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Detection of Intracranial In-Stent Restenosis Using Quantitative Magnetic Resonance Angiography

Sepideh Amin-Hanjani, MD; Ali Alaraj, MD; Mateo Calderon-Arnulphi, MD; Victor A. Aletich, MD; Keith R. Thulborn, MD, PhD; Fady T. Charbel, MD

Background and Purpose—In-stent restenosis (ISR) after angioplasty/stenting for intracranial stenosis has been reported in up to 25% to 30% of patients. Detection and monitoring of ISR relies primarily on serial catheter angiography, because noninvasive imaging methods are typically hampered by stent-related artifact. We examined the value of serial vessel flow measurements using quantitative magnetic resonance angiography (QMRA) in detection of ISR.

Material and Methods—Records of patients undergoing stenting for intracranial symptomatic stenosis >50% between 2005 and 2009 were retrospectively reviewed. Angiographic images were graded by a blinded neurointerventionalist for stenosis pretreatment, immediately after treatment, and during follow-up. Flow in the affected vessel measured by QMRA was recorded; >25% reduction in flow was considered indicative of an adverse change. Clinical data regarding neurological outcome were also collected.

Results—Twenty-eight patients underwent stenting during the time interval studied. Of these, 12 patients (mean age, 55.5 years; 8 female) had contemporaneous angiography and QMRA and were analyzed. Median follow-up was 9 months. Six patients (50%) demonstrated angiographic restenosis 2 to 12 months after treatment; all had an analogous decrease in flow in the vessel of interest. Of 3 patients with more severe flow decrement (>50%), 2 experienced stroke. None of the patients without angiographic ISR demonstrated a flow decrease on QMRA.

Conclusions—In this preliminary series, flow decrease on QMRA is highly predictive of angiographic ISR. Additionally, the degree of flow decrement correlates with symptomatic ISR. QMRA may provide a useful noninvasive tool for serial monitoring after intracranial stenting. (*Stroke*. 2010;41:2534-2538.)

Key Words: angioplasty ■ intracranial stenosis ■ magnetic resonance angiography ■ stent ■ stroke

Intracranial atherosclerosis is an increasingly recognized etiology of stroke, responsible for 8% to 10% of all ischemic strokes in the United States.^{1,2} Symptomatic intracranial stenosis has a high risk of recurrent stroke despite medical therapy.³ In recent years, endovascular angioplasty combined with stenting has emerged as the favored interventional treatment for recurrently symptomatic intracranial stenosis over angioplasty alone. However, recent series of intracranial stenting have reported in-stent restenosis (ISR) to be a significant issue, occurring in up to 25% to 35% of patients.^{4–7} Currently, detection of ISR relies primarily on serial conventional catheter angiography. Although a noninvasive alternative would be desirable, imaging with noninvasive modalities, such as computed tomographic angiography and magnetic resonance angiography (MRA), is typically hampered by stent-related artifact. A potential alternative is measurement of the blood flow within the stented vessel to identify ISR based on its physiological effects on flow, rather than its anatomic appearance. Large vessel flow measurements of this type can be performed with quantitative MRA

(QMRA) using phase-contrast MR technique. In this report, we examine the value of serial vessel flow measurements using QMRA in the detection of ISR.

Patients and Methods

Patient Selection

A retrospective review of all patients undergoing intracranial angioplasty/stenting for intracranial stenosis over a 4-year period from January 2005 through December 2009 was performed with Institutional Review Board approval. Patients who had undergone contemporaneous imaging follow-up with angiography and QMRA were selected and analyzed. Clinical data regarding neurological symptoms and outcome were collected.

Blood Flow Measurements Using QMRA

Flow measurements of the major intracranial vessels were performed using the technique of blood flow quantification by QMRA previously described⁸ and implemented with commercially available software called Noninvasive Optimal Vessel Analysis (NOVA) (VasSol Inc., Chicago, Ill). Briefly, an axial 2-dimensional or 3-dimensional time-of-flight MRA is first performed. The acquired images are then transmitted to a computer workstation where the

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Table. Patient Characteristics

	Age, yr	Gender	Location	Initial Stenosis, %	Stenosis After Treatment, %	Follow-Up Stenosis, %	Flow After Treatment	Follow-Up Flow, mL/min	Follow-Up, mo	Outcome	ISR	Flow Decrease
No ISR												
1	52	F	MCA	74	33	50	103*	111	20	No new symptoms	No	No
2	68	F	MCA	88	5	5	127	139	22	No new symptoms	No	No
3	63	M	BA	75	13	35	95*	94	9	No new symptoms	No	No
4†	52	M	VA	91	36	17	180*	140	30	No new symptoms	No	No
5	57	M	VA	84	56	67	196	158	6	No new symptoms	No	No
6‡	49	F	VA†	81	30	26	179	207	9	No new symptoms	No	No
ISR with >25% flow decrease												
7	49	F	ICA	86	38	71	222	145	2	TIA at 4 mo, stenosis 78%, flow N/A, re-plasty	Yes	>25%
8	54	F	ICA	90	30	75	300	218	5	No symptoms at 5 mo, re-plasty	Yes	>25%
9‡	68	M	VA	80	17	77	151	90	12	No new symptoms	Yes	>25%
ISR with >50% flow decrease												
10	37	F	ICA	76	46	83	367	94	4	Stroke at 4.5 mo, stenosis 90%, flow 33, re-plasty	Yes	>50%
11	72	F	ICA	81	41	80	341	98	12	Stroke at 12 mo, re-plasty	Yes	>50%
12	45	F	MCA	79	46	84	139	20	6	Cognitive decline at 6 mo, re-plasty	Yes	>50%

BA indicates basilar artery; F, female; ICA, internal carotid artery; ISR, in-stent restenosis; M, male; MCA, middle cerebral artery; N/A, not available; VA, vertebral artery.

*Initial flow measurement performed 4 months after stenting.

†Flow measurements in BA indicated as left vertebral artery flow not measured in studies (patient with occluded right vertebral artery).

‡Patients treated with stents other than Wingspan: patient 4, Biodiv Ysio stent (Abbott Laboratories, Abbott Park, Ill); patient 6, Cypher drug-eluting stent (Cordis Corporation, Bridgewater, NJ); patient 9, Taxus drug-eluting stent (Boston Scientific Corporation, Natick, Mass).

NOVA software is used to create a rotating 3-dimensional surface rendering of the vasculature, including the circle of Willis, using a marching cube algorithm.⁸ From the scan line calculated by a line-fitting algorithm, a double-oblique scan is performed using gated 2-dimensional phase-contrast MRI perpendicular to the vessel axis. A flow report including the mean volumetric flow rate (mL/min) on each vessel of interest is created using the NOVA software. All the images were acquired with the use of 1.5-T or 3-T MRI scanner (General Electric, Milwaukee, Wis). The flow values relevant to the stented vessel were recorded and followed-up over serial QMRA measurements. For patients with short segment disease, or in long vessel segments (such as the internal carotid artery), the scan line for flow measurement was preferentially placed proximal to the diseased segment to reduce the effect of turbulent flow. Otherwise, flow was measured within the stented segment using a dedicated thin slab technique, whereby a single slab with high-resolution images (10-mm slab consisting of 10 1-mm-thick slices) prescribed perpendicular to the expected flow direction within the long axis of the stent was performed. A consistent site for measurement relative to the stent was used for any given patient.

A >25% reduction in flow compared to that of initial QMRA after treatment was considered indicative of an adverse change based on existing literature on cerebral blood flow and perfusion thresholds, which indicates that flow compromise in the 20% to 25% range is correlated with cerebral ischemia.⁹⁻¹²

Angiographic Evaluation

The angiographic images of the selected patients were reviewed by a blinded neurointerventionalist unfamiliar with the flow measurements on QMRA. The regions of most severe stenosis on pretreatment, immediately after stenting, and follow-up angiograms were graded by Warfarin-Aspirin Symptomatic Intracranial Disease criteria.¹³ ISR on follow-up angiography was defined as recurrent stenosis >50%, except in patients with residual stenosis >30% immediately after stenting, in whom an increase in stenosis more

than half of the difference between stenosis before and after treatment was designated as ISR, eg, if initial stenosis is 80% and poststent stenosis is 40%, then ISR would be defined as restenosis ≥60%. This additional criteria was utilized for patients with significant residual stenosis; otherwise, even a small degree of further stenosis would qualify as ISR. In our retrospective series, absolute vessel measurements were not available to allow use of previous criteria relying on absolute luminal loss in such patients.⁶

Analysis

The data were analyzed for a correlation between flow decrement, angiographic ISR, and new neurological events. All statistical analyses were performed with Stata (Intercooled version 8.2; Stata Corporation, College Station, Tex).

Results

Patient Demographics

During the period reviewed, 28 patients underwent stenting for symptomatic intracranial stenosis. The indication for stenting in all cases was recurrent ischemic symptoms despite optimal medical therapy including antiplatelet agents in the setting of >50% stenosis. Of this group, 12 patients had both angiography and QMRA performed during follow-up and were analyzed. The group consisted of 8 (75%) females and 4 males, with a mean age of 55.5 years (Table). Stenosis affected the anterior circulation in 7 (58%) patients and the vertebrobasilar system in 5 patients. The majority of patients (75%) were treated with the Wingspan self-expanding intracranial stent (Boston Scientific Corporation, Natick, Mass).

ISR and Blood Flow Measurements

Angiographic ISR was encountered in 6 patients (50%). Time interval to ISR was 2 to 12 months (median, 5.5 months), and

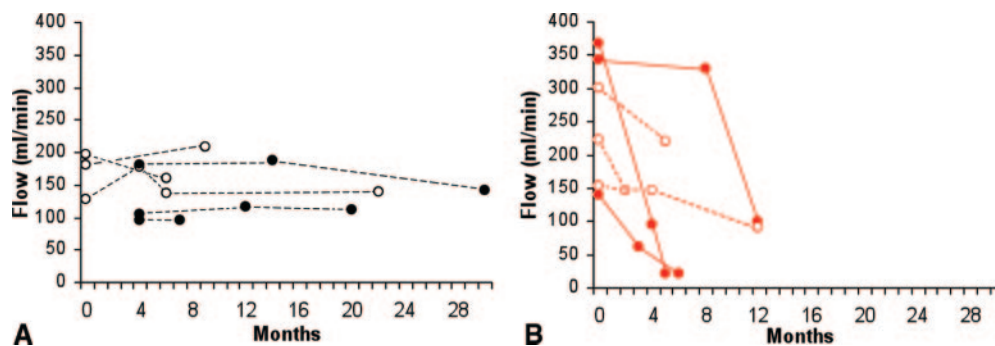


Figure 1. Flow (mL/min) in stented vessel over time in patients without (A) and with (B) angiographic in-stent restenosis. Solid black circles indicate patients with initial flow measurement at 4 months after stent. Solid red circles and lines indicate >50% flow decrease.

all episodes of angiographic ISR demonstrated an analogous decrease in flow of >25% in the vessel of interest compared to poststenting baseline (Figure 1B). None of the 6 patients without angiographic ISR demonstrated a decrease in flows on QMRA (Figure 1A, Figure 2) over a follow-up of 6 to 30 months.

Of the patients without flow decrease, none experienced new neurological symptoms over the course of follow-up. Of the patients with flow decrease, 3 demonstrated a more severe flow decrement >50% compared with initial post-treatment flow that decreased to, or below, pretreatment baseline flow (Figure 3). Among these, all were symptomatic; 2 had recurrent stroke in the territory of the affected vessel and the other (a patient with Down syndrome) had cognitive decline and decreased functioning, although no new strokes were evident on imaging. Among the 3 patients with less severe flow decrease, 1 experienced a subsequent TIA and underwent re-angioplasty at that time (Table). In considering stroke outcome, the patients with severe flow decrease experienced a stroke event rate of 67% compared to 0% in the remainder of the cohort ($P=0.05$).

Discussion

In a small cohort of patients with intracranial disease undergoing angioplasty and stenting, a flow decrement of >25% detected by QMRA was found to be indicative of angiographic ISR. Furthermore, a more severe flow decrement of

>50% relative to immediate post-treatment flow was associated with symptomatic ISR.

Despite the increased feasibility and procedural safety of intracranial stenting, recent published series of the Wingspan self-expanding stent and other intracranial stents have demonstrated a high rate of early ISR, ranging from 25% to 34.5% of cases.^{5,6,14} Risk factors for ISR included younger age (younger than 55 years) and anterior circulation disease.¹⁵ The relatively higher incidence of ISR in our study may reflect the younger age of our selected cohort compared to the previous registries.

A noninvasive method for detecting ISR would avoid invasive conventional angiography and its associated 1% risk of procedural complications.¹⁶ The utility of QMRA for measurement of intracranial vessel flow measurement already has been demonstrated for a variety of cerebrovascular conditions,^{9,17} including carotid stenosis and vertebrobasilar disease, and may have a role in the primary evaluation of intracranial stenosis by identifying flow-limiting disease.⁹ Its value for serial monitoring also has been previously reported in evaluation of extracranial-intracranial bypass surgery, whereby QMRA flow measurements through the graft accurately identified stenosis or diminution of the bypass based on critically low or rapidly decreasing (>30%) flow compared to baseline.¹⁸ QMRA has been useful in the detection of ISR in extracranial vessels in individual reported cases¹⁹ and was recently demonstrated to have a high sensitivity for detection

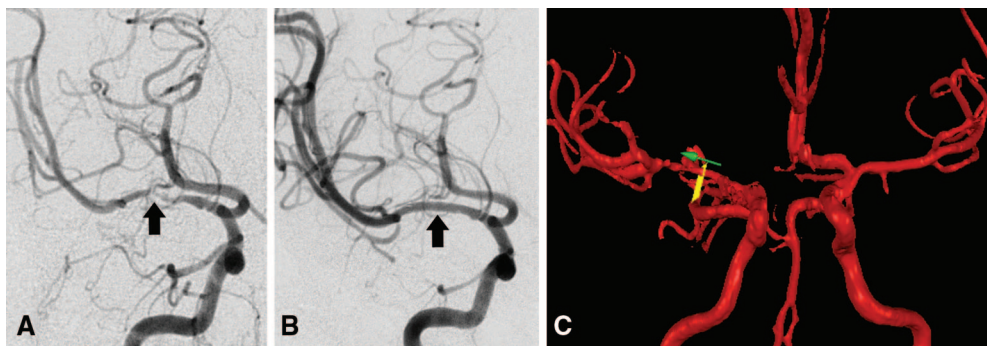


Figure 2. A, Conventional catheter angiogram demonstrating 88% stenosis of the right middle cerebral artery (MCA; arrow). QMRA indicated very poor flow in the MCA at <10 mL/min. B, Angiogram after angioplasty and Wingspan stent placement demonstrates minimal residual stenosis (arrow). C, NOVA system 3-dimensional surface rendering of the cerebral vasculature after stenting (arrow indicates direction of flow) improved to 127 mL/min. Flow remained stable over the course of follow-up, which was last measured as 139 mL/min 22 months after stenting.

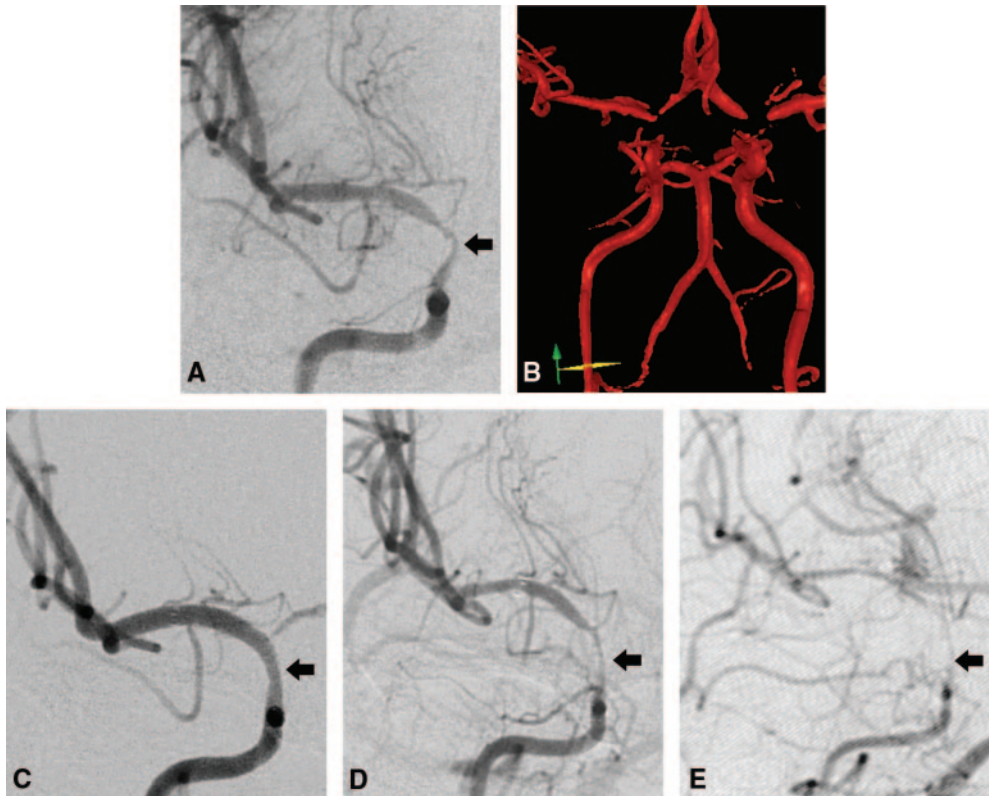


Figure 3. A, Conventional catheter angiogram demonstrating 76% stenosis of the supraclinoid right internal carotid artery (ICA). B, NOVA system 3-dimensional surface rendering of the vasculature demonstrating the scan line on the ICA proximal to the region of disease (arrow). QMRA measured a flow of 139 mL/min before treatment. C, Immediately after angioplasty and Wingspan stent placement, mild residual stenosis (arrow) is demonstrated. QMRA flow improved to 367 mL/min. D, At 4 months of follow-up, angiography reveals in-stent restenosis (ISR) with 83% recurrent stenosis (arrow) and flow decrease to 94 mL/min. Two weeks later, the patient had a right hemispheric stroke. E, Angiogram after the stroke demonstrated progressive ISR >90%, with further decrease in flow on QMRA to 33 mL/min.

of in-stent stenosis intracranially in a study of 14 patients with stents placed primarily for wide-neck intracranial aneurysms (1 stent placed for atherosclerotic stenosis).²⁰ The authors found that vessel flow >20% lower than normative ranges was indicative of the presence of angiographic stenosis >50%.²⁰ Our study is the first report to our knowledge to exclusively study a cohort of patients with intracranial stenosis and to document the value of flow decrease in detecting angiographic ISR. Our approach does not rely on normative flow ranges, because the flow within a vessel can vary widely based on age, cerebrovascular anatomy, and residual stenosis after treatment. Comparison to post-treatment baseline flow provides an internal control for follow-up flow measurements.

ISR appears to be the primary etiology for recurrent stroke in the follow-up period, after the periprocedural risk phase,^{4,5,7} and is amenable to retreatment with either angioplasty alone or restenting with apparent safety. In the U.S. Wingspan registry, for example, 29 patients underwent retreatment for ISR, with a low 2.4% procedural risk.²¹ Detection of high-risk ISR, therefore, would identify a subgroup of patients with restenosis who may benefit from early retreatment. Our data would suggest that QMRA may have the potential to identify such a group, specifically those with more severe flow decrease.

Our study is limited by the small sample size and retrospective nature of data collection. We attempted to limit bias by using a neurointerventionalist blinded to the QMRA results for measurement of angiographic stenosis. However, determination of clinical end points is still subject to ascertainment bias. Additionally, because all of the patients undergoing stenting in the study period could not be included because of lack of contemporaneous QMRA and angiography, there is a potential for selection bias. Our data do not address the optimal timing for flow measurement after stenting, and some patients may experience an initial period of hyperperfusion. Comparing immediate poststent flow to vessel-specific normative values²² may help to identify this possibility; however, ultimately, future examination of flow at more frequent intervals would be needed to determine optimal timing. Prospective validation of our findings in a larger cohort would be important in confirming the utility of QMRA for detection of ISR.

Conclusion

Our data suggest that QMRA may provide a useful noninvasive method for detecting ISR by identifying flow decrease in the stented vessel. Furthermore, the extent of flow decrement may be predictive of ISR at high risk for recurrent stroke.

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