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Natural history of hemodynamics in vertebrobasilar disease: temporal changes in the VERiTAS Study cohort

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Abstract

Background and Purpose: The role of regional hypoperfusion as a contributor to stroke risk in atherosclerotic vertebrobasilar (VB) disease has recently been confirmed by the observational Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) Study. We examined the stability of hemodynamic status over time and its relationship to stroke risk in patients from this prospective cohort.

Methods: VERiTAS enrolled patients with recently symptomatic ≥50% atherosclerotic stenosis/occlusion of vertebral and/or basilar arteries. Large vessel flow in the VB territory was assessed using quantitative magnetic resonance angiography (QMRA), and patients were designated as low or normal flow based on distal territory regional flow, incorporating collateral capacity. Patients underwent standard medical management and follow-up for primary outcome event of VB

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Supplemental Materials:
Supplemental methods
Supplemental table
Study Group listing

territory stroke. QMRA imaging was repeated at 6, 12 and 24 months. Flow status over time was examined relative to baseline, and relative to subsequent stroke risk using a cause-specific proportional hazard model, with flow status treated as a time-varying covariate. Mean blood pressure was examined to assess for association with changes in flow status.

Results: Over 19±8 months of follow-up, 132 follow-up QMRA studies were performed in 58 of the 72 enrolled patients. Of 13 patients with serial imaging who had low flow at baseline, 7 (54%) had improvement to normal flow at the last follow-up. Of the 45 patients who had normal flow at baseline, 3 (7%) converted to low flow at the last follow-up. The mean blood pressure did not differ in patients with or without changes in flow status. The time-varying flow status remained a strong predictor of subsequent stroke (hazard ratio HR 10.3, 95% CI 2.2 – 48.7).

Conclusions: There is potential both for improvement and worsening of hemodynamics in patients with atherosclerotic VB disease. Flow status, both at baseline and over time, is a risk factor for subsequent stroke, thus serving as an important prognostic marker.

Clinical Trial Registration -—URL: https://clinicaltrials.gov. Unique identifier: NCT00590980.

Keywords

Vertebrobasilar disease; Atherosclerosis; Magnetic resonance angiography; Flow measurement

Subject terms:

Atherosclerosis; Imaging; Ischemic Stroke; Magnetic Resonance Imaging (MRI); Stenosis

Introduction

Posterior circulation strokes account for approximately 30% of all ischemic strokes, a prominent source of which is vertebrobasilar (VB) atherosclerotic disease.[1–4] The role of regional hypoperfusion as an important contributor to recurrent stroke risk in atherosclerotic VB disease has recently been highlighted by the observational Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) study.[5] Patients with recently symptomatic atherosclerotic VB disease and hemodynamic impairment in the posterior circulation were found to have a five-fold risk of subsequent stroke (22% vs 4%) at 1 year compared to those without hemodynamic impairment. This finding echoes the increased risk of stroke associated with hemodynamic compromise in occlusive diseases affecting the anterior circulation, including carotid occlusion.[6–8]

Previous studies have demonstrated the capacity for improvement in cerebral hemodynamic impairment over time in the setting of carotid disease.[9–11] Based on the VERiTAS Study cohort, we sought to determine if VB disease has the same potential for temporal evolution in hemodynamic status and whether such changes impacted VB stroke risk.

Methods

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Patient Cohort

The design, cohort characteristics and primary results of the VERiTAS study have been previously published.[12,13] Briefly, patients presenting with VB distribution transient ischemic attack (TIA) or stroke and ≥ 50% vertebral and/or basilar stenosis at five North American centers were prospectively enrolled over a five year period. Stenosis was documented on conventional or computed tomographic angiography. Cases of dissection, fibromuscular dysplasia, vasculitis, radiation-induced vasculopathy, or other non-atherosclerotic disease were excluded, as were cases with known cardioembolic stroke risk or hematologic dyscrasias. At the time of enrollment, blinded quantitative magnetic resonance angiography (QMRA) measurement of flow was performed at pre-specified locations in the vertebral artery (VA), basilar artery (BA), and posterior cerebral artery (PCA) to evaluate hemodynamic status. QMRA was performed with a standardized protocol using commercially available noninvasive optimal vessel analysis (NOVA, VasSol Inc., River Forest, IL) software to process and analyze time of flight and phase contrast imaging to provide flow measurements in vessels of interest, as previously described[12] (please see supplemental methods, https://www.ahajournals.org/journal/strsupplement). Patients were followed for a minimum of 12 months, and up to 24 months, blinded to QMRA results, while receiving standard maximal medical therapy, as recommended by published guidelines at the time.[14–17] This entailed an antithrombotic regimen (aspirin 50–235 mg/day monotherapy, aspirin with dipyridamole, or clopidogrel monotherapy), antihypertensive therapy (goal <140/90 mmHg or 130/90 mmHg with diabetes mellitus or chronic kidney disease), anti-lipid therapy (target LDL-C <100 mg/dL, or <70 mg/dL with multiple risk factors), diabetes therapy (target HbA1c <7.0%), and counseling for smoking cessation, diet, and physical activity. Follow-up QMRA imaging was scheduled at 6, 12, and up to 24 months. The study was approved by the local institutional review boards, and all subjects provided informed consent.

Flow status designation

Low flow was designated *a priori* as more than 20% reduction below normative lower limits of flow in the BA (<120 cc/min) or PCA (<40 cc/min).[18] The PCA flow was not considered in flow status determination if the PCA anatomy was fetal (determined based on absent P1 on QMRA). In patients with reduced distal demand from bilateral fetal PCAs, the BA flow threshold was adjusted to <40 cc/min. In patients with two normal-configuration PCAs but flow in one PCA below the normative limit and flow in the other PCA above the normative limit, flow status was considered borderline and additional clinical and radiographic criteria were applied to determine the flow status as low versus normal.

Interval flow status

Serial flow status evaluations were compared for individual patients to determine the rate of improvement or worsening. Interval QMRAs were scheduled at pre-specified 6, 12, and 24

months of follow-up. Not all follow-up QMRAs occurred according to this schedule, but were included for analysis at the time of acquisition. Further clinical and radiographic assessments were censored at the time of subsequent VB territory stroke.

Blood pressure

To determine if blood pressure (BP) management influences change of flow status over time, we compared mean systolic BP (SBP) and diastolic BP (DBP) between patients who had a different flow state at last follow-up than at the baseline QMRA, and patients with the same flow state at last follow-up. Each patient's BP was measured at pre-specified 6 month interval clinic follow-ups during trial participation. Recordings were made with the patient sitting at rest for ≥5 minutes with the arm supported at the level of the heart. If the initial BP reading was >140/90 mm Hg, a second reading was taken at the end of the visit and the lower of the two readings was recorded. BP recordings for each patient were averaged over the study period; only BPs recorded prior to a primary endpoint of VB territory stroke were included.

Statistical Analysis

Flow status over time was examined relative to baseline, and relative to subsequent stroke risk. The predictive value of flow status at the time of enrollment (baseline) was previously analyzed and reported by comparing the group with low baseline flow and normal baseline flow using Cox proportional hazards regression modeling.[5] To assess the predictive value of interval QMRA over time, serial QMRA flow measurements were considered as a time varying covariate over the subsequent follow-up intervals in addition to the baseline until an event or the end of the study occurred. The results were reported as hazard ratio (HR) with its 95% confidence interval and p-value. This analysis was repeated with adjustment for baseline age, coronary artery disease, diabetes mellitus, and physical activity, which were found to be predictors in the previously reported study.[5] A Nelson-Aalen approach was used to estimate the cumulative hazards at 30 and 180 days.[19] This analysis was conducted in R version 3.4.1 (Vienna, Austria) by using 'survival' and 'mvna' packages, and $p<0.05$ was considered as statistical significance.[20–22]

The mean SBP and DBP were compared using a two-tailed independent t-test with no assumptions regarding the variance of the groups using SAS software (SAS Institute Inc., Cary, NC, USA).

Results

The VERiTAS cohort consisted of 72 patients with a mean age of 65.6±10.3 years, with 44% female, 25% black race and 11% Hispanic/Latino ethnicity.[5,13] 18 patients had low flow and 54 patients had normal flow at baseline imaging. There were 132 follow-up QMRA studies during the study period in 58 of the 72 enrolled subjects. Follow-up imaging was not obtained in 14 patients: 6 suffered primary endpoint prior to the scheduled follow-up imaging and were censored, 1 patient died a non-vascular death prior to interval imaging, 6 continued clinical follow-up but were unable to return for MRI or developed a

contraindication to MRI, and 1 patient was lost to follow-up due to withdrawal from the study.

Over 19±8 months of follow-up, 7 of the 13 low flow patients (54%) with follow-up imaging had improved their flow status (low at baseline to normal at final imaging follow-up, Figure 1A) while 3 of 45 normal flow patients (7%) had worsened (Figure 1B). The baseline demographics and vascular risk factors of these patients did not differ significantly from those without a change in flow status (see Supplemental Table I, https://www.ahajournals.org/journal/strsupplement) The 3 cases which converted to low flow all had multifocal disease involving the basilar and the vertebral arteries. In contrast, of the 7 cases that converted to normal flow from a baseline low flow state, only one had multifocal disease, and the remainder had focal single vessel stenosis/occlusion.

The mean BP over follow-up did not differ between patients who did or did not have a change in flow status. For patients with low flow at baseline QMRA, there was no difference in the mean BP of patients who remained in the low flow group compared to those who changed designation to a normal flow (SBP 142 vs. 139, DBP 77 vs. 77 mm Hg, $p>0.50$). A corollary finding was observed in the normal flow patients (SBP 143 vs. 141, DBP 80 vs. 76 in stable normal flow status vs. changing normal-to-low flow status, $p>0.50$)

Baseline flow status was previously demonstrated to be an independent stroke risk predictor in VERiTAS (Table 1).[5] After including flow status over follow-up, flow status remained a strong predictor of subsequent stroke (unadjusted HR 3.9, 95% CI 1.1–14.6), even when adjusting for age, coronary artery disease, diabetes, and physical activity (HR 10.3, 2.2–48.7, Table 1). The interval cumulative hazard of stroke for patients with low flow was 6% at 30 days and 11% at 6 months, compared to 0%, and 4%, respectively, for normal flow patients (Table 2).

Discussion

Flow status based on QMRA flow measurements is a validated binary state of characterizing hemodynamics in VB steno-occlusive disease which predicts subsequent stroke risk in the posterior circulation.[5] Our data indicate that VB flow status measured at baseline presentation often persists, but may also improve or worsen. This is similar to the carotid circulation, where hemodynamic compromise and stroke risk have been demonstrated in both preclinical and clinical studies to change over the course of several months.[9–11,23] In pre-clinical models and a subsequent prospective PET study, stroke-risk measures were more likely to improve than worsen.

Fundamentally, VB flow status designation in the VERiTAS cohort is dependent on distal territory flow, incorporating collateral capacity, so changes are presumed to reflect alterations in either primary or collateral flow. In general, several mechanisms could explain improvements in hemodynamic status.[24] Early studies demonstrated that there was improvement in carotid-circulation hemodynamic compromise over time, but were unable to distinguish between changes in metabolic demand versus changes in cerebrovascular supply.[9,25] PET measurements of metabolic rate subsequently demonstrated that improvement in

hemodynamics, when observed, was due to improving flow from compensatory collateral circulation.[11] In the setting of misery perfusion (increased oxygen extraction fraction (OEF) on PET), but in the absence of subsequent stroke or surgical intervention, the OEF improved over time, without changes in cerebral oxygen metabolic rate. This implied no changes in the metabolic demand, but suggested an increased supply. Although human studies have relied on inference regarding development of collaterals as the source of improved flow, murine models have directly observed increasing collateral supply over time in response to misery perfusion.[26] The current study supports, again by inference, a similar phenomenon in the VB circulation. It is notable that the cases which improved from low to normal flow status were predominantly single vessel disease, and thus potentially more capable of augmenting or recruiting collateral pathways over time. In contrast, the cases where flow status worsened from normal to low, the underlying VB disease was uniformly multifocal, which may limit the development of collaterals and make both the likelihood and consequences of progression of disease more unfavorable.

Regression of stenosis may also contribute to improved flow status. In studies using serial MRA or transcranial doppler measurements of intracranial stenosis, between 8–26% of cerebral arteries, including the basilar artery, have reduction of stenosis.[27–30] However, this improvement was observed over the course of 1–5 years, and the study focusing on basilar stenosis reported 20% interval ischemic stroke during 15 months of follow-up, with an annual stroke rate of 17%.[28] In our series, patients with VB stenosis and hemodynamic compromise had an 11% six-month cumulative hazard of stroke. Therefore, despite the potential for future improvement in stenotic disease and hemodynamic compromise, even the subset of patients who eventually improve are exposed to a window of particularly high recurrent stroke risk.

Regarding the cases of worsening hemodynamic compromise, this may reflect disease progression. There is little description of the anatomic natural history of VB stenosis. Although subsequent stroke risk has been characterized, interval anatomic imaging to evaluate progression of stenosis has not been performed by historic or recent larger scale studies.[1,2,31] A single center cohort of 153 patients found progression in 12% of patients with symptomatic basilar stenosis based on a mean 14.6 month follow-up MRA.[28] In the anterior circulation, similar single-center studies of 50–100 patients reported progression of stenosis in 8–22% of patients on MRA over 2–6 years.[27,30,32–34]

Apart from changes in collaterals and disease status, it is possible that, given perturbations in autoregulatory mechanisms in chronic cerebrovascular occlusive disease states, alterations in blood pressure could impact flow status.[35] In this cohort, all patients were managed to a target normotensive range as dictated by guidelines of that era, and average BP over follow-up was no different in patients who changed flow status. This suggests that differential BP management was not a major contributor to flow status changes over time.

Despite spontaneous improvement in flow status in 7 of the original cohort of 18 low flow patients, it is important to note that 4 of the cohort suffered strokes before follow-up imaging could even be obtained (Figure 1A). Thus, interventions to augment flow rapidly remain an attractive treatment goal. Endovascular approaches such as angioplasty and stenting present

feasible mechanisms to improve blood flow in vertebrobasilar stenosis. Although small studies have shown promise with qualitative improvements in cognition and perfusion imaging after intervention,[36–38] recent randomized trials have been unable to demonstrate benefit in stroke risk in comparison with medical therapy.[39–43] These studies, however, have not targeted hemodynamically selected high-risk patients. The current study highlights that despite changes in flow status in a portion of the original cohort over time, interval measurement continues to predict stroke risk in subsequent follow-up, and the strength of prediction of flow status over time is similar to the strength of prediction from baseline flow status only, with a HR 10.3 compared to 11.6, respectively.[5] Such high-risk patients, therefore, represent a logical subset for future evaluations of revascularization strategies.

Interpretation of this study may be limited by the post-hoc nature of the analysis on a cohort recruited primarily for the evaluation of the predictive value of baseline, rather than follow-up, QMRA flow. Although the study protocol defined fixed intervals for serial imaging, not all imaging was performed within the pre-specified windows, and patients were censored from further imaging after suffering a primary endpoint, limiting the number of serial observations. Although we cannot make definitive determinations regarding optimal timing of imaging follow-up, changes in flow status were seen in as little as 6 months. Thus, serial imaging at 6 month intervals would be a reasonable timeframe.

Conclusion

Patients suffering VB TIA or stroke may merit ongoing evaluation of their quantitative flow, which continues to predict posterior circulation stroke risk over repeated measures. VB hemodynamics are not static and can change in as little as 6 months. Although the hemodynamic status more commonly improves for patients from a high-risk stratum, it can also worsen for patients in a low-risk stratum. Further research, including clinical trials, is needed to determine how flow status may affect management of these complex and high-risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BA	basilar artery
BP	blood pressure
DBP	diastolic blood pressure
HR	hazard ratio
NOVA	noninvasive optimal vessel analysis
OEF	oxygen extraction fraction
PCA	posterior cerebral artery
QMRA	quantitative magnetic resonance angiography
SBP	systolic blood pressure
TIA	transient ischemic attack
VA	vertebral artery
VB	vertebrobasilar
VERiTAS	Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke

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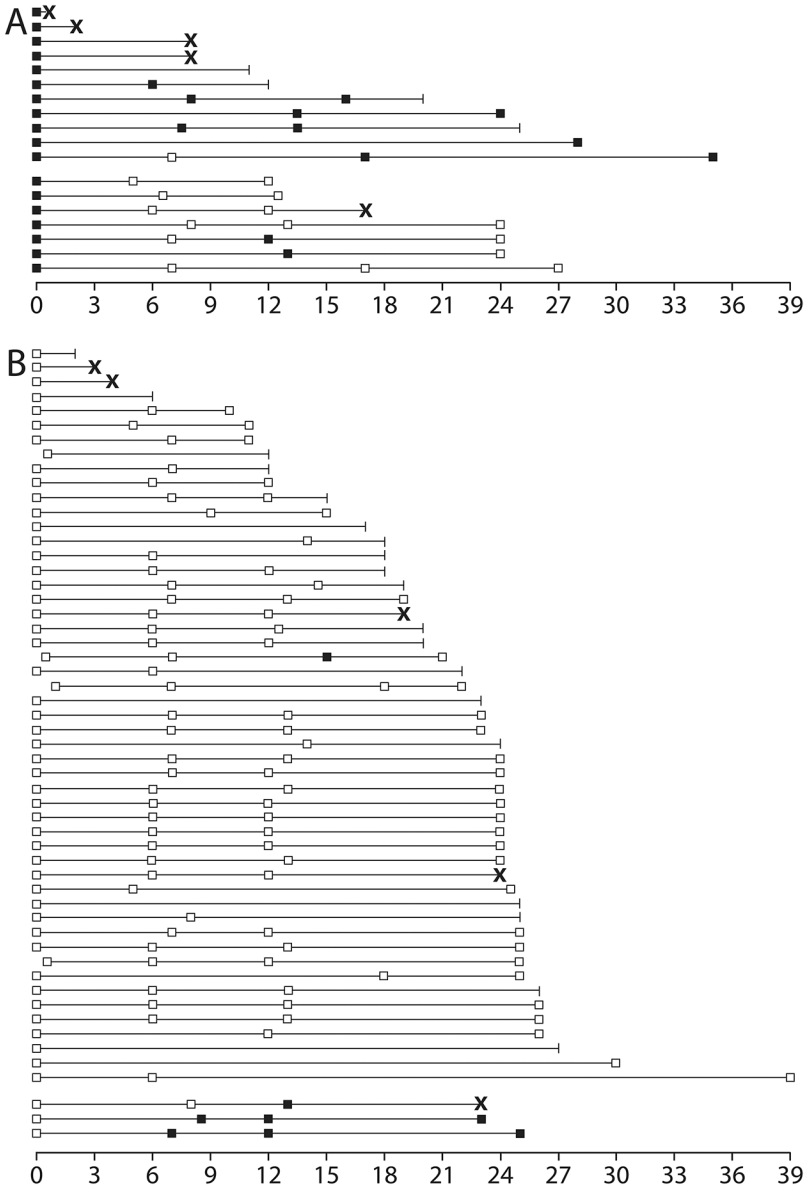

Figure 1.

Timeline plots of flow status and follow-up for patients. The x axis indicates months of follow-up starting at enrollment. Boxes represent timing of imaging assessing flow designations. Solid boxes represent low-flow designation, hollow boxes represent normal-flow designations. The short vertical bars at the end of a line indicate the end of clinical follow-up, which often coincides with timepoints of imaging follow-up. The x marks indicate a stroke event along the timeline, following which further clinical and radiographic follow-up was censored A. Flow status over time for patients with low flow at baseline. B. Flow status over time for patients with normal flow at baseline.

Table 1.

Hazard of recurrent vertebrobasilar stroke over the follow-up interval as a function of flow status

Risk Factor	Unadjusted Hazard Ratio (95% CI)	p-value	Adjusted Hazard Ratio (95% CI)*	p-value
Low flow status at the time of enrollment	3.4 (1.0 – 11.8)	0.05	11.6 (1.9 – 71.0)	0.008
Time varying low flow status	3.9 (1.1 – 14.6)	0.04	10.3 (2.2 – 48.7)	0.003

*Adjustment made for age, coronary artery disease, diabetes mellitus, and physical activity

Table 2.

Cumulative hazard of recurrent vertebrobasilar stroke at 30 and 180 days for patients with low flow and with normal flow

Time	Estimated cumulative hazard of stroke	95% CI
30 days		
Normal flow	0.00	(0–0) *
Low flow	0.06	0.01 – 0.39
180 days		
Normal flow	0.04	0.01 – 0.15
Low flow	0.11	0.03 – 0.46

* This result should be interpreted cautiously; given that no events occurred within 30 days, there is no variation available to generate an appropriate nonzero confidence interval for the normal flow group.