Current diagnosis and management of symptomatic intracranial atherosclerotic disease

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Abstract

Purpose of review—Intracranial atherosclerotic disease (IAD) is likely the most common cause of stroke world-wide, and is associated with a very high risk of recurrence. It results in cerebral ischemia due to a variety of mechanisms, including artery-to-artery embolism, hemodynamic failure and occlusion of penetrating arteries. New imaging modalities focused on physiological consequences of IAD have become available and recent treatment trials have been completed.

Recent findings—We review the traditional imaging modalities, emphasizing the advantages and limitations of each method, and discuss novel physiological approaches that interrogate physiological process to indicate specific mechanisms of ischemia. These allow deeper understanding of the pathophysiological processes that underlie IAD-related ischemia. The key findings of recent therapeutic trails are reviewed, including the landmark randomized studies showing advantage of antiplatelet agents and risk factor modification, and a significant risk of complications with endovascular approaches.

Summary—Current evidence argues for aggressive medical management and suggests caution with interventional treatments. We propose that mechanistic information will further refine the risk assessment of patients with IAD to offer targeted therapy.

Keywords

stroke; intracranial atherosclerosis; stroke etiology; stroke therapy; intracranial stenting

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Introduction

Intracranial atherosclerotic disease (IAD) is a common cause of stroke; its incidence and prevalence vary by ethnicity. IAD is more common in Asians, Hispanics, and those of African descent, compared to Caucasians. It causes approximately 10% of all strokes in the US. [1,2] From Asian studies, IAD accounts for 33–50% of all strokes in China, 47% in

Thailand, 48% in Singapore, and 10–25% in Korea.[3] Given these numbers and the shift in world populations, IAD may well be the most common subtype of ischemic stroke worldwide.[3,4] Furthermore, population based studies of stroke-free adults with vascular risk factors have shown a prevalence of asymptomatic IAD of 8.6%.[5] This review focuses on key findings and recent advances both in diagnosis, with an emphasis on novel approaches to defining the underlying mechanisms of stroke in IAD, and in treatment, including medical and endovascular approaches.

Imaging of Intracranial Stenosis

Diagnosing IAD and defining the mechanism of cerebral ischemia is important, as it will lead to targeted and aggressive treatment to lower recurrent stroke risk. While anatomic diagnosis of arterial narrowing is made with reasonable accuracy, ascribing an etiology for the stenosis remains challenging as radiographic mimics of IAD such as partial embolus recanalization, dissection, vasculitis, and vasospasm are often encountered and may require repeat or multi-modal imaging to distinguish between them. Furthermore, determining whether the stenosis is symptomatic or asymptomatic may not be straightforward, as cardioembolism, extracranial large artery disease and small artery occlusion can co-exist with IAD; up to 19% of recurrent strokes in IAD may be due to another mechanism.[6]

Diagnosis of intracranial stenosis

Catheter-based digital subtraction angiography (DSA), the reference standard of neurovascular imaging, provides excellent visualization of vessel contour, anatomic localization, and assessment of the degree and length of stenosis, and of collateral circulation. Three-dimensional reconstruction provides even greater detail. The risk of peri-procedural neurologic injury, associated access site injury, and dye-related complications limit its use.[7,8]

Transcranial Doppler (TCD) correlates blood flow patterns and velocity changes with arterial diameter. Since direct anatomic visualization is unavailable, its performance depends greatly on technical expertise. Color-coded duplex can overcome this limitation but needs more study.[9] Given its performance characteristics in IAD excellent sensitivity, specificity, and negative predictive (NPV) but only modest positive predictive (36–75%) value (PPV),[10–12] TCD is useful to exclude significant IAD with high certainty but requires confirmatory testing when stenosis is suggested.

Magnetic resonance angiography (MRA) measures flow signal intensity on time-of-flight (TOF) MRA to visualize changes in the flow of blood. Motion artifact and flow directional changes from vertical to horizontal can render ambiguous or erroneous results.[13,14] Its inability to distinguish between high-grade stenosis and occlusion is another major disadvantage.[14] In addition, it has limited to no use in morbidly obese and claustrophobic patients and those with implanted metallic objects. Overall, studies suggest MRA has the similar performance characteristics to TCD in diagnosing IAD: high sensitivity, specificity, and NPV, but modest PPV (59–66%).[10,15] Given their modest PPV, TOF-MRA requires confirmatory diagnostic testing. Contrast-enhanced MRA provides better anatomic visualization, particularly in regions of changing blood flow directions; however, visualization of smaller arteries remains limited.[16,17] Quantitative MRA (QMRA), utilizing phase-contrast techniques, has shown promise to diagnosis hemodynamic failure in posterior circulation stenosis[18] and screen for stenosis of intracranial stents.[19,20] High-resolution MRI (HR-MRI) is capable of characterizing plaque morphology, and discriminating from other non-atherosclerotic etiologies.[21,22] Further study using these novel modalities may increase the diagnostic utility of MRA and provide valuable prognostic data.

Computed tomography angiography (CTA) provides better anatomic visualization compared to MRA,[15,23] and is superior in assessing high-grade stenosis. However, it can be degraded by local calcium or metallic artifacts. Compared to DSA, the high sensitivity (81–98%), specificity (97–99%), PPV (79–93%), and NPV (98–100%) of CTA make this an excellent, and perhaps preferred, non-invasive diagnostic test for intracranial stenosis. [9,15,24] Its disadvantages, besides radiation exposure, are contrast reactions and nephrotoxicity.

The choice of non-invasive imaging modality is guided by availability, cost, advantages and disadvantages (table 1) but other factors should be considered: CTA can better visualize high-grade stenoses than MRA since the latter tends to overestimate the degree of stenosis, while MRA is better at evaluating the petrous and cavernous carotid as bony artifacts affect CTA. The concordance of any two non-invasive tests results obviates the need for confirmatory DSA.

Stroke mechanisms and imaging markers of stroke risk

The mechanisms of ischemia in IAD include impaired antegrade flow, artery-to-artery embolism, penetrator vessel occlusion, and impaired collateral flow and cerebrovascular reserve. It is likely that these mechanisms interact and co-exist in the same patient.[25–28] Non-invasive imaging can provide physiologic data on these mechanisms, which may be useful in calibrating stroke risk, developing mechanism-specific prevention and treatment strategies, and assisting in patient selection for endovascular therapies.

Anterograde blood flow at and distal to the site of stenosis can be quantified by QMRA; it exploits the phase shift in the signal of flowing blood, which is proportional to flow velocity, to quantify flow rate in medium and large vessels.[29] QMRA can quantify the physiologic significance of the anatomic degree of stenosis in IAD. For instance, at similar degrees of stenosis, patients may have different flow rates representing differential risk, as exemplified in the figure. In a study of 47 patients symptomatic vertebral or basilar 50–100% disease (72% with intracranial disease), low flow on QMRA was noted in one-third of patients; at 24 months, 97.5% of those with normal QMRA flow were event-free, compared to 81.5% with low flow.[18]

Serial monitoring of flow velocities by TCD detects progression of IAD. Progression was noted in upto one-third of patients with symptomatic middle cerebral artery (MCA) stenosis at 26-month follow-up and was associated with a near 3-fold increased risk of recurrence. [30] Others have noted progression of stenosis in 9–13% of patients at shorter time intervals even with aggressive medical therapy.[28,31] TCD monitoring can also detect embolic signals (ES) in approximately 33% of patients with symptomatic MCA stenosis in the acute phase.[32–34] MRI studies have confirmed that ES correlate with multiple strokes indicative of an embolic process, [35] and their presence is predictive of early recurrent ischemic events.[32]

Impaired cerebral hemodynamics is a well-established predictor in large artery stroke. [26,36,37] Cerebral perfusion pressure distal to a high-grade stenosis or occlusion depends on collateral sources of blood flow. The anterior and posterior communicating arteries provide most collateral flow in internal carotid and basilar artery stenosis (primary collaterals), while distal pial and leptomeningeal anastomoses (secondary collaterals) are important in MCA stenosis [26]. Collateral flow on DSA was found to be absent in 69% of patients with symptomatic IAD and an independent predictor of recurrent ipsilateral stroke. [38,39]

Autoregulatory vasodilation in response to a vasodilatory challenge, such as hypercapnia or acetazolamide, defines vasomotor reactivity (VMR), a measure of dynamic cerebrovascular reserve capacity.[36] Impaired VMR has been used to identify those patients who are at a high-risk for stroke in both intra- and extracranial large vessel disease.[37,40] TCD with CO_2 challenge correlates with degree of stenosis in IAD.[41] Using acetazolamide Xenon-SPECT, impaired VMR has been reported in 14–33%, with annual risk of ipsilateral stroke 17.4–21.8% versus 0.6–2.4% in those with impaired and normal VMR.[42,43].

Perfusion imaging of the brain using MRI, CT, and positron emission tomography (PET) measures tissue-level perfusion distal to a stenosis; it may reflect the true net effect of antegrade and collateral flow. Although extensively studied in acute ischemic stroke,[44,45] little data exist in chronic IAD.[26] Ongoing studies may provide further evidence of the prognostic value of perfusion defects in IAD.

A high-risk profile of physiologic markers emerges by combining these modalities (table 2). Therefore, markers of antegrade and collateral flow, static tissue perfusion, dynamic cerebrovascular reserve, and plaque features of embolic potential and morphology, may refine risk stratification adding to clinical and anatomic (i.e. percent stenosis) predictors of stroke risk.

Management

After stroke or TIA, the 1-year risk of ischemic stroke, intracerebral hemorrhage, or vascular death is 12–15%, while the risk of recurrent stroke in the same territory is 11–12%.[46,47] The most important predictors of stroke recurrence are the degree of stenosis and time from event.[48] Symptomatic IAD with 70–99% stenosis has greater risk compared to those with 50–69% stenosis (hazard ratio [HR] 2.08). The first 2–3 weeks are also particularly perilous (HR 1.67 for symptoms ≤ 17 days). Other factors are less clearly associated with increased risk, although women may have a marginally increased risk. The type of event, stroke vs. TIA, is not an independent predictor, but when stratified with degree of stenosis, can be used to stratify risk; for example, those with a stroke and high-grade 70–99% stenosis have an eightfold risk of stroke compared with those with a TIA and moderate stenosis. In sum, these clinical data may identify a high-risk population eligible for more aggressive treatment interventions.

Antithrombotic therapy

Warfarin is not more efficacious and is associated with greater risk than aspirin in IAD. The seminal Warfarin-Aspirin Symptomatic Intracranial Disease trial (WASID)[47] compared aspirin 1200 mg/day vs. warfarin (target INR 2–3) in symptomatic IAD with 50–99% stenosis. There was no difference between the treatment arms; ischemic stroke, intracerebral hemorrhage, or vascular death occurred at a staggering 22% during 1.8 years of follow-up (annual rate of 16%). Warfarin was associated with a two-fold increase in death and almost a three-fold increase in major hemorrhages. There was no benefit of warfarin for those who had their initial event on antiplatelet therapy.[49] As most events occur early after the initial event, a brief course of anticoagulation was considered to decrease risk while avoiding the long-term risks of warfarin.[50] However, nadroparin for 10 days followed by aspirin was not superior to aspirin alone when started even within 2 days of symptoms.[51]

The combination of aspirin and clopidogrel was tested in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial.[46] Patients with a non-disabling stroke or TIA due to IAD with 70–99% stenosis within 30 days of symptoms, a high-risk population,[48] were treated with the combination of aspirin 325 mg/day and clopidogrel 75 mg/day for 90 days followed by

aspirin 325 mg/day and aggressive treatment of other vascular risk factors, and randomized to angioplasty and stenting or medical therapy alone. As detailed below, the study was stopped due to excess complications in the angioplasty and stenting arm. Patients with medical management alone had a 30-day rate of stroke or death of 5.8%, lower than the anticipated 10.7% rate from the WASID sub-analysis of similar patients. The 1-year risk of stroke or death at 30 days or recurrent ischemic stroke in the territory of the stenotic vessel beyond 30 days was estimated at 12.2%. These data also imply that the combination of aspirin and clopidogrel for a short period of time, combined with statins and antihypertensive agents, is effective and probably superior to aspirin alone and standard risk factor modification.

Other antiplatelet drug combinations have also been evaluated. A randomized study comparing cilostazol and clopidogrel vs. cilostazol and aspirin in patients ischemic stroke within 2 weeks of symptoms did not find a difference between the treatment arms in progression of stenosis (primary outcome) or recurrent stroke, new ischemic lesions on MRI and hemorrhagic complications (secondary outcomes).[31] Combination antiplatelet therapy was associated with a 6.1% risk of stroke, major hemorrhage and vascular death during a follow-up period of 7 months, similar to the observed rates in SAMMPRIS.

Risk factor modification

Patients with IAD have a high burden of vascular risk factors and their control is associated with a lower rate of recurrent events. In the WASID trial, a recurrent stroke was more likely in those with poor control of risk factors during follow up; systolic blood pressure (SBP) ≥140 mm Hg (HR 1.58), total cholesterol >200 mg/dL (HR 1.95), and no alcohol consumption (HR 1.76) were significant risk factors.[52] Initial concern that blood pressure reduction would cause hypoperfusion was dispelled in further analysis of the WASID study: a recurrent stroke in the territory of the stenotic artery occurred at similar rates for SBP categories of <120, 120–139, and 140–159 mm Hg, and a higher risk was noted for those with SBP ≥160 mm Hg during follow-up,[53] although this analysis did not involve the acute post-stroke period. The SAMMPRIS study managed vascular risk factors in an intense manner with goal SBP <140 mm Hg (<130 mm Hg in diabetics) and LDL < 70 mg/dL, protocol-driven control of other risk factors and institution of a lifestyle modification program. After 4 months, important reductions in SBP (11 mm Hg), LDL (20–25 mg/dL), and tobacco use (7–10%) and an increase in moderate or vigorous exercise (22–27%) were achieved, demonstrating the feasibility of significantly altering vascular risk factors with intense medical treatment. These interventions likely stabilize the atherosclerotic plaque and prevent further IAD progression.

Revascularization strategies

Extracranial to intracranial (EC/IC) bypass surgery has not been successful; in the EC/IC bypass surgery, patients with severe middle cerebral artery stenosis had worse outcomes with surgery.[54] Endovascular approaches with angioplasty alone, angioplasty and stenting with balloon mounted stents (BMS) and self-expanding stents (SES) have been tested in IAD. Intracranial endovascular treatment is challenging as the intracranial vessels are accessed through a tortuous path, they are not embedded within tissue but free floating in CSF, have a thinner media, and have small penetrators arising at right angles. These characteristics underlie the complications encountered in intracranial procedures including peri-procedural stroke, vessel rupture, hyperperfusion syndrome, stent thrombosis and restenosis.

Angioplasty alone has been evaluated in a number of case series reporting wide ranges of periprocedural complications. Larger series where angioplasty was performed electively

documented relatively low complication rates,[55] but lesion recoil, restenosis and dissection are potential complications.[56] Indirect comparison of angioplasty and stenting case series suggest that angioplasty alone may be inferior to stenting,[57] but this intervention has not been evaluated in a randomized manner with blinded adjudication.

Balloon mounted stents offer the advantage of a one-step procedure and less residual stenosis, but the rigid delivery system makes it more difficult to navigate through tortuous anatomy. That BMS can be deployed was indicated by the SSYLVIA study,[58] a non-randomized study of vertebral stenosis treated with a BMS, but a 6.6% peri-procedural stroke rate plus a 7.3% subsequent risk of stroke was similar to the risk found with medical management in the WASID study.[47] A number of subsequent single center series employing a variety of stents analyzed in systematic reviews show a peri-procedural risk of stroke of 7.7%,[59] similar to large single center series,[60,61] although variability in peri-procedural complications and unblinded outcome ascertainments may bias results. Available data suggest that when the index event is related to occlusion of a perforating artery, the risk of peri-procedural stroke is higher.[62] There is little data on drug eluting stents (DES) in IAD, but DES do not overcome the challenges posed by other BMS, and may increase the risk of thrombogenicity.[63] Furthermore, DES did not show an advantage on restenosis in a small case series.[64]

Self-expanding stents require a two-step procedure (subtotal angioplasty stent deployment), but offer easier delivery through tortuous vessels, and were thought to have less peri-procedural complications. In the US, the Wingspan stent and Gateway balloon are approved by the FDA for IAD with >50% stenosis and recurrent events on medical therapy. Three registries using this system showed a 4.4–7.5% peri-procedural risk of stroke and death, and a 7.1–31.2% risk of restenosis.[65–69] However, the SAMMPRIS study, which employed the Wingspan/Gateway system, was stopped due to excess complications in the stented arm, with a 30-day risk of stroke or death of 14.7%, higher than the anticipated rate from the registries. The peri-procedural complications included ischemic strokes (70%) and intracranial hemorrhages (30%), many likely related to reperfusion. After 30 days, the risk of recurrent stroke was similar for both medical and stenting arm, and therefore a beneficial late effect of stenting is unlikely.[46] Long term follow-up in two Wingspan registries confirm that post-procedural beyond 30 days events continue to occur at a rate of 4–10%, with few events beyond one year, and associated with restenosis and antiplatelet cessation. [70,71]

There has been no head-to-head comparison of BMS and SES, but systematic reviews of case series have not shown significant differences in complications and equivocal benefit of BMS on restenosis rates.[59,60]

Conclusions

Intracranial atherosclerosis is associated with very high risk of recurrence, which can be modified by aggressive medical management (table 3). The role of stenting in the management of IAD is still unclear; the surprising high rate of complications in the SAMMPRIS study has given pause to recommending stenting for IAD. The current American Heart Association guidelines stating that endovascular approaches with angioplasty or stenting may be considered for symptomatic IAD >70% that failed medical therapy (class 2b recommendation, level of evidence C)[72] may need to be revised. Stenting, if used at all, should only be performed by experienced operators[73] in the setting of recurrent cerebral ischemia due to high-grade stenosis despite *maximal* medical therapy. It remains to be seen whether stenting will play a more prominent role in the future treatment of IAD as hardware, training, and experience improve. It is likely that advances in

neuroimaging may refine risk stratification. There is evidence that poor collateral flow, impaired vasomotor reactivity, and presence of microembolic signals predict risk. Future studies integrating pathophysiological mechanisms into risk stratification may identify specific high-risk groups and time windows to offer targeted therapies that may modify the course of this condition.

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Key Points

- IAD may well be the most common world-wide cause of ischemic stroke and is associated with various mechanisms of cerebral ischemia.

- Current diagnostic methods assess the degree of stenosis but novel physiological markers provide mechanistic information that may refine risk stratification and lead to more targeted interventions.

- Recent trials have shown that antiplatelet therapy and aggressive risk factor modification reduce the risk of stroke recurrence.

- The role of endovascular treatment of IAD is still unclear given the high risk of complications.
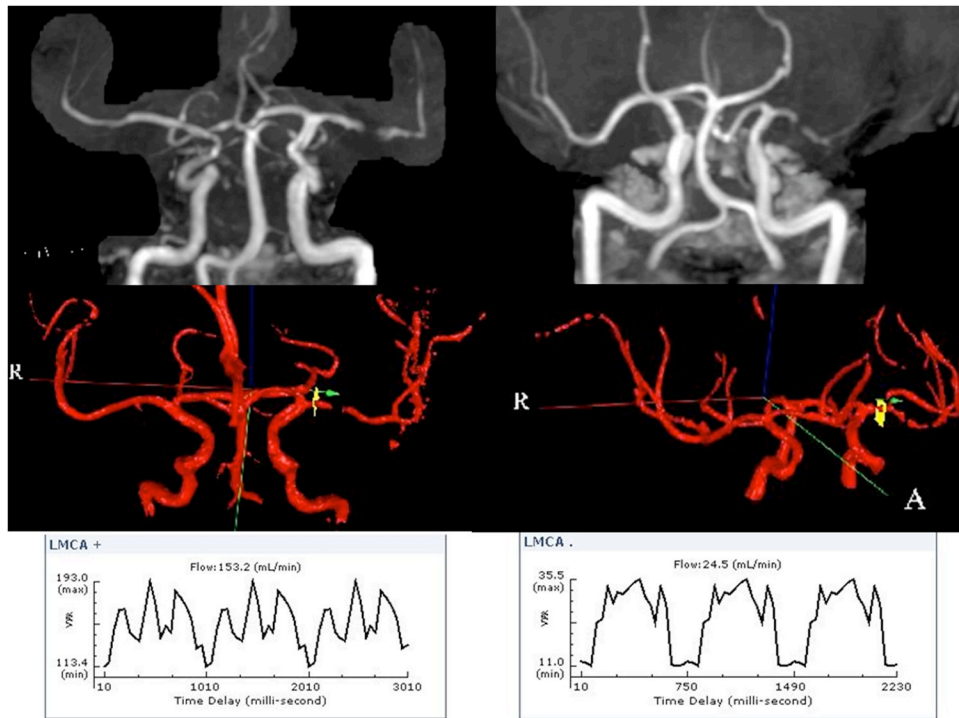
Figure. QMRA in two patients with similar stenosis by MRA but different volumetric flow rate
On the right, the top panel shows a left middle cerebral artery flow gap. The QMRA, shown in the right middle and right lower panels, shows the area interrogated and a low volumetric flow rate of 24.5 mL/min. The left upper panel depicts a similar left middle cerebral artery stenosis, but the volumetric flow rate shown in the left lower panels is *not* decreased at 153.2 mL/min.

Table 1

Comparison of commonly used diagnostic tests for intracranial stenosis

Test	Advantages	Disadvantages
DSA	High resolution (microns) Measure stenosis precisely Measure antegrade and collateral flow Gold standard	Invasive Radiation risks Contrast risks Availability Costs
TCD	Non-invasive Inexpensive Serial examination High specificity and NPV Emboli detection Vasomotor reactivity testing	Low PPV Reliability Technical limits (i.e. absent windows)
MRA	Non-invasive High specificity and NPV Modest cost No radiation Widely available	Motion artifact Magnet contraindications Overestimates stenosis Low PPV
CTA	High sensitivity, specificity, NPV Good PPV Modest cost Widely available	Radiation risk Contrast risk and contraindications Calcium and metal artifacts

Table 2

Mechanisms and surrogate imaging markers of stroke risk in intracranial stenosis

Mechanism	Marker (s)	Imaging modality
Decreased antegrade flow	VFR	QMRA
	TICI flow grade	DSA
	Flow velocity	TCD
Progression of stenosis	Changes in:	
	VFR	QMRA
	TICI flow grade	DSA
	Flow velocity	TCD
Poor collateral flow	Collateral flow grade	DSA
	COW collaterals	DSA, TCD, QMRA
Impaired vasomotor reactivity	Cerebrovascular reactivity	
	Breath-holding index	TCD
	CO2 inhalation	TCD
	Acetazolamide	SPECT
Poor tissue perfusion	CBF, CBV, transit time	MRP or CTP
	Metabolic rate, oxygen extraction	PET
Artery-to-artery embolism	Microembolic signals	TCD
Vulnerable plaque	Plaque enhancement/hemorrhage	HR-MRI

Abbreviations: VFR-volumetric flow rate; TICI-thrombolysis in cerebral infarction; CO2-carbon dioxide; CBF-cerebral blood flow; CBV-cerebral blood volume; DSA-digital subtraction angiography; TCD-transcranial Doppler; MRA-magnetic resonance angiography; QMRA-quantitative magnetic resonance angiography; SPECT-spectral emission computerized tomography; PET-positron emission tomography; MRP-magnetic resonance perfusion; CTP-computerized tomography perfusion; HR-MRI-high-resolution magnetic resonance imaging

Table 3

Treatment recommendations for recently symptomatic IAD

- Antiplatelet agents are superior to anticoagulants in IAD.

- In symptomatic high-grade IAD, combination of aspirin and clopidogrel for 3 months followed by aspirin appears to be safe and superior to aspirin alone.

- Statin use with goal LDL <70 mg/dl is recommended.

- Tight control of hypertension is recommended beyond the acute stroke period.

- Other vascular risk factors should be controlled.

- Stenting should be carefully considered, as it is associated with a high rate of complications.