Measurement of Local Cerebral Hematocrit with MRI

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Purpose: Propose and assess a method to measure local cerebral hematocrit using MRI.

Introduction: Red blood cells carry O_2 to tissue and transport CO_2 back to lungs. The percentage blood volume occupied by red blood cells is known as hematocrit (Hct). Whereas it is straightforward to measure Hct in large arteries (e.g. blood sample), it is very challenging to do it in brain microvasculature (i.e. cerebral Hct, Hct_{tissue}). Currently, this can only be done using invasive methods, such as with PET, SPECT, and autoradiography[1–3], but their use is very limited. Local variations in cerebral Hct have been reported in various brain abnormalities (e.g. stroke, vascular disease, and tumours).[4–6] Knowledge on cerebral Hct is also important for dynamic-susceptibility contrast (DSC) MRI and perfusion CT, since their contrast agents reside in blood plasma. These methods, therefore, commonly rely on assumed (uniform) literature values[7], which can lead to errors. We propose here a MRI method to image cerebral Hct, which relies on combining data from two MRI measurements of hemodynamic parameters: one that provides *Hct-weighted* values, and another one that provides *Hct-independent* values of the same parameter. By combining these two measurements, it is possible to isolate local cerebral Hct, thus providing an easily obtainable measurement of this important physiological parameter.

Methods: There are various ways to combine MRI measurements to calculate cerebral Hct (see Discussion). We describe one approach in detail here, which relies on data from (*i*) a DSC-MRI study in absolute units (e.g.[8,9]) and (*ii*) an arterial spin labelling (ASL) study.[10] In this case, a DSC-MRI deconvolution analysis[7] provides a *Hct-weighted* CBF (CBF_{Hct}) in *absolute* units, i.e. $CBF_{DSC\text{-}MRI}=CBF_{Hct}=CBF/k_{Hct}$, where k_{Hct} is the large-to-small vessel size plasma volume ratio:[7] $(1-Hct_{art})/(1-Hct_{tissue})$, and Hct_{art} is the Hct in a large artery. Note that, for most DSC-MRI studies, this scaling factor is considered a nuisance (i.e. neglected or fixed to an assumed literature value), but its presence is central to the method proposed here. From a complementary ASL measurement, known to provide *absolute* CBF measurements (i.e., CBF_{ASL}=CBF),[10] one can calculate k_{Hct} as the ratio: $k_{Hct}= CBF_{ASL}/CBF_{Hct}$, which therefore leads to cerebral Hct as:

$$\boldsymbol{Hct_{tissue}=1-(CBF_{Hct}/CBF_{ASL})\times(1-Hct_{art})}. \quad \text{[Eq.1]}$$

Data acquisition: Data from 17 healthy subjects were included, each scanned twice on a 3T Philips MRI scanner. DSC-MRI was carried out using the pre-bolus method[9] to obtain quantitative CBF-measurements: contrast agent pre-bolus (0.02 mmol/kg) and segmented EPI (single slice, temporal resolution=0.81s, 1.72×1.72×5 mm^3). The pre-bolus scan was followed by the actual single-dose DSC-MRI study (0.1 mmol/kg), using single-shot gradient-echo EPI (1.72×1.72×5 mm^3, 20 slices, TE/TR=29/1243ms). ASL was carried out using background-suppressed single-shot EPI pCASL (1.65s label duration, 1.6s post-labelling delay, 2.29×2.29×5 mm^3, 16 slices, TE/TR=14/4000 ms, 30 repetitions); a reference M_0 scan was performed without labelling or background suppression, TR=10s, and 4 repetitions.

Data analysis: Hct-weighted CBF (from DSC-MRI) was obtained by scaling the AIF by the VOF area from the pre-bolus experiment,[9] and using oSVD deconvolution.[11] Hct-independent CBF (from ASL) was calculated using a model resembling the recent consensus recommendations.[10] CBF maps were normalized to MNI152 template using SPM8. Cerebral Hct was estimated using Eq.1. Since no Hct_{art} measurements were available, this value was set to 0.45.[12] However, to investigate the sensitivity to the assumed Hct_{art}, the analysis was repeated for Hct_{art}=0.3–0.6. For more detailed analysis, regions in cortical and subcortical grey matter structures were manually defined. Test-retest reproducibility was assessed using Bland–Altman analysis.

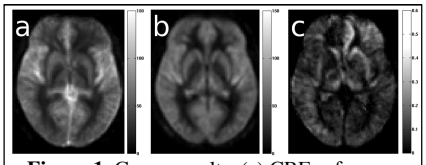

Figure 1. Group results. (a) CBF_{Hct} from DSC-MRI; (b) CBF from ASL; (c) Hct_{tissue}. CBF colorbars in ml/100g/min (range 0-150); Hct colorbar is unitless (range 0-0.6).

Results: Fig. 1 shows population average results, including average CBF and Hct_{tissue} maps. Fig. 2 shows the population average Hct_{tissue} maps in 3 MNI space projections. Fig. 3 shows the cerebral-to-arterial Hct ratio in subcortical and cortical regions, as a function of the assumed Hct_{art}: the ratio is, in general, consistent with literature values.[1,2] The method had good reproducibility, with a Bland–Altman bias (and limits of agreement) for the subcortical structures of 0.007 (0.115), and for cortical structures 0.018 (0.102).

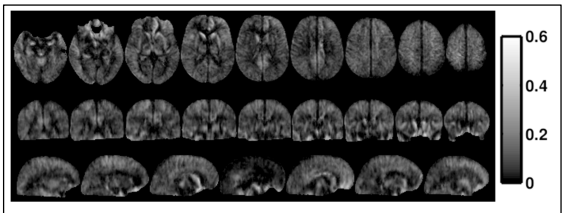

Figure 2. Population averaged Hct_{tissue}, in axial (top), coronal (middle), and sagittal (bottom) projections.

Discussion: An MRI method to measure cerebral Hct was proposed, which relies on combining measurements from 2 MRI techniques, one that provides Hct-dependent and another one with Hct-independent values. The method was illustrated using DSC-MRI and ASL data on a group of healthy subjects, and was shown to measure cerebral Hct in general agreement with literature values,[1,2] with good test-retest reproducibility. The proposed MRI method could have important applications in various neurological diseases, such as stroke and tumours.

Alternative implementations of this method could be done using CBV measurements instead of CBF (e.g. combining DSC-MRI with either steady-state T_1 data[13] or calibrated VASO data[14]), or combining steady-state T_1 and T_2 CBV measurements (which are in fast and slow exchange, respectively)[15]. CBV-based implementations are likely to be more robust, given that these do not rely on deconvolution. Furthermore, these alternative implementations are likely to be more suited for white matter Hct_{tissue}, given the known difficulties with quantifying white matter CBF using ASL. In particular, the steady-state implementation, when combined with blood pool agents, may open up the possibility of mapping cerebral Hct with high resolution and SNR. Finally, more robust measurements will be obtained when individual Hct_{art} are available, to account for its inter-subject variability.

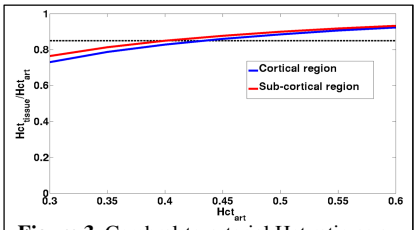

Figure 3. Cerebral-to-arterial Hct ratio as a function of assumed Hct_{art}, for subcortical (red line) and cortical (blue line) regions. The classical literature value[1,2] of 0.85 is shown as dashed line.

References: [1] Lammertsma AA et al, *J Cereb Blood Flow Metab* 1984; 4: 317–322. [2] Sakai F et al, *J Cereb Blood Flow Metab* 1985; 5: 207–213. [3] Bereczki D et al, *J Appl Physiol* 1985 1992; 73: 918–924. [4] Loutfi I et al, *Am J Physiol Imag* 1987; 2: 10–16. [5] Sakai F et al, *Acta Neurol Scand Suppl* 1989; 127: 9–13. [6] Brooks DJ et al, *Microvasc Res* 1986; 31: 267–276. [7] Calamante F et al, *J Cereb Blood Flow Metab* 1999; 19: 701–735. [8] van Osch MJP et al, *Magn Reson Med* 2003; 49: 1067–1076. [9] Knutsson L et al, *Magn Reson Med* 2014;72: 996-1006. [10] Alsop DC et al, *Magn Reson Med* 2014; doi: 10.1002/mrm.25197. [11] Wu O et al, *Magn Reson Med* 2003; 50: 164–174. [12] Purves WK et al, *Life: The Science of Biology*. W.H. Freeman & Co Ltd, 2004. [13] Shin W et al, *Magn Reson Med* 2007; 58: 1232–1241. [14] Lu H et al, *Magn Reson Med* 2005; 54: 1403–1411. [15] Donahue KM et al, *J Magn Reson Imaging* 1997; 7: 102–110.