Bolus delay and dispersion: implications for tissue predictor models in stroke

F. Calamante[1], D. G. Gadian[1], A. Connelly[1]

[1]Institute of Child Health, University College London, London, UK, United Kingdom

Introduction: Dynamic-susceptibility contrast MRI (DSC-MRI) can be used to calculate maps of cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT). These maps, in combination with diffusion- and T2-weighted images, are being used in models to predict the fate of the tissue in acute stroke, with the final aim to identify the patients that are more likely to benefit from therapy. However, it has been shown that the presence of bolus delay/dispersion can introduce significant errors in CBF (i.e. underestimation) and MTT (i.e. overestimation) [1]. This potential bias can have very important implications in the outcome of the predictor models. While deconvolution methods insensitive to the degree of delay have been proposed (e.g. [2,3]), the effect of dispersion is more difficult to deal with; it requires a model for the vascular bed [4,5], or the use of a locally defined arterial input function (AIF) [6,7]. The relationship between the degrees of delay and dispersion has not been fully investigated *in vivo*; if a simple relationship were identified, it could be used in the design of vascular models (e.g. by estimating the degree of dispersion from the much more easily calculated bolus delay). This study presents an assessment of the relationship between the degrees of delay and dispersion in a group of patients with a range of cerebral arterial abnormalities.

Methods: Patients included in the study had unilateral abnormalities in major cerebral arteries, and at least one region of bolus arrival delay. Data were acquired on a 1.5T Siemens Symphony scanner using a GE-EPI sequence (TE/TR=47/1500 ms) after the injection of a bolus of 0.15 mmol/kg of Gd-DTPA using an MR-compatible power injector (Medrad). For each patient, the local AIF was defined using our recently proposed method based on independent component analysis [7]. On this dataset, a number of characteristic *dispersed* AIF (AIF_{disp}) examples were measured in the ipsilateral hemisphere (typically 1-3, depending on the patient's local AIF distribution). A *normal* AIF (AIF_{normal}) was also measured in the M1 segment of the contralateral middle cerebral artery (MCA). Since AIF_{normal} can be considered to represent the AIF in the absence of dispersion, the two AIFs were assumed related by the convolution $AIF_{disp}(t)= AIF_{normal}(t)\otimes VTF(t)$, where VTF is the vascular transport function [5]. For each AIF_{disp}, the degree of delay with respect to AIF_{normal} was calculated (including taking into account the time delay between the acquisitions of the corresponding slices). To quantify the degree of dispersion, the VTF was obtained by deconvolution using Tikhonov regularization [8], and the normalized first moment of the VTF ($VTF^{(1)}$) was calculated. This parameter was used because of its analogy to MTT (i.e. the first moment of the *tissue* transport function [9]). Before deconvolution, the AIF curves were fitted using a gamma-variate function, the data subsampled to a 0.05sec resolution, and the delay removed by realigning the curves. The latter was done to isolate the dispersion from the delay effects. The subsampling is required to avoid discretization errors in the calculation of $VTF^{(1)}$; this parameter can be much shorter than the MTT, and the original TR would lead to large inaccuracies in the numerical integration required in the first moment. The relationship between the degrees of delay and dispersion was then investigated. The CBF errors introduced by the bolus dispersion were assessed using a similar methodology to that in [7]: the tissue concentration $C(t)$ was measured in a region around the place where AIF_{disp} was sampled, and two estimates of CBF were obtained by deconvolution of $C(t)$ using either the local (dispersed) AIF or the contralateral AIF.

Results: Fifteen patients were identified; their abnormalities included stenosis, occlusion or dissection of a major cerebral artery. Twenty-one AIF_{disp} were defined, with a range of delays between ~0-4sec, and dispersion (i.e. $VTF^{(1)}$) between ~0.5-3sec. Figure 1 shows a plot of the first moment as a function of delay. As can be seen in the plot, there is no correlation between the amount of delay and the degree of dispersion; in particular one patient had dispersion without delay (this patient had another region that showed delay and dispersion), and others with relatively small dispersion had delay >2sec. It should also be noted that the longest delay found in this group of patients did not correspond to the largest dispersion. The lack of correlation is not a consequence of the range of vascular abnormalities in the patients included in the study; for example, the 6 patients (corresponding to 8 AIF_{disp}) with MCA abnormalities also show no correlation (circled points in the figure).

The errors in the quantification of DSC-MRI data introduced by dispersions in the range observed are not negligible. Most of the cases studied have a dispersion of $VTF^{(1)} \approx$ 1sec, which produces a 25-30% CBF underestimation when the non-dispersed (contralateral) AIF is used. However, cases were also observed with dispersion >2sec, which introduces CBF errors >50%, if the dispersion is not accounted for.

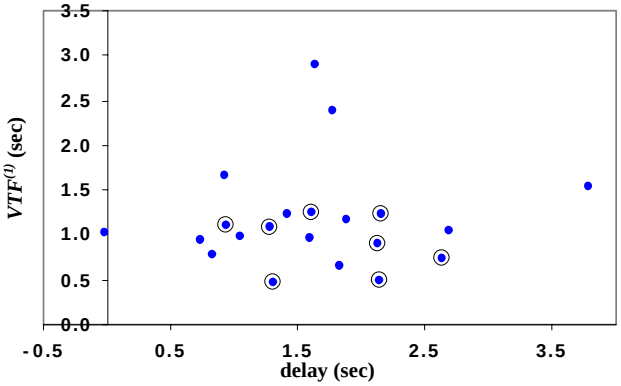

Figure 1. Degree of dispersion (measured as the first moment of the VTF) as a function of bolus delay. Data measured on patients with a range of abnormalities in major cerebral arteries. No correlation can be observed between the delay and the dispersion. The circled points correspond to patients with MCA abnormalities.

Discussion: There are two main findings in this study: *(i)* No correlation between the amount of delay and the degree of dispersion was observed in the patients studied; *(ii)* The bias introduced by the unaccounted dispersion is not negligible, and its range can be quite significant (10-60% underestimation of CBF). While the errors due to delay can be accounted for (e.g. [2,3]), the degree of dispersion present in a given patient cannot be inferred from the amount of delay. Therefore, if a local AIF is not used to minimize the dispersion, it is not possible to predict the extent of the bias that will be present in the data. These findings have very important implications for the models currently being used for determining the tissue outcome in stroke. This bias can lead to tissue misclassification, and finally to the inappropriate selection of patients for treatment, such as arterial thrombolysis.

References: [1] Calamante F et al, *Magn Reson Med* 2000;44:466. [2] Wu O et al, *Magn Reson Med* 2003;50:164. [3] Smith AM et al, *Magn Reson Med* 2000;43:559 [4] Østergaard L et al, *J Cereb Blood Flow Metab* 1999;19:690. [5] Calamante F et al, *NeuroImage* 2003; 19:341. [6] Alsop DC et al, Proc ISMRM 2002,659. [7] Calamante F et al, *Magn Reson Med* 2004;52:789. [8] Calamante F et al, *Magn Reson Med* 2003;50:1237. [9] Østergaard L et al, *Magn Reson Med* 1996;36:715.