Assessment of the significance of temporal delays in the BOLD signal response to a CO2 stimulus

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Introduction

The blood transit time provides useful information for the diagnosis of cerebrovascular disease. It is commonly measured using dynamic susceptibility contrast (DSC) imaging. Cerebrovascular reactivity (CVR) imaging is a promising and relatively non-invasive technique to investigate the brain's autoregulatory capacity. BOLD MRI can be used to measure the response to the vasodilatory effect of inhaled CO2. Although a reactivity parameter is obtained from the intensity of the BOLD response, a time delay parameter can also be extracted. In this study, we investigate the temporal response of the BOLD signal to the CO2 stimulus and evaluate whether delayed responses in patients are indicative primarily of delayed vascular transit time of the CO2 stimulus or delayed arteriolar response to the arriving stimulus.

Materials and Method

Ninety eight patients with vascular disease (Carotid stenosis and Moya Moya) were imaged on a 3T GE MRI system.

For the CVR experiment, hypercapnia is induced by inhaling a gas mixture of 8% CO2 balanced with oxygen via a re-breathing device described previously by Vesely and al [1]. $ETpCO_2$ in all patients varied from normocapnia ($ETpCO_2$ ~ 40 mmHg) to hypercapnia ($ETpCO_2$ ~ 50 mmHg) several times while $ETpCO_2$ was recorded.

CVR images were acquired using BOLD (EPI readout) with TE=30ms, TR=2s.

Six out of the 98 patients had DSC images acquired during the same session, using a 15cc injection of gadolinium.

Anatomical T1-weighted images were acquired for co-registration purposes.

Analysis:

Each dataset was transformed into Talairach space using AFNI software.

Excluding voxels with negative reactivity (likely caused by a steal phenomenon), BOLD signal averages of the right and left middle cerebral territories (MCT) were fed into an AFNI program (Hilbert Delay98) to calculate their relative time delay (ΔTD) by finding the maximum of their cross-correlation.

By standard regression analysis of the BOLD signal with the $ETpCO_2$, a reactivity map expressed in percentage BOLD signal change per millimeter of mercury (% / mmHg) was obtained and reactivity difference (ΔCVR) of the right and left MCT was calculated.

A correlation between the ΔCVR and ΔTD was then calculated.

For 6 of the 98 patients who had DSC images acquired during the same session, a time to minimum (TM) map was generated using the GE Advantage Workstation's FuncTool, and a correlation between ΔTD and ΔTM was calculated.

Results

With 98 patients the correlation between ΔCVR and ΔTD is significant ($r = 0.74$, $p < 0.0001$) (see Fig 1).

As well, the correlation on 6 of those patients between ΔTD and ΔTM is significant ($r = 0.97$, $p < 0.002$) (see Fig 2).

Fig1. *TD difference between right and left MCT plotted against CVR difference*

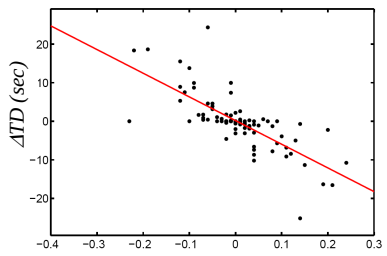


Fig2. *TD difference between right and left MCT plotted against TM difference*

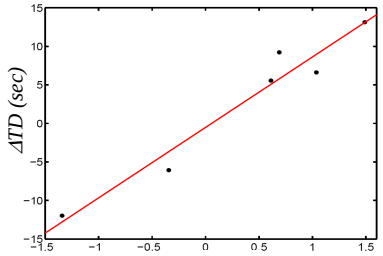
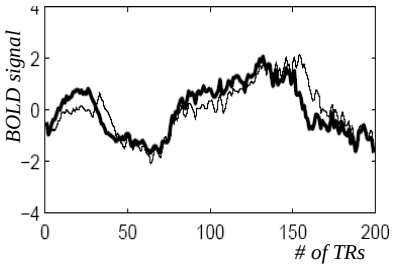


Fig3. *BOLD signal time courses extracted from the normal (in bold) and the diseased side of the brain*



Conclusion

We found that he CVR delay parameter correlates well with the CVR itself and the DSC-based TM measure. Even though the correlation between ΔTD and ΔTM is significant, the ΔTD values are an order of magnitude greater than the ΔTM measure and clearly reflect different physiological mechanisms. Whereas ΔTM reflects a vascular transit time, the much longer CVR-based ΔTD is presumably dominated by an arteriolar response time. As previously reported in a transcranial doppler ultrasound study by A. Hezel and al. [2], we have also observed that the main time delay occurs not on onset of hypercapnia but arises from a late return to baseline after the $ETpCO_2$ has already decreased (see Fig 3) This implies a non-linearity in the response and future work will assess whether modeling this effect can improve CVR analysis.

[1] Vesely et al., MRI mapping of cerebrovascular reactivity using square wave changes in end-tidal PCO_2. Magn Reson. Med. 2001;45(6):1011-1013

[2] Hetzel et al, Time Delay as a Parameter for Cerebrovascular Reactivity in Patients with Severe Carotid Stenosis. Cerebrovasc Dis. 2003;16(1):14-20