Intracranial Stenosis

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Definition

"Intracranial stenosis" is pathological narrowing of an intracranial blood vessel.

Etiology

The predominant mechanism of intracranial stenosis is atherosclerotic plaque formation commonly affecting Asians and African Americans. However, it is also increasingly found in Hispanics and Caucasians. Sickle cell anemia, endothelial proliferation, smooth muscle spasm, arterial dissection and non-occlusive thrombosis can also cause pathological narrowing of intracranial vessels. However, using the term stenosis implies atheromatous etiology rather than other conditions.

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W. C. Ziai, C. L. Cornwell (eds.), *Neurovascular Sonography*,
https://doi.org/10.1007/978-3-030-96893-9_9

Complications

Intracranial stenosis can cause "downstream" ischemic injury by hemodynamic compromise, athero-thrombosis, or artery-to-artery embolism. Atherosclerotic changes are common in the intracranial vasculature with increasing incidence with age across all demographics. Modifiable risk factors include tobacco use, hypertension, dyslipidemia and hyperglycemia.

Differential Diagnosis

The main differential diagnosis to be considered with evidence of narrowing of a vessel is congenital physiological atresia as a normal variant. There are many variants of normal and hypoplastic segments within the circle of Willis, such that a "complete" and symmetric circle of Willis is found in only a minority of patients. The length of the narrowed vessel (longer favoring atresia, short segment stenosis favoring pathology) and the presence or absence of compensatory velocity or vasculature changes on imaging serve as clues to help differentiate pathological stenosis *versus* atresia.

Transcranial Doppler Results

Transcranial Doppler [1] (TCD) measures a shift in frequency when echoes are reflected off of moving red blood cells, and from these shifts the velocity of the flowing blood is calculated. There are published normative data [2] that suggest a broad range of normal across primarily age strata and to a lesser degree gender.

First, to best understand TCD results, one must recall the key physical principles of:

- The assumed zero angle of insonation
- Flow dynamics, namely the Bernoulli and Hagen-Poiseuille principles
- The Spencer curve [3]

Handheld, non-imaging TCD instruments are generally calibrated to measure echoes at a 0° or 180° angle, and sampling a vessel at an unknown angle of intercept will give a fraction of the "true" velocity; the practical implication is that one can insonate only the most proximal segments of the basal intracranial vessels because of the limitation of traditional windows of insonation and typical vascular neuroanatomy to make a diagnosis of intracranial stenosis.

The purpose of brain vasculature is to maintain continuous flow in systolic and diastolic phases of the cardiac cycle to ensure uninterrupted supply of blood with oxygen and glucose to neurons. Blood flow to the brain depends on the cerebral vasculature being a low-pressure "sink" such that it is a path of least resistance. The pressure gradient (ΔP) is – in a simplified way – quantified by the Hagen-Poiseuille as $8\mu LQ/\pi r^4$ where μ is the viscosity, L is the length of the vessel, Q is the volume flow rate, and r is the vessel radius. The expression $8\mu L/\pi r^4$ can be thought of more broadly as "resistance to flow" and given the label R. The formula can be rearranged, then, to $Q = \Delta P/R$; in words, the volume flow rate is directly related to the pressure gradient and indirectly related to the resistance to flow. By these expressions, a progressively shrinking vessel radius will lead to an increase in resistance to flow, necessitating a corresponding drop in pressure gradient to maintain volume flow rate.

The Bernoulli principle states, as an extension of conservation of energy, that any change in potential (hydrostatic or pressure) energy must be met with a corresponding change in kinetic (velocity) energy such that total energy is equal at all points along a streamline. Therefore, in our example of a dropping pressure gradient due to increased resistance to flow, the drop in pressure (potential energy) theoretically necessitates an increase in kinetic energy, or velocity, which is exactly what we observe clinically when diagnosing intracranial stenosis with flow velocity increase across short and focal stenosis.

From the Hagen-Poiseuille and Bernoulli principles, Drs. Merrill Spencer and John Reid published a theoretical model [3] of flow velocity changes in the setting of an idealized stenosis – focal, axis-symmetric – which yielded a complex curve with

exponentially increasing velocity with decreasing lumen diameter up to approximately 80% stenosis, where beyond that critical level of stenosis velocity begins to exponentially decrease until it reaches zero with complete occlusion. This model, now referred to as "The Spencer Curve," although idealized and conceptualized for cervical carotid stenosis, has since become recognized as a foundational concept for developing diagnostic criteria for cerebrovascular hemodynamics, including intracranial vessels [4]. See Fig. 1.

Complementary to the observation of very elevated or very diminished mean flow velocity in the setting of intracranial steno-

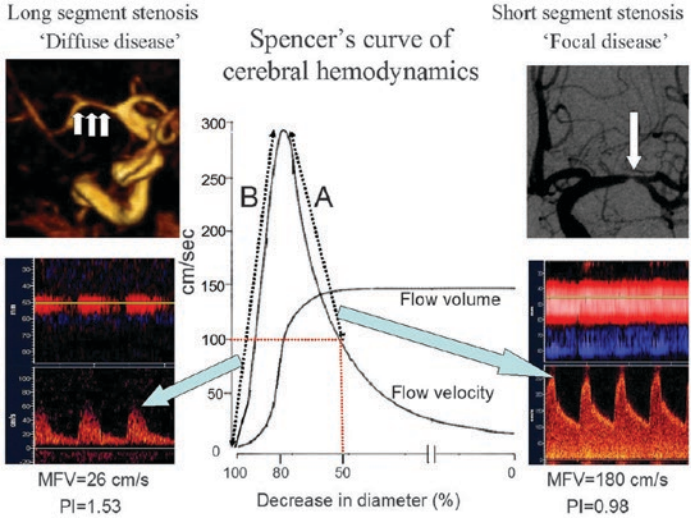

Fig. 1 Spencer's curve of cerebral hemodynamics [21]. Blood flow patterns in the intracranial arteries due to stenosis are predicted by their position on the Spencer's curve of cerebral hemodynamics. Dotted line A corresponds to abnormally elevated flow velocity on the "up slope" of the curve caused by short, focal stenoses of ≥50%, as is depicted in the DSA (upper right) with corresponding elevated TCD velocity (lower right). Dotted line B shows the "down slope" of the Spencer's curve when the velocities decrease due to increasing resistance to flow with the most severe and/or elongated lesions. The CTA image (top left) shows an elongated (>1 cm) stenosis with low mean velocity and high pulsatility on TCD (bottom left)

sis, the Thrombolysis in Brain Ischemia (TIBI) grading scale was introduced by Demchuk, et al. [5] This scale (see Fig. 2) essentially enumerated "where on the Spencer curve" – the accelerating slope on the right half or the decelerating slope on the left – the waveform profile associated with intracranial steno-occlusive disease happens to be and associated those strata with increasingly worse response to systemic thrombolysis and overall outcome with decreasing TIBI score. Increasing TIBI scores reflect the recanalization process, or "climbing back out to the other side" of the Spencer's Curve. See Fig. 2.

Given the individually unique complex nature of neurovascular anatomy, the typically axis-asymmetric nature of the pathological processes that cause intracranial stenosis, variability in operator technique and differences in ultrasound hardware, there are no discrete mean flow velocity cut-points that reliably identify significant intracranial stenosis with perfect granularity in all patients. Akin to best practices with carotid ultrasonography [6],

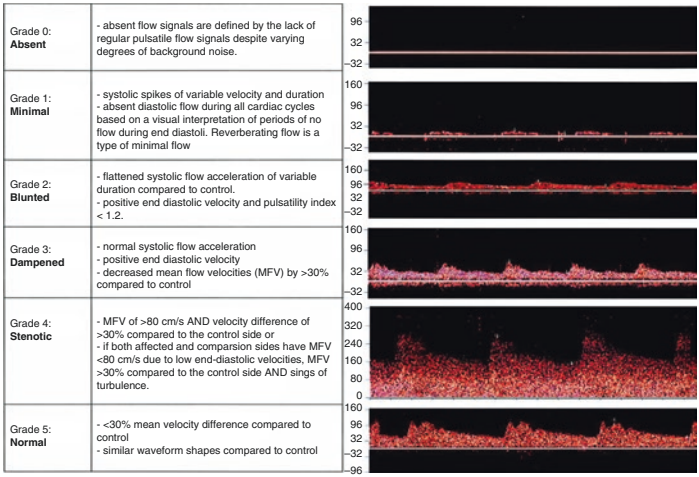

Fig. 2 Thrombolysis in brain ischemia (TIBI) flow grades. The TIBI grading scale. Lower scores are associated with worse response to systemic tPA and outcome. Grades 3–0 reflect progressive descent down the "left half" of the Spencer Curve

specific velocity values and corresponding degree of stenosis must be internally derived as a matter of routine quality assurance. That said, published clinical investigations have established reasonable starting points for new neurovascular laboratories. See Table 1. When following standard technique, TCD can be sensitive, specific and accurate for the diagnosis of intracranial stenosis or occlusion in patients with acute ischemic stroke [7].

TCD monitoring techniques also have a role in the diagnosis and management of intracranial stenosis. More specifically, longitudinal non-invasive surveillance can determine if the stenosis is stable, progresses or regresses after risk factor modification and best medical therapy that could be motivational to the patient. TCD also can assess vasomotor reactivity (VMR) and microembolic signal (MES) monitoring that further refine diagnosis, prognosis and management of intracranial stenosis. Vasomotor reactivity testing has been done primarily in the setting of cervical carotid artery stenosis, but there are series focusing on intracranial stenosis that have demonstrated findings similar to that which is published in the setting of cervical internal carotid artery stenosis, namely that impaired vasomotor reactivity "downstream" from an intracranial stenosis is associated with current ischemic stroke, history of stroke, and poorer prognosis as compared to a normal

Table 1 Published "starter" mean flow velocity cut points of intracranial artery stenosis [13, 19, 20]

Vessel	≥50%	≥80%
MCA	100 cm/s	240 cm/s
ICA	90 cm/s	120 cm/s
ACA	80 cm/s	–
PCA	80 cm/s	–
VA	90 cm/s	110 cm/s
BA	90 cm/s	130 cm/s

Legend: *MCA* middle cerebral artery, *ICA* internal carotid artery, *ACA* anterior cerebral artery, *PCA* posterior cerebral artery, *VA* vertebral artery, *BA* basilar artery, *cm/s* centimeters per second

vessel with normal VMR [8–10]. A series of MES monitoring of middle cerebral artery stenosis demonstrated that MES are common with stenosis (22%) and independently predicted ipsilateral stroke within 1 year [11].

Other Procedures

Both invasive and non-invasive angiography can be used to glean similar and complementary information as compared to TCD. Direct subtraction angiography (DSA), or "conventional" angiography, remains the "gold standard" for evaluating vessel lumen due to extremely high spatial and temporal resolution. CT and MR angiography (CTA or MRA, respectively) are non-invasive means of imaging intracranial vessel lumen with high (but not as high as DSA) spatial resolution but represent a "snapshot in time" such that there is no objective hemodynamic data other than opacification of a vessel. A seminal prospective comparison of DSA to TCD (as well as MRA) came in a subset of the WASID trial [12] called the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial [13]. In brief, this study demonstrated substantial negative predictive value of 50–99% stenosis, 86% across all vessels, of TCD as compared to DSA. Positive predictive value was low at 36%. The trial method and findings established that a normal TCD can reliably exclude intracranial stenosis, however, since no TCD standardization has been performed across participating centers, positive predictive values were less than optimal. An international multi-center group that validated TCD scanning protocols and adopted same diagnostic criteria showed that WASID-SONIA criteria perform reliably with high sensitivity and specificity [14]. Furthermore, TCD provides additional complementary information such as embolization, collateralization and steal that are not obtained by CTA. See Fig. 3 [15].

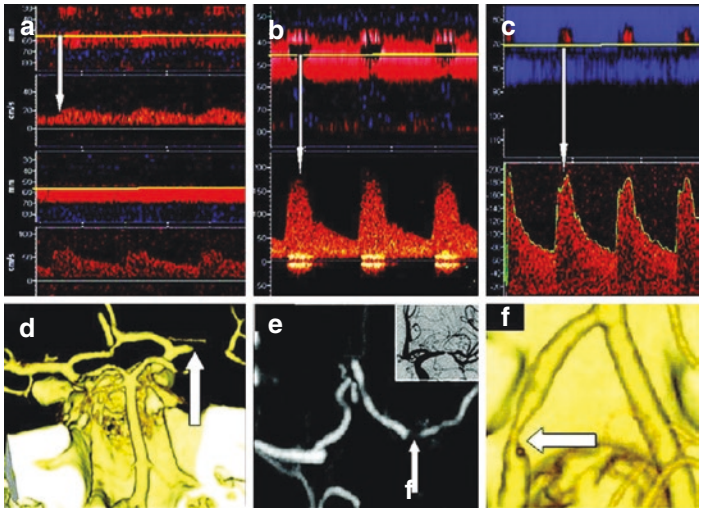

Fig. 3 CTA and TCD correlation [15]. (**a**) Power-motion TCD showing left M1-MCA occlusion with blunted signals at 54 mm and normal contralateral MCA below; (**b**) left M1-MCA stenosis with elevated velocities and systolic bruit at 48 mm; (**c**) right terminal VA stenosis with MFV of 113 cm/s at 70 mm. TCD findings (**a** through **c**) were confirmed by CTA (**d** through **f**, respectively). Insert in (**e**) represents urgent DSA image in the patient with M1-MCA stenosis

Treatment

The treatment of intracranial stenosis depends on the mechanism – again, most commonly atherosclerosis – and whether or not the patient is experiencing symptoms in association with the stenosis. Asymptomatic intracranial atherosclerotic stenosis is incidentally diagnosed and does not necessarily require directed medical or surgical therapy outside of maximizing control of common health concerns such as hypertension, dyslipidemia and hyperglycemia. Symptomatic intracranial atherosclerotic stenosis – whether it manifests as stroke or transient ischemic attack – bears high risk of stroke recurrence directly proportionate to the number of vessels affected and increases with increasingly severe

degree of stenosis. It is treated with antiplatelet medications, thoughtful blood pressure control (to avoid both hypotension or persistently elevated pressure) and high intensity statin therapy in addition to maximal control of the aforementioned common health concerns. The use of two antiplatelet agents is common for 90 days after a cerebral ischemic event suggestive of symptomatic intracranial stenosis. TCD is particularly helpful in diagnosing MES distal to an intracranial stenosis, which are a predictor of ipsilateral stroke [11, 16] and informs treatment, namely necessitating dual antiplatelet [17, 18] and occasionally anticoagulation if refractory.

Stenosis caused by other, less common conditions such as sickle cell anemia, endothelial proliferation ("vasospasm"), dissection, arterial smooth-muscle spasm or non-occlusive thrombus require different means of evaluation and management. For example, most spasmodic disease – vasospasm of aneurysmal subarachnoid hemorrhage or that of Call- Fleming syndrome (reversible cerebral vasoconstriction syndrome) calls for calcium channel blockade and supportive care of what is usually a time-limited pathology that resolves within 3 weeks to 3 months, but antithrombotic medications are not indicated. Arterial dissection and non-occlusive thrombosis, on the other hand, calls for lifelong antiplatelet medication and occasionally anticoagulation because of transitory (but at least weeks) to permanent alteration in a vessel lumen causing disturbance of laminar flow of arterial blood.

TCD is perhaps best known and most widely used to screen for the occurrence and to monitor the dynamic nature of vasospasm after subarachnoid hemorrhage. Serial studies can help guide treatment as severe cases often necessitate endovascular reperfusion therapies such as angioplasty and/or local calcium channel blocker injection to avoid ischemic injury. As seen in Fig. 4 there can also be thrombotic complications of the intravascular hardware needed to coil an aneurysm, such that this TCD recording indicated the need for both antiplatelet medication and intra-arterial therapy, neither of which would have been indicated without TCD diagnosis of a MES and mean velocity elevation in the range of severe vasospasm, respectively.

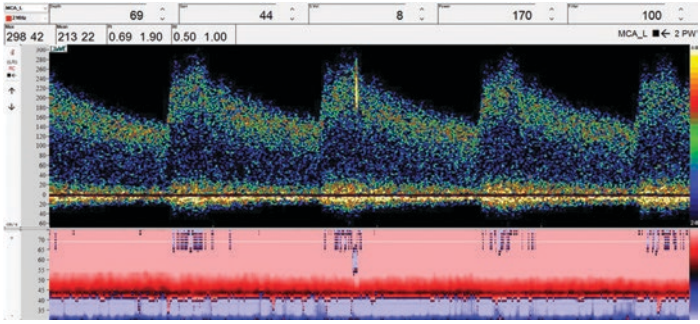

Fig. 4 TCD to diagnose complications of aneurysmal subarachnoid hemorrhage. Bedside TCD of the left MCA after left terminal ICA aneurysm coiling. Mean flow velocity is elevated into a range concerning for moderate to severe vasospasm and there was a spontaneous microembolic signal, seen as a bright "streak" in the single gate and a "backslash" in the multigate window

Conclusions

Intracranial stenosis, caused by various mechanisms, is an unfortunately common and morbid if not mortal condition, and the ability to diagnose the presence or absence of it is essential to not only stroke care but general wellness. TCD can reliably rule out hemodynamically significant stenoses in the intracranial vasculature and, in the hands of trained experts, can accurately diagnose and localize treatable lesions in concordance with both DSA and non-invasive angiography as well as provide complementary real-time flow related and embolic data that only ultrasound can provide.

Personal Perspectives

TCD is a necessity of daily stroke practice at our institution. We listen to intracranial stenoses on a serial basis – much like one would listen to a patient's lungs when dealing with and recovering from pneumonia – to ascertain whether or not our treatments have been effective in reducing the degree of stenosis or otherwise

restoring cerebral perfusion to an afflicted hemisphere. That it can be deployed rapidly, safely and noninvasively affords us the opportunity to rapidly diagnose and accurately manage acute neurological decline in the hospital setting, where it is imperative for the patient that we rapidly and reliably rule in or out the presence of intracranial steno-occlusive disease. VMR and MES monitoring can differentiate asymptomatic from concerning, hemodynamically significant stenoses that require further blood pressure and/or antithrombotic therapy. TCD is a reliable bedside diagnostic for the practicing vascular neurologist.

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