Evaluating Intracranial Atherosclerosis Rather Than Intracranial Stenosis

Xinyi Leng, PhD; Ka Sing Wong, MD; David S. Liebeskind, MD

Intracranial atherosclerosis (ICAS) is an important cause of ischemic stroke throughout the world, accounting for ≈30% to 50% and 10% of ischemic stroke and transient ischemic attack in Asians and whites, respectively. Several imaging modalities, such as transcranial Doppler (TCD), magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and digital subtraction angiography (DSA), are used commonly in routine clinical practice to detect and assess ICAS, as well as in selection criteria of clinical trials. Although some of these imaging modalities yield flow information, such as TCD revealing velocity data or waveform turbulence and time-of-flight MRA (TOF-MRA) depicting arterial patterns based on blood flow, most attention has been drawn to the maximal percent stenosis of the arterial lumen. The focus on severity of stenosis has been reinforced because severe (70%–99%) atherosclerotic stenosis was demonstrated as an independent predictor for stroke recurrence in the territory of the stenotic artery, with the risk of ≈20% at 1 year, in the Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial. However, those patients with a traditionally considered moderate (50%–69%) atherosclerotic stenosis were also at considerable risk of recurrent stroke, ≈10% at 1 year in the WASID study. In more recent studies, the role of percent stenosis in predicting subsequent stroke risk has been superseded by collateral flow and hemodynamics in the same patient cohort. Characterization of the atherosclerotic lesion is also represented poorly by percentage of stenosis measured at the narrowest vessel diameter alone. Beyond the maximal luminal stenosis, many other features may reflect the characteristics of ICAS, such as plaque morphology and components, which might also be promising markers in risk stratification of patients with symptomatic ICAS. However, from the view of intracranial stenosis, it could also be attributed to causes other than atherosclerosis, such as moyamoya disease and arterial dissection (not covered in the current review). The designation of ICAS as intracranial stenosis is insufficient and misleading with respect to the diagnosis, characterization of such lesions, and risk stratification for the prevention of subsequent stroke.

In this article, we redefine the diagnosis and evaluation of ICAS, removing the focus on luminal stenosis alone, drawing on data from recent imaging studies and we reconsider practical implications of this renewed emphasis on atherosclerotic plaque morphology and hemodynamic impact on downstream brain tissue. Our survey of currently available diagnostic techniques emphasizes potential surrogate markers for risk stratification in symptomatic ICAS.

Diagnostic Modalities for ICAS

TCD and Transcranial Color-Coded Duplex

TCD is a safe, noninvasive, and inexpensive method to diagnose ICAS. Although the accuracy of TCD in grading percent stenosis has varied among prior studies, it is superior in providing real-time flow information and evidence for direction of flow, collateralization, embolization, and steal phenomenon, as compared with static images of CTA and MRA. For instance, TCD detection of microembolic signals has been associated with specific infarct patterns on diffusion-weighted MR images. Persistence of microembolic signals may also indicate subsequent worsening of neurological deficits during the acute phase of ischemic stroke. Furthermore, microembolic signals have been reported as an independent predictor for stroke recurrence in patients with symptomatic ICAS. In addition, TCD vasomotor reactivity quantification may reflect the capacity of cerebral autoregulation, often globally impaired in patients with ICAS and a possible risk factor for stroke. Most recently, the use of transcranial color-coded duplex has advanced the diagnostic accuracy of ICAS by incorporating anatomic definition of the arterial lumen and has been applied increasingly to evaluate cerebral arteries in studies of revascularization therapies.

Magnetic Resonance Angiography

TOF-MRA and contrast-enhanced MRA are now commonly used for assessment of the intracranial vasculature. TOF-MRA, based on the contrast mechanism known as flow-related enhancement, accentuates hemodynamic features and therefore generally overestimates the degree of stenosis, especially in cases with low flow distal to the ICAS. But the flow information carried by TOF-MRA is likely to play a role in the assessment of hemodynamic impact of the lesion, which is discussed in detail below. Contrast-enhanced MRA, acquired with a combined head and neck coil, permits simultaneous imaging of the entire supra-aortic...
vasculature, from extracranial segments to distal intracranial branches.\textsuperscript{15} It may provide better morphological visualization as compared with TOF-MRA, especially for a high-degree stenosis with low flow, but its sensitivity to detect intracranial lesions is lower than that of extracranial lesions.\textsuperscript{15} Quantitative MRA, based on a phase-contrast technique and using TOF-MRA to facilitate vessel localization, is a relatively novel application of MRA to measure blood flow through vessels of interest.\textsuperscript{16} Quantification of blood flow by quantitative MRA has been found promising in identifying patients at high risk of stroke recurrence, assessing intracranial in-stent stenosis and revealing pathophysiology in various cerebrovascular disorders.\textsuperscript{17,18}

**High-Resolution MRI**

Recent research using modern MRI techniques, such as high-resolution MRI (HR-MRI), and other advanced technology, such as the computational fluid dynamics (CFD) technique as detailed below, produce important information to improve understanding of pathophysiology and diagnosis of intracranial atherosclerotic disease. Translation of HR-MRI from the depiction of coronary and carotid plaques to intracranial applications (Figure 1) has enabled imaging of intracranial plaque and the adjacent arterial wall, possibly identifying intracranial plaques because of atherosclerosis or other causes, revealing plaque morphology and constituents, including intraplaque hemorrhage, lipid core, and fibrous cap.\textsuperscript{19} Imaging features of intracranial plaque on HR-MRI (7 Tesla) have been reported to be closely correlated with plaque components by histopathologic analysis in a postmortem, in vitro study.\textsuperscript{19} HR-MRI was also been reported recently to be helpful in guiding endovascular intervention of atherosclerotic disease of the basilar artery.\textsuperscript{6} Further studies exploring the relationships between plaque features by HR-MRI and subsequent stroke risk may provide additional insight on the plaque stability and corresponding intervention strategy in patients with symptomatic ICAS.

**Computed Tomographic Angiography**

As a minimally invasive imaging modality, CTA provides better delineation of the anatomy of intracranial arteries, thus yielding higher diagnostic accuracy of the luminal stenosis of ICAS as compared with TCD and MRA, with DSA as the reference standard, although the visualization of petrous and cavernous segments of ICA by CTA may be affected by bony artifacts. Unlike TOF-MRA, the nature of CTA is not based on flow in the vessel, which is an advantage in depicting the vessel morphology but a disadvantage in the way that it tends to eliminate any temporal information about blood flow. Recently, CTA has been used increasingly in evaluating collateralization in ICAS, including leptomeningeal collateral routes, which have been correlated with risk of recurrent events.\textsuperscript{20,21} CTA images are a good source for geometric reconstruction in preparation for blood flow simulation by CFD techniques, which is discussed below.

**Digital Subtraction Angiography**

DSA is currently considered as the reference standard for diagnosing intracranial vascular diseases including ICAS, because of its superb spatial and contrast resolution to depict the vessels, as well as its ability to reveal temporal information on antegrade and collateral flow.\textsuperscript{10} It is almost always used as the reference standard in studies testing the accuracy of other imaging modalities to grade the luminal stenosis of ICAS. For the evaluation of collaterals, DSA may clearly reveal patent segments and the direction of flow across segments of the circle of Willis, and it has been demonstrated of good to very good inter/intraobserver agreement to grade leptomeningeal collateralization although grading methods have varied.\textsuperscript{21} However, as an invasive method, DSA could lead to periprocedural complications, including transient or even permanent neurological deficits.

**Perfusion Imaging**

Hypoperfusion serves as a common cause for ischemic stroke in patients with ICAS.\textsuperscript{22} CT perfusion and perfusion-weighted MR imaging have been used to detect hypoperfused territories in acute ischemic stroke during the past decade, which allows for the identification of potentially salvageable tissue or the ischemic penumbra.\textsuperscript{23} Mismatch between the hypoperfused tissue and the infarct core on multimodal CT and MR images has been used as an indicator for reperfusion therapies in clinical trials, which is altering the traditional concept of time windows.\textsuperscript{23} Recently, selective arterial spin-labeling MR imaging has been used to reveal the perfusion territories and measure cerebral blood flow of individual cerebral arteries.\textsuperscript{24} This technique also enables visualization and quantification of the actual collateral flow information in the setting of ICAS.\textsuperscript{24} These perfusion imaging methods
CFD of ICAS

Beyond the methods detailed above to evaluate the presence of ICAS, CFD techniques can also be applied to the study of ICAS to investigate hemodynamic impact of a specific lesion.\(^{25-27}\) Three-dimensional (3D) geometry of the diseased vessels may be reconstructed from angiographic images for simulation of blood flow, through which hemodynamic features of the lesion, including pressure gradients across the atherosclerotic plaque or fractional flow, may be analyzed.\(^{25}\) CFD simulation based on biplanar DSA images revealed low fractional flow in only 40% of the severe (70%-99%) stenoses in Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial,\(^{25}\) again underscoring the considerable need for more comprehensive evaluation of ICAS rather than arbitrarily grading it as moderate or severe based on the maximal luminal stenosis.

Stenosis Versus Lesion Identification

Despite the above-mentioned methods to profile different aspects of the lesions in patients with symptomatic ICAS, percentage of luminal stenosis has been the leading or only indicator for patient selection in successive clinical trials, and those with 70% to 99% stenosis have been almost exclusively targeted as the high-risk population in recent studies.\(^{2,3}\) Mounting evidence on the importance of collaterals, hemodynamic impact, and other factors in determining subsequent stroke risk in patients with symptomatic ICAS\(^ {7,8,25}\) suggests that the diagnosis and evaluation of intracranial atherosclerotic disease should be redirected from grading of stenosis to hemodynamic and embolic character, to optimally identify those who are truly at high risk.

Overall Problem With Studies on Diagnostic Tests Focusing on Stenosis Rather Than Other Measures

Noninvasive imaging modalities of TCD, MRA, and CTA, although widely used to detect ICAS, their diagnostic abilities have not been rigorously tested in large, prospective studies. The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial, as a companion study to WASID and the first prospective, multicenter study to test the diagnostic ability of these imaging modalities against DSA, focused solely on the maximal degree of luminal stenosis as many other preceding studies did, which is only one among many aspects to properly characterize the lesions.\(^{10}\) This might be one of the most important reasons why this study showed poor consistency across these imaging modalities. More recently, the predictive ability of percent stenosis measured via TOF-MRA for the risk of stroke recurrence has been surpassed by that of the hemodynamic impact of ICAS derived from TOF-MRA as detailed below, in subsequent analyses of the MRA archives of SONIA study.\(^ {9}\) Thus, the degree of stenosis may not be an appropriate target for studies investigating diagnostic tests for ICAS, which needs to be addressed in future studies.

Role of Collateralization in ICAS

Collateral status has been demonstrated to correlate with acute and final infarct volume and infarct volume expansion in patients with acute ischemic stroke.\(^ {24,26}\) Collateral perfusion is also predictive of response to intravenous thrombolysis and endovascular therapies, with good collaterals reducing hemorrhagic transformation while enhancing revascularization rate.\(^ {30,31}\) Most importantly, the degree of collateral circulation has been found to be significantly correlated with functional outcomes of patients with symptomatic ICAS.\(^ {20,32}\) In the WASID trial, collateral status was identified as an independent predictor for stroke recurrence in the symptomatic arterial territory, altering the stroke risk that otherwise would be different if only predicted based on the severity of luminal stenosis.\(^ {7}\) More extensive collaterals reduced the risk of recurrent territorial stroke in 70% to 99% stenoses (none versus good collaterals: hazard ratio, 4.60; 95% confidence interval, 1.03–20.56; poor versus good collaterals: hazard ratio, 5.90; 95% confidence interval, 1.25–27.81; \(P=0.0427\)), whereas increased risk in 50% to 69% stenoses (none versus good collaterals: hazards ratio, 0.18; 95% confidence interval, 0.04–0.82; poor versus good collaterals: hazards ratio, 1.78; 95% confidence interval, 0.37–8.57; \(P<0.0001\)). Collateral flow therefore is one of the most essential mediators in cerebral ischemia because of ICAS and hence an important indicator in risk prediction and treatment allocation in patients with symptomatic ICAS. However, it has not been systematically investigated, and little is known about the process of collateral recruitment or arteriogenesis in progressive ICAS, which warrant further studies.

Role of Fractional Flow in ICAS

Translation of recent advances in the cardiology field has inspired vascular neurologists to apply novel measures to characterize ICAS. The paradigm shift in ischemia-related coronary artery disease (CAD), from anatomic measures of percent stenosis to hemodynamic impact of lesions, may be paralleled in the diagnostic approach and decision making of ICAS. Fractional flow reserve (FFR), measured as the ratio of pressures distal and proximal to a coronary lesion under induced hyperemia by floating a pressure wire during percutaneous coronary angiography, has become the gold standard to assess the hemodynamic significance of CAD.\(^ {33}\) Large clinical trials on FFR have demonstrated the unreliability of percent stenosis as an indicator to define a hemodynamically significant CAD, especially in cases with anatomically moderate stenoses.\(^ {34}\) For instance, in the Fractional Flow Reserve versus Angiography in Multivessel Evaluation study, 35% of lesions with an angiographically moderate severity (50%-70% stenosis) were found to be functionally significant.\(^ {35}\) Moreover, FFR-guided coronary revascularization has been demonstrated safe and superior to angiography-guided strategy in reducing major cardiac events and composite adverse events.\(^ {36}\) More recently, the CFD technique has been applied to coronary CTA to noninvasively quantify FFR.\(^ {34}\) The noninvasive FFR has been proven of good diagnostic accuracy for the hemodynamic significance of CAD, with invasive FFR as the reference.\(^ {34}\) Although cerebral arteries in many ways differ...
from coronary arteries, these findings in cardiology further aroused the need for neurologists to divert the solely focus on the degree of stenosis to more sound and reasonable ways to evaluate ICAS.

Similar to the application of noninvasive FFR in the coronary arteries, the CFD technique may also be used to assess fractional flow across ICAS lesions. As mentioned above, CFD modeling based on the SAMMPRIS angiography disclosed hemodynamic effects of ICAS, with decreased pressure identified distal to the ICAS lesions.25 Besides, we have performed a pilot study of 10 cases on CFD modeling of ICAS based on intracranial CTA, which have confirmed the feasibility to reconstruct CFD models out of routinely obtained intracranial CTA source images (Figure 2). For CFD modeling of an ICAS lesion based on CTA, 3D geometry of a target arterial segment containing the lesion could be extracted and reconstructed from the CTA source images, which could then be meshed for simulation of the blood flow across the lesion. The simulated CFD models showed decreased pressure and increased flow velocity in situ and beyond the ICAS lesions, as shown in Figure 2. Although the CFD-based fractional flow in ICAS has yet to be correlated with subsequent stroke risk, it provides a fertile ground for next steps in the clinical research on the diagnosis and optimal treatment of ICAS.

Besides the CFD-based evaluation of fractional flow, we developed another method including use of the TOF-MRA termed signal intensity ratio, based on its flow-related signal contrast mechanism, to systematically gauge the hemodynamic effects of an ICAS. Signal intensity ratio of an ICAS was measured as the ratio of distal and proximal signal intensities within the vessel lumen, adjusted by the background signal intensity on the maximum intensity projection images (Figure 3).14 We have preliminarily explored the clinical significance of signal intensity ratio.8,37 It was found to be significantly related to acute infarct volume on diffusion-weighted MR images in a preliminary study.37 Moreover, it was identified as an independent predictor for recurrent stroke in the territory of the diseased artery in the SONIA-WASID cohort.9 Therefore, signal intensity ratio by TOF-MRA, as a noninvasive, easy-to-perform, and highly reproducible method, may be a useful tool to differentiate high-risk ICAS.26,38

**Practical Considerations for ICAS**

Although ICAS has been established as a prominent cause of ischemic stroke and transient ischemic attack, it has been relatively understudied during the past decades. Compared with numerous studies on symptomatic and asymptomatic carotid artery disease, the relatively limited interest on ICAS has hindered progress in relevant research and clinical areas. Insufficient evidence on specific treatment effects in large clinical studies has produced considerable gaps between research and practical risk stratification and decision making in patients with ICAS. This may partly explain why the clinical diagnosis and treatment of ICAS continues to be based solely on luminal stenosis, despite recent findings for many other potential predictors of subsequent stroke risk. In coming years, more diagnostic test data concerning the above imaging modalities will further identify denominators of cases with high risks and validate the roles of perfusion imaging and other novel imaging methods in the evaluation of hemodynamic effects of ICAS, which will allow us to truly identify high-risk ICAS but not highly selected and biased cases of intracranial stenosis. In the clinical diagnosis and assessment
of ICAS, as well as in future relevant clinical studies, the following practical considerations are important to address this common disease worldwide.

Need for Noninvasive Detection of ICAS
Despite the use and accuracy in evaluating anatomic severity, antegrade and collateral flow in ICAS, the invasive nature and potential peri-procedural risk of DSA prevent its extensive and repeated use in indicated patients, and the high costs and dependence on experienced operators further limit its use as a routine examination for intracranial arteries in all patients with ischemic stroke. Therefore, noninvasive methods, such as TCD, MRA, and CTA, are still used commonly for the diagnosis of ICAS in clinical scenarios. Although these currently available noninvasive imaging modalities also have limitations, detailed below, comprehensive interpretation of noninvasively obtained intracranial vascular images, in combination with perfusion imaging and other methods reflecting different aspects of ICAS, may avoid the need to proceed with an invasive angiography procedure.

Limitations of Noninvasive Diagnostic Modalities and Need for Reasonable Interpretation
Based on the inherent nature of TCD, TOF-MRA, and CTA, they address different aspects of the lesion when characterizing ICAS, yet the severity of stenosis remains the primary focus despite enormous information on flow and other aspects of ICAS often ignored by clinicians. Paradoxically, the percentage of stenosis itself is not concordant among these imaging modalities.10 Furthermore, each of these noninvasive methods has its specific limitations. TCD, as a low-cost and useful tool to provide real-time cerebral flow information, requires thorough skill training and is highly operator-dependent, which therefore is still underused throughout the world ≈30 years after its first use in cerebrovascular diseases.12 TOF-MRA and CTA, as the most commonly used noninvasive methods to depict the morphology of major intracranial arteries, respectively, based on the blood flow and vascular geometry, could complement each other with respect to the evaluation of hemodynamic and lumen-narrowing effects of ICAS, yet may incorrectly reflect severity of the lesion if interpreted alone in the evaluation of ICAS. In addition, although CTA provides a reliable method to assess the leptomeningeal collateral circulation, inconsistency in the scaling methods impedes generalization of recent findings on the correlations between noninvasive leptomeningeal collateral grading and the clinical outcomes.34 Therefore, application of these imaging methods and interpretation of the results should be based on the unique characteristics of each modality, to permit a comprehensive assessment of the lesion.

Recurrent Risk in Patients With ICAS of Mild or Moderate Luminal Stenosis
In contrast to intracranial atherosclerotic lesions resulting in 70% to 99% reduction of the vessel caliber, which are considered severe and high-risk in relevant studies, ICAS of <50% and 50% to 69% luminal stenosis is usually regarded as nonsignificant, or defined as mild and moderate lesions, respectively.24 However, despite the high risk of stroke recurrence in patients with symptomatic 70% to 99% stenosis, ICAS of nonsevere luminal stenosis may also be at risk of recurrent events. In the WASID and the Chinese ICAS (CICAS) studies, nearly half of the recurrent stroke occurred in patients with 50% to 69% stenosis.25 Few data are available on the prognosis of those with ICAS of mild (<50%) stenosis. According to large parallel cardiovascular studies performed in patients with acute coronary syndromes, those with CAD of <50% luminal stenosis also faced a non-negligible risk of death and reinfection, although relatively lower than that of those with obstructive lesions.39 Among the limited data concerning outcomes of patients with ICAS of <50% luminal stenosis, a considerable risk of recurrent stroke was observed in the CICAS cohort, yet the percentages of luminal stenosis in these mild lesions were not specifically reported.8 Therefore, recurrent risks in patients with ICAS of <70% stenosis need to be fully appreciated in future studies, so that high-risk patients would not be missed because of the artificially graded severity of ICAS by the degree of luminal stenosis.

Need for Correlating With Subsequent Clinical Events, Not Percent Stenosis
Increasing evidence on potential determinants of subsequent stroke risk beyond the severity of stenosis calls for changes in the concept of how to diagnose ICAS. The traditional method to grade ICAS by the maximal percentage of luminal stenosis is irrational, in light of the considerable risk of stroke recurrence in patients with ICAS of <70% luminal stenosis and the complex effects of different aspects of ICAS on stroke risk. Thus, the currently defined high-risk ICAS based on the angiographic severity of stenosis may be misleading. For this reason, evaluation of ICAS based on its correlations with subsequent clinical events rather than the percent stenosis may be of higher clinical significance, supported by recent findings in the roles of collateral status, plaque characteristics, and hemodynamic features in determining recurrent risks in symptomatic ICAS.28,29

Need to Develop Methods to Evaluate All Stroke Cases With ICAS
Because of the widely adopted philosophy of grading ICAS by the severity of luminal stenosis, successive observational and interventional studies tend to be performed in restricted populations with a certain degree of stenosis, for instance, the WASID-SONIA and the SAMMPRIS trials specifically focused on patients with symptomatic ICAS of 50% to 99% and 70% to 99% luminal stenosis.2,3,10 Given the increasingly emerging evidence for other potential indicators altering subsequent stroke risks in symptomatic ICAS, it is in great need to establish more reasonable and generalizable methods for the evaluation of all stroke cases with ICAS, regardless of the degree of stenosis. Future studies with broader considerations of this patient subset will provide abundant information on the diagnosis and treatment of all symptomatic ICAS and embrace better understanding of this important cause of ischemic stroke.
Table. Key Messages of the Review

1. The designation of ICAS as intracranial stenosis is insufficient and misleading with respect to diagnosis, characterization, and risk stratification of such lesions
2. Plaque morphology and stability, presence of collaterals, downstream perfusion status, and fractional flow across the lesion, etc. besides the percentage of luminal stenosis, may also facilitate risk stratification of patients with symptomatic ICAS
3. In the evaluation of ICAS, results of currently available imaging methods should be comprehensively interpreted based on the unique characteristics of each modality, rather than focusing solely on the severity of luminal stenosis
4. Symptomatic ICAS of <70% luminal stenosis, usually considered as mild or moderate lesions, are not without risk of recurrence, which also need to be fully appreciated in future studies and clinical practice, as with ICAS of ≥70% luminal stenosis
5. Diagnosis and evaluation of ICAS based on its correlations with subsequent clinical events rather than the percent stenosis may be of higher clinical significance.

ICAS indicates intracranial atherosclerosis.

Stroke Risk of Asymptomatic ICAS
Identifying asymptomatic intracranial atherosclerotic lesions with high risk of first-ever ischemic stroke or transient ischemic attack will be a further step in advancing the management of such a patient subset, yet data concerning the stroke risk and prognostic factors in asymptomatic ICAS have been scarce to date. Although previous studies reported a relatively benign clinical course of asymptomatic ICAS as compared with symptomatic lesions, these findings have not been verified in large, prospective, population-based studies. In addition, in patients with symptomatic intracranial atherosclerotic lesions, recurrent stroke may also occur in the territories of concomitant asymptomatic ICAS, for which case little is known about the clinical course and mechanisms. Exploration of the natural history and stroke risks in individuals with asymptomatic ICAS in future studies will undoubtedly facilitate primary prevention of stroke.

Conclusions
Key messages of this review article are summarized in the Table. In patients with ICAS, the roles of collateral status, plaque stability, hemodynamic impact, and other potential factors may surpass that of percent stenosis in predicting the risk of subsequent recurrent events. The diagnostic emphasis on ICAS rather than intracranial stenosis is fundamental in risk stratification and rational decision making with respect to available therapies. Errorneously estimating the risk of stroke recurrence based on the maximal degree of luminal stenosis without consideration of hemodynamic features may be devastating. Currently available imaging methods should be comprehensively evaluated based on specific advantages in each technique rather than focusing solely on the severity of stenosis. After many years with a persistent focus on percent stenosis, redefinition of ICAS based on other diagnostic test information may facilitate the development of novel treatment strategies for patients with ICAS around the world. In coming years, increasing application of perfusion imaging and other novel methods to evaluate directly or indirectly the hemodynamic impact of ICAS will promote a broader understanding of this common cerebrovascular disorder. Future studies correlating various aspects of ICAS with subsequent stroke risk will facilitate diagnosis of high-risk or severe intracranial atherosclerotic lesions, instead of an arbitrary measure of maximal luminal stenosis.

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References


34. Taylor, CA, Fonte, TA, Min, JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *Am Coll Cardiol*. 2013;61:2233–2241.


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Intracranial atherosclerosis (ICAS) is a worldwide important cause of ischemic stroke, accounting for 30–50% and 10% of ischemic stroke and transient ischemic attack (TIA) in Asian and white populations, respectively. Currently, various imaging methods are used for clinical diagnosis and evaluation of ICAS, such as transcranial Doppler (TCD), magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and digital subtraction angiography (DSA). Some imaging methods can provide flow-related information, for example, TCD can provide flow velocity and detect turbulence, while time-of-flight MRA (TOF-MRA) can reflect vessel morphology based on flow conditions. However, in the evaluation of ICAS, most attention is still focused on the degree of vessel narrowing. In the Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) study, "severe" (70–99%狭窄) intracranial atherosclerotic stenosis was proved to be an independent risk factor for recurrent ischemic stroke in patients with disease-related vessel stenosis. This finding further emphasizes the overemphasis on the degree of vessel narrowing in ICAS evaluation. However, in the WASID study, the "moderate" (50–69% narrowing) ICAS patients still had a one-year recurrent stroke risk of 10%, which was not negligible. In recent studies, the severity of vessel narrowing is less important than collateral circulation and hemodynamics in predicting recurrent ischemic stroke risk. Additionally, plaque morphology and components may have potential value for risk stratification in affected patients, such as plaque morphology and composition. Moreover, the etiology of intracranial stenosis is not only atherosclerosis, but also other diseases such as moyamoya disease, arterial dissection, etc. Therefore, using ICAS to denote ICAS is not correct and misleading.

TCD for ICAS may provide higher accuracy than CTA and MRA in diagnosing ICAS. TCD may provide flow velocity, detect turbulence, and other information such as collateral circulation and microembolic signals (MES). Some studies have shown that TCD-detected MES may be associated with specific stroke types on diffusion-weighted imaging (DWI) and may predict worsening cerebral function when detected during acute ischemic stroke. TCD can also provide quantitative assessment of cerebrovascular reactivity, which may reflect impaired cerebral autoregulation, a potential risk factor for ischemic stroke. Transcranial color-coded duplex (TCCD) has recently been used to improve the accuracy of ICAS diagnosis with both ultrasound and color Doppler signals. In current research, TCCD is increasingly used to evaluate cerebral revascularization in patients with intracranial stenosis. Magnetic resonance angiography (MRA) is currently used to evaluate the intracranial arterial system. TOF-MRA relies on the signal enhancement related to blood flow, and CE-MRA uses contrast agents to improve vessel visualization. The superior imaging of CE-MRA in evaluating intracranial ICAS is more prominent in severe stenosis compared with TOF-MRA. Furthermore, in severe stenosis of ICAS, CE-MRA can provide lower sensitivity than TOF-MRA. Quantitative MRA (QMRA) is a relatively new MRA technique that can measure blood flow in the intracranial arteries and can help predict recurrent stroke risk and provide information on the pathophysiology of ICAS. High-resolution magnetic resonance imaging (HR-MRI) has been used extensively to evaluate ICAS and other cerebrovascular diseases. In recent years, the combination of high-resolution MRI and computational fluid dynamics (CFD) has been used to simulate hemodynamics in the intracranial arteries and can help predict recurrent stroke risk.
样硬化性颅内斑块及其他原因所致的颅内斑块，并可反映颅内动脉斑块的形态及成分，例如斑块内出血、脂核及纤维帽。在一项尸检体外标本研究中，HR-MRI（7 Tesla）所反映的颅内斑块成分与病理诊断结果非常接近。此外，近期有研究发现 HR-MRI 有助于指导基底动脉粥样硬化性病变的血管内介入治疗。对于症状性颅内动脉粥样硬化患者，进一步探索 HR-MRI 颅内斑块特征与卒中复发风险之间的关系，可能有助于判断斑块稳定性及指导相应干预措施。

计算机断层扫描血管成像 CTA 是一种需要造影剂的影像学检查方法，能够比 TCD 和 MRA 更好地反映颅内动脉的解剖学特征。以 DSA 为金标准。CTA 在诊断 ICAS 管腔狭窄程度上的准确性高于 TCD 和 MRA；但是 CTA 对颅内动脉血管图像中的管腔狭窄性病变的血管内介入治疗。对于症状性颅内动脉粥样硬化患者，进一步探索 HR-MRI 颅内斑块特征与卒中复发风险之间的关系，可能有助于判断斑块稳定性及指导相应干预措施。

数字减影血管造影 由于 DSA 具有很高的空间分辨率，并且可以反映颅内动脉粥样硬化性病变的血流动力学信息，目前被认为是诊断颅内动脉病变的金标准。包括颅内动脉粥样硬化性病变，但在一些研究中发现 DSA 与 MRA 的管腔狭窄程度存在明显的差异。此外，对于颅内动脉粥样硬化性病变的血管内介入治疗，CTA 的应用越来越受到重视。CTA 可以在不造影剂的情况下，清楚地显示颅内动脉的解剖学特征，对于评估颅内动脉粥样硬化性病变的血流动力学和血流情况具有重要意义。

ICAS 的计算机流体动力学建模 除了上述讨论的影像学诊断和评价方法，CFD 技术也可应用于 ICAS 血流动力学建模的研究。通过 CFD 技术，可以模拟 ICAS 病变血流动力学效应的分布，这对于评估 ICAS 病变血流动力学效应（如血流速度和压力梯度）具有重要价值。此外，研究还发现 CFD 技术对于评估 ICAS 病变血流动力学效应（如血流速度和压力梯度）具有重要价值。而且 CFD 技术还可以评估 ICAS 病变血流动力学效应的分布，这对于评估 ICAS 病变血流动力学效应（如血流速度和压力梯度）具有重要价值。CTA 的应用越来越受到重视。CTA 可以在不造影剂的情况下，清楚地显示颅内动脉的解剖学特征，对于评估颅内动脉粥样硬化性病变的血流动力学和血流情况具有重要意义。

对狭窄进行评估，还是对病变进行综合评估？尽管上文所讨论的影像学方法可反映症状性 ICAS 病变的各方面特征，但在近年的相关临床研究中，病变的管腔狭窄百分比仍然是首要纳入标准。而且在这些研究中，管腔狭窄程度为 70-99% 的 ICAS 病变通常被认为是“中度”或“重度”病变。这可能是该研究显示各个影像学方法之间一致性很差的原因之一。最近，对 SONIA 研究中接受 MRA 检查的患者进行的亚组分析表明，基于 TOF-MRA 所评价的 ICAS 病变的血流动力学特征与 DSA 所评价的 ICAS 病变的血流动力学特征一致。然而，作为一种有创性的影像学检查方法，DSA 可能导致围手术期并发症，甚至引起一过性或永久性神经功能损伤。

灌注成像 低灌注是 ICAS 患者发生缺血性卒中的常见机制之一。近十年来，CT 灌注成像（CT perfusion, CTP）及磁共振灌注加权成像（perfusion-weighted imaging, PWI）开始被经常应用于急性缺血性卒中的诊断和治疗。然而，CTA 作为一项无创性影像学检查方法，对于诊断 ICAS 病变的血流动力学特征和血流情况具有重要意义。CTA 的应用越来越受到重视。CTA 可以在不造影剂的情况下，清楚地显示颅内动脉的解剖学特征，对于评估颅内动脉粥样硬化性病变的血流动力学和血流情况具有重要意义。
流力学效应对受累患者的卒中复发风险的预测价值，超过了基于该检查方法对评价的管腔狭窄程度的预测价值；这种通过 TOF-MRA 上信号强度变化评估 ICAS 病变血流力学效应的方法将在下文进行详细描述。因此，在评价 ICAS 影像学诊断方法准确性的相关研究中，病变部位的管腔狭窄程度可能并非合适的评价指标；在未来的相关研究中需要解决这个问题。

侧枝循环对 ICAS 的意义

在急性缺血性卒中患者中，侧枝循环的状态被证实与急性及最终梗死灶体积，以及梗死体积增大相关。28, 29 同时，侧支灌注可预测急性缺血性卒中患者对静脉溶栓和血管内治疗的反应；较好的侧枝循环可以减少出血转化，并增加血管再通率。30, 31 更重要的是，侧枝循环的开放程度与症状性 ICAS 患者的功能预后显著相关。20, 32 在 WASID 研究的症状性 ICAS 患者中，侧枝循环的程度被证实为目标颅内动脉供血区域卒中的独立预测因素，可以改变基于病变动脉管腔狭窄程度所预测的卒中复发风险。7 有研究证实，10-99% 狭窄的管腔狭窄程度 50-70% 的冠脉病变被发现具有显著的功能异常。35 此外，研究证实 FFR 指导下的冠脉病变血运重建术不仅安全，而且优于传统冠脉造影指导下的血运重建术；最后如显降低主要心脏事件及复合不良事件的发生率。36 在最近的研究中，CFD 技术可应用于 CTA, 从而进行无创性的 FFR 模拟分析。24 侧枝循环对 ICAS 的意义

血流动力学效应(或血流分数)对 ICAS 的意义

近年来，一些心脏科的新进展促使血管神经病学家将这些新方法应用于 ICAS 的诊断和评价。目前，血流动力学效应与 ICAS 病变的血流动力学效应(或血流分数)已被证实具有显著的临床意义。25 例如，在血流储备分数与冠脉病变血运重建端复血管位置的压力比(图 3)。34 我们已经在一些小样本研究中探索了 SIR 的临床意义；26, 38 该指标在一项初步研究中被证实与受累患者急性梗死灶体积显著相关。37 此外，在 SONIA-WASID 研究人群中，该指标被证实为目标病变动脉供血区域内卒中复发的独立预测因素。38 因此，ICAS 病变的 SIR 作为一种无创性、简单易行且具有高度可重复性的方法，可能有助于高风险 ICAS 病变的判定。26, 38
ICAS 相关的实际问题

尽管 ICAS 已经被证实是缺血性卒中和 TIA 的重要病因，但是仍未被全面研究。与症状性和无症状性颈动脉粥样硬化疾病的大量研究相比，ICAS 研究的力度及广度都远小于其他血管病变。与症状性和无症状性颈动脉粥样硬化疾病的大量研究相比，ICAS 相关领域的关注度较低，这妨碍了 ICAS 的研究及临床进展。

ICAS 治疗方法相关的大型临床试验数据不足，这使得相关研究结果与患者的临床实际分层和临床决策之间存在很大差距。这可能解释了为什么相关研究已经发现了其他可预测卒中复发的危险因素，而 ICAS 患者的临床诊断和治疗仍然以病变管腔的狭窄程度为唯一参照标准。未来几年内，更多关于上述影像学检查方法诊断效能的研究可进一步确定高危患者的决定因素，并验证 CT/MR 灌注成像及其他新的影像学方法在评价 ICAS 病变血流动力学效应中的作用；这样我们才能真正确定具有高复发风险的“颅内动脉粥样硬化”病变，而非存在偏倚且高度选择性的“颅内动脉狭窄”。作为一种世界范围内常见的疾病，在 ICAS 的临床诊断与评估，以及未来的相关临床研究中，以下实际问题需要引起重视。

需要对 ICAS 进行无创性检查

尽管 DSA 在诊断 ICAS 病变狭窄程度及前向或侧枝血流中具有很高的准确性，但是其有创性的特征及潜在的围手术期风险使其无法在患者中广泛和重复应用；此外，DSA 花费较高，而且非常依赖操作者的经验，所以无法作为缺血性卒中患者颅内动脉粥样的常规检查方法。因此，在临床实践中，TCD、MRA 和 CTA 等无创性检查方法仍然常用于 ICAS 的诊断。尽管这些检查方法同样存在局限性（于下文中详述），将无创性检查方法获得的颅内血管影像与灌注成像和其他 ICAS 成像方法的结果相结合并进行综合评价，可能避免进行有创性血管检查。

无创性检查方法的局限性及合理评估的必要性

基于 TCD、TOF-MRA 及 CTA 的特征，它们可以反映 ICAS 不同方面的特征，然而，病变的管腔狭窄程度仍是目前临床医生的首要关注目标，而大量的血流信息及其他方面的特征经常被临床医生忽视。事实上，即使是病变的狭窄程度本身在这些检查方法之间也并不一致。10 此外，上述无创性检查方法各自具有不同的局限性。TCD 作为一种经济的检查方法可提供实时脑血流信息，但该方法需要检查者接受全面的培训，其检查结果高度依赖于检查者；因此，在 TCD 首次用于脑血流研究 30 年之后，该技术仍未在世界范围内充分使用。12 TOF-MRA 及 CTA 是评价颅内动脉粥样硬化中常用的无创性影像学方法，二者成像分别基于血流和血管形态学，因此在评价 ICAS 的血流动力学效应及管腔狭窄程度上可以互补；然而，在评价 ICAS 时将二者的结果分开进行独立分析，则可能无法准确反映病变的严重程度。此外，尽管 CTA 可以有效评价软脑膜侧枝循环，但不同评价方法之间的差异使得近期关于无创性软脑膜侧枝循环分级和临床结局之间的关系的发现无法推广。21 因此，上述影像学检查方法的临床应用及结果诠释需要基于各自的特征，从而对 ICAS 病变进行全面的评价。

轻中度管腔狭窄的 ICAS 患者的卒中复发风险

管腔狭窄 70-99% 的 ICAS 病变通常被认为是“重度”或“高危”病变；与此类 ICAS 病变相比，管腔狭窄程度 <50% 和 50-69% 的 ICAS 病变常常被忽视，或者分别被定义为“轻度”和“中度”病变。2 然而，不仅管腔狭窄 70-99% 的症状性 ICAS 患者具有高复发风险，非重度管腔狭窄的 ICAS 病变也具有卒中复发风险。在 WASID 研究及中国颅内动脉粥样硬化 (Chinese Intracranial Atherosclerosis, CICAS) 研究人群中，近一半卒中复发发生于管腔狭窄 50-69% 的症状性 ICAS 患者。5, 6 目前，关于轻度(<50%)管腔狭窄 ICAS 患者预后的数据较少。根据在急性冠脉综合征患者中进行的多项大型心血管病研究，管腔狭窄<50% 的 CAD 患者心梗复发和死亡风险尽管低于存在严重管腔狭窄的患者，但仍不可忽视。20 在目前关于管腔狭窄<50% 的 ICAS 患者预后的有限研究中，CICAS 研究发现该患者群体不可忽视的卒中复发风险；然而该研究中这些“轻度”病变具体的管腔狭窄程度并未披露。因此，我们需要在未来的研究中对管腔狭窄程度<70% 的 ICAS 患者的卒中复发风险进行进一步评估，这样我们才不会因为人为地根据管腔狭窄程度判定 ICAS 病变的严重程度而忽略掉真正的高危患者。

需要根据临床事件风险而非狭窄程度对 ICAS 进行评价

对于 ICAS 患者，越来越多的证据支持除了病变狭窄程度之外的其他可能决定卒中复发风险的因素，这些证据提示我们需要对 ICAS 的诊断方法进行改进，考虑到管腔狭窄程度<70% 的 ICAS 患者同样具有不可忽视的卒中复发风险，而且 ICAS 病变不同方面的特征均可能影响卒中复发风险，传统上仅仅根据病变最大管腔狭窄百分比来判定其严重程度的方法是不合理的。因此，目前根据病变管腔狭窄程度判定的“高危”ICAS 病变可能具有误导性。最新的关于侧枝循环、斑块特征及血流动力学特征在 ICAS 患者卒中复发风险中作用的相关发现提示，结合 ICAS 与继发临床事件分析其管腔狭窄程度对其卒中复发风险可能具有更大的临床意义。

需要建立评价所有 ICAS 病例的方法

根据管腔狭窄程度对 ICAS 的严重程度进行分级的理念被广泛接受，因此近年来相关的观察性和干预性临床研究多将研究人群限制为一定程度管腔狭窄的患者，例如 WASID-SONIA 研究和 SAMMPRIS 研究分别集中于管腔狭窄 50-99% 和 70-99% 的症状性 ICAS 患者。2, 3, 10 基于越来越多的证据提示其他因素在症状性 ICAS 患者卒中复发风险中的作用，我们亟需建立一种更合理且更全面地评价所有 ICAS 病例的方法，不论其管腔狭窄程度如何。未来的相关研究可以为症状性 ICAS 的诊断和治疗提供大量信息，并使我们更好地理解这种缺血性卒中的重要病因。
无症状性 ICAS 的卒中风险

确定具有出血性卒中或 TIA 高发风险的无症状性 ICAS 病变可以进一步促进对此类患者的治疗,然而目前关于无症状性 ICAS 卒中风险和预测因素的数据尚非充分。尽管以往有研究报道,与症状性 ICAS 患者相比,无症状性 ICAS 患者卒中预后较好,但这些发现尚需在大型、前瞻性的、基于人群的研究中证实。此外,在症状性 ICAS 患者中,卒中也可能是因于卒中的无症状性 ICAS 病变在动脉供血区域,这些区域具有颈部及颈动脉狭窄程度而不考虑血流动力学因素的影响。因此,对 ICAS 病变的自然病程进行研究无疑可以帮助我们提高卒中一级预防。

结论

本综述中最重要的信息和观点已总结于表 1 中。对于症状性颅内动脉粥样硬化患者,侧枝循环、斑块稳定性的病变血流动力学效应及其他因素对复发事件的预测作用可能超过病变的管腔狭窄程度。对颅内动脉粥样硬化进行全面评价而非仅仅诊断颅内动脉狭窄,在受累患者的危险分层及合理临床决策中至关重要。仅根据 ICAS 的管腔狭窄程度而不考虑血流动力学因素的影响,错误估计患者的卒中复发风险,其结果可能很严重。现有影像学方法的检查结果应根据各个方法的优缺点进行综合评估,而非仅仅关注 ICAS 的管腔狭窄程度。经历了过去很多年的对 ICAS 病变狭窄程度的过分关注之后,基于其他影像学信息对 ICAS 进行重新定义与评价可促进世界范围内 ICAS 患者的新的治疗策略的确定。在未来几年内,对可直接或间接评价 ICAS 血流动力学效应的成像方法及其他新的影像学方法的越来越多的应用,可能加深我们对这种常见血管疾病的理解。未来的关于 ICAS 不同特征与卒中风险之间的研究可以促进高危或严重 ICAS 病变的诊断,从而替代现有的根据管腔狭窄程度判断病变严重程度的片面方法。

参考文献