DSC-MRI errors due to bolus delay and dispersion in sub acute stroke patients: implications for extending the therapeutic time window

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Introduction

In many cases of ischaemic stroke, diffusion MRI lesions are surrounded by a perfusion abnormality where reduced and collateral blood flows are able to preserve the tissue for a limited time (1). The perfusion-diffusion (P/D) mismatch tissue may be amenable to salvage using thrombolytic drugs (2). Although treatment is most effective when administered up to 3 hours after symptom onset, individual patients may benefit from treatment within 6 hours and beyond (3). Since the risk of a drug-induced intracerebral haemorrhage increases with time, assessing the patient specific risk outside the hyper acute window requires reliable perfusion measurements.

The most common MRI method for measuring perfusion in stroke is bolus tracking. However, in patients with cerebrovascular abnormalities the bolus may become delayed and/or dispersed en route to the tissue through stenosed or collateral vessels. This distortion causes a significant underestimation of perfusion calculated using standard methods such as Singular Value Decomposition (SVD) (4, 5), which may explain the observations of several studies where areas of apparent hypoperfusion do not necessarily progress to infarction (e.g. 6). More advanced techniques such as circular SVD (oSVD) (7) provide delay-insensitive perfusion estimates, but these are still bias by bolus dispersion. Since the presence of bolus delay and/or dispersion cannot be known a priori (8), balancing the benefit and risk of treatment is therefore difficult when using the potentially biased SVD or oSVD perfusion estimates. Furthermore, at later time points (the sub acute period) bolus delay and/or dispersion are expected to be more significant. Therefore, if the 6 hour treatment window is to be extended, the identification and correction of the related perfusion errors is important. In this work we demonstrate a methodology that identifies and corrects dispersion related perfusion measurement errors in a group of sub acute patients.

Background

Cerebral Blood Flow (CBF) is estimated from the maximum of the response function CBF·R(t), which is calculated by deconvolving the bolus concentration measured in a major artery, the Arterial Input Function (AIF), from that measured in the tissue C(t): $C(t)=CBF(AIF(t)\otimes R(t))$ (4). In regions where the bolus is delayed /dispersed, the measured AIF poorly represents the true tissue input. Reliable perfusion estimates are only possible when the effect of delay and dispersion is removed from the deconvolution by finding the true tissue input (9, 10).

Method

A Maximum-Likelihood Expectation-Maximisation (MLEM) algorithm regularised using an oscillation index and wavelet thresholding (oMLEMw) (11) was used for the deconvolution. This algorithm is able to characterise CBF·R(t) with sufficient accuracy to identify bolus delay/dispersion, and hence regions where an improved AIF is necessary. A regional AIF (rAIF) was found from within each identified region, by performing the Independent Component Analysis (ICA) decomposition of the C(t) within the region (12), using a Bayesian information criterion to decide the number of components (9). The time-course component with an early arrival and spatially localised within the arteries was selected for the rAIF in that region, and the oMLEMw was re-performed within the region. This methodology was repeated until delay/dispersion were minimised within the affected regions. Finally the global AIF and rAIF deconvolution regions were combined. We call this whole method rAIF-oMLEMw.

We compare the Mean Transit Time (MTT) maps calculated using SVD, oSVD and rAIF-oMLEMw in six stroke patients (mean age 64yrs, range 31-84yrs) imaged sub acutely and selected because of a P/D mismatch on the SVD MTT map. The data were acquired on a 1.5T GE scanner: PWI: TR/TE=2000/60ms, 0.1mmol/kg Gd-DPTA; DWI: b=0,1000s/mm^2. The bolus concentration data were denoised prior to deconvolution using ICA, and a global AIF was measured in a branch of contra-lateral middle cerebral artery.

Results

The P/D mismatch was assessed by measuring its severity (the magnitude of the MTT values) and extent (the size of the abnormal MTT area). In all six patients the oSVD and rAIF-oMLEMw mismatches are less severe and/or less extensive than the SVD mismatch. This suggests that the SVD mismatch is exaggerated by bolus delay. A comparison of the oSVD and rAIF-oMLEMw mismatches is given in Table 1. In three of the patients (c, e, and f) the extent of the mismatch region is smallest using the rAIF-oMLEMw analysis, suggesting that the SVD and oSVD mismatch areas are overestimated because of bolus dispersion. In two of these patients (e and f) the severity of the mismatch is also less using rAIF-oMLEMw. In three patients (a, b, and d) the extent of the oSVD and rAIF-oMLEMw mismatches are equal, suggesting that there is little dispersion, and that the larger SVD mismatch observed is purely an artefact of delay. In two patients (b and d) the oSVD mismatch is the same extent, but less severe than the rAIF-oMLEMw mismatch; these mismatch regions are located in the white matter where there is naturally a small bolus delay, which is accounted for by cSVD but not oMLEMw. The rAIF analysis is not possible in small white matter regions because a more appropriate rAIF can not be found. Figure 1 illustrates patient 'e', where both the severity and extent of the mismatch were significantly reduced using rAIF-oMLEMw.

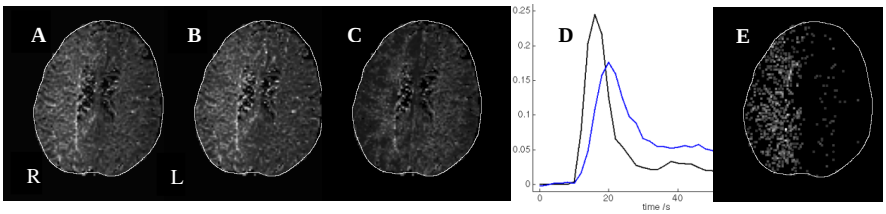

Figure 1: MTT maps calculated for patient 'e' using (A) SVD, (B) oSVD and (C) rAIF-oMLEMw. (D) The global AIF (black) and the regional AIF (blue) used for the right hemisphere of (C). (E) Highlighted voxels are affected by dispersion when using the global AIF. The rAIF is clearly dispersed with respect to the global AIF. The fact that this patient had no observable DWI abnormality in this slice is consistent with the apparent perfusion abnormality being mainly caused by dispersion errors.

Discussion

The safe administration of thrombolytic agents requires reliable perfusion estimates especially in sub acute patients. Using standard analyses, it is impossible to know whether a region of hypoperfusion is real, partly real or wholly artefact. In this sub acute group of patients, the severity and extent of the abnormalities were overestimated when bolus delay/dispersion were not accounted for. Even using oSVD, uncorrected dispersion exaggerated the extent of the abnormality. When bolus delay/dispersion are removed using the rAIFs, the rAIF-oMLEMw analysis can theoretically provide more accurate perfusion estimates (11), and therefore improved perfusion maps in patients with cerebrovascular abnormalities. Even in this small group, the rAIF-oMLEMw method reduces the mismatch extent in half of the patients, demonstrating the potential impact of dispersion in sub acute perfusion measurements. It is important to identify and correct for dispersion, since an overestimation of the mismatch region (e.g. Figure 1) could lead to dangerous mistreatment. More accurate quantification is therefore essential if the treatment window is to be extended. Given the logistical problems of treating patients within a short 6 hour time window, extending this period will lead to an increased number of patients identified as likely to benefit from treatment. This study therefore suggests that a more comprehensive investigation on sub acute patient outcome is required.

	oSVD *vs.* rAIF-oMLEMw	
	Severity	Extent
a	=	=
b	<	=
c	=	>
d	<	=
e	>	>
f	>	>

Table 1: oSVD *vs* rAIF-oMLEMw P/D mismatch.
=: rAIF-oMLEMw and oSVD are equal
>: rAIF-oMLEMw is less severe or smaller extent than oSVD
<: oSVD is less severe or smaller extent than rAIF-oMLEMw

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