Effects of collateral circulation on haemodynamic flow status in intracranial artery stenosis depicted by computational fluid dynamics

TWH Leung *, SY Fan, HL Ip, AYL Lau, DYW Siu, EYL Dai, LKS Wong, DS Liebeskind

KEY MESSAGES

1. Risk of stroke recurrence is not solely affected by the degree of anatomical stenosis.
2. Haemodynamic changes across the stenosed vessel are as important as the degree of luminal narrowing in terms of implication on stroke risk.
3. Studying haemodynamic changes in the cerebral circulation is feasible with computational fluid dynamics technique coupling to various imaging modalities, including computed tomographic angiography.

Hong Kong Med J 2019;25(Suppl 5):S18-21
HMRF project number: 01120466

TWH Leung, SY Fan, HL Ip, AYL Lau, DYW Siu, EYL Dai, LKS Wong, DS Liebeskind

Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong

* Principal applicant and corresponding author: drtleung@cuhk.edu.hk

Introduction

Intracranial atherosclerotic steno-occlusive disease (ICAS) is a major cause of stroke. Stroke results in significant morbidity and mortality. In Hong Kong, stroke has been the commonest cause of permanent disability in adulthood and the fourth leading cause of death in the past 10 years. Although there are a lot of studies on effective means to reduce stroke incidence and improve stroke outcome in ICAS, remarkable progress is yet to be seen. One key element of successful intervention is to identify patients most vulnerable to stroke relapse and in need of timely adjunctive treatments.

In ICAS, the degree of arterial stenosis is predictive of stroke risk. In the Warfarin-Aspirin Symptomatic Intracranial Disease trial, the 1-year stroke risk for patients with symptomatic ICAS of ≥70% was up to 18%. Yet, emerging evidence showed that the degree of arterial stenosis may not be the only factor governing stroke risk. Other factors, particularly those that impact on the haemodynamics across ICAS, including the extent of collateralisation[1] and plaque morphology, may play a role.

The novel technique of computational fluid dynamics (CFD), coupled with various angiographic modalities, enables assessment of haemodynamics in the cerebral circulation.

We aimed to measure the haemodynamic parameters of a symptomatic high-grade intracranial stenosis in a CFD model derived from computed tomographic angiography (CTA), and correlated these factors to the extent of collateralisation as depicted by digital subtraction angiography (DSA) in patients with symptomatic ICAS. We aimed to explore the feasibility and potential of coupling of CFD technique to CTA as a non-invasive means to assess anatomical and functional severity of ICAS.

Methods

We recruited patients from the neurovascular intervention registry in the Division of Neurology, Department of Medicine and Therapeutics, Prince of Wales Hospital from November 2006 to June 2012. These ischaemic stroke patients were aged 18 to 80 years and underwent both DSA and CTA within 1 month of stroke as part of vascular workup. Patients were eligible if DSA confirmed a stenotic lesion of ≥50% in a relevant intracranial large artery. Patients were excluded if they had (1) suspected non-atherosclerotic ICAS such as vasculitis, dissections or Moya-Moya disease, (2) suspected cardioembolic stroke, (3) prior intervention or surgical procedures in intra- or extra-cranial ICAS, or (4) DSA or CTA examinations performed in other hospitals where source data could not be retrieved.

We recorded the baseline demographics, neurological status, and risk factor profile of the patients. These included gender, age, blood pressure, fasting blood glucose level, glycated haemoglobin level and lipid profile on presentation; prior medical history of diabetes mellitus, dyslipidaemia, prior history of ischaemic heart disease and peripheral vascular disease, prior history of stroke and transient ischaemic attacks, smoking and drinking history, baseline NIH Stroke Scale and modified Rankin score on presentation.

Relevant arterial stenosis on DSA was measured based on the Warfarin-Aspirin

Symptomatic Intracranial Disease Trial. The extent of collateralisation was assessed based on the American Society of Interventional and Therapeutic Neuroradiology collateral flow grading system.[2] Grade 0 or 1 is regarded as poor collateral flow, and grade 2 or above is regarded as good collateral flow.

The arterial segment with the relevant symptomatic ICAS was visually identified and selected on CTA images. The source images were used for construction of simulated model using commercially available software and programs, including ANSYS ICEM-CFD (ANSYS Inc), ANSYS CFX software, and Cray CX1 cluster (Cray Inc) program.

Simulated models were analysed using CFD techniques. The ANSYS CFX-post software was used for extraction and evaluation of haemodynamic parameters. For each symptomatic ICAS, haemodynamic parameters across the lesion were evaluated, including pressure difference, pressure ratio, pressure gradient, shear strain rate (SSR) ratio, wall shear stress (WSS) ratio, and velocity ratio (Fig).

The baseline demographics and risk factors were summarised with their means and prevalence in the cohort presented. For modified Rankin score and National Institute of Health Stroke Score were non-parametric variables and thus median and interquartile ranges were presented. The haemodynamic parameters demonstrated skewed distribution upon testing for normality with the Kolmogorov-Smirnov test, so their median and interquartile ranges were presented. Spearman's correlation test was used to explore the correlation between the haemodynamic parameters and the extent of collateralisation. Two-sided P values of <0.05 were considered statistically significant. Linear regression technique was used to adjust for the effects of age, blood pressure, and glucose level.

Results

A total of 55 patients were recruited. Three patients had outlying values in the haemodynamic parameters in the post-processed CFD models and were excluded from analysis. The demographic characteristics and risk factor profiles of the remaining 52 patients are shown in Table 1.

The mean of arterial stenosis was 75.1%. 46 (88.5%) patients had ICAS in anterior circulation; four lesions were in internal carotid arteries and 42 lesions were in middle cerebral arteries. Six patients had ICAS over intracranial segments of

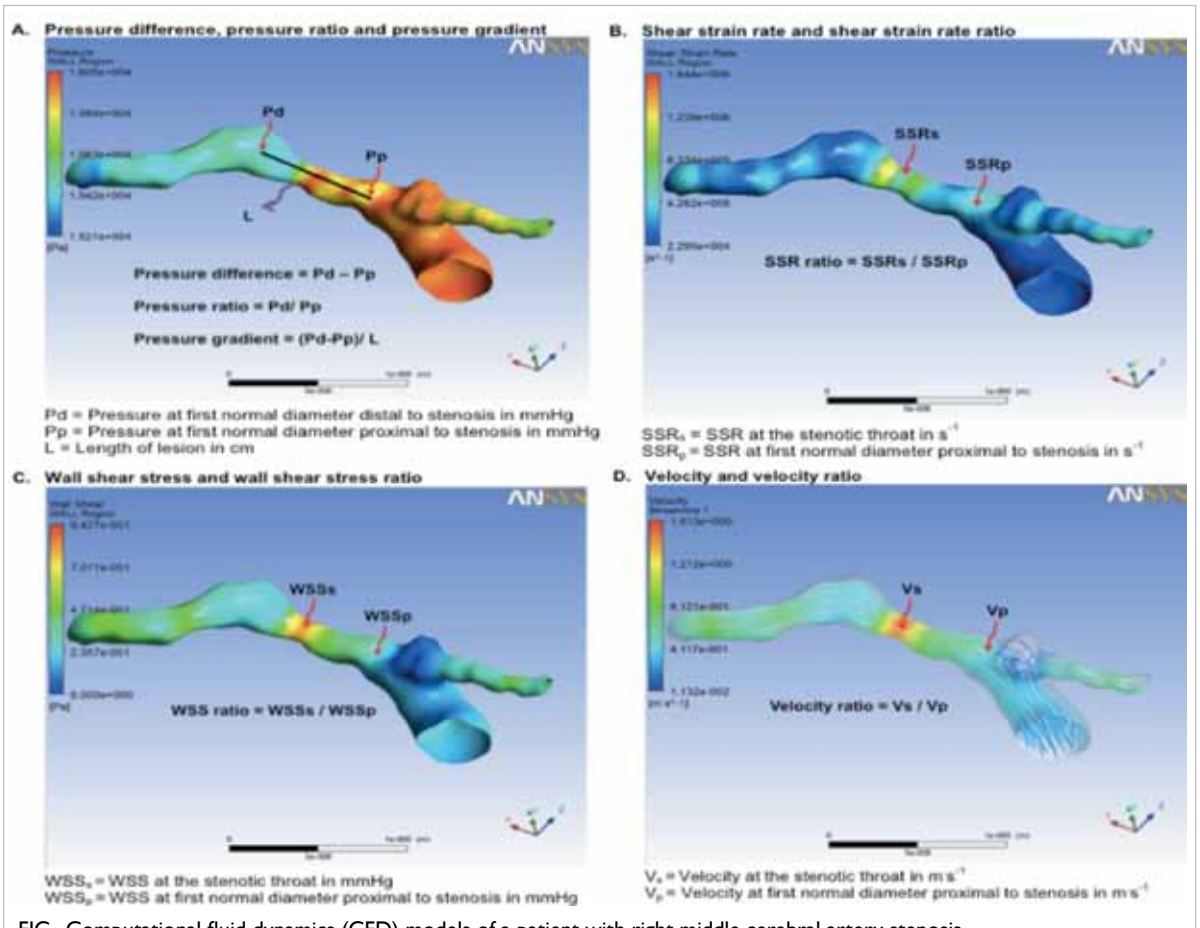

FIG. Computational fluid dynamics (CFD) models of a patient with right middle cerebral artery stenosis

vertebrobasilar arteries.

The extent of collateralisation showed weak but significant correlations with pressure difference (r_s= -0.28, P=0.04), pressure ratio (r_s=0.31, P=0.03), and pressure gradient (r_s= -0.29, P=0.03) [Table 2]. After adjustments for age, blood pressure, and glucose level, the correlations became insignificant. No correlation was found with SSR ratio, WSS ratio, or velocity ratio, or among patients with symptomatic lesions in anterior circulation or posterior circulation, or with moderate (50%-69% stenosis) or severe (70%-99% stenosis) ICAS.

TABLE 1. Baseline demographics of 52 patient

Characteristic	Value*
Age, y	63.2±10.5
Male	37 (67.3)
History of hypertension	40 (76.9)
History of diabetes mellitus	17 (32.7)
History of hyperlipidaemia	48 (92.3)
History of ischaemic heart disease or peripheral vascular disease	0
History of stroke or transient ischaemic attack	13 (25)
Smoking history	21 (40.4)
Drinking history	7 (13.5)
National Institute of Health Stroke score	2 (1-3)
Modified Rankin score	1 (1-2)
Systolic blood pressure, mmHg	162.6±25.6
Diastolic blood pressure, mmHg	86.8±15.2
Low density lipoprotein-cholesterol, mmol/L	3.6±1.1
Triglycerides, mmol/L	1.5±0.7
High density lipoprotein-cholesterol, mmol/L	1.2±0.3
Fasting glucose, mmol/L	6.5±2.5
Glycated haemoglobin, %	6.4±1.6

* Data are presented as mean ± standard deviation, No. (%) of patients, or median (range)

Discussion

Pressure ratio and pressure gradients reflect the more 'static' aspect of the haemodynamics across ICAS, whereas the SSR ratio, WSS ratio, and velocity ratio reflect the more 'dynamic' aspect of it. Shear strain rate of blood flow reflects the spatial gradient of flow velocity. To understand such concept, the blood volume inside the vessel should be considered as many thin layers of blood flow. SSR refers to the relative changes of flow velocity between these infinitesimally thin layers of blood flow. Turbulent flow at the stenotic throat increases the relative flow velocities between the layers and leads to increased SSR. WSS of blood flow reflects flow induced stress and can be conceptualised as frictional force of viscous blood. Turbulent blood flow across the stenotic lesion increases the wall shear stress. Therefore, the ratio of SSR, WSS, and velocity at the stenotic throat and the proximal normal segment of vessel were examined to reflect the haemodynamic changes.

From our study, the extent of collateralisation showed weak correlation with pressure difference, pressure ratio, and pressure gradient, such correlation became insignificant after adjustments for age, blood pressure, and glucose level. There were no correlations with SSR ratio, WSS ratio, and velocity ratio.

The presence of multiple cardiovascular risk factors (hypertension, diabetes, and hyperlipidaemia) promotes the formation of an atherosclerotic plaque in a vessel. Plaque formation results in narrowing of the vessel lumen and disturbs the normal laminar blood flow. During an acute ischaemic event, blood flow across the diseased vessel is disturbed and reduced, leading to a pressure drop downstream. Such a pressure drop leads to collateral circulation by

TABLE 2. Correlations between the extent of collateralisation and various haemodynamic parameters

	Correlations between the extent of collateralisation and											
	Pressure difference		Pressure ratio		Pressure gradient		Shear strain rate ratio		Wall shear stress ratio		Velocity ratio	
	r_s	P value	r_s	P value	r_s	P value	r_s	P value	r_s	P value	r_s	P value
Entire cohort	-0.28	0.04	0.31	0.03	-0.29	0.03	-0.01	0.95	-0.13	0.37	-0.17	0.24
Entire cohort (adjusted for age, blood pressure and glucose level)	-0.11	0.49	0.11	0.46	-0.17	0.26	-0.16	0.28	-0.05	0.73	-0.12	0.41
Anterior circulation stroke/ transient ischaemic attack	-0.22	0.14	0.25	0.1	-0.24	0.1	0.03	0.85	-0.14	0.36	-0.12	0.42
Posterior circulation stroke/ transient ischaemic attack	-0.62	0.19	0.62	0.19	-0.63	0.18	-0.21	0.69	-0.41	0.41	-0.62	0.19
50%-69% stenosis	-0.25	0.36	0.31	0.24	-0.16	0.54	-0.53*	0.03	-0.16	0.54	-0.29	0.28
70%-99% stenosis	0.11	0.53	-0.12	0.51	0.08	0.63	0.14	0.42	0.04	0.81	0.12	0.48

activating the endothelium and stimulating a cascade of signalling events, involving a number of cytokines release and inflammatory cells. The process was known as arteriogenesis.[3] Such process can occur within hours of an acute event and remain active weeks to months afterwards. The interplay between collateral flow and arterial occlusion is complicated. Study correlating collateral flow status with the haemodynamics across ICAS was scarce and yielded conflicting results. On the one hand, in an acute event, good collateral circulation was associated with less severe stroke and better stroke outcome. It was also associated with better clinical response and lower rate of haemorrhagic transformation during thrombolysis and recanalisation therapies. On the other hand, in patients with chronic arterial stenosis, the recruitment of collateral flow often signifies severe stenotic lesions compromising flow downstream, therefore implying higher risk of stroke. Thus, the age of the lesion and the timing of imaging of collateral flow impact on the assessment and interpretation of the effect of collateral flow on haemodynamics across ICAS. This may contribute to the largely negative findings in our current study.

CTA is a useful tool for anatomical and functional assessments of ICAS when coupled to CFD techniques. Being non-invasive and more widely available, it is more acceptable by patients, physicians, and researchers in the field to investigate the hidden haemodynamic aspect of ICAS. More studies are needed to determine the effect of collateralisation on haemodynamics of ICAS, the correlation between different haemodynamic parameters and risk of recurrent stroke and clinical outcome. This may revolutionise and rationalise our management on stroke patients in the near future. With better understanding on the haemodynamic characteristics in ICAS, selection of patients with high risk of stroke recurrence for more aggressive treatments could be facilitated. The financial and social burdens of stroke could thus be minimised.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#01120466). We thank the hard work and dedicated support from the medical and research teams of the Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong.

References

1. Liebeskind DS, Cotsonis GA, Saver JL, et al. Collaterals dramatically alter stroke risk in intracranial atherosclerosis. Ann Neurol 2011;69:963-74.
2. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke 2013;44:2650-63.
3. Liu J, Wang Y, Akamatsu Y, et al. Vascular remodeling after ischemic stroke: mechanisms and therapeutic potentials. Prog Neurobiol 2014;115:138-56.