SVN Stroke & Vascular Neurology

Cerebral haemodynamics in symptomatic intracranial atherosclerotic disease: a narrative review of the assessment methods and clinical implications

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To cite: Liu Y, Li S, Tian X, *et al*. Cerebral haemodynamics in symptomatic intracranial atherosclerotic disease: a narrative review of the assessment methods and clinical implications. *Stroke & Vascular Neurology* 2023;**8**: e002333. doi:10.1136/svn-2023-002333

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2023-002333).

Received 30 January 2023
Accepted 7 April 2023
Published Online First 24 April 2023

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ABSTRACT

Intracranial atherosclerotic disease (ICAD) is a common cause of ischaemic stroke and transient ischaemic attack (TIA) with a high recurrence rate. It is often referred to as intracranial atherosclerotic stenosis (ICAS), when the plaque has caused significant narrowing of the vessel lumen. The lesion is usually considered 'symptomatic ICAD/ICAS' (sICAD/sICAS) when it has caused an ischaemic stroke or TIA. The severity of luminal stenosis has long been established as a prognostic factor for stroke relapse in sICAS. Yet, accumulating studies have also reported the important roles of plaque vulnerability, cerebral haemodynamics, collateral circulation, cerebral autoregulation and other factors in altering the stroke risks across patients with sICAS. In this review article, we focus on cerebral haemodynamics in sICAS. We reviewed imaging modalities/methods in assessing cerebral haemodynamics, the haemodynamic metrics provided by these methods and application of these methods in research and clinical practice. More importantly, we reviewed the significance of these haemodynamic features in governing the risk of stroke recurrence in sICAS. We also discussed other clinical implications of these haemodynamic features in sICAS, such as the associations with collateral recruitment and evolution of the lesion under medical treatment, and indications for more individualised blood pressure management for secondary stroke prevention. We then put forward some knowledge gaps and future directions on these topics.

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is a common cause of ischaemic stroke and transient ischaemic attack (TIA), especially in populations of African, Asian and Hispanic ancestries.[1] It is often referred to as intracranial atherosclerotic stenosis (ICAS), when the plaque has caused significant narrowing of the vessel lumen. The lesion is usually considered 'symptomatic ICAD/ICAS' (sICAD/sICAS) when it has caused an ischaemic stroke or TIA.

The risk of recurrent stroke in trials of sICAS has been declining in the past two decades. For instance, the risk of recurrent stroke or death was up to 15%–17% at 1 year, among those with 50%–99% sICAS treated with aspirin or warfarin, in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial published in 2005, which was higher in those with 70%–99% sICAS.[2] The risk of any stroke or death was 18% at 1 year in patients with 70%–99% sICAS receiving aggressive medical management, including short-term dual followed by long-term mono antiplatelet plus stringent vascular risk factor management (often referred as 'best medical treatment' now), in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial published in 2011.[3] In the China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) trial published in 2022, the risk of 30-day stroke or death and same-territory stroke beyond 30 days through 1 year was further reduced to 7% in similarly, medically treated patients with 70%–99% sICAS.[4] The significant reduction in stroke risk in sICAS in recent trials, especially in CASSISS, could be partly attributed to more refined patient recruitment criteria, and to the more effective secondary prevention strategies and more standardised clinical practice and possibly improved patient compliance in recent years. However, the residual risk of stroke recurrence in sICAD under such treatment is still considerable. One of the possible reasons could be the limited understanding and appreciation of various aspects of the sICAD lesion and the stroke mechanisms in formulating secondary stroke prevention strategies.

Indeed, the severity of luminal stenosis has long been established as a prognostic factor for stroke relapse in sICAS, for example, in the WASID trial patients.[5] However, it is not the only factor that governs the stroke recurrence risk in sICAS, when nearly half of the recurrent strokes occurred in patients with 'moderate' (50%–69%) sICAS in WASID,[5] and there are strokes in those with 'mild' (<50%) ICAS in other studies.[6] It is definitely not the only factor that determines the stroke mechanisms in ICAD/ICAS, either, when ICAD/ICAS can cause an ischaemic stroke by occluding penetrating arteries, plaque rupture to embolise distal arteries, hypoperfusion or mixed mechanisms.[7] In the past few years, accumulating studies have reported the important roles of plaque characteristics (eg, morphology, components and vulnerability), cerebral haemodynamics, collateral circulation, cerebral autoregulation and other factors in altering the stroke risks in sICAD. In this review article, we focus on cerebral haemodynamics in sICAD, including global and focal haemodynamic features, such as blood flow velocity, cerebral blood flow (CBF) and volume (CBV), perfusion time metrics, cerebral vasoreactivity (CVR) and translesional changes in pressure and wall shear stress (WSS). We shall review the assessment methods of these cerebral haemodynamic metrics in sICAD and the clinical implications, especially the prognostic value for stroke recurrence. Of note, most of the evidence reviewed below comes from studies on sICAS (with >50% stenosis), when sICAD with no or mild stenosis was seldom investigated in previous relevant studies.

HAEMODYNAMICS IN SICAS: ASSESSMENT METHODS AND PROGNOSTIC VALUES

Various imaging methods based on ultrasound, CT, MRI or digital subtraction angiography (DSA) can be used to quantitatively or semi-quantitatively assess cerebral haemodynamics in different aspects. By combining with advanced computational techniques, for example, computational fluid dynamics (CFD) modelling,[8 9] more cerebral haemodynamic metrics could be illustrated. We herein briefly review the principles and applications of these imaging methods, and more importantly, the significance of haemodynamics in governing lesion progression and stroke risks in sICAS, in the hope of informing future research on secondary prevention of sICAS from the haemodynamic perspective. All imaging methods and haemodynamic metrics discussed below are illustrated in the figure 1.

Positron emission tomography, single-photon emission CT and xenon-enhanced CT

Imaging modalities available to measure cerebral haemodynamics have evolved over time. In earlier days, positron emission tomography (PET), single-photon emission CT (SPECT) and xenon-enhanced CT (xenon CT) were used to provide measurements of cerebral perfusion or metabolism metrics, which have been associated with prognosis of ischaemic stroke with sICAS.[10–13] They can also be used to define cerebral hypoperfusion stages, which is further discussed in the section below.

PET provides regional measurement of important physiological parameters, such as CBF and oxygen metabolism. Oxygen extraction fraction (OEF), an important parameter for gauging haemodynamic and metabolic impairment, can be obtained by using 15-oxygen (^{15}O) as a tracer in a PET exam. In patients with symptomatic occlusive internal carotid artery (ICA) or middle cerebral artery (MCA), increased OEF (compared with normal OEF) was significantly associated with increased 1-year risk of ipsilateral ischaemic stroke,[10] which was also an independent predictor of the 5-year stroke risk.[11]

SPECT is a reliable method for measuring CBF and detecting alterations in CBF in the first few hours after a stroke. Xenon-133, ^{99m}Tc-labelled hexamethylpropyleneamine oxime and ethylcysteinate dimer have been commonly used compounds in SPECT, which can be taken up by the brain tissue in a manner proportional to CBF.[14] In addition, SPECT in conjunction with the acetazolamide challenge test allows for measurement of regional CVR, a marker of the cerebral autoregulation capacity, when patients with severely impaired regional CVR might have an increased risk of subsequent stroke.[12]

Xenon CT is another imaging technique that combines the stable non-radioactive element xenon with CT scan to quantify CBF. Stable xenon, inhaled by the examinee, will rapidly cross the blood-brain barrier and distribute proportionally to the blood flow and lipid content. The distribution of xenon contrast enhancement can then be converted into quantitative CBF maps. A study that combined xenon CT with the acetazolamide challenge test showed a significantly increased risk of subsequent ipsilateral stroke, in patients with symptomatic ICA stenosis or occlusion with compromised CVR and low CBF at baseline.[13]

Overall, these imaging methods have provided early evidence regarding the clinical implications and prognostic values of cerebral haemodynamics in patients with sICAS. But they are extremely infrequently used for clinical or research purpose in recent years, due to the complexity of the examination procedures, the high radiation burden and low spatial resolution.

Transcranial Doppler and carotid duplex ultrasound

Transcranial Doppler (TCD) is a non-invasive, inexpensive and convenient method that allows measurement and real-time monitoring of cerebral haemodynamics, of which the prognostic values in stroke and patients with sICAS have been profoundly validated in the past two decades. For instance, mean flow velocity (MFV) and the ratio of pulsatility index (PI) and MFV in MCA by TCD were independent prognostic factors for recurrent stroke within 2 years, in patients with minor ischaemic stroke/TIA.[15] In addition, CVR can also be measured by TCD, for example, by a breath-holding manoeuvre. In the Mechanisms of Early Recurrence in Intracranial Atherosclerotic

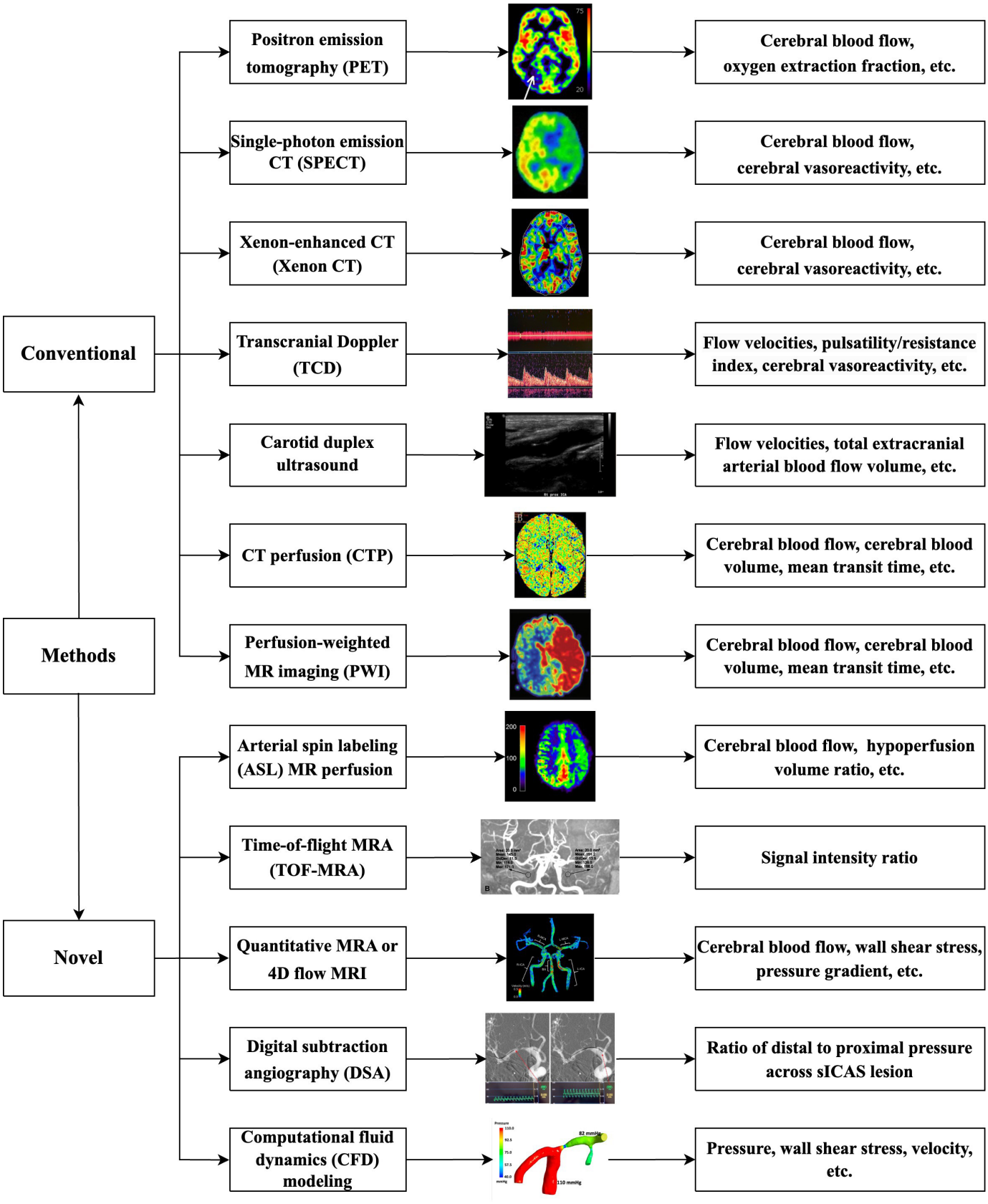

Figure 1 Illustration of imaging methods for assessing cerebral haemodynamics in stroke and/or intracranial atherosclerotic disease. Key perfusion and haemodynamic parameters provided by these imaging methods are listed on the right side. Most of the images were reproduced from previous publications with permissions, with the references provided in the online supplemental appendix. MRA, magnetic resonance angiography; sICAS, symptomatic intracranial atherosclerotic stenosis.

Disease (MyRIAD) study, low CVR (defined as a TCD breath-hold index <0.69) was present in nearly 70% of patients with sICAS, although it was not significantly associated with stroke recurrence.[16]

Another ultrasound-based method, carotid duplex ultrasound can also be used to quantify extracranial and intracranial haemodynamics. In addition to the flow velocities, colour velocity imaging quantification based on carotid duplex can estimate the total extracranial arterial blood flow volume, a lower level of which was associated with an increased risk of recurrent stroke, in patients with mildly to moderately severe ischaemic stroke.[17]

In summary, although ultrasound-based techniques are highly operator-dependent and may be inaccurate in quantification of the haemodynamic metrics, they are simple and repeatable imaging methods that can be widely used in clinical practice and research, to provide flow data that complement the vascular structure data obtained from other advanced vascular imaging modalities.

Contrast-dependent CT or MR perfusion imaging

CT perfusion (CTP) and dynamic susceptibility contrast (DSC) perfusion-weighted MR imaging (PWI) use intravascular contrast agents and temporal sequence of images to quantify blood flow through the brain parenchyma.[18] Several perfusion parameters, including CBF, CBV, mean transit time (MTT), time-to-peak (TTP) and time-to-maximum (Tmax), could be obtained through CTP and DSC-PWI. They are valuable in selecting patients with acute ischaemic stroke suitable for hyperacute intravenous or endovascular reperfusion treatments, which may also provide prognostic information in the setting of sICAS. Based on the perfusion parameters, the cerebral haemodynamic impairment in patients with steno-occlusive cervico-cerebral artery diseases can be divided into three stages: stage I, cerebral autoregulation, when distal cerebrovascular resistance reduces with compensatory vasodilatation to maintain CBF, in response to reduced cerebral perfusion pressure (CPP); CBV and MTT could increase in this scenario. Stage II, misery perfusion or 'benign oligaemia', when CBF falls passively with reduced CPP, with overwhelmed autoregulatory capacity; MTT usually increases to allow the brain to extract more oxygen from the blood passing through, to avoid metabolic compromise. Stage III, end-organ compromise/dysfunction, the increased oxygen extraction rate is unable to maintain normal oxygen metabolism, when CBF continues to fall with even further reduced CPP.[19]

In a retrospective study of patients with 50%–99% sICAS, sustained CBF with prolonged MTT in CTP, that is, stage I haemodynamic impairment, was significantly associated with recurrence of ipsilateral ischaemic stroke (HR 7.01, 95% CI 1.86 to 26.46; p=0.004), but not with ipsilateral TIA, during 2 years of follow-up.[20] The findings may be related to the underlying stroke mechanisms. Plaque rupture and subsequent artery-to-artery embolisation is a common stroke mechanism in ICAD.[7] With sufficient, rapid CBF, the small emboli in distal regions released from proximal vulnerable plaques could be cleared, so patients may have TIA due to transient embolisation. However, with prolonged cerebral perfusion, impaired clearance of the emboli may lead to permanent ischaemic lesions (infarctions) in the affected regions.

In two studies, using Tmax >6 s to define penumbra, distal hypoperfusion (defined by penumbra volume ≥15 mL distal to the sICAS lesion on CTP/PWI) or unfavourable perfusion status (defined by a penumbra and infarct core mismatch volume of ≥15 mL on PWI) was significantly associated with an increased risk of recurrent ischaemic stroke within 90 days despite aggressive medical management, in patients with acute ischaemic stroke with sICAS.[21 22] However, there was no significant association between haemodynamic impairment and recurrent ischaemic events in patients with sICAS in the MyRIAD study, with different PWI thresholds to define haemodynamic impairment, that is, ≥10 mL brain tissue with TTP >4 s.[16]

Overall, contrast-dependent CT or MR perfusion imaging has been widely used in clinical practice for evaluating cerebral haemodynamics in patients with acute ischaemic stroke. However, the thresholds to define distal hypoperfusion or haemodynamic impairment in ICAS remain to be established in CTP or PWI, so that findings from different studies may be comparable or generalisable.

Contrast-independent arterial spin labelling MR perfusion imaging

Arterial spin labelling (ASL) MR perfusion imaging is independent of exogenous contrast agent, which has been available for more than two decades. A critical innovation of ASL over conventional perfusion imaging is using the arterial blood as an endogenous contrast agent, to visualise and quantify territorial cerebral perfusion by magnetically labelling the inflowing blood through an artery of interest with radiofrequency pulses.[23]

Appropriate selection of the postlabelling delay (PLD) time is critical in accurate perfusion measurements by ASL, which relies on an estimate of the mean arterial transit time (ATT) from the labelling region to the capillary exchange site.[24] The ATT may be longer in patients with arterial stenosis or occlusion (eg, ICAS).[25] Moreover, compared with antegrade blood flow across ICAS, collateral flow that is retrograde or from an alternative and longer route may lead to an even longer ATT.[25] Thus, if the PLD is too short, the labelled bolus may not reach the imaging plane that can lead to underestimation of CBF in ICAS.[24] From this perspective, a multi-delay ASL approach (usually with >5 PLDs) provides improved accuracy in the measurement of CBF and other haemodynamic metrics, and better visualisation of the collateral circulation in sICAS, compared with single-delay ASL.[25 26]

Cerebral haemodynamics assessed by ASL have been indicated in several studies to predict clinical outcomes in acute stroke, which may also have prognostic values in patients with ICAS.[27] For instance, hypoperfusion volume ratio (HVR) was proposed in a recent study to

quantify haemodynamic impairment in sICAS in three-dimensional pseudocontinuous ASL (3D pCASL), which was calculated as the ratio of the hypoperfusion volume in the CBF maps generated respectively with a PLD of 2.5 s and 1.5 s. Severe haemodynamic impairment defined as an HVR value ≥50% was significantly associated with recurrent stroke within 1-year follow-up, in patients with severe MCA stenosis (adjusted OR 12.93, 95% CI 1.57 to 106.24; p=0.017).[26] The clinical significance of HVR in patients with ICAS warrants further validation in future studies.

Compared with DSC-PWI, ASL allows quantification of cerebral perfusion metrics in patients with contraindications to intravenous contrast material (eg, renal failure). However, the variability in ATT and the uncertainty in PLD in different settings may interfere with the accuracy of ASL to quantify CBF and other haemodynamic metrics, particularly in the presence of ICAS when there is often prolonged ATT. Further studies are needed to explore for optimal PLD times, preferably using a multi-delay ASL approach, to more accurately quantify cerebral haemodynamic metrics in ICAS and to further reveal their clinical implications.

Time-of-flight magnetic resonance angiography

Time-of-flight magnetic resonance angiography (TOF-MRA) is a widely used, non-invasive, contrast-independent imaging method for intracranial arteries.[28] The degree of enhancement of flowing blood on TOF-MRA, that is, the signal intensity (SI) in the vessel lumen, increases non-linearly with the absolute flow velocity. Therefore, diminished SI distal to ICAS may indicate disturbed or reduced blood flow downstream.[29] Thus, changes in SIs across an ICAS lesion may yield information on its haemodynamic and functional severity. An index named SI ratio (SIR) has been developed to quantify the haemodynamic significance of ICAS in TOF-MRA, which was the ratio of SIs distal and proximal to the ICAS lesion, adjusted by the background SI; SIR=(mean poststenotic SI–mean background SI)/(mean prestenotic SI–mean background SI).[29] It has been demonstrated of high intra-observer and inter-observer reproducibility.[30] A lower SIR indicates a haemodynamically more severe ICAS lesion.

In a cohort of patients with unilateral MCA stenosis, SIR was significantly lower in those with stage II and stage III cerebral hypoperfusion (mean SIRs: 0.86 and 0.72), compared with those with normal perfusion (mean SIR 0.93).[31] Such findings were echoed in a study using ^{123}I-iodoamphetamine SPECT with CVR test to grade the cerebral hypoperfusion stages in patients with unilateral MCA stenosis, which also revealed lower mean SIR in symptomatic than asymptomatic MCA stenoses.[32] Among a subset of patients with intracranial ICA or MCA stenosis with sustained CBF in CTP, a lower SIR was significantly correlated with prolonged or delayed perfusion, reflected by higher ipsilateral MTT and ipsilateral/contralateral MTT ratio.[28] All these studies supported the value of SIR in gauging the haemodynamic significance of an ICAS lesion.

Although there has been no established threshold of SIR to define a haemodynamically significant ICAS lesion, SIR <0.9 was independently associated with an increased risk of recurrent stroke in the same territory, in WASID trial patients with 50%–99% sICAS (adjusted HR (aHR) 10.9, 95% CI 2.0 to 58.9; p<0.001).[33] There were also studies using a simpler method to assess the change in SIs across ICAS in TOF-MRA, that is, by grading the visibility of branch arteries distal to ICAS.[34] In 153 patients with symptomatic, unilateral MCA trunk stenosis (70%–99%) in TOF-MRA, reduced visibility in distal MCA branches was associated with presence of internal borderzone infarction and an increased risk of stroke recurrence.[34]

Overall, these studies reinforced SIR in TOF-MRA as a simple, reproducible and non-invasive but useful tool to assess the haemodynamic significance of sICAS, which also has value in risk stratification of the patients. However, factors such as vessel tortuosity, vessel calibre tapering and arterial branching can affect SIs in the vessel lumen in TOF-MRA, which have limited the application of SIR in ICAS lesions across tortuous arterial segments or adjacent to a bifurcation. In addition, variable imaging and postprocessing parameters of TOF-MRA across institutions can also impact the acquisition of SIs in the vessel lumen.[31] With most studies on SIR in ICAS being retrospective analyses with a limited study scale, the clinical implications of SIR warrant further verification in prospective, longitudinal, multicentre studies.

Quantitative magnetic resonance angiography

Quantitative magnetic resonance angiography (QMRA) is a non-invasive method that combines TOF and two-dimensional phase-contrast MRA, which can simultaneously characterise intracranial vascular anatomy and quantify cerebral haemodynamics. A 20% reduction below the normative lower limits of the vessel-specific and age-specific average has been used as a threshold to define compromised CBF.[35]

In the prospective, observational, multicentre Vertebrobasilar Flow Evaluation and Risk of Transient Ischaemic Attack and Stroke (VERiTAS) study, low distal flow was identified by QMRA in 25% of patients with symptomatic vertebrobasilar atherosclerotic stenosis and/or occlusion, which was an independent predictor for subsequent vertebrobasilar territory stroke (aHR 11.55, 95% CI 1.88 to 71.00; p=0.008).[36] In the MyRIAD study of patients who mostly had a sICAS in the anterior circulation, a low flow state was similarly detected by QMRA in 25.5% of the patients. However, no significant association was found between flow compromise in QMRA and subsequent ischaemic stroke in the MyRIAD cohort, possibly due to the small sample size and small number of the recurrent ischaemic events.[16]

As a novel and non-invasive method to quantify cerebral perfusion, QMRA, however, is limited by inadequate anatomical coverage and unreproducible manual

placement of multiple planes.[37] Four-dimensional (4D) flow MRI (ie, time-resolved 3D phase-contrast MRI with 3-directional velocity-encoding) has additional benefits over QMRA, which allows retrospective flow quantification at any vessel location within the imaging volume and 3D blood flow visualisation of the entire vasculature,[37] and provides several other haemodynamic parameters such as WSS and pressure gradient (PG) across an arterial segment of interest.[38] Further studies are needed to elucidate the clinical significance of cerebral haemodynamics by QMRA or 4D flow MRI in ICAS in anterior and posterior circulations.

Digital subtraction angiography

To date, conventional angiography or DSA remains the reference standard in assessing the degree of luminal stenosis in coronary artery disease (CAD), and extracranial and intracranial stenosis. The fractional flow reserve (FFR), a ratio of poststenotic and prestenotic pressures obtained with induced hyperaemia during a coronary angiography examination, is currently the reference standard in assessing the haemodynamic severity of CAD.[39] The pressures can be measured by advancing a pressure guidewire across the stenotic lesion and administering vasodilatory agents (eg, adenosine) to induce hyperaemia.[39] For coronary revascularisation, patient selection based on FFR to detect haemodynamically significant CAD lesions is associated with better clinical outcomes, compared with patient selection based solely on the degree of luminal stenosis.[40] FFR ≤0.80 or 0.75 is recommended in the 2018 European Society of Cardiology and European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularisation, to guide clinical decisions on coronary revascularisation in patients with different extent and/or symptoms of CAD.[41]

In the last few years, there have been preliminary attempts to test the feasibility of assessing the fractional flow (Pd/Pa) across sICAS during a DSA exam. In these studies, the mean distal pressure (Pd) and proximal pressure (Pa) were mostly measured under resting rather than hyperaemic conditions, given the unclear risk of using vasodilatory agents and the various degrees of impairment in cerebral autoregulation in these patients.[42 43] In ICAS studies, Pd/Pa was not, or only modestly, correlated with the severity of luminal stenosis measured by DSA.[43 44] This reinforced that the anatomical severity of ICAS is not fully representative of its haemodynamic or functional severity. In a pilot study, Pd/Pa ≤0.7 was used to guide patient selection for stenting treatment in sICAS.[42] In 12 patients with 40%–69% sICAS, 8 patients with a Pd/Pa ≤0.7 were suggested for stenting, among whom only a patient who refused stenting treatment had a recurrent TIA within 6 months of follow-up.[42]

In summary, invasive angiography-based fractional flow measurement provides valuable information for understanding the pathophysiology of ICAS, but there remain technical and ethical difficulties. Furthermore, it is unclear whether the pressure guidewire itself would interfere with the flow across a small-calibre intracranial artery and a stenotic lesion of further reduced lumen area, which could affect the accuracy of the measurement. By far, with limited evidence from small-scale studies, there are many unanswered questions, for instance, the cut-off value for Pd/Pa in defining a haemodynamically severe ICAS lesion and its value in facilitating clinical decisions regarding interventional treatment. It is also debatable whether we could or should conduct larger-scale studies, with the limitations as discussed above.

Computational fluid dynamics modelling

CFD, a branch of fluid mechanics, can solve blood flow-related problems using numerical methods.[8] Based on the vessel anatomy from a vascular imaging exam and reasonable assumptions on the conditions of the vessel wall, inlet/outlet(s) and the blood per se, a CFD model can be built to simulate blood flow across an arterial stenotic lesion and quantify the haemodynamic features of the lesion.

CFD modelling in arterial diseases usually involves the following steps: (1) extraction of the 3D vessel geometry of the area of interest from angiographic images (eg, MRA/CTA); (2) mesh creation in the surface, inlet/outlets and vessel lumen domains; (3) application of assumptions of generic or patient-specific boundary conditions and blood properties (eg, Newtonian or non-Newtonian fluid); (4) simulation of the blood flow by solving fluid dynamics equations and (5) postprocessing of the models for measurement of the haemodynamic metrics.[8 45] These can be done with some commercially available software or in-house developed programmes.

Starting from the late 2000s, a non-invasive FFR computed by CFD models based on CTA (ie, FFR_{CT}) has been vigorously tested in CAD, which has shown high diagnostic performance for detecting haemodynamically severe CAD lesions, against the invasive FFR obtained with a coronary angiography as discussed above.[46] In cerebrovascular diseases, the CFD technique has been more maturely used in simulating blood flow in intracranial aneurysms in the last two decades, which has clinical implications in predicting the risk of rupture and guiding surgical planning and other managements.

However, the application of CFD modelling in ICAD has been limited until the past few years. CFD models are built based on neurovascular imaging, to simulate the blood flow across sICAS and quantify cerebral haemodynamic metrics. For instance, the translesional pressure ratio (PR), a non-invasive measure similar to the Pd/Pa obtained through DSA as discussed above, represents the relative, translesional PG across ICAS that governs the residual antegrade flow through the lesion.[47] In addition, WSS, which is associated with development and vulnerability of atherosclerotic plaques,[9] as well as velocity and vorticity, etc, could also be quantified with CFD models in ICAS.[8] In a cohort study of 245 patients with sICAS, a low translesional PR (ie, a large translesional PG) and a high translesional WSS ratio (ie, excessively elevated

WSS at the stenotic throat) as quantified using CTA-based CFD models were independently, respectively associated with an increased risk of recurrent ischaemic stroke in the same territory within 1 year.[9] Furthermore, a combination of both a low translesional PR and a high translesional WSS ratio was associated with a significantly higher risk of this outcome, compared with a combination of normal PR and WSS ratio (aHR 7.52, 95% CI 1.94 to 29.20; p=0.004).[9] There are other implications of the cerebral haemodynamic metrics obtained with CFD models in sICAS, for example, in plaque evolution and collateral recruitment, which are discussed in relevant sections below.

Overall, the CFD method has advantages in studying cerebral haemodynamics in ICAS. Compared with the invasive method to quantify Pd/Pa, it provides an opportunity to identify haemodynamically significant ICAS based on non-invasive neurovascular imaging. It can also quantify other global and focal haemodynamic metrics such as flow velocity and WSS that cannot be obtained with conventional perfusion imaging. Moreover, the CFD method could also simulate blood flow with idealised ICAS models, which can aid in understanding the generalised associations between lesion geometry, haemodynamics and the biomechanical behaviour of the lesion.[48] In the meantime, however, this technique also has many challenges, especially in the modelling methodology that has varied across different studies and research teams. To date, it is mainly used in the research field for ICAD but not in clinical practice. Future studies are needed to test and establish more reasonable, reproducible and accurate CFD modelling methodology in ICAS, and more importantly, the clinical implications of the haemodynamic metrics. In the near future, this method could be ultimately applied in clinical practice for the assessment and risk stratification of ICAD, and guiding clinical decisions, for example, for interventional versus medical treatment, or for more individualised blood pressure (BP) management target as discussed in the relevant section below. The CFD tools may also be integrated in the imaging system, for quicker assessment and analyses in aiding clinical decisions.

OTHER CLINICAL IMPLICATIONS OF HAEMODYNAMICS IN SICAS

Haemodynamics and collateral circulation in sICAS

Cerebral collateral circulation refers to preexisting or newly emerging vascular channels to compensate CBF when the primary vascular pathways fail, in the presence of extracranial or intracranial arterial stenosis or occlusion due to atherosclerosis, in situ thrombosis, embolisation or other causes.[49] In patients with ICAS, the residual antegrade flow and the distal leptomeningeal collateral (LMC) flow could be complementary in sustaining the cerebral perfusion downstream to the lesion.[47]

Primary cerebral collaterals include the arterial segments of the circle of Willis, and secondary collateral routes involve the ophthalmic artery and LMCs.[49] Collateral routes may partially exist before appearance of a critical arterial stenosis/occlusion, but the routes and capacity could dynamically evolve over time.[49] The underlying mechanisms of cerebral collateral formation and/or recruitment are not fully clear. Taking LMCs for an example, a large translesional PG across a sICAS lesion may be a driving force for LMC recruitment, as revealed in a CTA-based CFD study in patients with symptomatic, atherosclerotic MCA-M1 stenosis.[50] The large translesional PG could open pre-existing collateral anastomoses and result in increasing fluid shear stress in the distal vascular bed, which subsequently facilitates collateral recruitment, growth or arteriogenesis.[51] In other words, the LMC status in sICAS may depend more on the haemodynamic significance, rather than the luminal stenosis, of the lesion, which explains why there are sometimes good LMCs in sICAS lesions of 'moderate' (50%–69%) luminal stenosis but haemodynamic significance.[50] Good LMCs may identify a subgroup of patients in whom the 'moderate' sICAS is haemodynamically compromised. Such inference is also supported by the findings from WASID that good LMCs had a protective effect against ipsilateral stroke recurrence in sICAS of severe (70%–99%) luminal stenosis, which, however, was a risk factor for recurrent stroke in those with moderate (50%–69%) stenoses.[52]

Future studies delineating the dynamic evolution of collateral circulation in ICAS with serial neurovascular imaging tests are warranted. In addition to cerebral haemodynamics, several other factors such as metabolic syndrome, hyperuricaemia and cerebral small vessel disease are also associated with the cerebral collateral status,[53 54] which could be considered simultaneously in future studies, to further reveal the pathophysiology of collateral recruitment in ICAS and to provide potential therapeutic markers to intervene.

Haemodynamics and plaque vulnerability and evolution in sICAS

In addition to systemic vascular risk factors (such as hypertension and dyslipidaemia), focal haemodynamics could also have a significant role in the formation, development and evolution of atherosclerotic plaques and in determining the plaque vulnerability.[55] This has been intensively studied in experimental models and clinical studies of coronary and carotid atherosclerotic disease, which have indicated that the relationships of WSS with atherosclerotic plaque vulnerability or evolution are not simply linear.[55 56]

Based on coronary and carotid artery studies, in early stages of atherosclerosis, low and oscillatory WSS is in general atherogenic, by stimulating endothelial cell mechanoreceptors and eliciting a network of intracellular cascades to trigger overexpression of pro-atherosclerotic genes, while high WSS may have an anti-atherosclerosis effect by reducing endothelial cell counts and converting contractile to synthetic phenotype of smooth muscle cells.[55 57] With plaque growth, however, both high and

low WSS have been reported to be associated with higher or increasing plaque vulnerability.[55] For instance, ulceration and some vulnerability-related components, such as macrophages and matrix metalloproteinase-9, mostly colocalise at the upstream of coronary and carotid plaques, where the WSS is in average higher than that in the downstream regions.[56] Moreover, positive (outward) remodelling, another feature of vulnerable plaques, has been observed more commonly in coronary arterial segments with high WSS, which may be accompanied by regression in the luminal stenosis.[58] However, there were also studies indicating that low WSS may promote the transformation to vulnerable phenotypes in CAD, with an increasing necrotic core and dense calcium.[59]

Yet, relevant research in ICAD has been limited, due to the lack of mature, non-invasive imaging methods to quantify focal haemodynamic metrics adjacent to the lesion. CFD modelling based on neurovascular imaging may be a promising tool in such investigations, which can quantify WSS and other focal haemodynamic metrics in ICAD. In CFD studies in sICAS, elevated WSS upon the plaque was associated with multiple cortical infarcts or territorial infarcts that indicates artery-to-artery embolism,[60] which was also associated with a higher risk of same-territory stroke recurrence despite medical treatment as mentioned above.[9] Therefore, similar to the findings in coronary and carotid arteries, high WSS may also be associated with a higher plaque vulnerability and higher tendency to rupture in sICAS. In addition, in a study conducted in patients with 50%–99% sICAS, higher WSS at the stenotic throat and throughout the sICAS lesion as quantified in CFD models was associated with regression in the luminal stenosis under contemporarily optimal medical treatment.[61] Although no vessel wall imaging was employed in the study to reveal the arterial remodelling patterns, we may speculate that there may be positive remodelling in the lesions with regressed luminal stenosis, which needs verification in future studies.

The studies above further demonstrate the importance of haemodynamics in governing the vulnerability and evolution of ICAD/ICAS lesions, which in the meantime also put forward more questions to be answered, for example, over the complex relationships of WSS with plaque vulnerability and evolution. These questions could be answered with further advances in the CFD technology and in combination with other imaging methods (eg, vessel wall MR imaging), to reveal a clearer picture of ICAD evolution under current treatment regimens and to provoke explorations of more personalised treatments based on the findings.

Haemodynamics and blood pressure management in sICAS

BP control is an essential part of secondary stroke prevention in patients with sICAS. The latest guidelines for secondary stroke prevention recommend a goal of BP of <140/90 mm Hg for patients with sICAS of 50%–99% stenosis.[62] However, the relationships between long-term BP levels and risk of recurrent stroke in sICAS may be altered by the cerebral perfusion status. For instance, long-term systolic blood pressure (SBP) <130 mm Hg may increase the risk of ipsilateral stroke recurrence in sICAS with impaired cerebral perfusion in PET, with significant SBP-impaired cerebral perfusion interaction on the stroke risk (p for interaction <0.01).[63 64] More recently, post hoc analysis of the VERiTAS study demonstrates an association between BP <140/90 mm Hg during follow-up and an increased risk of subsequent stroke, among patients with haemodynamically compromised (by QMRA), symptomatic, vertebrobasilar artery stenosis.[65] In another study using a CTA-based CFD model to quantify cerebral haemodynamics in sICAS, the translesional PG altered the relationship between SBP during follow-up and the risk of stroke recurrence; when lower SBP during follow-up was associated with a reduced risk of same-territory stroke recurrence in patients with sICAS with a small translesional PG, but an increased risk in those with a large translesional PG (reflecting reduced antegrade flow).[66]

Impaired cerebral autoregulation in patients with stroke and ICAS, when cerebral perfusion may be further reduced with lower BP levels, may underlie such findings. We therefore may need more individualised BP management strategies for secondary stroke prevention in patients with sICAS. Indeed, 'determining the interaction between haemodynamic function and BP management' has been listed as one of the future research priorities in sICAS, in the 2021 American Heart Association/American Stroke Association secondary stroke prevention guideline.[62]

CONCLUSIONS AND FUTURE DIRECTIONS

In this review article, we have provided an overview of the principles and applications of imaging modalities/methods to quantify cerebral haemodynamics in ICAD/ICAS, for example, cerebral perfusion metrics, pressure and WSS. More importantly, we have also highlighted the significance of haemodynamic features of sICAS, in governing lesion evolution and risk of stroke recurrence, driving collateral recruitment and affecting BP management strategies in secondary stroke prevention in patients with sICAS.

Despite the clinical implications of cerebral haemodynamics in sICAS, some of the imaging methods reviewed in this article are not yet widely available in clinical practice, for example, QMRA and CFD modelling that are mostly used in research studies. Moreover, there is no consensus on the selection of certain imaging methods/metrics in assessing different aspects in haemodynamics in ICAD/ICAS, or in different clinical scenarios. Furthermore, there are numerous unanswered questions that are discussed with more details in the sections above and summarised as follows, answers of which may extend the applications of these imaging methods in clinical practice in the near future.

First, more studies are needed to establish or validate the thresholds/cut-off values to define hypoperfusion or haemodynamic impairment downstream to ICAS, for example, in CT/MR perfusion imaging, SIR in TOF-MRA, fractional flow by Pd/Pa from cerebral angiography and translesional PR from CFD models. The agreement between different imaging methods also needs to be verified, for larger-scale investigations and generalisation of relevant findings in the near future. Second, stroke in ICAD can be caused by a spectrum of diverse mechanisms, which may carry different stroke risks.[7] On top of the prognostic values of cerebral haemodynamic metrics provided by these imaging/computational methods, more studies are needed to further reveal the role of cerebral haemodynamics in governing the stroke mechanisms, which may explain its association with the stroke risks and facilitate stroke mechanism-based, more individualised treatment. In such studies, a combination of imaging methods from different perspectives could provide a more integrated picture of the plaque characteristics and haemodynamics in ICAD, and their interactions, which will provide evidence for more accurate risk stratification of affected patients. Third, ICAD as a dynamic disease, the evolution of the lesion, the cerebral haemodynamic features and the collateral circulation, etc, need to be delineated by serial neurovascular imaging examinations and/or computational methods. More studies are needed to reveal the underlying mechanisms and modifiable factors for different evolution patterns, to provide novel therapeutic targets for primary and secondary stroke prevention in affected patients.

Contributors YL, XT and XL contributed to the concept of the manuscript. YL, SL and XL drafted the manuscript. TWL, LL and DSL provided critical comments/revisions of the manuscript.

Funding This work was supported by the General Research Fund (Reference Number 14106019) and Early Career Scheme (Reference Number 24103122), Research Grants Council of Hong Kong; Kwok Tak Seng Centre for Stroke Research and Intervention; and Li Ka Shing Institute of Health Sciences.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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