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Sustaining cerebral perfusion in intracranial atherosclerotic stenosis: The roles of antegrade residual flow and leptomeningeal collateral flow

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Abstract

We aimed to investigate the roles of antegrade residual flow and leptomeningeal collateral flow in sustaining cerebral perfusion distal to an intracranial atherosclerotic stenosis (ICAS). Patients with apparently normal cerebral perfusion distal to a symptomatic middle cerebral artery (MCA)-M1 stenosis were enrolled. Computational fluid dynamics models were built based on CT angiography to obtain a translesional pressure ratio (PR) to gauge the residual antegrade flow. Leptomeningeal collaterals (LMCs) were scaled on CT angiography. Cerebral perfusion metrics were obtained in CT perfusion maps. Among 83 patients, linear regression analyses revealed that both translesional PR and LMC scale were independently associated with relative ipsilesional mean transit time (rMTT). Subgroup analyses showed that ipsilesional rMTT was significantly associated with translesional PR ($p < 0.001$) rather than LMC scale in those with a moderate (50–69%) MCA stenosis, which, however, was only significantly associated with LMC scale ($p = 0.051$) in those with a severe (70–99%) stenosis. Antegrade residual flow and leptomeningeal collateral flow have complementary effects in sustaining cerebral perfusion distal to an ICAS, while cerebral perfusion may rely more on the collateral circulation in those with a severe stenosis.

Keywords

Cerebral perfusion, intracranial atherosclerotic stenosis, antegrade flow, collateral circulation, computational fluid dynamics

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Introduction

Intracranial atherosclerotic stenosis (ICAS) is a leading cause for ischemic stroke and transient ischemic attack (TIA) in Asian populations, accounting for 30–50% of ischemic strokes in Asia.[1,2] Hypoperfusion could be a common mechanism in ischemic strokes attributed to ICAS.[3] Moreover, those with impaired cerebral perfusion distal to symptomatic ICAS may have a higher risk of ipsilateral stroke recurrence.[4] Robust collateral circulation may alleviate or even revert the perfusion deficits caused by ICAS; hence, a considerable proportion of ICAS patients have apparently normal distal perfusion despite of the stenotic lesion that restricts

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antegrade cerebral blood flow. However, there may be interactions between the severity of luminal stenosis and the collateral status on the risk of recurrent stroke in patients with symptomatic ICAS. According to the retrospective analysis of the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial data, good collaterals were a protective factor against ipsilateral stroke recurrence in patients with a severe (70–99%) ICAS, but a risk factor for recurrent stroke in those with a moderate (50–69%) ICAS.[5] Mechanisms underlying the increased risk of recurrent stroke in moderate ICAS patients with good collaterals were unclear. It was speculated that presence of good collaterals may identify a subgroup of moderately luminal-narrowing but significantly flow-limiting ICAS lesions, which thus yield higher risk of recurrent stroke than otherwise.[5]

Therefore, there may exist complex inter-correlations between antegrade blood flow across the stenotic lesion, leptomeningeal collateral (LMC) flow, and cerebral perfusion in the arterial territory distal to an ICAS lesion, which have not been fully elucidated. In the current study, we preliminarily investigated such correlations in ICAS patients with apparently normal cerebral perfusion. We studied the roles of antegrade residual flow and LMC flow, in addition to conventional demographic and clinical factors, in governing the mean transit time (MTT) of blood flow in the middle cerebral artery (MCA) territory with sustained cerebral perfusion despite a symptomatic MCA stenosis.

Methods

Study design and subjects

This was a cross-sectional study, approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee, Hong Kong SAR, China, which was conducted according to the principles of Declaration of Helsinki. All participants provided informed consent. We recruited adult patients with acute ischemic stroke or TIA admitted to Prince of Wales Hospital, Hong Kong, from October 2006 to January 2016, based on the following inclusion criteria: (1) the index ischemic event was attributed to atherosclerotic stenosis (50–99%) of M1 segment of MCA (MCA-M1) as confirmed on CT angiography (CTA); (2) the cerebral perfusion status in the ipsilesional MCA territory was apparently normal, i.e. comparable to the contralateral side, defined as a relative difference in cerebral blood flow (CBF) $\leq 30\%$ between bilateral MCA territories on CT perfusion (CTP) maps; (3) the CTA/CTP exam was conducted within one month of stroke/TIA onset; (4) the patient provided informed consent. Patients were excluded if (1) the index ischemic event was attributed to non-atherosclerotic intracranial stenosis (e.g. Moyamoya disease, vasculitis or dissection); (2) there was evidence of possible cardioembolic stroke (e.g. atrial fibrillation); (3) there was known arterio-venous malformation or aneurysm; or (4) there was previous interventional or surgical procedures in ipsilesional extra- or intracranial arteries.

Demographics and the following medical histories of patients recruited were collected: smoking and drinking habits, histories of hypertension, diabetes, dyslipidemia, prior ischemic stroke or TIA, and prior ischemic heart disease. Blood pressure and neurological severity of the index ischemic stroke by National Institutes of Health Stroke Scale (NIHSS) were also collected at admission. The results of laboratory tests were retrieved during hospitalization. Anatomic severity of the qualifying MCA stenotic lesions was assessed on CTA images by radiologists using the WASID method, and further categorized into moderate (50–69%) and severe (70–99%) stenoses. We used a computational fluid dynamics (CFD) model based on routine CTA images to simulate CBF across an MCA stenotic lesion and obtain a translesional pressure ratio (PR), which could quantitatively reflect the residual antegrade flow diminished by the stenotic lesion.[6–9] The LMC status was graded on CTA. Cerebral perfusion metrics in bilateral MCA territories were measured on CTP maps. The correlations between these parameters were analyzed in univariate and multivariate analyses, among all patients recruited or in subgroups of patients with moderate or severe MCA stenoses.

Multimodel CT exam

All patients underwent a routine multimodal CT brain exam, including pre-contrast CT scan, CTA, and CTP. All CT exams were performed on a 64-slice CT scanner (Lightspeed VCT, GE Healthcare, USA). For CTA, intravenous contrast (Omnipaque 300) was injected via the antecubital vein at a rate of 3–3.5 ml/s with a total volume of 70 ml, and images were obtained with 120 kVp, 550 mAs, 0.625 mm slice thickness and 0.4 s rotation. For CTP, 50 mL of Iopamiro 300 was injected intravenously at a rate of 4 ml/s. The scan was performed with the following parameters: 80 kVp, 200 mAs, 250 mm field of view, and 5 mm slice thickness.

CFD modeling and assessment of antegrade residual flow

One investigator (LL) built CFD models based on CTA source images and measured the translesional PR across MCA lesions blinded to clinical information, using the ANSYS software package (ANSYS, Inc., Canonsburg, PA, USA) on a DELL Precision T7610

Workstation. The inter-rater reproducibility of CFD modeling and translesional PR assessment was tested between two investigators (LL and XL) in 14 cases in a previous study, when inter-rater agreement (an absolute difference in translesional PR ≤ 0.05) was achieved in 12 (85.7%) cases.[10]

Major procedures of CFD modeling in ICAS were as follows: (1) Three-dimensional geometry of ipsilesional terminal internal carotid artery (ICA), MCA-M1, and A1 segment of anterior cerebral artery (ACA) was extracted from CTA source images. (2) A mesh was then created on the vessel wall and lumen in ANSYS ICEM CFD, with the maximal element sizes of 0.1 for the ICA inlet and MCA/ACA outlet surfaces and 0.25 for other parts. The total number of tetrahedral cells was more than 0.5 million in each case. (3) Generic boundary conditions and properties of blood flow were applied on the mesh in ANSYS CFX-pre: a mean pressure of 110 mmHg was applied at the ICA inlet; mass flow rates were applied at the MCA and ACA outlets, estimated based on mean flow velocities of the elderly from a population-based study;[11] the arterial wall was assumed rigid, with a no-slip condition; and the blood was assumed as an incompressible Newtonian fluid with a constant viscosity of $0.0035\,kg{\cdot}m^{-1}{\cdot}s^{-1}$ and a density of $1060\,kg{\cdot}m^{-3}$. (4) Steady-state blood flow simulation was fulfilled by solving the Navier–Stokes equations in ANSYS CFX; convergence was achieved when the root mean square residual value reached below 10^{-4}. More detailed CFD modeling procedures have been described in our recent review article.[12]

Hemodynamic characteristics of the symptomatic MCA stenotic lesions in the CFD models were assessed in ANSYS CFD-post. We used a translesional PR $\left(\text{Transleisonal } PR = \frac{\text{Post}-\text{stenotic pressure}}{\text{Pre}-\text{stenotic pressure}}\right)$ to quantitatively reflect the antegrade fractional or residual flow in the presence of MCA stenosis, irrespective of the collateral status and other systemic conditions.[13] The post-stenotic pressure was measured at the first normal diameter of MCA distal to the stenotic lesion, and the pre-stenotic pressure was measured at terminal ICA. A smaller translesional PR means a larger translesional pressure drop, which reflects reduced antegrade flow restricted by the MCA stenotic lesion.

Assessment of LMCs

Two investigators (LL, XL) independently graded the extent of LMCs blinded to clinical information, by defining the laterality of bilateral ACAs and posterior cerebral arteries (PCA) on two-dimensional, axial and coronal reconstructions of CTA with 20-mm-thick slabs and 0.625 mm increment in OsiriX (Version 8.0.1, Pixmeo, Switzerland). LMC graded with this method had been proved significantly correlated with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral scale.[14] The extent of ipsilesional ACA pials was scaled as 0, 1, or 2, when the distal pials in ipsilesional ACA territory was less than, equal to, or more prominent than the contralateral side. The extent of ipsilesional PCA pials was scaled similarly (examples shown in Figure 3). We summed up the ACA and PCA pial scores to represent the overall extent of ipsilesional LMCs (scores 0–4) and defined good and poor LMC status by scores 3–4 and 0–2, respectively. Any disagreement between the two investigators was resolved by consensus. It should be noted that the ACA/PCA laterality grading method was a measure of collateral recruitment rather than collateral filling, so "poor LMC" as defined in the current study referred to no or poor LMC recruitment from ipsilesional ACA/PCA, rather than flow limitation to the MCA territory.

Assessment of cerebral perfusion

CTP imaging was processed using a delay-insensitive deconvolution algorithm and the perfusion metrics were measured in CT perfusion 4.0 (GE Healthcare, USA) as previously described.[15,16] Absolute values of CBF and MTT in bilateral MCA territories were measured at the basal ganglia level, by drawing symmetrical regions of interest in the two hemispheres on perfusion maps. Any region of old or new infarct was excluded from such measurement. Relative CBF (rCBF) of ipsilesional MCA territory was calculated as the ratio of ipsilesional and contralesional absolute CBF values. Relative MTT (rMTT) was calculated similarly.

Statistical analysis

Data are presented as means ± standard deviation, medians (interquartile range, IQR) or numbers (percentage). Continuous or categorical variables were compared between two groups by independent t tests, Mann–Whitney tests, or Chi-square tests. The correlations between translesional PR and rMTT, and between LMC score and rMTT, were analyzed using Pearson correlation coefficients. Univariate and multivariate linear regression models were used to identify independent predictors for rMTT in overall subjects, and in subgroups of subjects with moderate or severe MCA stenoses. Variables with a p value <0.1 in univariate analysis were put in multivariate linear regression models. The percent luminal stenosis was not included in the multivariate linear regression models due to its significant collinearity with translesional

PR. All analyses were performed using IBM SPSS software (Version 20.0). Two side $p \leq 0.05$ was considered statistically significant.

Results

Clinical and imaging characteristics

Among 106 patients with apparently normal cerebral perfusion distal to a symptomatic, atherosclerotic stenosis of MCA-M1 who had CTA/CTP exam within 1 month of stroke or TIA onset, 18 were excluded due to poor image quality or complex vessel geometry that did not allow vessel geometry reconstruction for CFD modeling, and 5 were excluded due to poor image quality that did not allow collateral assessment (Supplemental Figure I). Thus, 83 patients were analyzed in the current study. The mean age was 61 ± 11 years, and 69.9% were male. Twenty-two patients had TIA and 61 had ischemic stroke as the index cerebral ischemic event. The median interval from symptom onset to the multimodel CT exam was seven (IQR 4–16) days. Detailed characteristics of the patients are presented in Table 1.

Table 1. Baseline patient characteristics.

Patient characteristics	Overall (N = 83)
Age, years	61.4 ± 11.0
Male	58 (69.9)
TIA	22 (26.5)
NIHSS at admission	3 (1–4)
History of smoking	34 (41.0)
History of hypertension	54 (65.1)
History of diabetes mellitus	26 (31.3)
History of dyslipidemia	50 (60.2)
Prior ischemic stroke or TIA	17 (20.5)
Prior ischemic heart disease	4 (4.8)
Systolic blood pressure at admission, mmHg	159.2 ± 29.9
Diastolic blood pressure at admission, mmHg	89.6 ± 17.0
Laboratory test results	
Fasting glucose, mmol/L	6.22 ± 2.12
Triglycerides, mmol/L	1.54 ± 0.95
High-density lipoprotein, mmol/L	1.25 ± 0.44
Low-density lipoprotein, mmol/L	3.21 ± 1.16
Imaging characteristics	
Interval from onset to multimodal CT exam, days	7 (4–16)
Percentage of MCA-M1 luminal stenosis, %	64 (56–70)
Severe (70–99%) MCA-M1 stenosis	29 (34.9)
Translesional PR	0.92 (0.87–0.96)
LMC score	2 (2–3)
Good LMC status	35 (42.2)
CTP measures in ipsilesional MCA territory as relative to the contralateral side	
rCBF	1.00 ± 0.15
rMTT	1.06 ± 0.10

Note: Values are means ± SD, medians (IQR) or numbers (%).
TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale; MCA-M1: M1 segment of middle cerebral artery; PR: pressure ratio; LMC: leptomeningeal collateral; CTP: CT perfusion; rMTT: relative mean transit time; rCBF: relative cerebral blood flow.

Overall, there were 54 (65.1%) patients with a moderate MCA-M1 stenosis and 29 (34.9%) with a severe stenosis. Patients with severe stenosis had significantly lower translesional PR than those with moderate stenosis (0.79 ± 0.23 vs. 0.90 ± 0.11, $p = 0.015$). Figure 1 shows a trend of lowered translesional PR values with an increased severity of luminal stenosis. Forty-eight (57.8%) patients had poor ipsilesional LMC status and 35 (42.2%) had good LMCs. Patients with severe MCA-M1 stenosis were more likely to have good LMC status than those with moderate stenosis (56.7% vs. 34.5%, $p = 0.079$).

The roles of antegrade residual flow and collateral circulation in determining MTT in ipsilesional MCA territory

The mean rCBF in ipsilesional MCA territory was 1.00 ± 0.15, and the mean ipsilesional rMTT was

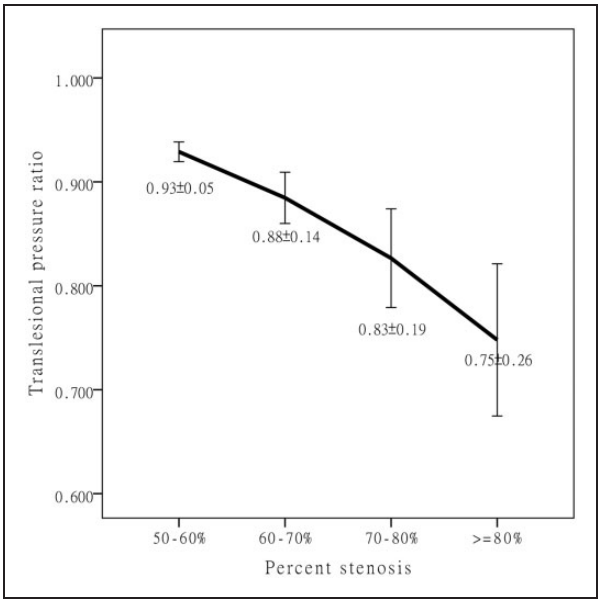

Figure 1. Mean translesional pressure ratios in patient subgroups with different severities of luminal stenosis in MCA-M1.

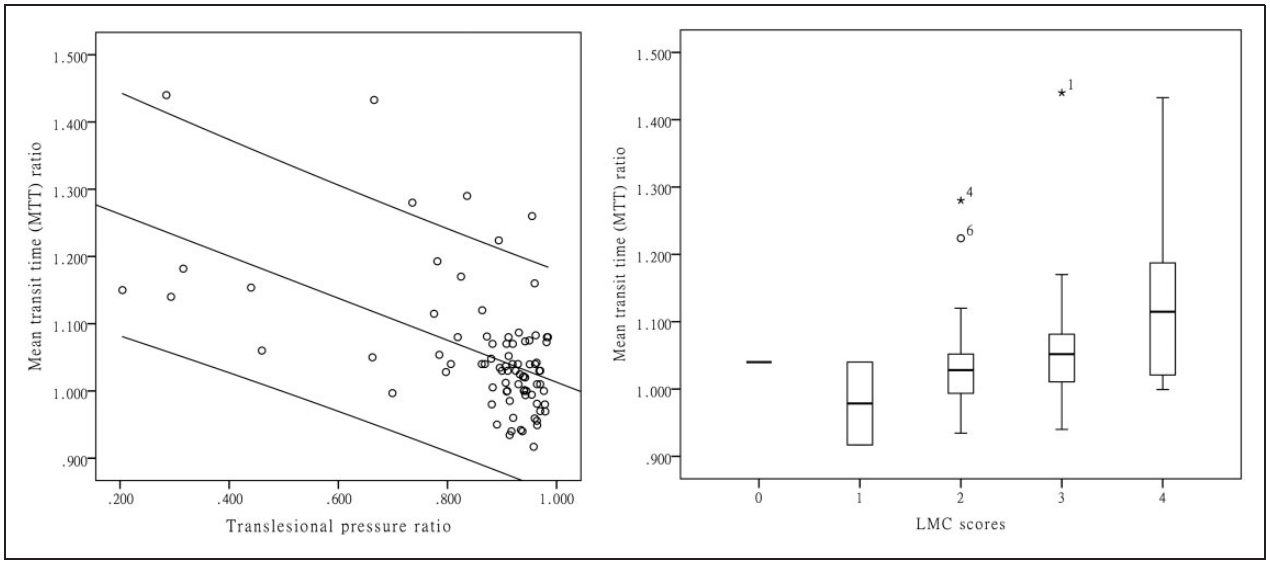

Figure 2. Scatterplots showing the correlation between translesional pressure ratio and rMTT (left panel), and the correlation between LMC scores and rMTT (right panel), among all patients recruited. rMTT increased with a smaller translesional pressure ratio (i.e. a larger translesional pressure drop), and with more prominent LMCs.
LMC: leptomeningeal collateral; rMTT: ratio of mean transit time in hemispheres ipsilateral and contralateral to the qualifying intracranial stenotic lesion.

1.06 ± 0.10. Univariate linear regression indicated that the percentage of MCA luminal stenosis ($p = 0.016$), translesional PR ($p < 0.001$) and LMC scores ($p < 0.001$) was significantly associated with ipsilesional rMTT. There was significant linear correlation between a lower translesional PR and a longer rMTT in ipsilesional MCA territory (Pearson correlation $r = -0.534$, $p < 0.001$), as well as between a better LMC status and a longer ipsilesional rMTT (Pearson correlation $r = 0.392$, $p < 0.001$; Figure 2). In addition, age ($p = 0.055$) also tended to correlate with rMTT (Table 2).

Further multiple linear regression in the overall cohort revealed that both translesional PR ($\beta = -0.257$, $p < 0.001$) and LMC scores ($\beta = 0.026$, $p = 0.018$) were independently associated with ipsilesional rMTT after adjusting for age (Table 2). Figure 3 shows a case (upper panel) with a low translesional PR across an MCA stenosis and a good ipsilateral LMC status, who had prolonged MTT but normal CBF in the ipsilesional MCA territory; and another case (lower panel) with a high translesional PR but poor LMC status, who had sustained CBF and normal MTT in the ipsilesional MCA territory.

Divergent effects of antegrade residual flow and LMC circulation on MTT in moderate and severe MCA stenoses

In the 54 patients with moderate MCA stenoses, univariate linear regression showed that both translesional PR ($\beta = -0.634$, $p < 0.001$) and LMC scores ($\beta = 0.037$, $p = 0.026$) were associated with ipsilesional rMTT. Further multivariate linear regression indicated that only translesional PR was independently associated with ipsilesional rMTT ($\beta = -0.605$, $p < 0.001$), while the LMC scores were not significantly related to rMTT ($\beta = 0.019$, $p = 0.109$). Among the 29 patients with severe MCA stenoses, univariate linear regression showed that translesional PR ($\beta = -0.165$, $p = 0.047$) and LMC scores ($\beta = 0.046$, $p = 0.013$) were associated with ipsilesional rMTT. However, in multivariate linear regression, only LMC scores ($\beta = 0.038$, $p = 0.051$), but not translesional PR ($\beta = -0.107$, $p = 0.192$), tended to independently relate with ipsilesional rMTT. Such findings indicated that cerebral perfusion distal to a moderate MCA stenosis might be more dependent on the antegrade residual flow, while LMC circulation might play a more important role in sustaining ipsilesional cerebral perfusion in patients with severe MCA stenosis.

Discussion

Among patients with apparently normal downstream perfusion despite a symptomatic MCA stenosis, we found that antegrade residual flow and LMC flow were independently associated with the MTT of blood flow in the ipsilesional MCA territory, which suggested their important roles in sustaining cerebral perfusion in such patients. More importantly, we found divergent effects of antegrade residual flow and LMC flow in governing ipsilesional MTT in subgroups of patients with moderate and severe MCA stenoses, when rMTT

Table 2. Univariate and multivariate linear regression analyses for independent predictors for rMTT of the MCA territory ipsilateral to an MCA-M1 stenosis.

Variables	β	*P*
Univariate linear regression		
Age	0.002	0.055
Gender	0.009	0.708
TIA as the index ischemic event	−0.011	0.652
Systolic blood pressure at admission	<0.001	0.911
Diastolic blood pressure at admission	<0.001	0.495
History of smoking	−0.006	0.796
History of drinking	0.048	0.160
History of hypertension	0.021	0.341
History of diabetes mellitus	−0.027	0.243
History of dyslipidemia	−0.018	0.408
Interval from onset to multimodal CT exam	−0.001	0.394
Percentage of MCA-M1 luminal stenosis	0.002	0.016
Translesional PR	−0.312	<0.001
LMC scores	0.044	<0.001
Multivariate linear regression		
In all subjects (N=83)		
Age	0.001	0.207
Translesional PR	−0.257	<0.001
LMC scores	0.026	0.018
In patients with moderate MCA-M1 stenosis ($n = 54$)		
Translesional pressure ratio	−0.605	<0.001
LMC scores	0.019	0.109
In patients with severe MCA-M1 stenosis ($n = 29$)		
Translesional pressure ratio	−0.107	0.192
LMC scores	0.038	0.051

rMTT: relative mean transit time; MCA: middle cerebral artery; TIA: transient ischemic attack; PR: pressure ratio; LMC: leptomeningeal collateral.

was more significantly associated with translesional PR (reflecting residual antegrade flow) in patients with moderate MCA stenoses but more significantly related to the LMC status in the presence of severe MCA stenoses. Such findings indicated that downstream cerebral perfusion depends more on antegrade residual flow in moderate MCA stenosis but more on LMC flow in severe MCA stenosis.

In patients with ischemic stroke and extra- or intra-cranial arterial occlusive disease, impaired cerebral perfusion was significantly associated with an increased risk of recurrent stroke, according to numerous studies conducted over the past two decades.[17–20] Understanding factors that govern cerebral perfusion in such occasions could provide therapeutic markers in secondary prevention of affected patients. There have been efforts exploring the roles of severity of cervico-cerebral arterial luminal stenosis and collateral circulation status in determining cerebral perfusion in relevant patients.[21–24] However, the residual antegrade flow (relying mostly on the geometric features of stenosis) and collateral status have seldom been investigated simultaneously for their independent correlations with cerebral perfusion metrics in patients with ICAS. In the current study, we used a translesional PR to gauge the antegrade residual flow across an arterial stenosis, when a smaller translesional PR indicated more significant flow-limiting effect of a stenotic lesion. In the meantime, we graded ipsilesional LMC flow by comparing the visibility and extent of distal pials in bilateral ACA and PCA territories. We demonstrated the complementary roles of antegrade residual flow and LMC flow in sustaining cerebral perfusion distal to a symptomatic ICAS lesion, with a comparable or prolonged perfusion time as compared with the contralateral side.

As mentioned above, opposite effects of good collateral circulation have been noted in the WASID

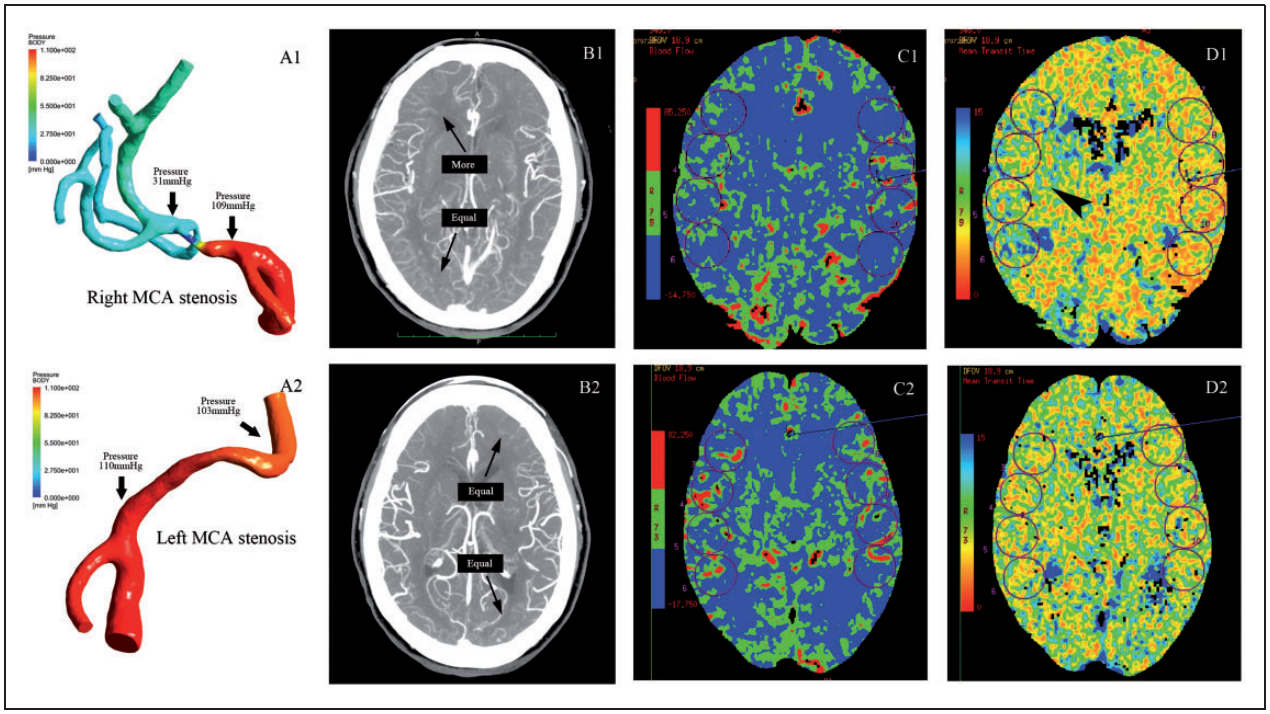

Figure 3. Illustration of the translesional PR, LMC and cerebral perfusion status in two patients with symptomatic MCA-M1 stenosis. Upper panel: sustained CBF but prolonged MTT in the territory distal to a 68% MCA stenosis, when there was severely restricted antegrade flow across the stenotic lesion but good ipsilesional leptomeningeal collaterals. (A1) A significant pressure drop across the stenosis as revealed in the CFD model, with a translesional pressure ratio of 0.285. (B1) More prominent pials in the ipsilesional ACA territory than the contralateral side and comparable pials in bilateral PCA territories in CTA images, with an ipsilesional LMC score of 3. (C1/D1) Comparable CBF (ipsilateral/contralateral CBF ratio 1.01) in bilateral MCA territories, but significantly prolonged MTT (arrow, ipsilateral/contralateral MTT ratio 1.44) in ipsilesional MCA territory in CTP maps. Lower panel: sustained CBF and normal MTT in the territory distal to a 50% MCA stenosis with slightly declined antegrade flow; comparable pial vessels were observed in the bilateral ACA and PCA territories. (A2) No significant pressure drop across the stenosis with a translesional pressure ratio of 0.936. (B2) Comparable pials in bilateral ACA and PCA territories, with an ipsilesional LMC score of 2. (C2/D2) Sustained CBF (ipsilateral/contralateral CBF ratio 0.91) and normal MTT (ipsilateral/contralateral MTT ratio 1.00) in ipsilesional MCA.

PR: pressure ratio; LMC: leptomeningeal collateral; CBF: cerebral blood flow; MTT: mean transit time; MCA: middle cerebral artery; CFD: computational fluid dynamics; ACA: anterior cerebral artery; PCA: posterior cerebral artery; CTA: computed tomography angiography; MTT: mean transit time; CTP: computed tomography perfusion.

cohort—good collaterals were, respectively, a protective factor and risk factor for recurrent stroke in patients with severe and moderate symptomatic ICAS.[5] One possible explanation is that in patients with a moderate ICAS, presence of good collaterals may imply a hemodynamically significant stenotic lesion, while in patients with severe ICAS when antegrade flow was usually inadequate to perfuse downstream brain tissue, a good collateral circulation compensates the perfusion insufficiency and hence reduces the risk of recurrent stroke.[5] Such theory was supported by our previous findings and the current study.[9] When an MCA stenosis causes a certain translesional pressure drop, CBF in the downstream territory could remain normal but the MTT could be prolonged due to the flow-limiting effects of the stenotic lesion, e.g. in a majority of cases with moderate MCA stenosis. However, when the MCA stenosis significantly diminishes antegrade flow across the lesion (e.g. a tight arterial stenosis), it may induce hemodynamic and pathophysiological changes in the distal arterial bed, which may open pre-existing collateral paths and facilitate formation of new collateral anastomoses.[9] In such a circumstance, the collateral circulation would be critical in restoring the territorial CBF, commonly with a prolonged MTT as well. One important fact to be noted is that the correlations between the degree of luminal stenosis, collateral circulation and cerebral perfusion are not constant, for instance around one-third of patients with moderate MCA stenosis in the current study had good LMCs, which indicated that a considerable proportion of ICAS lesions of <70% luminal narrowing are hemodynamically significant. Moreover, the current study only offered a snapshot of the correlations between

these factors, which in vivo could be far more complicated and dynamic.

In this study, we employed a CFD model to obtain the translesional PR, to reflect the fractional or residual flow across a stenotic artery irrespective of the collateral status. Application of the uniform boundary conditions in CFD modeling procedures ensured that the translesional PR calculated in the current study was solely based on the geometry of the narrowed artery but not confounded by other factors. We also graded LMCs in ACA and PCA territories but not in MCA territories to avoid confounding of antegrade residual flow in distal MCA territories. Only in this way we could investigate the separate and independent effects of antegrade residual flow and LMC flow on cerebral perfusion. It should be noted that the 'true' translesional PR in vivo is subject to a dynamic equilibrium between antegrade residual flow and LMC flow, and could possibly be higher than the translesional PR calculated in the current study.[9]

There were several limitations of this study. First, we used an ACA/PCA laterality method to assess the recruitment of LMCs in single-phase CTA images, which could not reveal the direction of blood flow. While future studies with multi-phase CTA or CTA reconstructions from CTP raw data should allow more accurate discrimination of the flow directions within the ACA/PCA pial areas and the MCA territory. Second, as mentioned above, in patients with a symptomatic ICAS, the stenotic lesion per se, the collateral extent, and the cerebral perfusion status dynamically evolve after the ischemic event,[25–27] while the current analysis captured only a snapshot of the inter-correlations between these metrics. Future studies with repeated assessment of these imaging measures may shed light on the pathophysiological process in achieving a dynamic balance between the antegrade flow through the steno-occlusive lesion and the distal compensating collateral flow, which may help early identification of those who are unable to sustain cerebral perfusion distal to an ICAS lesion and hence more likely to have a recurrent ischemic event in the same territory.

Summary

Both antegrade residual flow and LMC flow play important roles in sustaining cerebral perfusion in patients with a symptomatic MCA stenosis, while cerebral perfusion was more significantly dependent on antegrade residual flow in patients with moderate MCA stenoses but more significantly dependent on collateral flow in patients with severe MCA stenoses. The current findings need further verification in larger, longitudinal studies with repeated imaging exams to delineate the dynamic evolution in the stenotic lesion, collateral circulation and the perfusion status, and clinical follow-up to correlate with these imaging markers. Such studies will further uncover the roles of antegrade residual flow and LMC flow in sustaining cerebral perfusion and governing the subsequent recurrent risk in patients with symptomatic ICAS. In addition, the study once more reinforced the value of CFD modeling technique in clinical research into ischemic stroke and intracranial atherosclerotic disease.

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Declaration of conflicting interests

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Authors' contributions

Linfang Lan: study design, patient recruitment, imaging processing, statistic analysis, data interpretation, drafting the manuscript
Xinyi Leng: study design, imaging processing, statistic analysis, data interpretation, manuscript editing.
Vincent Ip: patient recruitment, comments to the manuscript.
Yannie Soo: patient recruitment, comments to the manuscript.
Jill Abrigo: image retrieving and assessment, comments to the manuscript.
Haipeng Liu: imaging processing.
Florence Fan: patient recruitment.
Sze Ho Ma: patient recruitment.
Karen Ma: patient recruitment.
Bonaventure YM Ip: patient recruitment.
Ka Lung Chan: imaging processing.
Vincent CT Mok: comments to the study design and manuscript.
David S Liebeskind: comments to the imaging assessment and manuscript.
Ka Sing Wong: comments to the study design and manuscript.
Thomas W Leung: study design, manuscript editing.

Supplementary material

Supplementary material for this paper can be found at the journal website: http://journals.sagepub.com/home/jcb

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