ischemic lesions in the follow-up MRI.11,23–25 In $\leq 20\%$ of patients without cerebral infarction, time-related maps, such as MMT and time to peak, showed a perfusion deficit, whereas CBF showed a perfusion deficit in 5% of the patients without infarction.11 Our results indicate that infratentorial perfusion deficits, which sometimes are regarded as false-positive, can actually have a pathophysiologic background. However, one has to keep in mind that time-related maps are particularly susceptible for perfusion alterations and always have to be interpreted along with CBF and CTA. This particularly holds true if qualitative relative assessment method in comparison with the contralateral side is being chosen. To date, it has been shown that the frequency of V AH is increased in patients with PCI, suggesting that V AH confers an increased probability of ischemic stroke.5–7,13 It has been demonstrated that V AH is associated with PICA and lateral medullary infarctions.4,7,8,26 The authors attributed the underlying mechanism to atherosclerosis of the V AH because of abnormal hemodynamics.7 Park et al4 found that patients with V AH were more susceptible to stenosis of the distal VA. This was considered to relate to the slow blood flow in the VA, which might increase the susceptibility to thrombosis and poor clearance of thrombi resulting in stenosis of the distal artery. Our results indicate that, in addition to the mechanisms mentioned above, a pre-existing relative hypoperfusion of the PICA territory caused by V AH might confer to the pathogenesis of cerebellar infarcts. Future studies should address whether patients with a pre-existing PICA hypoperfusion indeed have an increased risk for PCI and represent a high-risk collective among patients with V AH.

The present study has limitations. First, perfusion deficits were assessed visually by 2 readers without the use of quantitative tools. The determination of reliability and reproducibility might be the subject of additional studies. Our approach, however, reflects clinical practice in stroke CTP reading. As we could also detect CTP deficits in patients without V AH, artifacts were probably present, potentially resulting in an overestimation of the hemodynamic effect of V AH. Another possible explanation for regional perfusion alterations might be a crossed cerebellar diaschisis, which might lead to a cerebellar hypoperfusion in patients with acute supratentorial stroke.27

Second, we acknowledge that cerebellar arterial anatomy is variable among individuals,28,29 and that there is a considerable interindividual variability of the PICA territory.30 Even though we used a high-resolution CTA for the assessment of the vascular tree, we cannot entirely rule out that small vascular variants or large interindividual differences might have influenced the results. Third, the study was not conducted in healthy subjects but in patients who were admitted to our hospital because of suspected stroke. This might constitute a selection bias with overestimation of V AH frequency, provided that the patients of our sample generally had a worse vascular status. Finally, the study was designed as a retrospective single-center study. More detailed prospective studies with larger cohorts are, therefore, necessary to determine the pathophysiological and causative relationship between V AH and PCI. With respect to concerns on radiation exposure, however, a corresponding prospective study could not use functional CT but should use other imaging methods, such as MRI.

Conclusions

Our study shows that V AH is a common vascular variant with a prevalence of 15.6% in patients with suspected stroke. V AH is associated with a relative hypoperfusion in the dependent PICA territory in $\leq 42\%$ of the patients, as identified by WB-CTP. Additional studies are required to determine the pathophysiological relevance of V AH for PCI further and whether the assessment of cerebellar perfusion using CTP allows the identification of a high-risk subset among patients with V AH.

Disclosures

None.

References

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