Clinical Radiology 77 (2022) 833–839

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Association between cerebral blood flow changes and blood–brain barrier compromise in spontaneous intracerebral haemorrhage

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ARTICLE INFORMATION

Article history:
Received 28 January 2022
Received in revised form
26 May 2022
Accepted 30 May 2022

AIM: To quantitatively evaluate blood–brain barrier (BBB) permeability in the perihaematomal region of spontaneous intracerebral haemorrhage (ICH) and investigate the association between the alterations in cerebral blood flow and BBB permeability around the haematoma.

MATERIALS AND METHODS: Spontaneous ICH patients underwent unenhanced computed tomography (CT) and CT perfusion (CTP) simultaneously. Haematoma volume was measured on CT. The values of cerebral haemodynamic parameters including cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), time to peak (TTP), and permeability–surface area product (PS) were measured in the perihaematomal region and the contralateral mirror region, and then relative values were calculated for statistical analysis. Linear regression was used to evaluate associations between BBB permeability and variables.

RESULTS: A total of 87 ICH patients were included in this study. The focally elevated BBB permeability was observed in the perihaematomal region in ICH patients. Linear regression showed that reduced rCBF ($\beta = -0.379$, p=0.001) and increased rCBV ($\beta = 0.412$, p=0.000) correlated independently with increased relative PS (rPS) value in deep ICH, while only increased rCBV ($\beta = 0.423$, p=0.071) correlated to increased rPS value in patients with lobar ICH.

CONCLUSIONS: BBB permeability is focally elevated in the region around the haematoma. Cerebral haemodynamic alterations are associated with increased BBB permeability. Cerebral hypoperfusion may aggravate BBB compromise, and a compensatory increase in CBV may lead to reperfusion injury on BBB.

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https://doi.org/10.1016/j.crad.2022.05.028
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Introduction

Intracerebral haemorrhage (ICH) is the most devastating subtype of stroke with high mortality and poor functional outcomes.[1] Severe functional impairment is associated with primary brain damage resulting from the mechanical injury of haematoma formation.[2,3] More importantly, secondary brain injuries, such as vasogenic oedema formation and blood–brain barrier (BBB) compromise are thought to contribute to the unfavourable ICH-related outcomes.[4–6]

The BBB is a neurovascular unit consisting of endothelial cells, tight junctions, basement membrane, pericytes, and astrocytic endfeet, and plays a fundamental role in maintaining the homeostasis of the cerebral nervous system (Fig 1).[7] In experimental models of ICH, the toxic effects of thrombin, haemoglobin breakdown products, and some inflammatory mediators have been observed to result in elevated BBB permeability, and further contribute to the formation of vasogenic oedema around the haematoma.[3,8,9] In ICH patients, previous studies have reported BBB compromise leading to perihaematomal oedema formation, which is a known radiological marker of secondary injury.[3,10,11] Therefore, BBB compromise may be an important factor in secondary brain injury caused by ICH, and it could serve as a potential target for therapeutic interventions focused on alleviating cerebral oedema in patients with ICH.

BBB compromise may lead to the leaking of contrast agent into the extravascular space, and the permeability–surface area product (PS) can be calculated by the rate of iodinated contrast medium extravasation during computed tomography (CT) perfusion (CTP) acquisition. The PS value, as a quantitative indicator of BBB permeability, may be used to evaluate the extent of BBB compromise.[12] In previous studies of ICH patients, CTP has been used to identify and assess BBB permeability and cerebral perfusion around the haematoma after ICH.[13,14] Reduced cerebral perfusion and increased BBB permeability have been demonstrated in the perihaematomal region after ICH[13–15]; however, whether the perihaematomal hypoperfusion is related and contributes to the BBB compromise is unclear. It was hypothesised that the reduced cerebral blood flow may aggravate BBB compromise in the perihaematomal region after ICH.

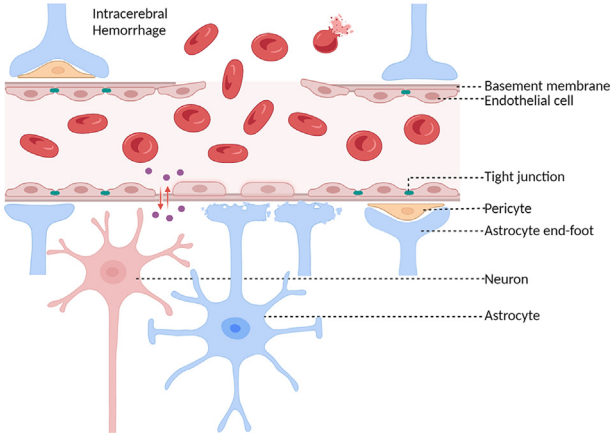

Figure 1 BBB compromise around the haematoma. BBB compromise presents multiple structural injures including the swelling of endothelial cells, the opening of tight junction, swelling and disintegration of astrocyte end-feet, degradation of basement membranes, and microvascular rupture (Created with https://biorender.com/.).

The present study aimed to quantify BBB permeability and investigate the association between cerebral haemodynamic changes and BBB permeability alterations in the region around the haematoma in spontaneous ICH patients using CTP, to provide valuable information for poor outcome evaluation and therapeutic intervention in patients with ICH.

Materials and methods

Population and clinical data

The study protocol was approved by the institutional review board. No informed consent was required because of the retrospective nature of the study. Processed data that support the findings of this study are available from the corresponding author on reasonable request.

Eighty-seven patients who presented with a spontaneous supratentorial ICH from the emergency, outpatient, and inpatient departments from September 2019 to March 2020 were analysed retrospectively. The following inclusion criteria were applied for this study: (1) age ≥18 years; (2) supratentorial parenchyma haemorrhage confirmed by baseline CT; (3) presence of follow-up CTP examination. Patients with the following characteristics were excluded: (1) ICH secondary to intracranial aneurysm, cerebral infarction, vascular malformation, brain tumours, trauma, vasculitis, illicit drug usage, septicaemia, and other rarer causes; (2) haemorrhage breaking into the ventricles and subarachnoid space; (3) stereotactic therapy before CTP; (4) a history of large cerebral infarction; (5) cases with severe complications resulting from the functional failure of vital organs; (6) lack of clinical data; (7) poor CTP image quality.

For included patients, demographic and clinical data including age, sex, and time from ICH onset to CTP imaging were recorded. Comorbid conditions, such as the history of hypertension, diabetes mellitus, previous stroke, smoking, and alcohol abuse were also recorded. National Institutes of Health Stroke Scale (NIHSS) score, Glasgow Coma Scale (GCS) score, admission systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded. BP was managed according to the American Heart Association/American Stroke Association guidelines.[16] Based on the ICH onset to CTP scan time, the patients were further subdivided into four groups: within 1 day, 1–3 days, 4–7 days, and 8–14 days.

Image acquisition

CT examinations including CT and CTP were performed on a Revolution CT machine (GE Healthcare, Milwaukee, WI, USA). Unenhanced CT was performed with the following

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parameters: 120 kVp, 300 mA, 512 × 512 image matrix, 5-mm section thickness, 5-mm intersection interval. CT perfusion was performed with the injection of 50 ml of iodinated contrast material (iohexol [Omnipaque], 350 mg iodine/ml; GE Healthcare, Shanghai, China) into an antecubital vein at a rate of 6 ml/s, followed by 20 ml saline flush at the same injection rate. The following technical settings were applied: 80 kVp, 150 mAs, 512 × 512 image matrix, 1 second rotation time, 5-mm section thickness with no interval. A total of 512 sections was obtained with a total scan time of 44 seconds.

Image analysis

Post-processing of raw CTP source images was performed on a standard Advantage Workstation (AW4.7, GE Healthcare). The anterior cerebral artery and the superior sagittal sinus were chosen to obtain arterial input function and venous output function, respectively. Then parametric maps of PS, cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP) were generated by the CT Perfusion 4D (GE Healthcare) from the raw CTP data.

The measurements of all data were completed in form of parametric maps. Regions of interest (ROIs) were drawn on CTP base image and were superimposed onto the PS, CBF, CBV, MTT, and TTP maps. ROIs included eight 50 mm^2 circles approximately equably distributed in the perihaematomal region (defined as 1 cm away from the rim of haematoma) at the image section with the maximum scale of haematoma. Then, the contralateral mirror ROIs were obtained by the midline as the axis of symmetry (Fig 2). Special care was taken to avoid the major blood vessels, sulcus, ventricles, calcifications, and bones. The mean values of the eight ROIs were calculated and then the relative values including rCBF, rCBV, rMTT, rTTP, and rPS were obtained by the ratio of the ipsilateral to contralateral values. PS indicates that the amount of contrast agent that leaks from intravascular into extravascular space per minute in 100 g of brain tissue.[17] The unit for PS is millilitres per 100g per minute and its value is affected by the change in CBF. Given this, as done in the previous studies,[18] the relative permeability of the BBB was defined as the ratio of rPS to rCBF, to eliminate the inherent impact of the change in CBF on PS. Haematoma volume was measured using semi-automated Hounsfield unit thresholding on unenhanced CT. The data were measured independently by two investigators.

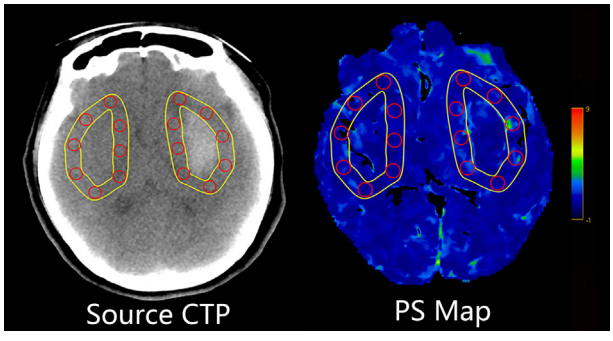

Figure 2 Regions of interest (ROIs) on CTP image and PS map. The inner yellow line is the rim of haematoma, and a 1-cm perihaematomal zone is outlined between the two yellow lines. Red circles define ROIs drawn in the perihaematomal region and the contralateral mirror region.

Statistical analysis

All statistical analyses were performed on SPSS (version 25.0, IBM-SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]) and discrete variables as count (percentage). Comparison between continuous variables was made using *t*-test or Mann–Whitney U-test. The chi-square test was used to compare discrete variables.

The relative PS value (rPS) was log-transformed to approximate normality and then univariable linear regression was used to evaluate unadjusted associations between log-transformed rPS value and variables. The covariates with $p<0.1$ were included in the multivariable linear regression model. Independent associations were identified with multivariable linear regression using a step-wise model building method. Collinear factors were removed based on the variance inflation factor. Furthermore, the correlation between rPS/rCBF and rCBF was performed to confirm the validity of the initial result. All tests of significance were two-tailed, and $p<0.05$ indicated statistical significance.

Results

Patient characteristics

A total of 87 patients with ICH within 14 days after onset were included in this study, consisting of 68 with deep ICH and 19 with lobar ICH. Sixty-two patients (71.3%) were men, and the mean age of all patients was 51 ± 12 years, with a range from 18 to 76 years. The median (interquartile range) NIHSS score at admission was 7 (11) and the median (interquartile range) GCS score at admission was 15 (2). Sixty-one patients (70%) had a history of hypertension. The mean admission SBP and DBP were 161 ± 20 and 92 ± 14 mmHg, respectively. Among these ICH patients, 16% had a previous ischaemic stroke and 6% had a previous ICH. There was no significant difference in clinical characteristics between the deep ICH ($n=68$) and lobar ICH ($n=19$). The demographic and clinical characteristics of all patients are summarised in Table 1.

Cerebral haemodynamics

Among the 87 patients, the CBF and CBV were decreased significantly around the haematoma ($p=0.000$). In addition, 30 patients presented slightly increased rCBV relative to the contralateral homologous region. The MTT and TTP around haematoma were significantly delayed than those in the contralateral region ($p=0.000$). There was no significant difference in perihaematomal relative haemodynamic

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parameters, rCBF, rCBV, rMTT, and rTTP, between deep and lobar ICH.

BBB permeability

The regions of increased BBB permeability showed a high colour level in the PS map, and the higher the colour level, indicating proportionally severe BBB compromise. The regions of focally elevated BBB permeability were found in the area adjacent to the haematoma in 84 patients (p=0.000). BBB permeability had significantly highest values at 8–14 days after ICH than that at other periods in all patients (p=0.008) and in deep ICH patients (p=0.029).

Relationship between cerebral haemodynamics and BBB permeability

The perihaematomal rCBF, rCBV and rMTT correlated significantly with BBB permeability rPS value in deep ICH patients (Table 2). Perihaematomal rCBF and rCBV remained significantly correlated with rPS value after adjustment for potential confounders. The reduced rCBF (β = −0.379, p=0.001) and increased rCBV (β=0.412, p=0.000) were independently related to BBB permeability in deep ICH, as shown in Table 3. The rPS/rCBF was observed to be inversely correlated with rCBF (β = −0.605, p=0.000) as shown in Fig 3(b), indicating increased BBB permeability to be associated with reduced CBF. In lobar ICH, rCBV was observed to be related to increased rPS but the association did not reach statistical significance (β=0.423, p=0.071) and there was also no correlation between rCBF and rPS value.

Table 1
Baseline intracerebral haemorrhage patients characteristics.

	All (n=87)	Deep (n=68)	Lobar (n=19)
Sex, M	62 (71%)	46 (68%)	16 (84%)
Age, years, mean ± SD	51 ± 12	52 ± 10	46 ± 17
Clinical characteristics			
Hypertension, *n*	61 (70%)	48 (71%)	13 (68%)
Diabetes, *n*	17 (20%)	15 (22%)	2 (11%)
Previous ischaemic stroke, *n*	14 (16%)	10 (15%)	4 (21%)
Previous ICH, *n*	5 (6%)	3 (4%)	2 (11%)
Alcohol abuse, *n*	34 (39%)	27 (40%)	7 (37%)
Smoking, *n*	47 (54%)	36 (53%)	11 (58%)
NHISS, median (IQR)	7 (11)	6 (11)	9 (14)
GCS, median (IQR)	15 (2)	15 (2)	14 (6)
SBP, mmHg, mean ± SD	161 ± 20	163 ± 23	157 ± 21
DBP, mmHg, mean ± SD	92 ± 14	93 ± 14	89 ± 14
Time to CTP, days, median (IQR)	2.2 (5.3)	2.3 (5.8)	2.1 (4.6)
HV, ml, median (IQR)	10.2 (21.6)	9.5 (18.9)	24.2 (26.3)
PHE, ml, median (IQR)	11.3 (17.7)	12.1 (19.6)	10.1 (15.2)
Perihaematomal rPS, median (IQR)	1.64 (0.88)	1.67 (0.89)	1.57 (0.88)
0–24 h (n=26)	1.54 (0.79)	1.54 (0.68)	1.28 (2.97)
1–3 days (n=22)	1.57 (0.90)	1.62 (0.95)	1.50 (0.52)
4–7 days (n=22)	1.59 (0.62)	1.61 (0.68)	1.57 (0.50)
8–14 days (n=17)	2.18 (2.24)	2.17 (2.21)	3.18 (none)
P value	0.008	0.029	0.394
Haemodynamic parameters			
rCBF, mean ± SD	0.67 ± 0.15	0.67 ± 0.16	0.66 ± 0.13
rCBV, mean ± SD	0.94 ± 0.13	0.94 ± 0.13	0.93 ± 0.13
rMTT, mean ± SD	1.64 ± 0.41	1.63 ± 0.42	1.67 ± 0.39
rTTP, mean ± SD	1.19 ± 0.25	1.19 ± 0.27	1.20 ± 0.19
rPS/rCBF, median (IQR)	2.60 (1.66)	2.65 (1.61)	2.51 (1.97)

DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; HV, haematoma volume; IQR, interquartile range; NCCT, unenhanced computed tomography; NIHSS, National Institutes of Health Stroke Scale; PHE, perihaematomal oedema; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; rMTT, relative mean transit time; rTTP, relative time to peak; rPS, relative permeability–surface area product; SBP, systolic blood pressure; SD, standard deviation.

Discussion

The present study demonstrated using CTP that haemodynamic changes and BBB compromise occur around the haematoma, and a significant association was observed between cerebral haemodynamic parameters and BBB permeability in a cohort of 87 spontaneous ICH patients. Perihaematomal rCBF and rCBV were independently associated with the increased BBB permeability. These findings suggest that haemodynamic abnormality may play a role in the course of BBB injury. The targeted regulation of cerebral blood flow may guide future therapeutic interventions aimed at the amelioration of BBB compromise and oedema growth in ICH patients.

The present study showed the presence of a hypoperfused area around the haematoma and abnormal cerebral perfusion, such as the changes of rCBF, rCBV, rMTT, and rTTP. Similar observations have been reported by Rosand *et al.*[19] who found a gradient of hypoperfusion surrounding the haematoma. Reduced CBF was also reported in several single-photon-emission CT (SPECT) and magnetic resonance imaging (MRI) studies aimed at investigating perihaematomal perfusion.[20–22] Collectively, these studies indicate the presence of haemodynamic changes in the perihaematomal region. The observed haemodynamic abnormalities, which particularly the reduced CBF, could be the result of compression of the microcirculation and decline of vascular bed volume due to the mass effect of the haematoma. In addition, there is evidence to suggest that the reduced CBF normalised by 3–5 days after ICH onset[23]; however, it has been suggested that hypoperfusion could persist into subacute and chronic phases after ICH.[24] This discrepancy in the regain of perfusion may be affected by

Table 2
Univariable linear regression of perihaematomal rPS.

Covariate	Deep		Lobar	
	β (SE)	*p*-Value	β (SE)	*p*-Value
Age	0.054 (0.002)	0.661	-0.316 (0.003)	0.188
Sex (male versus female)	-0.172 (0.046)	0.160	-0.005 (0.130)	0.984
Interval time (days)	0.282 (0.006)	0.020	0.348 (0.015)	0.144
rCBF	-0.285 (0.147)	0.019	0.084 (0.259)	0.731
rCBV	0.324 (0.166)	0.007	0.423 (0.303)	0.071
rMTT	0.208 (0.012)	0.089	-0.054 (0.018)	0.827
rTTP	0.150 (0.101)	0.222	-0.042 (0.139)	0.863
Haematoma volume	0.073 (0.001)	0.555	-0.252 (0.003)	0.299

rCBF indicates relative cerebral blood flow; rCBV, relative cerebral blood volume; rMTT, relative mean transit time; rTTP, relative time to peak; rPS, relative permeability–surface area product.

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Table 3
Multivariable analysis of perihaematomal relative log-transformed rPS in deep ICH.

Covariate	Deep ICH	
	β (SE)	*p*-Value
rCBF	-0.379 (0.138)	0.001
rCBV	0.412 (0.158)	0.000

rCBF indicates relative cerebral blood flow, rCBV indicates relative cerebral blood volume.
ICH, intracerebral haemorrhage; rCBF indicates relative cerebral blood flow; rCBV, relative cerebral blood volume; rPS, relative permeability–surface area product.

individual differences in haematoma volumes, the condition of blood vessels and collateral flow.

Using CTP parametric maps, as indicated by elevated PS, focally increased BBB permeability was observed in the perihaematomal region. The areas of BBB compromise were distributed non-uniformly in the perihaematomal region with severe compromise located mainly in the brain tissue immediately adjacent to the haematoma where the reduction in CBF was the most severe.[19,24] Previous experimental studies observed a similarly increased BBB permeability at 12 or 24 h and continued up to 14 days after ICH.[21] In another study, Yang *et al.*[25] observed that BBB permeability decreased after an initial peak at 3 days, and returned to normal level at 11 days after ICH. The present study found that the BBB permeability peaked at 8–14 days after ICH onset. It seems that these studies yielded inconsistent results on the changes of BBB permeability, but these studies collectively indicate that the changes of BBB permeability are dynamic and multiphasic during the ICH progression. This inconsistency might be attributed to methodological differences, as BBB permeability was obtained by a plurality of single measurements at different time points rather than continuous monitoring.

The present study also showed a significant relationship between CBF and BBB permeability around the haematoma. The reduced CBF was independently associated with increased BBB permeability, which suggested that the decreased cerebral blood perfusion may induce ischaemic injury of the BBB structure. Previous MRI studies have observed ischaemic lesions after ICH. Kidwell *et al.*[26] demonstrated reduced values of the apparent diffusion coefficient within 6 h of ICH, an imaging marker of ischaemic injury in the perihaematomal region. Moreover, several studies have demonstrated that ischaemic lesions could be presented on diffusion-weighted imaging (DWI) at baseline, 5 days, and 1 month after ICH onset.[27,28] The present results suggest that reduced rCBF is correlated with elevated BBB permeability, and is an important factor of BBB compromise after ICH. The integrity of BBB is regulated by various cells, proteins, and molecules together.[7,29,30] Existing evidence from animal studies suggests that ischaemia or hypoxia

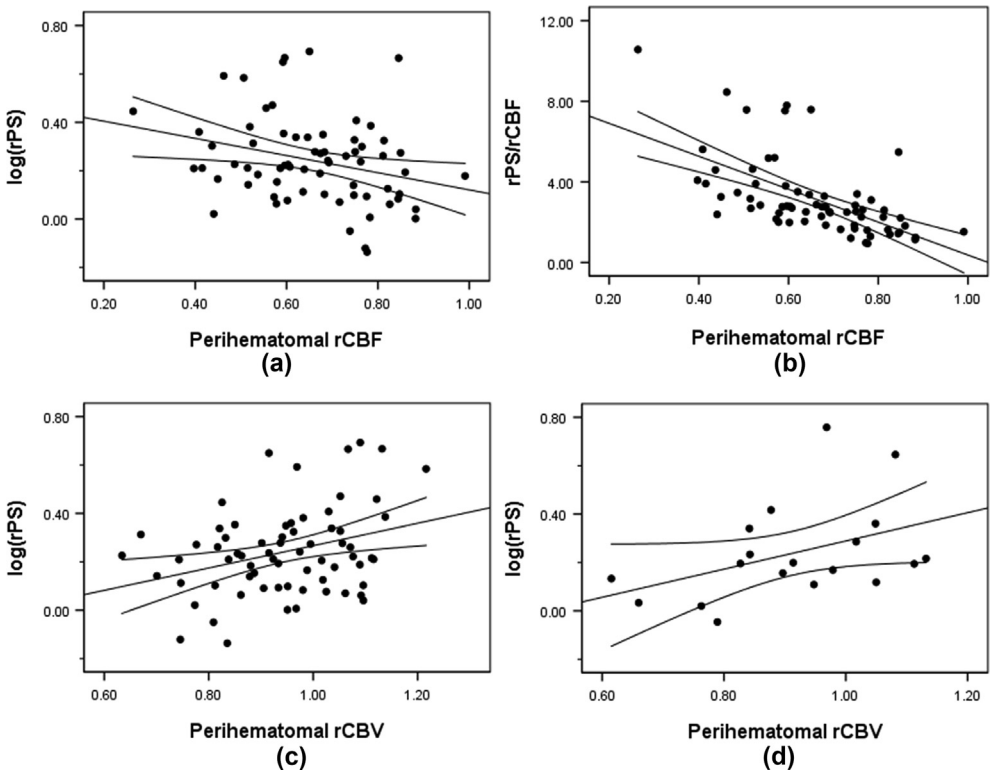

Figure 3 Scatter plots showed the relationship between perihaematomal rCBF, rCBV and log-transformed rPS. (a) The BBB permeability was related inversely to rCBF (β= -0.379, *p*=0.001) in deep ICH, and (b) rPS/rCBF was correlated with rCBF (β -0.605, *p*=0.000), which confirmed the validity of the first result. (c) The log (rPS) was related positively to rCBF (β= 0.412, *p*=0.000) in deep ICH. (d) The BBB permeability was related positively to rCBV (β= 0.423, *p*=0.071) in lobar ICH.

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could activate multiple pathways to injure the structure of BBB, and then lead to BBB dysfunction.[29,31] Therefore, the persistence of cerebral blood hypoperfusion may induce tissue hypoxia adjacent to the haematoma, and further lead to perihaematomal BBB compromise.

Apart from CBF, CBV is another important cerebral perfusion parameter that measures the volume of blood within the brain tissue, and it indirectly quantifies the compensatory mechanisms undertaken by the body to counter the effects of reduced CBF by enlargement of the blood vessels. The present study showed a mild increase in CBV in a subset of ICH, and increased rCBV was independently associated with increased BBB permeability. This finding suggests that the reperfusion characterised by the CBV compensatory increase may exacerbate BBB compromise. There are limited studies that investigated the association between CBV and BBB permeability after ICH. In an ischaemic stroke study, Latour *et al.*[32] found that BBB compromise was more common in patients with reperfusion than those without reperfusion, and demonstrated that reperfusion was independently correlated with BBB disruption, which was further confirmed by Warach *et al.*[33] To the authors' knowledge, this is the first report demonstrating the influence of compensatory increased CBV on BBB permeability, and further studies are needed to confirm this preliminary result.

Interestingly, there was no association between cerebral haemodynamics and BBB permeability in patients with lobar ICH in the present study. The smaller sample size of lobar ICH patients might be the main reason for the failure to detect the association. Another explanation for the present results may be that they reflect differences that existed in brain structures between lobar and deep locations. These regions, especially the basal ganglia and thalamus, may be more highly susceptible to BBB damage, while cerebral lobes contain a profuse blood flow and may remove toxic substances rapidly in the surrounding tissues of lobar haematoma.

There is some evidence to suggest that BBB compromise around the haematoma plays an important role in the unfavourable outcome of ICH patients.[4–6] The present study found a significant correlation between perihaematomal perfusion changes and increased BBB permeability, but also confirmed for the first time that CBF was an important factor in BBB compromise. In addition, to the authors' knowledge, this is the first report demonstrating that the compensatory increase in CBV may lead to reperfusion injury on BBB structure after ICH.

There are some limitations to the present study, including determining haematoma volume and measuring perihaematomal BBB permeability and cerebral haemodynamics such as CBF, CBV, MTT and TTP. The sample size is small in this study, especially in patients with lobar ICH, which limits the confidence with the relationship between cerebral haemodynamics and BBB permeability. Another limitation is that a single measurement of BBB permeability and cerebral haemodynamics was undertaken rather than undertaking serial measurements. A longitudinal study with imaging data collection at multiple time points would have been more useful to understand the evolution of BBB permeability damage in human ICH; however, such a longitudinal study could not be performed due to the restriction on the irradiation dose received by patients undergoing CT examinations. Potential inaccuracies in quantifying BBB permeability by measuring the mean rPS values of eight ROIs may affect slightly the assessment of BBB permeability, but some preliminary results on cerebral haemodynamics and BBB permeability have been obtained. Additionally, ICH patients enrolled in the present study were from symptom onset to 14 days after ICH. Long intervals increased the heterogeneity of the sample. Finally, selection bias was present when ICH patients with GCS Scores <5 we excluded as they were not allowed to undergo CTP. Further studies with a larger sample size are needed to gather data of sequential dynamic imaging of ICH patients at multiple time points, to investigate the evolution of BBB disruption and secondary brain injury as well as the longer-term effect of BBB compromise on functional outcome in spontaneous ICH patients.

In conclusion, the present study found evidence of BBB disruption around the haematoma in spontaneous ICH patients using CTP imaging. Cerebral haemodynamic abnormalities and increased BBB permeability were observed in the perihaematomal region in ICH patients. Changes of cerebral haemodynamics were associated with increased BBB permeability around the haematoma. Furthermore, reduced CBF may aggravate BBB compromise and increased CBV may lead to reperfusion injury of perihaematomal BBB. Quantitative assessment of BBB damage after ICH may reflect the severity of secondary brain injury, and guide future therapeutic interventions to maximise alleviation of perihaematomal tissue injury.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This study was supported by a grant from the National Key Research and Development Program of China (2018YFC1312200).

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