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Li, S., Tian, X., Ip, B., Feng, X., Ip, H. L., Abrigo, J., Lan, L., Liu, H., Zheng, L., Liu, Y., Liu, Y., Ma, K. KY., Fan, F. SY., Ma, S. H., Fang, H., Xu, Y., Lau, A. Y., Leung, H., Soo, Y. OY., Mok, V. CT., & 3 others



**Original citation & hyperlink:**
Li, S, Tian, X, Ip, B, Feng, X, Ip, HL, Abrigo, J, Lan, L, Liu, H, Zheng, L, Liu, Y, Liu, Y, Ma, KKY, Fan, FSY, Ma, SH, Fang, H, Xu, Y, Lau, AY, Leung, H, Soo, YOY, Mok, VCT, Wong, KS, Leng, X & Leung, TW 2023, 'Cerebral hemodynamics and stroke risks in symptomatic intracranial atherosclerotic stenosis with internal versus cortical borderzone infarcts: A computational fluid dynamics study', Journal of Cerebral Blood Flow and Metabolism, vol. (In-Press), pp. (In-Press).
https://doi.org/10.1177/0271678x231211449

DOI 10.1177/0271678x231211449
ISSN 0271-678X
ESSN 1559-7016

Publisher: SAGE Publications

# Cerebral hemodynamics and stroke risks in symptomatic intracranial atherosclerotic stenosis with internal versus cortical borderzone infarcts: A computational fluid dynamics study

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**Running headline:** Hemodynamics and stroke risk in borderzone infarct

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**Total word count:** 4118

**Number of tables:** 3; **figures**: 3; **references:** 21

**Supplementary Material:** 1 Supplementary Table

**Abstract**

There may be different mechanisms underlying internal (IBZ) and cortical (CBZ) borderzone infarcts in intracranial atherosclerotic stenosis. In 84 patients with symptomatic, 50-99% atherosclerotic stenosis of M1 middle cerebral artery (MCA-M1) with acute borderzone infarcts in diffusion-weighted imaging, we classified the infarct patterns as isolated IBZ (n=37), isolated CBZ (n=31), and IBZ+CBZ (n=16) infarcts. CT angiography-based computational fluid dynamics models were constructed to quantify translesional, post-stenotic to pre-stenotic pressure ratio (PR) in the MCA-M1 lesion. Those with IBZ infarcts were more likely to have a low PR (indicating impaired antegrade flow across the lesion) than those without (p=0.012), and those with CBZ infarcts were more likely to have coexisting small cortical infarcts (indicating possible embolism) than those without (p=0.004). In those with isolated IBZ or CBZ infarcts, low PR was independently associated with isolated IBZ infarcts (adjusted odds ratio=4.223; p=0.026). These two groups may also have different trajectories in the stroke risks under current medical treatment regimen, with a higher risk of same-territory ischemic stroke recurrence within 3 months in patients with isolated IBZ infarcts than isolated CBZ infarcts (17.9% versus 0.0%; log-rank p=0.023), but similar risks later in 1 year.

**Keywords**: Borderzone infarct, cerebral hemodynamics, intracranial atherosclerotic disease, ischemic stroke, prognosis.

## Introduction

Intracranial atherosclerotic stenosis (ICAS) is a major cause of ischemic stroke. Infarcts in the internal or cortical borderzone (IBZ or CBZ) are commonly seen in patients with symptomatic ICAS (sICAS), e.g., in over 60% of sICAS patients in our previous study, either isolated or combined with other infarct patterns.[1] IBZ infarcts are usually small, chain-like infarcts in centrum semiovale and/or corona radiata along or above the lateral ventricles, which are junctional areas between the deep perforating arteries and penetrating cortical branches of anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA). CBZ infarcts are usually wedge-shaped/ovoid infarcts in the cortical and adjacent subcortical areas between the supplying territories of ACA and MCA, or PCA and MCA.[2]

Hypoperfusion has been considered a major mechanism underlying IBZ or CBZ infarcts in sICAS.[2] However, there are also studies indicating possible differences in the pathogenesis underlying these two infarct patterns. For instance, in a previous study in patients with acute ischemic stroke in the MCA territory, more patients with IBZ infarcts had MCA stenosis or occlusion, while more patients with CBZ infarcts had concomitant small cortical infarcts (implying probable embolization).[3] Investigating differences in the clinical and imaging features (including hemodynamic features) of sICAS patients with IBZ and CBZ infarcts could help understanding the potential

differences in the pathogenesis in these two circumstances, which has not been fully appreciated in previous studies.

In a series of studies, we have been using a computer tomographic angiography (CTA)-based computational fluid dynamics (CFD) model to investigate flow dynamics across sICAS. We measured the relative pressure gradient across a sICAS lesion, i.e., the translesional (post-stenotic to pre-stenotic) pressure ratio (PR), which quantitatively reflects the impairment in antegrade flow across the lesion.[4, 5] In this study, we aimed to investigate the differences in clinical and imaging features (including the translesional PR) in patients with atherosclerotic stenosis in M1 segment of MCA (MCA-M1) who had IBZ and/or CBZ infarcts, to further reveal the pathogenic mechanisms underlying these two infarct patterns. We also aimed to compare the risks of early and later recurrent strokes in patients with IBZ and CBZ infarcts, under current medical treatment regimens.

## Material and Methods

### *Study design and subjects*

This was a substudy of the Stroke Risk and Hemodynamics in Intracranial Atherosclerotic Disease (SOpHIA) study, a cohort study investigating the prognostic values of hemodynamic features of sICAS, approved by local institutional review board

(Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee; ethic number: 2014.329) with informed consent from all patients.[5] The study obeyed the Declaration of Helsinki, as amended by the World Medical Association General Assembly in October 2013. Patients screened for the SOpHIA study at Prince of Wales Hospital (PWH) in Hong Kong and the First Affiliated Hospital of Zhengzhou University in Zhengzhou, were sifted and analyzed in the current substudy, if they: 1) had an acute ischemic stroke, attributed to 50-99% atherosclerotic stenosis in MCA-M1 confirmed by CTA; 2) had IBZ and/or CBZ infarcts, with or without infarcts in other regions, confirmed in diffusion-weighted imaging (DWI) and apparent diffusion coefficient sequence within 14 days of ictus. Exclusion criteria were: 1) nonatherosclerotic intracranial stenosis (e.g., dissection, vasculitis, Moyamoya disease); 2) potential cardioembolic stroke; 3) tandem stenosis in ipsilateral common carotid artery or internal carotid artery; 4) any interventional or surgical procedure of intracranial or extracranial arteries (e.g., angioplasty or carotid endarterectomy) within one month before the index ischemic stroke; 5) any serious comorbidity with a life expectancy of <1 year since the stroke onset.

Demographics, NIH Stroke Scale (NIHSS), cardiovascular risk factors, blood pressure, laboratory test results of each patient were collected at baseline. The percentage of MCA-M1 luminal stenosis was measured on baseline CTA using the Warfarin-Aspirin

Symptomatic Intracranial Disease (WASID) method,[6] and dichotomized as moderate (50%-69%) and severe (70%-99%).

*Assessment of acute infarcts in DWI*

Acute infarcts were identified as hyperintense signals in DWI and hypointense signals in apparent diffusion coefficient map. In patients with symptomatic MCA-M1 stenosis, IBZ infarcts were usually large, confluent, cigar-shaped infarcts, or small, discrete (≥ 3 lesions), chain-like infarcts each with a diameter ≥ 3mm, paralleled with the centrum semiovale or corona radiata, the junctional regions between superficial and perforating arteries of MCA. To differentiate IBZ infarcts with lenticulostriate infarct – the latter was usually small single subcortical infarct (diameter ≤ 20 mm) at lower portion of the basal ganglia, indicating parent artery (MCA-M1 in this study) atherosclerosis occluding penetrating artery as a probable stroke mechanism.[1, 7] CBZ infarcts were wedge-shaped or ovoid infarcts in the cortical and adjacent subcortical regions between MCA and ACA territories, or MCA and PCA territories.[1, 2, 8] The borderzone infarct patterns in individual patient were classified to three categories, isolated IBZ or CBZ infarcts (IBZ infarcts or CBZ infarcts only), and coexisting IBZ and CBZ infarcts (IBZ+CBZ infarcts). The borderzone infarcts were also analyzed by the presence of IBZ (regardless of presence of CBZ) or CBZ (regardless of the presence of IBZ) infarcts. In

addition, presence of small cortical infarct(s) (diameter<10mm) in the MCA territory was recorded, indicating probably concomitant artery-to-artery embolism.[1, 3]

*Assessment of translesional PR of MCA-M1 lesion in CFD models*

We constructed a steady-state CFD model in each patient based on the CTA images and assessed the hemodynamic significance of the symptomatic MCA-M1 lesion using the ANSYS software package (ANSYS version 15.0; ANSYS Inc., Canonsburg, PA, USA), with more detailed methodology described in our previous study.[5] Briefly, CTA images were employed to extract the geometry of distal internal carotid artery and proximal segments of MCA and ACA. A mesh was then created in the vessel surface and lumen in ANSYS ICEM CFD, with at least 0.5 million tetrahedral cells in each case. The maximum size of the mesh was 0.1 mm at the inlet and outlet surface, and 0.25 mm in the remaining parts. Boundary conditions and blood flow properties were set up in ANSYS CFX-pre as follows: noncompliant vessel wall with no-slip flow condition, incompressible blood flow with constant viscosity of 0.0035 kg/m·s and density of 1,060 $kg/m^3$; mean pressure of 110 mmHg at the inlet, and mass flow rates at the outlets estimated based on mean flow velocities from a published study[9] multiplied by the cross-sectional areas of the corresponding outlet. The blood flow was then simulated by solving Navier-Stokes equations in ANSYS CFX. Convergence was achieved when the root mean square residual value reached below $10^{-4}$.

Translesional PR across an the MCA-M1 lesion was measured in the CFD model, which was the ratio of pressures measured at the 1st normal diameter distal to the lesion ($Pressure_{post\text{-}stenotic}$) and a proximal normal vessel segment ($Pressure_{pre\text{-}stenotic}$).[5] A lower PR indicates a larger translesional pressure drop and hence reduced antegrade residual flow across the lesion. PR ≤ median in all patients, or in a subgroup of patients of interest, was defined as low PR; otherwise a normal PR.[5] Of note, the leptomeningeal collateral (LMC) status was not incorporated in CFD modeling, hence the PR obtained with CFD models represented only the degree of impairment in antegrade flow across the lesion, while the LMCs that could reflect retrograde compensate the flow was assessed separately (with details provided below).

*Assessment of leptomeningeal collaterals in CTA*

We evaluated the ipsilesional LMC status by comparing the laterality in the visibility of distal vessels in the ACA and PCA territories ipsilateral and contralateral to the MCA-M1 lesion, in the maximum intensity projections of axial and coronal planes reconstructed from CTA source images using OsiriX (version 8.0.1, Pixmeo, Geneva, Switzerland). The extent of ipsilesional ACA or PCA pials was graded as 0, 1, 2 when the distal vessels in ipsilesional ACA or PCA territories were less than, equal to or more than the contralateral side. Then the scores of ipsilesional ACA and PCA pials were

summed up to represent the overall extent of ipsilesional LMCs (scores 0-4). A score of 3-4 was defined as good LMCs, otherwise (scores 0-2) poor LMCs.[10, 11]

*Treatment and follow-up*

All patients were followed up for 1 year. Patients at PWH were followed up at 1, 3, 6, 9 and 12 months by neurologists at an out-patient clinic, most of whom received optimal medical treatment according to the contemporary guidelines, including antiplatelet, statin therapy and other vascular risk factor management.[5, 12] A small proportion of PWH patients received interventional treatment (angioplasty with or without stenting) as clinically indicated, or because of enrollment in a clinical trial on interventional treatment of sICAS. Patients at the First Affiliated Hospital of Zhengzhou University were followed up at 1 year at an out-patient clinic or by telephone, all of whom received optimal medical treatment. Recurrent ischemic stroke in the same territory (SIT) of the index artery within 3 months and 1 year were recorded. A recurrent ischemic stroke was defined as newly developed neurological deficits accompanied by any new infarct(s) revealed on CT or MRI; or diagnosed by a neurologist with newly developed neurological deficits lasting more than 24 hours, if there was no CT/MRI at recurrence.[5]

*Statistical analysis*

Software IBM SPSS Statistics (version 25.0) was used to conduct data analysis. Two-sided $p<0.05$ was considered to be of statistical significance. Categorical variables were presented as numbers (percentage) and continuous variables as medians (interquartile ranges, IQR).

We first conducted statistical analyses in all patients. We compared patient characteristics and other variables in those with presence of IBZ infarcts versus otherwise, using Pearson Chi-square, Fisher's exact tests and Mann-Whitney U tests for categorical and continuous variables. Similar analyses were conducted for those with presence of CBZ infarcts versus otherwise.

We then analyzed data in patients with isolated IBZ or CBZ infarcts. We compared patient characteristics and other variables between these two groups in univariate analyses. Multivariate binary logistic regression analysis including variables with $p<0.1$ in univariate analyses were performed to reveal independent predictors for isolated IBZ infarcts; adjusted odds ratio (OR) and 95% confidence interval (CI) were obtained. Survival analyses were conducted for SIT within 3 months or 1 year, in patients receiving medical treatment alone (but not interventional treatment) before stroke recurrence (if any) or by the end of 3 months or 1 year. Kaplan-Meier curves were plotted to present the cumulative probabilities of recurrent SIT within 3 months or 1 year by isolated IBZ or CBZ infarcts, with the differences examined by log-rank tests.

## Results

A study flow chart is presented in Figure 1. Overall, 84 sICAS patients with borderzone infarct were recruited, with a median age of 62 (IQR 53-69) years and 59 (70.2%) being males. The median NIHSS at baseline was 2 (IQR 1-5). The median interval between symptom onset and MRI scan was 5 (IQR 2-7.5) days. Regarding the infarct patterns, 37, 31 and 16 patients had isolated IBZ, isolated CBZ and IBZ+CBZ infarcts, respectively. 49 (58.3%) patients had severe luminal stenosis in the MCA-M1 lesion. Translesional PR was obtained from 71 patients who had a successfully constructed CFD model, with a median PR of 0.89 (IQR 0.73-0.93) and 36 (50.7%) patients with a low PR. The ipsilesional LMC status was evaluated in 70 patients, and 35 (50.0%) had good LMCs.

*Clinical and imaging features of patients with/without IBZ or CBZ infarcts*

Univariate comparisons of baseline features between patients with/without IBZ infarcts or CBZ infarcts are presented in Table 1. Compared with those without IBZ infarcts, patients with IBZ infarcts tended to have a higher NIHSS (p=0.055), severe luminal stenosis (p=0.020) and a low PR (p=0.012) in the MCA-M1 lesion, as well as good ipsilesional LMCs (p=0.027). Compared with those without CBZ infarcts, patients with CBZ infarcts were more likely to have a history of diabetes mellitus (p=0.081),

concomitant small cortical infarcts (p=0.004), but less likely to have good ipsilesional LMCs (p=0.086). Three cases with IBZ and/or CBZ infarcts in DWI, and different PR of the MCA-M1 lesions in CFD models are presented in Figure 2.

*Clinical and imaging features of patients with isolated IBZ versus CBZ infarcts*

Among the 68 patients with isolated IBZ infarcts (n=37) or isolated CBZ infarcts (n=31), 38 (55.9%) had severe MCA-M1 stenosis and 25 (36.8%) had small cortical infarcts. In 55 patients with a successfully constructed CFD model, the median PR was 0.90 (IQR 0.80-0.93), with 28 (50.9%) patients having a low PR. The ipsilesional LMC status was evaluated in 54 patients, 26 (48.1%) had good LMCs. Demographics, clinical features and laboratory results were similar between patients with isolated IBZ and isolated CBZ infarcts (Table 2). More patients with isolated IBZ infarcts had severe MCA-M1 stenosis (p=0.034), low PR (p=0.022), and good LMCs (p=0.029), while more patients with isolated CBZ infarcts had concomitant small cortical infarcts (p=0.020).

In multivariate logistic regression analysis, low PR (adjusted OR=4.223, 95% CI 1.18-15.06; p=0.026) and good LMCs (adjusted OR=4.219, 95% CI 1.18-15.05; p=0.026), but not severe stenosis in sICAS or small cortical infarcts, were significantly associated with isolated IBZ infarcts (Table 3).

*Stroke recurrence in patients with isolated IBZ versus CBZ infarcts receiving medical treatment*

Among the 68 patients with isolated IBZ or isolated CBZ infarcts, 55 received medical treatment alone, with 28 and 27 patients respectively having isolated IBZ and CBZ infarcts at baseline. Five (9.1%) patients had a recurrent SIT within 3 months, all of whom had isolated IBZ infarcts at baseline. Nine (16.3%) patients had a recurrent SIT within 1 year: 6 of them had isolated IBZ infarcts at baseline, with isolated IBZ infarcts upon the recurrent SIT in 4 patients, no acute infarct in MRI or no CT/MRI examination upon recurrence with symptom lasting >24h in 2 patients; 3 patients had isolated CBZ infarcts at baseline, 1 with isolated CBZ infarcts, 1 with isolated IBZ infarcts and 1 with cortical infarcts upon the recurrent SIT (Supplemental Table).

The risk of recurrent SIT within 3 months was significantly higher (17.9% versus 0.0%; log-rank p=0.023) in patients with isolated IBZ infarcts than those with isolated CBZ infarcts (Figure 3.A). However, the cumulative risks of 1-year recurrent SIT were not significantly different between these two groups (21.4% versus 11.1%; log-rank p=0.271), when the difference in the cumulative risks attenuated beyond the first 3 months (Figure 3.B).

## Discussion

In this study of patients with MCA-M1 stenosis and borderzone infarcts, we found a significant, independent association between low PR (representing reduced antegrade flow across the lesion) and IBZ infarcts, while more patients with CBZ infarcts had concomitant small cortical infarcts (indicating possible embolism) than those with IBZ infarcts. These findings implied different pathogenic mechanisms behind IBZ and CBZ infarcts. More importantly, the study revealed a significantly higher risk of recurrent SIT in the first 3 months after an index ischemic stroke in those with isolated IBZ infarcts than isolated CBZ infarcts, who received optimal medical treatment according to contemporary guidelines. Yet, such risks beyond 3 months were similar in these two groups.

Lying between the supplying areas of perforating arteries and penetrating cortical branches of ACA, MCA and PCA, the IBZ is vulnerable to hypoperfusion in the presence of large artery occlusive disease.[13] Hemodynamic impairment has long been considered as a main cause of IBZ infarcts, supported by previous studies. For instance, in positron emission tomography/single photon emission computed tomography studies, elevated oxygen extraction fraction that indicates insufficient blood supply, was more commonly seen in patients with IBZ infarcts than those with CBZ infarcts.[8] In the current study, a low translesional PR in symptomatic MCA-M1 stenosis, which represents reduced antegrade flow across the lesion, was independently associated with isolated IBZ infarcts (versus isolated CBZ infarcts). The findings further supported

hemodynamic impairment, mostly reduced antegrade flow, as a mechanism underlying IBZ infarcts in the presence of MCA-M1 stenosis.

Of note, good LMCs were also independently associated with isolated IBZ (versus isolated CBZ) infarcts in this study. On one hand, presence of good ipsilateral LMCs in the presence of MCA-M1 stenosis implies probable hemodynamic significance of the lesion, since a larger translesional pressure drop (low PR) could be a driving force in recruiting the pial collaterals, as indicated in our previous study.[10] On the other hand, this also indicates that blood flow from pial collaterals may not reach the IBZ, which locates deep inside the brain. Interestingly, the severity of MCA-M1 luminal stenosis was associated with isolated IBZ infarcts in univariate analyses, but the association was neutralized after considering other imaging features in multivariate analysis. This is probably because the severity of luminal stenosis is one, but not the only factor, that governs the hemodynamic significance of an ICAS lesion and the residual antegrade flow across the lesion, as indicated in previous studies using an adjusted distal to proximal signal intensity ratio in time-of-flight MR angiography to gauge hemodynamic impairment of sICAS.[14] Although not closely relevant to the aims of this study, this again reinforces the need to reshape the current paradigm in gauging the severity of ICAS by a single measure of the luminal stenosis, while a more reasonable or more comprehensive approach is needed.[15]

Regarding CBZ infarcts, a previous study revealed concomitant small cortical infarcts in nearly 2/3 of patients with CBZ infarcts.[3] Such rate was comparable in the current study of patients with sICAS in MCA-M1. Another interesting finding of the current study was the worse LMCs in patients with isolated CBZ infarcts than IBZ infarcts, independent of other confounders in multivariate analysis. These findings on one hand suggested embolism as an underlying pathogenic mechanism in the occurrence of CBZ infarcts in MCA stenosis. Further, as the CBZ region is spatially far away from the MCA-M1 lesion, cerebral perfusion in the CBZ region is more closely related with flow from the distal cortical branches and arterioles from ACA/MCA/PCA, than with the antegrade flow across the MCA lesion (indeed 2/3 of patients with isolated CBZ infarcts had a normal PR of the MCA lesion). Therefore, poor LMCs in this study could indicate hypoperfusion in CBZ, which may reduce the clearance of emboli stranded in this region and increase the risk of developing CBZ infarcts.

Several studies have associated IBZ infarcts with a worse clinical course early after an index stroke (e.g., in the first week) and a worse functional outcome at 3 months, compared with other infarct patterns including CBZ infarcts.[16, 17] Previous studies also reported a higher risk of stroke recurrence in sICAS patients with borderzone infarcts than those with other infarct patterns, especially in the first 3 months, but IBZ and CBZ infarcts were mostly mixed in these analyses.[18-20] In another retrospective study, IBZ infarcts, rather than CBZ infarcts, was a predictor for recurrent cerebrovascular events

within 90 days in sICAS patients.[21] In our study, although we did not record early neurological deterioration of the patients within the first few days after the index stroke, we investigated the risks of recurrent SITs in 3 months and 1 year in those with isolated IBZ and CBZ infarcts. The recurrent SITs in the first 3 months all occurred in those with isolated IBZ infarcts at baseline, while SITs were more likely to recur beyond 3 months in patients with isolated CBZ infarcts at baseline. These findings suggested that the contemporary medical treatment strategy for sICAS patients, including up to 90 days of dual antiplatelet treatment and stringent vascular risk factor management, may be effective for early stroke prevention in those with CBZ infarcts, while switching to mono antiplatelet treatment after 3 months may be insufficient to prevent stroke recurrence in those with CBZ infarcts (when embolism may play a role). On the other hand, this treatment regimen may be insufficient, or even inappropriate, for early stroke prevention in those with IBZ infarcts when hypoperfusion is a major stroke mechanism. Indeed, our previous work has revealed a higher risk of stroke recurrence in sICAS patients with an impaired antegrade blood flow (low PR), when the systolic blood pressure was controlled strictly below 130 mmHg versus 130-150 mmHg.[4] This is possibly related with impaired cerebral autoregulation in these patients, when stringent controlled blood pressure would further reduce cerebral perfusion. Therefore, more individualized treatments may be needed for sICAS patients with IBZ and CBZ infarcts, for instance, considering less stringent blood pressure control or even cerebral blood

flow augmentation measures in patients with IBZ infarcts, and longer-term or more intensive antiplatelet and statin treatment in those with CBZ infarcts. These warrant further investigations.

Our study had strengths. First, to study borderzone infarcts, it is very important to separately assess blood flow from different routes to the borderzone regions. In the current study, we used CFD models to simulate cerebral blood flow across the sICAS lesion and obtained a translesional PR to quantitatively reflect the effects of the lesion on the antegrade flow; we also assessed the LMCs in the distal vascular bed that could reflect retrograde compensating flow. To the best of our knowledge, this has not been done before in investigations of borderzone infarcts. Second, blood flow to the IBZ and CBZ regions may be differently affected in those with sICAS proximal or distal to the circle of Willis. For instance, a proximal internal carotid artery stenosis could affect blood flow in the entire anterior circulation territory, including the CBZ regions between ACA and MCA territories, while LMC flow may compensate blood flow in the CBZ region between ACA/MCA and PCA/MCA territories in those with MCA stenosis. Therefore, we have limited the analyses to patients with sICAS at MCA-M1 in the current study.

This study also had limitations. First, we inferred embolism as a possible mechanism underlying the small cortical infarcts in this study, while the inference would be more

solid with validation by transcranial Doppler-based microembolic monitoring. Second, with the strict inclusion criteria, the sample size was small, and hence the small number of patients with the outcome events. This has prevented multivariate analyses on the outcomes. Moreover, we used the median value to dichotomize the translesional PR as in our previous studies, while more studies are needed to explore for an appropriate cut-off value to define a "low PR". In addition, future studies are also needed to verify indicators for the coexistence of IBZ and CBZ infarcts and their clinical outcomes, which has not been investigated in the current study due to the small number of cases with IBZ+CBZ infarcts.

Despite these limitations, we found that in patients with atherosclerotic MCA-M1 stenosis and borderzone infarcts, IBZ infarcts are more closely related with hemodynamic compromise across the ICAS lesion than CBZ infarcts, while embolism may be a possible pathogenic mechanism underlying CBZ infarcts. Moreover, under the current medical treatment regimen, IBZ infarcts at baseline may be associated with a higher risk of same-territory stroke recurrence within 3 months than CBZ infarcts, while such risks beyond 3 months may be similar in these two groups. More individualized treatments may be needed for sICAS patients with IBZ and CBZ infarcts, which warrants further investigations.

**Funding:** Early Career Scheme (Reference number 24103122), Research Grants Council of Hong Kong; Li Ka Shing Institute of Health Sciences.

**Acknowledgements**

We thank all participants and investigators who participated in this study.

**Disclosures of conflicting interests**

The Author(s) declare(s) that there is no conflict of interest

**Author contribution statement**

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

**Supplemental material**

Supplemental material for this article is available online.

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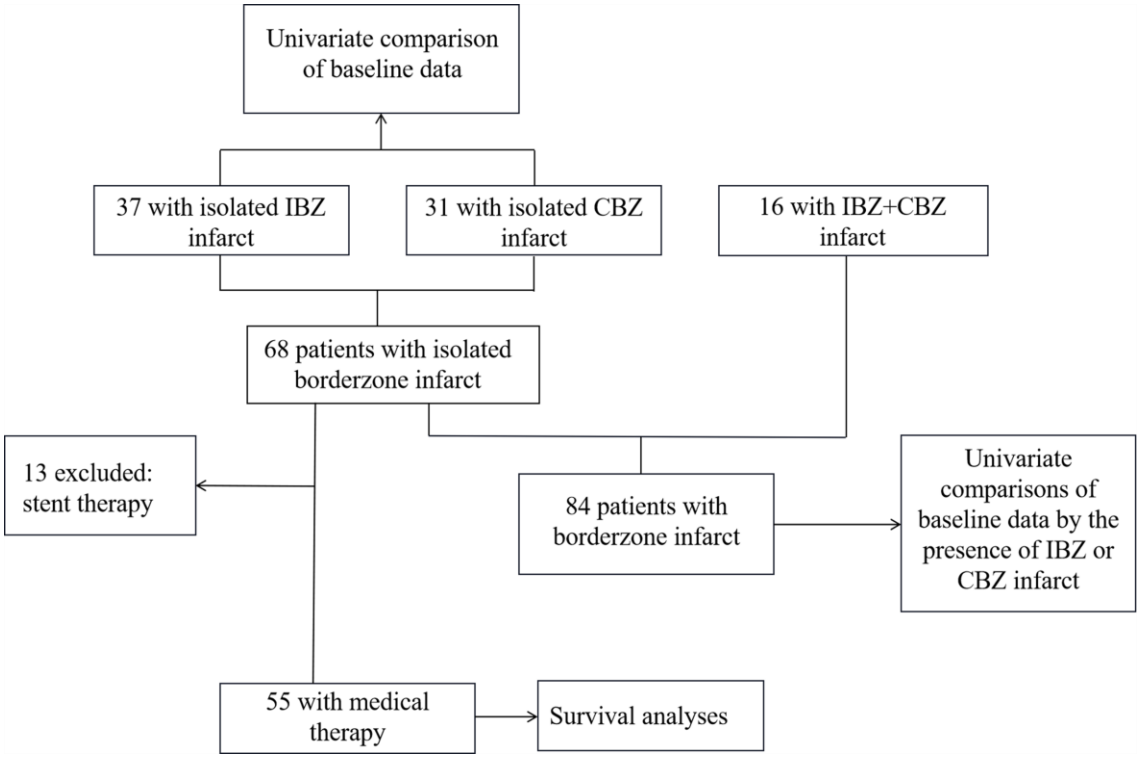


**Figure 1:** Flow chart of this study.

IBZ, internal borderzone; CBZ, cortical borderzone.

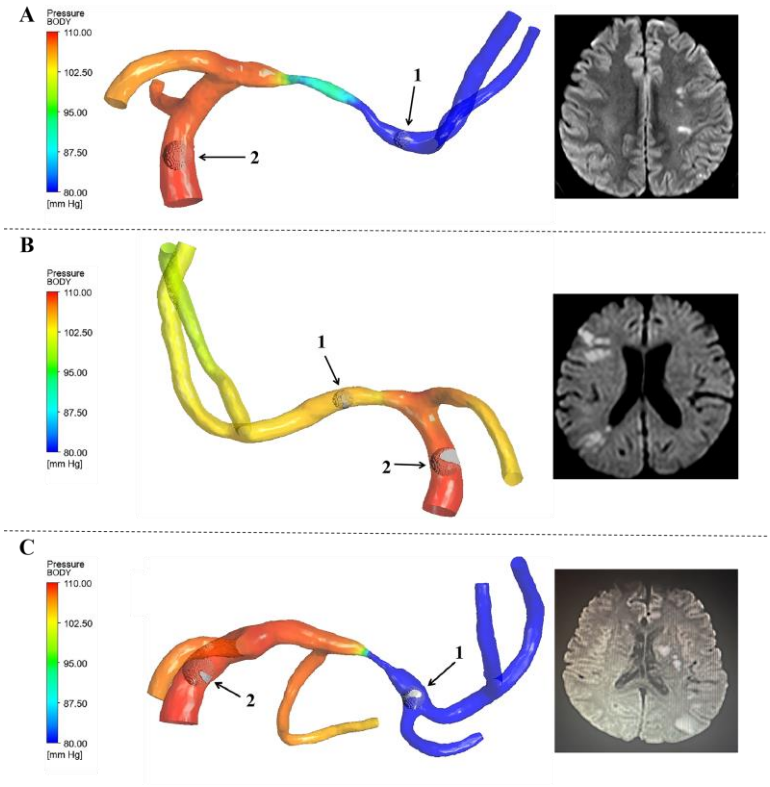


**Figure 2:** Pressure distribution across symptomatic M1 segment of middle cerebral artery (MCA-M1) stenosis in the computational fluid dynamics (CFD) models (left panel) and the infarct patterns in diffusion-weighted images (DWI, right panel) in 3 patients. Translesional pressure ratio (PR)= $Pressure_{post\text{-}stenotic}$/$Pressure_{pre\text{-}stenotic}$. Locations for measuring the $Pressure_{post\text{-}stenotic}$ and $Pressure_{pre\text{-}stenotic}$ in the CFD models are marked with arrows 1 and 2, respectively.

A. Low PR (PR=0.71) of left MCA-M1 stenosis noted in the CFD model, indicating a significant pressure gradient and hence impaired antegrade flow across the lesion. Multiple small chain-like infarcts noted in the left IBZ in DWI.
B. Normal PR (PR=0.96) of right MCA-M1 stenosis noted in the CFD model, indicating a small translesional pressure gradient. Wedge-shaped infarcts noted in the right anterior and posterior CBZ noticed in DWI.
C. Low PR (PR=0.42) of left MCA-M1 stenosis noted in the CFD model, indicating a significant pressure gradient and hence impaired antegrade flow across the lesion. Wedge-shaped infarcts in the left posterior CBZ and multiple small chain-like infarcts noted in the ipsilateral IBZ.

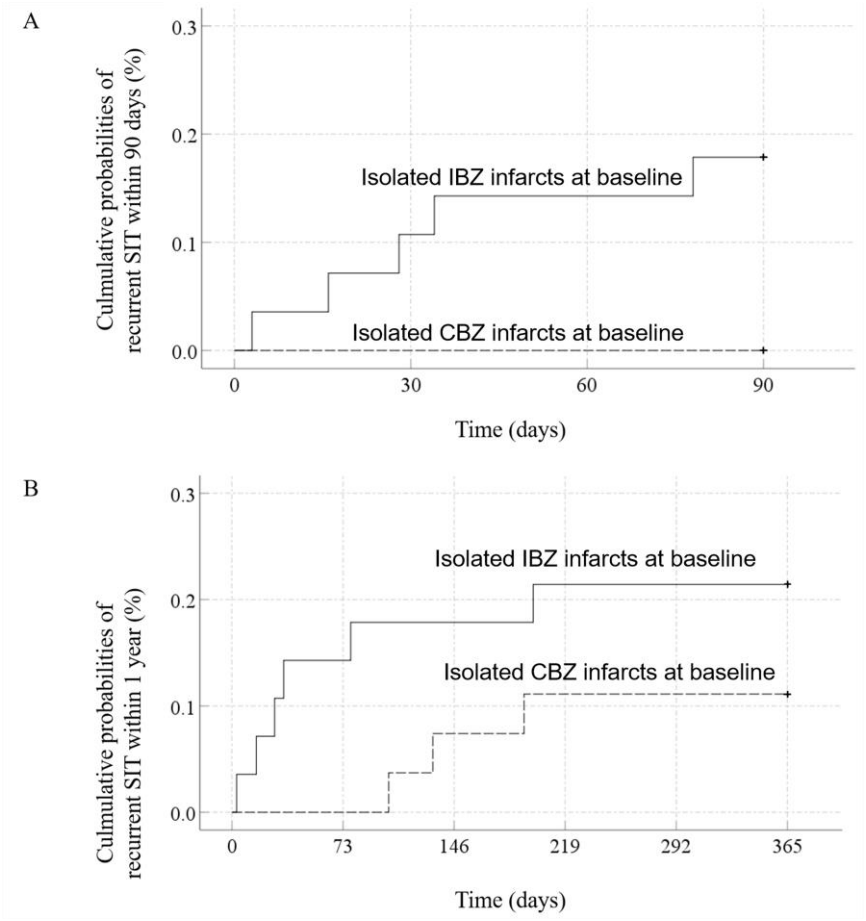


**Figure 3:** Cumulative probabilities of recurrent ischemic stroke in the same territory (SIT) within 3 months (A) and 1 year (B) in patients with isolated internal borderzone (IBZ) or cortical borderzone (CBZ) infarcts at baseline.

A. Significant difference in the cumulative risks of recurrent SIT within 3 months in patients with isolated IBZ and CBZ infarcts at baseline (17.9% versus 0.0%; log-rank p=0.023).
B. The cumulative risks of recurrent SIT within 1 year were not significantly different between patients with isolated IBZ and CBZ infarcts at baseline (21.4% versus11.1%; log-rank p=0.271). Of note, the difference in the cumulative risks between the two groups seems narrowed beyond the first 3 months.

**Table 1. Baseline features of patients with or without IBZ infarcts/CBZ infarcts**

| | Presence of IBZ infarcts | | | Presence of CBZ infarcts | | |
|---|---|---|---|---|---|---|
| Characteristics | Yes (n=53) | No (n=31) | P value | Yes (n=47) | No (n=37) | P value |
| Age, year | 62 (53-69) | 61 (53-68) | 0.760 | 61 (53-69) | 62 (54-68) | 0.868 |
| Male | 37 (69.8) | 22 (71.0) | 0.911 | 35 (74.5) | 24 (64.9) | 0.339 |
| Smoking | 24 (45.3) | 16 (51.6) | 0.575 | 21 (44.7) | 19 (51.4) | 0.543 |
| Hypertension | 34 (64.2) | 23 (74.2) | 0.342 | 35 (74.5) | 22 (59.5) | 0.144 |
| Diabetes mellitus | 18 (34.0) | 11 (35.5) | 0.887 | 20 (42.6) | 9 (24.3) | 0.081 |
| Hyperlipidemia | 30 (56.6) | 19 (61.3) | 0.674 | 27 (57.4) | 22 (59.5) | 0.853 |
| Ischemic heart disease | 3 (5.7) | 1 (3.2) | 1.000 | 3 (6.5) | 1 (2.7) | 0.625 |
| Previous stroke/TIA | 5 (9.4) | 3 (9.7) | 1.000 | 5 (10.9) | 3 (8.1) | 0.727 |
| Baseline NIHSS | 3 (1-5) | 2 (1-3) | 0.055 | 2 (1-4) | 3 (1-6) | 0.599 |
| SBP, mmHg | 150 (131-168) | 148 (135-169) | 0.739 | 150 (134-167) | 153 (131-172) | 0.787 |
| DBP, mmHg | 80 (70-92) | 85 (76-97) | 0.176 | 84 (72-95) | 79 (72-92) | 0.300 |
| Mean BP, mmHg | 103 (93-117) | 108 (99-114) | 0.276 | 105 (96-116) | 103 (93-119) | 0.643 |
| **Laboratory results** | | | | | | |
| Fasting glucose, mmol/L | 5.7 (5.1-7.1) | 5.6 (5.0-8.1) | 0.883 | 5.7 (5.1-8.5) | 5.4 (5.0-6.9) | 0.228 |
| HbA1c, % | 6.1 (5.6-6.8) | 6.0 (5.6-7.1) | 0.948 | 6.3 (5.6-7.4) | 5.9 (5.6-6.7) | 0.105 |
| Triglyceride, mmol/L | 1.6 (1.1-2.2) | 1.3 (1.0-1.9) | 0.345 | 1.4 (1.0-2.1) | 1.4 (1.1-2.1) | 0.707 |
| HDL, mmol/L | 1.1 (0.9-1.3) | 1.1 (1.0-1.4) | 0.466 | 1.1 (0.9-1.3) | 1.1 (0.9-1.5) | 0.619 |
| LDL, mmol/L | 3.2 (2.3-3.9) | 2.9 (2.4-4.0) | 0.881 | 2.8 (2.3-3.9) | 3.3 (2.6-4.0) | 0.124 |
| **Imaging features** | | | | | | |
| MCA-M1 luminal stenosis, % | 71 (66-82) | 65 (55-75) | 0.017 | 70 (60-77) | 70 (63-81) | 0.376 |
| Severe (70%-99%) MCA-M1 stenosis | 36 (67.9) | 13 (41.9) | 0.020 | 24 (51.5) | 25 (49.0) | 0.128 |
| Small cortical infarcts | 19 (35.8) | 16 (51.6) | 0.157 | 26 (55.3) | 9 (24.3) | 0.004 |
| [a]Translesional PR | 0.84 (0.67-0.91) | 0.92 (0.88-0.95) | <0.001 | 0.90 (0.77-0.94) | 0.87 (0.70-0.91) | 0.103 |
| [a]Low PR | 27 (62.8) | 9 (32.1) | 0.012 | 21 (47.7) | 15 (55.6) | 0.522 |
| [b]Good LMCs | 26 (60.5) | 9 (33.3) | 0.027 | 18 (41.9) | 17 (63.0) | 0.086 |

[a] PR: obtained in 71 patients

[b] LMCs: evaluated in 70 patients

Abbreviations: IBZ: internal borderzone; CBZ: cortical borderzone; SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure; TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale; HbA1c: glycosylated hemoglobin; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; MCA-M1: M1 segment of middle cerebral artery; PR: pressure ratio; LMCs: leptomeningeal collaterals.

**Table 2. Baseline features of patients with isolated IBZ versus isolated CBZ infarcts**

| Characteristics | Isolated IBZ infarcts (n=37) | Isolated CBZ infarcts (n=31) | P value |
|---|---|---|---|
| Age, year | 62 (54-68) | 61 (53-68) | 0.786 |
| Male | 24 (64.9) | 22 (71.0) | 0.592 |
| Smoking | 19 (51.4) | 16 (51.6) | 0.983 |
| Hypertension | 22 (59.5) | 23 (74.2) | 0.201 |
| Diabetes mellitus | 9 (24.3) | 11 (35.5) | 0.314 |
| Hyperlipidemia | 22 (59.5) | 19 (61.3) | 0.878 |
| Ischemic heart disease | 1 (2.7) | 1 (3.2) | 1.000 |
| Previous stroke/TIA | 3 (8.1) | 3 (9.7) | 1.000 |
| Baseline NIHSS | 3 (1-6) | 2 (1-3) | 0.186 |
| SBP, mmHg | 153 (131-172) | 148 (135-169) | 0.917 |
| DBP, mmHg | 79 (72-92) | 85 (76-97) | 0.181 |
| Mean BP, mmHg | 103 (93-119) | 108 (99-114) | 0.349 |
| **Laboratory results** | | | |
| Fasting glucose, mmol/L | 5.4 (5.0-6.9) | 5.6 (5.0-8.1) | 0.399 |
| HbA1c, % | 5.9 (5.6-6.7) | 6.0 (5.6-7.1) | 0.864 |
| Triglyceride, mmol/L | 1.4 (1.1-2.1) | 1.3 (1.0-1.9) | 0.610 |
| HDL, mmol/L | 1.1 (0.9-1.5) | 1.2 (1.0-1.4) | 0.074 |
| LDL, mmol/L | 3.3 (2.6-4.0) | 2.9 (2.4-4.0) | 0.061 |
| **Imaging features** | | | |
| MCA-M1 luminal stenosis, % | 70 (63-81) | 65 (55-75) | 0.067 |
| Severe (70%-99%) MCA-M1 stenosis | 25 (67.6) | 13 (41.9) | 0.034 |
| Small cortical infarcts | 9 (24.3) | 16 (51.6) | 0.020 |
| [a]Translesional PR | 0.87 (0.70-0.91) | 0.92 (0.88-0.95) | 0.003 |
| [a]Low PR | 18 (66.7) | 10 (35.7) | 0.022 |
| [b]Good LMCs | 17 (63.0) | 9 (33.3) | 0.029 |

[a] PR: obtained in 55 patients.

[b] LMCs: evaluated in 54 patients.

Abbreviations: IBZ: internal borderzone; CBZ: cortical borderzone; SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure; TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale; HbA1c: glycosylated hemoglobin; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; MCA-M1: M1 segment of middle cerebral artery; PR: pressure ratio; LMCs: leptomeningeal collaterals.

**Table 3. Logistic regression analyses for factors associated with isolated IBZ infarcts (versus isolated CBZ infarcts)**

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Severe (70%-99%) MCA-M1 stenosis | 2.89 (1.07-7.77) | 0.036 | 1.50 (0.42-5.39) | 0.539 |
| Small cortical infarcts | 0.30 (0.11-0.84) | 0.022 | 0.72 (0.19-2.70) | 0.628 |
| Low PR | 3.60 (1.18-10.95) | 0.024 | 4.22 (1.18-15.06) | 0.026 |
| Good LMCs | 3.40 (1.11-10.40) | 0.032 | 4.22 (1.18-15.05) | 0.026 |

Abbreviations: IBZ: internal borderzone; CBZ: cortical borderzone; OR: odds ratio; CI: confidential interval; MCA-M1: M1 segment of middle cerebral artery; PR: pressure ratio; LMCs: leptomeningeal collaterals

**Supplemental Table. Infarct patterns at baseline and recurrent SIT in patients with SIT within 1 year**

| Number | Interval between stroke onset and recurrent SIT (days) | Infarct pattern at baseline | Infarct pattern at recurrent SIT |
|---|---|---|---|
| 1 | 3 | Isolated IBZ infarcts | Isolated IBZ infarcts |
| 2 | 16 | Isolated IBZ infarcts | Isolated IBZ infarcts |
| 3 | 28 | Isolated IBZ infarcts | No MRI, symptoms lasting > 24h |
| 4 | 34 | Isolated IBZ infarcts | Isolated IBZ infarcts |
| 5 | 78 | Isolated IBZ infarcts | No acute infarct in MRI, but symptoms lasting >24h |
| 6 | 103 | Isolated CBZ infarcts | Scartter cortical infarcts |
| 7 | 132 | Isolated CBZ infarcts | Isolated IBZ infarcts |
| 8 | 192 | Isolated CBZ infarcts | Isolated CBZ infarcts |
| 9 | 198 | Isolated IBZ infarcts | Isolated IBZ infarcts |

Abbreviations: SIT, stroke in the same territory; IBZ, internal borderzone; CBZ, cortical borderzone; MRI, magnetic resonance image.