Illustrative Teaching Case
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Symptomatic Intracranial Atherosclerosis
With Impaired Distal Perfusion
A Case Study
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Case Description
An 82-year-old woman with a history of hypertension presented to the emergency department with a 1-week history of 3 episodes of word-finding difficulty and right arm weakness lasting for a few minutes each without any known triggers or associated neurological symptoms.

On arrival, her blood pressure was 174/84 mmHg. Her general and neurological examination showed mild expressive aphasia. Neuroimaging was immediately undertaken with computerized tomographic angiogram of the brain and neck, demonstrating high-grade proximal left M1 stenosis without cervical artery stenosis (Figure 1). She then underwent magnetic resonance imaging (MRI) of the brain with perfusion imaging with rapid processing of perfusion and diffusion (RAPID), which demonstrated delayed perfusion in the left middle cerebral artery territory and small left hemispheric infarcts (Figure 2, top). She was started on aspirin, clopidogrel, and high-intensity statin therapy and admitted to the stroke unit. A transthoracic echocardiogram was unremarkable, her glycosylated hemoglobin was 5.7%, and low-density lipoprotein was 131 mg/dL. Her stroke was attributed to intracranial atherosclerosis. She was discharged on dual antplatelet therapy and high-intensity statin therapy with persistent mild expressive aphasia.

Two weeks after discharge, she represented with right hemiplegia and severe near-global aphasia. Her blood pressure was 130/82 mmHg. Computerized tomographic angiogram of the head and neck was stable. A repeat brain MRI with RAPID showed expansion of infarcts to involve the left corona radiata (Figure 2, bottom). Because of the large hypoperfused penumbra on MRI and suspected pressure-dependent examination, decision was made to augment cerebral blood flow, and she was placed on norepinephrine with a goal of systolic blood pressure ≈ 120 mmHg, which led to regaining of speech; however, her right hemiplegia persisted. She was then started on oral midodrine and fludrocortisone, her home blood pressure medications were held, and she was slowly weaned off norepinephrine after 48 hours. During her hospital stay, her blood pressure goal was initially liberalized to 160 to 180 mmHg systolic and then 140 to 160 mmHg systolic. Her examination subsequently stabilized after 1 week with mild-to-moderate global aphasia and severe right hemiparesis. Follow-up brain MRI RAPID showed improvement in the perfusion deficit (Figure 2), and she was discharged to a skilled nursing facility. On discharge, her blood pressure goal was liberalized to normotension with a goal of ≤ 140 mmHg systolic. The patient’s recurrent symptoms were felt to be attributable to a pressure-dependent examination, often referred to as misery perfusion.

Discussion
Intracranial atherosclerotic disease (ICAD) is an important stroke mechanism, accounting for 9% to 17% of all strokes.1 Certain demographic and clinical factors predispose to intracranial atherosclerosis; the incidence seems to be the highest in blacks and those of Asian descent, with whites having the lowest incidence. Additionally, hypertension, diabetes mellitus, hyperlipidemia, and age are associated with the risk of developing ICAD. Angiography is considered the gold standard for diagnosis of ICAD; however, noninvasive tests, such as computerized tomographic angiography, magnetic resonance angiography, and transcranial Doppler ultrasound, are often used.2

ICAD can cause strokes by way of 3 mechanisms: artery-to-artery embolism, flow failure or hypoperfusion, and branch-atheromatous disease; of these, artery-to-artery embolism seems to be the most common.2 Studies have shown a relatively high risk of recurrent cerebrovascular events in patients with symptomatic ICAD. The SAMMPRIS study (Stenting Versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) showed that the risk of recurrent events is ≈ 12% at 1 year and 20% at 2 years from the initial event.3 However, the SAMMPRIS trial excluded patients with worsening deficits during the 24 hours preceding stent placement. So it did not address the subpopulation of patients with worsening neurological symptoms, despite medical therapy, such as our patient during her second admission. Other studies have shown that the highest risk of recurrence or worsening in patients with intracranial or
extracranial large-vessel atherosclerotic disease is in the first few days after the initial event.4,5

Perfusion-based imaging has been recently used to aid with acute stroke treatment decisions in patients with emergent proximal large-vessel anterior circulation intracranial occlusion. At our institution, we use RAPID—a software, which computes quantitative perfusion maps and can calculate the ratio of ischemic infarct on diffusion weighted imaging to the hypoperfused penumbra.6 Recent data demonstrates the benefit from mechanical thrombectomy using perfusion-based imaging selection with RAPID software beyond 6 hours from symptom onset.7 This may also be the case in patients with ICAD where there has been increased use of perfusion imaging to predict stroke risk with a recent study showing an increased risk of recurrent stroke in patients with impaired distal blood flow.8 In addition to perfusion, 1 study demonstrated that absent or poor collaterals portended a high risk of stroke recurrence rate, whereas rapid filling of collateral vessels was relatively protective against stroke recurrence.9

To date, aggressive medical treatment with antiplatelet agents, statins, and risk-factor modification remains the treatment of choice for patients with symptomatic ICAD.1 Aggressive medical treatment, however, may help stabilize atherosclerotic plaques and reduce the risk of embolization, but it is unlikely to significantly and acutely improve blood flow to tissue at risk and prevent neurological deterioration. In fact, impaired distal blood flow detected by noninvasive imaging has been shown to predict stroke risk in patients with extracranial and ICAD, despite medical therapy.8

Hence, patients with symptomatic ICAD and impaired blood flow remain a therapeutically challenging subgroup. Although small trials and case reports have demonstrated the clinical phenomenon of vasopressor-responsive flow failure, there are no randomized clinical trials studying this phenomenon.10 Given that pressure dependence is theoretically predicated on the presence of a penumbra, it is possible that the widespread implementation of perfusion imaging may help identify patients in whom a higher blood pressure target may be beneficial. Induced hypertension, however, is not an ideal treatment because the duration and blood pressure target are widely variable among patients and there are potential significant adverse events from prolonged use of vasopressors. In the SAMMPRIS trial, blood pressure lowering appeared to be safe and was included as part of the medical management arm.

Furthermore, patients with symptomatic ICAD and unfavorable perfusion may benefit from revascularization therapy beyond aggressive medical management alone. This has already been suggested regarding treatment of extracranial large-artery stenosis in a pooled analysis of completed randomized trials of carotid endarterectomy. In patients with ICAD, the 2 prior randomized trials that assessed interventions for intracranial atherosclerotic stenosis, SAMMPRIS1 and VISSIT (Vitesse Intracranial Stent Study on Ischemic Therapy),11 did not select patients based on perfusion status. In SAMMPRIS, the periprocedural complication rate was ≈15% in the first 30 days. Recently, results from the WEAVE (Wingspan Stent System Post Market Surveillance Study) registry of symptomatic ICAD showed a relatively low risk of periprocedural complications (~5% at 30 days) with stenting when compared with the reported rates in the SAMMPRIS study (NCT02034058). The authors attribute this to increased operator experience with the device and perhaps because of a submaximal angioplasty alone strategy. Because of the high recurrence risk in patients with symptomatic ICAD and impaired perfusion, these patients may be a distinctive group in whom the safety of revascularization and reperfusion against the risk of neurological deterioration in medically treated patients may be studied.

In addition to endovascular treatment, surgical revascularization by way of external carotid to internal carotid bypass through connecting the superficial temporal artery to the middle cerebral artery has been studied but failed to benefit patients with severe middle cerebral artery stenosis.12 More recent studies have explored indirect bypass by way of encephaloduroarteriosynangiosis, wherein the superficial temporal artery is transposed directly onto the brain, allowing it to form collaterals. Preliminary studies of this procedure in patients with moyamoya have been more promising than with atherosclerotic disease, where small prospective trials have shown no benefit.13,14

Our patient had minor neurological symptoms but had evidence of impaired distal blood flow on the initial brain MRI RAPID and exhibited neurological deterioration, despite aggressive medical treatment. Clinical trials investigating the safety of reperfusion treatment in this patient population are needed with an ultimate goal to reduce the risk of neurological deterioration in patients with symptomatic ICAD causing impaired distal blood flow.
Figure 2. The patient's sequential rapid processing of perfusion and diffusion (RAPID) magnetic resonance imaging (MRI) demonstrates the evolution of the perfusion deficit. The top of the figure shows the initial RAPID MRI with punctate left hemispheric infarcts and delayed perfusion in the left middle cerebral artery territory with 61-mL volume of brain tissue with T max >6-s delay. Middle of figure shows second RAPID MRI with infarct expansion and 61-mL volume of brain tissue with T max >6-s delay. The bottom of the figure shows the last RAPID MRI after blood pressure augmentation showing stable left hemispheric infarcts without areas of brain tissue with T max >6-s delay. ADC indicates apparent diffusion coefficient.
TAKE-HOME POINTS

• Intracranial atherosclerosis can cause stroke by artery-to-artery embolism, branch artery atherosclerosis, or hypoperfusion.
• Stenting is not routinely recommended for symptomatic intracranial atherosclerosis because of increased risk of stroke compared with medical management.
• Antiplatelet therapy, blood pressure control, and treatment of hyperlipidemia are recommended for intracranial atherosclerosis.
• A small subset of patients with severe intracranial stenosis may demonstrate pressure dependence or deterioration with lowering of blood pressure beyond a threshold value.
• Pressure dependence can be demonstrated clinically and is treated with augmentation of blood pressure until it can be weaned without deterioration.
• Clinical trials investigating the safety of reperfusion treatment in this patient population are needed with an ultimate goal to reduce the risk of neurological deterioration in patients with symptomatic intracranial atherosclerotic disease causing impaired distal blood flow.

Disclosures
None.

Acknowledgments
K. Dakay contributed in the preparation of manuscript and literature review and Dr Yaghi in preparation of manuscript, literature review, and critical review.

References

KEY WORDS: aspirin • blood pressure • humans • hypertension • troponin
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Stroke. published online November 22, 2017;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 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/early/2017/11/21/STROKEAHA.117.019173.citation

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