Vascular dynamics and BOLD fMRI: CBF level effects and analysis considerations

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Changes in the cerebral blood flow (CBF) baseline produce significant changes to the hemodynamic response. This work shows that increases in the baseline blood flow level produce blood oxygenation-level dependent (BOLD) and blood flow responses that are slower and lower in amplitude, while decreases in the baseline blood flow level produce faster and higher amplitude hemodynamic responses. This effect was characterized using a vascular model of the hemodynamic response that separated arterial blood flow response from the venous blood volume response and linked the input stimulus to the vascular response. The model predicted the baseline blood flow level effects to be dominated by changes in the arterial vasculature. Specifically, it predicted changes in the arterial blood flow time constant and venous blood volume time constant parameters of +294% and −24%, respectively, for a 27% increase in the baseline blood flow. The vascular model performance was compared to an empirical model of the hemodynamic response. The vascular and empirical hemodynamic models captured most of the baseline blood flow level effects observed and can be used to correct for these effects in fMRI data. While the empirical hemodynamic model is easy to implement, it did not incorporate any explicit physiological information.

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Introduction

Vasculature dynamics play a very important role in hemodynamics, especially in the generation of the blood oxygenation-level dependent (BOLD) response observed during brain activation using functional magnetic resonance imaging (fMRI) (Ogawa et al., 1990; Kwong et al., 1992). The vascular response is believed to arise in response to the metabolic needs of the working brain, in particular, the supply and delivery of oxygen and glucose (Fox et al., 1988; Magistretti et al., 1999). Temporally, the vascular response is slower compared to the changes in neuronal activity, questioning the degree to which the vasculature may be under direct neuronal control. This is not necessarily detrimental to studies that make inferences on working brain patterns from information encoded in the hemodynamic response since vascular responses have been measured to stimuli tens of milliseconds in duration (Savoy et al., 1995; Menon et al., 1998; Lewis and Miall, 2003). However, the close temporal correlation between the vascular and BOLD responses to brain stimulation is affected by properties of the vascular response that are not dependent on the neuronal activity. For example, the vascular response has been shown to vary as a function of the blood flow level (Bandettini and Wong, 1997; Cohen et al., 2002; Riecker et al., 2003; Kamurpatti et al., 2003).

A hypercapnia challenge is known to increase cerebral blood flow (CBF) globally in the brain. Hypercapnia manipulations have been shown to also increase the BOLD baseline (Davis et al., 1998; Cohen et al., 2002) with regional variations that may be related to differences in baseline cerebral blood flow and/or volume (Kastrup et al., 1999). Moreover, visual stimulation under normocapnia and hypercapnia conditions produces different BOLD fMRI responses although these manipulations do not produce known changes in oxygen metabolism (Cohen, 2002). Cohen et al. (2002), reported slower BOLD responses with increases in the baseline blood flow and faster BOLD responses with decreases in the baseline blood flow level. This is not the only known non-linear behavior of the BOLD response; other non-linear properties have been reported, such as non-linearities in the hemodynamic response with respect to stimulus duration (Vazquez and Noll, 1998; Miller et al., 2001).

The objective of this manuscript is to characterize the effect of the cerebral blood flow baseline on the hemodynamic response using a vascular hemodynamic model. The vascular hemodynamic model provided a means to characterize the effect of the baseline blood flow level on the hemodynamic response and to test the hypothesis that increases in baseline blood flow produce slower and lower amplitude hemodynamic responses, while decreases in baseline blood flow produce faster and higher amplitude responses, respectively.
model implemented provided a separate characterization of arterial and venous properties of the vascular response given blood flow and BOLD fMRI responses. Additionally, the model linked the vascular response to the stimulus via an assumed neuronal tissue response. The vascular model was compared to an empirical model of the hemodynamic response that also captured the baseline blood flow level effects on the hemodynamic response. Both vascular and empirical hemodynamic models provide guidance on how to account and correct for these effects in fMRI data analysis.

Materials and methods

Two experiments were performed to investigate the impact of the vascular dynamics on the hemodynamic response. One experiment measured evoked BOLD responses under increases and decreases in the blood flow baseline, while the other experiment measured blood flow and BOLD evoked responses under increases in the blood flow baseline. The data from these experiments were used to estimate the parameters of the vascular hemodynamic model.

Experiment 1: Visual BOLD fMRI data at 7 T

The first experiment consisted of two sessions for which subjects were recruited and scanned. In the first session, visual stimuli were presented to the subjects during normocapnia and hypercapnia conditions (Cohen et al., 2002). The visual stimulus consisted of a full-field black and white checkerboard alternating at a frequency of 4.5 Hz for 4 s followed by 41 s of rest (uniform grey screen). The first stimulus in each scan was presented after 30 s of rest and the stimulus and rest periods were repeated 9 times. Hypercapnia was induced at the onset of the third stimulus in the scan and maintained for 3 min via the administration of a 5% carbon dioxide, 95% oxygen gas mixture (i.e., carbogen) and hypocapnia conditions in similar fashion to the previous session. Hypocapnia was induced by rehearsed hyperventilation. The scans in each session were repeated 3 to 6 times.

The scans in this experiment were performed using a 7 T MRI scanner (Magnex Scientific, Abingdon, UK) controlled with a Varian Unity console (Varian, Palo Alto, CA, USA) at the University of Minnesota. For further details please refer to Cohen, 2002.

Experiment 2: Motor FAIR and BOLD fMRI data at 3 T

In the second experiment the subjects were instructed to perform a visually cued motor task (finger opposition) while being scanned. The subjects performed the motor task under hyperoxia and hyperoxic–hypercapnia conditions. Hypercapnia and hyperoxia were induced in this experiment using a 5% carbon dioxide, 95% oxygen gas mixture (i.e., carbogen) and 100% oxygen gas, respectively. The duration of the motor task varied over the scan session with durations of 12 and 6 s and resting periods of 38 and 34 s, respectively. Each stimulation and rest condition was repeated 20 times in each experiment. Hyperoxia was induced prior to the beginning of each scan and hypercapnia was induced at the onset of the 10th stimulus and lasted for the following 10 stimuli and rest conditions. One additional experiment was performed under hyperoxia conditions where the stimulus and rest periods lasted 60 s each, repeated 10 times.

The imaging in this experiment was performed using a standard quadrature birdcage head coil and a 3 T MRI scanner (GE Medical Systems, Milwaukee, WI USA) at the University of Michigan. Blood flow and BOLD measurements were performed in this experiment using a flow-sensitive alternating inversion recovery (FAIR), gradient-echo acquisition (Kim, 1995). A single axial slice (7 mm thick) over the motor cortex of the subjects, localized from a whole-brain block design BOLD acquisition, was scanned using a dual-echo, gradient-echo FAIR acquisition with spiral readouts. The imaging parameters were: 20 × 20 cm² FOV, 64 × 64 matrix, 2,0× inversion slab width, 8 ms TE (echo 1), 28 ms TE (echo 2), 1900 ms TI, 2000 ms TR and 90° flip angle. The data from the first echo was used to determine the CBF changes while the data from the second echo was used to determine the BOLD signal changes. The images from the selective and non-selective inversion conditions of the FAIR acquisition were linearly interpolated to every TR in order to obtain CBF and BOLD images at every TR. Informed consent was obtained from all subjects in this experiment (n = 8) in accordance with the University of Michigan Institutional Review Board. All subjects were screened to be in good health.

Vascular Hemodynamic Model

A vascular model of the hemodynamic response was used to characterize the vascular effects present in the data by describing the arterial vascular response to neuronal stimulation and the eventual generation of the BOLD effect in the venous side. This model is referred to in this manuscript as the vascular hemodynamic model or the vascular model (Fig. 1, top).

The vascular hemodynamic model consisted of a pre-vascular portion that linked the stimulus (of duration w) to the vascular response via the neuronal tissue response. A summary of the parameters of the vascular hemodynamic model is provided in Table 1. The neuronal response (fneu) was assumed to resemble neuronal adaptation effects observed with cortical local field potential (LFP) measurements as well as the possibility of a sustained neuronal response following evoked stimulation (Logothetis et al., 2001; Muller et al., 1999). The sustained neuronal response was modeled as a prolonged neuronal response period of additional duration (wexp) while the neuronal adaptation effect was represented by the product of the stimulus with a time-locked exponential function of amplitude N and time constant kexp (Eq. (1)). The time constant for the neuronal adaptation effect was fixed to 1/1.5 s⁻¹ (Logothetis et al., 2001). These sharp changes in the neuronal response were smoothed prior to producing the vascular response using a first-order linear model, analogous to a passive intermediary process (U in Eq. (2)). The time constant of this intermediary process (τn) was fixed to 2 s and can be related to the diffusion of small vasoactive chemicals across a distance of about 100 μm.

\[ f_{\text{neu}} = S(w + w_{\text{exp}}, t - t_0)(1 + N \exp(-k_{\text{exp}}(t - t_0))) \]  
\[ \frac{dU}{dt} = \frac{1}{\tau_n} (f_{\text{neu}}(S) - U(t)) \]
Vascular Model

![Diagram of the vascular model]

Empirical Model (for comparison)

Fig. 1. (Top) The vascular model of the hemodynamic response produces the blood flow response via neuronal and intermediate responses. The BOLD response was calculated considering the blood flow, blood oxygen extraction into tissue and the venous volume properties. The hemodynamic response dependence on the baseline blood flow level was assessed through the model parameters that directly influence the vascular response, namely, the arterial blood flow time constant ($\tau_a$) and the venous blood volume time constant ($\tau_v$). (Bottom) An empirical model of the hemodynamic response that captures the effects of the baseline blood flow level was used to compare the results of the vascular model. The input stimulus is transformed by the hemodynamic response function (HRF) to produce the BOLD response. The parameters of hemodynamic response function (HRF) were determined from the normocapnia or hyperoxia fMRI analyses.

First-order process with time constant $\tau_a$ (Eq. (3)). Note that arterial blood flow response to stimulation is described by a first-order linear system with two time constants ($\tau_a$ and $\tau_v$) and that this response is always positive. The venous out-flow ($F_{out}$) responded via changes in the venous volume ($V_v$) with time constant $\tau_v$, as proposed in the balloon model (Eqs. (4) and (5); Buxton et al., 1998). The second term in Eq. (5) determined the changes in blood volume given changes in blood flow via Grubb’s relationship (Grubb et al., 1974). As in the balloon model, the venous mean transit time (MTTv) describes the average filling time of the venous compartment while the venous volume time constant ($\tau_v$) describes further changes in venous volume with changes in blood flow (Buxton et al., 1998).

\[
\frac{dF_{in}}{dt} = \frac{1}{\tau_a} \left( (k_a U(t) + 1) - F_{in}(t) \right)
\]

(3)

\[
\frac{dV_v(t)}{dt} = \frac{1}{MTTv} \left[ F_{in}(t) - \left( V_v^{1/0.4} + \tau_v \frac{dV_v}{dt} \right) \right]
\]

(4)

\[
F_{out}(V_v) = V_v^{1/0.4} + \tau_v \frac{dV_v}{dt}
\]

(5)

Finally, the BOLD response was estimated to be proportional to the amount of venous deoxy-hemoglobin ($q$) calculated using an expression for the oxygen extraction fraction ($E$; see Eqs. (6)–(8); refer to Buxton et al., 1998; Buxton et al., 2004 for further details). The expressions for the arterial blood in-flow ($F_{in}$), venous out-flow ($F_{out}$), venous blood volume ($V_v$) and deoxygenated hemoglobin amount ($q$) in Eqs. (3)–(7) have been normalized to their respective baseline value.

\[
\frac{dq}{dt} = \frac{1}{MTTv} \left( F_{in} \frac{E}{E_0} - q \frac{F_{out}}{V_v} \right)
\]

(6)

\[
E = 1 - (1 - E_0)^{\frac{1}{\tau_v}}
\]

(7)

\[
BOLD = k_v \left[ 116.78 T_v E_0 (1 - q) + 2 \left( 1 - \frac{q}{V_v} \right) + (2E_0 - 0.2) (1 - V_v) \right]
\]

(8)

Data analyses

The time series of the data from Experiment 1 were correlated with a reference waveform to identify the ROIs in each subject tested. The reference waveform was generated by convolving the experimental paradigm with a Poisson function. The ROI consisted of the voxels that satisfied a threshold of $p < 0.01$. In Experiment 2, the ROI was obtained by correlating the FAIR and BOLD blocked experiment with stimulus and rest conditions that lasted 60 s each with a rectangular waveform for the stimulus conditions. Only contiguous areas ($n_v > 1$) over a threshold of half the maximum correlation coefficient were selected for each map, but only those voxels common to both maps were considered for further analysis in each subject studied. This procedure was tested on pilot data to insure that the ROIs were large enough so as not to bias the data from a subgroup of subjects. Average BOLD and
Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Range constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Stimulus temporal pattern</td>
<td>Function of time(^a)</td>
<td></td>
</tr>
<tr>
<td>(w)</td>
<td>Stimulus duration</td>
<td>4, 60, 12 or 6 s</td>
<td></td>
</tr>
<tr>
<td>(w_{ex})</td>
<td>Neuronal sustained response duration</td>
<td>0–2 s</td>
<td></td>
</tr>
<tr>
<td>(t_{0})</td>
<td>Stimulus onset</td>
<td>0–5 s</td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td>Neuronal adaptation effect amplitude</td>
<td>Unconstrained</td>
<td></td>
</tr>
<tr>
<td>(k_{bpf})</td>
<td>Neuronal adaptation effect time constant</td>
<td>1/1.5 s(^{-1})</td>
<td></td>
</tr>
<tr>
<td>(U)</td>
<td>Intermediary process response time constant</td>
<td>Function of time(^a)</td>
<td></td>
</tr>
<tr>
<td>(\tau_{in})</td>
<td>Intermediary process time constant</td>
<td>2 s</td>
<td></td>
</tr>
<tr>
<td>(F_{m})</td>
<td>Arterial blood flow response</td>
<td>Function of time(^a)</td>
<td></td>
</tr>
<tr>
<td>(k_{a})</td>
<td>Arterial blood flow amplitude change</td>
<td>Unconstrained</td>
<td></td>
</tr>
<tr>
<td>(\tau_{a})</td>
<td>Arterial blood flow time constant</td>
<td>Unconstrained</td>
<td></td>
</tr>
<tr>
<td>(V_{v})</td>
<td>Venous blood volume response</td>
<td>Function of time(^a)</td>
<td></td>
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<tr>
<td>(F_{out})</td>
<td>Venous out-flow response</td>
<td>Function of time(^a)</td>
<td></td>
</tr>
<tr>
<td>(\text{MTT}_v)</td>
<td>Venous transit time</td>
<td>Unconstrained</td>
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<tr>
<td>(\tau_v)</td>
<td>Venous volume time constant</td>
<td>0–5 s</td>
<td></td>
</tr>
<tr>
<td>(E)</td>
<td>Oxygen extraction response and fraction</td>
<td>Function of time(^a)</td>
<td></td>
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<tr>
<td>(E_0)</td>
<td>Baseline extraction fraction</td>
<td>0.2–0.8</td>
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</tr>
<tr>
<td>(q)</td>
<td>Venous deoxyhemoglobin amount</td>
<td>Function of time(^a)</td>
<td></td>
</tr>
<tr>
<td>(k_{v})</td>
<td>BOLD gain factor (related to the venous blood volume fraction)</td>
<td>Unconstrained</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) These model expressions have been included to provide a complete picture of the model variables. These variables represent expressions for the various responses and are not free parameters of the model.

BOLD time series for the various conditions tested were generated for further analyses.

The BOLD data from Experiment 1 and BOLD and FAIR data from Experiment 2 were fit to the vascular hemodynamic model. The parameters of the vascular hemodynamic model \((t_{0}, w_{ex}, N, k_{a}, \tau_{a}, \tau_{v}, \text{MTT}_v, E_0\) and \(k_v\); see Table 1) were fit to the normocapnia data of Experiments 1 and hyperoxia data of Experiment 2 to obtain a set of baseline model parameters for each experiment using a uniform non-linear least-squares algorithm. The vascular effects produced on the hypcapnia and hypercapnia hemodynamic responses were assessed by fitting only the arterial blood flow time constant \((\tau_{a})\) and the venous blood volume time constant \((\tau_{v})\) parameters to these data while appropriately adjusting the venous transit time \((\text{MTT}_v)\), baseline oxygen extraction fraction \((E_0)\) and BOLD gain \((k_v)\) parameters to the altered blood flow baseline. In this fashion, the effects of the manipulation in baseline blood flow were assessed through the model parameters that directly influence the vascular response. The fractional amplitude change of the arterial blood flow response \((k_v)\) was assumed to remain constant as a function of the baseline blood flow level. Note that the appropriate changes to the venous transit time and baseline extraction fraction with the baseline blood flow level change the hemodynamic response function features (i.e., overshoot and undershoot amplitudes and durations). Since this model produced estimates for the blood flow and BOLD responses, the FAIR and BOLD data when available were fit to the model simultaneously. In this case, the error for the optimization routine was weighted by the maximum of the respective data.

Model comparison (empirical hemodynamic model)

An empirical hemodynamic model that captures the effects of the baseline blood flow level on the hemodynamic response in the context of linear analyses was used to compare the results of the vascular model. This model is referred to in this manuscript as the empirical hemodynamic model or the empirical model (Fig. 1, bottom).

The empirical hemodynamic model was based on that previously developed by our group to describe the non-linear properties of the BOLD effect with respect to the stimulus amplitude and duration (Vazquez and Noll, 1998). In summary, the temporal pattern of the stimulus is the input to a hemodynamic response function characterized by overshoot and undershoot time constants and is broadened by convolution with a rectangular filter (Eqs. (9) and (10)). This empirical model was used to obtain an estimate of the normocapnia or hyperoxia hemodynamic response function (HRF) given the stimulus. The effects of manipulating the blood flow baseline were captured by modifications made to the stimulus amplitude and duration necessary to represent the data (referred to as the apparent stimulus or \(S_{app}\) in Eq. (10)), while the HRF remained fixed (Fig. 1, bottom).

\[
\text{HRF} = A_{hrf} \text{rect} \left( \frac{t}{w_{hrf}} \right) \left( k_1 e^{-t/\tau_1} + k_2 e^{-t/\tau_2} \right) \quad (9)
\]

\[
\text{BOLD} = S_{app} (t - t_0, w_{app}, A_{app}) \text{*HRF} \quad (10)
\]

In this fashion, the BOLD data from Experiment 1 and BOLD and FAIR data from Experiment 2 were also fit to the empirical hemodynamic model. A weighted non-linear least-squares routine implemented in Matlab (Mathworks Inc., Natick MA) was used to estimate the normocapnia (Experiment 1) and hyperoxia (Experiment 2) hemodynamic response function parameters (HRF; \(A_{hrf}, w_{hrf}, k_1, \tau_1, k_2, \tau_2\) for the BOLD and blood flow responses independently. Note that Eq. (10) can also be used to estimate the blood flow response using the hyperoxia FAIR data to estimate the blood flow HRF. The weighting criterion selected doubled the error over the stimulus duration period and the following 12 to 16 s, biasing the estimates to fit the response overshoot more than the undershoot. Preliminary testing showed that the empirical model performed best at fitting only the positive BOLD response. For this reason the empirical model was biased to fit the positive response. The optimization routine was then used to estimate the hypercapnia and hypcapnia effects in terms of the
apparent stimulus amplitude \((A_{app})\) and duration \((w_{app})\) while maintaining the HRF parameters constant (see Fig. 1, bottom). The apparent stimulus temporal pattern was represented by a rectangular function. In this fashion, linear model analysis can consider, at least in part, the possible blood flow baseline effects via modifications to the apparent stimulus temporal pattern.

The effectiveness of the vascular and empirical hemodynamic models in accounting for the BOLD and FAIR changes with the hypocapnia and hypercapnia manipulations was assessed by the sum of the residual squared error (SSE). The improvement in the ratio between the SSE of the model fit to the hypercapnia or hypocapnia data and the SSE of the hypercapnia or hypocapnia data with respect to baseline (the total error) was reported (Eq. (11)). In this fashion, the error introduced by the CBF manipulation (denominator in Eq. (11)) can be compared to that explained by the model (numerator of Eq. (11)).

\[
\text{error explained} = 100\% \left[1 - \frac{\text{SSE}_{\text{hyper or hypo fit}}}{\text{SSE}_{\text{hyper or hypo data}}}\right]
\]  

(11)

Results

Experiment 1: Visual BOLD fMRI Data at 7 T

Short periods of visual stimulation (4 s) produced average increases in the peak BOLD fMRI signal of 4.3%, 4.6% and 3.0% under normocapnia, hypocapnia and hypercapnia conditions, respectively (Fig. 2, dashed lines). The hypocapnia BOLD response was observed to be 6.8% larger with respect to the normocapnia condition response while the hypercapnia BOLD response was observed to be 30.7% smaller. The BOLD overshoot during stimulus onset and post-stimulus undershoot are evident in the data and, more importantly, these temporal features were observed to depend on the blood flow baseline level. A higher blood flow baseline (hypercapnia condition) produced a slower BOLD response, while decreases in the blood flow baseline (hypocapnia condition) produced a faster response. Although measurements of the baseline blood flow for these conditions were not performed, the average end-tidal CO2 tension was measured to be 36 mm Hg, 46 mm Hg and 27 mm Hg during normocapnia, hypercapnia and hypocapnia conditions, respectively. This suggests that the hypercapnia manipulation increased the baseline blood flow by 27.8% and the hypocapnia manipulation decreased blood flow by 25.0% assuming normal physiology (Kety and Schmidt, 1948).

The vascular hemodynamic model was fit to the normocapnia BOLD data in order to obtain a set of normocapnia parameter estimates. The predictions of these parameters are presented in Table 2 and the resulting fits are presented in Fig. 2 (left panels, solid lines). The baseline extraction fraction was estimated to be 0.716, the mean venous transit time to be 1.0 s, and the BOLD gain factor to be 1.8%. These parameters were then appropriately adjusted to the change in blood flow baseline produced by hypocapnia and hypercapnia, assumed to be \(-25.0\%\) and \(+27.8\%\), respectively. The arterial flow time constant \((s_a)\) and venous volume time constant \((s_v)\) parameters were then fit to the hypocapnia and hypercapnia BOLD data while appropriately adjusting the baseline oxygen extraction fraction \((E_0)\), venous transit time \((\text{MTTv})\) and BOLD gain factor \((k_v)\) parameters to the altered blood flow level. (B) All of the empirical hemodynamic model parameters were fit to the normocapnia data in order to estimate the hemodynamic response function (HRF) given the stimulus. The model was then fit to the hypercapnia and hypocapnia data with the HRF fixed and the input stimulus represented by apparent amplitude \((A_{app})\), duration \((w_{app})\) and onset time \((t_0)\) parameters. This way the blood flow baseline effects were captured by changes in the apparent stimulus duration and amplitude. Qualitatively, the vascular hemodynamic model captured the hypercapnia changes with little residual error. However, it did not represent the hypocapnia changes very well due to the lack of an accentuated post-stimulus overshoot, which the model predicted. The empirical model accounted for much of the error introduced by the blood flow baseline manipulation, however, discrepancies in the estimation of the post-stimulation undershoot are evident, especially in the hypercapnia condition. Note that the empirical model fits are biased to fit the overshoot portion of the response better than the post-stimulus undershoot, while the vascular model fits were not biased. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
volume time constant ($\tau_v$) parameters were fit to the hypocapnia and hypercapnia BOLD data, such that the vascular effects produced by the change in blood flow baseline were characterized by these vascular parameters (see Table 2 and Fig. 2). In summary, the arterial flow time constant decreased by 78.2% while the venous volume time constant increased by 15.7% due to hypocapnia, and the arterial flow time constant increased by 294.9% while the venous volume time constant decreased by 24.8% due to hypercapnia. This model accounted for 90.3% and 98.9% of the total error produced by the hypocapnia and hypercapnia manipulations, respectively. Note that the vascular hemodynamic model did not perform very well in predicting the hypocapnia BOLD response because of the lack of an accentuated post-stimulus undershoot which the model predicts. (Fit results of the vascular hemodynamic model weighted to the positive portion of the BOLD response are included in the supplementary material of this article in the journal website.)

The empirical hemodynamic model was then fit to the normocapnia BOLD data (Fig. 2, right panels, solid lines). The hemodynamic response function parameters from the normocapnia BOLD response (HRF) were fixed and the input stimulus was parametrized by apparent amplitude ($A_{app}$) and width ($w_{app}$) parameters. These parameters were fit to the hypercapnia and hypocapnia BOLD data. The hypocapnia fits required the apparent stimulus width to be 1.7 s shorter (from 4.0 s or −42.9%) and 60.4% higher in amplitude, and the hypercapnia fits required the apparent stimulus width to be 4.0 s longer (+100.0%) and 56.5% lower in amplitude with respect to normocapnia (Fig. 2, left panels). The residual errors of the hypercapnia and hypocapnia model predictions were still significant indicating that a simple modification of the stimulus input is not sufficient to completely capture the blood flow baseline effects. However, this approach did account for a very large portion of the total error, 95.1% and 90.7% for the hypocapnia and hypercapnia manipulations, respectively.

An additional analysis was performed using the empirical model to study the benefits of using this model to correct for CBF baseline changes in the responses. The amplitude of the following two HRFs were fit to the normocapnia data (akin to a general linear model analysis): (1) the normocapnia HRF amplitude convolved with the stimulus, and (2) the amplitude of the normocapnia HRF convolved with an apparent stimulus width 42.9% shorter and 100.0% longer than the true stimulus duration (as above) for the hypocapnia and hypercapnia cases, respectively. Manipulating the apparent stimulus duration improved the MSE by 62.9% and 72.8%, reported as the ratio in MSE between the latter and the former fits, for the hypocapnia and hypercapnia BOLD response predictions, respectively. The predicted amplitude was overestimated by 70.1% and underestimated by 28.1% (reported as the ratio of the latter and the former amplitude estimates) for the hypocapnia and hypercapnia BOLD responses, respectively.
amplitude to be 12.7% and 24.1% lower, respectively (Fig. 5, right panels). This model accounted for 97.9% and 87.4% of the total squared error due to the hypercapnia manipulation in the 12 s and 6 s FAIR responses. Although these quantities were computed for the FAIR responses to 6 s of motor stimulation, the data are too noisy to draw any conclusions for this case.

As before, an additional analysis was performed using the empirical model to study the benefits of using this model to correct for CBF baseline changes in the responses. The amplitude of the following two HRFs were fit to the hypercapnia data (akin to a general linear model analysis): (1) the hyperoxia HRF amplitude convolved with the stimulus (12 s and 6 s), and (2) the amplitude of the hyperoxia HRF convolved with an apparent stimulus width +17.0% longer than the true stimulus duration (this is the average of the increase in width reported above). Increasing the apparent stimulus duration improved the MSE by 95.4% and 19.1%, reported as the ratio of the latter and the former fits, for the 12 s and 6 s hypercapnia BOLD response predictions, respectively. The predicted amplitude was underestimated by 8.4% and 5.9% (reported as the ratio of the latter and the former amplitude estimates) for the 12 s and 6 s hypercapnia BOLD responses, respectively. Similarly, increasing the apparent stimulus duration improved the MSE by 86.3% and 5.7% for the 12 s and 6 s hypercapnia FAIR response predictions, respectively. The amplitudes were also underestimated by 8.4% and 5.8% for the 12 s and 6 s hypercapnia FAIR response predictions, respectively.

The apparent widths and amplitude correction factors calculated above for Experiments 1 and 2 were collected and plotted in Fig. 6. A quadratic polynomial was fit to the data in Fig. 6 (right-side panels) to obtain apparent width and amplitude correction factors for each subject given the baseline change in CBF for each subject. The second-order polynomial for the apparent width and amplitude correction factor were determined to be $4.39x^2 +2.54x +0.94$ and $7.45x^2 +2.87x +0.93$, respectively. Then, the analysis performed above was repeated on the 12 s motor stimulation BOLD responses on a subject-by-subject basis. The ratio of the MSE of the latter fit over the former fit on the hypercapnia BOLD data was on

![Fig. 3. FAIR and BOLD responses to 12 s (top-left panels) and 6 s (top-right panels) of motor stimulation under hyperoxia (100% O2, blue lines) and hyperoxic–hypercapnia (5% CO2, 95% O2, green lines) conditions measured at 3 T. The FAIR and BOLD measurements were performed simultaneously using a dual-echo gradient-echo FAIR acquisition (TEs of 8 and 28 ms, TR of 2000 ms and TI 1900 ms). The onset of hypercapnia increased the blood flow baseline by 10%. Increasing the baseline blood flow using the hypercapnia manipulation produced BOLD and FAIR responses that were slower and lower in amplitude in comparison to their respective hyperoxia responses, in agreement with the results presented in Fig. 2. (Bottom panels) Average FAIR and BOLD fMRI time series during 60 s of motor stimulation under hyperoxia conditions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](image-url)
average 67.8% ± 23.9% (s.d.), indicating a significant improvement due to the modified HRF. After correction, the ratio of the amplitudes improved from \(-12.1\% ±19.5\% (s.d.)\) to 5.1% ±25.4% (s.d.), indicating that, in this case, the bias in the amplitude term was reduced though a small overestimation of the amplitude remained.

Discussion

The results presented show that changes to the blood flow baseline produce significant changes in the evoked BOLD and blood flow responses. Increases in the baseline blood flow level produce stimulation-evoked blood flow and BOLD responses that are slower and lower in amplitude, and decreases in the baseline blood flow level produce faster and higher amplitude hemodynamic responses. A vascular hemodynamic model was used to characterize the effect of the blood flow baseline level on the hemodynamic response. The vascular hemodynamic model linked the blood flow response to the input stimulus via an assumed neuronal tissue response and separated the arterial blood flow and venous blood volume responses. In combination with FAIR and BOLD data, the model determined that this baseline blood flow dependence is dominated by changes in the arterial flow time constant, and to a smaller extent by changes in the venous volume time constant. Specifically, it predicted an increase in the arterial blood flow time constant of 294% for a 27% increase in the baseline blood flow, and a 78% decrease in the arterial flow time constant for a 25% decrease in the baseline blood flow. Also, the model predicted changes in the venous volume time constant.

Table 3

Selected vascular hemodynamic model parameter estimates for the FAIR and BOLD fMRI data fits in experiment 2

<table>
<thead>
<tr>
<th></th>
<th>t0</th>
<th>wex</th>
<th>N</th>
<th>k0</th>
<th>(\tau_a)</th>
<th>(\tau_v)</th>
<th>MTTv</th>
<th>E0</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 s visual stimulation</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>1.99 (1.43)</td>
<td>0.13 (0.23)</td>
<td>0.0 (0.0)</td>
<td>0.645 (0.750)</td>
<td>2.97 (5.65)</td>
<td>6.12 (12.29)</td>
<td>2.06 (1.29)</td>
<td>0.681 (0.710)</td>
</tr>
<tr>
<td>Hyperoxic–hypercapnia</td>
<td>1.51 (1.22)</td>
<td>0.52 (0.51)</td>
<td>0.0 (0.0)</td>
<td>0.621 (0.690)</td>
<td>4.10 (6.65)</td>
<td>4.05 (10.52)</td>
<td>1.94 (1.22)</td>
<td>0.646 (0.676)</td>
</tr>
</tbody>
</table>

| 12 s visual stimulation |         |         |        |        |            |            |        |        |
| Hyperoxia      | 1.51 (1.22) | 0.52 (0.51) | 0.0 (0.0) | 0.621 (0.690) | 2.31 (4.07) | 3.92 (8.68) | 2.06 (1.29) | 0.681 (0.710) |
| Hyperoxic–hypercapnia | 1.51 (1.22) | 0.52 (0.51) | 0.0 (0.0) | 0.621 (0.690) | 4.10 (6.65) | 4.05 (10.52) | 1.94 (1.22) | 0.646 (0.676) |

| 6 s visual stimulation |         |         |        |        |            |            |        |        |
| Hyperoxia      | 1.84 (1.71) | 1.91 (1.70) | 0.0 (0.0) | 0.500 (0.500) | 0.89 (2.20) | 3.17 (8.28) | 2.06 (1.29) | 0.681 (0.710) |
| Hyperoxic–hypercapnia | 1.84 (1.71) | 1.91 (1.70) | 0.0 (0.0) | 0.500 (0.500) | 1.19 (2.68) | 1.95 (6.54) | 1.94 (1.22) | 0.646 (0.676) |

Items in parenthesis represent the parameter estimates if only the BOLD data is considered.
constant of −24% and +15% for a +27% and −25% change in the baseline blood flow, respectively. The vascular model performance was compared to that of a non-physiological, empirical model of the hemodynamic response. Both vascular and empirical hemodynamic models captured most of the baseline blood flow level effects on the hemodynamic response, accounting for over 90% of the error in most cases. The residual discrepancies in the fits between the vascular and empirical model were mostly due to mismatches in fitting both the overshoot and post-stimulation undershoot features of the BOLD response. The magnitude of this discrepancy reflects the remaining inaccuracies of the vascular model at capturing the BOLD fMRI response. While both models can be used to correct for these effects in fMRI data, the empirical hemodynamic model did not incorporate any physiological information. Nonetheless, the ability of the empirical model to effectively capture the baseline blood flow effects by modifications to the apparent stimulus provides a simple alternative to correct for these effects in standard data analysis (e.g., within SPM). The empirical hemodynamic model determined that the apparent stimulus amplitude and duration changed by as much as −56% and +100%, respectively, with a 27% increase in baseline blood flow, and by +60% and −42%, respectively, with a 25% decrease in baseline blood flow. A sample analysis performed on the individual data from each subject showed a reduction in the bias of the amplitude estimate from 12% to 5% for the case investigated (12 s motor stimulation data from Experiment 2) using the empirical model results in Fig. 6 to correct for the change in CBF baseline. More pronounced reductions in the bias of the BOLD response amplitude due to changes in the CBF baseline (as large as 70%) were obtained for the average data in Experiment 1.

In terms of the BOLD amplitude, the results showed that decreases in the baseline blood flow level of 25% increase the BOLD amplitude by 7%, and increases in the baseline blood flow level of 10% and 28% decrease the BOLD response amplitude by 7% and 31%, respectively. Although the results from Experiments 1 and 2 may be dependent on factors such as the blood flow baseline manipulation, stimulus duration or the vasculature of different cortical areas, the results of these experiments were consistent. More importantly, while this effect of the blood flow baseline on the hemodynamic response amplitude might not hamper the detectability of hemodynamic changes, it can have profound effects in the estimation of hemodynamic response parameters.

The vascular hemodynamic model was used to characterize the effect of the changes in the baseline blood flow level on the hemodynamic response through the vascular parameters of the model (τ_a and τ_v). The hypocapnia and hypercapnia manipulations in Experiments 1 and 2 were assumed to only affect blood flow globally across the brain (Kety and Schmidt, 1948). The data from Experiment 2 showed that the effect of these manipulations on the hemodynamic response is mostly arterial since it is present in both FAIR and BOLD responses. As presented in Fig. 6 (top-left), the arterial time constant (τ_a) increases monotonically with the baseline blood flow level,
where increasing the blood flow baseline increased the arterial time constant by as much as 294% and decreasing the blood flow baseline decreased the arterial time constant by as much as 78%. This dependence of the arterial time constant on the baseline blood flow level suggests the arterial vasculature possess a flow dependent relaxation property. In fact, arterial smooth muscle has been shown to possess visco-elastic creeping properties (Fung, 1993). This parameter \( \tau_a \) regulates the rate of the changes in the demand of blood flow by the tissue. In the model, changes to this parameter can be interpreted as a loading of the arterial vasculature that produces different arterial dilation characteristics (represented by the changes in blood flow \( F_{\text{a}} \)) depending on the arterial vascular properties (described by the value of \( \tau_a \)) and the baseline blood flow level. This rationale assumes that the same stimulus produces the same loading demand on the arteries. The venous volume time constant \( \tau_v \) was predicted to decrease with increases in the baseline blood flow (Fig. 6, bottom-left). Increasing the blood flow baseline decreased the venous volume time constant by 17 to 24%, and decreasing the blood flow baseline increased the venous volume time constant by 15%. This effect is evident on the fast and slow return to baseline of the respective BOLD responses (Figs. 2 and 4). The venous volume time constant can be related to the resistance-compliance product considering flow down a pressure gradient in the veins. Therefore, these changes in the venous volume time constant may indicate a pressure-dependent compliance considering that the effective venous compliance varied as a function of the baseline blood flow level. The source of these changes may also include the changes in intracranial pressure that accompany the hypercapnia manipulation. The change in the overshoot and undershoot time constants were partially accounted for in this model by the adjustments made to the mean venous transit time and mean extraction fraction as a function of the baseline blood flow level. However, these parameters did not account completely for the effects observed. While the vascular model predicted a longer post-stimulus undershoot duration, it also predicted a more negative undershoot, contrary to the hypocapnia BOLD data in Fig. 2. This discrepancy may be due to other vascular or physiological effects that were not incorporated in the model, such as intracranial pressure effects or a sustained oxygen consumption response after stimulation offset.

The vascular hemodynamic model implemented assumed that the amplitude of the change in arterial blood flow \( k_a \) did not

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**Fig. 6.** The behavior of the arterial blood flow time constant \( \tau_a \) (top-left panel) and the venous volume time constant \( \tau_v \) (bottom-left panel) parameters of the vascular model as a function of the change in the baseline blood flow level are presented. The changes in the apparent stimulus amplitude (top-right panel) and duration (bottom-right panel) parameters of the empirical model as a function of the changes in the baseline blood flow level are also presented. These results were obtained by combining data from Experiments 1 and 2, which consisted of 4 s of visual stimulation and blood flow baseline changes of −25% and +27% relative to normocapnia (Experiment 1; solid line), and 6 s and 12 s of motor stimulation and a blood flow baseline change of +10% relative to hyperoxia (Experiment 2; dashed line). A polynomial was fit to the apparent stimulus amplitude (black-dots, bottom-right) and the inverse of the apparent stimulus amplitude (amplitude correction; black-dots, top-right), and used to correct for the CBF baseline levels effects.
depend on the baseline blood flow level. That is, a given stimulus was assumed to always produce a blood flow response that is proportional to the baseline blood flow level. To this extent, the peak amplitude of the blood flow response predicted by the vascular hemodynamic model depended on the neuronal response duration and the arterial blood flow time constant. The model fits presented in Fig. 4 suggest this assumption may not hold, indicating an additional non-linearity of the blood flow and BOLD responses with respect to the baseline blood flow level.

The vascular hemodynamic model made predictions of the blood flow response, which is affected only by the arterial change, and the BOLD response, which is affected by both arterial and venous time constants. The venous volume time constant determined the venous blood volume response and therefore it influences the duration of the BOLD undershoot according to the model. Although it is possible to distinguish the arterial and venous behavior from BOLD data, incorporating blood flow data was used to make more robust predictions of these parameters. In addition, it is worth noting that the baseline oxygen extraction fraction and venous mean transit time estimated were larger than commonly accepted (see Tables 2 and 3). This is in part due to the hyperoxic control condition in Experiment 2, where the baseline CBF level is likely to be somewhat lower than that of normoxia. In addition, the model used for oxygen delivery (Eq. (7)) may overestimate the baseline oxygen extraction fraction if the change in oxygen consumption produced by activation is larger than a few percent (e.g., 5%) (Buxton and Frank, 1997).

Although the blood flow baseline can be decreased to reduce the arterial blood flow time constant, the fastest blood flow response possible is still constrained to the mechanism behind the neurovascular coupling. The vascular hemodynamic model coupled these via a first-order system where the time constant (τ_a) was fixed to 2 s (Eq. (2), Fig. 7). Many individual processes may be involved in this intermediary process, such as the diffusivity of vasoactive chemicals around regional arterioles controlling blood flow. The principal role of vasoactive chemicals in the regulation of regional cerebral blood flow has been established (Edvinsson, 1993). Hence, the time constant selection for the intermediary process was made based on this primary mechanism controlling blood flow. Considering the diffusion coefficient of vasoactive substances like nitric oxide or carbon dioxide (~1 × 10⁻⁵ cm²/s) over a distance that exceeds the mean inter-capillary distance (30 µm) suggests the diffusion time is around 0.2 s (Orrison, 1989). On the other hand, extending this distance to that of half a mean capillary length (300 µm) suggests the diffusion time is around 27 s. Considering the complex cortical vascular architecture and these diffusion times, the intermediary process time constant (τ_a) was fixed to 2 s. However, it is worth noting that this simple representation may not properly capture the behavior of this coupling or even potential non-linearities in this coupling. For example, the non-linearity of the BOLD response with respect to stimulus duration in the vascular model proposed may require a stimulus-dependent intermediary process time constant. This is evident in Table 3, since the arterial flow time constant, a parameter that should be independent of the stimulus, varied with stimulus duration. Moreover, the absolute value of the intermediary process time constant (τ_a) also affects the absolute value of the arterial flow time constant (τ_a). That is, there is an upper bound to τ_a considering the range of values the arterial blood flow time constant can adopt, especially as the CBF baseline level decreases (see Table 2). Preliminary simulations have indicated that a value of 2 s for τ_a is near the upper bound of its range of possible values.

The vascular hemodynamic model was compared to the empirical hemodynamic model in Eqs. (9) and (10). This model, and its variants, is widely used in fMRI data analyses for detection and estimation of the fMRI responses. In addition to comparing the results, the empirical hemodynamic model was also used to highlight the physiological content of the vascular hemodynamic model.

The empirical hemodynamic model showed that manipulating the apparent stimulus amplitude and duration accounts for much of the error introduced to the BOLD and FAIR responses by the changes in the baseline blood flow. A monotonically increasing trend is observed for the apparent change in stimulus duration, while a monotonically decreasing trend is observed for the apparent stimulus amplitude as a function of the baseline blood flow level (Fig. 6, right panels). The results also showed that for general linear model analyses, the effect of the baseline blood flow level can be captured (to the extent shown in Figs. 2 and 5) by appropriately adjusting the apparent stimulus amplitude and duration prior to convolution with a hemodynamic response function (HRF) as indicated in Fig. 6. Similar approaches have been reported to account for other non-linear BOLD response behavior (Wager et al., 2005). However, the empirical model also showed that a simple modification to the stimulus is not sufficient to completely describe the changes in the BOLD response, in particular, to the overshoot and undershoot characteristics of the responses (Fig. 2). It is expected that the time constants of the vascular changes depend on the blood flow baseline since there is a blood flow level for which blood flow cannot change further, equivalent to an infinite time constant. Thus, for a better description of the data,
the time constants of the HRF also need to be adjusted as a function of the blood flow baseline. This change in the HRF time constants is predicted, at least in part, by the vascular hemodynamic model. The empirical hemodynamic model fit to the FAIR data in Experiment 2, although noisier, appears to show the same behavior in terms of the apparent stimulus amplitude and duration with respect to the baseline blood flow level.

Other models have been used to investigate the effects of the CBF baseline on the BOLD response dynamics (Vazquez et al., 2003; Behzadi and Liu, 2005a; Behzadi and Liu, 2005b). Behzadi et al., proposed a biomechanical model to link the stimulus with the vascular response in terms of the arterial compliance. They suggested changes in the arterial compliance rate parameter of about +10% and −17% (or inversely by −8% and +20%) for changes in the CBF baseline of −20% and +30%, respectively. They also reported changes to the venous time constant (deflation) of −7% and −27% to changes in the CBF baseline of −20% and +30%, respectively. While the model presented by Behzadi focuses on the compliance properties of arterial muscle, the vascular model presented in this paper generalizes the compliance properties to a time constant; however, both models use similar venous volume and BOLD signal representations. In general, the differences and similarities of these models are reflected in the results obtained in this work where the changes to the venous volume time constant are similar to their results, while the changes to the arterial time constant are significantly different in magnitude (but with the same direction). There are at least a few possibilities for these differences. First, different operating points for these parameters affect their magnitude change. The value of the intermediary process time constant used in this work is different than their equivalent parameter (k_n, a free parameter of their fit); however, decreasing r_n in the vascular model to match their equivalent value for k_c was not sufficient to approach their results. Similarly, their changes in arterial compliance depend on the operating point selected for the arterial radius and thickness. Another possibility may be differences in the routine used to estimate the baseline parameters (for example, E_0 and MTT,) and the temporal window used to estimate the parameters. Qualitatively, nonetheless, both model results appeared to fit the stimulation positive response better than the post-stimulation undershoot indicating that both models do not seem to capture the post-stimulation undershoot well with decreases in the CBF baseline level in comparison to similar increases in the CBF baseline level.

The data from Experiment 2 are consistent with previous BOLD non-linearity findings with respect to stimulus duration. The predicted BOLD responses of longer duration stimuli from those of shorter stimuli estimate responses that are higher in amplitude and narrower in duration. The source of this non-linearity has thought to be neuronal. To this extent, the vascular hemodynamic model was implemented with neuronal adaptation and sustained responses that can potentially capture non-linear effects with respect to the stimulus duration. The effect of the neuronal adaptation parameter (N) on the predictions in Experiment 2 was not significant, indicating that this non-linearity was not captured by the model. On the other hand, the temporal smoothing property of the intermediary process (U) filtered much of the potentially fast neuronal response changes including the neuronal adaptation response (Fig. 7). Therefore, it is possible that this effect may be present in the data but with an amplitude that prevented the model from capturing it. Also, it may also be that shorter stimulus durations are necessary to highlight this property of the BOLD response by model since the non-linear properties of the BOLD response are more evident for short stimuli (less than 4 s) (Vazquez and Noll, 1998). The vascular model predictions obtained for Experiments 1 and 2 suggest that a post-stimulation neuronal sustained response that prolongs the neuronal and hemodynamic responses captures this non-linearity more effectively. The FAIR data exhibited similar non-linearities to those reported in the literature; however, the dominant non-linear feature was the amplitude of the blood flow response. It is possible that the noise in the FAIR data accentuated the amplitude non-linearities over the temporal non-linearities.

There are numerous situations where the effects presented in this work affect routine functional MRI experiments. These situations include respiratory fluctuations (e.g., breath holds that last tens of seconds), caffeine intake, vascular reactivity effects of drugs and anesthetics, age effects, hypertension and others (Kastrup et al., 2001; Liu et al., 2002; Mulderink et al., 2002; D’Esposito et al., 2003; Pouratian et al., 2003; Riecker et al., 2003; Sicard et al., 2003; Cohen et al., 2004; Devonshire, 2004; Liu et al., 2004; Dickerson et al., 2004; Sicard and Duong, 2005). It is very important to consider how these different situations affect the BOLD response in different brain areas within and between subject populations. These results advocate for careful screening of the subjects participating in a BOLD fMRI experiment and either calibrating the BOLD response via a vascular reactivity test or at least obtaining periodic measurements of the baseline blood flow level. Models such as the ones used in this work, in combination with measurements of vascular reactivity and/or blood flow levels, serve to diminish possible vascular response artifacts and strengthen inferences based on hemodynamic data. For example, the decrease in arterial distensibility linked to aging and hypertension can be related in the vascular hemodynamic model to a larger arterial blood flow time constant. Vascular models such as the one used in this paper not only serve to expand our knowledge of the vascular response, but also to narrow the gap between the hemodynamic response and the neuronal response, making the BOLD response more quantitative.

Conclusions

The results presented show that changes in the blood flow baseline are associated with significant changes in the blood flow and BOLD responses. Increases in the baseline blood flow level lead to blood flow and BOLD responses that are slower and lower in amplitude while decreases in the baseline blood flow level lead to faster and higher amplitude hemodynamic responses. This dependence of the hemodynamic response on the blood flow baseline level needs to be accounted for, especially in studies that draw inferences on neuronal function based on the hemodynamic response amplitude, as is frequently done in studies comparing different groups or populations. The models used characterized this dependence of the blood flow and BOLD responses on the baseline blood flow level and provide guidance on how to account for this dependence. The vascular hemodynamic model in combination with FAIR and BOLD data determined that the baseline blood flow
dependence of the hemodynamic effect is dominated by changes in the arterial flow time constant, and to a smaller extent by changes in the venous volume time constant. The arterial flow time constant changed by +294% and −78% while the venous volume time constant changed by −24% and +15% with changes in the baseline blood flow level of +27% and −25%, respectively.

Acknowledgments

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Appendix A. Supplementary data


References


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