Hemodynamic Features of Symptomatic Vertebrobasilar Disease

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Background and Purpose—Atherosclerotic vertebrobasilar disease is an important cause of posterior circulation stroke. To examine the role of hemodynamic compromise, a prospective multicenter study, Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS), was conducted. Here, we report clinical features and vessel flow measurements from the study cohort.

Methods—Patients with recent vertebrobasilar transient ischemic attack or stroke and ≥50% atherosclerotic stenosis or occlusion in vertebral or basilar arteries (BA) were enrolled. Large-vessel flow in the vertebrobasilar territory was assessed using quantitative MRA.

Results—The cohort (n=72; 44% women) had a mean age of 65.6 years; 72% presented with ischemic stroke. Hypertension (93%) and hyperlipidemia (81%) were the most prevalent vascular risk factors. BA flows correlated negatively with percentage stenosis in the affected vessel and positively to the minimal diameter at the stenosis site (P<0.01). A relative threshold effect was evident, with flows dropping most significantly with ≥80% stenosis/occlusion (P<0.05). Tandem disease involving the BA and either/both vertebral arteries had the greatest negative impact on immediate downstream flow in the BA (43 mL/min versus 71 mL/min; P=0.01). Distal flow status assessment, based on an algorithm incorporating collateral flow by examining distal vessels (BA and posterior cerebral arteries), correlated neither with multifocality of disease nor with severity of the maximal stenosis.

Conclusions—Flow in stenotic posterior circulation vessels correlates with residual diameter and drops significantly with tandem disease. However, distal flow status, incorporating collateral capacity, is not well predicted by the severity or location of the disease. (Stroke. 2015;46:1850-1856. DOI: 10.1161/STROKEAHA.115.009215.)

Key Words: magnetic resonance angiography ■ magnetic resonance imaging ■ regional blood flow ■ stroke ■ vertebrobasilar ischemia

Large-vessel atherosclerotic disease of the vertebrobasilar system, both intracranial and extracranial, is a significant cause of posterior circulation stroke, accounting for approximately one third of ischemic events in this territory.1,2 Symptomatic vertebrobasilar disease carries a high annual risk of recurrent events, averaging 10% to 15% per year, despite medical therapy.3-6 In addition to thromboembolism as a contributing factor, regional hypoperfusion is considered an important potential contributor to stroke risk in vertebrobasilar disease.7 Evaluation of hemodynamic status has been traditionally limited to assessment of tissue perfusion in anterior circulation disease, with imaging techniques which translate poorly into assessment of the more compact posterior circulation territory.8 Retrospective data, however, suggest that...
measurement of large-vessel flow using quantitative magnetic resonance angiography (QMRA) provides a useful surrogate for hemodynamic assessment in the posterior circulation and may be predictive of future stroke risk.9

To examine the use of QMRA in assessment of hemodynamic compromise and prediction of stroke risk in symptomatic vertebral disease, a prospective observational multicenter study, Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) was undertaken.10 In this article, we evaluate the affected vessel, immediate downstream and distal hemodynamic impact of vertebral disease.

Methods

Study Design
Details of the VERiTAS study design have been previously published.10 Briefly, the study is a multicenter prospective cohort study of patients with ≥50% extracranial or intracranial atherosclerotic vertebral basilar stenosis or occlusion based on conventional digital subtraction angiography (DSA) or computed tomographic angiography presenting with referable vertebral basilar distribution transient ischemic attack (TIA) or stroke within 60 days. The clinical criteria for enrollment are further detailed in Methods in the online-only Data Supplement. In addition to standard clinical assessments, eligible patients underwent QMRA imaging to assess their cerebrovascular hemodynamic status; the results of this imaging were interpreted centrally as low or normal distal flow status and kept blinded from the treating clinicians. The patients were prospectively followed up on medical regimens consistent with national guidelines for a minimum of 1 year, up to a planned maximum of 2 years, and evaluated for recurrent ischemic events. The study was approved by the local institutional review boards, and all subjects provided informed consent.

After the initiation of the study, interim analysis of flow and angiographic data after enrollment of the initial 35 patients resulted in 2 additional exclusion criteria, as follows. First, interim analysis of distal flow status revealed a 4:1 ratio of normal flow to low flow subjects when compared with the 2:1 ratio, which had been used in initial sample size calculations; thus, decision was made to exclude further enrollment of patients with unilateral vertebral disease (stenosis or occlusion) because distal flow status in such previously enrolled subjects was normal in the vast majority (8:1 ratio). Second, interim review of angiographic data raised concern that subjects already enrolled with unilateral vertebral occlusion as the only finding on imaging could not reliably be distinguished as atherosclerosis or dissection as the underlying cause; given the differing prognostic and potential stroke mechanisms of these 2 entities, an exclusion criteria was imposed to exclude from subsequent analyses all patients with unilateral vertebral occlusion in the absence of concomitant basilar disease.

Baseline Study Assessments

Baseline Evaluation
Standard neurological evaluation was performed, and data gathered including demographic information, nature and frequency of cerebral ischemic events, medications at the time of enrollment, vascular risk factors, and available laboratory and imaging data. Hypertension was defined as self-reported history or use of antihypertensive medication; diabetes mellitus was defined as self-reported history or use of insulin or oral hypoglycemic treatment; hyperlipidemia was defined as self-reported history or current treatment with lipid-lowering therapy; coronary artery disease was defined as reported history of myocardial infarction, angina pectoris, positive stress test, or cardiac surgery/intervention; renal dysfunction was defined as chronic renal failure (need for dialysis) and chronic renal insufficiency (as per criteria of the National Kidney Foundation for chronic kidney disease including decreased glomerular filtration rate for ≥3 months). Smoking history was obtained and specified as current (smoked within the past 12 months), former (not within past 12 months, but smoked for >1 year previously), or never. Alcohol intake history was recorded as number of drinks per day in the past year. Body mass index was calculated from recorded height and weight data and classified as normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), class 1 obesity (30–34.9 kg/m²), class 2 obesity (35–39.9 kg/m²), or class 3 obesity (≥40 kg/m²).

Enrollment angiographic data (DSA or computed tomographic angiography) was centrally reviewed by a blinded interventional neuroradiologist for final determination of degree of stenosis using the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) method,11 further detailed in Methods in the online-only Data Supplement. Measurements of residual lumen and vessel diameters were obtained from site review of the angiographic imaging.

Magnetic Resonance Imaging
A magnetic resonance imaging protocol including QMRA was performed within 7 to 14 days of enrollment using a standardized protocol on a 3 Tesla MR scanner. The QMRA portion of the imaging was performed with a protocol using noninvasive optimal vessel analysis (VasSol, Inc) software as previously described12 and is further detailed in Methods in the online-only Data Supplement. Flow measurements were performed on prespecified locations of each major cerebral artery, including the vertebral arteries (VA, straight segment proximal to posterior inferior cerebellar artery), basilar artery (BA, proximal to superior cerebellar arteries, distal to stenosis if present), and posterior cerebral arteries (P2 segment distal to the posterior communicating arteries). The study was remotely supervised at the time of the imaging by a certified noninvasive optimal vessel analysis technician to ensure correct parameters and vessel placement for flow measurement, and the data were transferred automatically via secured internet-based transfer to the clinical coordinating center at University of Illinois at Chicago for central review. The results of the imaging remained blinded to the patient and participating site personnel including the evaluating study physician.

Hemodynamic Analysis

Anterograde flow in the affected vessel was examined relative to degree of stenosis and minimal vessel diameter at the site of stenosis using correlation analysis for patients with exclusively VA or BA stenosis. Any vessels with retrograde flow were designated as 0 mL/min anterograde flow for the purposes of this analysis (BA: n=3; VA, n=2). VA or BA occlusions were excluded from this correlation analysis, which aimed to assess the impact of stenosis on anterograde local flow. Similarly, any patients with tandem VA and BA disease were excluded from this analysis because the flow in the affected vessel would be influenced not only by that vessel’s disease but also by the tandem disease.

Next, anterograde immediate downstream flow in the BA was assessed by examining the BA flow in all subjects, including those with BA or VA occlusion and tandem disease. Retrograde flow was designated as 0 mL/min anterograde flow (BA, n=5). For purposes of analyzing the relationship of immediate downstream flow to severity of disease, subjects were characterized as moderate (50%–69%), severe (70%–99%), or occlusion based on their most severe disease in either the VA or BA.

Finally, distal flow status was assigned for all subjects as a measure of regional flow, and designated as low or normal based on a previously published algorithm (Figure 1 in the online-only Data Supplement) defining flow compromise as ≥20% reduction below normative lower limits of flow in distal vessels, namely the BA and posterior cerebral arteries. Conceptually, the algorithm incorporates any sources of collateral flow (eg, via the posterior communicating arteries) by their effect on the blood flow within these distal vessels.
Statistical Analysis
After completion of study enrollment, aggregate clinical data were collated from the baseline assessments. Clinical presentation relative to disease location, severity, and flow status was assessed using \( \chi^2 \) analysis with Fisher exact test where appropriate. The relationship between degree of stenosis/diameter and blood flow in the affected vessel was assessed using Pearson correlation analysis; the relationship was also examined using linear regression analysis. The impact of increasing degrees of stenosis was evaluated using \( t \) test. Downstream flow rates in the BA were averaged, and comparisons relative to location and severity of disease performed using \( t \) test or analysis of variance methods with post hoc Tukey test, where appropriate; flow status comparisons were performed using \( \chi^2 \) analysis with Fisher exact test. A value of \( P<0.05 \) was considered significant. All analysis was performed with SAS (version 9.4; SAS Institute, Cary, NC).

Results

Study Population
The study was open for enrollment from August 2008 to July 2013, with an initial target sample size of 80 patients. During this period, 200 patients were screened, 89 of whom meet eligibility criteria, and 82 of whom consented to participate and were enrolled. After central angiographic review, 8 patients with unilateral vertebral occlusions were excluded, and an additional patient was determined to have a vertebrobasilar junction fenestration, rather than atherosclerotic stenosis; 1 patient with angiographic basilar occlusion at time of enrollment demonstrated complete resolution of the occlusion without evidence of underlying atherosclerotic disease on baseline QMRA imaging and was excluded. Consequently, 72 patients with centrally adjudicated atherosclerotic vertebrobasilar disease \( \geq 50\% \) comprised the study cohort analyzed.

Baseline Characteristics
Demographics and Vascular Risk Factors
The cohort consisted of 40 (56\%) men, with mean age of 65.6 (median, 65.7; range, 40–90) years. Baseline characteristics, including race, ethnicity, and vascular risk factors are outlined in Table 1. Both hypertension and hyperlipidemia were present in a majority of patients, as well as elevated body mass index.

Angiographic Characteristics
DSA was performed in 44 (60\%) cases as enrollment imaging when compared with computed tomographic angiography in the remaining cases (except 1 patient who had previously undergone DSA, but the only imaging at time of qualifying event was MRA). The profile of vertebrobasilar vessel involvement is outlined in Table 1. The majority of patients harbored only intracranial disease (78\%), with predominantly exclusive basilar artery disease (40\%). In terms of the worst disease severity in a given patient, severe stenosis (70–99\%) was predominant, accounting for 44\% of the cohort.

Clinical Presentation
With regard to their qualifying event, 52 (72\%) patients presented with stroke, and the rest with TIA. Stroke was confirmed by imaging in the vast majority of patients (n=49); in the remaining minority and those with diagnosis of TIA, all patients presented with a constellation of symptoms consistent

| Table 1. Baseline Clinical and Angiographic Characteristics |
|--------------|-----------------|
| Characteristics | n=72 (\%) |
| Mean age, y | 65.6±10.3 |
| Sex | |
| Men | 40 (56) |
| Women | 32 (44) |
| Race | |
| Black | 18 (25) |
| White | 49 (68) |
| Other | 5 (7) |
| Ethnicity | |
| Hispanic or Latino | 64 (89) |
| Not Hispanic or Latino | 8 (11) |
| Qualifying event | |
| Stroke | 52 (72) |
| TIA | 20 (28) |
| History of previous posterior circulation event (\%) | 42 (58) |
| Vascular risk factors | |
| Hypertension | 67 (93) |
| Diabetes mellitus | 23 (32) |
| Hyperlipidemia | 58 (81) |
| Coronary artery disease | 16 (22) |
| Chronic renal insufficiency/failure | 2 (3) |
| Smoking (\%) | |
| Never | 31 (43) |
| Former | 17 (24) |
| Current | 24 (33) |
| Alcohol use (\%) | |
| None | 44 (61) |
| <1 drink/d | 24 (33) |
| >1 drink/d | 4 (6) |
| BMI (\%) | |
| Normal | 13 (18) |
| Overweight | 33 (46) |
| Class 1–3 obesity | 26 (36) |
| Physical activity (\%) | |
| Exercise enough to raise a sweat at least twice/wk | 24 (33) |
| Vessel involvement | |
| Basilar only | 29 (40) |
| Vertebral only | 22 (30) |
| Unilateral | 7 |
| Bilateral | 15 |
| Basilar and vertebral (mixed) | 21 (29) |
| Intracranial or extracranial | |
| Intracranial only | 56 (78) |
| Extracranial only | 7 (10) |
| Both | 9 (12) |
| Disease severity: worst disease | |
| Occlusion | 24 (33) |
| Severe (70–99\% stenosis) | 32 (44) |
| Moderate (50–69\% stenosis) | 16 (22) |

BMI indicates body mass index; and TIA, transient ischemic attack.
with posterior circulation cause. Patients with vertebral-only disease presented with stroke slightly less frequently (59%) than those with basilar (76%) or vertebrobasilar involvement (81%), but not statistically significant (P=0.29). Patients with exclusively extracranial disease also presented with stroke less frequently (43%) than those with exclusively intracranial disease (75%) or both (78%), but this difference was not statistically significant (P=0.21). The severity of disease (occlusion versus severe versus moderate) did not impact the frequency of stroke as the presenting symptom nor did the distal flow status (P>0.50). The majority of patients presented with a symptom complex indicative of pontine syndrome (44%). The frequency of clinical syndromes relative to location of disease is shown in Table I in the online-only Data Supplement.

Forty-two (58%) patients had a history of a previous posterior circulation ischemic event (TIA or stroke). The majority of these previous stroke or TIAs occurred within 30 days of the qualifying event (Figure II in the online-only Data Supplement).

**Hemodynamic Assessment**

**Affected Vessel Flow**

Flows within the affected vessels were examined in patients with exclusively BA or VA stenosis, to evaluate the impact of the stenosis on proximate flow within the vessel. Flows correlated moderately well with degree of stenosis in the affected vessel for the BA (ρ=-0.49; P=0.01) but not for the VA (ρ=-0.09; P=0.66; Figure 1). For the BA, the largest and most statistically significant drop in vessel flow was first encountered at a threshold of 80% stenosis (P=0.02; Figure 2). The correlation between flow and the residual diameter at the site of stenosis was more robust and evident both in the BA (p=0.65; P<0.01 for BA) and in the VA (p=0.62; P<0.01; Figure 1).

**Immediate Downstream Flow**

The immediate downstream effect of stenosis was examined by assessing BA flow. Flow reduction was significantly related to severity of stenosis (P<0.01; Table 2). Tandem disease also had
a significant impact on downstream flow: 43 mL/min in multifocal disease (concomitant BA and VA) compared with 71 mL/min in the patients with only BA or only VA disease (P=0.01).

**Distal Flow Status**

Of the cohort, 18 (25%) patients were designated low flow based on the predetermined regional flow algorithm, which incorporates collateral flow. Unlike the immediate downstream flow, distal flow status was independent of tandem disease (Table 3). Similarly, distal flow status was largely independent of disease severity with 89% of low flow patients demonstrating severe stenosis or occlusion (≥70%) compared with 75% of normal flow patients (P=0.08; Table 3).

**Discussion**

We report here, for the first time, vessel flow measurements and clinical characteristics in a cohort of patients with symptomatic vertebrobasilar disease, correlated with severity and location of disease. Clinically, our cohort resembles those reported in other prospective studies of similar patients. Both a hospital-based cohort of 58 patients and a population-based cohort of 37 patients with ≥50% symptomatic vertebrobasilar stenosis demonstrate a similar mean age, and male predominance, with hypertension and hyperlipidemia as the most common vascular risk factors. Also similar to these previous studies, the majority of patients presented with stroke rather than with TIA. We did not find a significant relationship between presentation with stroke and disease location although exclusively VA or extracranial disease trended toward the less severe presentation of TIA. Interestingly, the severity of stenosis and distal flow status both showed no relationship to presentation. Over one half of our patients reported a previous posterior circulation ischemic event, primarily within the previous 30 days, in keeping with data reporting a high risk of recurrent stroke early after TIA or minor stroke in general.

In our hemodynamic analysis, we examined the impact of vessel stenosis in the posterior circulation in several ways: at the level of the affected vessel, downstream in the BA as the major conduit immediately distal to the vertebrobasilar disease, and finally, as a regional distal flow status incorporating collateral capacity. The importance of hemodynamics in predicting stroke risk has been evident in other settings. Even in carotid stenosis, where the underlying cause of recurrent stroke is widely considered to be thromboembolism, hemodynamic factors may be relevant. The hemodynamic impact of stenosis within a vessel was first postulated by Spencer and Reid as a curve that predicts no substantive decline in flow until ≥70% stenosis and a steep threshold in flow drop at ≥80% (Figure 3). Carotid stenosis risk seems to largely correspond to these thresholds, with moderate (50%–69%) stenosis having a more benign prognosis than severe stenosis, and a progressive increase in stroke risk with higher degrees of stenosis beyond 70%. However, flow restriction within the affected vessel may ultimately be less relevant than distal regional flow. In this regard, the importance of collaterals in influencing stroke risk has been demonstrated in the setting of both carotid disease and intracranial stenosis. Post hoc analysis of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) data demonstrated that even in patients with severe stenosis, the relative rate of recurrent stroke was much lower in patients with robust collaterals than those without angiographic collaterals. Similarly, in subsequent analysis of patients with both anterior and posterior circulation intracranial stenosis from the WASID trial, angiographic collaterals had a marked influence on stroke risk, with good collaterals significantly reducing risk in those with severe stenosis.

Recent data from large-vessel flow measurements in carotid disease further support the importance of regional flow by demonstrating that flow compromise in the distal territory measured in the middle cerebral artery territory was more frequently associated with symptomatic presentation, whereas flow decline in the internal carotid alone was not predictive.

In our cohort, we established that flows in affected vessels correlate with residual diameter and stenosis, as would generally be expected, but has not been previously demonstrated in the posterior circulation. The relationship was strongest with diameter, and only evident with stenosis in the BA but not in the VAs. This latter finding likely reflects the frequent variability encountered in VA size, where asymmetries in luminal diameter are not uncommon. As such, the same percentage stenosis leads to a markedly smaller residual diameter in a hypoplastic 2-mm vertebral compared with a dominant 5-mm VA and likely accounts for the lack of correlation between flow and percentage stenosis in the VA. In the BA, although flow declines with increasing stenosis, our data further support the tenets of the curve of Spencer and Reid, by demonstrating the most significant drop in flows at the 80% stenosis threshold.

When looking at the immediate downstream flow in the BA in the full cohort, both severity of disease and tandem...
stenosis have a significant impact. Contrary to this, however, hemodynamic assessment of the distal flow status in the posterior circulation, which incorporates the contribution of any large-vessel collateral flow, is not well predicted by either the severity or the location of the disease. Thus, we illustrate for the first time in the posterior circulation that the distal flow status provides a hemodynamic assessment, which, by incorporating collateral capacity, is distinct from anatomic measures such as stenosis and diameter and, as such, can be independent of the local hemodynamic impact of the disease. The importance of distal flow status in predicting stroke risk, when compared with the traditional reliance on anatomic features such as stenosis severity, has preliminary support from previous data: in a retrospective single center cohort of 48 patients with >50% vertebrobasilar stenosis or occlusion, patients designated as low distal flow status demonstrated a significantly worse stroke-free survival of 71% at 24 months compared with 100% stroke-free survival in the normal distal flow status group. On multivariate analysis, distal flow status remained an independent predictor of recurrent stroke after adjusting for stenosis severity and location of disease. Although compelling, such retrospective data have drawbacks that limit definitive conclusions. The ultimate determination of the relevance of this form of hemodynamic assessment to predicting stroke risk will be available from future outcome data from the prospective VERiTAS cohort.

**Limitations**
The patients in this study are a selected population, rather than representing a population-based cohort; however, their demographic and clinical characteristics resemble other published prospective series. Only stenosis, and not diameter, was centrally adjudicated because of inability to perform reliable absolute vessel measurements from centrally transmitted images; the lack of central verification and the use of both DSA and computed tomographic angiography images may introduce some inaccuracies or variability in the diameter measurements. Patients with unilateral VA disease in the cohort may skew assessments of immediate downstream flow or distal flow status because even severe stenosis or occlusion in just 1 VA is less likely to impact distal flow and could dilute an otherwise predictive value of severe disease on these parameters; however, unilateral VA occlusions were excluded from the cohort, and unilateral VA stenosis was limited by the eligibility criteria such that these cases comprise <10% of the cohort. Vessel flows can potentially be affected by systemic factors, such as blood pressure, for which our flow data have not been adjusted because of lack of standardized blood pressure measurements at the time of QMRA imaging. Although data from healthy volunteers suggest that intracranial blood flow is not affected by blood pressure, it is possible that in this cohort with underlying cerebrovascular disease and a high prevalence of preexisting hypertension, autoregulation is altered, with flows affected by blood pressure variation.

**Conclusions**
Flow in stenotic posterior circulation vessels correlates with residual diameter and stenosis and drops most significantly when stenosis exceeds 80%, or in the setting of tandem disease. However, distal flow status, incorporating collateral capacity, is not well predicted by the severity or location of the disease. Final clinical outcome results from the VERiTAS study will further clarify the relevance of hemodynamic assessment to predicting stroke risk in patients with vertebrobasilar disease.

**Appendix**

**VERiTAS Study Group**
Clinical Coordinating Center: University of Illinois at Chicago—PI: Sepideh Amin-Hanjani, MD, and Project Manager: Linda Rose-Finnell, MPA, CCRA. Data Management Center: Center for Stroke Research, University of Illinois at Chicago—Director: DeJurian Richardson, PhD, and Dilip Pandey, MD, PhD; Biostatisticians: Xinjian Du, MD, MPH, and Hui Xie, PhD; Database Administrator: Xinjian Du, MD, MPH. Participating sites (in descending order of number of enrollees): University of Illinois at Chicago—Site PI: Sepideh Amin-Hanjani, MD; Project Manager: Linda Rose-Finnell, MPA, CCRA; Site MR Team: Keith Thulborn, MD, PhD, Michael P. Flannery, and Hagai Ganin; Study Physician(s): Sean Ruland, DO, Rebecca Grysiewicz, DO, Aslam Khaja, MD, Laura Pedelty, MD, Fernando Testai, MD, Archie Ong, MD, Noam Epstein, MD, Humima Muqtadar, MD; Coordinator(s): Karriem Watson, MD, Nada Mlinarevich, RN, and Maureen Hillmann.
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Disclosures
Dr Amin-Hanjani received material research support (no direct funds) from GE Healthcare and VasSol, Inc. Dr Liebeskind is a consultant for Stryker, Coviden. Dr Derdeyn is a consultant for Microvention, Silk Road, Penumbra; serves on Scientific Advisory Board, Pulse Therapeutics; stock options in Pulse Therapeutics. Dr Gorelick served as the founder and director/codirector of the Clinical Coordinating Center for the Lundbeck sponsored Desmoteplase in Acute Ischemic Stroke (DIAS 4) trial. Dr Charbel has financial interest in VasSol, Inc.

References
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on behalf of the VERiTAS Study Group

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SUPPLEMENTAL MATERIAL

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Supplemental Methods

Eligibility criteria
Inclusion Criteria:
1. Symptomatic (TIA or stroke) in the vertebrobasilar territory*.
2. Conventional angiography or CTA demonstration of ≥ 50% stenosis or occlusion of extracranial or intracranial vertebrobasilar artery.
3. Symptoms within 60 days of enrollment.
4. Age 18 and above.
5. Able to provide informed consent.

Exclusion Criteria:
1. Neurologic criteria:
   • Major disabling stroke prohibiting return for follow-up assessment.
   • Any neurological disease which would confound follow-up assessment.
2. Medical criteria:
   • Any severe co-morbidity condition with <12 month life expectancy.
   • Known cardiac disease associated with cardioembolic risk e.g. atrial fibrillation, prosthetic valves, endocarditis, left atrial/ventricular thrombus, cardiomyopathy with EF<25%, cardiac myxoma.
   • Blood dyscrasias e.g. polycythemia vera, essential thrombocytosis, sickle cell disease.
3. Disease criteria:
   • Non-atherosclerotic disease vertebrobasilar disease including dissection, fibromuscular dysplasia, vasculitis, radiation induced vasculopathy.
   • Unilateral vertebral disease**
4. Patient criteria:
   • Unable or unwilling to undergo MRI.
   • Unable to undergo conventional angiography or CTA
   • Pregnancy.
   • Concurrent participation in interventional trial for treatment of vertebrobasilar disease.

*Symptoms or signs indicative of vertebrobasilar circulation ischemia were defined as outlined by the Special Report from the National Institute of Neurological Disorders and Stroke, Classification of Cerebrovascular Diseases III, as follows:
   a. Motor dysfunction (weakness, paralysis, or clumsiness) of any combination of upper and lower extremities and face, left and/or right.
   b. Sensory symptoms (loss of feeling, numbness, or paresthesia) involving the left, right, or both sides.
   c. Loss of vision in one or both homonymous visual fields.
   d. Loss of balance, vertigo, unsteadiness or disequilibrium, diplopia, dysphagia, or dysarthria.

Ischemic stroke in the vertebrobasilar territory was characterized by new infarct on CT or MR in a region of brain supplied by the vertebrobasilar system, or (in the absence of an infarct on brain imaging) defined clinically as the above symptoms/signs lasting at least 24 hours.
Vertebrobasilar system TIA was characterized by the rapid onset of the above symptoms/signs
lasting less than 24 hours. Loss of balance, vertigo, unsteadiness, or disequilibrium, diplopia
dysphagia or dysarthria, although characteristic were not considered as a TIA when any of these
symptoms occurred alone. The presenting stroke or TIA symptoms were required to be within
the territory of the qualifying vertebrobasilar disease for inclusion criteria to be met.

**Additional exclusion criteria added after initiation of study to exclude further enrollment of
patients with unilateral vertebral stenosis or occlusion, and to exclude all prior patients with
unilateral vertebral occlusion in the absence of concomitant basilar disease form subsequent
analysis due to uncertainty of underlying disease process (atherosclerosis vs dissection)

**Angiographic Data**
Enrollment angiographic data (CTA and DSA) were centrally reviewed per the WASID criteria²,
as follows:

\[ \% \text{ stenosis} = \left[ 1 - \frac{D_{\text{stenosis}}}{D_{\text{normal}}} \right] \times 100, \]

where

- \(D_{\text{stenosis}}\) = the diameter of the artery at the site of the most severe stenosis
- \(D_{\text{normal}}\) = the diameter of the normal artery, determined by the following criteria:
  1\text{st choice}: the diameter of the proximal part of the artery at its widest, non-tortuous,
normal segment
  2\text{nd choice}: if the proximal artery is diseased (e.g. origin stenosis), the diameter of the
distal portion of the artery at its widest parallel, non-tortuous normal segment
  3\text{rd choice}: if the entire intracranial artery is diseased, the most distal, parallel, non-
tortuous normal segment of the feeding artery

**QMRA technique**
All subjects underwent phase contrast quantitative magnetic resonance angiography (QMRA)
performed on a 3.0 Tesla magnetic resonance (MR) system. The volume flow rate measurements
were acquired with the Noninvasive Optimal Vessel Analysis (NOVA) software (VasSol, Inc.,
River Forest, IL)³. To visualize the vessels, a 3D MRA TOF of the head was first obtained. The
following parameters were used for GE systems (equivalent parameters were used for Siemens
and Phillips MR machines): TR/TE, 23/3.3 ms; flip angle, 20; FOV, 200mm; section thickness,
1mm; matrix, 512 X256. MRA TOF images were received by the NOVA software on a separate
workstation in order to reconstruct a 3D surface-rendering of the vasculature for determining the
perpendicular scan plane to vessels of interest. Volume flow measurements based on these
positions were performed (TR, 10-13ms; TE, 4-7ms; flip angle, 15; NEX, 4; slice thickness, 5
mm for carotid, 4 mm for basilar and 3 mm for all other vessels; FOV, 160 mm for vertebral and
carotid arteries, and 140 mm for all other arteries; matrix, 256x128 for carotid, and 256x192 for
all other arteries. Velocity encoding was automatically adjusted by the NOVA software. All
QMRA flow measurements were performed using an oblique 2D fast phase contrast sequence
with retrospective gating. Volumetric flow rate (ml/min) in each artery was processed on the
NOVA workstation after phase contrast images had been acquired.
Supplemental Table

Table I: Posterior circulation TIA/stroke syndromes*

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Basilar only</th>
<th>Vertebral only</th>
<th>Basilar and Vertebral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major basilar artery syndrome</td>
<td>6 (21%)</td>
<td>2 (9%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Midbrain syndrome</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Pontine syndrome</td>
<td>17 (59%)</td>
<td>5 (23%)</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Medullary syndrome</td>
<td>1 (3%)</td>
<td>5 (23%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Pure cerebellar</td>
<td>4 (14%)</td>
<td>5 (23%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Other Posterior Circulation syndrome</td>
<td>1 (3%)</td>
<td>4 (18%)</td>
<td>3 (14%)</td>
</tr>
</tbody>
</table>

*Assignment of syndrome based on best clinical impression of site investigator
Supplemental Figures

Figure I

Flow algorithm for designation of distal flow status (reprinted with permission from Amin-Hanjani et al, Stroke, 2005;36:1140-1145):

*In the case of fetal PCAs, determination of flow status is as follows: if one PCA is fetal, only the flow in the non-fetal PCA is considered; if both PCAs are fetal, only flow in the BA is considered (low flow if <40 cc/min)

¶ Additional criteria in borderline cases: ominous BA flow waveform oscillating around zero, ominous symptom complex (symptoms exacerbated with change in position, related to effort or exertion, or related to recent (<7 days) introduction or increase of an antihypertensive agent), or flow in non-occluded proximal BA <40 cc/min.

Note: Within the described cohort, 8 of 72 patients were borderline cases and required use of additional criteria for designation of final flow status.
Figure II

Distribution of the time interval between most recent posterior circulation event and qualifying event in those presenting with recurrent symptoms (n=42).
Supplemental References