Infarct Patterns in Patients with Atherosclerotic Vertebrobasilar Disease in Relation to Hemodynamics

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Keywords
Stroke · Vertebrobasilar ischemia · Magnetic resonance angiography · Regional blood flow

Abstract
Introduction: Distal territory blood flow is independently associated with subsequent strokes in symptomatic vertebrobasilar atherosclerotic disease. We aimed to assess infarct patterns in relation to hemodynamic status in the prospective Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) study. Methods: Distal territory blood flow was measured using quantitative magnetic resonance angiography (MRA) in 72 patients with symptomatic atherosclerotic vertebrobasilar disease, and then dichotomized into normal ($n = 54$) and low ($n = 18$) flow. Patients were followed longitudinally on standard medical management. Two observers blinded to flow status independently reviewed the imaging performed at the time of subsequent strokes, in order to adjudicate the likely mechanism based on infarct patterns. The frequency of stroke mechanisms was qualitatively compared based on flow status. Results: During a median follow-up period of 23 months, 10/72 patients had a subsequent stroke; 5 of these had low distal flow. Infarct patterns were adjudicated to be

ClinicalTrials.gov Identifier: NCT00590980. https://clinicaltrials.gov/ct2/show/NCT00590980.
consistent with hemodynamic \((n=2)\), embolic \((n=4)\), and junctional plaque/perforator \((n=4)\) infarcts. Hemodynamic infarcts were seen in 40\% \((2/5)\) low-flow patients, in comparison to 0\% \((0/5)\) normal-flow patients. **Conclusion:** In contrast to normal-flow patients, those with low distal flow seem to be uniquely susceptible to hemodynamic infarctions, although other patterns of infarction can also be seen in these hemodynamically impaired patients.

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Published by S. Karger AG, Basel

**Introduction**

Approximately one-third of ischemic strokes occur in the posterior circulation, commonly caused by atherosclerotic disease, which carries a high risk for recurrent stroke [1]. To identify the highest-risk patients, the Vertebrobasilar flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) study examined hemodynamic insufficiency as a potential biomarker for subsequent stroke in the setting of vertebrobasilar atherosclerotic disease. The study demonstrated that low blood flow in the distal posterior circulation, measured on quantitative MRA (QMRA), was an independent predictor of future stroke [2]. In this study, we sought to examine the mechanism of recurrent strokes in relation to hemodynamic status within the VERiTAS cohort.

**Materials and Methods**

The VERiTAS study was a prospective, multicenter, observational study on patients with a recently symptomatic \(\geq 50\%\) atherosclerotic stenosis/occlusion affecting the vertebral and/or basilar arteries. Details of the trial design and cohort baseline features have been previously published [2, 3] and data are available from the corresponding author upon reasonable request.

Participants underwent QMRA to determine their hemodynamic status, by using vertebrobasilar large-vessel flows. QMRA was performed using standardized NOVA (noninvasive optimal vessel analysis, VasSol, Inc.) software which has been extensively validated in vitro and in vivo [4, 5]. A blinded QMRA reviewer assessed whether distal flow status was “low” or “normal” based on an algorithm using flows in the basilar and nonfetal posterior cerebral arteries [6]. Participants were followed regularly by their treating physicians who provided routine medical management. New neurologic events were adjudicated by an independent panel of stroke neurologists blinded to the patients’ hemodynamic status.

Participants who had suffered a new vertebrobasilar territory ischemic stroke during follow-up were included in the study. Two blinded observers (S.E.K., F.L.S.) reviewed the MR images (DWI/ADC and T2W-FLAIR), and then independently assessed the most likely stroke mechanism according to infarct patterns in relation to the location of steno-occlusive disease on the baseline angiogram. The following stroke patterns and plausible stroke mechanisms were determined according to the classification proposed by the WASID Trial Investigators [7]:

1. **Embolic infarct:** \(\geq 1\) infarct distal to the stenotic artery restricted to the territory supplied by a single intracranial artery.
2. **Junctional plaque occluding a perforator:** infarct in the distribution of a perforating artery originating from the site of stenosis.
3. **Hemodynamic infarct:** \(\geq 1\) infarct in a border zone between the posterior inferior and anterior inferior cerebellar arteries, between the anterior inferior and superior cerebellar arteries, and between the posterior and middle cerebral arteries [8].

The raters reached consensus for discrepancies. Given the small sample size, the relative frequency of these stroke mechanisms was qualitatively compared based on flow status.
Results

During a median follow-up period of 23 (IQR: 14–25) months, 10/72 enrolled subjects (mean age 58 years; 6 females) had a vertebrobasilar territory stroke at a median of 8 (IQR: 3–19) months after enrollment. Multiple infarcts were recorded for 3 patients in the posterior circulation and 2 additional patients in both the anterior and posterior circulation. The interobserver agreement for stroke mechanism was substantial (weighted $\kappa = 0.77$; 95% CI 0.49–1.00). Two patients were classified as having hemodynamic infarcts, 4 as having embolic infarcts, and 4 as having junctional plaque/perforator occlusion. Five strokes occurred in patients with a low-flow status (Table 1). Hemodynamic infarcts were seen in 40% (2/5) low-distal-flow patients compared to 0% (0/5) in normal-flow patients.

In 3 patients, the degree of stenosis had progressed since the time of enrollment, 2 of whom had low distal flow at baseline. Two patients died; one patient had low distal flow and succumbed to multiple hemodynamic infarcts and the other death was related to myocardial infarction.

Fig. 1. a Embolic infarct. A 64-year-old male with extracranial left vertebral artery occlusion, 60% right vertebral artery stenosis and normal distal flow develops cerebellar infarcts distal to the stenosis. b Junctional infarct. A 55-year-old female with a 60% basilar artery stenosis and normal distal flow develops a left ventral paramedian pontine infarct at the level of the stenosis consistent with branch artery occlusion. c Hemodynamic infarct. A 58-year-old female with bilateral intracranial vertebral artery occlusions and low distal flow develops multifocal infarcts in the mesencephalon, cerebral peduncles, and central pons, adjudicated to be hypoperfusion mechanism.
Discussion

The VERITAS study previously demonstrated that low distal flow measured with QMRA predicts a 5-fold-higher risk of subsequent stroke at 1 year (22 vs. 4%) in patients with symptomatic vertebrobasilar disease [2]. This study, utilizing the VERITAS cohort demonstrates that, in addition to embolic and perforator strokes, patients with low distal flow are at risk for hemodynamic infarction.

Given that infarct patterns in patients with low distal flow were not restricted to a solely hemodynamic pattern, it might be surmised that low flow is merely a marker for atherosclerotic burden and is not itself the underlying mechanism for stroke. If so, correcting hemodynamic compromise by endovascular interventions may fail to improve stroke risk, unless the interventions have additional beneficial effects (e.g., on plaque stability). In fact, trials of intra/extracranial stenting thus far have shown no benefit over medical management for vertebrobasilar disease [9–11], albeit the patients were not selected based on hemodynamic factors. Importantly, however, our data demonstrate a notable incidence of hemodynamic pattern infarction in low-flow patients, accounting for 40% of the stroke types encountered, and low flow may well potentiate other underlying mechanisms of stroke; synergy between low flow and emboli is a well-recognized concept attributed to reduced “washout” of embolic debris leading to strokes [12].

The failure of prior stenting trials may be caused by a combination of (1) the failure to select the highest-risk hemodynamically compromised subgroup, thereby diluting a possible treatment effect, and (2) the high periprocedural risks associated with stenting, particularly in the intracranial circulation where plaque debris is presumed to “snowplow” over perforator orifices. Interestingly, recent small series of submaximal angioplasty without stenting, being less disruptive to plaques, have shown a promising periprocedural safety profile [13]. A more recent single-arm study to assess the periprocedural safety of intracranial stenting for severe symptomatic intracranial stenosis that failed medical management demonstrated an event-free procedure in 97.4% of cases [14]. Ultimately, the high-risk patients identified using QMRA may benefit from lower risk procedures.

An important corollary of our results is that it was not exclusively hemodynamic infarct patterns that were seen in patients with a low-flow status. Infarct patterns in the WASID Trial of warfarin versus aspirin, and the SAMMPRIS Trial of stenting versus medical management for intracranial stenosis, similarly suggest that poor collaterals, being a surrogate marker for hypoperfusion, do not specifically correlate with hemodynamic infarcts [7, 11, 15, 16]. These convergent results lend further credence to the hypothesis that there is an interplay between hypoperfusion and other stroke mechanisms [17]. Consequently, caution should be exercised in relying solely on infarct patterns to deduce hemodynamic compromise. Rather, measurement of blood flow, as provided by techniques such as QMRA, are needed to identify high-risk flow-compromised patients.

### Table 1. Stroke mechanisms and flow status

| Stroke mechanism        | All strokes (n = 10) | Normal distal flow (n = 5) | Low distal flow (n = 5) |
|-------------------------|---------------------|---------------------------|------------------------|
| Embolic infarct         | 4 (40%)             | 3 (60%)                   | 1 (20%)                |
| Junctional plaque       | 4 (40%)             | 2 (40%)                   | 2 (40%)                |
| Hemodynamic infarct     | 2 (20%)             | 0 (0%)                    | 2 (40%)                |
| Multiple infarcts       | 5 (50%)             | 3 (60%)                   | 2 (40%)                |
The VERITAS cohort is unique in using quantitative hemodynamic assessment to characterize hemodynamic impairment and stroke risk in the posterior circulation; its prospective nature and blinding of stroke mechanism adjudication were additional strengths of the analysis. However, given the small numbers, conclusions must be considered speculative regarding differences in stroke mechanism related to distal flow. Another limitation is the uncertainty regarding stroke mechanisms attributed to infarct patterns, a classification which has not been specifically validated, especially in the posterior circulation. The substantial interobserver agreement is at least reassuring with regard to internal validity.

**Conclusion**

In contrast to normal-flow patients, those with low distal flow seem to be uniquely prone to hemodynamic infarctions, although other infarction patterns can also be seen in these hemodynamically impaired patients.

**Acknowledgement**

We thank the VERITAS Study Group (online suppl. Material; for all online suppl. material, see www.karger.com/doi/10.1159/000503091).

**Statement of Ethics**

The institutional review boards at each site approved the study protocol; all participants provided written informed consent.

**Disclosure Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

National Institute of Neurological Disorders and Stroke (R01-NS-059745); Dr. Ralph and Marian Falk Research Trust Foundation; other research support (no direct funds) was provided by VasSol, Inc.

**Author Contributions**

Joanna D Schaafsma: data acquisition, analysis, and interpretation; manuscript drafting. Frank L Silver and Scott E Kasner: data acquisition and interpretation; manuscript revision. Louis R Caplan, Linda Rose-Finnell, Fady T Charbel, and Dilip K Pandey: data interpretation; manuscript revision. Sepideh Amin-Hanjani: conception and design; data acquisition and interpretation; manuscript revision.
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