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Hypoperfusion Symptoms Poorly Predict Hemodynamic Compromise and Stroke Risk in Vertebrobasilar Disease

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Abstract

Background and Purpose: Cerebral hypoperfusion symptoms (defined as symptoms related to change in position, effort or exertion, or recent change in antihypertensive medication) have been used in stroke studies as a surrogate for detecting hemodynamic compromise. However, the validity of these symptoms in identifying flow compromise in patients has not been well established. We examined whether hypoperfusion symptoms correlated with quantitative

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CONFLICTS OF INTEREST/DISCLOSURES

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measurements of flow compromise in the prospective, observational Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) study.

Methods: VERiTAS enrolled patients with recent vertebrobasilar transient ischemic attack or stroke and ≥50% atherosclerotic stenosis or occlusion in vertebral and/or basilar arteries. Hemodynamic status using vertebrobasilar large vessel flow was measured using quantitative magnetic resonance angiography (QMRA), and patients were designated as low, borderline, or normal flow based on distal territory regional flow, incorporating collateral capacity. The presence of qualifying event hypoperfusion symptoms was assessed relative to the quantitatively determined flow status (normal vs. borderline/low), and also examined as a predictor of subsequent stroke risk.

Results: Of the 72 enrolled subjects, 66 had data on hypoperfusion symptoms available. On initial QMRA designation, 43 subjects were designated as normal flow vs. 23 subjects designated as low flow (n=16) or borderline flow (n=7). Of these, 5 (11.6%) normal flow and 3 (13.0%) low/borderline flow subjects reported at least one qualifying event hypoperfusion symptom (p=0.99, Fisher's exact test). Hypoperfusion symptoms had a positive predictive value of 37.5% and negative predictive value of 65.5% for low/borderline flow status. Compared to flow status, which strongly predicted subsequent stroke risk, hypoperfusion symptoms were not associated with stroke outcome (p=0.87, log rank test).

Conclusions: These results suggest that hypoperfusion symptoms alone correlate poorly with actual hemodynamic compromise as assessed by QMRA and subsequent stroke risk in vertebrobasilar disease, and are not a reliable surrogate for flow measurement.

Keywords

blood flow; hypoperfusion; magnetic resonance imaging; stroke; vertebrobasilar disease; Cerebral Blood Flow; Cerebrovascular Stroke; Magnetic Resonance Imaging (MRI); Magnetic Resonance Angiography (MRA); Stroke; Vertebrobasilar insufficiency

INTRODUCTION

Hemodynamic compromise has been identified as a risk factor for stroke associated with cerebrovascular occlusive diseases affecting both the anterior[1, 2] and posterior circulations[3]. While this association has been best demonstrated in studies using quantitative imaging assessment of cerebral blood flow, other studies have used clinical symptoms purported to be indicative of hemodynamic impairment as a surrogate for hemodynamic compromise.[4, 5] Clinical hypoperfusion symptoms are typically defined as neurological symptoms related to: 1) change in position (i.e., supine to seated), 2) effort or exertion, or 3) recent change in antihypertensive medication. However, the validity of these symptoms in identifying actual flow compromise has not been well established. In the present study, we examined whether clinical hypoperfusion symptoms correlated with imaging-based assessment of flow compromise in the prospective, observational Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) study cohort.

METHODS

VERiTAS enrolled patients with recent vertebrobasilar transient ischemic attack (TIA) or stroke and ≥50% atherosclerotic stenosis or occlusion affecting the vertebral and/or basilar arteries. The details of the trial design and baseline features of the study cohort have been previously published,[6, 7] and all data are available from the corresponding author upon reasonable request. Hemodynamic status using large vessel flow in the vertebrobasilar territory was measured using quantitative magnetic resonance angiography (QMRA),[8] and patients were designated as low, borderline or normal flow based on distal territory regional flow, incorporating collateral capacity, as previously reported.[6, 9] The presence of qualifying event hypoperfusion symptoms was assessed relative to the quantitatively determined flow status (normal vs. borderline/low) using $\chi 2$ analysis with the Fisher exact test. Receiver operating characteristic (ROC) curve analysis was performed examining the area under the curve (AUC) using a logistic regression model to test the accuracy of hypoperfusion symptoms in predicting flow status. Flow status and hypoperfusion symptoms were examined as predictors of subsequent stroke risk using Kaplan-Meier analysis with log rank statistics. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC).

RESULTS

Of the 72 enrolled subjects, 66 had data on hypoperfusion symptoms available. Based on QMRA, 43 subjects were designated as normal flow vs. 23 subjects designated as low flow (n=16) or borderline flow (n=7). Of these, 5 (11.6%) normal flow and 3 (13.0%) low/borderline flow subjects reported at least one qualifying event hypoperfusion symptom (p=0.99, Fisher exact test). The specific hypoperfusion symptoms were the following: change in position only (n=2 normal flow, n=2 low flow); recent change in antihypertensive medication only (n=2 normal flow, n=1 low flow); recent change in antihypertensive medication in the setting of effort or exertion (n=1 normal flow). Hypoperfusion symptoms had a positive predictive value of 37.5% (95% CI 8.5% to 75.5%) and negative predictive value of 65.5% (95% CI 53.3% to 77.8%) for low/borderline flow status, respectively. ROC curve analysis demonstrated that hypoperfusion symptoms were a poor indicator of actual flow status (AUC=0.51, 95% CI 0.42 to 0.59). Compared to flow status, which strongly predicted subsequent stroke risk in VERiTAS (p=0.03, log rank test; Figure 1A), hypoperfusion symptoms were not associated with stroke outcome (p=0.87; Figure 1B).

DISCUSSION

In cerebrovascular atherosclerotic disease in general, and in vertebrobasilar disease in specific, mechanisms of TIA and stroke include distal hypoperfusion and thromboembolism.[10] The accurate determination of hemodynamic compromise associated with atherosclerotic stenosis can identify patients most at risk for hypoperfusion and, therefore, subsequent TIA and stroke. The importance of intracranial hemodynamic compromise as a stroke risk factor is well established in the carotid circulation[1, 2], and has recently been demonstrated in the posterior circulation with the results of the VERiTAS study[3]. In the VERiTAS cohort, vertebrobasilar disease patients with impaired distal flow measured using QMRA were

found to be at significantly higher risk of subsequent vertebrobasilar stroke, with a 22% one-year stroke risk compared to 4% in patients with normal distal flow.[3] The present analysis of the VERiTAS study cohort demonstrates that qualifying event hypoperfusion symptoms poorly predict actual hemodynamic compromise as evaluated by QMRA, with low positive and negative predictive values. More importantly, unlike measured flow status, hypoperfusion symptoms were not associated with subsequent stroke risk in vertebrobasilar disease.

To the best of our knowledge, no prior studies have examined the accuracy of clinical hypoperfusion symptoms relative to actual measurement of flow compromise. Prior stroke studies which have defined hemodynamic impairment based solely on hypoperfusion symptoms have had conflicting results regarding their association with stroke risk. In the Groupe d'Etude des Sténoses Intra-Crâniennes Athéromateuses symptomatiques (GESICA) study[4], hemodynamically significant stenosis, as defined by clinical hypoperfusion criteria, was reported in 28 of 102 enrolled patients, and these patients were more likely to suffer a recurrent stroke or TIA (60.7% vs. 39.3%; p=0.009). On the other hand, of 227 patients enrolled into the medical arm of the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial, 31 (13.6%) had qualifying event hypoperfusion symptoms, and subsequent two-year stroke risk was unexpectedly lower in this group (7.1%) than in patients without hypoperfusion symptoms (15.1%).[5] Furthermore, as with the full cohort, patients with hypoperfusion symptoms did not achieve a benefit of stenting, with two-year stroke risk of 7.1% and 5.6%, respectively.

Despite the post hoc nature of our analysis, limitation to posterior circulation disease, and the relatively small sample size, our data highlight that clinical criteria should not be assumed to be reliable for determination of hemodynamic compromise. Consequently, dismissing the role of hemodynamic impairment as a stroke risk factor, or its ability to identify subgroups which may benefit from interventions to restore blood flow, based on clinical hypoperfusion symptoms alone is not well justified. Methods for quantitative measurement of blood flow have now been validated as stroke risk biomarkers in the anterior and posterior circulation, and should not be substituted by clinical criteria.

CONCLUSION

These results suggest that hypoperfusion symptoms alone correlate poorly with actual hemodynamic compromise as assessed by QMRA and subsequent stroke risk in vertebrobasilar disease, and are not a reliable surrogate for flow measurement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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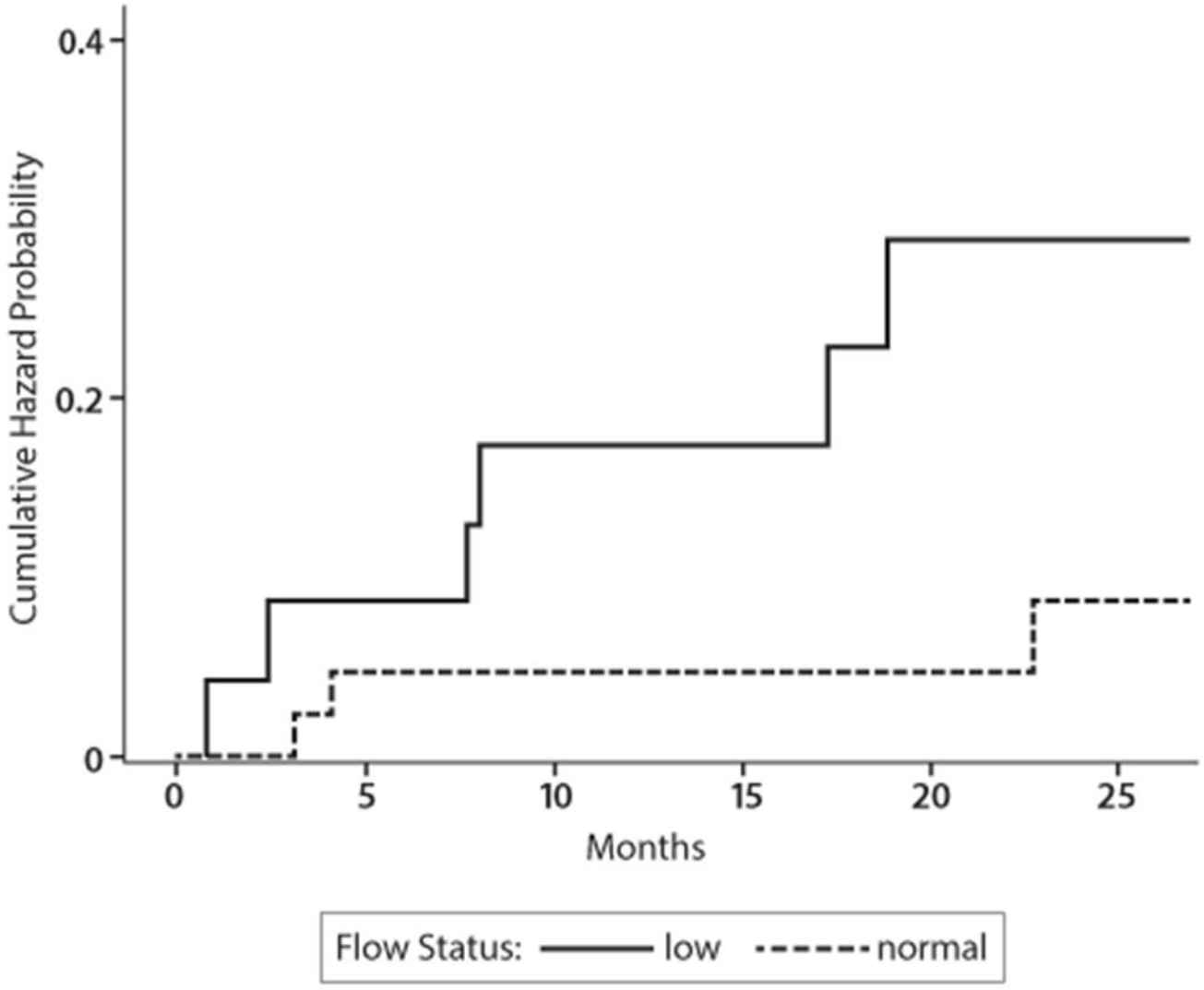

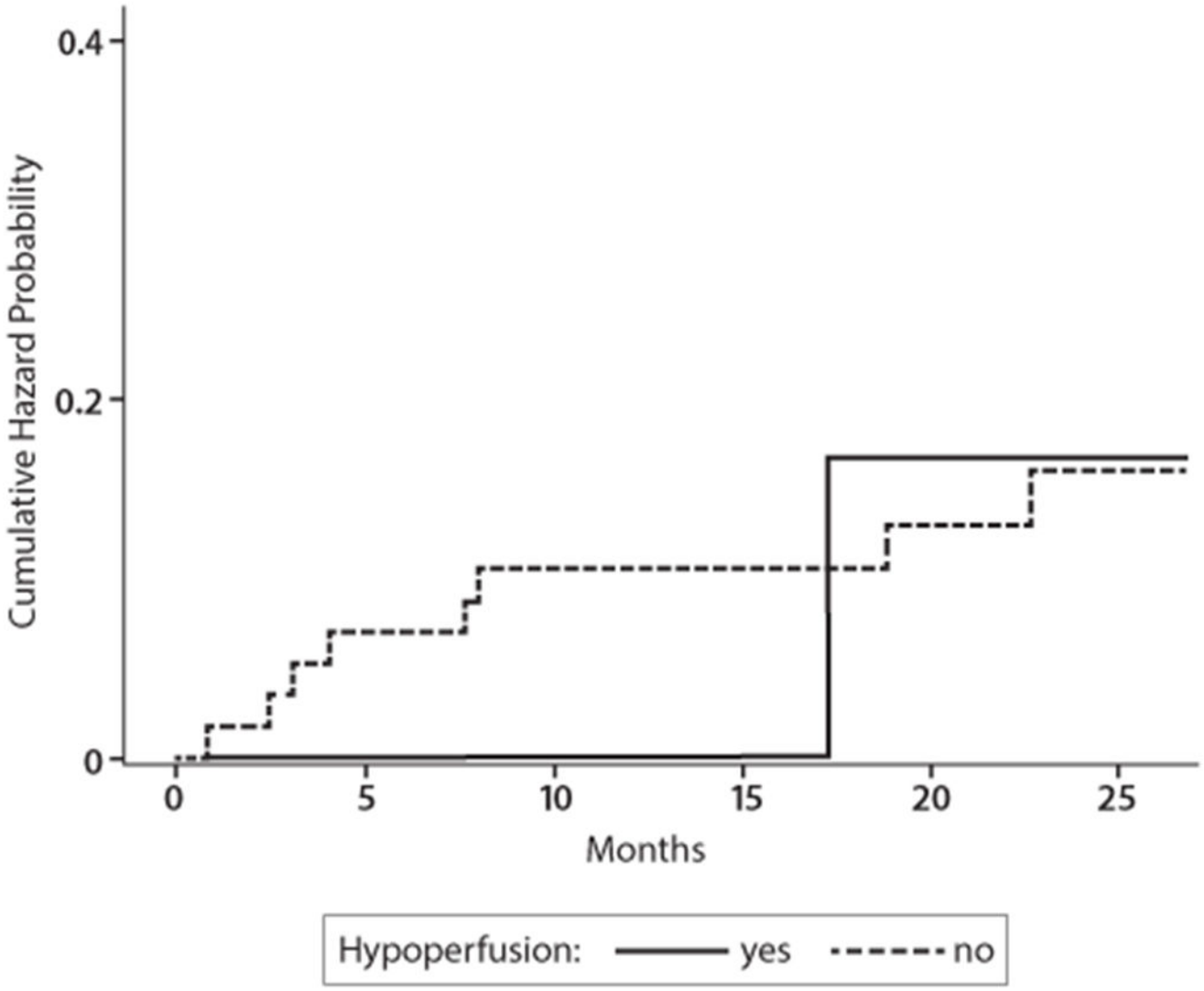

Figure 1:
Cumulative hazard curve for the primary end point of vertebrobasilar territory stroke, according to **(A)** flow status as assessed by quantitative magnetic resonance angiography (p=0.03) and **(B)** qualifying event hypoperfusion symptoms (p=0.87).