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Hemodynamic Features of Symptomatic Vertebrobasilar Disease

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Abstract

Background and Purpose—Atherosclerotic vertebrobasilar (VB) disease is an important etiology of posterior circulation stroke. To examine the role of hemodynamic compromise, a prospective multi-center study, Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic

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Attack and Stroke (VERiTAS), was conducted. Here we report clinical features and vessel flow measurements from the study cohort.

Methods—Patients with recent VB TIA or stroke and 50% atherosclerotic stenosis or occlusion in vertebral (VA) and/or basilar (BA) arteries were enrolled. Large vessel flow in the VB territory was assessed using quantitative MRA.

Results—The cohort (n=72, 44% female) 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 VAs had the greatest negative impact on immediate downstream flow in the BA (43 ml/min vs. 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 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.

Keywords

INTRODUCTION

Large vessel atherosclerotic disease of the vertebrobasilar (VB) system, both intracranial and extracranial, is a significant etiology of posterior circulation stroke, accounting for approximately one third of ischemic events in this territory[1, 2]. Symptomatic VB disease carries a high annual risk of recurrent events, averaging 10-15% per year despite medical therapy[3-6]. In addition to thromboembolism as a contributing etiology, regional hypoperfusion is considered an important potential contributor to stroke risk in VB 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].

In order to examine the utility of QMRA in assessment of hemodynamic compromise and prediction of stroke risk in symptomatic VBD, a prospective observational multi-center study, Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) was undertaken[10]. In this paper, we evaluate the **affected vessel, immediate downstream and distal** hemodynamic impact of VB disease.

METHODS

Study design

Details of the VERiTAS study design have been previously published[10]. Briefly, the study is a multi-center prospective cohort study of patients with 50% extracranial or intracranial atherosclerotic VB stenosis or occlusion based upon conventional digital subtraction angiography (DSA) or computed tomographic angiography (CTA) presenting with referable VB distribution TIA or stroke within 60 days. The clinical criteria for enrollment are further detailed in the supplemental methods (please see http://stroke.ahajournals.org). 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 on medical regimens consistent with national guidelines for a minimum of one year, up to a planned maximum of two 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 following enrollment of the initial 35 patients resulted in two additional exclusion criteria, as follows. First, interim analysis of distal flow status revealed a 4:1 ratio of normal flow to low flow subjects, as compared to 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) as 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 etiology; given the differing prognosis and potential stroke mechanisms of these two 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 (HTN) was defined as self-reported history or use of antihypertensive medication; diabetes mellitus (DM) was defined as self-reported history or use of insulin or oral hypoglycemic treatment; hyperlipidemia (HL) 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 (CRF, need for dialysis) and chronic renal insufficiency (CRI, as per criteria of the National Kidney Foundation for chronic kidney disease including decreased GFR 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 (BMI) was calculated from recorded height and weight data and classified as normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m m^2), class 1 obesity (30 to 34.9 kg/m^2), class 2 obesity (35 to 39.9 kg/m^2), or Class 3 obesity (40 kg/m^2).

Enrollment angiographic data (DSA or CTA) 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 the supplemental methods (please see http://stroke.ahajournals.org). Measurements of residual lumen and vessel diameters were obtained from site review of the angiographic imaging.

MR imaging—A magnetic resonance (MR) imaging protocol including QMRA was performed within 7-14 days of enrollment using a standardized protocol on a 3 Tesla MR scanner. The QMRA portion of the imaging was performed with a protocol utilizing NOVA (Noninvasive Optimal Vessel Analysis, VasSol, Inc.) software as previously described[10], and is further detailed in the supplemental methods (please see http://stroke.ahajournals.org). Flow measurements were performed on pre-specified 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 (PCA, P2 segment distal to the posterior communicating arteries). The study was remotely supervised at the time of the imaging by a certified NOVA technician to ensure correct parameters and vessel placement for flow measurement, and the data were transferred automatically via secure internet based transfer to the clinical coordinating center at University of Illinois at Chicago (UIC) 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 cc/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 as the flow in the affected vessel would be influenced not just 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 cc/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[9] (please see http://stroke.ahajournals.org, supplemental figure I) defining flow compromise as >20% reduction below normative lower limits of flow in distal vessels, namely the BA and PCAs. Conceptually, the algorithm incorporates any sources of collateral flow (e.g. via the posterior communicating arteries) by their effect on the blood flow within these distal vessels.

Statistical Analysis

Following 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 χ^2 analysis with Fisher's 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 χ^2 analysis with Fisher's exact test. $P<0.05$ was considered significant. All analysis was performed with SAS (version 9.4, SAS institute, Cary, NC, USA).

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. Following 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; one 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 VB disease ≥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 years (median 65.7, range 40 to 90). Baseline characteristics, including race, ethnicity, and vascular risk factors are outlined in Table 1. Both HTN and HL were present in a majority of patients, as well as elevated BMI.

Angiographic characteristics—DSA was performed in 44 (60%) of cases as enrollment imaging, as compared to CTA in the remaining cases (except one 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—As regards 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 with posterior circulation etiology. Patients with vertebral only disease presented with stroke slightly less frequently (59%) than 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 vs. severe vs. 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 supplementary table I (please see http://stroke.ahajournals.org).

Forty two (58%) of patients had a history of a prior posterior circulation ischemic event (TIA or stroke). The majority of these prior stroke or TIAs occurred within 30 days of the qualifying event (Supplementary Figure II).

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 (rho=−0.49, p=0.01) but not for the VA (rho=−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 (rho=0.65, p<0.01 for BA) and VA (rho=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 to 71 ml/min in the patients with only BA or only VA disease (p=0.01).

Distal Flow Status—Of the cohort, 18 (25%) were designated low flow based on the pre-determined 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 VB 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 VB stenosis demonstrate a similar mean age, and male predominance, with HTN and HL as the most common vascular risk factors[12, 13]. Also similar to these prior studies, the majority of patients presented with stroke rather than TIA. We did not find a significant relationship between presentation with stroke and disease location, although exclusively VA or extracranial disease trended towards the less severe presentation of TIA. Interestingly, the severity of stenosis and distal flow status both showed no relationship to presentation. Over half of our patients reported a prior 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[14], and after VB TIA or stroke in specific[13].

In our hemodynamic analysis, we examined the impact of vessel stenosis in the posterior circulation in a number of ways: at the level of the affected vessel, downstream in the BA as the major conduit immediately distal to the VB 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[15]. Even in carotid stenosis, where the underlying etiology of recurrent stroke is widely considered to be thromboembolism, hemodynamic factors may be relevant[16]. The hemodynamic impact of stenosis within a vessel was first postulated by Spencer and Reid as a curve which predicts no substantive decline in flow until ~70% stenosis and a steep threshold in flow drop at ~80%[17] (Figure 3). Carotid stenosis risk appears 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%[18]. 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 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[16]. 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[19]. 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[20].

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 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 % stenosis leads to a markedly smaller residual diameter in a hypoplastic 2 mm vertebral compared to a dominant 5 mm VA, and likely accounts for the lack of correlation between flow and % stenosis in the VA. In the BA, although flow declines with increasing stenosis, our data further support the tenets of Spencer and Reid's curve, 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 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, as compared to the traditional reliance on anatomic features such as stenosis severity, has preliminary support from prior data[9]: in a retrospective single center cohort of 48 patients with >50% VB stenosis or occlusion, patients designated as low distal flow status demonstrated a significantly worse stroke free survival of 71% at 24 months compared to 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 which 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 due to inability to perform reliable absolute vessel measurements from centrally transmitted images; the lack of central verification, and the use of both DSA and CTA 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, as even severe stenosis or occlusion in just one 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 impacted by systemic factors such as blood pressure, for which our flow data has not been adjusted due to lack of standardized blood pressure measurements at the time of QMRA imaging. Although data from healthy volunteers suggest that intracranial blood flow is not impacted by blood pressure[21], it is

possible that in this cohort with underlying cerebrovascular disease and a high prevalence of pre-existing HTN, autoregulation is altered, with flows affected by blood pressure variation.

CONCLUSION

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 VB disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

APPENDIX: VERiTAS study group

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(in descending order of number of enrollees)

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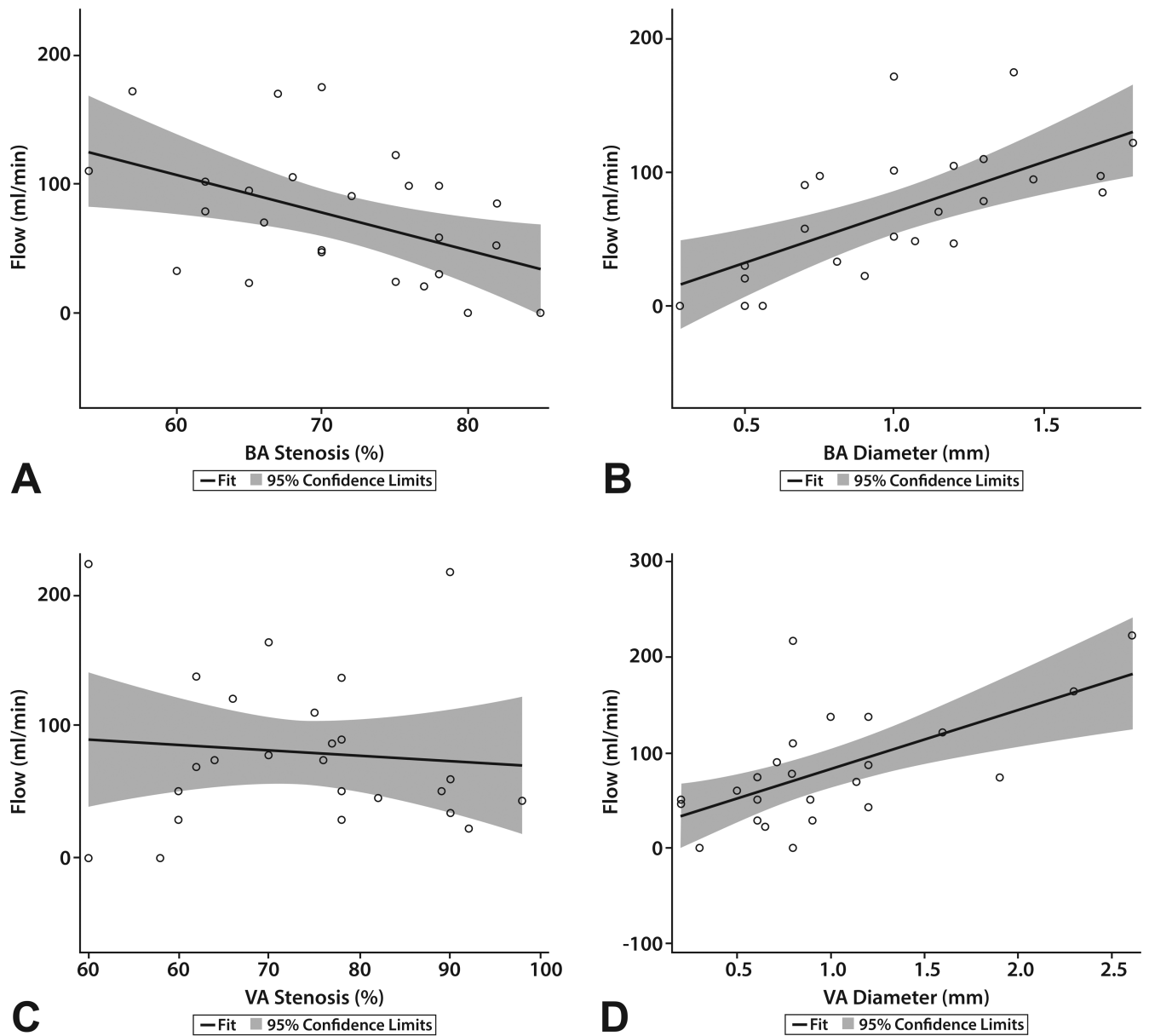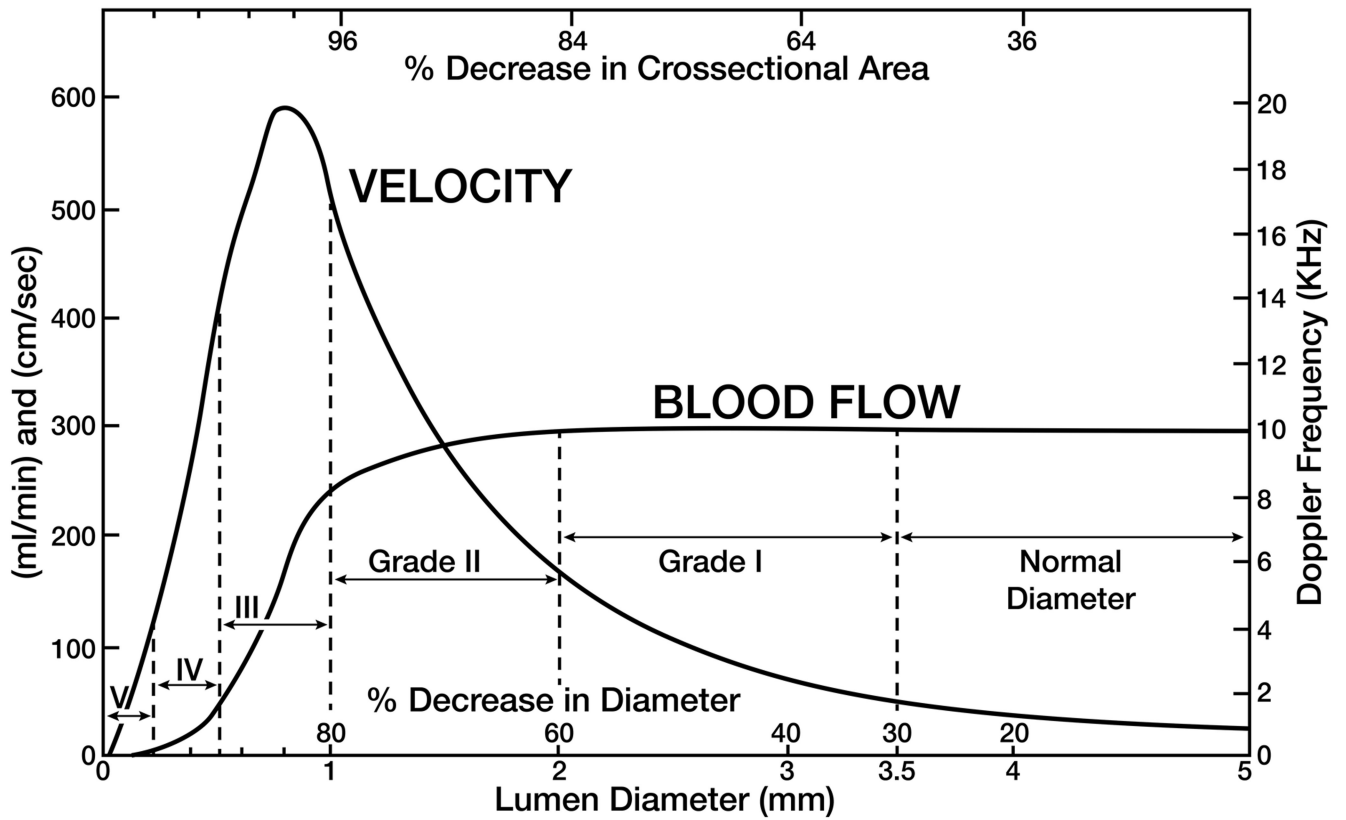
Figure 1.
Correlation between flow in the BA in relation to stenosis (A) and to minimal BA luminal diameter (B) in a linear regression model.
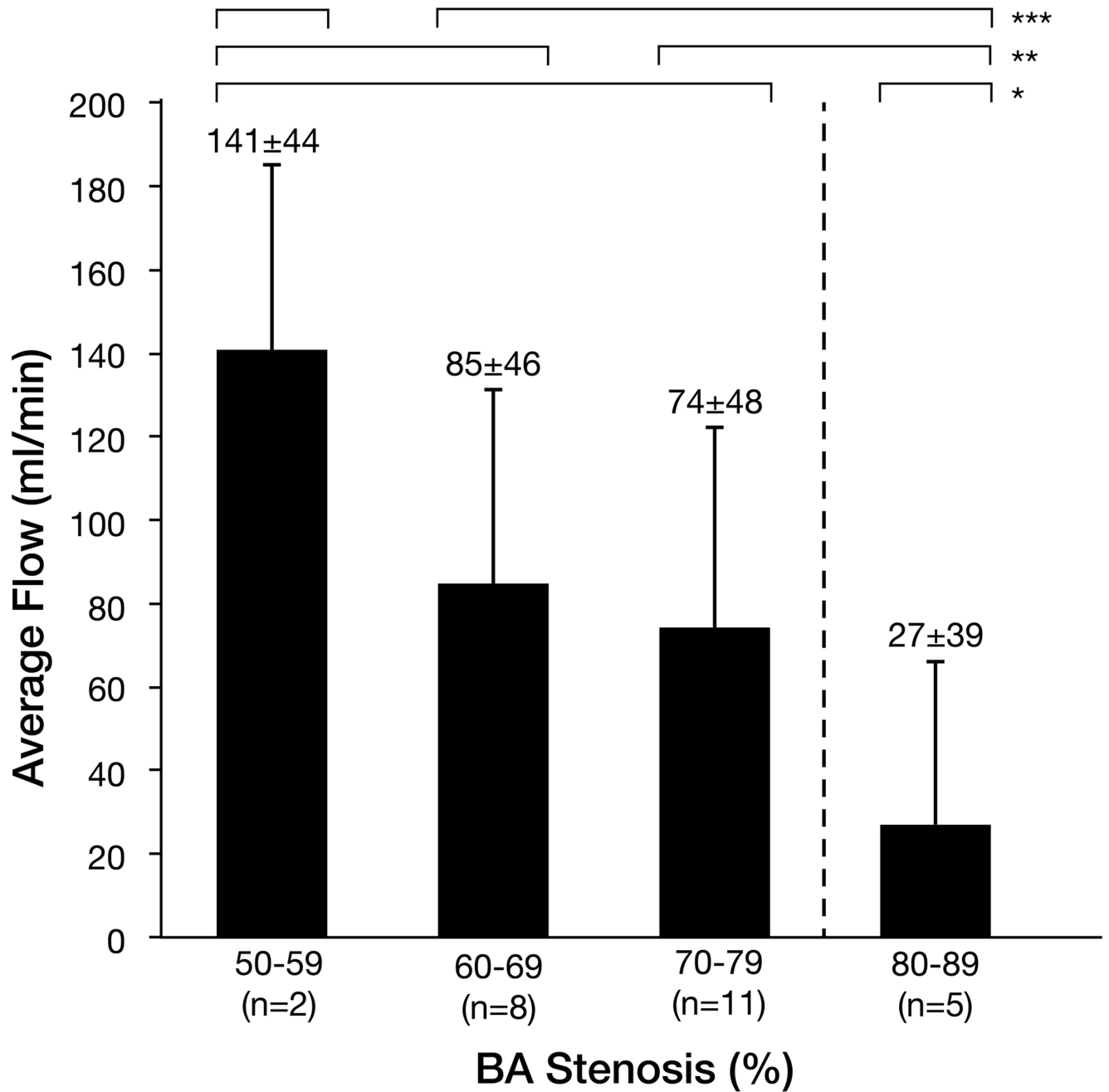
Figure 2.
Mean flows in the BA relative to degree of stenosis. * p= 0.02, ** p=0.08, *** p=0.05 using t-test comparison of groupings.

Figure 3.
Theoretical relationships between blood flow and graded vessel stenosis (adapted, with permission, from Spencer MP and Reid JM[17])

Table 1

Baseline Clinical and Angiographic Characteristics

Characteristics	n = 72 (%)
Mean age (yrs)	65.6 ± 10.3
Sex	
Male	40 (56)
Female	32 (44)
Race	
Black	18 (25)
Caucasian	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 Prior 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/day	24 (33)
> 1 drink/day	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/week	24 (33)
Vessel Involvement	
Basilar Only	29 (40)
Vertebral Only	22 (30)
Unilateral	7

Characteristics	n = 72 (%)
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)

Table 2

Immediate Downstream Flow in the Basilar Artery relative to Severity of Stenosis and Tandem disease

	Flow (ml/min)	p value
Disease Severity – worst disease		<0.01[*]
Occlusion (n=24)	33 ± 37	
Severe (70-99% stenosis) (n=32)	72 ± 54	
Moderate (50-69% stenosis) (n=16)	88 ± 51	
Vessel Involvement		0.01
Basilar Only or Vertebral Only (n=51)	71 ± 56	
Basilar and Vertebral (n=21)	43 ± 35	

[*] Occlusion vs. Severe, p<0.05; Occlusion vs. Moderate, p<0.05 on post hoc Tukey test

Table 3

Distal Flow Status relative to Severity of Stenosis and Tandem Disease

	Low Flow	Normal Flow	p value
Disease Severity – worst disease			0.08
Occlusion (n=24)	10 (42%)	14 (58%)	
Severe (70-99% stenosis) (n=32)	6 (19%)	26 (81%)	
Moderate (50-69% stenosis) (n=16)	2 (12%)	14 (88%)	
Vessel Involvement			0.65
Basilar Only or Vertebral Only (n=51)	12 (24%)	39 (76%)	
Basilar and Vertebral (n=21)	6 (29%)	15 (71%)	