MRI measurement of blood-brain barrier leakage: filling the gaps

Citation for published version:
Thrippleton, MJ 2018, 'MRI measurement of blood-brain barrier leakage: filling the gaps' Journal of Physiology. DOI: 10.1113/JP277425

Digital Object Identifier (DOI):
10.1113/JP277425

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published in:
Journal of Physiology

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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 five percent or lower over twenty minutes. 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. published in the current issue of *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) will be familiar to fellow researchers in the field, as will the phenomenon of negative $K_i$ estimates (Figure 4).

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 transvascular water exchange, is also eagerly anticipated.


Additional Information
**Competing interests:** The author has no competing interests.

**Funding:** MJT acknowledges financial support from the NHS Lothian Research and Development Office.