Effects of Extracranial Carotid Stenosis on Intracranial Blood Flow

Sophia F. Shakur, MD; Tomas Hrbac, MD, PhD; Ali Alaraj, MD; Xinjian Du, MD; Victor A. Aletich, MD; Fady T. Charbel, MD; Sepideh Amin-Hanjani, MD

Background and Purpose—The hemodynamic effects of extracranial carotid stenosis on intracranial blood flow are not well characterized. We sought to determine the impact of degree of stenosis, stenosis length, and residual lumen on intracranial blood flow in patients with extracranial carotid stenosis.

Methods—Carotid stenosis patients who had undergone both vessel flow rate measurements using quantitative magnetic resonance angiography and digital subtraction angiography were examined. The impact of the anatomic measurements of the stenosis relative to ipsilateral internal carotid artery (ICA) flow and ipsilateral-to-contralateral middle cerebral artery (MCA) flow ratio were assessed.

Results—Forty-four patients (mean age, 67 years; 64% symptomatic) were included. Higher percentage stenosis and smaller residual lumen were associated with a significant decrease in ICA flow (P<0.01 and 0.04, respectively). On multivariate analysis, percentage stenosis remained as the primary predictor of ICA flow (P<0.001). MCA flow ratio was not significantly associated with percentage stenosis, stenosis length, or residual lumen. However, mean MCA flow ratio was significantly lower in symptomatic compared with asymptomatic patients (0.92 versus 1.22; P=0.001). In contrast, mean ICA flow ratio was similar among these 2 groups (0.55 versus 0.55; P=0.99).

Conclusions—Percentage stenosis and residual lumen are significantly associated with ICA but not MCA flow, suggesting that local hemodynamic effects of carotid stenosis do not translate directly to distal vasculature, because intracranial flows can be maintained through collaterals. The lower MCA flow ratio in symptomatic patients highlights the potential importance of distal hemodynamics in symptomatic presentation. (Stroke. 2014;45:3427-3429.)

Key Words: carotid arteries • carotid stenosis • magnetic resonance angiography

A pproximately 20% of ischemic strokes in the United States are attributed to extracranial carotid artery stenosis.1 Prior trials have shown that a higher degree of stenosis is associated with increased stroke risk, thereby establishing percentage stenosis as the key determinant in treatment decision making.2–4 The predominant pathophysiological mechanism underlying ischemia is thought to be thromboembolic, but hemodynamically consequential narrowing of the vessel lumen can also result in cerebral hypoperfusion and may even potentiate the effects of distal embolization.1–6 The relationship between carotid disease features—such as degree of stenosis, stenosis length, and residual lumen—and intracranial blood flow have not been well defined.7 In this study, we aimed to determine the hemodynamic effects of extracranial carotid artery stenosis on intracranial blood flow.

Methods

Patient Selection
Baselne clinical data for consecutive patients with ≥50% carotid stenosis who underwent revascularization at our institution between 2004 to 2012 were collected and retrospectively reviewed (n=105). Patients with ≥50% contralateral stenosis were excluded (n=24). Of the remainder, patients were included if both anatomic (based on conventional angiography) and flow data were available (n=44).

Flow and Vessel Measurements
Patients in this study had undergone quantitative flow measurements of the extracranial and intracranial arteries using quantitative magnetic resonance angiography (Figure I in the online-only Data Supplement). This technique has been described previously4 and was implemented using the commercially available software (Noninvasive Optimal Vessel Analysis; VasSol, Inc, River Forest, IL); further details are provided in the online-only Data Supplement. To provide an internal control for factors such as age and blood pressure, flow ratios (ipsilateral/contralateral vessel flow) were generated for the internal carotid artery (ICA) and middle cerebral artery (MCA). Measurements of degree of stenosis, stenosis length, and residual lumen were made from digital subtraction angiography. Degree of stenosis was determined using the North American Symptomatic Carotid Endarterectomy Trial criteria.3 The vessel residual lumen was measured at the point of maximal stenosis (Figure II in the online-only Data Supplement).

Statistical Analysis
Spearman correlation was used to assess the relationship between plaque characteristics and flow. Multivariate analysis was used to
determine the effect of covariates showing significance of $P<0.05$. Mean flows were compared using paired 2-tailed Student t test. All analyses were performed with SPSS (version 21; IBM, Inc).

Results

Patient Characteristics
The study cohort consisted of 44 patients with a mean age of 67 years, and degree of stenosis averaging 76%. Sixty-four percent of patients presented with symptomatic stenosis. Patient and lesion characteristics are summarized in the Table.

Flow Versus Percentage Stenosis, Residual Lumen, and Stenosis Length
The mean ICA flow decreased as percentage stenosis increased (Figure 1) as follows: 206.4 (50–59% stenosis), 188.0 (60–69% stenosis), 180.9 (70–79% stenosis), 118.6 (80–89% stenosis), and 91.4 mL/min (90–98% stenosis). The difference in mean ICA flow between the 70% and 80% stenosis groups (180.9 versus 118.6 mL/min) was statistically significant ($P=0.02$). As percentage stenosis increased, there was also a corresponding significant decrease in ipsilateral ICA flow ratio ($P<0.01; \rho=-0.55$). MCA flow ratio was not significantly associated with percentage stenosis ($P=0.70; \rho=-0.06$) and remained essentially unchanged even in patients with severe ICA stenosis (Figure 2).

Smaller residual lumen was significantly associated with decreased ICA flow ratio ($P=0.04$) but not with MCA flow ratio ($P=0.78$; Figure III in the online-only Data Supplement). Neither ICA flow ratio ($P=0.82; \rho=+0.04$) nor MCA flow ratio ($P=0.86; \rho=-0.03$) was significantly correlated with plaque length.

Multivariate analysis showed that percentage stenosis ($P<0.001, 0.003$), but not residual lumen ($P=0.64, 0.88$) or stenosis length ($P=0.94, 0.54$) was an independent predictor of ICA flow and ICA flow ratio, respectively.

Intracranial Flow and Symptomatic Presentation
Mean ICA flow ratios were not significantly different among asymptomatic versus symptomatic patients (0.55 versus 0.55; $P=0.99$). However, mean MCA flow ratio was significantly lower in symptomatic patients (0.92 versus 1.22; $P=0.001$).

Discussion
Since Fisher 4 reported in 1951 that carotid artery occlusive disease can cause cerebral ischemia and infarcts, the pathophysiology of this phenomenon has been of keen interest. 5,9 Thromboembolism is presumed to be the most common cause of symptoms,9,10 yet the correlation of severity of stenosis with increased stroke risk implicates hypoperfusion as an alternative mechanism.2,3 Caplan et al9 have postulated that vessel narrowing and wall abnormalities are thromboembolic sources but that hypoperfusion may synergistically impair clearance of distal emboli.

According to Poiseuille’s law, the resistance to flow of a fluid with viscosity $\eta$ is equal to $8\eta L/\pi (d/2)^4$, where $L$ is the length of the tube and $d$ is the diameter. Thus, the effects of carotid artery disease on cerebral hemodynamics may entail consideration of factors other than percentage stenosis alone. Plaque length and residual lumen, in addition to percentage stenosis, have been previously demonstrated as variables predictive of ICA flow,7 but intracranial hemodynamics as measured by MCA flow has not been previously assessed. Here, we report that as percentage stenosis increases, ipsilateral ICA flow ratio on average decreases

### Table. Cohort Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>59</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>67 (41–82)</td>
</tr>
<tr>
<td>Symptomatic, %</td>
<td>64</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>84</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>51</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>23</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>28</td>
</tr>
<tr>
<td>Vessel measurements</td>
<td></td>
</tr>
<tr>
<td>Mean percentage stenosis (range)</td>
<td>76 (50–98)</td>
</tr>
<tr>
<td>Mean residual lumen, mm (range)</td>
<td>1.7 (0.4–3.2)</td>
</tr>
<tr>
<td>Mean stenosis length, mm (range)</td>
<td>9.0 (1.3–17.0)</td>
</tr>
<tr>
<td>ICA flows</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral ICA mean, mL/min (range)</td>
<td>146 (28–321)</td>
</tr>
<tr>
<td>Contralateral ICA mean, mL/min (range)</td>
<td>272 (173–478)</td>
</tr>
<tr>
<td>ICA flow ratio mean (range)</td>
<td>0.56 (0.11–1.17)</td>
</tr>
<tr>
<td>Intracranial (MCA) flows</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral MCA mean, mL/min (range)</td>
<td>117 (55–193)</td>
</tr>
<tr>
<td>Contralateral MCA mean, mL/min (range)</td>
<td>110 (53–208)</td>
</tr>
<tr>
<td>MCA flow ratio mean (range)</td>
<td>1.03 (0.4–2.17)</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; and MCA, middle cerebral artery.
Figure 2. Flow ratio vs percentage stenosis. A decrease in ipsilateral internal carotid artery (ICA) flow ratio but not middle cerebral artery (MCA) flow ratio is significantly associated with increasing percentage stenosis.

significantly, whereas MCA flow ratio remains maintained, even in patients with severe ICA stenosis. Similarly, smaller residual lumen was significantly associated with decreased ICA flow ratio but not with MCA flow ratio. These findings are consistent with those described by Powers et al using positron emission tomography, which demonstrated that the severity of a cervical carotid lesion alone cannot be used to extrapolate the intracranial hemodynamic status. The existence of collateral pathways can provide intracranial compensation for flow compromise within the ICA. These findings overall support the notion of thromboembolism as the primary culprit in ischemia related to carotid stenosis. However, we also found that MCA flow ratio was significantly lower in symptomatic patients (0.92 versus 1.22; P=0.001) suggesting that less effective collaterals with impairment of distal hemodynamics is also associated with ischemia. This observation potentially implicates intracranial hemodynamics in symptomatic presentation.

Limitations of our study are its retrospective design and small sample size. Nonetheless, our cohort is the largest to date to measure intracranial blood flow using quantitative magnetic resonance angiography in the setting of extracranial carotid stenosis. The possibility for blood flow to be affected by physiological parameters, including age, blood pressure, and effect of medications, is a potential concern when comparing flow measurements among patients. Consequently, ipsilateral-to-contralateral flow ratios indexing the stenotic ICA to the contralateral unaffected ICA were used to control for patient-specific systemic confounders, which may otherwise impact absolute flow measurements.

Conclusions

Based on our results, we conclude that percentage stenosis and residual lumen are significantly associated with ICA but not MCA flow, because intracranial flows can be maintained through collaterals. MCA flow, however, was compromised among symptomatic patients, highlighting the potential importance of distal hemodynamics in ischemia. Moreover, our study reveals the utility of quantitative magnetic resonance angiography as a noninvasive tool to quantitatively assess the hemodynamic impact of carotid artery stenosis. With further study, flow rates could potentially indicate critical thresholds prognostic of high stroke risk or disclose limited collateral supply that can be used to guide recommendations for revascularization.

Sources of Funding

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Disclosures

Dr Du receives salary support from the Dr Ralph and Marian Falk Research Trust. Dr Charbel has financial interest in VasSol, Inc. Dr Amin-Hanjani receives material research support (no direct funds) from GE Healthcare and VasSol Inc. The other authors report no conflicts.

References

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/11/3427

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/09/16/STROKEAHA.114.006622.DC1
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Supplemental Methods

**QMRA technique**

All subjects underwent phase contrast quantitative magnetic resonance angiography (QMRA) performed on a 1.5 Tesla or 3.0 Tesla magnetic resonance (MR) system (Sigma VHi, GE Medical system, Milwaukee, WI) using a 4-channel neurovascular coil. The volume flow rate measurements were acquired with the Noninvasive Optimal Vessel Analysis (NOVA) software (VasSol, Inc., River Forest, IL). To visualize major extracranial arteries in the neck, 2-dimensional (2D) MRA time-of-flight (TOF) technique (TR/TE, 23 ms/4.6 ms; flip angle, 60; FOV, 200mm; slice thickness, 2 mm; matrix, 256/192; NEX, 1) was performed first. Then, a 3D MRA TOF of the head was obtained with the following parameters: TR/TE, 23/3.3 ms; flip angle, 20; FOV, 220mm; 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, 10-15ms; TE, 4-7ms; flip angle, 15; NEX, 4; slice thickness, 3 mm for intracranial arteries and 5 mm for neck arteries; FOV, 140 mm for intracranial arteries and 180mm for neck arteries; matrix, 256x192 for intracranial arteries and 256x128 for neck 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.

The accuracy and precision of QMRA flow measurements using NOVA software have been published previously.²
Supplemental Figures

Figure I

Location of flow measurement using QMRA
A. Extracranial flow measurement: internal carotid artery
B. Intracranial flow measurement: middle cerebral artery
Blood vessel measurements from digital subtraction angiography: Vessel residual lumen was measured at the point of maximal stenosis. Length of stenosis was measured as demonstrated by the line with arrowheads. Degree of stenosis was determined using the NASCET criteria: 1 - diameter of maximal stenosis/diameter of normal distal segment x100, as shown.³
Flow ratio versus residual lumen: increased residual lumen is significantly associated with increased internal carotid artery (ICA) flow ratio ($P=0.04$, rho=+0.32) but not with middle cerebral artery (MCA) flow ratio ($P=0.78$, rho=+0.04).
Supplemental References


두개강외 경동맥협착이 두개강내 혈류에 미치는 효과

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(Stroke. 2014;45:3427-3429.)

Key Words: carotid arteries • carotid stenosis • magnetic resonance angiography

배경과 목적 두개강외 경동맥협착이 두개강내 혈류에 미치는 혈역학적 효과에 대해서는 잘 알려져 있지 않다. 본 연구는 두개강외 경동맥협착을 가지고 있는 환자에서 혈류의 정도, 길이, 잔여 내경이 두개강내 혈류 변화에 미치는 영향을 평가하였다.

방법

정량적 자기공명영상과 다지털감란형영상을 모두 시행받은 경동맥협착 환자들을 조사하였다. 혈류의 측정 지표가 동측의 내경동맥 혈류와 동측-반대측 중대뇌동맥 혈류비에 미치는 영향을 평가하였다.

결과

본 연구는 44명의 환자(평균 연령 67세, 증상성 64%)를 대상으로 진행하였다. 혈류 정도가 심하고(P<0.01) 잔여 내경이 작을수록(P=0.04) 내경동맥 혈류 감소와 유의한 연관이 있었다. 다변량 분석에서 혈착 정도는 두개강내 혈류의 유의한 연관 변수였다(P<0.001). 중대뇌동맥혈류비는 혈착 정도, 혈착 길이, 잔여 내경과 유의한 연관성을 보이지 않았다. 평균 중대뇌동맥혈류비는 무증상 환자보다 증상성 환자에서 더 낮았고(1.22 vs 0.92; P=0.001), 반대로 평균 내경동맥혈류비는 두 그룹에서 비슷하였 다(0.55 vs 0.55; P=0.99).

결론

혈착 정도와 잔여 내경은 내경동맥 혈류와 유의한 연관성이 있었지만, 중대뇌동맥 혈류와는 관계 없었다. 두개강내 혈류는 측부순환으로 유지될 수 있기 때문에 경동맥협착에 의한 혈역학적 효과는 원위부의 혈관까지 작용하지 않는다는 것을 시사한다. 증상성 환자에서 관찰된 낮은 중대뇌동맥 혈류비는 원위부 혈역학적 상태가 증상 발생에 중요하다는 잠재적인 가능성을 시사한다.

Figure 1. Mean internal carotid artery (ICA) flow for incremental categories of percentage stenosis. The difference in flow between the 70% to 79% and 80% to 89% stenosis groups was statistically significant.