Hemodynamic significance of intracranial atherosclerotic disease and ipsilateral imaging markers of cerebral small vessel disease

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Title: Hemodynamic Significance of Intracranial Atherosclerotic Disease and Ipsilateral Imaging Markers of Cerebral Small Vessel Disease

Running Head: Hemodynamics and CSVD in sICAD

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ABSTRACT

Introduction: Cerebral small vessel disease (CSVD) commonly exists in patients with symptomatic intracranial atherosclerotic disease (sICAD). We aimed to investigate the associations of hemodynamic features of sICAD lesions with imaging markers and overall burden of CSVD.

Patients and methods: Patients with anterior-circulation sICAD (50-99% stenosis) were analyzed in this cross-sectional study. Hemodynamic features of a sICAD lesion were quantified by translesional pressure ratio (PR=$Pressure_{post\text{-}stenotic}/Pressure_{pre\text{-}stenotic}$) and wall shear stress ratio (WSSR=$WSS_{stenotic\text{-}throat}/WSS_{pre\text{-}stenotic}$) via CT angiography-based computational fluid dynamics modeling. PR ≤median was defined as low ("abnormal") PR, and WSSR≥ 4th quartile as high ("abnormal") WSSR. For primary analyses, white matter hyperintensities (WMHs), lacunes and cortical microinfarcts (CMIs) were assessed in MRI and summed up as overall CSVD burden, respectively in ipsilateral and contralateral hemispheres to sICAD. Enlarged perivascular spaces (EPVSs) and cerebral microbleeds (CMBs) were assessed for secondary analyses.

Results: Among 112 sICAD patients, there were more severe WMHs, more lacunes and CMIs, and more severe overall CSVD burden ipsilaterally than contralaterally (all $p<0.05$). Abnormal PR&WSSR (versus normal PR&WSSR) was significantly associated with moderate-to-severe WMHs (adjusted odds ratio=10.12, p=0.018), CMI presence (5.25, p=0.003) and moderate-to-severe CSVD burden (12.55; p=0.033), ipsilaterally, respectively independent of contralateral WMHs, CMI(s) and CSVD burden. EPVSs and CMBs were comparable between the two hemispheres, with no association found with the hemodynamic metrics.

Discussion and Conclusion: There are more severe WMHs and CMI(s) in the hemisphere ipsilateral than contralateral to sICAD. The hemodynamic significance of sICAD lesions was independently associated with severities of WMHs and CMI(s) ipsilaterally.

Keywords: cerebral small vessel disease; hemodynamics; intracranial atherosclerotic disease; white matter hyperintensity; cortical microinfarct

Abbreviations and Acronyms

ADC=apparent diffusion coefficient;

aOR=adjusted odds ratios

CFD=computational fluid dynamics;

CI=confidence interval;

CMBs=cerebral microbleeds;

CMIs=cortical microinfarcts；

CSVD=cerebral small vessel disease;

CTA=CT angiography;

DWMHs=deep white matter hyperintensities;

DWI=diffusion-weighted imaging;

EPVSs= enlarged perivascular spaces;

FLAIR=fluid-attenuated inversion recovery;

ICAD=intracranial atherosclerotic disease;

IC-ICA=the intracranial portion of internal carotid artery;

IQR=interquartile range;

MCA-M1=M1 middle cerebral artery;

MRI=magnetic resonance imaging;

OR=odds ratio;

PR=pressure ratio;

PWMHs=periventricular white matter hyperintensities;

sICAD=symptomatic intracranial atherosclerotic disease;

SOpHIA=the StrOke risk and Hemodynamics in Intracranial Atherosclerotic disease;

SWI=susceptibility-weighted imaging;

T2*GRE= T2*-weighted gradient-recalled echo sequence;

TIA=transient ischemic attack;

WASID=Warfarin-Aspirin Symptomatic Intracranial Disease;

WMHs=white matter hyperintensities;

WSS=wall shear stress;

WSSR=wall shear stress ratio.

INTRODUCTION

Cerebral small vessel disease (CSVD) is usually diagnosed with imaging markers in brain magnetic resonance imaging (MRI), such as white matter hyperintensities (WMHs), lacunes, enlarged perivascular spaces (EPVSs) and cerebral microbleeds (CMBs).[1] These CSVD imaging markers and cortical microinfarcts (CMIs), an emerging marker of CSVD,[1] as well as more severe overall CSVD burden, were associated with decreased performance in all cognitive domains, and increased risks of stroke, dementia and death.[2]

Intracranial atherosclerotic disease (ICAD) is an important cause of ischemic stroke or transient ischemic attack (TIA). CSVD commonly coexists with ICAD in stroke patients.[3-5] Some studies have indicated a positive correlation between presence of ICAD and severity of CSVD, and a vicious circle of aggravation between the macro- and micro-circulations in the brain resulting from cross-talks between large and small arteries.[6] This may partly explain the increased risks of recurrent stroke and worse functional outcomes in stroke patients with coexisting ICAD and CSVD.[6, 7]

However, data have been limited for an overall picture of CSVD burden in ICAD patients, and the mechanisms underlying development and progression of CSVD in the presence of ICAD have not been fully understood. In addition to some shared risk factors (e.g., smoking and hypertension),[7] altered cerebral hemodynamics in ICAD may also play an important role in governing the presence and severity of CSVD. For instance, cerebral hypoperfusion has been associated with more severe WMHs in the general population and in patients with symptomatic ICAD (sICAD).[8, 9] Moreover, thromboembolism and cerebral hypoperfusion have been associated with presence of CMIs.[10] These all need further investigations.

In previous studies, we had proposed two hemodynamic metrics, translesional pressure ratio (PR) and wall shear stress (WSS) ratio (WSSR) in computational fluid dynamics (CFD) models based on CT angiography (CTA), to reflect the translesional changes of pressure and WSS in sICAD and quantify its hemodynamic significance.[11] In the current study, we aimed to compare imaging markers and the overall burden of CSVD in the cerebral hemispheres ipsilateral and contralateral to a sICAD lesion, and to investigate the associations of hemodynamic significance of sICAD (by translesional PR and WSSR) with CSVD imaging markers and the overall burden in ipsilateral and contralateral hemispheres.

METHODS

Study design and subjects

This was a cross-sectional study, screening and recruiting patients from the StrOke risk and Hemodynamics in Intracranial Atherosclerotic disease (SOpHIA) study.[11] Adult patients with acute ischemic stroke or TIA attributed to 50-99% atherosclerotic stenosis in the intracranial portion of internal carotid artery (IC-ICA) or M1 middle cerebral artery (MCA-M1) in CTA, who were admitted to Prince of Wales Hospital in Hong Kong and First Affiliated Hospital of Zhengzhou University in Zhengzhou from Jan 2009 to Dec 2017 in SOpHIA, were screened for the current study. Those who received a 3.0T brain MRI exam at baseline, including axial T1/T2-weighted images, fluid-attenuated inversion recovery (FLAIR) imaging, diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) and T2*-weighted gradient-recalled echo sequence (T2*GRE) or susceptibility-weighted imaging (SWI), with a successfully constructed CTA-based CFD model, were analyzed.

Patients' demographics and clinical features were collected. Luminal stenosis of the sICAD lesion in CTA by the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) method,[12] and presence of ≥50% stenosis or occlusion of contralateral IC-ICA or MCA-M1, were recorded. Ipsilesional leptomeningeal collateral status (dichotomized as good or poor) was assessed by the laterality of distal branches in anterior/posterior cerebral artery territories in CTA source images, as described in our previous work.[11] CFD model was built based on CTA images to quantify the hemodynamic features of a sICAD lesion (translesional PR and WSSR).[11] The CSVD imaging markers and burden were assessed in 3.0 T brain MRI, as detailed below and in Supplemental Methods. We compared the individual imaging markers and overall burden of CSVD between ipsilateral and contralateral hemispheres. We investigated the associations of the hemodynamic features of sICAD with individual imaging markers and overall burden of CSVD, in ipsilateral and contralateral hemispheres.

CFD modeling and quantification of hemodynamic features of sICAD

CFD model was constructed based on CTA, to simulate blood flow across a sICAD lesion and to quantify its hemodynamic features, using the ANSYS software package version 15.0 (ANSYS, Inc., Canonsburg, PA, USA). Detailed modeling steps and boundary conditions were described in our previous work.[11]

We quantified the relative changes of pressure and WSS across each sICAD lesion to reflect its hemodynamic significance, by obtaining the translesional PR and WSSR in CFD model.[11] Translesional PR was the ratio of post-stenotic and pre-stenotic pressure ($Pressure_{post\text{-}stenotic}/Pressure_{pre\text{-}stenotic}$). Translesional WSSR was the ratio of WSS upon the stenotic throat and pre-stenotic normal vessel segment ($WSS_{stenotic\text{-}throat}/WSS_{pre\text{-}stenotic}$).

There was substantial inter-rater reproducibility of measuring translesional PR and WSSR in sICAD lesions.[11]

Translesional PR was then dichotomized by the median, with PR ≤ median as a low ("abnormal") PR, indicating a larger pressure drop or pressure gradient across sICAD lesion, which may restrict antegrade perfusion; otherwise a "normal" PR. Translesional WSSR was dichotomized by the 4^{th} quartile, with WSSR ≥ the 4^{th} quartile as a high ("abnormal") WSSR, indicating more significantly elevated WSS upon sICAD lesion; otherwise a "normal" WSSR. We further classified the hemodynamic status of sICAD lesions to 3 categories by simultaneously considering both hemodynamic features: 1) normal hemodynamic status - normal PR & normal WSSR; 2) intermediate status - normal PR & abnormal WSSR, or abnormal PR & normal WSSR; and 3) abnormal status - abnormal PR & abnormal WSSR.[11]

Assessment of individual imaging makers and overall burden of CSVD in MRI

The 3 CSVD imaging markers (WMHs, lacunes and CMIs) that have been associated with an ischemic pathophysiology or hemodynamic disturbances, and an overall CSVD burden score composed based on these 3 markers, were investigated in primary analyses in the current study. Secondary analyses included separate analyses of periventricular WMHs (PVWMHs) and deep WMHs (DWMHs), and another two commonly seen CSVD imaging markers that were previously assumed not associated with an ischemic pathophysiology or hemodynamic disturbance (EPVSs and CMBs).[12]

Blinded to clinical information and the CFD modeling results, one trained reader (L.Z.) assessed the presence/severity of CSVD imaging markers in 3.0 T brain MRI using OsiriX MD version 12.0 (Pixmeo, Switzerland), respectively in the cerebral hemispheres ipsilateral and contralateral to the sICAD lesion. The reader was also

asked to be blinded to the location and severity of the sICAD lesion. Regions of acute ischemic lesions (high intensities in DWI and low intensities in ADC) were avoided in CSVD assessment. A second reader (X.L.) was consulted upon uncertainty. Inter-rater (L.Z. and X.T.) reliabilities of assessing the CSVD imaging markers were assessed in 35 cases. Detailed methods of assessing these CSVD imaging markers are described in Supplemental Methods. An overall CSVD burden score (0-7 points) of each hemisphere was calculated by summing up the severities of the 3 imaging markers possibly associated with an ischemic pathophysiology or hemodynamic disturbance (WMHs, lacunes and CMIs), with 0, 1, 2, 3 points for WMHs with the Fazekas scale[13] of 0, 1, 2 and 3; 0, 1, 2 points for 0, 1 and ≥2 lacunes; and 0, 1, 2 points for 0, 1 and ≥2 CMIs (Supplemental Table S1). An overall CSVD burden score of 0-4 and 5-7 was respectively defined as none-to-mild and moderate-to-severe overall CSVD burden.

Statistical analyses

Medians (interquartile range, IQR) or numbers (%) were used for descriptive statistics. Inter-rater reliabilities of assessing CSVD imaging markers were assessed with Cohen's κ statistic. CSVD imaging markers and overall burden in ipsilateral and contralateral hemispheres were compared using Wilcoxon signed-rank tests for continuous variables and McNemar's tests or marginal homogeneity tests for categorical variables.

The associations between the hemodynamic features of sICAD lesion and an individual CSVD imaging marker in ipsilateral hemisphere were analyzed with Wilcoxon rank sum, chi-square or Fisher's exact tests, and then univariate and multivariate logistic regression (adjusting for this particular CSVD imaging marker in the contralateral hemisphere). The associations between the hemodynamic features of sICAD lesions

and ipsilateral moderate-to-severe overall CSVD burden were analyzed similarly in univariate comparisions, and then using univariate and multivariate logistic regression (adjusting for variables with $p<0.05$ in univariate comparisons). Crude and adjusted odds ratios (OR/aOR) and 95% confidence intervals (CI) were obtained. The two hemodynamic features of sICAD, translesional PR and WSSR, were analyzed as continuous and categorical variables in univariate comparisons and as categorical variables in univariate and multivariate logistic regression analyses. Similar analyses were conducted for the overall burden and individual imaging markers of CSVD in the contralateral hemisphere. Sensitivity analyses were conducted to detect the associations between the hemodynamic features of sICAD lesions and ipsilateral moderate-to-severe overall CSVD burden in patients with MCA-M1 stenosis.

Statistical significance was defined by 2-sided p value <0.05. All analyses were conducted using SPSS version 26.0 (IBM Co., USA).

RESULTS

Among 174 potentially eligible patients in the SOpHIA cohort, 112 (median age 63 years; 62.5% males) were included in the current analyses (Supplemental Figure S1). Characteristics of all patients included are presented in Supplemental Table S2. The qualifying sICAD lesions respectively located in IC-ICA and MCA-M1 in 13 (11.6%) and 94 (83.9%) cases, and 5 (4.5%) cases had a tandem lesion across IC-ICA and MCA-M1. Sixty-seven (59.8%) patients had 50-69% luminal stenosis and 45 (40.2%) had 70-99% stenosis. Ten (8.9%) patients had ≥50% contralateral intracranial stenosis/ occlusion. Leptomeningeal collateral status was assessed in 80 patients, with good leptomeningeal collaterals in 34 (42.5%) patients. The median translesional PR was 0.93 (IQR 0.82-0.97) and median translesional WSSR was 12.0 (IQR 6.3-19.7). When

considering the two hemodynamic metrics simultaneously, 46 (41.1%), 43 (38.4%) and 23 (20.5%) sICAD lesions respectively had normal (normal PR&WSSR), intermediate (normal in one and abnormal in the other metric), and abnormal (abnormal PR&WSSR) hemodynamic status.

WMHs, lacunes and CMIs and overall burden of CSVD in ipsilateral versus contralateral hemispheres

There was substantial inter-rater agreement in the assessment of WMHs, lacunes and CMIs in 35 cases (κappa=0.78, 0.82 and 0.87, respectively), with detailed data presented in Supplemental Table S3.

WMHs, lacunes and CMIs were significantly more severe in the ipsilateral than contralateral hemisphere (all $p<0.05$). Moreover, the patients had a higher proportion of moderate-to-severe overall CSVD burden based on these 3 imaging markers (14.3% versus 3.6%, $p=0.005$), in the ipsilateral than contralateral hemisphere (Table 1 and Supplemental Figure S2).

Hemodynamic features of sICAD and ipsilateral WMHs, lacunes and CMIs

Translesional PR was significantly lower and WSSR was significantly higher in those with moderate-to-severe (versus none-to-mild) ipsilateral WMHs, and those with (versus without) ipsilateral CMIs, in univariate comparisons (all $p<0.05$). Abnormal hemodynamic status of sICAD (abnormal PR&WSSR) was significantly associated with moderate-to-severe ipsilateral WMHs and presence of ipsilateral CMI(s) in univariate logistic regression (both $p<0.05$; Supplemental Table S4).

In multivariate logistic regression, high WSSR was significantly associated with moderate-to-severe ipsilateral WMHs (aOR=6.75; $p=0.011$), independent of contralateral WMHs. Low PR (aOR=3.26; $p=0.005$) and high WSSR (aOR=2.82;

p=0.022) were respectively, significantly associated with presence of ipsilateral CMI(s), independent of contralateral CMI(s). Abnormal hemodynamic status of sICAD was also independently associated with moderate-to-severe ipsilateral WMHs (aOR=10.12; p=0.018) and ipsilateral CMI(s) (aOR=5.25; p=0.003; Supplemental Table S4).

None of the hemodynamic features was significantly associated with presence of lacune(s) in univariate or multivariate analyses (Supplemental Table S4). Two patients with different hemodynamic features/status of the sICAD lesion and different severities of ipsilateral CSVD markers/burden are illustrated in Figure 1.

Hemodynamic features of sICAD and ipsilateral overall CSVD burden

Compared with those with none-to-mild overall CSVD burden ipsilaterally, more patients with moderate-to-severe CSVD burden ipsilaterally (based on WMHs, lacunes and CMIs) had severe luminal stenosis in the sICAD lesion, and moderate-to-severe overall CSVD burden contralaterally (both $p<0.05$; Table 2). Clinical features of the patients, or other imaging features, were not significantly different between the two groups (Table 2).

Regarding the hemodynamic features of sICAD, patients with moderate-to-severe overall ipsilateral CSVD burden had a lower translesional PR (medians 0.81 versus 0.94; p=0.003) and a higher WSSR (medians 19.9 versus 10.8; p=0.004) than those with none-to-mild ipsilateral CSVD burden. More patients with moderate-to-severe ipsilateral CSVD burden had a low PR (81.3% versus 50.0%; p=0.020), a high WSSR (50.0% versus 20.8%; p=0.025), and an abnormal hemodynamic status (50.0% versus 15.6%; p=0.006; Table 2).

In multivariate logistic regression, low PR (aOR=8.18; 95%CI 0.98-68.38; p=0.052) and high WSSR (aOR=3.52; 95%CI 1.04-11.99; p=0.044) were respectively associated

with moderate-to-severe ipsilateral CSVD burden, adjusting for the degree of luminal stenosis in sICAD and contralateral overall CSVD burden (Table 3). When simultaneously considering translesional PR and WSSR, those with abnormal hemodynamic status of the sICAD lesion (low PR & high WSSR) were more likely to have moderate-to-severe CSVD burden in the ipsilateral hemisphere, than those with normal hemodynamic status (aOR=12.55; 95%CI 1.35-116.75; p=0.033; Table 3), independent of the degree of luminal stenosis in the sICAD lesion and contralateral CSVD burden.

Hemodynamic features of sICAD and contralateral WMHs, lacunes, CMIs and CSVD burdern

None of the hemodynamic features of sICAD was significantly associated with moderate-to-severe WMHs, lacune(s), CMI(s), or the overall burden of CSVD contralaterally (all p>0.05, Supplemental Table S5 & S6).

Sensitivity Analyses

Among the 94 patients with MCA-M1 stenosis only, the associations between the hemodynamic features and ipsilateral moderate-to-severe overall CSVD burden were similar with that in the overall analyses (Supplemental Table S7).

Analyses of PVWMHs, DWMHs, EPVSs and CMBs

There was substantial inter-rater agreement in the assessment of EPVSs and CMBs in 35 cases (κappa=0.87 and 0.85, respectively; Supplemental Table S3).

PVWMH(s) and DWMH(s) were more severe in ipsilateral than contralateral hemispheres (Table 1), but EPVSs and CMBs were comparable between the two hemispheres (Supplemental Table S8, all p>0.05).

In separate analyses of PVWMHs and DWMHs, no hemodynamic feature of sICAD lesion was significantly associated with moderate-to-severe ipsilateral PVWMHs or DWMHs (Supplemental Table S4). In addition, none of the hemodynamic features was significantly associated with moderate-to-severe EPVSs or presence of CMB(s), in the ipsilateral (Supplemental Table S4) or contralateral hemisphere (Supplemental Table S5).

DISCUSSION

In this study, we found a higher CSVD burden in ipsilateral than contralateral hemisphere to sICAD. A larger translesional pressure gradient across sICAD lesion (i.e., a low PR) and excessively elevated WSS at the stenotic throat (i.e., a high WSSR) were significantly, independently associated with moderate-to-severe WMHs, presence of CMI(s) and moderate-to-severe overall CSVD burden (based on WMHs, lacunes and CMIs) ipsilaterally, but not presence of lacune(s), moderate-to-severe EPVSs or presence of CMB(s). None of the hemodynamic features was significantly associated with individual imaging markers or the overall burden of CSVD contralaterally. The study indicated the role of hemodynamic significance of sICAD lesion in governing the severity of certain CSVD markers (WMHs and CMIs).

The prevalence of moderate-to-severe WMHs, lacune(s) and CMI(s) ipsilaterally to sICAD in this study were consistent with previous reports.[5, 14, 15] Moreover, we observed more severe WMHs, lacunes and CMIs in the ipsilateral than contralateral hemisphere to sICAD. These findings were consistent with a previous study reporting a higher volume of WMHs in ipsilateral than contralateral hemisphere to sICAD.[8] Recent studies also found more prevalent CMIs in the cerebral hemisphere ipsilateral than contralateral to a stenosed/occluded proximal ICA.[16, 17] So far, there seemed to be

limited data regarding the inter-hemisphere difference of lacune(s) in ICAD patients. Of note, EPVSs and CMBs, another two commonly seen CSVD imaging markers, were found comparable between the ipsilateral and contralateral hemispheres to sICAD, consistent with previous findings that they were less likely associated with an ischemic pathophysiology or hemodynamic disturbances in situations like ICAD.[12]

Previous studies had indicated the role of hemodynamics in CSVD etiology in the presence of large artery occlusive disease. For instance, we had associated the hemodynamic significance of MCA-M1 stenosis, assessed in time-of-flight MR angiography, with more severe WMHs and presence of CMI(s) ipsilaterally.[14, 18] Lower cerebral blood flow had been reported as a causal factor of CMI development, in patients with proximal ICA occlusion.[16] In this study, we further analyzed the associations of hemodynamic features of sICAD by two novel hemodynamic metrics obtained from CFD modeling, with imaging markers and overall burden of CSVD in bilateral hemispheres. A low PR indicated reduced antegrade flow through a sICAD lesion, possibly leading to cerebral hypoperfusion if there is no adequate retrograde collateral flow.[12] A high WSSR might aggravate plaque vulnerability and cause microembolisms by inducing endothelial dysfunction, weakening the plaque surface and increasing the necrotic core.[19, 20] Low PR and high WSSR, separately and synergistically, were significantly associated with a higher risk of recurrent stroke in the same territory in sICAD patients in the SOpHIA cohort.[11]

In the current study, patients with abnormal hemodynamic status of sICAD (low PR & high WSSR) were more likely to have moderate-to-severe WMHs and CMI(s) than those with normal hemodynamic status (normal PR&WSSR), but no association was observed with presence of lacune(s). These results might be partly explained by the

different mechanisms underlying the 3 CSVD markers. WMHs were reported secondary to reduced cerebral blood flow, which leads to a cascade of neurovascular unit dysfunction secondary to hypoxia, blood-brain barrier leakage, inflammation, edema and oligodendrocyte dysfunction, and eventually loss of myelin sheath and gliosis.[21] However, the association of WMHs with the hemodynamic features of sICAD were weakened, when it was further distinguished as PVWMHs and DWMHs. It is possible that a hemodynamically significant sICAD lesion could affect perfusion in the entire distal vascular bed rather than in specific regions, which may have weakened the associations in separate analyses of PVWMHs and DWMHs. Further larger-scale studies with more detailed assessment of the location, morphology and volume of WMHs may reveal the possible reasons underlying such findings. Regarding CMIs, in addition to hypoperfusion and in situ small vessel disease (e.g., cerebral amyloid angiopathy and arteriolosclerosis), vulnerable plaques in proximal arteries with possibly increased risk of microembolism could also be a pathogenic mechanism.[10, 17] Moreover, reduced cerebral perfusion may impair the clearance of microemboli,[22, 23] which explains the synergistic effects of low PR and high WSSR in leading to more severe CSVD, particularly the CMI(s). However, lacunes were possibly more associated with in situ small vessel disease, but with the regional cerebral blood flow or microembolism,[24] hence the negative findings over PR or WSSR with lacunes in this study. The “negative” findings over PR and WSSR with EPVSs and CMB(s) further indicated the little effect of hemodynamics in governing these two CSVD imaging markers. The association of the hemodynamic features of sICAD and the ipsilateral overall CSVD burden were therefore mostly driven by their associations with WMHs and CMIs. The more severe CSVD burden in ipsilateral than contralateral hemisphere to sICAD could also be explained by the relatively higher chance of hypoperfusion and

microembolism in the ipsilateral hemisphere, although we did not assess the hemodynamics contralaterally, which was a limitation of the current study.

This study had strengths. First, we used a CFD-based cerebral blood flow simulation method to quantify the hemodynamic features of sICAD. The two hemodynamic parameters, translesional PR and WSSR, represent two different dimensions of the hemodynamic significance of sICAD, in contrast to conventional perfusion imaging methods that can only provide perfusion metrics. The study therefore revealed two possible mechanisms associated with individual imaging markers and overall burden of CSVD in sICAD. Moreover, we assessed individual markers and overall CSVD burden separately in two cerebral hemispheres, and associated hemodynamic features of sICAD with ipsilateral CSVD, adjusting for contralateral CSVD and other confounders. The associations between hemodynamic features of sICAD and ipsilateral CSVD were therefore independent of contralateral CSVD.

However, there were also limitations. First, the acute ischemic regions were avoided in CSVD assessment, which may result in underestimation of ipsilateral CSVD burden, though the trend of the overall findings should remain unchanged (if not stronger) if CSVD in such regions could be assessed. Future studies in those with asymptomatic ICAD (hence no acute ischemic lesions) may further verify current findings. In addition, although avoiding acute ischemic regions in CSVD assessment could prevent mixing WMHs-like acute ischemic lesions with chronic WMHs, we were unable to distinguish WMHs evolving from old infarcts due to isolated small artery occlusion or ICAD with "classical" CSVD-associated WMHs. Second, the readers were asked to be blinded to the ICAD information when reading the CSVD imaging markers, but it might be inevitable that in some cases they could notice the ICAD lesion in MR angiography

images stored together with images of other MRI sequences. This might result in potential bias. Third, this cross-sectional study cannot justify causal relationships of the hemodynamic features of ICAD with progression of CSVD and subsequent cognitive outcomes. Further longitudinal investigations are warranted, using repeated, non-invasive imaging methods to monitor the CSVD markers, cerebral perfusion status and possible embolic sources, and serial assessments to picture the cognitive trajectory. Yet, we need to keep in mind the different therapeutic options of individual CSVD imaging markers that may confound such investigations in longitudinal studies. Moreover, the study findings need to be verified in other populations.

Conclusions

In sICAD patients, WMH(s), lacune(s) and CMI(s) were more prevalent, and the overall CSVD burden based on these 3 imaging markers was more severe, in the ipsilateral than contralateral hemisphere. A larger translesional pressure gradient (low PR) and significantly elevated WSS upon the sICAD lesion (high WSSR) were associated with moderate-to-severe WMHs, presence of CMI(s) and moderate-to-severe overall CSVD burden ipsilaterally, independent of contralateral CSVD marker or burden. Yet, no association was found of these hemodynamic metrics with EPVSs and CMB(s). This study demonstrated an important role of cerebral hemodynamics in governing the severity of coexisting CSVD (particularly WMHs and CMIs) in sICAD patients. The findings need to be verified in those with asymptomatic ICAD, and in longitudinal studies with serial CSVD and cognitive assessments.

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Guarantor: XL.

Contributorship: LZ and XL designed the study, analyzed the data, interpreted the findings and wrote the manuscript; LZ, XT and JA assessed the images; HF, BYMI, YL, SL, YL, LL, HL, HLI, FSYF, SHM and KM contributed to data collection and analyses; AYL, YOYS, HL, VCTM, KSW, YX, LL and TWL provided critical comments/revisions of the manuscript. XL and TWL are equally responsible for the overall content.

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Data Availability: Data related to the current study are available from the corresponding author on reasonable request.

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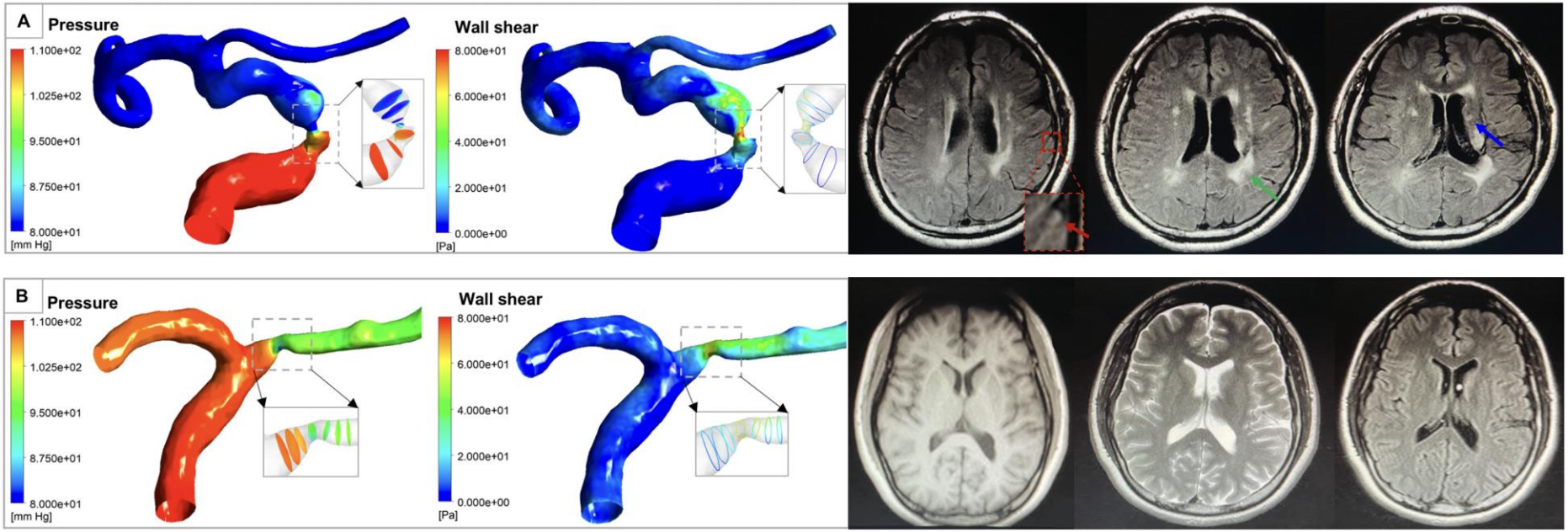

Figure 1. Hemodynamic metrics of the sICAD lesions in CFD models and CSVD markers in MRI in two patients.

(A) Abnormal hemodynamic status of a sICAD lesion in left intracranial ICA in the CFD model, with an abnormal PR (0.74) and abnormal WSSR (55.4). Moderate-to-severe WMHs (green arrow), 1 lacune (blue arrow) and 1 CMI (red arrow and box) in the ipsilateral hemisphere illustrated in FLAIR images, with a moderate-to-severe overall ipsilateral CSVD burden (score=5).

(B) Normal hemodynamic status of a sICAD lesion in left MCA revealed in the CFD model, with a normal PR (0.94) and normal WSSR (14.3). No CSVD imaging markers seen in T1, T2-weighted and FLAIR images in the ipsilateral hemisphere, hence a none-to-mild overall ipsilateral CSVD burden (score=0).

Table 1. Comparisons of individual CSVD imaging markers and overall CSVD burden between cerebral hemispheres ipsilateral and contralateral to sICAD*

Imaging markers and overall burden of CSVD	Ipsilateral	Contralateral	p value
Presence of CSVD imaging marker			
WMH(s)			0.109
None-to-mild	92 (82.1)	98 (87.5)	
Moderate-to-severe	20 (17.9)	14 (12.5)	
PVWMH(s)			0.219
None-to-mild	96 (85.7)	100 (89.3)	
Moderate-to-severe	16 (14.3)	12 (10.7)	
DWMH(s)			0.125
None-to-mild	95 (84.8)	100 (89.3)	
Moderate-to-severe	17 (15.2)	12 (10.7)	
Lacune(s)			0.100
0	72 (64.3)	82 (73.2)	
≥1	40 (35.7)	30 (26.8)	
CMI(s)			0.136
0	68 (60.7)	79 (70.5)	
≥1	44 (39.3)	33 (29.5)	
Severity of CSVD imaging marker			
WMH(s) - Fazekas score			0.005
0	43 (38.4)	50 (44.6)	
1	49 (43.8)	48 (42.9)	
2	16 (14.3)	12 (10.7)	
3	4 (3.6)	2 (1.8)	
PVWMH(s) - Fazekas score			0.016
0	62 (55.4)	70 (62.5)	
1	34 (30.4)	30 (26.8)	
2	12 (10.7)	10 (8.9)	
3	4 (3.6)	2 (1.8)	
DWMH(s) - Fazekas score			0.018
0	60 (53.6)	63 (56.3)	
1	34 (30.4)	37 (33.0)	
2	17 (15.2)	12 (10.7)	
3	1 (0.9)	0 (0.0)	
Lacune(s) - number			0.017
0	72 (64.3)	82 (73.2)	
1	16 (14.3)	16 (14.3)	
≥2	24 (21.4)	14 (12.5)	
CMI(s) - number			0.018
0	68 (60.7)	79 (70.5)	
1	17 (15.2)	21 (18.8)	
≥2	27 (24.1)	12 (10.7)	
Overall CSVD Burden score	2 (1-3)	1 (0-2)	0.001
Overall CSVD Burden (binary)			0.005
None-to-mild	96 (85.7)	108 (96.4)	
Moderate-to-severe	16 (14.3)	4 (3.6)	

* Values are medians (interquartile range) or numbers (%).

CSVD, cerebral small vessel disease; sICAD, symptomatic intracranial atherosclerotic disease; WMH, white matter hyperintensity; PVWMH, periventricular white matter hyperintensity, DWMH, deep white matter hyperintensity and CMI, cortical microinfarct.

Table 2. Comparisons between patients with moderate-to-severe and none-to-mild overall CSVD burden in the cerebral hemisphere ipsilateral to sICAD*

Characteristics	None-to-mild (n=96)	Moderate-to-severe (n=16)	p value
Age, year	63 (54-68)	64 (60-72)	0.118
Male	57 (59.4)	13 (81.3)	0.094
Risk factors			
Current smoker	40 (41.7)	8 (50.0)	0.533
Hypertension	58 (60.4)	12 (75.0)	0.265
Diabetes mellitus	29 (30.2)	8 (50.0)	0.119
Dyslipidemia	57 (59.4)	10 (62.5)	0.813
Prior stroke or TIA	12 (12.5)	4 (25.0)	0.241
Ischemic stroke as the index cerebral ischemic event	68 (70.8)	13 (81.3)	0.550
Admission NIH Stroke Scale score (among ischemic stroke patients)	3 (1-5)	3 (1-5)	0.840
Blood pressure at admission, mmHg			
Systolic	157 (135-170)	169 (140-193)	0.075
Diastolic	84 (76-97)	92 (80-102)	0.118
Lab testing results during hospitalization			
Fasting glucose, mmol/L	5.4 (4.9-7.0)	5.9 (5.0-9.6)	0.302
Hemoglobin A1c, %	6.1 (5.6-6.8	6.4 (5.8-7.1)	0.364
Low-density lipoprotein cholesterol, mmol/L	3.1 (2.2-3.9)	2.8 (2.3-3.8)	0.874
Interval from stroke/TIA onset to MRI, days	3 (1-5)	2 (1-11)	0.763
Interval from stroke/TIA onset to CTA, days	7 (4-13)	9 (4-20)	0.340
Location of the sICAD lesion			1.000
IC-ICA	12 (12.5)	1 (6.3)	
MCA-M1	80 (83.3)	14 (87.5)	
IC-ICA & MCA-M1 tandem lesion	4 (4.2)	1 (6.3)	
Luminal stenosis of the sICAD lesion			0.049
50-69%	61 (63.5)	6 (37.5)	
≥70%	35 (36.5)	10 (62.5)	
Contralateral intracranial stenosis (≥50%)/occlusion	8 (8.3)	2 (12.5)	0.615
Good leptomeningeal collateral status	30 (43.5)	4 (36.4)	0.751
Hemodynamic features of sICAD lesions quantified in CFD models			
Translesional PR	0.94 (0.87-0.97)	0.81 (0.74-0.93)	0.003
PR ≤ median (low PR)	48 (50.0)	13 (81.3)	0.020
Translesional WSSR	10.8 (5.9-17.3)	19.9 (12.3-58.1)	0.004
WSSR ≥ 4th quartile (high WSSR)	20 (20.8)	8 (50.0)	0.025
Hemodynamic status of sICAD lesions by translesional PR & WSSR			0.006
Normal	43 (44.8)	3 (18.8)	
Intermediate	38 (39.6)	5 (31.3)	
Abnormal	15 (15.6)	8 (50.0)	
Overall CSVD burden in the contralateral hemisphere			0.009

None-to-mild	95 (99.0)	13 (81.3)
Moderate-to-severe	1 (1.0)	3 (18.8)

[*] Values are medians (interquartile range) or numbers (%).

CSVD, cerebral small vessel disease; sICAD, symptomatic intracranial atherosclerotic disease; TIA, transient ischemic attack; MRI, magnetic resonance imaging; CTA, computed topography angiography; IC-ICA, the intracranial portion of internal carotid artery; MCA-M1, M1 middle cerebral artery; CFD, computational fluid dynamics; PR, pressure ratio and WSSR, wall shear stress ratio.

Table 3. Univariate and multivariate logistic regression analyses for the associations between hemodynamic features of sICAD and ipsilateral moderate-to-severe CSVD burden

	Univariate Analysis		Multivariate Analysis*	
	OR (95% CI)	**p value**	**aOR (95% CI)**	**p value**
Hemodynamic features of sICAD lesions				
Translesional PR ≤ median (low PR)	4.33 (1.16-16.18)	0.029	8.18 (0.98-68.38)	0.052
Translesional WSSR ≥ 4th quartile (high WSSR)	3.80 (1.27-11.38)	0.017	3.52 (1.04-11.99)	0.044
Hemodynamic status of sICAD lesions by translesional PR & WSSR				
Normal	ref		ref	
Intermediate	1.89 (0.42-8.42)	0.406	4.12 (0.44-38.47)	0.215
Abnormal	7.64 (1.79-32.63)	0.006	12.55 (1.35-116.75)	0.033

* Adjusted for luminal stenosis of sICAD lesion and contralateral overall CSVD burden.

sICAD, symptomatic intracranial atherosclerotic disease; CSVD, cerebral small vessel disease; PR, pressure ratio; WSSR, wall shear stress ratio; OR, odds ratio; aOR, adjusted odds ratio and CI, confidence interval.