The Role of Vascular Resistance in BOLD Responses to Progressive Hypercapnia

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Abstract: The ability of the cerebral vasculature to regulate vascular diameter, hence resistance and cerebral blood flow (CBF), in response to metabolic demands (neurovascular coupling), and perfusion pressure changes (autoregulation) may be assessed by measuring the CBF response to carbon dioxide (CO₂). In healthy individuals, the CBF response to a ramp CO₂ stimulus from hypocapnia to hypercapnia is assumed sigmoidal or linear. However, other response patterns commonly occur, especially in individuals with cerebrovascular disease, and these remain unexplained. CBF responses to CO₂ in a vascular region are determined by the combined effects of the innate vascular responses to CO₂ and the local perfusion pressure; the latter ensuing from pressure-flow interactions within the cerebral vascular network. We modeled this situation as two vascular beds perfused in parallel from a fixed resistance source. Our premise is that all vascular beds have a sigmoidal reduction of resistance in response to a progressive rise in CO₂. Surrogate CBF data to test the model was provided by magnetic resonance imaging of blood oxygen level-dependent (BOLD) signals. The model successfully generated all the various BOLD-CO₂ response patterns, providing a physiological explanation of CBF distribution as relative differences in the network of vascular bed resistance responses to CO₂. *Hum Brain Mapp* 38:5590–5602, 2017. © 2017 Wiley Periodicals, Inc.

Key words: cerebral blood flow; carbon dioxide; model; cerebral vascular resistance

Additional Supporting Information may be found in the online version of this article.

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INTRODUCTION

Cerebral blood flow (CBF) is regulated to maintain an appropriate blood supply to the diverse regions of the brain. This regulation relies on control of vascular diameter to alter vascular resistance, and parenchymal arterioles, the last smooth muscle-containing vessels upstream of the capillary bed [Hirsch et al., 2012], account for about 30% of the total resistance [Faraci and Heistad, 1990]. Their role is divided between pressure autoregulation, whereby an

appropriate capillary perfusion pressure is maintained under both normal and pathologic alterations in systemic blood pressure [Hill et al., 2006; Lucas et al., 2010; Osol et al., 2002; Tan and Taylor, 2014], and neurovascular coupling, whereby local increases in metabolic demand are satisfied by functional hyperemia [Attwell et al., 2011; Iadecola, 2004; Wells et al., 2015]. Because vascular resistance also changes in response to vasoactive substances like carbon dioxide (CO_2), the CBF changes in response to the end-tidal partial pressures of CO_2 (PETCO_2) can be used to assess a region's ability to regulate its blood flow [Sobczyk et al., 2015, 2016].

In healthy subjects, the CBF response to PETCO_2 in major arteries like the middle cerebral artery is sigmoidal [Battisti-Charbonney et al., 2011], providing that arterial blood pressure remains constant [Regan et al., 2014]. More detailed regional responses can be seen in studies using magnetic resonance imaging (MRI) where the blood oxygen level-dependent (BOLD) signal provides a surrogate measure of CBF. In healthy subjects, changes in the BOLD signal are mostly uniform throughout the gray matter (GM) and white matter (WM), again increasing sigmoidally as a function of PETCO_2 [Bhagal et al., 2014, 2015; Sobczyk et al., 2014]. However, in some regions, BOLD responses deviate from a sigmoidal or linear relation to PETCO_2 , especially in patients with cerebrovascular disease, but also in some healthy subjects [Fisher et al., 2017]. These BOLD- CO_2 response patterns are of particular interest in patients because they may be related to the pathophysiology of vascular disease [Sobczyk et al., 2014]. We therefore sought a physiological explanation for these various BOLD- CO_2 response patterns in terms of changes in vascular resistance with PETCO_2 .

CBF responses to PETCO_2 in a vascular region are determined by the combined effects of the innate vascular resistance response to CO_2 and the local perfusion pressure. The innate vascular resistance response to CO_2 is necessarily of sigmoidal shape, due to the limits of vasodilation and vasoconstriction, with resistance highest in hypocapnia and lowest in hypercapnia. Local perfusion pressure is determined by pressure-flow interactions within the cerebral vascular network as overall CBF changes in response to CO_2 . When vessels dilate and CBF increases, the perfusion pressure distal to the major supply arteries decreases, lowering the local perfusion pressure. This aspect is particularly prominent in the cerebral vasculature because of the high resistance of the cerebral arterial supply system—the highest of all body organ vascular supply systems [Faraci and Heistad, 1990]. The net result is that, in brain regions with a robust vasodilatory capacity, increases in blood flow may be accompanied by reductions in regional perfusion pressure. Blood flow may then fall in vascular beds with less robust vasodilatory capacity. The latter situation has been labeled the cerebrovascular steal phenomenon [Conklin et al., 2010; Sobczyk et al., 2014].

To describe the combined effects of the innate vascular resistance responses to CO_2 and the network local

Figure 1.

A simple 2-vascular-bed model of a cerebral vascular region. **(A)** A theoretical illustration of two brain vascular territories both supplied in parallel by a major supply artery with resistance. Their vasodilatory responses are shown as shading. **(B)** A simple resistance circuit model. Reference and examined vascular beds with resistances $R1$ and $R2$ are perfused via an arterial flow resistance (R_{art}) from mean arterial blood pressure (MAP). The pressure perfusing the two branches (P_{branch}) and their respective resistances establishes flows through each branch ($F1$ and $F2$), that sum to F_{total} . Given $F1$ and $F2$ as BOLD measures for the reference and examined voxels, $R1$ and $R2$ can be calculated by considering the model as an analog of an electrical circuit.

perfusion pressure changes, we used a simple model of two vascular beds with independent resistance profiles, perfused from the same supply vessel. The resistance model (Fig. 1A) was kept as simple as possible, following the form described by [Sobczyk et al., 2014]. As shown in Figure 2, we suggest that this model, expanded in a fractal pattern of vessels and vessel beds perfused in parallel by a feeding vessel, exists at all scales from individual capillaries up to inter-hemispheric vascular beds [Lorthois and Casot, 2010]. To test this model, we used the measured BOLD responses to a ramp change in PETCO_2 from hypocapnia to hypercapnia as the flow changes in the model vascular beds, and calculated the changes of resistance with PETCO_2 . We thought that if the model correctly describes how blood flow is distributed in the brain, then, for all patterns of the BOLD- CO_2 responses to progressive PETCO_2 , the calculated changes in resistance with PETCO_2 should be characterized by sigmoid functions. In turn, these sigmoidal resistance- CO_2

Figure 2.

An illustration of the concept that this model, expanded in a fractal pattern of vessels and vessel beds perfused in parallel by a feeding vessel, exists at all scales from individual capillaries up to inter-hemispheric vascular beds.

functions, when applied to the model, should correctly generate the various observed BOLD- CO_2 response patterns [Fisher et al., 2017], thus through “changes in vascular resistance,” providing a physiological explanation for them.

METHODS

Resistance Model

Description

The model electrical circuit analog (Fig. 1B) consists of two vascular beds, each with resistance (R_1 and R_2) and flows (F_1 and F_2), perfused by a common major arterial vessel of fixed resistance (R_{art}), so that the local perfusion pressure (P_{branch}) changes with the total flow through the two branches (F_{total}). The model assumes a resting state, where metabolic and neural activation is neglected so that the only determinant of vasoactivity is PETCO_2 . Under conditions where intracranial pressure and venous backpressure are not limiting, the overall cerebral perfusion pressure is determined by the arterial blood pressure (MAP).

F_1 and F_2 are the BOLD responses to CO_2 for a reference voxel, chosen to represent a standard healthy voxel, and any other examined voxel respectively. The standard voxel response acts as a summation of all vascular responses that determine the changes in the local perfusion pressure (P_{branch}) experienced by the examined voxel during a CO_2 challenge. It should therefore be

chosen from a voxel in a region of robust response. While not reproducing the flow that determines the actual local perfusion pressure, which is unknown, the standard voxel response provides a challenge that is the same for all examined voxels. In this way, the resistance response calculated for any examined voxel is relative to that of any other examined voxel so that comparisons can be made between voxels and vascular regions. Thus, despite not measuring absolute vascular resistance, we consider the calculated resistance response patterns to reflect the changes in vascular resistance with PETCO_2 that determine the BOLD response patterns that measure cerebrovascular reactivity (CVR).

Solution

Figure 3 illustrates the processing flow for solving the model. As BOLD is not an absolute measure of flow it was scaled to the model as % changes from 100% at resting PETCO_2 , so that F_1 and $F_2 = 100\%$ and the total flow through R_{art} is 200%. Assuming the pressure loss in R_{art} to be 30% of the total perfusion pressure (MAP) at resting PETCO_2 , [Faraci and Heistad, 1990], then, with MAP as 100 mmHg, $R_{art} = \text{pressure loss divided by total flow} = 30/200 = 0.15$ (mm Hg/%). The model is analogous to an electrical circuit with the following equations applied at each PETCO_2 of the ramp stimulus:

$$F_{total} = F_1 + F_2 \quad (1)$$

$$P_{branch} = MAP - R_{art} * F_{total} \quad (2)$$

$$R_1 = P_{branch}/F_1 \quad (3)$$

$$R_2 = P_{branch}/F_2 \quad (4)$$

The resistance model solution was automated using a specially written computer program (LabVIEW, National Instruments, TX), which also used the Levenberg–Marquardt algorithm to fit the calculated variations in R_1 and R_2 with PETCO_2 using the following sigmoid function illustrated in Figure 4:

Figure 3.

A diagram showing the data processing flow.

Figure 4.

The sigmoidal relation between resistance and $P_{ET}CO_2$ showing the parameters that define it.

$$R = a + b / (1 + e^{-(PCO_2 - c)/d}) \quad (5)$$

Where:

R = resistance (pressure/flow, mmHg/%), a function of $P_{ET}CO_2$

a = maximum flow resistance in hypocapnia, R_{max}

b = amplitude = minimum – maximum resistance

c = sigmoid midpoint $P_{ET}CO_2$ where slope (sensitivity) is maximum (mmHg)

d = $P_{ET}CO_2$ range over which resistance is linear (mmHg)

To determine the quality of fit of the resistance sigmoidal fitted to the examined voxel we calculated the r^2 . The fitted resistance sigmoidal responses to $P_{ET}CO_2$ for R1 and R2 were then used to calculate the model flow responses, which should fit the measured BOLD- CO_2 responses, and we recorded the r^2 of the examined voxel BOLD fit.

Experimental Protocol

Subjects

The example data used to illustrate the functioning of the model originated from a 57-year-old male patient in our database with left internal carotid occlusion that had undergone a standardized testing protocol as a result of participation in a Research Ethics Board (REB) approved study at our institution. This subject was chosen as typical of those with voxel BOLD responses to a ramp increase in $P_{ET}CO_2$ displaying the four types of response pattern seen in an earlier study [Fisher et al., 2017]. The study conformed to the standards set by the latest revision of the Declaration of Helsinki, and was approved by the REB of the University Health Network and Health Canada. All subjects in the database were competent and gave written informed consent.

Figure 5.

$P_{ET}CO_2$ (mm Hg, squares) and mean whole brain BOLD ($\Delta\%$ from mean, circles) versus time. The step response is used in another analysis for speed of response, and the ramp response used in this study is shown delineated between the dashed lines.

Data acquisition

For testing, subjects breathe via a face mask, connected to a sequential gas delivery breathing circuit [Somogyi et al., 2005]. The CO_2 stimulus sequence consists of clamping $P_{ET}CO_2$ at the subject's resting baseline for 1 min, a step increase by 10 mm Hg for 2 min followed by 2 min at baseline. $P_{ET}CO_2$ is then slowly reduced by 10 mm Hg over 30 sec, followed by a steady rise in $P_{ET}CO_2$ to 15 mm Hg above baseline over 4.3 min, and a return to baseline for 2 min. This stimulus pattern, shown in Figure 5, was programmed into a computer-controlled gas blender (RespirAct™, Thornhill Research, 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].

The BOLD acquisitions with echo planar imaging gradient echo (TR/TE = 2,400/30 ms, 3.5 mm voxels, field of view 24×24 cm, 39 slices, slice thickness 3.5 mm, matrix size 64×64 , number of frames = 405, flip angle = 70°) were obtained using a 3.0-Tesla Signa HDx scanner with an 8-channel phased-array receiver coil (GE Healthcare, Milwaukee, Wisconsin). The acquired MRI and $P_{ET}CO_2$ data were analyzed using AFNI software [Cox, 1996]. BOLD images were then 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, matrix size 256×256 , field of view 22×22 cm, slice thickness = 1 mm, and flip angle = 15°) that was acquired during the same scan session [Saad et al., 2009]. $P_{ET}CO_2$ data were re-sampled at TR, and time-shifted to the point of coincidence with the mean brain BOLD signal where $P_{ET}CO_2$ abruptly decreased at the end of the ramp.

Data analysis

CVR was calculated from the slope of a linear least-squares fit of the BOLD signal data series to the PetCO_2 data series over the range of PetCO_2 represented by the ramp portion of the CO_2 sequence on a voxel-by-voxel basis. The slope of the relation between the BOLD signal and PetCO_2 was color-coded [see Appendix in Poubanc et al., 2015] to a spectrum of colors corresponding to the direction (positive or negative) and the magnitude of the slope to form CVR maps.

As previously described [Fisher et al., 2017], there are four shapes of BOLD- CO_2 response patterns resulting from ramp changes in PetCO_2 from hypocapnia to hypercapnia; rising, falling, U-shaped, and inverted U-shaped. These pattern shapes are classified according to the signs of the linear slopes of the BOLD versus PetCO_2 relations in the hypocapnic and hypercapnic ranges and color coded to form type maps [Fisher et al., 2017] as follows:

- Rising, Type A (+/+); BOLD increases in both hypocapnic and hypercapnic ranges of PetCO_2 .
- Inverted U-shaped, Type B (+/-); BOLD increases in hypocapnia but decreases in hypercapnia.
- Falling, Type C (-/-); BOLD decreases in both hypocapnic and hypercapnic ranges of PetCO_2 .
- U-shaped, Type D (-/+); BOLD decreases in hypocapnia but increases in hypercapnia.

The model was used to calculate resistance- CO_2 responses for all voxels, using their BOLD- CO_2 responses as the examined branch flow F2 and the reference voxel BOLD- CO_2 response, chosen as previously described, as the reference branch flow F1. These calculated resistance- CO_2 responses for the reference voxel R1 and the examined voxel R2 were fitted with sigmoid functions to obtain their sigmoid parameters. In turn, the fitted resistance sigmoids for the examined voxel R1 and reference voxel R2 were then used to derive the reference and examined voxel BOLD- CO_2 responses. Illustrations of these procedures are shown in Figures 6–9 of the results.

Statistical analyses

The signal/noise ratios (SNR) of the BOLD responses to PetCO_2 for each response type were calculated as the ratio of the CVR to the mean square error of the linear fit, with the assumption that CVR was representative of the magnitude of the BOLD response to CO_2 , and the mean square error of the linear fit was representative of the response noise. The quality of the model fitting for the sigmoidal resistance responses to PetCO_2 for examined voxels and the derived fitting of the measured BOLD responses to PetCO_2 for examined voxels were assessed as the r^2 of the fits. Comparison of these r^2 values between linear CVR and model fits of the examined voxel BOLD responses to PetCO_2 were assessed by signed

rank tests for each of the four types of response (SigmaPlot 12.5) as the measures were not normally distributed.

RESULTS

Examples of Model Fitting

Figures 6 to 9 illustrate the use of the model to calculate the sigmoidal resistance- CO_2 responses for voxels with type A +/+, B +/-, C -/-, and D -/+ patterns of BOLD- CO_2 response. The graphs show the reference voxel in black and the examined voxel in purple. The BOLD- CO_2 data were acquired from a 57-year-old patient with left internal carotid occlusion. Two more patient examples showing similar figures are included in Supporting Information.

Model Assessment

These individual voxel examples illustrate the sigmoidal nature of the resistance- CO_2 response patterns calculated from the observed BOLD- CO_2 response patterns, no matter which of the four response types is examined. To assess the appropriateness of the sigmoidal fitting of the resistance- CO_2 responses, we calculated the r^2 values for all voxels in this example patient for each pattern type, and Table I displays the median values for each type. Using the fitted sigmoidal resistance- CO_2 responses, the BOLD- CO_2 response pattern types can be generated for all voxels, and we calculated these r^2 values to compare with the r^2 values of the linear fit CVR. Table I lists the median values of these r^2 fits as well as the median SNR values. Signed rank tests showed that the r^2 values for the model prediction of the BOLD- CO_2 responses are an improvement over the r^2 values for CVR, except for Type C (-/-).

Overall View

To gain an overall view of the resistance- CO_2 response sigmoid patterns for each of the four types of BOLD- CO_2 response pattern types, we used the commonly observed values of the resistance- CO_2 response sigmoid parameters to generate the resistance- CO_2 response sigmoids, and these are shown in Figure 10. As these resistance response patterns show, type A +/+ responses are the most robust and type C -/- the least, with the amplitudes of B +/- and D -/+ types intermediate. The midpoints of all four types tend to the resting PetCO_2 of this patient (40 mm Hg), with D -/+ types often slightly above resting PetCO_2 and B +/- types often slightly below resting PetCO_2 as in Figures 7 and 9. The range of PetCO_2 over which the sigmoid is linear is similar for all types, about 5 mm Hg.

DISCUSSION

In this study, we move our investigation of the regional brain vascular regulation cause-and-effect cascade upstream;

Figure 6.

The reference voxel compared to a type A (+/+) voxel, CVR = 0.508. **(A)** The CVR map for an axial slice shows the position of the reference voxel (white cursors) and the type A +/+ voxel (purple cursors). **(B)** Similarly, the type map shows the positions of the chosen voxels. **(C)** The model flow responses to PETCO₂ for the type A +/+ voxel (purple open circles, blue type line fits) and the reference voxel (black open circles). The curves for the type A +/+ (purple line) and

reference (black line) voxels were calculated from the model resistance sigmoidal responses. **(D)** The model resistance-CO₂ responses calculated from the model flow responses for the type A +/+ voxel (purple open circles) and the reference voxel (black open circles). Sigmoid curves (lines) were fitted to the resistance-CO₂ responses for each voxel. **(E)** The model branch pressure change with PETCO₂.

instead of simply observing flow responses to CO₂, which are responses to remote, as well as local effects, we calculate the pattern of the underlying local changes in vascular resistance. For our examination of the hypothesized vascular network, where flow interactions between vascular beds result in perfusion pressure changes, we deliberately used the simplest model of a vascular region. It consists of a resistor circuit analogue of two vascular beds perfused in parallel via a fixed resistance; a conceptual model previously described by [Sobczyk et al., 2014]. We suggest that this model can be scaled fractally throughout the brain as illustrated in Figure 2. With this model, we related the differing patterns of BOLD-CO₂ responses observed in different regions, to their underlying physiologic determining factor: relative changes in vascular resistance.

Model Assumptions

A major premise of the model was that the resistance-CO₂ response is sigmoidal. With the effect of CO₂ on cerebral vessel smooth muscle to alter vessel diameter, and anatomical limits for changes in vascular diameter with CO₂, a sigmoidal relationship results for resistance. Consequently, if local perfusion pressure remains constant, then a sigmoidal resistance-CO₂ response produces a sigmoidal flow response to CO₂. Indeed, in healthy subjects the flow response to CO₂ for an artery such as the middle cerebral that perfuses a region containing both GM, with highly reactive vessels, as well as WM with less reactive vessels, is sigmoidal [Battisti-Charbonney et al., 2011]. Moreover, both GM and WM responses of healthy subjects may be

Figure 7.

The reference voxel compared to a type B (+/-) voxel, CVR = 0.241. Explanation as for Figure 6.

fitted with sigmoids, similar to the whole brain response [Bhogal et al., 2014]. These observations support a linkage between sigmoidal resistance- CO_2 responses and resulting sigmoidal flow responses, as in health, the various vascular beds perfused in parallel have balanced changes in resistance resulting in organized and coordinated changes in brain blood flow in response to a global vasoactive stimulus. However, in pathophysiology that balance is disturbed, and manifests as unbalanced distributions of brain blood flow with asymmetric BOLD responses to hypercapnia [Han et al., 2008; Silvestrini et al., 2000; Poubanc et al., 2013].

A second major assumption was that the reference voxel BOLD- CO_2 response acts as a summation of all vascular responses that determine the changes in the local perfusion pressure experienced by the examined voxel during a CO_2 challenge. The justification for this assumption lies in the known vascular physiology of blood flow distribution in the complex network of vessels, where regions of high CVR affect regions of low reactivity, so that blood flow distribution is determined by their relative CVR [Sobczyk et al., 2014]; the extreme case being the cerebrovascular

steal phenomenon [Conklin et al., 2010]. By choosing a reference voxel flow that interacts with the examined voxel flow to determine the model local perfusion pressure changes with CO_2 , the model provides a challenge to the examined voxel that represents the vascular network perfusion pressure changes with CO_2 . While this challenge is not the actual change in perfusion pressure experienced by a voxel, it nevertheless serves to expose the resistance pattern of response. By using a standard reference that is the same for all examined voxels, the resistance responses can be compared between voxels.

The model assumes a constancy of neural activation, cerebral tissue metabolic state and cerebral perfusion pressure during a ramp CO_2 challenge. Although subjects are instructed to minimize movement during BOLD- CO_2 response measurements, nevertheless neural activation may occur with changing cognitive and sensory activity, but the degree to which model results would be affected is unknown and assumed to be low. Regardless whether hypercapnia is an isometabolic stimulus or not [Yablonskiy, 2011], the vigorous flow responses to the large hypercapnic stimulus of over 10 mm Hg change in PETCO₂ will

Figure 8.

The reference voxel compared to a type C (–/–) voxel, $CVR = -0.069$. Explanation as for Figure 6.

strongly dominate the BOLD response. Perfusion pressure, conversely, may pose a problem in some subjects as blood pressure may be increased in response to CO_2 . If so, it is a confounder of the model that cannot be overcome [Regan et al., 2014]. For this reason, it is advisable to monitor blood pressure during testing. Our experience with subjects, supine in MRI tests, is that most maintain MAP within a small, probably physiological range, and the present analysis would be largely unaffected.

The model assumes aggregated parameter resistances for the vascular beds and a fixed supply artery resistance, whereas both are of course in reality spatially distributed. The fixed supply artery resistance can be criticized because although CO_2 may be thought to primarily affect the arterioles and precapillary sphincters [Atkinson et al., 1990; Busija and Heistad, 1984; Edvinsson and Krause, 2002], all cerebral vessel smooth muscles are relaxed by CO_2 [Willie et al., 2014], with small vessels the most sensitive [Wei et al., 1980], so that in reality the supply artery resistance would decrease somewhat with hypercapnia. Nevertheless, we suggest that none of these model enhancements

have a significant effect on the conclusions drawn from its application.

Finally, we offer an alternative interpretation of our modeling; we suggest that the model may be viewed as a BOLD- CO_2 response-fitting exercise. The model is simply a way of providing a standardized method based on the physiological assumptions of perfusion pressure changes due to vascular network interactions and a sigmoidal change in resistance with CO_2 .

Model Performance

Sigmoidal patterns of resistance- CO_2 responses are to be expected, not only based on the principle of physical limitations of vasoconstriction and vasodilation but also on the observation of sigmoidal BOLD- CO_2 responses in healthy tissues [Bhagal et al., 2014, 2015; Sobczyk et al., 2014]. Indeed, for all of the four BOLD- CO_2 response patterns we previously catalogued [Fisher et al., 2017], we found that the model calculated resistance responses to CO_2 that were well fitted by sigmoids, an observation supported by

Figure 9.

The reference voxel compared to a type D $(-/+)$ voxel, $CVR = -0.021$. Explanation as for Figure 6.

the high r^2 found for the sigmoidal fits, especially in light of the low SNR of some of the data. That this standardized fitting procedure consistently generates sigmoidal resistance curves for the variety of BOLD- CO_2 response patterns observed, suggests that the sigmoid parameters

provide physiological meaning, that is, characterize the relative changes in local vascular resistance with CO_2 . Further support for the model was evident from higher r^2 values for the model predicted BOLD- CO_2 responses compared to the r^2 of the CVR, in all but type C $-/-$ responses.

TABLE I. Median values of r^2 fits for the resistance sigmoids, BOLD- CO_2 responses derived from the resistance sigmoids, and the CVR fit to the BOLD- CO_2 responses, and SNR

Type	Resistance sigmoid	Model BOLD- CO_2 response	CVR	SNR
A $(+/+)$	0.782	0.641	0.619	0.17
B $(+/-)$	0.455	0.165	0.067	0.03
C $(-/-)$	0.236	0.061	0.062	0.05
D $(-/+)$	0.563	0.239	0.172	0.06

Signed rank tests for each type detected significant differences ($P < 0.001$) between CVR fit r^2 and model BOLD- CO_2 fit r^2 with higher values bolded.

Physiological Interpretation

In the following paragraphs, we examine the calculated resistance- CO_2 responses to address the physiological and pathophysiologic implications associated with the four types of BOLD- CO_2 response patterns. We consider the examined voxel resistance sigmoid parameters to characterize the relative ability of the various tissues to control blood flow, and offer the following interpretations.

The resistance sigmoid amplitude value describes the overall ability of the voxel to decrease resistance as $PETCO_2$ increases from hypocapnia to hypercapnia, and as expected, is greatest for type A $+/+$ vessels where both the examined and standard reference voxels have strong (high amplitude) reductions in resistance. As a result, the

Figure 10.

Resistance- CO_2 response sigmoids for the four types of BOLD- CO_2 response pattern based on the values of the sigmoid parameters calculated for all voxels in the example patient. The midpoints are shown as dots and the dashed line shows the resting PETCO_2 .

BOLD- CO_2 response is sigmoidal, that is, healthy physiology. By contrast, Type C $-/-$ vessel resistance amplitudes are small, reflecting the near loss of ability to vasodilate in response to CO_2 , so that these vessels are almost completely passive in behavior and become susceptible to steal. Although both Type B $+/-$ and D $-/+$ vessels are capable of responding to CO_2 with similar amplitudes, their amplitudes are intermediate between those of types A $+/+$ and C $-/-$, and it is their sigmoid midpoints that characterize them.

The resistance sigmoid midpoints of type A $+/+$ voxels tend to resting PETCO_2 , where the maximum sensitivity to CO_2 occurs, thereby providing the optimum regulation of flow with respect to PETCO_2 . For the type C $-/-$ BOLD- CO_2 response pattern pictured in Figure 8, the resistance sigmoid midpoint is similar to that of the reference type A $+/+$ voxel. We suggest that this similarity is a consequence of the degree to which type C $-/-$ voxel vessels act as passive conduits. In that case, type C $-/-$ voxel flows will then reflect the flow changes of type A $+/+$ voxels so that the BOLD- CO_2 response patterns are mirror images; the reference type A $+/+$ voxel steals flow from the type C $-/-$ voxel [Sobczyk et al., 2014].

For the type D $-/+$ voxel flow response pattern pictured in Figure 9, the resistance sigmoid has a midpoint PETCO_2 higher than that of the reference type A $+/+$ voxel. As a result, the hypocapnic half of the flow response has a negative slope as the reference type A $+/+$ voxel vessels respond, but the D $-/+$ type voxel vessels do not, so that steal occurs as PETCO_2 increases from hypocapnia to resting. However, in hypercapnia the type D $-/+$ voxel vessels do respond and vasodilate, while the reference type A $+/+$ voxel vessels are reaching their maximum vasodilation and no longer steal. With respect

to the elevated midpoint of D $-/+$ type voxel vessels, we note that the speed of response [Blockley et al., 2011; Duffin et al., 2015; Poublanc et al., 2015] could have an effect on the midpoint if the ramp increase in PETCO_2 was too fast. The response to a ramp stimulus in a first-order system remains a ramp but is displaced later in time proportional to the system time constant, and since PETCO_2 is proportional to time in a ramp, the response to PETCO_2 would be displaced to a higher value. This effect could explain the midpoint increase observed for type D responses if they were very slow: with the initial increase in CO_2 , a delay in the reduction of resistance results in a redistribution of their blood flow toward vessels with an immediate response. Then, as CO_2 increases further, and vessels with fast responses approach their minimal resistance, the slowly responding vessels now reduce their resistance and increase their flow relative to other vessels. Whether this hypothesis accounts for the increased type D $-/+$ midpoints requires further investigation.

A complementary response pattern describes the type B $+/-$ voxel in Figure 7, where the voxel resistance sigmoid has a midpoint below that of the type A $+/+$ reference voxel. In the hypocapnic range, the type B $+/-$ voxel vessels vasodilate and are able to increase flow, but in hypercapnia these vessels reach their maximum vasodilation before the reference type A $+/+$ voxel vessels. Further vasodilation by the type A $+/+$ vessels diverts flow from the type B $+/-$ voxel vessels.

Limitations

First, it is acknowledged that this model is elementary compared to more comprehensive models [Lorthois et al., 2011; Ursino and Giannessi, 2010], which could be used for the same purpose. However, our model is simpler to understand and the resulting equations are easily solved by applying standard electrical circuit principles, first to convert the BOLD derived flow data to resistance data and then, after fitting the resistance data with sigmoids, converting the fitted resistance data to fitted flow data, enabling modeling of all voxel response patterns. It should be noted that the model is limited in its application, requiring a slow ramp stimulus pattern where it is assumed that the speed of response does not influence the relations between flow distribution and CO_2 [Blockley et al., 2011; Duffin et al., 2015; Poublanc et al., 2015].

The response pattern examples used to develop the model are based on BOLD measurements, which were assumed to represent the patterns of CBF- CO_2 responses. While there are methods of assessing CBF other than BOLD such as Doppler arterial velocity measures and arterial spin labeling (ASL) MRI, such methods that are available do not have the temporal or spatial resolution necessary to supply data to our model. Nevertheless, we must stress that the use of BOLD as a surrogate measure of CBF for our model also involves a number of important

caveats. First, BOLD deviates from a linear relationship to CBF at very high flows [Hoge et al., 1999] because the concentration of deoxyhemoglobin is diluted with oxyhemoglobin as the oxygen extraction fraction (OEF) falls. Such a nonlinearity could affect the sigmoid fitting at very high PCO_2 . However, using Doppler ultrasound measurements of middle cerebral artery velocity, sigmoidal relationships were maintained at CO_2 tensions in excess of those in our study. In addition, the increases in BOLD we observed were <10%, which is within the linear BOLD–CBF relation according to the Davis [dHb] dilution model [Davis et al., 1998]. Moreover, experimental measurements of brain oxygenation using near infra-red spectroscopy [Alderliesten et al., 2014], and measurements of CVR using both BOLD and ASL MRI data [Tancredi et al., 2015] acquired using a 2-dimensional spin-echo flow-sensitive alternating inversion recovery sequence, have noted that even in patients with steno-occlusive disease, the BOLD MRI signal response to hypercapnia predominantly reflects changes in CBF [Mandell et al., 2008].

The second caveat is that BOLD measures are affected by cerebral blood volume (CBV), which also changes with hypercapnia. As the fractional change in CBV relative to baseline can be approximated by the fractional change in CBF relative to baseline raised to the power of 0.2 [Chen and Pike, 2010; Mark and Pike, 2012], we consider this effect to be minor and to have little effect on the sigmoidal responses we measured. BOLD may also reflect changes in cerebral metabolic rate, and changes in oxygen tension [Bulte et al., 2007; Prisman et al., 2008]. As discussed in [Yablonskiy, 2011] and [Yezhuvath et al., 2009], the assumption that hypercapnia does not change cerebral metabolic rate is debateable and must therefore be regarded as a caveat for these experiments. As for changes in oxygen tension, we maintained normoxic isoxia during these tests. Finally, we note that the ΔBOLD – ΔPCO_2 relationship depends on the baseline PCO_2 [Cohen et al., 2002; Halani et al., 2015; Sobczyk et al., 2014], and so we used the subject's resting PCO_2 as baseline with the ramp from hypocapnia to hypercapnia passing through this PCO_2 .

A further aspect of using BOLD as a surrogate measure of CBF pertains to the fact that the maximum BOLD response in a particular region is set by the amount of deoxyhaemoglobin at rest, which is determined by resting CBF, OEF, and CBV. The only issue is WM voxels, where OEF is similar to GM but CBV is only 1/2 or 1/3, so that the BOLD range is only a fraction of GM BOLD range; that is, WM CBF is a fraction of GM CBF when using BOLD as a proxy for CBF. Therefore, in the model it may be wrong to equate WM and GM CBF at max PCO_2 . However, the mean BOLD at each voxel is set to 100% at resting PCO_2 and the range of CBF over the ramp is such that the range in resistance should correctly describe the response pattern.

In summary, we realize that our translation of BOLD into resistance depends on the assumption that BOLD is a

reasonable surrogate for CBF. As better measures of CBF become available, we suggest that the model we present here may be applied equally to these measurements to produce respectively improved measures of resistance

CONCLUSIONS

This modeling study demonstrated that the pattern of BOLD– CO_2 responses in an individual voxel resulting from a ramp CO_2 challenge can be derived from a simple model of interaction with the BOLD– CO_2 responses of other regions of the brain. It assumes there is a redistribution of flow between vascular beds perfused in parallel from a vessel with a significant resistance, which is brought about via changes in local perfusion pressure with CO_2 . The model adopts the unifying principle that all vascular bed resistance– CO_2 responses are sigmoidal, a characteristic to be expected based on vascular physiology. The model calculations determine the examined voxel resistance– CO_2 response utilizing a standard BOLD– CO_2 response reference, and so provide a relative estimate of a physiological parameter, resistance, that can be compared between regions. We suggest that the resistance– CO_2 responses provide physiological explanations for the various observed BOLD– CO_2 response patterns. Given that differences in amplitudes and midpoints of the resistance– CO_2 response sigmoids occur under pathological conditions, we speculate that maps of these characteristics would prove of clinical importance, and further development of the ideas proposed in this study could prove fruitful.

CONFLICT OF INTEREST

JAF is Chief Scientist and JD is Senior Scientist at Thornhill Research (TRI), a spin-off company from the University Health Network that developed the RespirAct™. RespirAct™ is currently a non-commercial research tool assembled, and made available by TRI to research institutions to enable CVR studies.

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APPENDIX

The model equations are as follows:

$$R1 = R1a - R1b / (1 + \exp(-(PCO_2 - R1c) / R1d)) \quad (A1)$$

$$R2 = R2a - R2b / (1 + \exp(-(PCO_2 - R2c) / R2d)) \quad (A2)$$

$$Re = R1 * R2 / (R1 + R2) \quad (A3)$$

$$R_{total} = R_{art} + Re \quad (A4)$$

$$F_{total} = MAP / R_{total} \quad (A5)$$

$$P_{branch} = MAP - CBF * R_{art} \quad (A6)$$

$$F2 = P_{branch} / R2 \quad (A7)$$

$$F1 = P_{branch} / R1 \quad (A8)$$

Where:

PCO₂ = the partial pressure of carbon dioxide affecting the branch resistances

R1 = the resistance of branch 1

R2 = the resistance of branch 2

Re = the equivalent resistance of the combined branches in parallel

R_{total} = the total resistance for the model tissue

F_{total} = the total flow through the model tissue

P_{branch} = the branch perfusion pressure

F1 = the flow through branch 1

F2 = the flow through branch 2

R1a and R2a are the maximum resistances in hypocapnia

R1b and R2b are the sigmoid amplitudes

R1c and R2c are the sigmoid midpoints

R1d and R2d are the sigmoid linear ranges