


TRANSLATIONAL PERSPECTIVES

MRI measurement of blood–brain barrier leakage: minding the gapsMichael Jonathan Thrippleton 

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Determination of blood–brain barrier (BBB) integrity is of substantial interest to researchers in several fields, including multiple sclerosis (MS), ageing, cerebral small vessel disease, stroke and dementia. A validated, reliable and minimally invasive technique for *in vivo* quantification is therefore a highly desirable goal. Although several imaging and biochemical techniques exist, dynamic contrast-enhanced (DCE-) magnetic resonance imaging (MRI) is considered the most useful for clinical research applications at present (Heye *et al.* 2014), since it provides quantitative estimates of contrast agent leakage at moderate spatial resolution, and is relatively convenient and safe if relevant guidance is followed. Briefly, a solution of paramagnetic gadolinium complex is injected intravenously, which enters the brain's capillaries and from there may leak across the BBB into the extracellular extravascular space. This uptake is detected via an increase in the T_1 -weighted MRI signal intensity, typically measured over a period of several minutes or longer. Image analysis methods can be used to estimate vascular properties including the cerebral blood volume (CBV or v_b) and contrast agent leakage rate across the vessel wall (reported variously as K^{trans} , K_i and PS) from the time-signal profile.

Despite widespread application of DCE-MRI in neuro-oncology and body imaging, measurement of leakage across relatively intact BBB is less common and is acknowledged to be difficult: leakage is slow, resulting in very small signal changes – typically 5% or lower over 20 min. The precision and accuracy of quantification are limited by noise, artefact, the temporal stability of MRI scanners and by assumptions inherent in the data modelling. In the language of quantitative imaging biomarkers, there is growing (e.g.

Wong *et al.* 2017) but limited evidence supporting the technical and biological validity; such evidence is difficult to obtain due to the need to administer repeat doses of contrast agent and the lack of suitable reference methods.

The article by Varatharaj *et al.* (2019) published in the current issue of *The Journal of Physiology* therefore contributes welcome proof-of-principle evidence of biological validity. They performed DCE-MRI in MS subjects and in healthy controls. Specifically, they report a grey matter (GM)/white matter (WM) CBV ratio of around 2, greater BBB leakage rate in contrast-enhancing MS lesions *versus* normal-appearing WM and greater leakage rate in the normal-appearing WM of MS subjects *versus* that of healthy controls – findings that are consistent with reasonable biological expectation. The authors also report faster leakage in GM compared with WM in healthy controls, plausibly suggesting that the greater CBV in GM corresponds to higher vascular surface area and therefore more overall leakage per unit tissue volume, assuming equal permeability and vessel radius in the two tissues. Whether or not this is the actual reason, it emphasises the important subtlety that DCE-MRI at best quantifies PS , the capillary surface area per unit volume multiplied by the permeability, not the permeability *per se*. Vascular surface area is also difficult to measure *in vivo*, and the potential influence of vascularity on PS may be especially relevant in studies of cerebrovascular diseases and in cohorts spanning a wide age range. The difficulty of probing low-level BBB leakage is also nicely illustrated in the article: signal changes that are small in relation to the temporal noise level (Figure 3, Varatharaj *et al.* (2019)) will be familiar to fellow researchers in the field, as will the phenomenon of negative K_i estimates (Figure 4, Varatharaj *et al.* (2019)).

An additional challenge to obtaining and interpreting BBB leakage data is the methodological heterogeneity found in the literature, with regard to both data acquisition and image analysis methods, which range from qualitative visual evaluation of permeability to various quantitative and semi-quantitative methods. Partly as a consequence, leakage values reported by different groups are often highly dissimilar or simply impossible to

compare. Nevertheless, there is a growing consensus in favour of the approach exemplified by Varatharaj *et al.*, which included pre-injection measurement of the T_1 relaxation time and pharmacokinetic analysis of the data using the Patlak model. It is an approach that has been developed and tested by the authors and by other groups over many years (Larsson *et al.* 2009; Barnes *et al.* 2016; Heye *et al.* 2016), and has advantages over simpler methods (e.g. signal enhancement at a single time point or area-under-curve calculation) since it aims to correct for protocol-dependent factors and to distinguish between intra- and extra-vascular contrast agent. On some aspects, however, such as measurement of contrast agent concentration in blood (the 'vascular input function'), and temporal resolution, practice remains varied.

The time is arguably now ripe for development of consensus-based multi-vendor MRI protocols for more standardised measurement of BBB leakage, coupled with further efforts towards quantitative imaging biomarker validation. One such harmonisation initiative is currently underway in the context of cerebral small vessel disease (<https://harness-neuroimaging.org>). This should help facilitate the larger, multi-centre studies required to investigate BBB pathophysiology. Parallel development of DCE-MRI and of other methods for probing the BBB, including those measuring trans-vascular water exchange, is also eagerly anticipated.

References

- Barnes SR, Ng TS, Montagne A, Law M, Zlokovic BV & Jacobs RE (2016). Optimal acquisition and modeling parameters for accurate assessment of low K^{trans} blood-brain barrier permeability using dynamic contrast-enhanced MRI. *Magn Reson Med* 75, 1967–1977.
- Heye AK, Culling RD, Valdes Hernandez Mdel C, Thrippleton MJ & Wardlaw JM (2014). Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI. A systematic review. *Neuroimage Clin* 6, 262–274.
- Heye AK, Thrippleton MJ, Armitage PA, Valdes Hernandez MDC, Makin SD, Glatz A, Sakka E & Wardlaw JM (2016). Tracer kinetic modelling for DCE-MRI quantification of subtle blood-brain barrier permeability. *Neuroimage* 125, 446–455.

Larsson HB, Courivaud F, Rostrup E & Hansen AE (2009). Measurement of brain perfusion, blood volume, and blood-brain barrier permeability, using dynamic contrast-enhanced T_1 -weighted MRI at 3 tesla. *Magn Reson Med* **62**, 1270–1281.

Wong SM, Jansen JFA, Zhang CE, Staals J, Hofman PAM, van Oostenbrugge RJ, Jeukens C & Backes WH (2017). Measuring subtle leakage of the blood-brain barrier in cerebrovascular disease with DCE-MRI: Test-retest reproducibility and its influencing factors. *J Magn Reson Imaging* **46**, 159–166.

Varatharaj A, Liljeroth M, Darekar A, Larsson HBW, Galea I & Cramer SP (2019). Blood–brain barrier permeability measured using dynamic contrast-enhanced magnetic resonance imaging: a validation study. *J Physiol* **597**, 699–709.

Additional information

Competing interests

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Sole author.

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