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The dynamics of cerebrovascular reactivity shown with transfer function analysis

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ABSTRACT

Cerebrovascular reactivity (CVR) is often defined as the increase in cerebral blood flow (CBF) produced by an increase in carbon dioxide (CO_2) and may be used clinically to assess the health of the cerebrovasculature. When CBF is estimated using blood oxygen level dependent (BOLD) magnetic resonance imaging, CVR values for each voxel can be displayed using a color scale mapped onto the corresponding anatomical scan. While these CVR maps therefore show the distribution of cerebrovascular reactivity, they only provide an estimate of the magnitude of the cerebrovascular response, and do not indicate the time course of the response; whether rapid or slow. Here we describe transfer function analysis (TFA) of the BOLD response to CO_2 that provides not only the magnitude of the response (gain) but also the phase and coherence. The phase can be interpreted as indicating the speed of response and so can distinguish areas where the response is slowed. The coherence measures the fidelity with which the response follows the stimulus. The examples of gain, phase and coherence maps obtained from TFA of previously recorded test data from patients and healthy individuals demonstrate that these maps may enhance assessment of cerebrovascular pathophysiology by providing insight into the dynamics of cerebral blood flow control and distribution.

Introduction

Cerebral blood flow (CBF) responds to changes in perfusion pressure (Dineen et al., 2010; Lucas et al., 2010; Panerai et al., 1999), tissue metabolism (Attwell et al., 2011; Iadecola and Nedergaard, 2007; Paulson et al., 2011) and carbon dioxide (CO_2) (Ainslie and Burgess, 2008; Battisti-Charbonney et al., 2011); an integration of these factors controls cerebral blood flow (Willie et al., 2014). Alterations in cerebral perfusion pressure cause changes in vascular diameter to regulate CBF, a process termed pressure autoregulation (Tzeng et al., 2014). And the CBF response to CO_2 is also thought to be mediated via changes in vascular diameter produced by a direct action of CO_2 on cerebral arteriolar vessels (Kontos et al., 1977; Lassen, 1968; Tian et al., 1995). Since tissue metabolism demand, CO_2 and pressure autoregulation all control vessel caliber independently, the latter two drawing on the same vascular dynamic range to control CBF (Harper and Glass, 1965), the flow response to manipulation of any of these three factors can be used to assess the health of the cerebral vasculature. However, manipulating tissue metabolism is not feasible because it requires a stimulus that would increase brain metabolism to the same degree over the whole brain. Therefore, to achieve a global stimulus either blood pressure manipulation (Tan et al., 2013) or a CO_2 challenge can be used, with the latter preferable in terms of clinical practicality and patient safety.

Applying carefully controlled CO_2 stimuli, the cerebrovascular response can be obtained using blood oxygen level dependent (BOLD) measurements during magnetic resonance imaging (MRI) as a surrogate for the CBF response (Fierstra et al., 2013). We used BOLD to measure CBF because it is implemented on most clinical scanners, whereas direct measurements of CBF may not always be available. Moreover, BOLD-based CVR values are well correlated to the more direct CBF-based CVR values, when isoxia is maintained (Mandell et al., 2008). Cerebrovascular reactivity (CVR) is then usually calculated as the slope of an assumed linear relationship between the BOLD response and the CO_2 stimulus, i.e. the change in BOLD signal divided by the increase in the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$). Although $P_{ET}CO_2$ is the stimulus measured, the actual stimulus is arterial PCO_2 ($PaCO_2$). CVR values for each voxel can be displayed using a color scale mapped onto the corresponding voxel of an anatomical scan to generate CVR maps showing the distribution of CVR. These CVR maps offer physiological interpretation (Sobczyk et al., 2014), and can also be used to detect pathology (e.g. Mandell et al., 2008), and assess the efficacy of surgical interventions (e.g. Han et al., 2011).

Nevertheless, CVR maps do not reflect the time course of response, other than through its effect on the amplitude of the CBF response to

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CO_2, and generally ignore the hemodynamics involved, which may be complex, reflecting the dynamic interaction of the CO_2 vasodilatory stimulus with the pressure autoregulation mechanism, and possibly the dynamic redistribution of blood flow between the various areas of the cerebrovasculature (Blockley et al., 2011; Regan et al., 2013). We hypothesized that a way of determining whether the response was rapid or slow (i.e. the speed of the response) is a valuable dimension in addition to the magnitude of response which characterizes the CVR.

We therefore analyzed the BOLD response and its $P_{ET}CO_2$ stimulus signals with a frequency analysis technique; transfer function analysis (TFA) which is already used to measure dynamic pressure autoregulation of the cerebrovasculature (Blaber et al., 1997; Tzeng et al., 2012; Zhang et al., 1998), and offers a means of characterizing the BOLD response to CO_2 that includes not only an estimate of the magnitude of the response, as CVR does, but also insight into the response dynamics. The latter is provided by the phase relationship between the response and the stimulus (Blockley et al., 2011). The phase difference between stimulus and response arises from two factors; a blood transit time delay and a response time as illustrated in Fig. 1. In our TFA method, CO_2 and BOLD signals are time aligned before analysis, and differences in time delay between regions were assumed to be less than the 2 s sampling period so that TFA phase primarily reflects the speed of the response. In this respect TFA phase corresponds to a time domain analysis where the stimulus is convolved with a mono-exponential 'dispersion' function and the time constant altered to provide the best fit with the BOLD response. Indeed maps of these time constant estimates are similar to the phase maps (unpublished data).

In this paper we describe the TFA approach, and illustrate its application with examples from our database of previously recorded and analyzed CVR experiments. One advantage of determining the speed of the response is distinguishing those voxels with reduced vasodilatory reserve from voxels with a slow response but otherwise normal reserve. As previously discussed (Regan et al., 2014), calculation of CVR using a linear analysis of BOLD vs. $P_{ET}CO_2$ can be confounded in tissues with a slowed response leading to artificially low values of CVR. Another key physiological insight provided by TFA is the finding that areas of slow positive gain often bordered areas of fast negative gain (steal) indicating that latter tissues behave passively representing steal physiology.

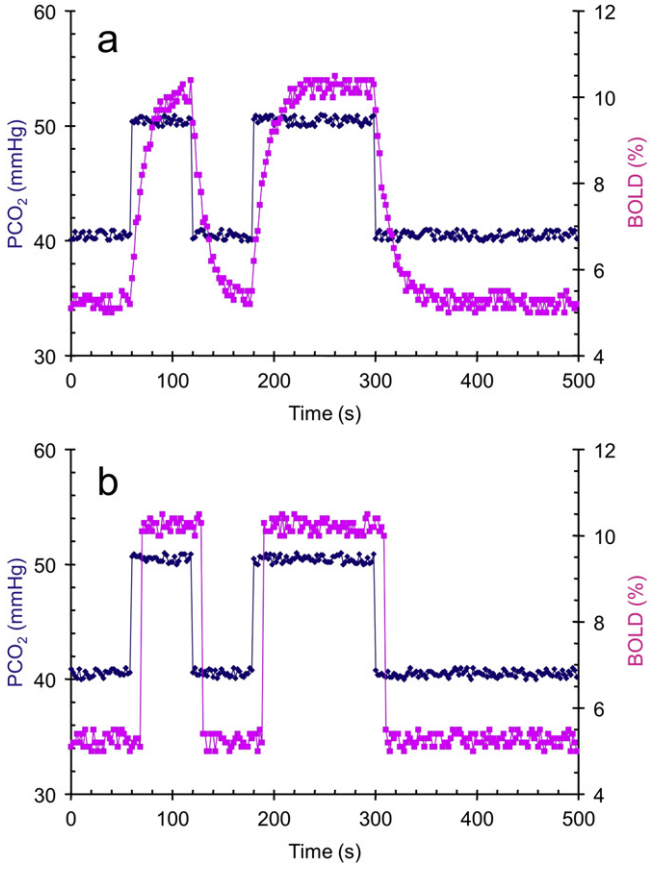

Fig. 1. Model simulation examples showing the effects of transit delay and speed of response on the TFA phase parameter; random noise (10% of step changes) was added to the PCO_2 and BOLD signals. (a) A simulated slowed response (exponential rise with time constant of 15 s) with no transit delay produced a TFA phase = −0.46 (radians). (b) A simulated transit delay of 10 s produced a TFA phase = −0.45 (radians).

Methods

Subjects

The examples shown were assembled from 2 healthy individuals and 10 patients drawn from our CVR database; the latter diagnosed with a known cerebrovascular disease (Moyamoya) (Scott and Smith, 2009). All had undergone a standardized CVR testing protocol as a result of participation in ERB approved CVR studies at our institution. These studies therefore conformed to the standards set by the latest revision of the Declaration of Helsinki, and were approved by the Research Ethics Board of the University Health Network. All subjects were competent and gave written informed consent. The anthropomorphic and pathophysiological characteristics of the subjects are summarized within their corresponding figures.

Apparatus

The application of a standardized CO_2 stimulus using prospective end-tidal gas control has been described in detail elsewhere (Fierstra et al., 2013). Subjects were fitted with a face mask, connected to a sequential gas delivery breathing circuit (Somogyi et al., 2005), and a step CO_2 stimulus was implemented, consisting of the following sequence: baseline $P_{ET}CO_2$ for 60 s at the subject's resting $P_{ET}CO_2$, step to a hypercapnia of 10 mm Hg above baseline for 45 s, baseline for 90 s, hypercapnia for 120 s, and return to baseline for 60 s, all during isoxic normoxia. Throughout these tests isoxia was maintained at normoxic values ($P_{ET}O_2$ = 100 mm Hg). These patterns of $P_{ET}CO_2$ and $P_{ET}O_2$ were programmed into the automated gas blender (RespirAct™, Thornhill Research Inc., Toronto, Canada) running a prospective gas targeting algorithm (Slessarev et al., 2007), which has been shown to control the CO_2 stimulus such that $P_{ET}CO_2$ is equivalent to $PaCO_2$ (Ito et al., 2008; Willie et al., 2012).

A 3.0-Tesla HDx scanner using an 8-channel phased-array receiver coil (Signa; GE Healthcare, Milwaukee, Wisconsin) was used for MRI; consisting of BOLD acquisitions with echo planar imaging (EPI) gradient echo (TR/TE = 2000/30 ms, 3.75 × 3.75 × 5 mm voxels, field of view 24 × 24 cm, 39 slices, slice thickness 5 mm, matrix size 64 × 64, number of frames = 254, flip angle (FA) = 85°).

CVR analysis

The BOLD MRI response and corresponding $P_{ET}CO_2$ stimulus were analyzed using AFNI software (National Institutes of Health, Bethesda, Maryland; http://afni.nimh.nih.gov/afni; Cox, 1996), as described in greater detail elsewhere (Fierstra et al., 2010). The BOLD images were first volume registered and slice-time corrected and co-registered to an axial 3-D T1-weighted Inversion-Recovery prepared Fast Spoiled Gradient-Echo (IR-FSPGR) volume (TI/TR/TE = 450/8/3 ms, voxel size 0.86 × 0.86 × 1.0 mm, matrix size 256 × 256, field of view 22 × 22 cm, slice thickness = 1 mm, FA = 15°) that was acquired at the same time (Saad et al., 2009). The end-tidal PCO_2 stimulus recording was resampled and interpolated at the BOLD sampling frequency of 0.5 Hz, and then time-aligned to the point of maximum correlation with the whole brain average BOLD signal. A linear, least-squares fit of