Leptomeningeal collaterals (LMCs) play a pivotal role in sustaining cerebral perfusion in patients with sten-occlusive disease of the internal carotid artery (ICA) and middle cerebral artery (MCA). Indeed, patients with inadequate LMC have increased stroke risk caused by hypoperfusion or impaired washout of thromboemboli. Consequently, structural and functional assessment of LMC is used to guide management decisions in these patients.1

Digital subtraction angiography (DSA) remains the gold standard for determining LMC structure and anatomy despite its invasive nature.1 On the other hand, positron emission tomography and single-photon emission computed tomography or transcranial Doppler combined with a vasodilator have been used for functional assessment of LMC by measuring the autoregulatory capacity of cerebral blood flow or cerebrovascular reserve (CVR).3 Quantitative magnetic resonance angiography (QMRA) is another noninvasive technique that can be used to measure flow before and after Diamox challenge and has several advantages over the above methods, namely, flow changes are provided in all intracranial vessels without the use of radiotracers or ionizing contrast agents.4,5

In this study, we examined the relationship between the degree of LMC and the flow change with Diamox challenge measured using QMRA, hypothesizing that these flow changes correlate with indicators of impaired CVR and thus may be used to evaluate CVR in chronic carotid artery or MCA steno-occlusive disease. (Stroke. 2016;47:1658-1660. DOI: 10.1161/STROKEAHA.116.013015.)

**Key Words:** acetazolamide ▼ angiography, digital subtraction ▼ hemodynamics ▼ magnetic resonance angiography ▼ middle cerebral artery

---

**Background and Purpose**—Impaired cerebrovascular reserve in chronic steno-occlusive disease has been shown to be associated with poor leptomeningeal collaterals (LMCs) on digital subtraction angiography and increased stroke risk.2 We examined the relationship between the degree of LMCs and the flow change with Diamox challenge measured using quantitative magnetic resonance angiography (QMRA).

**Methods**—Patients with steno-occlusion in the internal carotid artery or middle cerebral artery (MCA) at our institution between 2007 and 2013 were retrospectively studied. Intracranial flows were obtained using QMRA, and flow change with Diamox (QMRA_{Δd}) was calculated as follows: ([flow after Diamox−flow before Diamox]/[flow before Diamox])×100%. Poor LMC was defined as grade 1 or 2, and robust LMC was defined as grade 3 or 4 based on the ASITN/SIR (American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology) grading system on digital subtraction angiography.

**Results**—Thirty-eight patients had angiographic and flow data. Ipsilateral MCA QMRA_{Δd} was significantly lower versus the contralateral side (flow, 85.5 versus 135.9 mL/min; P<0.001 and QMRA_{Δd}, 24.0% versus 45.6%; P=0.01). If LMCs were robust (n=12), MCA QMRA_{Δd} was significantly higher (21.4% versus −26.8%; P=0.04) compared with patients with poor LMC (n=4).

**Conclusions**—We show that patients with more robust LMC have better MCA QMRA_{Δd}. Therefore, QMRA_{Δd} may be used for the functional assessment of LMC as a surrogate for cerebrovascular reserve in chronic internal carotid artery or MCA steno-occlusive disease.
LMC Grading
Collaterals were assessed with the ASITN/SIR (American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology) grading system. These grades include 0=no LMCs visible to MCA territory, 1=slow LMCs to the periphery of MCA territory, 2=rapid LMCs to the periphery of MCA territory, 3=LMCs with slow but complete angiographic blood flow to MCA territory, and 4=complete and rapid LMCs to the MCA territory. Subsequently, collaterals were categorized as poor (grade 1 or 2) and robust (grade 3 or 4).

We did not include patients with grade 0 or the absence of LMC in our binary scale as most of our subjects had ICA steno-occlusive disease, and the absence of LMC in these patients indicates robust primary collateral pathways that supply the MCA territory through anterograde flow.

Blood Flow Measurements Before and After Diamox
All patients underwent flow measurements of the extracranial and intracranial arteries before and after Diamox administration using QMRA.

MCA flow change with Diamox (QMRA $\Delta d$) was calculated as follows: $\frac{(\text{flow after Diamox} - \text{flow before Diamox})}{\text{flow before Diamox}} \times 100\%$.

Statistical Analysis
Ipsilateral and contralateral MCA QMRA $\Delta d$ were compared using paired 2-tailed Student t tests. Ipsilateral QMRA $\Delta d$ was compared between poor and robust LMC groups using independent 2-tailed Student t tests. The relationship between QMRA $\Delta d$ and degree of LMC was assessed using Spearman correlation. Analyses were performed with SPSS (version 22; IBM, Inc).

Results
Patient Characteristics
Our cohort consisted of 38 patients with a mean age of 60 years. Mean percentage stenosis was 93% (range, 50%–100%), 90% had severe stenosis $\geq 70\%$, and 10% had moderate stenosis defined as 50% to 70%. Fifty-seven percent of LMC were grade 0, 2% grade 1, 8% grade 2, 2% grade 3, and 31% grade 4.

Relationship Between QMRA $\Delta d$ and Degree of LMC
Mean ipsilateral MCA QMRA $\Delta d$ was significantly impaired compared with the contralateral side (24.0% versus 45.6%; $P=0.01$). Among patients with poor LMC (n=4), mean MCA QMRA $\Delta d$ was significantly lower compared with the mean MCA QMRA $\Delta d$ in patients with robust LMC (n=12; $-26.8\%$ versus $21.4\%$; $P=0.04$; Figure 1). Spearman correlation between MCA QMRA $\Delta d$ and the degree of LMC demonstrated a positive but nonsignificant relationship ($\rho=+0.36$; $P=0.18$).

Discussion
This is the first study to investigate the relationship between flow changes with Diamox challenge (QMRA $\Delta d$) measured using QMRA and degree of LMC determined from DSA in patients with chronic ICA or MCA steno-occlusive disease. We showed that patients with robust LMC (grade 3 or 4) had significantly better MCA QMRA $\Delta d$ than patients with poor LMC (grade 1 or 2; $21.4\%$ versus $-26.8\%$; $P=0.04$). Illustrative cases are shown in Figures 2 and 3. Therefore, QMRA $\Delta d$ measured using QMRA with Diamox challenge may be used for the functional assessment of LMC and as a surrogate for CVR.

Robust collateral perfusion has been shown to compensate for compromised cerebral hemodynamics and has been linked to better CVR. Consequently, identification of patients with poor collateral flow and impaired CVR can guide treatment decision making in chronic steno-occlusive disease. Compared with existing modalities used to measure CVR, such as positron

Figure 1. Middle cerebral artery (MCA) flow change with Diamox (QMRA $\Delta d$) vs degree of leptomeningeal collateral (LMC). MCA QMRA $\Delta d$ was significantly higher in the presence of robust versus poor collateralization (21.4% vs $-26.8\%$; $P=0.04$).

Figure 2. A–C, Illustrative case 1, patient with left internal carotid artery (ICA) occlusion and robust collateralization. A, Arterial phase of digital subtraction angiography (DSA) after right ICA injection showing robust collateralization. B, Capillary phase of DSA after right ICA injection showing robust collateralization. C, Quantitative magnetic resonance angiography flow map with right middle cerebral artery (MCA) flow change with Diamox measured as 21% (right box).
emission tomography, single-photon emission computed tomography, and transcranial Doppler. QMRA provides objective and direct measurement of flow changes after Diamox challenge in all principal intracranial vessels simultaneously without exposing subjects to radiotracers or iodinated contrast dye.\textsuperscript{4,5}

Previously, multiple studies focused primarily on the correlation of CVR and pattern of collateralization rather than LMC grade in patients with ICA stenosis and reported conflicting results. These studies used varying modalities to measure CVR and to determine the presence of LMC, including transcranial Doppler. Some studies concluded that the presence of LMC is associated with poor CVR.\textsuperscript{10-12}

In this study, we examined the importance of functional status and grade of LMC in compensating for cerebral hemodynamic impairment instead of the presence of LMC alone. Indeed, we showed that robust rather than poor LMC is associated with higher QMRA\textsubscript{\Delta d}. We did not find a statistically significant correlation between all grades of LMC and MCA QMRA\textsubscript{\Delta d}, possibly because our patients were not equally distributed among different LMC subgroups.

\textbf{Study Limitations}

Our study is a retrospective review with a small sample size. In addition, patients were not distributed homogeneously across LMC subgroups. These limitations highlight the need for a larger prospective study on patients with different degrees of MCA or ICA stenosis with baseline QMRA\textsubscript{\Delta d} and LMC grade who are followed up over time for development of stroke.

\textbf{Conclusions}

We show that patients with more robust LMC have better MCA QMRA\textsubscript{\Delta d}. Therefore, QMRA\textsubscript{\Delta d} may be used for the functional assessment of LMC as a surrogate for CVR in chronic ICA or MCA steno-occlusive disease.

\textbf{Acknowledgments}

We thank Dr Dilip K. Pandey, director of clinical research, for reviewing the article.

\textbf{Disclosures}

Dr Alaraj received research grant from National Institutes of Health (NIH) and is a consultant for Cordis-Codman. Dr Amin-Hanjani received research grant from NIH and research support (no direct funds) from GE Healthcare and VasSol Inc. Dr Charbel received ownership interest from VasSol Inc and is a consultant for Transonic. The other authors report no conflicts.

\textbf{References}


Angiographic Correlates of Cerebral Hemodynamic Changes With Diamox Challenge Assessed by Quantitative Magnetic Resonance Angiography
Mersedeh Bahr-Hosseini, Sophia F. Shakur, Sepideh Amin-Hanjani, Fady T. Charbel and Ali Alaraj

Stroke. 2016;47:1658-1660; originally published online April 19, 2016; doi: 10.1161/STROKEAHA.116.013015
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/47/6/1658

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/