Cerebral Blood Flow Estimation using Local Tissue Reference Functions

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Introduction

The arterial input function (AIF) remains a large source of error in quantitative dynamic susceptibility contrast (DSC) MR perfusion cerebral blood flow (CBF) estimates. Absolute AIF tracer concentration measurements are subject to error arising from partial volume effects (PVE) – causing variation in both the degree of AIF underestimation and in the AIF dependency on complex field inhomogeneities from surrounding tissues - are prone to signal saturation (*i.e.*, DSC-MR signal is below noise level) [1] and have dispersion errors since the AIF is not local to a given tissue region.[2] As a result, CBF values are often cross-calibrated using a normal human-based CBF average from a reference region in order to provide meaningful CBF values for clinical purposes such as acute ischemic stroke diagnosis. In a study assessing DSC-MR CBF operator variability, Niven *et al.*[3] reported that the effect of AIF selection was not statistically significant while the PVE correction factor from cross-calibration was significant. Interestingly, a similar finding was reported using bolus-tracking CT perfusion by Sanelli *et al.*[4] where CBF estimates were robust to AIF selection but were impacted up to a factor of 3 by selection of the venous output function used to provide a patient-specific AIF PVE correction factor. Based on this evidence, it would appear that CBF is more sensitive to the PVE correction method then to the AIF itself.

Tracer concentration measurements from white matter (WM) and gray matter (GM) have a higher signal-to-noise ratio (*i.e.*, do not saturate), have less operator PVE variation and also may be less affected by AIF dispersion errors, since LRFs are chosen locally at the tissue level rather than distally as with AIFs. Therefore, it seems logical that the tissue signals we use for CBF cross-calibration may serve as better *reference signals* for deconvolution given the technical and practical errors associated with AIF measurement.

The purpose of this work is to investigate the concept of deriving CBF by replacing the traditional AIF with the DSC-MR signal from normal WM tissue. It is our hypothesis that if the CBF overestimation effects resulting from AIF PVE errors are addressed using cross-calibration, then there will be negligible difference between CBF estimates generated using AIFs versus normal WM local reference functions (LRF).

Methods

Thirty acute ischemic stroke patients were imaged at 3 T (Signa; GE Healthcare, Waukesha, WI) with a T2*-weighted single-shot gradient-recalled echo echo-planar sequence (TR/TE/flip = 1750 ms/30 ms/45°, 144 × 144 acq. matrix, 24 cm field of view). A power-injector (Medrad; Pittsburgh, PA) delivered 20 ml of contrast agent (Magnevist; Berlex, Wayne, NJ) to each patient at a rate of 5 ml/s. PerfTool [6] was used to process CBF maps using delay-insensitive reformulated singular value decomposition [7] with a relative regularization threshold fixed at 20% for an AIF from the middle cerebral artery and for a LRF, both contralateral to the ischemic hemisphere. The peak height of the Fourier-interpolated residue functions [8] were then cross-calibrated so that the mean of a region of interest (ROI) placed in centrum semiovale WM contralateral to the ischemic hemisphere was 22 ml/min/100 g.[8] ROIs were also placed in putamen GM contra-lateral to ischemia and in ischemic tissue using apparent-diffusion coefficient maps to evaluate infarct for ischemic ROI selection. Mean and standard deviation measurements for each ROI (excluding mean WM CBF due to cross-calibration) were analyzed using a repeated measures multivariate analysis of variance (MANOVA) with the reference function (*i.e.*, AIF or LRF) as a within-subject factor. Univariate analyses of individual tissue CBF measures were performed as appropriate. Statistical significance thresholds were established, with $p > 0.05$ indicating no difference between LRF and AIF measurements.

Results

The MANOVA analysis revealed that the effect of reference function type on the CBF measurements was not significant ($p = 0.11 > 0.05$). As an example of differences between AIFs and LRFs, the Figure shows CBF maps generated using AIFs and LRFs for two of the acute stroke patients.

Discussion

In patients, we found little difference between CBF estimates from AIFs and LRFs after cross-calibration. Although normal WM CBF cross-calibration still requires validation for the pathology considered, this method is often still used clinically to scale DSC-MR CBF as WM has relatively constant CBF in normal humans across age and sex. LRFs generally yield similar relative differences across CBF maps to AIFs, but are less impacted by acquisition limitations, are easier to select and may reduce operator variability as WM suffers from less variable ROI PVE. Thus, LRFs appear to yield essentially the same CBF information as AIFs but provide several practical advantages for clinicians in the time-critical diagnosis of acute stroke.

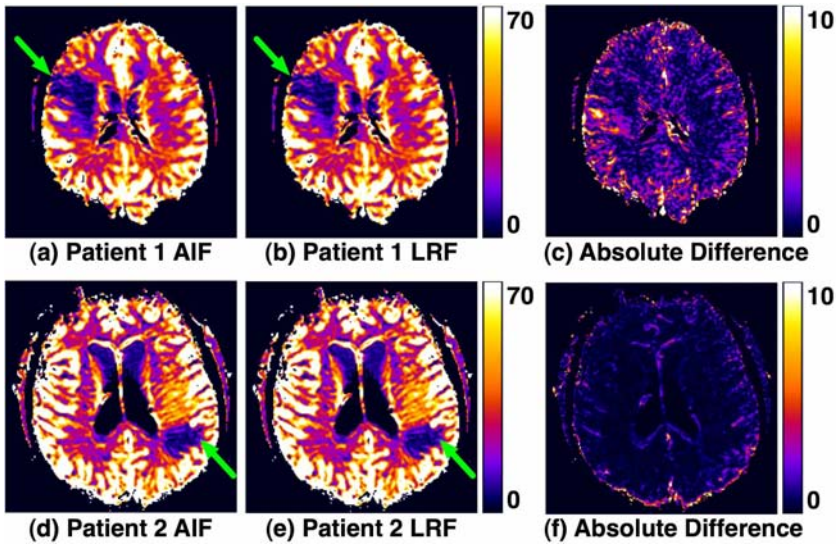

Figure: AIF vs. LRF. Cross-calibrated CBF maps produced with AIFs (a,d) and LRFs (b,e) from two ischemic stroke patients (arrows depict ischemia) visually resemble one another and show negligible differences from one another in the ischemia. The largest differences occur in vasculature and in cerebral spinal fluid (CSF) that was not removed prior to CBF post-processing. Even still, the mean absolute difference across the whole brain (including vasculature and CSF) in (c) and (f) were 2.5 and 0.8, respectively. In thirty ischemic stroke patients, the MANOVA analysis indicated no significant differences between AIFs and LRFs ($p = 0.11 > 0.05$).

References

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