Numerous recent and ongoing technical advances offer the potential to substantially enhance the MRI evaluation of moyamoya disease (MMD). These include high-resolution volumetric imaging, high-resolution vessel wall characterization, improved cerebral angiographic and perfusion techniques, high-field imaging, fast scanning methods, and artificial intelligence. This review discusses the current state-of-the-art MRI applications in these realms, emphasizing key imaging findings, clinical utility, and areas that will benefit from further investigation. Although these techniques may apply to imaging of a wide array of neurovascular or other neurological conditions, consideration of their application to MMD is useful given the comprehensive multidimensional MRI assessment used to evaluate MMD. These MRI techniques span from basic cross-sectional to advanced functional sequences, both qualitative and quantitative.

The aim of this review was to provide a comprehensive summary and analysis of current key relevant literature of advanced MRI techniques for the evaluation of MMD with image-rich case examples. These imaging methods can aid clinical characterization, help direct treatment, assist in the evaluation of treatment response, and potentially improve the understanding of the pathophysiology of MMD.

https://thejns.org/doi/abs/10.3171/2019.9.FOCUS19616

KEYWORDS moyamoya disease; vessel wall imaging; magnetic resonance angiography; cerebrovascular reactivity; cerebral perfusion
T1 weighting, T2 weighting), technological advancements have ushered in a variety of techniques that improve tissue characterization, speed, and spatial resolution. Recent research continues to offer insight into the utility of various pulse sequences for the assessment of MMD. Examples emphasizing cross-sectional techniques used for the evaluation of MMD are shown in Figs. 1 and 2. An overview of the utility of key imaging techniques presented in this review is presented in Table 1.

First, high-spatial-resolution 3D techniques for many pulse sequence categories are now employed in many clinical practices, particularly with 3T MRI, which allow multiplanar reformating in any image plane from a single acquisition. These techniques can facilitate advanced analysis such as structural and lesion characterization with automated segmentation and artificial intelligence computer learning algorithms. Three-dimensional imaging is also beneficial for postprocessing such as 3D surface-rendered images for the assessment of regional cortical thickness analysis in MMD.59 It is likely that such analyses will serve a role in research and clinical applications for MMD going forward. Additionally, clinicians and radiologists need to be aware that the precise image contrast and appearance of normal and pathologically deranged anatomy may differ between 2D and 3D techniques.

The utility of the T2 FLAIR sequence for the assessment of MMD has been extensively investigated.21,22,28,43,48,63 The “ivy sign,” an indicator of slow or retrograde flow in cortical vessels, can help characterize the origins of collateral supply, correlates with cerebrovascular reactivity (CVR), and can improve in response to revascularization surgery, or it can temporarily worsen after revascularization in the setting of hyperperfusion.21,28,48 In the cerebral white matter, linear T2 hyperintense streaks perpendicular to the lateral ventricle, referred to as “medullary streaks,” have been described.63 The pathophysiology of medullary streaks is incompletely understood, but is thought to be associated with ischemia and these may represent collateral vasculature, increased CSF, and edema.63 Additionally, Komatsu et al. reported that T2 FLAIR can demonstrate areas of parenchymal white matter T2 hyperintensity that variably reverse after revascularization.53

The appearance of T2 FLAIR images depends on the precise technique. For example, the ivy sign was shown to be less well depicted with 3D FLAIR than with 2D FLAIR in MMD in a study by Kakeda et al.26 Further-
more, the signal within the subarachnoid space can be affected by recent gadolinium administration or other leptomeningeal pathology. T2-weighted FLAIR images derived from synthetic imaging, a fast imaging method discussed later, can demonstrate flow and noise artifact.65

Susceptibility-weighted imaging (SWI) is a technique that utilizes both the phase and magnitude of signal arising from imaged tissue, whereas most traditional techniques completely discard the phase information. Haacke et al, provided a comprehensive technical review of SWI,19 but, in brief, it can be useful for the assessment of hemorrhage and blood vessels in MMD. The sequence is exquisitely sensitive to areas of chronic microhemorrhage, which are seen with an increased incidence in MMD and may be associated with increased risk of intracranial hemorrhage.29,56,72 The brush sign of prominent deep medullary veins on SWI may be associated with likelihood of infarct, low cerebral blood flow (CBF), and low CVR.22 Asymmetrically prominent superficial cortical vessels on SWI are associated with elevated deoxyhemoglobin content with increased oxygenation extraction; with revascularization, this finding may reverse and may predict potential to improve CBF.72

Advanced techniques have been developed to evaluate the microstructure of the brain by measuring the degree and orientation of water diffusion. Methods of assessment include diffusion tensor imaging (DTI) with fractional anisotropy determination, and diffusion kurtosis imaging (DKI), which is a more advanced technique that typically requires a longer scanning time and is less widely available. DKI may provide complementary information to DTI and may be more sensitive to white matter alterations in MMD.30 These techniques have been used to characterize structural white matter change of connectivity and

FIG. 2. Diffuse hypoperfusion, extensive collateral blood supply with ivy sign, and acute superimposed on chronic parenchymal sequela in a 14-year-old girl with MMD and no prior surgical intervention. A: Three-dimensional TOF MIP MR angiogram demonstrating severe stenosis of the bilateral cavernous ICAs, supraclinoid ICAs, and M, segments. The internal maxillary arteries (arrows) are enlarged, providing collateral flow via the ophthalmic arteries, with prominent collaterals within the bilateral cavernous sinus regions but a lack of identifiable ICAs (arrowheads). Prominent thalamoperforator and lenticulostriate collateral vessels are present centrally. The anterior cerebral artery (ACA) and MCA are widely patent beginning at the second-order branches. B: Diffusion-weighted image demonstrating a small acute infarct in the left subinsular white matter (arrow). C: Axial 2D T2 FLAIR image demonstrating a small chronic infarct in the right lateral frontal lobe (arrow) and additional areas of confluent bilateral white matter with T2 hyperintensity. D: Axial 2D T2 FLAIR image further demonstrating the ivy sign, which is most marked in the occipital regions (arrows), greater on the right than the left. E: Axial reformatted image from a high-resolution volumetric T1-weighted variable flip angle sequence with gadolinium demonstrating small vessels and small areas of enhancement with greater detail than typically seen with traditional spin echo techniques. F: Color CBF image derived from ASL perfusion without intravenous contrast, demonstrating diffuse cortical hypoperfusion (diffuse blue) with mild sparing of the medial left occipital region (arrow) and sparing of the thalamus.
microstructure in MMD that cannot be visibly assessed in so-called normal-appearing white matter.\textsuperscript{24,30,31} Such changes have been correlated to clinical status, such as cognitive measures with frontal lobe white matter involvement; there is evidence that these imaging and clinical changes can improve after revascularization.\textsuperscript{31}

**Functional Connectivity**

Resting-state functional MRI (rsfMRI) techniques are being applied to study functional connectivity patterns and alterations in MMD by assessment of low-frequency oscillations of blood oxygen level–dependent (BOLD) activity in a task-negative state. Initial data from rsfMRI suggest that patients with MMD have alterations in functional connectivity, including that of key networks such as the default mode network.\textsuperscript{60} Recent evidence indicates that this reduced functional connectivity is associated with certain clinical features depending on the anatomical area of involvement and can improve after revascularization, both ipsilateral and contralateral to the bypass.\textsuperscript{31,60} However, rsfMRI in the setting of MMD may lead to inaccurate results without appropriate expertise and corrections for temporal alterations of blood flow when assessing patterns of spontaneous brain activity.\textsuperscript{23} rsfMRI requires hardware and software and specialized data processing and interpretation that is not universally available clinically.

**Luminal Angiographic Techniques**

Catheter angiography remains the gold standard examination for the evaluation of intracranial vasculature and external carotid artery (ECA) branches with high spatial resolution and dynamic information, but it is invasive, requires contrast, results in radiation exposure, and has a small but definite risk of complications. CTA also involves radiation and contrast exposure and lacks the spatial and temporal resolution of catheter angiography. Intracranial MRA can be accomplished with several techniques. Cross-sectional methods of angiography such as CTA or

---

**TABLE 1. Key MRI techniques for evaluation of moyamoya disease**

| Technique                        | Utility                                                                                                                                 |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| **Cross-sectional MRI**         |                                                                                                                                        |
| Volumetric techniques          | Allow high-resolution imaging & multiplanar reformatting. Facilitate creation of 3D images & advanced image processing such as cortical thickness determination. |
| T2 FLAIR                        | Demonstrates the leptomeningeal “ivy sign” & medullary streaks. Allows assessment of regions of white matter T2 hyperintensity. Image appearance depends on technique (2D, 3D, recent Gd administration, synthetic MRI). |
| SWI                             | High sensitivity for most states of blood product, including chronic microbleeds. Can demonstrate prominent cortical & periventricular vasculature w/ increased deoxyhemoglobin & oxygen extraction. |
| Contrast-enhanced T1-weighted MRI | Demonstrates vascular enhancement corresponding to collateral arteries. Can demonstrate enhancing subacute infarcts.                             |
| DWI                             | High sensitivity for acute infarcts.                                                                                                       |
| DTI & DKI                       | Allow assessment of anatomic connectivity btwn brain regions & can serve as an indicator of white matter integrity.                             |
| **rsfMRI**                      | Demonstrates the degree of functional connectivity btwn brain regions.                                                                          |
| **MRA**                         |                                                                                                                                        |
| 3D-TOF                          | Delineates the lumen of major ICA & ECA branches w/o the need for intravenous contrast.                                                        |
| 2D phase contrast               | Allows assessment of direction of blood flow & approximation of flow velocity.                                                           |
| Time-resolved contrast enhanced | Can demonstrate arterial stenosis & progressive filling of collateral arteries.                                                             |
| **Techniques to assess perfusion & CVR** |                                                                                                                                          |
| DSC                             | Can assess multiple perfusion parameters using a bolus of intravenous Gd. Interpretation can be quantitative or qualitative.                |
| ASL                             | Facilitates assessment of CBF w/o the need for intravenous contrast. Interpretation can be quantitative or qualitative.                     |
| BOLD                            | Indirect representation of perfusion parameters w/o need of intravenous contrast. Interpretation is qualitative.                            |
| VWI                             | A wide variety of techniques w/ high spatial resolution & suppression of signal from flowing blood Differentiate btwn different causes of arterial stenosis. May serve as an indicator of MMD activity. Adjunct for assessment of the lumen. |

---
MRA are typically acquired with a high-spatial-resolution technique, which permits evaluation in multiple imaging planes. Maximum intensity projection (MIP) images are produced, allowing a more global view of a volume of intracranial vasculature when projected onto a 2D image. A common MRA technique that does not require intravenous contrast utilized clinically is 3D time-of-flight (3D-TOF), which demonstrates signal based on “flow-related enhancement.”

Three-dimensional TOF can depict the lumen of the main cerebral arteries as well as the ECA branches, including superficial temporal artery (STA) assessment after ECA–middle cerebral artery (MCA) bypass procedures. Recent studies have demonstrated that 3D-TOF is highly suitable for application of compressed sensing to reduce acquisition time, including in the setting of MMD. Current 3D-TOF technique remains susceptible to artifacts in some cases and can falsely indicate complete occlusion in areas of very high-grade stenosis and focal pseudolesions of trepanation segment bypass.

The reported utility of 3D-TOF continues to expand; for example, comparison of the signal intensity of the lumen upstream and downstream of a stenosis may approximate the fractional flow. However, 3D-TOF does not provide quantitative information and does not indicate the precise direction of blood flow. In distinction, 2D phase-contrast MRA can indicate the direction of flow and approximate flow velocities within the major intracranial arteries.

Numerous established fast methods of MRI data acquisition have enabled dynamic MRA with a reasonable temporal resolution. For example, time-resolved contrast-enhanced MRA can demonstrate internal carotid artery (ICA) stenosis and progressive filling of collateral vessels, although it has not been widely applied due to the relatively low spatial and temporal resolution relative to conventional angiography. Another technique, 4D pseudo-continuous arterial spin labeling (ASL), can demonstrate fill from leptomeningeal collaterals.

Overall, these luminal techniques can demonstrate the areas of stenosis or occlusion of the basal arteries, collateral vasculature, and ECA-MCA bypass graft status, and can identify associated aneurysms which may occur in either the basal arteries or peripheral arteries such as moyamoya vessels. Therefore, the modified Suzuki stage can potentially be established with these MRA luminal techniques without the need for formal catheter angiography. Examples highlighting methods of luminal MRA are shown in Figs. 3 and 4.

### Cerebral Perfusion and Cerebrovascular Reactivity

Standard angiographic and cross-sectional imaging techniques may be used to diagnose MMD, but they lack functional information of cerebral hemodynamic status, which may better guide treatment and prognosis. Cerebral hemodynamics may be assessed with a variety of perfusion imaging techniques, including several nuclear medicine methods, contrast-bolus or xenon CT, and several MRI methods that have been extensively reviewed previously. These vary in both qualitative or quantitative capability and type of information provided, but in general provide measures of CBF, cerebral blood volume (CBV), mean transit time (MTT), time to peak (TTP), and/or relative oxygen extraction. An understanding of the underlying pathophysiology is essential for the application and interpretation of imaging examinations that assess cerebral perfusion and CVR.

Specifically, progressive intracranial arterial stenosis of MMD results in reduction in cerebral perfusion pressure. Mechanisms to maintain CBF in the setting of reduced cerebral perfusion pressure include cerebral auto-regulation and recruitment of collateral vessels. Cerebral autoregulation acts to maintain CBF by vasodilatation of the downstream arterioles; this ability to maintain CBF is termed “cerebrovascular reserve.” If CBF is unable to meet needs for oxygen metabolism, the oxygen extraction fraction (OEF) will increase, and the tissue will be at increased risk for ischemia. Typical findings on perfusion imaging in patients with MMD are decreased CBF, increased CBV and OEF, prolonged MTT, and impaired CVR. While these findings have been found to be reproducible in the pediatric population, findings in adults have been more heterogeneous.

There are several methods to assess such cerebral perfusion with MRI. A common method is dynamic susceptibility contrast (DSC) MR perfusion. DSC perfusion signal is derived from T2*-susceptibility signal loss of gadolinium, allowing assessment of relative CBV, relative CBF, and MTT. ASL is a method that can determine CBF without the need for intravenous contrast through labeling of flowing blood with magnetic saturation techniques and imaging after a predefined “postlabel delay.” Technical parameters such as the postlabel delay time need to be defined to perform ASL. An understanding of these parameters is particularly critical in the evaluation of steno-occlusive disease such as MMD. Both DSC and ASL techniques may render qualitative or quantitative data. Another newer, but less well-established, method to assess cerebral perfusion without intravenous contrast is intravoxel incoherent motion (IVIM), a modification of diffusion-weighted imaging (DWI), which has been applied to MMD, but it still needs further evaluation before widespread adoption. Christen et al. reported that temporal analysis of the rsfMRI BOLD signal can produce perfusion delay maps similar to those acquired with DSC perfusion, but without the need for intravenous contrast.

Furthermore, in cerebrovascular diseases such as MMD, the cerebral vasculature may be maximally dilated at baseline, limiting the ability to compensate in the setting of increased demand and placing patients at risk for ischemia. CVR, defined as the ability to increase CBF with increased demand or application of a stimulus, is therefore an important indicator of stroke risk in MMD and can facilitate treatment planning and assessment to treatment response. Specifically, CVR may be used to monitor patients and determine when cerebrovascular reserve is waning and revascularization would be beneficial. It may also be used to follow patients after revascularization.
In particular, patients with an intermediate disease stage (modified Suzuki stage II or III) have been found to have variable hemodynamics, and evaluation of CVR is of particular use to guide therapy. Evaluation of CVR before and after surgical revascularization has shown that revascular of a preoperative CVR impairment corresponds with collateral formation on DSA and successful revascularization. Furthermore, evaluation of both the degree and extent of reduced CVR is important in clinical evaluation.

To evaluate CVR, perfusion imaging techniques may be performed without and with a vasoactive, isometabolic stimulus, which elicits a change in CBV and CBF without a change in metabolic demand. Vasoactive stimuli include exogenous pharmaceutical agents (acetazolamide) and hypercapnia, both of which cause a decrease in the local pH, vascular smooth muscle relaxation, and vasodilation. The various available vasoactive stimuli used for CVR measurements have been detailed in prior reviews. In brief, acetazolamide is the most commonly clinically implemented pharmaceutical stimulus in part due to its ease of administration. Hypercapnia is commonly achieved with a breath-hold technique, although this can also be accomplished with use of a rebreathing face mask, nonrebreathing face mask, or computer-controlled gas delivery system. In addition to the typical perfusion methods, CVR can also be assessed via the BOLD response on fMRI without the need for gadolinium. Findings on MRI perfusion and CVR examinations are illustrated in Figs. 2, 4, and 5.

**High-Resolution Vessel Wall Imaging**

Intracranial high-resolution vessel wall imaging (VWI) consists of a variety of MRI techniques with high spatial resolution (typically submillimeter resolution both in-plane and slice thickness) and suppression of signal from flowing blood (“black blood”) to facilitate evaluation of the vessel wall and diminish apparent wall enhancement.
The basic findings of MMD on VWI include luminal stenosis or occlusion reflective of intimal thickening and decreased diameter of the vessel (negative remodeling).\textsuperscript{8,39} Vessel wall enhancement on T1-weighted or proton density (PD)–weighted images seems to be variable, with reports ranging from absent to marked.\textsuperscript{8,39,49,50,57,58,69} Variable wall enhancement can also be seen within a single patient with simultaneous nonenhancing and enhancing segments. Vessel wall findings are typically circumferentially concentric and less commonly eccentric. In distinction, causes of secondary moyamoya syndrome (MMS), which demonstrate an angiographic pattern resembling MMD but are associated with another identifiable pathology, tend to have other patterns of vessel wall abnormality reflective of the underlying pathology. For example, atherosclerosis is most often associated with eccentric vessel wall involvement and heterogeneous internal T2 signal with a thin T2 hyperintense cap and can demonstrate positive remodeling.\textsuperscript{49} When VWI is strongly supportive of secondary MMS or idiopathic MMD, the findings can have a substantial effect on immediate medical treatment strategy.

Nonetheless, VWI findings of stenosis due to MMD and other etiologies can overlap in some cases (Fig. 6). Additionally, the criteria used to differentiate MMD from MMS with VWI in some studies have included VWI findings themselves as definitive histopathological confirma-
tion is typically absent.\textsuperscript{1,49} For example, in some instances, circumferential vessel wall enhancement was defined to indicate presumptive vasculitis.\textsuperscript{1} Other reports indicate that such enhancement can be seen with MMD,\textsuperscript{49,57,69} demonstrating a challenge with interpreting study results. Although MMD classically involves the distal ICA segments bilaterally, unilateral isolated M\textsubscript{1} disease with vessel wall findings most suggestive of MMD has been reported.\textsuperscript{1}

Limited evidence indicates that high-grade vessel wall enhancement is associated with an incidence of territorial infarct and progressive stenosis of that segment on follow-up examination.\textsuperscript{50,57,69} Roder et al. found a pattern of increasing and then decreasing vessel wall enhancement roughly 6–8 months before and after clinical and radiographic disease progression.\textsuperscript{37} That study employed an imaging technique with high in-plane spatial resolution but a relatively large slice thickness up to 2 mm; replication with higher-resolution techniques to confirm these findings may be useful. However, the association of vessel wall enhancement to infarcts and progression is not entirely consistent, even within a given patient (Fig. 7). Additionally, there is limited evidence that vessel wall enhancement of stenotic M\textsubscript{1} segments can decrease after application of steroids with a presumptive diagnosis of vasculitis,\textsuperscript{7} although correlation of the degree of enhancement to medication administration in MMD and other steno-occlusive disease needs more work.

Although VWI is primarily used to assess the vessel wall, recent studies have demonstrated utility for luminal characterization.\textsuperscript{3,32} For example, Kim et al. found that lumen diameter measurements of the major intracranial arteries with or without stenosis using VWI black blood images are similar to those obtained with 3D-TOF.\textsuperscript{32} Bai et al. demonstrated similar findings in the MCA using inverted black/white MIP images to highlight the vessels.\textsuperscript{3} VWI may be useful for lumen assessment in areas of artifact on 3D-TOF and segments of very high-grade stenosis.\textsuperscript{31}

In many cases, these VWI studies need confirmation with additional work to show reproducibility and validity in various patient populations if these findings are to be used to heavily influence clinical care. Readers should take into account spatial resolution and type of flow-suppression technique, as these technical factors can impact the appearance of vessel wall\textsuperscript{12} and vessel wall enhance-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Images obtained in an adult female with MMD and a history of right STA bypass. A–D: DSC perfusion with gadolinium permits evaluation of numerous parameters, including CBF (A), CBV (B), MTT (C), and TTP (D). There is decreased CBF and CBV (arrows) compatible with a large chronic infarct in the right cerebral parietal lobe. Some vascular perfusion persists with an elevated MTT and TTP (C and D, arrows), compatible with slow delayed flow within nonviable tissue. In the bilateral ACA territory, CBF and CBV are without substantial abnormality, compatible with adequate blood supply. DSC perfusion parameters in the left MCA and left posterior cerebral artery territories are also unremarkable. E: CVR was assessed with a 20-second breath-hold BOLD response superimposed on an axial 3D T2-weighted FLAIR image, demonstrating reduced CVR in the right ACA territory as a blue overlay (arrow), compatible with vascular steal. F: Three-dimensional TOF MIP image demonstrating focal stenosis of the bilateral distal supraclinoid ICAs. The STA bypass is also visualized with mild signal loss and narrowing near the level of the calvaria (arrows) but is otherwise patent.}
\end{figure}
ment. Additionally, the methods of image interpretation and criteria used to establish the final diagnosis need careful consideration. Histopathological correlation of vessel walls that enhance is lacking. Although some recent evidence has challenged the prevailing notion that MMD is a noninflammatory condition, it remains unclear if vessel wall enhancement represents inflammation, angiogenesis, cell proliferation, or another factor. Finally, VWI sequences are time consuming. While compressed sensing can be applied to decrease scan time, published reports of effect on image quality and diagnostic accuracy are currently lacking.

**High-Field MRI**

High-field MRI such as 7T has now moved into both the research and clinical practice realms at some institutions. This may have several advantages for the assessment of MMD, including gains in signal-to-noise ratio and contrast-to-noise ratio that facilitate improved visualization of the basal arteries and moyamoya vessels with VWI, 3D-TOF MRA, T1 MPRAGE (magnetization-prepared ra-

diofrequency pulses and rapid gradient echo) MRA, improved assessment of BOLD response, and increased sensitivity for areas of microbleed with SWI. There are also limitations, including limited availability of certain pulse sequences, increased incidence of susceptibility artifact near the skull base (and thus cavernous ICA levels), the need to account for differing contrast properties (e.g., the T1 and T2 relaxation times/appearance and BOLD response are field strength dependent), and more stringent patient exclusion criteria. Limited evidence indicates that, compared with 3T, 7T examinations better depict moyamoya vessels within the basal ganglia, but may not be advantageous for determination of the Suzuki stage, ivy sign depiction, or measurement of the intracranial ICA diameter. However, true assessment of impact on imaging assessment and patient management needs further investigation.

**Emerging Advanced Methods to Decrease MRI Acquisition Time**

As briefly introduced in the preceding sections, a num-

---

**FIG. 6.** VWI appearance of alternative causes of stenosis of the basal arteries with axial PD images demonstrating multiple distinct vessel wall features, although these vessel wall features can overlap in some cases. **A:** Eccentric plaques along the walls of the left M1 segment (arrows) without negative remodeling are most consistent with atherosclerosis. **B:** In another case with focal short-segment stenosis, moderate associated vessel wall enhancement (arrow), and negative remodeling, the VWI findings are less specific; the favored diagnosis was atherosclerosis given the short segment involvement as seen on conventional angiography (not shown) and clinical presentation. Although atherosclerosis typically demonstrates normal vessel diameter or positive remodeling, it can occasionally demonstrate negative remodeling. **C:** Marked circumferential enhancement of the luminal surface of the right cavernous ICA wall (arrow) in a 75-year-old man with giant cell arteritis. **D:** Image obtained in a 66-year-old woman with primary angitis of the CNS, demonstrating marked enhancement of the luminal border of the walls of both cavernous (arrows) and supraclinoid (not shown) ICAs with normal vessel diameter. **E:** Image obtained in a 46-year-old woman with a diagnosis of unilateral MMD, demonstrating marked circumferential vessel wall enhancement with negative remodeling (arrow). **F:** Dissection of the right M1 segment demonstrating a thin linear flap (arrow) along the length of the vessel segment, separating the true lumen anteriorly from the dissected lumen posteriorly.
ber of emerging techniques show potential to substantially reduce scanning time and facilitate a comprehensive multimodal MRI assessment within a reasonable appointment time. Such methods may be applied to each of the main areas of MRI assessment of MMD, including standard cross-sectional MRI, MRA, MR perfusion, and VWI.

For example, reduced acquisition of redundant imaging data can be accomplished with the compressed sensing technique. Synthetic MRI can produce multiple sequences from a single acquisition. MR fingerprinting applies a novel method of image reconstruction of multiple sequences from raw data based on computer pattern matching to an index library of signal patterns from different tissues. Unlike other common MRI techniques, MR fingerprinting also allows for quantitative assessment of tissue signal intensity. Another approach to decrease scan time is the concurrent acquisition of data from multiple slices using simultaneous multislice imaging techniques. While the premise of simultaneous multislice is not new, recent technological advancements have enhanced the capabilities of these techniques and facilitated increasing clinical implementation.

All of these have been most extensively evaluated in the technical literature, although reports of clinical evaluation in MMD and other conditions are emerging. The availability of these techniques currently varies by vendor and software package, and not all techniques are approved by the Food and Drug Administration within the United States. Further evaluation of effect on image quality and diagnostic utility, technique optimization, and practical practice implementation is also needed.

**FIG. 7.** A: A 31-year-old woman presented with bilateral border zone infarcts on DWI. B: Three-dimensional TOF MR angiogram obtained at presentation, demonstrating moderate stenosis of the bilateral distal supraclinoid ICAs and proximal M1 segments (arrows). C: Axial PD VWI study with gadolinium, demonstrating mild to moderate circumferential vessel wall enhancement of the left supraclinoid segment (arrow) and no appreciable enhancement of the right ICA vessel wall. D: Axial PD VWI study with gadolinium obtained at the 8-month follow-up, demonstrating increased enhancement of the stenotic left segment (arrow). E: Axial 3D-TOF MR angiogram demonstrating progressive stenosis of both the nonenhancing right and enhancing left stenotic segments (arrows). This case demonstrates that infarcts and progressive stenosis can be associated with either enhancing or nonenhancing segments and that vessel wall enhancement can evolve over time.

**Artificial Intelligence**

Artificial intelligence techniques have numerous potential applications to evaluate MMD, including automated image segmentation, image grading, clinical/imaging prediction scoring, and use to improve image quality of advanced fast scanning techniques. For example, one group has described the technical feasibility of an automated method of intracranial VWI segmentation. Machine learning has been utilized for recognition of MMD on the basis of skull plain radiographs. Although to date there are few reports on the application of artificial intelligence algorithms specifically for the evaluation of cross-sectional imaging examinations in MMD, such methods will like-
ly impact evaluation in the future, given the multimodal imaging evaluation required.

**Application of Multimodal MRI Findings to Clinical Practice**

The multimodal MRI techniques discussed can help determine patient prognosis, direct medical or surgical treatment, and assess treatment response. As the prior sections have demonstrated, there is a wide variety of techniques available, and those used will depend on local resources and expertise. There is no universally standardized imaging protocol for moyamoya patients, standardized methods of imaging assessment are generally lacking, and there is much more to learn. However, some studies have proposed various approaches to help guide clinical management.

Most patients with a diagnosis of MMD undergo regular clinical and imaging surveillance (approximately every 6 months) to monitor disease progression and guide management. Imaging may include DSA and/or MR, including MRA, structural imaging, and perfusion or CVR measurements as discussed above. As these patients are generally young, it is useful to utilize MRI since it lacks radiation and provides multiple facets of information. Some of the proposed methods to evaluate the MR techniques for clinical decision-making are outlined below.

Perfusion and CVR may be used to assess clinical status and timing of revascularization, guide perioperative management, and assess success of revascularization. In general, a decrease in CBF, increase in MTT, and decrease in CVR indicate increased risk of ischemia and may be used as an indicator for revascularization. In perioperative patient management, there is evidence that increased CBV or reduced OEF is associated with an increased risk of perioperative cerebral hyperperfusion. Assessment of these findings could be useful to prompt heightened vigilance and monitoring. Finally, perfusion and CVR have been applied to monitor success of revascularization.

Methods of systematic analysis of perfusion parameters have been proposed by Lin et al. and Yun et al. While such assessment is not standardized, these authors normalized perfusion to the cerebellum and defined vascular territories for assessment. Using a simple qualitative visual analysis, Lin et al. divided each cerebral hemisphere into 14 segments, normalized perfusion to the cerebellum, and assessed the TTP on each segment over time. The TTP delay improved on serial examinations over a 6-month time period, and the improvement correlated with the Matsushima grade. This or similar modifications can be applied to clinical practice. Although such an approach is straightforward, consideration of multiple perfusion parameters likely provides a more complete, albeit descriptive, picture of clinical status.

Others have incorporated perfusion/CVR with additional MR metrics. Ladner et al. proposed the PIRAMD (Prior Infarcts, Reactivity, and Angiography in Moyamoya Disease) scoring system, which incorporates assessment of infarcts, CVR, and angiographic findings on MRI into a scoring system of grades 1–3 for each hemisphere. Higher grade correlated with symptoms, but this study is retrospective and further assessment is needed.

In the absence of recurrent ischemic or hemorrhagic symptoms or sequelae, clinical assessment of response to revascularization can be challenging. In addition to perfusion/CVR metrics, many of the cross-sectional imaging findings (ivy sign, brush sign, medullary streaks, parenchymal T2 FLAIR signal, DTI findings, and even cortical volume loss) may improve after revascularization. These imaging findings can help the clinician determine if there has been a positive treatment response and provide concrete findings to convey to the patient.

Until widely accepted standardized imaging protocols and methods of interpretation are established, application of a consistent imaging protocol that includes components from the key categories discussed herein is a reasonable approach. Consistent application of one of the few available scoring systems discussed or an adaptation of the scoring system to another related imaging technique seems reasonable. Ultimately, use of imaging findings to facilitate patient counseling and care will require some subjectivity, clinical judgement, and consideration of other patient factors.

**Conclusions**

Numerous recent technological advances offer potential to substantially enhance the multidimensional MRI evaluation of MMD. These include high-resolution volumetric imaging, high-resolution vessel wall characterization with suppression of signal from flowing blood, improved angiographic and perfusion techniques, high-field imaging, fast scanning methods, and potential applications of artificial intelligence. These imaging methods can aid clinical characterization, help direct treatment, assist in the evaluation of treatment response, and elucidate the pathophysiology of MMD.

**References**

1. Ahn SH, Lee J, Kim YJ, Kwon SU, Lee D, Jung SC, et al: Isolated MCA disease in patients without significant atherosclerotic risk factors: a high-resolution magnetic resonance imaging study. Stroke 46:697–703, 2015
2. Alsop DC, Detre JA, Golay X, Günther M, Hendrikse J, Hernandez-Garcia L, et al: Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magn Reson Med 73:102–116, 2015
3. Bai X, Lv P, Liu K, Li Q, Ding J, Qu J, et al: 3D black-blood luminal angiography derived from high-resolution MR vessel wall imaging in detection MCA stenosis: a preliminary study. AJNR Am J Neuroradiol 39:1827–1832, 2018
4. Bang OY, Fujimura M, Kim SK: The pathophysiology of moyamoya disease: an update. J Stroke 18:12–20, 2016
5. Bang OY, Ryoo S, Kim SJ, Yoon CH, Cha J, Yeon JY, et al: Adult moyamoya disease: a burden of intracranial stenosis in East Asians? PLoS One 10:e0130663, 2015
6. Bipin Mehta B, Coppo S, Frances McGivney D, Ian Hamilton J, Chen Y, Jiang Y, et al: Magnetic resonance fingerprinting: a technical review. Magn Reson Med 81:25–46, 2019
7. Brinjikji W, Lehman V, Huston J III, Luetmer PH, Lanztino G, Rabinstein AA: Decreased vessel wall enhancement as a biomarker for response to corticosteroids in a patient with CNS vasculitis. J Neurosurg Sci 63:100–101, 2019
8. Brinjikji W, Mossa-Basha M, Huston J, Rabinstein AA, Lanzino G, Lehman VT: Intracranial vessel wall imaging for evaluation of steno-occlusive diseases and intracranial aneurysms. J Neuroradiol 44:123–134, 2017
9. Chen Q, Qi R, Cheng X, Zhou C, Luo S, Ni L, et al: Assessment of extracranial-intracranial bypass in Moyamoya disease using 3T time-of-flight MR angiography: comparison with CT angiography. Vasa 43:278–283, 2014
10. Christen T, Jahanian H, Ni WW, Qu D, Moseley ME, Zaharchuk G: Noncontrast mapping of arterial delay and functional connectivity using resting-state functional MRI: a study in Moyamoya patients. J Magn Reson Imaging 41:424–430, 2015
11. Cipolla MJ: Control of cerebral blood flow, in Cipolla MJ: The Cerebral Circulation. San Rafael, CA: Morgan & Claypool Life Sciences, 2009 (https://www.ncbi.nlm.nih.gov/books/NBK53081/) [Accessed September 27, 2019]
12. Cogswell PM, Siero JCW, Lants SK, Waddle S, Davis LT, Gilbert G, et al: Variable impact of CSF flow suppression on quantitative 3.0T intracranial vessel wall measurements. J Magn Reson Imaging 48:1120–1128, 2018
13. Deng X, Zhang Z, Zhang Y, Zhang D, Wang R, Ye X, et al: Comparison of 7.0- and 3.0-T MRI and MRA in ischemic-type moyamoya disease: preliminary experience. J Neurosurg 124:1716–1725, 2016
14. Dengler NF, Madai VI, Wuerfel J, von Samson-Himmelstjerna FC, Dusek P, Niendorf T, et al: Moyamoya vessel pathology imaged by ultra-high-field magnetic resonance imaging at 7.0 T. J Stroke Cerebrovasc Dis 25:1544–1551, 2016
15. Donahue MJ, Ayad M, Moore R, van Osch M, Singer R, Clemmons P, et al: Relationships between hypercarbic reactivity, cerebral blood flow, and arterial circulation times in patients with moyamoya disease. J Magn Reson Imaging 38:1129–1139, 2013
16. Fan AP, Guo J, Khalighi MM, Gulaka PK, Shen B, Park JH, et al: Long-delay arterial spin labeling provides more accurate cerebral blood flow measurements in moyamoya patients: a simultaneous positron emission tomography/MRI study. Stroke 48:2441–2449, 2017
17. Fierstra J, Sobczyk O, Battisti-Charbonney A, Mandell DM, Poublanc J, Crawley AP, et al: Measuring cerebrovascular reactivity: what stimulus to use? J Physiol 591:5809–5821, 2013
18. Ge X, Zhao H, Zhou Z, Li X, Sun B, Wu H, et al: Association of fractional flow on 3D-TOF-MRA with cerebral perfusion in patients with MCA stenosis. AJNR Am J Neuroradiol 40:1124–1131, 2019
19. Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng YC: Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. AJNR Am J Neuroradiol 30:19–30, 2009
20. Hara S, Horii M, Ueda R, Hagiwara A, Hayashi S, Inaji M, et al: Intravoxel incoherent motion perfusion in patients with Moyamoya disease: comparison with O-gas positron emission tomography. Acta Radiol Open 8:2058460119846587, 2019
21. Horie N, Morikawa M, Morofuji Y, Hiu T, Izumo T, Hayashi K, et al: De novo ivy sign indicates postoperative hyperperfusion in moyamoya disease. Stroke 45:1488–1491, 2014
22. Horie N, Morikawa M, Nozaki A, Hayashi K, Sueyama K, Nagata I: “Brush Sign” on susceptibility-weighted MR imaging indicates the severity of moyamoya disease. AJNR Am J Neuroradiol 32:1697–1702, 2011
23. Jahanian H, Christen T, Moseley ME, Zaharchuk G: Erroneous resting-state fMRI connectivity maps due to prolonged arterial arrival time and how to fix them. Brain Connect 8:362–370, 2018
24. Jeong H, Kim J, Choi HS, Kim ES, Kim DS, Shim KW, et al: Changes in integrity of normal-appearing white matter in patients with moyamoya disease: a diffusion tensor imaging study. AJNR Am J Neuroradiol 32:1893–1898, 2011
25. Juttukonda MR, Donahue MJ: Neuroradiography of vascular reserve in patients with cerebrovascular diseases. Neuroimage 187:192–208, 2019
26. Kakeda S, Kurogi Y, Hiai Y, Ohnami N, Sato T, Hirai T: Pitfalls of 3D FLAIR brain imaging: a prospective comparison with 2D FLAIR. Acad Radiol 19:1225–1232, 2012
27. Kaku Y, Iihara K, Nakajima N, Kataoka H, Fukuda K, Masuoka J, et al: Cerebral blood flow and metabolism of hyperperfusion after cerebral revascularization in patients with moyamoya disease. J Cereb Blood Flow Metab 32:2066–2075, 2012
28. Kawashima M, Noguchi T, Takase Y, Nakahara Y, Matusshima T: Decrease in leptomeningeal ivy sign on fluid-attenuated inversion recovery images after cerebral revascularization in patients with Moyamoya disease. AJNR Am J Neuroradiol 31:1713–1718, 2010
29. Kazumata K, Shindo B, Ito M, Shichinohe H, Kuroda S, Nakayama N, et al: Spatial relationship between cerebral microbleeds, moyamoya vessels, and hematoma in moyamoya disease. J Stroke Cerebrovasc Dis 23:1421–1428, 2014
30. Kazumata K, Tha KK, Narita H, Ito YM, Shichinohe H, Ito M, et al: Characteristics of diffusional kurtosis in chronic ischemia of adult moyamoya disease: comparing diffusional kurtosis and diffusion tensor imaging. AJNR Am J Neuroradiol 37:1432–1439, 2016
31. Kazumata K, Tha KK, Tokairin K, Ito M, Uchino H, Kawabori M, et al: Brain structure, connectivity, and cognitive changes following revascularization surgery in adult moyamoya disease. Neurosurgery 85:E943–E952, 2019
32. Kim DK, Verdoorn JT, Gunderson TM, Huston Ii J, Brinjikji W, Lanzino G, et al: Comparison of non-contrast vessel wall imaging and 3-D time-of-flight MRA for atherosclerotic stenosis and plaque characterization within intracranial arteries. J Neuroradiol [epub ahead of print], 2019
33. Kim T, Heo J, Jang DK, Sunwoo L, Kim J, Lee KJ, et al: Machine learning for detecting moyamoya disease in plain skull radiography using a convolutional neural network. EBioMedicine 40:636–642, 2019
34. Koh DM, Collins DJ, Orton MR: Intravoxel incoherent motion in body diffusion-weighted MRI: reality and challenges. AJR Am J Roentgenol 196:1351–1361, 2011
35. Komatsu K, Mikami T, Noshiro S, Miyata K, Wanibuchi M, Mikuni N: Reversibility of white matter hyperintensity by revascularization in patients with moyamoya disease. J Stroke Cerebrovasc Dis 25:1495–1502, 2016
36. Ladner TR, Donahue MJ, Arteaga DF, Faraco CC, Roach BA, Davis LT, et al: Prior Infarcts, Reactivity, and Angiography in Moyamoya Disease (PIRAMD): a scoring system for moyamoya severity based on multimodal hemodynamic imaging. J Neurosurg 126:495–503, 2017
37. Lee M, Zaharchuk G, Guzman R, Achrol A, Bell-Stephens T, Steinberg GK: Quantitative hemodynamic studies in moyamoya disease: a review. Neurosurg Focus 26(4):E5, 2009
38. Lee S, Yun TJ, Yoo RE, Yoon BW, Kang KM, Choi SH, et al: Monitoring cerebral perfusion changes after revascularization in patients with moyamoya disease by using arterial spin-labeling imaging. Radiology 288:565–572, 2018
39. Lehman VT, Brinjikji W, Kallmes DF, Huston J, Lanzino G, Rabinstein AA, et al: Clinical interpretation of high-resolution vessel wall MRI of intracranial arterial diseases. Br J Radiol 89:20160496, 2016

12 Neurorsurg Focus Volume 47 • December 2019
40. Li J, Jin M, Sun X, Li J, Liu Y, Xi Y, et al: Imaging of moyamoya disease and moyamoya syndrome: current status. J Comput Assist Tomogr 43:257–263, 2019.

41. Liu YH, Kuo MH, Lu CJ, Lee CW, Yang SH, Huang YC, et al: Standardized MR perfusion scoring system for evaluation of sequential perfusion changes and surgical outcome of moyamoya disease. AJNR Am J Neuroradiol 40:260–266, 2019.

42. Liu MC, Chen HC, Wu CH, Chen WH, Tsuei YS, Chen CC: Time-resolved magnetic resonance angiography in the evaluation of intracranial vascular lesions and tumors: a pictorial essay of our experience. Can Assoc Radiol J 66:385–392, 2015.

43. Liu W, Xu G, Yue X, Wang X, Ma M, Zhang R, et al: Hyperintense vessels on FLAIR: a useful non-invasive method for assessing intracerebral collaterals. Eur J Radiol 80:786–791, 2011.

44. Lui YW, Tang ER, Allmendinger AM, Spektor V: Evaluation of CT perfusion in the setting of cerebral ischemia: patterns and pitfalls. AJNR Am J Neuroradiol 31:1552–1563, 2010.

45. Mandell DM, Mossa-Basha M, Qiao Y, Hess CP, Hui F, Matouk C, et al: Intracranial vessel wall MRI: principles and consensus recommendations of the American Society of Neuroradiology. AJNR Am J Neuroradiol 38:218–229, 2017.

46. Mejia-Munne JC, Ellis JA, Feldstein NA, Meyers PM, Connolly ES: Moyamoya and inflammation. World Neurosurg 100:575–578, 2017.

47. Mikulis DJ: Cerebral Moyamoya disease. Stroke 44 (Suppl 1):S55–S57, 2013.

48. Mori N, Magikura S, Higano S, Kaneta T, Fujimura M, Umetsu A, et al: The leptomeningeal “ivy sign” on fluid-attenuated inversion recovery MR imaging in Moyamoya disease: a sign of decreased cerebral vascular reserve? AJNR Am J Neuroradiol 30:930–935, 2009.

49. Mossa-Basha M, de Havenon A, Becker KJ, Hallam DK, Levitt MR, Cohen WA, et al: Added value of vessel wall magnetic resonance imaging in the differentiation of moyamoya vasculopathies in a non-Asian cohort. Stroke 47:1782–1788, 2016.

50. Muraoka S, Araki Y, Taoka T, Kawai H, Okamoto S, Uda K, et al: Prediction of intracranial arterial stenosis progression in patients with moyamoya vasculopathy: contrast-enhanced high-resolution magnetic resonance vessel wall imaging. World Neurosurg 116:e1114–e1121, 2018.

51. Ni W, Jiang H, Xu B, Lei Y, Yang H, Su J, et al: Treatment of aneurysms in patients with moyamoya disease: a 10-year single-center experience. J Neurosurg 128:1813–1822, 2018.

52. Oh BH, Moon HC, Baek HM, Lee YJ, Kim SW, Jeon YJ, et al: Comparison of 7T and 3T MRI in patients with moyamoya disease. Magn Reson Imaging 37:134–138, 2017.

53. Paschou AM, Leoni RF, Dos Santos AC, Paiva FF: Intravoxel incoherent motion MRI in neurological and cerebrovascular diseases. NeuroImage Clin 20:705–714, 2018.

54. Powers WJ: Cerebral hemodynamics in ischemic cerebrovascular disease. Ann Neurol 29:231–240, 1991.

55. Qiao PG, Zuo ZW, Han C, Zhou J, Zhang HT, Duan L, et al: Cortical thickness changes in adult moyamoya disease assessed by structural magnetic resonance imaging. Clin Imaging 46:71–77, 2017.

56. Qin Y, Ogawa T, Fuji S, Shinohara Y, Kitao S, Miyoshi F, et al: High incidence of asymptomatic cerebral microbleeds in patients with hemorrhagic onset-type moyamoya disease: a phase-sensitive MRI study and meta-analysis. Acta Radiol 56:329–338, 2015.

57. Roder C, Hauser TK, Ermemann U, Tatagiba M, Khan N, Bender B: Arterial wall contrast enhancement in progressive moyamoya disease. J Neurosurg [epub ahead of print May 24, 2019. DOI: 10.3171/2019.2.JNS19106].

58. Ryoo S, Cha J, Kim SJ, Choi JW, Ki CS, Kim KH, et al: High-resolution magnetic resonance wall imaging findings of Moyamoya disease. Stroke 45:2457–2460, 2014.

59. Ryu KH, Baek BH, Park SH, Ha JY, et al: Initial clinical experience of synthetic MRE as a routine neuroimaging protocol in daily practice: a single-center study. J Neuroadiol [epub ahead of print], 2019.

60. Sakamoto Y, Okamoto S, Maesawa S, Bagarinao E, Araki Y, Izumi T, et al: Default mode network changes in moyamoya disease before and after bypass surgery: preliminary report. World Neurosurg 112:e652–e661, 2018.

61. Shi F, Yang Q, Guo X, Qureshi T, Tian Z, Miao H, et al: Intracranial vessel wall segmentation using convolutional neural networks. IEEE Trans Biomed Eng 66:2840–2847, 2019.

62. Su P, Mao D, Liu P, Li Y, Pinho MC, Welch BG, et al: Multiparametric estimation of brain hemodynamics with MR fingerprinting ASL. Magn Reson Med 78:1812–1823, 2017.

63. Suzuki H, Kamikita T, Kuribara T, Yoshifuji K, Komatsu K, Akiyama Y, et al: Pathophysiologic consideration of medullary streaks on FLAIR imaging in pediatric moyamoya disease. J Neurosurg Pediatr 19:560–566, 2017.

64. Takagi Y, Kikuta K, Nozaki K, Hashimoto N: Histological features of middle cerebral arteries from patients treated for Moyamoya disease. Neurol Med Chir (Tokyo) 47:1–4, 2007.

65. Tanenbaum LN, Tsiouris AJ, Johnson AN, Naïdich TP, DeLano MC, Melhem ER, et al: Synthetic MRI for clinical neuroimaging: results of magnetic resonance image compilation (MAGiC) prospective, multicenter, multireader trial. AJNR Am J Neuroradiol 38:1103–1110, 2017.

66. Togao O, Hiwatashi A, Obara M, Yamashita K, Momosaka D, Nishimura A, et al: 4D ASL-based MR angiography for visualization of distal arteries and leptomeningeal collateral vessels in moyamoya disease: a comparison of techniques. Eur Radiol 28:4871–4881, 2018.

67. Uchino H, Kuroda S, Hirata K, Shiga T, Houkin K, Tamaki N: Predictors and clinical features of postoperative hyperperfusion after surgical revascularization for moyamoya disease: a serial single photon emission CT/positron emission tomography study. Stroke 43:2610–2616, 2012.

68. Urback AL, MacIntosh BJ, Goldstein BI: Cerebrovascular reactivity measured by functional magnetic resonance imaging during breath-hold challenge: a systematic review. Neurosci Biobehav Rev 79:27–47, 2017.

69. Wang M, Yang Y, Zhou F, Li M, Liu R, Guan M, et al: The contrast enhancement of intracranial arterial wall on high-resolution MRI and its clinical relevance in patients with moyamoya vasculopathy. Sci Rep 7:44264, 2017.

70. Watchmaker JM, Frederick BD, Fusco MR, Davis LT, Juttukonda MR, Lants SK, et al: Clinical use of cerebrovascular compliance imaging of evaluation revascularization in patients with moyamoya. Neurosurgery 84:261–271, 2019.

71. Weiqiang Q, Tikun S, Qiongqiong Q, Jinge Z, Chunchoa X, Yi L, et al: Asymmetric cortical vessel sign indicates hemodynamic deficits in adult patients with moyamoya disease. World Neurosurg 127:e137–e141, 2019.

72. Wenz H, Wenz R, Maros M, Ehrlich G, Al-Zghoul M, Groden C, et al: Incidence, locations, and longitudinal course of cerebral microbleeds in European moyamoya. Stroke 48:307–313, 2017.

73. Wintermark M, Sesay M, Barbier E, Borbély K, Dillon WP, Eastwood JD, et al: Comparative overview of brain perfusion imaging techniques. Stroke 36:e83–e99, 2005.

74. Yamamoto T, Okada T, Fushimi Y, Yamamoto A, Fujimoto K, Okuchi S, et al: Magnetic resonance angiography with compressed sensing: an evaluation of moyamoya disease. PLoS One 13:e0189493, 2018.
Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Lehman, Cogswell, Rinaldo, Huston, Lanzino. Acquisition of data: Cogswell. Drafting the article: Lehman. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lehman.

Correspondence

Vance T. Lehman: Mayo Clinic College of Graduate Medical Education, Rochester, MN. lehman.vance@mayo.edu.