



Blood-brain barrier permeability imaging as a predictor for delayed cerebral ischaemia following subarachnoid haemorrhage. A narrative review

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Abstract

Background Aneurysmal subarachnoid haemorrhage is associated with significant morbidity and mortality due to the myriad of complications contributing to early brain injury and delayed cerebral ischaemia. There is increasing interest in the exploration of the association between blood-brain barrier integrity and risks of delayed cerebral ischaemia and poor outcomes. Despite recent advances in cerebral imaging, radiographic imaging of blood-brain barrier disruption, as a biomarker for outcome prediction, has not been adopted in clinical practice.

Methods We performed a narrative review by searching for articles describing molecular changes or radiological identification of changes in BBB permeability following subarachnoid haemorrhage (SAH) on MEDLINE. Preclinical studies were analysed if reported structural changes and clinical studies were included if they investigated for radiological markers of BBB disruption and its correlation with delayed cerebral ischaemia.

Results There is ample preclinical evidence to suggest that there are structural changes in BBB permeability following SAH. The available clinical literature has demonstrated correlations between permeability imaging and outcomes following aneurysmal subarachnoid haemorrhage (aSAH).

Conclusion Radiological biomarkers offer a potential non-invasive prognostication tool and may also allow early identifications of patients who may be at risk of DCI.

Keywords Subarachnoid haemorrhage · Aneurysms · Blood-brain barrier · Tight junctions · Magnetic resonance imaging · Permeability imaging

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Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) accounts for approximately 80% of spontaneous non-traumatic SAH presentations. It accounts for up to 5% of all new stroke presentations and 5% of deaths from stroke, with a mean age at presentation of 55 years and an increase in incidence with age [50, 74]. The common complications associated with aSAH include re-bleeding in the acute period before definitive aneurysm treatment, hydrocephalus, cerebral vasospasm, delayed cerebral ischaemia, seizures, hyponatraemia, myocardial injuries and pulmonary oedema. Several factors are also associated with poor outcomes following aSAH including age, poor WFNS grade, delayed cerebral ischaemia and radiological haemorrhage burden.

Delayed cerebral ischaemia, defined as the development of new focal neurological deficit(s) or radiological evidence of new infarction(s), occurs in up to a third of patients following

the onset of aSAH and can result in significant morbidity and mortality [75]. The presence of thick cisternal blood and intraventricular haemorrhage (modified Fisher grade IV) increases the risk of a poor outcome for patients, with up to 40% risk of delayed cerebral ischaemia compared to computed tomography (CT)-negative aSAH (Fig. 1) [15]. Mean cerebral blood flow (CBF) has been shown to be significantly lower in patients with Fisher III–IV and poor-grade aSAH patients in comparison to patients with better clinical grades [86]. Historically, the terms “delayed cerebral ischaemia” (DCI) and “cerebral vasospasm” had been used interchangeably. This was because the mechanical relationship between narrowed blood vessels, reduced blood flow and cerebral ischaemia was thought to be intuitive. DCI, however, has now been shown to occur independent of cerebral vasospasm. In a study by Dankbaar et al., vasospasm, evident on CT angiography, was reported to correspond with the least perfused regions of the brain in only two-thirds of patients on CT perfusion. DCI was also evident in some patients who had no radiological evidence of vasospasm [18]. Furthermore, oral administration of nimodipine, an L-type calcium channel antagonist, has been shown to reduce the risk of DCI and poor outcome following aSAH [57]. However, this effect has not been shown to correlate with significant reduction in angiographic vasospasm in the patients administered nimodipine [3, 22]. There is also experimental evidence that the presence of oxyhaemoglobin in the perivascular and subarachnoid spaces results in the release of endothelin from the arterial walls. This

response has been implicated in the pathogenesis of vasospasm, due to the effects of endothelin on vasoconstriction. These findings prompted the CONSCIOUS trials (clazosentan to overcome neurological ischaemia and infarct occurring after subarachnoid haemorrhage) which assessed the effect of clazosentan on mortality and DCI. Clazosentan is an endothelin receptor antagonist with a molecular weight of 577.6 Da. In the CONSCIOUS trials, its efficacy and safety at three doses (1, 5 and 15 mg/h) on the prevention of vasospasm and DCI was assessed. There was a dose-dependent reduction in moderate and severe angiographic cerebral vasospasm with a 65% relative risk reduction at 15 mg/h. However, there was no significant effect on mortality, vasospasm-related neurological complications and functional outcomes [45–47], further supporting that the pathogenesis of DCI is not fully a result of vasoconstriction. Other factors, such as microcirculatory constriction, micro-thrombosis, platelet aggregation, cortical spreading ischaemia, delayed cellular apoptosis, neuroinflammation and increased blood-brain barrier (BBB) permeability, have been hypothesised as potential contributors to the pathophysiology of DCI [23, 26, 58, 66]. As a result, various multimodal monitoring systems such as continuous EEG, brain tissue oxygen, intracranial pressure (ICP) and imaging modalities such as transcranial Doppler ultrasound, CT perfusion (CTP) and digital subtraction angiography (DSA) have been used in early identification and response to treatment of vasospasm and cerebral ischaemia. Several preclinical studies have demonstrated increased

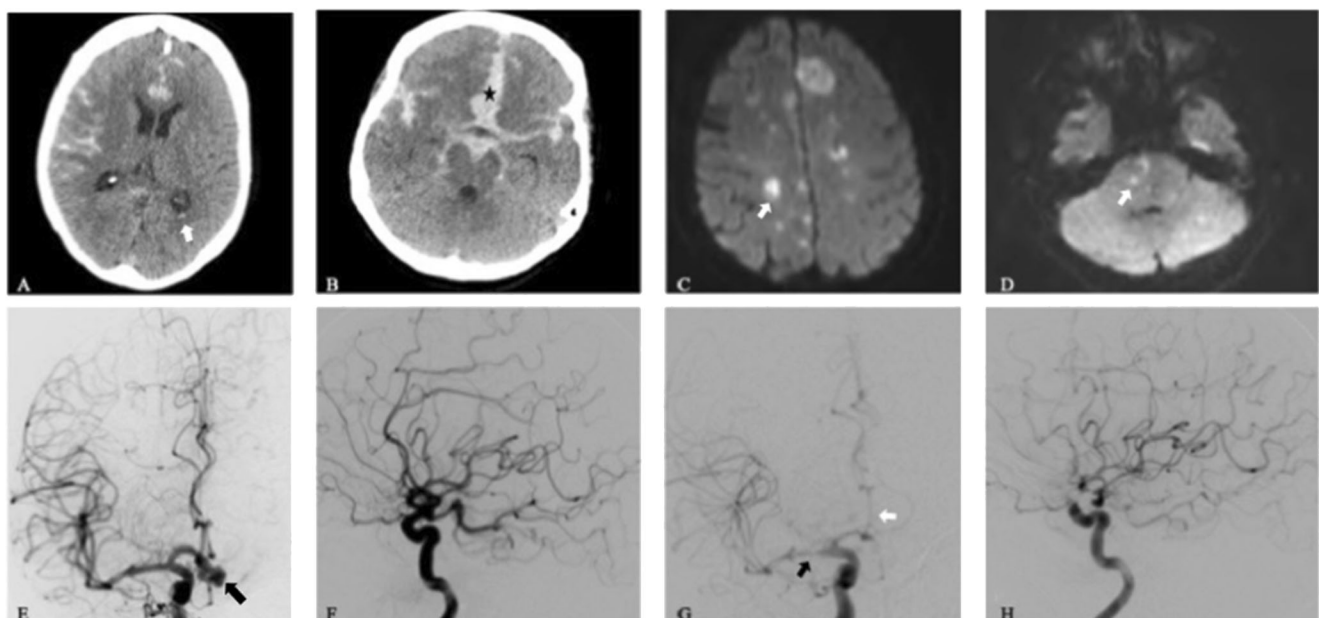


Fig. 1 **a, b** Axial CT brain obtained at presentation, showing Fisher IV aSAH (diffuse SAH (asterisk) with IVH (white arrow)); **c, d** Axial DWI MRI sequences obtained day 7 post-ictus showing areas of bi-hemispheric and pontine diffusion restriction representing infarction (white arrows); **e, f** Digital subtraction angiography (DSA) of cerebral vessels (**e** antero-posterior view, **f** lateral view) obtained on the day of

presentation showing anterior communicating artery aneurysm (black arrow on image **e**) with no significant large vessel vasospasm; **g, h** DSA of cerebral vessels (**g** antero-posterior view, **h** lateral view) obtained on day 7 prior to balloon angioplasty, showing severe right middle cerebral artery (black arrow) and anterior cerebral artery (white arrow) vasospasm

permeability of the BBB, at various time courses after subarachnoid haemorrhage, and its implications on early brain injury and DCI [40, 66]. However, there has been limited use of BBB imaging in clinical practice for the prediction and prognostication of DCI following aSAH. In this review, we discuss some of the mechanisms involved in BBB disruption following aSAH and the potential role of BBB integrity imaging in prediction of DCI and outcome prognostication following aSAH.

Methods

A systematic review of the literature was performed to identify peer-reviewed literature reporting association of radiological evidence of blood-brain barrier integrity with clinical or radiological outcomes following aSAH in humans. The approach for reporting was modelled on the PRISMA guidelines (Fig. 2). We conducted a literature search using the PubMed/MEDLINE database using the search terms “(subarachnoid haemorrhage OR SAH) AND (blood-brain barrier OR BBB) AND (magnetic resonance imaging OR MRI OR computed tomography OR CT OR imaging)”. Abstracts were screened for investigations of association of radiological evidence of

BBB permeability and clinical or radiological outcomes pertaining to DCI. Eight studies were included in the qualitative synthesis of the literature, presented as a narrative review describing the utility of permeability imaging in predicting DCI or poor outcomes in humans with aSAH [20, 34–36, 38, 43, 48, 62].

Disruptions to the blood-brain barrier in SAH

The basic anatomical structure of the BBB is a single layer of microvascular endothelial cells (ECs), lining the lumen of cerebral capillaries, supported by ensheathing pericytes and the foot processes of astrocytes (Fig. 3) [1, 14]. This complex network of cells restricts movement into the brain to lipophilic molecules with a molecular weight less than approximately 400 Da. The EC layer consists of luminal (blood-side) and abluminal (brain-side) membranes separated by ≈ 500 nm of cytoplasm. Cerebral ECs differ, morphologically, from peripheral ECs in 2 respects: (1) the presence of fluid-filled pinocytes and higher concentration of mitochondria in their cytoplasm, highlighting the important transport requirements and function of the BBB. (2) The high electrical resistance across the ECs is established in part by complex tight

Fig. 2 PRISMA flow diagram

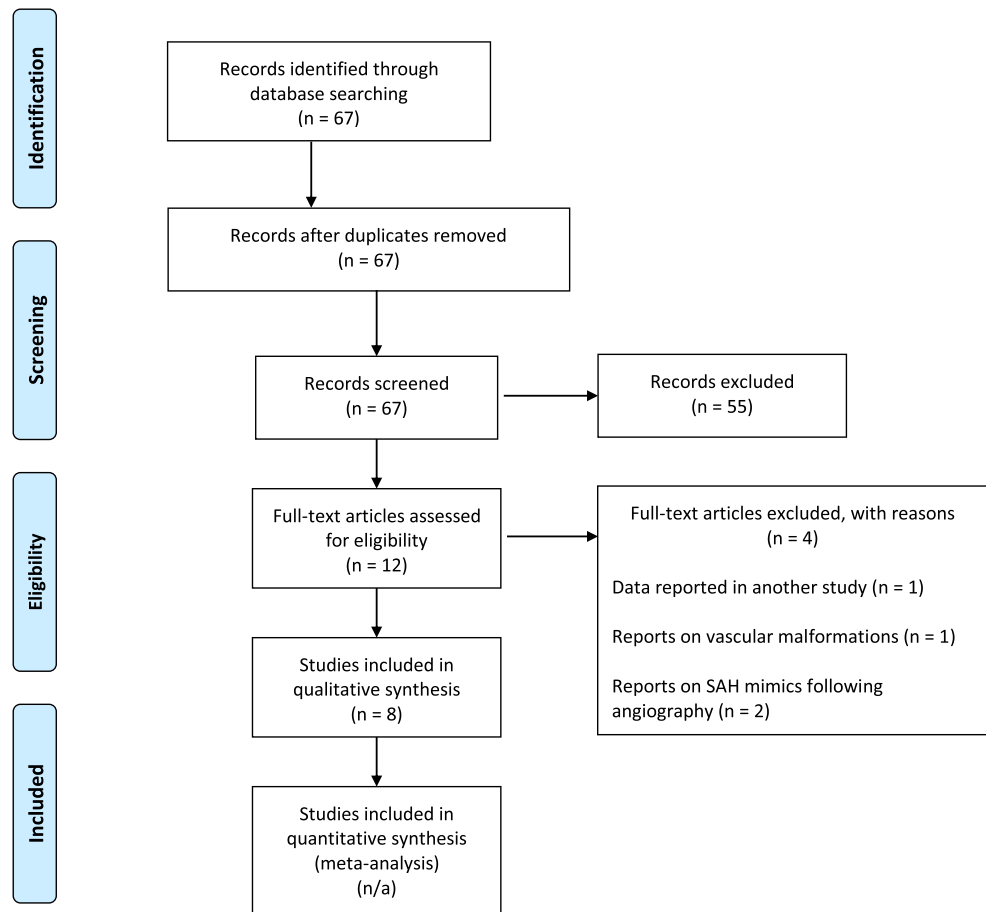
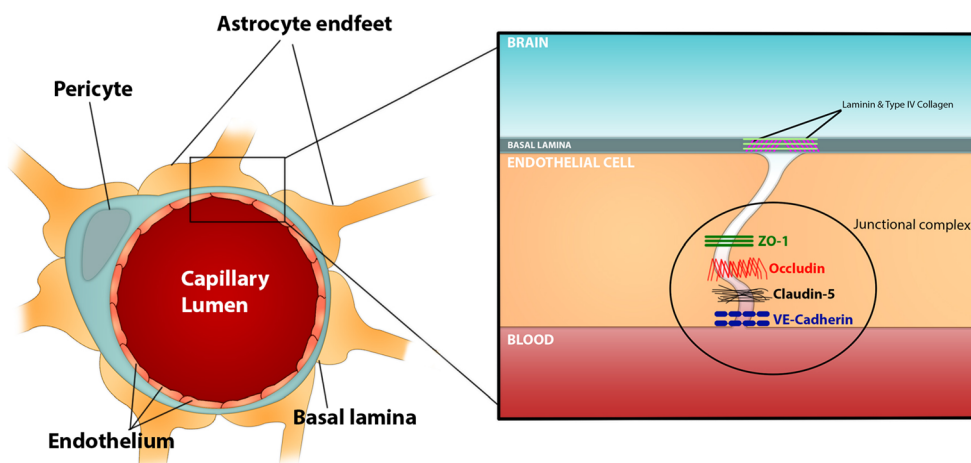


Fig. 3 Brief overview of cellular and molecular structure of the blood-brain barrier



junctions (TJs) connecting neighbouring ECs [53]. Tight junctions play an important role in maintaining the integrity of the BBB through very intimate, but gated, membrane apposition of neighbouring ECs. Proteins, such as claudins, occludins and zonula occludens (ZO), are expressed in rodent embryos shortly after cerebral angiogenesis, as early as day 12 of embryogenesis [17]. These proteins, with their connections, form a junctional complex with structural integrity to regulate transport of solutes through the paracellular pathway in and out of the brain. Increased BBB permeability has been demonstrated in rodent models with decreased expression of claudin-5. Likewise, upregulating the expression of claudin-5 at the BBB has been associated with reduced cerebral oedema and haemorrhagic transformation of the focal area of cerebral ischaemia in mice [33, 51].

Occludin is another integral membrane and TJ-associated component of the BBB, with expression reported in various mammals. Although its function in the BBB is still not fully understood, the expression of occludin has been shown to be modified when exposed to conditions such as hypoxia/reoxygenation, matrix metalloproteinase 9 (MMP-9) activation and interleukins (IL), amongst others [9, 37, 78, 79]. Initially, a fence-barrier function was suggested; however, occludin-deficient stem cells had the potential to differentiate into epithelial cells with functioning tight junctions [64].

Changes in the integrity of the BBB have been implicated in a number of neurological conditions, e.g. Alzheimer-associated dementias, TBI and stroke. BBB disruption, in the acute setting after subarachnoid haemorrhage, was reported by Doczi in 1985, showing some correlations between abnormal post-contrast enhancement on CT, vasospasm and poor clinical outcomes [19]. There have been a number of preclinical studies confirming the impairment of BBB integrity since this study. Changes in the BBB have been observed as early as 10 minutes after SAH, evident by partial degradation of the basal lamina and platelet migration across abluminal membranes of ECs in experimental rat models of

SAH [26]. The exact mechanism of BBB disruption following SAH remains poorly understood; however, a number of microvascular alterations have been reported in the literature.

One of the reported microvascular changes in the structure of the BBB in SAH is the focal destruction of collagen. Immunohistochemical studies of cerebral arteries in animal models of SAH have shown degradation of type IV collagen in the basal lamina [55, 67, 68]. This effect was not limited to the outer cortex exposed to subarachnoid blood. There was also a correlation between the observed collagen degradation and BBB dysfunction, as demonstrated by increased serum albumin content in the cortex of the animals in this cohort [67]. In normal physiological state, extravasation of albumin is limited by the BBB. The matrix metalloproteinase (MMP) system has been thought to contribute to the disruption of type IV collagen in a number of cerebral pathologies. Correlations have been established between a reduction in type IV collagen immune staining with increased matrix metalloproteinase 9 staining, as early as 3 hours after SAH [5, 54, 68]. A decrease in other basal lamina proteins, such as laminin, has also been reported in the context of SAH [77]. A correlation in the timing of basal lamina degradation and the increase in brain water further supports its role in early global vasogenic cerebral oedema following SAH [67, 76].

There has been a growing understanding of changes in the expression of BBB tight junction proteins in response to SAH. Experiments in rat models have reported alterations in expressions of claudin-5 [4, 8, 10, 11, 13, 24, 25, 32, 40, 44, 54, 60], occludin [4, 11, 13, 24, 27, 29, 30, 32, 40, 42, 44, 54, 60, 77, 80, 81, 84, 85] and ZO-1 [4, 11, 13, 24, 27, 29, 30, 32, 40, 42, 44, 54, 59, 60, 73, 77, 80, 81, 83–85] within 24–48 hours of exposure to SAH. While most studies have generally found a concurrent decrease in the expression of these proteins, Li et al. reported no decrease in claudin-5 expression. The temporal change in the expression of these proteins has also been explored in a few studies. While most studies have reported a monophasic decrease in TJ protein expression, Li et al.

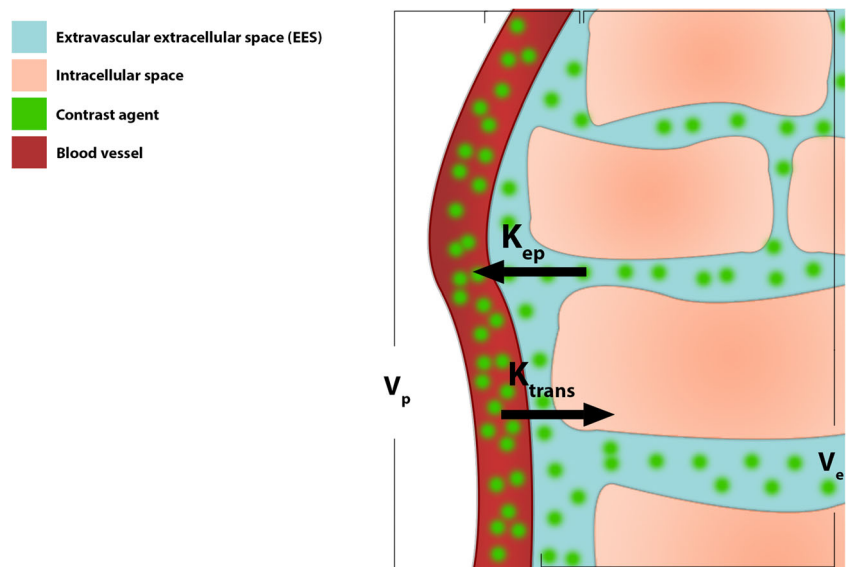
reported a biphasic response with decreased levels of ZO-1 and occludin [40]. Blecharz-Lang et al. showed a decrease in mRNA transcripts and protein expression for claudin-5 and vascular endothelial cadherin (VE-cadherin) at 8 hours and 24 hours following induction of SAH. However, although transcript levels of occludin remain unchanged at 8 hours, there was an increase in the protein expression. At 24 and 48 hours, there was a concurring decrease in both transcript and protein expressions of occludin [4]. The expression of other less-studied tight junction proteins, such as VE-cadherin, has also been shown to decrease following SAH [4, 29]. Interestingly, similar effects on basement membranes in extracranial organs have been described following experimental SAH in animals. These effects also seem to occur as a result of the same pathways reported in the BBB [12, 28].

BBB permeability imaging as a predictor of DCI

Global cerebral oedema (GCE), thought to be partially a result of increased BBB permeability, has been shown to be an independent predictor of morbidity and mortality in subarachnoid haemorrhage [16, 39]. A non-contrast computed tomography (CT) imaging of the brain can provide an easily accessible evaluation of cerebral oedema following aSAH. Although GCE may result from secondary pathological pathways leading to either increased brain water content or hyperaemia, the former has been demonstrated to correlate with regions of CT hypodensity more than the latter [49, 61]. This coupled with the concurrent increase of brain water content and structural changes in the BBB in preclinical studies supports the potential role of NCCT brain in the gross analysis of BBB integrity following aSAH in clinical practice

[67, 76]. CT perfusion has been utilised in the assessment of alterations in cerebral perfusion in the context of delayed cerebral ischaemia, with prolonged mean transit time (MTT) and reduced cerebral blood flow (CBF) being prognostic indicators for DCI [65]. Following on from this, a number of recent studies have analysed the correlations between DCI and global cerebral ischaemia with the severity of BBB permeability, using CT perfusion (CTP). The main measurable radiological parameter in permeability imaging is K^{trans} (Fig. 4). K^{trans} represents a measurement of capillary associated signal change after injection of a contrast agent and reflects the kinetic diffusion of this tracer across the BBB-associated endothelium. It represents the sum of all the processes contributing to the net rate of the influx of contrast agent from the intravascular space into the extravascular extracellular space EES. V_e denotes the volume of EES per unit volume of tissue, representing the potential volume of interstitium that can be occupied by the contrast agent. Similarly, V_p represents the fractional volume of plasma (intravascular space). K_{ep} is the time constant for contrast agent reflux from EES back into intravascular space, which is dependent on the former parameters, and permeability surface (PS) area product, representing flow from plasma to EES. Due to the selectivity of passage across an intact BBB, any observed change in BBB integrity is also significantly dependent on the molecular weight of the tracer (contrast agent) used. Ivanidze et al. analysed these parameters retrospectively from CTP in matched SAH patients who had radiological evidence of global cerebral oedema (GCE) and those who did not, within 72 hours of onset of SAH symptoms. They observed statistically significant decreased K^{trans} , k_{ep} , and v_p and increased V_e in the GCE group in comparison to non-GCE group [35]. The paradoxical decrease in K^{trans} observed was attributed to the dependence of the derivation of K^{trans} on cerebral blood flow rate, which can

Fig. 4 Simple illustrations of compartments and radiological parameters commonly utilised in blood-brain barrier permeability imaging



be reduced in the context of global cerebral oedema, likely as a result of elevated intracranial pressure. Subsequent studies have found correlations between increased PS and V_e and decreased k_{ep} and functional outcomes after SAH [34, 36].

One of the earliest reports of abnormal contrast enhancements, following aSAH, was by Doczi et al. [20]. The author described the utility of the quantitative measurement and comparison of Hounsfield units (HU) in regions of interest between NCCT brain and contrast-enhanced CT studies. The confinement of contrast agent by an intact BBB results in a slight increase in density of the cerebral parenchyma, since the cerebral blood volume represents 4–5% of the total brain volume. Therefore, normal white and grey matter exhibit a very slight hyper-attenuation in contrast-enhanced CT, on average, 1.9 HU for grey matter and 1.4 H for white matter. Hence, a significant increase in enhancement, to the effect of 4.5 HU, is considered evidence for abnormal permeability [63, 70, 71]. With analysis based on this threshold, Doczi et al. observed that 40% patients who had a post-contrast CT brain within 5 days of aSAH demonstrated abnormal enhancements, while 31% of patients scanned later than 5 days showed abnormal contrast enhancement. The enhancing regions were noted to be parenchymal suggesting disruption in BBB as an underlying factor. Interestingly, the authors reported a relationship between abnormal enhancements and outcome, such as infarction (DCI) and re-bleed, although the statistical significance of this finding is uncertain, given the small sample size [20].

Magnetic resonance imaging (MRI) is superior to CT for assessing tissue properties and subtle changes in regions of interest, although limited by longer time of image acquisition in comparison to CT. MRI has been used for the investigation of BBB permeability in a range of neurological conditions, i.e. neoplasm, TBI, neurodegenerative disorders, stroke and intra-cerebral haemorrhage [2, 31]. The basic principle of investigating BBB permeability using contrast-enhanced MRI is based on the potential of transmembrane efflux of paramagnetic contrast agents, typically gadolinium, from intravascular space, depending on degree of BBB disruption. Statistical differences in images before and after administration of contrast agents can be calculated in a static or dynamic fashion. One approach for evaluation of BBB integrity in preclinical and clinical studies using static contrast-enhanced MRI is the “post-pre” comparison method. This method uses enhancement differences between certain tissues with varying membrane permeability (muscle (permeable, no BBB), blood vessel and eyeball (intact blood-retina barrier)), as references for statistical calculations. For example, if the pre-contrast intensity of a region of interest (ROI) was in the range between the eyeball and blood vessel and there is a

significant change in its intensity after contrast administration, this ROI is considered as a permeable brain region. A slice-wise paired *t*-test is performed to identify any statistically significant differences in the pre- and post-contrast images for specific pixels in the ROI [6, 7]. Dynamic contrast-enhanced MRI (DCE-MRI) on the other hand is used to quantify BBB permeability by monitoring changes in tracer/contrast agent concentration, over a longer period of time, on repeated scans after administration of the contrast agent. There are a number of tracer-kinetic models described in the literature (Patlak, one compartment, Tofts, steady state, etc.), with Tofts model most commonly used. A “linear dynamic method” was proposed by Chassidim et al., whereby linear slopes of scans taken at multiple time points after contrast agent administration are analysed [7]. Detailed descriptions of commonly used pre-clinical and clinical models have been described by Sourbron et al. [72]. A number of studies predominantly preclinical have utilised non-contrast-enhanced MRI, i.e. T2 hyperintensity analysis, in the investigation of BBB permeability [11, 56, 82]. Lin et al. proposed a non-contrast water-extraction-with-phase-contrast-arterial-spin-tagging (WEPCAST) sequence as an alternative to contrast-enhanced studies. This was achieved by manipulation and modelling water signals using selective detection of arterial spin labelling signals [41].

A prospective cohort study by Serlin et al. reported an association of BBB disruption with development of recurrent cerebral infarction. They presented a case whereby a patient presenting with transient ischaemic attack (TIA) was re-admitted after a few days with a diffusion weighted imaging (DWI) positive ischaemic stroke in areas that had previously been DWI negative at initial presentation, however demonstrated radiological (DCE-MRI) evidence of BBB disruption [69]. This highlights the potential for use of BBB disruption as a radiological biomarker, in conjunction with clinical history and signs, for prediction and prognostication in various neurological pathologies. BBB disruption has also been implicated in the sequelae of mild repetitive traumatic brain injury [21]. DCE-MRI has been used to demonstrate dynamic alterations in BBB integrity following exposure to varying levels of repetitive head trauma in mixed martial arts (MMA) fighters and rugby players [52]. There are, however, currently limited clinical studies exploring MRI changes in BBB following SAH [43, 62].

BBB disruption, measured radiologically with DCE-MRI, has been associated with poor outcomes following subarachnoid haemorrhage in a clinical study. Using the Patlak linear regression analysis, Russin et al. observed significantly higher K^{trans} values ($2.28 \pm 0.09 \times 10^{-3} \text{ min}^{-1}$) in patients who subsequently developed DCI when compared to patients with radiographic only vasospasm ($1.85 \pm 0.12 \times 10^{-3} \text{ min}^{-1}$; $p < 0.05$) or no vasospasm/ischaemia ($1.74 \pm 0.07 \times 10^{-3} \text{ min}^{-1}$; p

< 0.01), with ROC curve analysis showing K^{trans} from DCE-MRI as an accurate radiological predictor of DCI [62]. A larger series by Lublinsky et al. also reported significant correlation between radiological quantification of BBB permeability and outcomes following aSAH. The post-imaging acquisition analysis used was the “post-pre” method described by Chassidim et al. The authors described abnormal brain tissue (ABT) as regions of apparently abnormal MRI signal (i.e. cytotoxic/vasogenic oedema, gliosis or haemorrhage). Interestingly, most voxels with BBBD were found in apparently normal brain tissue (NBT) and these were located within 1 cm from the core of a voxel of ABT. The extent of BBBD in ABT was associated with poor WFNS grades. There were no significant temporal changes in degree of BBBD in NBT between images acquired within 48 hours (t1) up to 19 days (t2 and t3) (Table 1), although some improvement was observed after 19 days (t4). On the other hand, worsening BBBD was observed in ABT at t2 and t3 with subsequent improvement at t4. As well as describing a temporal pattern of BBB changes, the serial DCE-MRI method used in this study demonstrated a significantly higher probability of transformation of NBT with BBBD to ABT, on follow-up imaging, when compared to initially intact voxels at t1. The degree of BBBD in both NBT and ABT was significantly larger in patients with poorer

extended Glasgow outcome scores and the inclusion of BBBD in predictive algorithms improved predictive accuracy for outcomes than when only traditional factors such as age and WFNS grades were used [43].

Conclusion

There is sufficient evidence from preclinical studies to suggest that alterations to the permeability of the BBB play a crucial role in the complex pathophysiology of DCI following SAH. Radiological biomarkers offer a potential non-invasive prognostication tool and may also allow early identifications of patients who may be at risk of DCI. Radiological evidence of BBB breakdown has been demonstrated in humans in a wide variety of neurological disorders, particularly, neurodegenerative conditions and TBI. However, there is currently a paucity of human studies investigating the association between BBB dysfunction and its severity, with the severity of delayed cerebral ischaemia and overall patient outcomes. With the recent advances in permeability imaging, it is imperative that potential associations between BBB disruption and early and delayed brain injuries are investigated in patients with aSAH.

Table 1 Clinical studies of radiological changes in blood-brain barrier permeability and associations with DCI and outcomes

Publication	Modality	Study design	Time to scan	Sample size	Outcome measures	Findings
Lublinsky et al. [43]	MRI	Retrospective analysis of data from prospective co-operative studies	t1 = 24–48 h t2 = 3–9 days t3 = 10–19 days t4 = > 59 days	124	Poor outcome = eGOS ≤ 5 Favourable outcome = eGOS > 5 Abnormal brain tissue BBB dysfunction	NBT with BBBD had higher probability of becoming ABT Brain volume with BBBD larger in progressive disease course vs non-progressive disease course
Russin et al. [62]	DCE-MRI	Prospective	Day 4	20	Development of DCI	$\uparrow K^{\text{trans}}$ in patients with DCI compared to radiographic only or no vasospasm/ischaemia
Ivanidze et al. [34].	CTP	Retrospective analysis of consecutive patients	Within 72 h	22	Permanent neurological deficit mRS 3–6 at discharge	$\uparrow PS$, V_e and $\downarrow k_{ep}$ associated with unfavourable outcome
Murphy et al. [48]	CTP	Prospective cohort	Within 72 h	50	Functional outcome (mRS) @ 3 months Radiological evidence of infarction (2 weeks to 3 months)	No associations between MTT, CBF, PS and mRS $\uparrow MTT$ in patients with subsequent DCI and infarction
Ivanidze et al. [36]	CTP	Prospective cohort	Within 72 h Day of deficit* Day 6–8**	21	Radiological evidence of infarction	$\uparrow PS$ predicts region of subsequent infarction No difference in CBF and MTT in regions of subsequent infarction
Kishore et al. [38]	CTP	Retrospective cohort	4–384 h	83	Prediction of BBBP	$\uparrow BBBP$ proportional to CBV and MTT

ABT abnormal brain tissue, BBBD blood-brain barrier dysfunction, BBBP blood-brain barrier permeability, CBF cerebral blood flow, CBV cerebral blood volume, CTP computed tomography perfusion, DCE dynamic contrast enhanced, DCI delayed cerebral ischaemia, eGOS extended Glasgow outcome scale, k_{ep} time constant, K^{trans} volume transfer constant, MRI magnetic resonance imaging, mRS modified Rankin score, MTT mean transit time, NBT normal brain tissue, PS permeability surface area, V_e fractional volume

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval For this type of study, formal consent is not required.

Informed consent This article does not contain any studies with human participants performed by any of the authors.

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Comments

The authors claim that the manuscript is a narrative review on the hypothesis that clinical imaging of the blood-brain barrier permeability may serve as a predictor for delayed cerebral ischaemia following subarachnoid haemorrhage.

They state that there has been limited use of BBB imaging in clinical practice for the prediction and prognostication of DCI following aSAH. Accordingly, they discuss some of the mechanisms involved in BBB disruption following aSAH and the potential role of BBB integrity imaging in prediction of DCI and outcome prognostication following aSAH.

The concept that detection of focal BBB damage following aneurysmal subarachnoid haemorrhage in the acute phase of the disease as shown by abnormal contrast enhancement may be an early indicator/biomarker of development of delayed vasospasm/focal DCI is rather old. The authors rightly point out that DCI, however, has now been shown to occur independent of cerebral vasospasm, i.e. the pathogenesis of DCI may not be fully a result of pathological vasoconstriction.

The authors performed an anecdotal search in the English literature looking for papers dealing with disruptions to the blood-brain barrier in SAH; BBB permeability imaging as a predictor of DCI. Based on their critical reading experiences, they conclude that there is sufficient evidence from preclinical and clinical studies to suggest that alterations to the permeability of the BBB play a crucial role in the complex pathophysiology of DCI following SAH.

Radiological biomarkers offer a potential non-invasive prognostication tool and may also allow early identifications of patients who may be at risk of DCI.

With the recent advances in permeability imaging, it is imperative that potential associations between BBB disruption and early and delayed brain injuries are investigated in patients with aSAH.

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