Diagnosis of Intracranial Stenosis

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Abstract: The diagnosis of intracranial stenosis has improved with the advent and availability of non-invasive vascular imaging tests. Vascular imaging modalities to consider include transcranial Doppler, magnetic resonance and computed tomographic angiography. While these have strengths and weaknesses, they provide anatomic information. Physiologic and/or hemodynamic data can be gleaned from perfusion imaging, vasomotor reactivity testing, positron emission tomography, and quantitative magnetic resonance angiography. These latter tests may be particularly useful in stratifying stroke risk in individuals with intracranial stenosis. While most cases are due to atherosclerotic disease, the astute clinician still needs to consider other etiologies including vasoconstriction, vasculitis, and dissection before embarking on treatment decisions.

Keywords: Magnetic resonance angiography, computed tomographic angiography, stroke risk, hemodynamics.

INTRODUCTION

The diagnosis of intracranial stenosis has improved with the advent and availability of non-invasive vascular imaging tests. Conventional catheter-based angiography remains the gold standard but has potentially serious risks and limited availability. Hence, magnetic resonance angiography (MRA), computerized tomographic angiography (CTA), and transcranial Doppler (TCD) are the most commonly employed non-invasive modalities in the diagnostic evaluation of intracranial stenosis. Each has its own attributes and limitations. Besides their utility in the anatomic diagnosis of intracranial stenosis, non-invasive imaging can also provide critical physiologic information (such as blood flow characteristics) which can assist in prognostication and recurrent stroke risk stratification (Fig. 1). In this review, we will consider the role of non-invasive screening, discuss established and emerging cerebrovascular imaging tools for the diagnosis of intracranial stenosis, and determine their role in management.

DIFFERENTIAL DIAGNOSIS

Despite the ability to make the anatomic diagnosis of intracranial stenosis, one still needs to differentiate among several known radiographic mimics of atherosclerotic intracranial stenosis such as partial recanalization of an embolus and non-atherosclerotic diseases such as dissection, vasculitis, vasospasm, and fibromuscular dysplasia. For example, central nervous system vasculitis, whether primary or secondary, can result in multifocal and distal sites of arterial narrowing that results in a "beaded" appearance, while athero-stenosis typically involves the proximal circle of Willis vessels and vertebrobasilar circulation (i.e. middle cerebral, proximal or mid basilar, distal vertebral, and distal internal carotid arteries). Reversible cerebral vasoconstriction syndromes are a generalized, self-limiting group of disorders often due to vaso-active substances [1] that cause multifocal vasoconstrictive changes in the intracranial vasculature presenting with symptoms such as thunderclap headache and focal neurologic signs. Fibro-muscular dysplasia and dissection, which typically affects the extracranial carotid arteries, is also a rare cause non-atherosclerotic stenosis in the intracranial circulation [2]. While a careful clinical history and physical examination can reasonably exclude many mimics, assuring high diagnostic certainty remains challenging. In some instances, repeat imaging may be required to evaluate mimic conditions that improve over time (i.e. complete recanalization of an embolus or resolution of vasospasm) versus persistent or worsening stenosis due to atherosclerosis.

Though atherosclerotic stenosis is the most common cause of intracranial arterial narrowing, assigning the appropriate stroke mechanism in a patient with intracranial atherosclerotic stenosis (i.e. determining whether the stenosis is symptomatic or asymptomatic) may still be far from straightforward. Besides large artery atherosclerosis, other stroke subtypes, particularly cardioembolic and lacunar strokes can co-exist in patients with intracranial stenosis. Furthermore, though recurrent strokes tend to have the same mechanism of action as the initial stroke event, up to 19% may be due to another mechanism including cardioem-bolism, extracranial large artery disease, and lacunar disease [3].

Consequently, cardioembolic and small-vessel etiologies need to be excluded in making the initial diagnosis of symptomatic intracranial stenosis and later in assessing the mechanism of recurrent ischemic events. These data suggest that even in patients with unequivocal intracranial athero-sclerotic stenosis, the mechanisms of stroke can be heterogenous and assigning causative etiology with absolute certainty may be difficult.

SCREENING

Intracranial stenosis is responsible for 5-10% of all ischemic strokes in the United States and up to 50% among

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certain ethnic sub-types in Asia [4, 5]. When symptomatic, it is associated with a 10-20% mortality rate [6-8]. Given the prevalence and severity of this disease, it is attractive to consider non-invasive neuroimaging as a means to screen at-risk populations before symptoms occur. For instance, diabetics, men, smokers, and non-Caucasians have the highest prevalence of intracranial stenosis [9-12] and may benefit from selected screening for the disease. However, the data supporting the benefits of asymptomatic screening are limited at best.

The risk of an ischemic stroke in asymptomatic intracranial stenosis is ten-fold less than that associated with symptomatic intracranial stenosis [13, 14]. However, in patients harboring both symptomatic and asymptomatic stenoses, 73% of recurrent ischemic strokes occurred in the symptomatic stenotic arterial territories while 27% were in previously asymptomatic regions [3]. Among out-of-territory recurrent strokes, 48% developed strokes distal to previously asymptomatic stenoses [3]. While the stroke risk due to asymptomatic intracranial stenosis is certainly lower than symptomatic stenosis, the actual risk is difficult to quantify and patients with asymptomatic stenosis coexisting with symptomatic stenosis may require careful risk assessment. Thus, despite the lack of robust, prospective data, selective

screening for asymptomatic stenoses may be useful in high-risk populations (i.e. diabetics) but generalized screening of the population is likely not cost-effective or beneficial [11, 12]. Further study assessing long-term outcomes following screening for intracranial stenosis is warranted.

ANATOMIC DIAGNOSIS OF INTRACRANIAL STENOSIS (FIG. 2)

The gold standard of neurovascular imaging remains the conventional (catheter-based) angiogram, or digital subtraction angiography (DSA) [15]. In comparing the efficacy of non-invasive imaging techniques, DSA is considered the reference standard. It provides excellent overall visualization of vessel contour, anatomic localization, measurement of degree and length of stenosis, and assessment of collateral circulation. Modern DSA also incorporates three-dimensional reconstructed images from the raw data to provide even greater detail. However, due to its invasive nature, there is a small but real risk (approximately 0.7%) of peri-procedural neurologic injury associated with DSA [16]. The most serious complications (ischemic and hemorrhagic stroke), should they occur, are noted within 24-72 hours of the procedure. In addition, DSA carries the nephrotoxic risk associated with iodinated
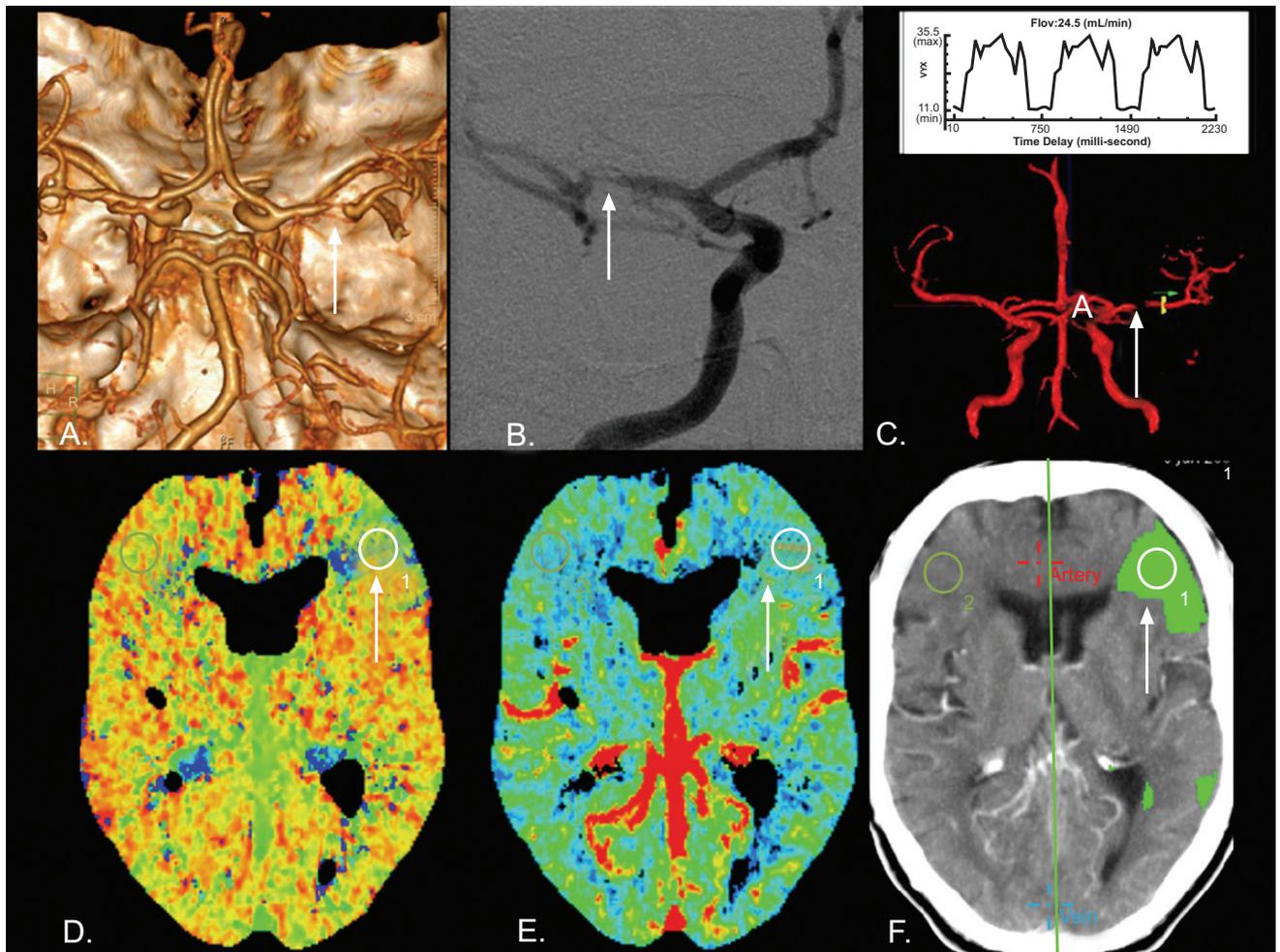
Fig. (1). Examples of imaging modalities (**A**, CTA; **B**, DSA; **C**, QMRA; **D-F**, CT perfusion). Arrows (white) indicate stenosis (**A-C**) and area of hypoperfusion (**D-F**).

contrast injection and the potential for access-related injury (i.e. groin hematoma and limb ischemia). Given these concerns and the limited availability of qualified cerebral angiographers, the diagnosis of intracranial stenosis was previously inferred without anatomic visualization or neglected altogether until recently when non-invasive imaging overcame many of these concerns.

Transcranial Doppler is a widely available and inexpensive non-invasive test used to diagnose intracranial stenosis. It is based on the principle that flow velocity increases with worsening arterial stenosis (decreasing vessel diameter). It is commonly used to screen for cerebral vasospasm following subarachnoid hemorrhage but has demonstrated utility in sickle cell anemia, brain death, microembolic signal detection, enhanced clot lysis, as well as the diagnosis of intracranial stenosis [17, 18]. The location and degree of stenosis is inferred by the transducer probe's position, depth, direction, and from the measured velocity and contour of the waveform within an arterial segment. However, since direct anatomic visualization is not performed with TCD, its performance depends greatly on technical expertise and experience. In large controlled studies, the sensitivity, specificity, positive and negative predictive values of TCD are as follows: 73-92%, 89-99%, 36-50%, and 85-86%, respectively [17, 19]. For distinguishing between low and high grade stenosis, the sensitivity, specificity, and NPV of TCD are slightly lower: 82%, 73%, 79% respectively [20]. Given the high specificity but low positive predictive values, TCD can serve as a reasonable test to exclude intracranial stenosis but often requires another confirmatory test (often another non-invasive test or DSA) when the diagnosis of intracranial stenosis is suggested.

Magnetic resonance angiography is another commonly employed non-invasive imaging modality used to identify intracranial stenosis. The technique measures flow signal intensity as a function of proton spin, as utilized in time-of-flight (TOF) MRA to visualize changes in the flow of blood. As a consequence, motion artifact, directional changes in arterial flow (i.e. from vertical to horizontal) can render the results ambiguous or even erroneous [15]. Its advantages are the absence of radiation exposure or radiocontrast risks [21]. Its major disadvantage, besides vulnerability to motion artifacts, is its inability to distinguish between high-grade stenosis and occlusion. A flow gap on TOF-MRA may represent high-grade stenosis or occlusion. In addition, it has limited to no use among patients who are morbidly obese, claustrophobic, or have implanted foreign metallic objects (i.e. pacemakers). Despite these limitations, MRA have shown 70% sensitivity in detecting intracranial stenosis > 50% and 81% sensitivity in detecting intracranial occlusion relative to DSA [15]. Overall, studies suggest MRA has the following performance characteristics in diagnosing intracranial stenosis: sensitivity 62-88%, specificity 86-97%, PPV 59-66%, and NPV 87-88% [15, 19, 22]. In clinical practice, MRA is considered a more useful modality than TCD, but given its low PPV, still requires further confirmatory diagnostic testing such as a second non-invasive test or DSA.

New innovations are expanding the role of MRA in intracranial stenosis. Contrast-enhanced MRA uses gadolinium dye to provide better anatomic visualization and overcome regions of changing blood flow directions [23]. Currently, it is the most widely used technique to visualize the external carotids [22] but it has been increasingly applied to the intracranial circulation. Quantitative MRA, utilizing phase-contrast techniques, has shown promise as a diagnostic test of intravascular blood flow to diagnosis hemodynamic failure in posterior circulation stenosis [24, 25] and screen for post-procedural stenosis at sites of stents or coils [26]. QMRA can also assess regional blood flow which can indicate the overall cerebral hemodynamic and collateral flow status [25]. Another emerging MR technique is high resonance imaging (HR-MRI), capable of visualizing and characterizing plaque morphology and behavior, and discriminating from other non-atherosclerotic etiologies [27, 28]. Further study using these novel modalities may increase the diagnostic utility of MRA and provide valuable prognostic data.

Compared to traditional time-of-flight MRA, CTA provides better anatomic visualization of the intracerebral vasculature [15, 29]. While MRA focuses on flow motion dynamics, CTA focus on the relative penetrance of radiocontrast agents within the blood vessels and image the vessels in the form of a "vessel cast" [15]. While it can overcome the limitation of accurate visualization of slow-flow lesions (i.e. high-grade stenosis), CTA can be degraded by local calcium or metallic artifacts [30]. Compared to DSA, the high sensitivity (98%), specificity (99%), PPV (93%), and NPV (100%) of CTA make this an excellent, and perhaps preferred, non-invasive diagnostic test for intracranial stenosis (Fig. **1**) [29, 30]. A major disadvantage is the small risk of radiocontrast reactions and possible severe anaphylaxis [20]. In addition, nephrotoxicity is a known complication that can arise from contrast dye administration. Therefore, it may be contraindicated in those with chronic renal insufficiency, pregnancy, or known contrast allergies.

The relative availability, costs, advantages and disadvantages, along with the pre-test probability and test performance characteristics, will determine which test is best suited for an individual patient; however, other circumstances may also guide the choice of non-invasive imaging modality. For example, CTA can better visualize high-grade stenoses than time-of-flight MRA since the latter tends to overestimate the degree of stenosis and has lower sensitivity and specificity [15, 22, 29, 30]. Furthermore, the relative accuracy of each test can vary depending on the location of the stenosis. The petrous ICA and cavernous ICA are susceptible to bony or calcium artifacts, and in this region, MRA tends to be more useful than CTA [15].

PHYSIOLOGIC IMAGING MARKERS OF STROKE RISK

As discussed earlier (Chapter 1), the mechanisms of ischemia in intracranial stenosis include progressive arterial narrowing, plaque instability (thrombo-embolism), and/or attenuated vasomotor reactivity due to impaired collateral flow. It is likely that these mechanisms interact in complex ways and co-exist in the same patient [31-33]. Identifying physiologic markers of the underlying vascular mechanism may be critical to determine stroke risk, develop mechanism-
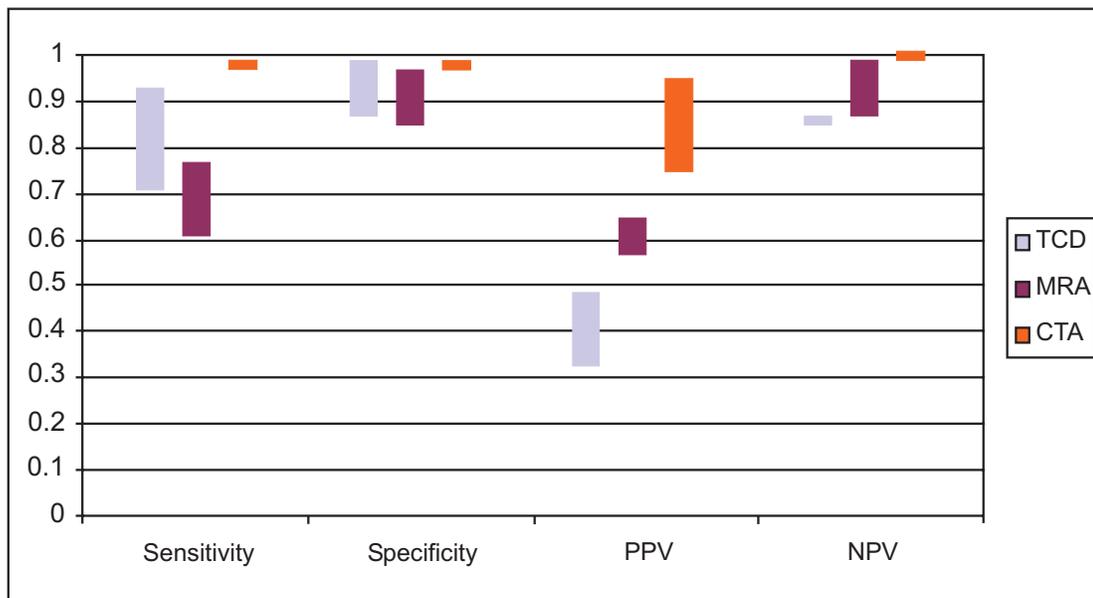
Fig. (2). Comparison of test performance for transcranial Doppler, magnetic resonance angiography, and computerized tomographic angiography in diagnosis of intracranial stenosis (conventional angiography is the reference standard); PPV-positive predictive value, NPV-negative predictive value.

specific prevention and treatment strategies, and assist in patient selection for endovascular therapies. Non-invasive imaging can provide critical physiologic data on anterograde flow, tissue perfusion, collateral flow, plaque morphology, and embolic signals and help in the determination of stroke mechanism (Fig. **3**).

Physiologic information related to the viability of cerebral blood flow distal to a stenotic lesion factoring in collateral blood flow would also be an important variable to estimate the natural history risk for recurrent stroke. Two stages of hemodynamic failure have been described [34]. Stage 1 involves vasodilation in response to poor perfusion which results in increased cerebral blood volume and prolongation of mean transit time to preserve cerebral blood flow and oxygen extraction fraction. Stage 2 shows falling cerebral blood flow and increased oxygen extraction fraction. Early investigations with hemodynamic imaging suggested that compromised cerebral blood flow reactivity predicted an increased risk of stroke [35]. A recent small study compared interventional treatment of patients who failed medical therapy with those who demonstrated impaired regional cerebral blood flow (CBF) and found a non-significant trend toward better long-term outcome in those with impaired regional CBF [36].
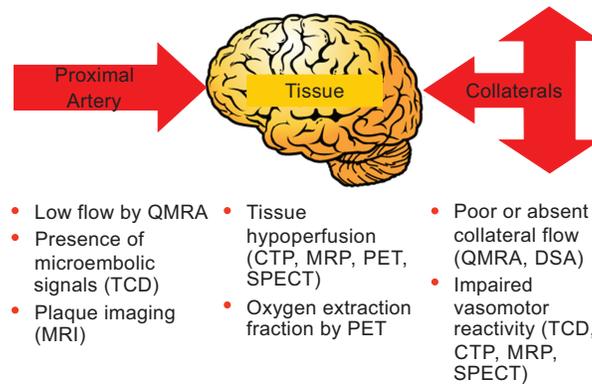
Anterograde blood flow at and distal to the site of stenosis can be measured and quantified by QMRA or phase-contrast MRA. In the setting of arterial stenosis, intravascular blood flow decreases with advancing stenosis. QMRA can quantify the physiologic significance of the anatomic degree of stenosis [24, 26]. For example, a patient with 60% stenosis who has preserved anterograde flow is at a lower risk of ischemic stroke than a patient with 60% stenosis and diminished anterograde flow.

Phase-contrast MRA exploits the phase shift in the signal of flowing blood, which is proportional to flow velocity. Phase velocity maps can be constructed for quantitative measurements of volumetric flow rate (VFR) through medium and large-sized vessels. The technique of blood flow quantification by phase-contrast MRA is now commercially available through software called Non-Invasive Optimal Vascular Analysis (NOVA, VasSol, Inc.,) and has been shown to be a reliable method for quantifying flow in the cerebral vasculature [37]. Volumetric blood flow measurement (mL/min) integrates flow velocity over the cross-sectional vessel area which correlates strongly with CBF at the tissue level.

Over the past decade, many studies have been performed using QMRA in the assessment of extracranial and intra-cranial arterial flow in patients with carotid stenosis and occlusion, vertebrobasilar ischemia, subclavian steal pheno-menon, and following treatments with carotid endarterec-tomy (CEA), stenting, and bypass surgery [24, 25, 38-41]. Recent reports have also demonstrated the utility of QMRA in the measurement of pre- and post-procedure vessel flow following angioplasty for vertebrobasilar stenosis and Wingspan stent placement for extracranial vertebral artery stenosis [42, 43].

The largest of these studies assessed the risk of recurrent ischemic stroke in 47 patients with posterior circulation ischemic stroke or TIA and > 50% stenosis or occlusion of the vertebral or basilar arteries (72% intracranial disease). The authors utilized a QMRA algorithm to stratify risk by VFR measured at baseline. Low flow (> 20% decrease from normal values) correlated with increasing degree of stenosis: among 23 patients with 80-99% stenosis, 8 (34.8%) had low flow while none of the 8 patients in the 50-80% stenosis group had low flow. At 24 months, 97.5% of those with normal QMRA flow rates were event- free, compared to 81.5% with low flow. In Cox proportional hazards models, QMRA flow status predicted event-free survival independent of other covariates [24].

- Low flow by QMRA
- Presence of microembolic signals (TCD)
- Plaque imaging (MRI)

- Tissue hypoperfusion (CTP, MRP, PET, SPECT)
- Oxygen extraction fraction by PET

- Poor or absent collateral flow (QMRA, DSA)
- Impaired vasomotor reactivity (TCD, CTP, MRP, SPECT)

Fig. (3). Schematic of physiologic markers that may help stratify stroke risk among patients with intracranial stenosis.

Transcranial Doppler can also characterize anterograde blood flow by measuring mean flow velocity and detecting embolic signals (ES). Initially, velocities increase appropriately in response to mild reductions in vessels' luminal diameter but then the vessels begin to accommodate less responsively as the stenosis progresses. Flow velocities and changes thereof among intracranial stenosis patients may indicate acute hemodynamically significant changes such as those incurred from infarcts by artery-to-artery embolism [33, 44, 45]. Serial TCDs can also distinguish between recanalized embolic processes and stenoses [46].

Embolic signals have been detected *in vivo* in various procedures and in conditions associated with stroke; [47, 48] TCD can detect ES suggestive of an embolic pattern of cortical or multiple infarcts in 33% of patients with symptomatic middle cerebral artery stenosis [49]. Furthermore, diffusion-weighted sequences in MRI studies have confirmed that abnormal ES patterns on TCD are indicative of an embolic process [32, 50, 51] while animal models have also supported ES as thrombotic particulate material from artery-to-artery embolism [45]. Though the majority of microemboli is washed out into the venous circulation [52], presence of ES on TCD may indicate active embolization [53, 54]. In *extracranial* carotid stenosis, ES are more common in symptomatic than asymptomatic patients, correlate with the degree of stenosis, and are associated with a greater risk of recurrent stroke [48]. In *intracranial* stenosis, most studies have focused on ES from the middle cerebral artery as it is the most accessible for monitoring. Embolic signals are noted in about 30% of stroke patients in the acute phase [32, 46, 47, 50, 51, 55]. In addition, the presence of ES appears to be prognostic of future events (OR 8.4, $P = 0.01$) with the majority of recurrent events occurring in the first month [50].

Another emerging modality, HR-MRI, creates sufficiently thin cuts through intracranial vessels that the plaque morphology and stability can be detected [27, 28, 56]. By visualizing enhancing or heterogeneous plaques (akin to extracranial carotid plaque evaluation), one can determine whether they are vulnerable (unstable) or stable plaques based on high-grade or low-grade wall shear forces. Preliminary studies have shown the utility of this modality in assessing plaque characteristics even in anatomically more elusive regions such as the cavernous ICA [57].

Impaired cerebral hemodynamics is a well-established predictor of future strokes among patients with large artery stroke [34-36, 58]. Cerebral perfusion pressure distal to a high-grade stenosis or occlusion may be reduced depending on the adequacy of collateral sources of blood flow. As a result, unless collateral flow is adequate, the delivery of oxygen to the tissue will be impaired. Normally, perfusion pressure is maintained by independent compensatory mechanisms such autoregulatory vasodilation and increased oxygen extraction [59]. Once these mechanisms are exhausted, and cerebral perfusion pressure decreases beyond the limits of compensation, CBF falls and tissue infarction ensues [60, 61]. In a small study, photon emission tomography (PET) study, there was strong correlation between MCA occlusion and hemodynamic compromise resulting in reduced oxygen extraction [62].

In addition to anterograde flow, perfusion distal to an arterial stenosis is determined compensatory collateral flow; thus, evaluating collateral circulation is critical to the understanding of stroke risk due to intracranial atherosclerotic disease. Primary collateral pathways provide a route for cerebral blood flow to ischemic regions through existing anastomoses at the circle of Willis; flow through the posterior and anterior communicating artery account for the majority of collateral flow in internal carotid and basilar artery stenosis. These can be visualized and quantified using phase-contrast MRA [38, 63-66]. Collaterals *via* pial and leptomeningeal (secondary collateral pathways) anastomoses may play an important role in middle cerebral artery stenosis [34, 62], which is distal to the circle of Willis (primary) collaterals, and can be assessed using tests of vasomotor reactivity (VMR).

Autoregulatory vasodilation in response to a vasodilatory challenge, such as carbon dioxide (CO_2), defines VMR [36]. Impaired VMR can be used to identify those patients who are at a high-risk for stroke in both intra- and extracranial large vessel disease [58, 67-72]. While the hemodynamics of extracranial large vessel disease has been more extensively investigated [36], hemodynamic compromise associated with intracranial occlusive disease may have even greater significance on outcome. In contrast to extracranial high-grade stenosis, collateral flow heavily depends on leptomeningeal arteries since large collaterals from the circle of Willis may not be recruited with more distal intracranial stenosis. A leptomeningeal collateral flow pattern has been associated with a higher prevalence of impaired VMR [73-75].

Sequential testing also suggests that impaired VMR due to intracranial disease is unlikely to recover on follow-up examinations [36]. In a study evaluating 70 cases with *intracranial* large vessel occlusion using Xenon-SPECT with acetazolamide challenge, one-third had impaired VMR. The annual risk of ipsilateral stroke with impaired VMR was 17.4% versus 1.2% with normal reactivity [68]. TCD with CO_2 challenge, performed by measuring the blood flow with breath-holding, evaluates the degree of dilatation that occurs in distal arterioles in response to hypercarbia [73, 74]. Noting the change in MFV in response to CO_2 challenge, one can also gauge VMR [68, 73, 74, 76].

Perfusion studies (CT and MRI) using the bolus-track method [77] can measure resting tissue perfusion as well as cerebrovascular reserve in patients with intracranial stenosis in response to a challenge [76]. While the optimal parameter to define reversible hypoperfusion (ischemia without infarction) has yet to be validated, mean transit time (MTT) and cerebral blood volume (CBV) have been the most studied and the most consistent. A increase in MTT with preservation of CBV indicates tissue-at-risk of infarction and may be a marker of high stroke risk [78]. Xenon-CT is also a reliable predictor of cerebrovascular reserve capacity and MTT [79]. PET scans can also assess oxygen extraction fraction within the tissue supplied by the stenotic vessel and provide a marker of advanced hemodynamic failure [67].

By studying cerebral perfusion and cerebrovascular reserve capacity before and after administering the vasoactive agents, one can evaluate the physiologic sequelae of the flow-limiting stenosis as a function of degree of hemodyanamic failure or compromise [80]. Much like diagnostic imaging modalities can complement one other, the available tools to identify physiologic markers are best utilized in combination to inform and calibrate stroke risk. In clinical practice, suspected patients with intracranial stenosis are evaluated with MRA, TCD, and/or CTA with DSA serving a final confirmatory test. While imaging techniques assessing key physiologic parameters associated with intracranial stenosis may prove more important than just an anatomic diagnosis, these techniques require further prospective study [36].

CONCLUSION

Modern neuroimaging has been critical to improving the capacity to diagnose intracranial stenosis routinely and also holds promise in unraveling putative mechanisms of stroke in this high-risk population. Understanding the strengths and limitations of each imaging tool and its diagnostic utility are essential to accurate and timely diagnosis and can assist in stroke risk stratification. A comprehensive approach that integrates both clinical and radiographic markers of risk will ultimately best.

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