A model for the regulation of cerebral oxygen delivery

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Hyder, Fahmeed, Robert G. Shulman, and Douglas L. Rothman. A model for the regulation of cerebral oxygen delivery. J. Appl. Physiol. 85(2): 554–564, 1998.—On the basis of the assumption that oxygen delivery across the endothelium is proportional to capillary plasma PO2, a model is presented that links cerebral metabolic rate of oxygen utilization (CMRO2) to cerebral blood flow (CBF) through an effective diffusivity for oxygen (D) of the capillary bed. On the basis of in vivo evidence that the oxygen diffusivity properties of the capillary bed may be altered by changes in capillary PO2, hematocrit, and/or blood volume, the model allows changes in D with changes in CBF. Choice in the model of the appropriate ratio of \( \Omega = (\Delta D/\Delta \text{CBF})/\text{CBF} \) determines the dependence of tissue oxygen delivery on perfusion. Buxton and Frank (J. Cereb. Blood Flow. Metab. 17: 64–72, 1997) recently presented a limiting case of the present model in which \( \Omega = 0 \). In contrast to the trends predicted by the model of Buxton and Frank, in the current model when \( \Omega > 0 \), the proportionality between changes in CBF and CMRO2 becomes more linear, and similar degrees of proportionality can exist at different basal values of oxygen extraction fraction. The model is able to fit the observed proportionalities between CBF and CMRO2 for a large range of physiological data. Although the model does not validate any particular observed proportionality between CBF and CMRO2, generally values of \( (\Delta \text{CMRO2}/\text{CMRO2})/(\Delta \text{CBF}/\text{CBF}) \) close to unity have been observed across ranges of graded anesthesia in rats and humans and for particular functional activations in humans. The model’s capacity to fit the wide range of data indicates that the oxygen diffusivity properties of the capillary bed, which can be modified in relation to perfusion, play an important role in regulating cerebral oxygen delivery in vivo.

UNDER BASAL CONDITIONS, most of the energy required for cerebral ATP generation is supplied by oxidation of glucose through the tricarboxylic acid cycle (60). Roy and Sherrington (58) suggested that the cerebral metabolic rates of oxygen and glucose use (i.e., CMRO2 and CMRGlc, respectively) are locally adjusted to meet the metabolic needs through local regulation of cerebral blood flow (CBF) and volume (CBV). The mechanisms for these couplings have remained elusive, and even the measured stoichiometries have been somewhat variable, reflecting a variety of experimental methods and conditions. Generally, tight proportionality between fractional changes in CMRO2 and CBF measured regionally has been observed at rest with a ratio of \( \sim 1:1 \) (29, 54). However, recent results from positron emission tomography (PET) have demonstrated that, during brain activation, CBF increases by a greater fraction than does CMRO2 (11, 12). The greater fractional increase in CBF than in CMRO2 has been interpreted as an uncoupling between perfusion and oxidative metabolism within the normal physiological range of activity. An important point is that although there is no requirement for a constant stoichiometry between fractional changes in CBF and CMRO2, there is a prescribed stoichiometric ratio between fractional changes in CMRO2 and CMRGlc, if oxidative glycolysis is to be maintained from rest to higher and/or lower levels of activity (60).

Recently, Buxton and Frank (6) presented a model in which the higher increase in CBF than in CMRO2 during cerebral activation (11, 12) is not uncoupling but rather represents a mechanistic limitation on the ability to increase cerebral oxygen delivery through CBF. There are two main assumptions in their model: 1) they assumed that cerebral tissue oxygen tension is low, for which there is considerable evidence (37–39, 41), such that the capillary-tissue PO2 gradient is determined primarily by the capillary PO2 (26, 33, 34); and 2) they assumed that oxygen delivery is only increased through perfusion. There is no change in the effective diffusivity of oxygen from blood to tissue; thus it was proposed that the capillary bed has no flexibility with respect to changes in CBF. Their model shows that as the capillary PO2 approaches the arterial input value, the relationship between changes in CBF and CMRO2 becomes highly nonlinear, because a large increase in CBF is required to achieve a small increase in the capillary PO2. Their model is able to fit the PET data of Fox and co-workers (11, 12), who reported a ratio of \( \sim 0.2:1 \) for relative changes in CMRO2 and CBF. With the assumptions made, their model predicts that the ability of the brain to increase oxygen consumption is severely limited, and low ratios for relative changes in CMRO2 and CBF should be the norm for all brain activations at the oxygen extraction fraction (OEF) values reported in the literature.

The stated goal of the model of Buxton and Frank (6) was to relate changes in CBF and CMRO2 during functional activation in awake humans and to compare results with PET activation data. A more comprehensive survey of the literature reporting changes in CBF and CMRO2, including measurements from additional PET activation studies and resting graded anesthesia studies, shows proportionalities not allowed by their model. For example, with sensory stimulation in awake humans, ratios of \( \sim 0.5:1 \) have been observed for relative changes in CMRO2 and CBF (59), and during cognitive stimulation, ratios of \( \sim 1:1 \) have been reported (56). In addition, PET studies have shown that, at rest, human cortical gray matter values of CBF, CMRO2, and CMRGlc are regionally coupled (17, 54, 56). Similar high ratios have been reported for local correlations in animals, showing close agreement with CBF, CMRO2,
and CMR_{glc} (5, 35, 64). A further limitation of their model is that it predicts a highly nonlinear relationship between CBF and CMRO_2, which does not agree with the close-to-linear relationships between CBF and CMRO_2 measured across ranges of graded anesthesia in rats (20, 24, 45, 46, 64) and humans (29, 51, 61).

We present an extended model where certain characteristics are derived from a number of recent models (3, 6, 8, 15, 16, 52, 55, 60, 68). Our model relaxes one of the constraints in the model of Buxton and Frank (6) by allowing for changes in effective diffusivity (D) of the capillary bed with changes in CBF. The change in effective diffusivity of the capillary bed may result from altering capillary PO_2, hematocrit, and/or blood volume, as has been reported on the basis of microscopic measurements (9, 10, 21, 31, 32, 36, 42, 43). Consequently, oxygen delivery is allowed to be responsive to perfusion by an increase in the effective diffusivity of the capillary bed. The model of Buxton and Frank (6) is the limiting case of the present model, in which the ratio (ΔD/ΔCBF) is equal to zero. The present model is able to fit the large body of data in which the observed ratios (ΔCMRO_2/ΔCMRO_2)/(ΔCBF/ΔCBF), although generally close to unity, are sometimes significantly smaller. The ability of the current model to fit the wide range of data indicates that the diffusivity properties of the capillary bed, which may be altered by changes in capillary PO_2, hematocrit, and/or blood volume, play an important role in regulating cerebral oxygen delivery in vivo.

However, the model does not validate any particular value of (ΔCMRO_2/ΔCMRO_2)/(ΔCBF/ΔCBF); only more reliable in vivo experiments can do that. Implications of this analysis for the interpretation of functional magnetic resonance imaging (fMRI) are also discussed.

Glossary

- **BOLD**: Blood oxygenation level dependent
- **CBF and CBV**: Cerebral blood flow and volume
- **CMR_O_2 and CMR_{glc}**: Cerebral metabolic rates of oxygen and glucose consumption
- **OEF**: Tissue oxygen extraction fraction
- **Y**: Venous blood oxygenation
- **D**: Effective diffusivity for oxygen in the capillary bed
- **C_a and C_v**: Arterial and venous oxygen concentrations
- **T**: Transit time of capillary bed
- **Ω and Ψ**: Coupling parameter for changes in D and CMR_2, with changes in CBF
- **[Hb(O_2)]_a**: Oxyhemoglobin concentration
- **[Hb]_a**: Deoxyhemoglobin concentration
- **[Hb(total)]_a**: Total hemoglobin concentration
- **S**: BOLD fMRI signal
- **A**: Magnetic field-dependent physiological constant
- **r_{max}**: Magnetic field-dependent deoxyhemoglobin susceptibility frequency shift

**THEORY AND METHODS**

Model. Oxygen in blood exists in two discrete components, hemoglobin and plasma, with the oxygen affinity and concentration significantly higher in the former.

Oxygen extraction by the tissue from an infinitesimally thin element of blood occurs during capillary transit and may be described by the temporal profile of the changing total oxygen content of blood [C_T(t)]. At any time during the transit the rate of loss of oxygen is proportional to the oxygen concentration in the plasma

\[
dC_t/\partial t = -kC_p
\]

The constant k is determined by the spatial gradients of PO_2 across the volume element and is the first-order rate constant of oxygen loss from the capillary (3, 6, 8, 15, 16, 52, 55). If it is assumed that the ratio of transient oxygen content values in plasma and blood is constant, i.e., \( r = C_p/C_T \), during an elapsed time of \( \Delta t \), then it can be shown that

\[
C_T(t + \Delta t) = C_T(t) \exp (-k r \Delta t)
\]

If \( \Delta t \) is the nth equivalent fraction of the capillary transit time \( T_c \), then it can be shown that

\[
C_T(T_c) = C_T(0) \exp \left[ -k (r)_{net} T_c \right]
\]

where \((r)_{net}\) is the net product for the whole transit time \( T_c \) (see APPENDIX A). If k is a constant all through transit, then Eq. 3 becomes

\[
C_T(T_c) = C_T(0) \exp \left[ -k (r)_{net} T_c \right]
\]

As pointed out by Gjedde (15), in this case \( r_{net} \) may be estimated from \( C_T(0), \text{OEF}, \) and the mathematical relationship between hemoglobin fractional oxygenation and \( C_p \). However, in the more general case, as presented here, the term \((r)_{net}\) in Eq. 3 may not be separated. Note that r is determined by the relationship between hemoglobin fractional oxygenation and the average capillary PO_2. Because of the cooperativity of oxygen binding, r will not be a constant but will vary with \( T_c \) in contrast to the model of Buxton and Frank (6). Although the mathematical description of Eq. 3 is similar to the Renkin-Crone relationship (8, 55) and the model of Buxton and Frank (6), there is no localization of the major point of resistance to the capillary endothelium. This localization may be inferred from the use of the permeability-surface area product in the Renkin-Crone relationship and from the assumption of Buxton and Frank that the PO_2 is negligible throughout the brain extracellular and intracellular space. The OEF around the capillary (OEFc) may be calculated (3, 6, 8,
15, 16, 52, 55, 60, 68) from
\[ \text{OEF}_c = \frac{[C_T(0) - C_T(T_c)]/C_T(0)}{\langle kr \rangle_{\text{net}} T_c} \]
(5)
which is equivalent to
\[ \text{OEF}_c = 1 - \exp\left[ -(\langle kr \rangle_{\text{net}} T_c) \right] \]
(6)
Because at steady state perfusion is constant at all points along the capillary, so \( T_c \) may be calculated from the relationship
\[ T_c = \frac{\text{CBV}_c / \text{CBF}_c}{1 - \text{OEF}_c} \]
(7)
where \( D_c \) is the effective diffusivity for oxygen from the capillary to the point of consumption, presumably the mitochondria, and is equal to
\[ D_c = \frac{\langle kr \rangle_{\text{net}} \text{CBV}_c}{1 - \text{OEF}_c} \]
(9)
Thus the net oxygen extraction per capillary can be described by the cumulative effect of an infinitesimally thin element of blood moving down a capillary during transit as it loses oxygen to the tissue and which experiences changing spatial PO2 gradients between transit as it loses oxygen to the tissue and which thin element of blood moving down a capillary during transit. The changing ratio of the traversing volume element and the abluminal side of the capillary endothelium. The changing ratio of total to plasma oxygen contents in the traversing volume element reflects the cooperative binding of oxygen by hemoglobin in whole blood within the capillary. Extension to the macroscopic picture is achieved through averaging across an ensemble of identical capillaries, which yields macroscopic terms: effective diffusivity of the capillary bed (\( D \)), transit time of the capillary bed (\( T_c \)), perfusion in the capillary bed (\( \text{CBF} \)), OEF, and \( \text{CMR}_O_2 \), such that
\[ \text{OEF} = 1 - \exp\left( -D / \text{CBF} \right) \]
(10)
Equation 10 is similar to previous analytic expressions of a microvascular tissue unit, which consists of a mass of tissue irrigated by a collection of identical capillaries that are uniformly separated (3, 6, 8, 15, 16, 52, 55, 60, 68), although the interpretation of the diffusivity constant, \( D \), is somewhat different here. It has been shown previously that, for a distribution of transit times, an expression similar to Eq. 10 is valid, provided the distribution is reasonably symmetrical and peaked about the average value (52, 68). An alternate expression for OEF determined from Fick's equation is given by (60)
\[ \text{OEF} = \frac{\text{CMR}_O_2 / (\text{CBF} \cdot C_a)}{[1 - \exp\left( -D / \text{CBF} \right)]} \]
(11)
Equation 12 shows that oxygen utilization is linked to perfusion via the effective diffusivity of the capillary bed. By rearrangement of Eq. 11, the relationship between fractional changes in \( \text{CMR}_O_2 \), \( \text{CBF} \), and OEF may be expressed as
\[ \frac{\Delta \text{CMR}_O_2 / \text{CMR}_O_2}{\Delta \text{CBF} / \text{CBF}} = (1 + \Delta \text{CBF} / \text{CBF})(1 + \Delta \text{OEF} / \text{OEF}) - 1 \]
(13)
In Eq. 13 and subsequently, the terms without and with \( \Delta \) indicate basal and relative differences, respectively, due to a physiological perturbation. In the present analysis, the effective diffusivity for oxygen permeability within the capillary bed is assumed to be coupled to perfusion according to a parameter \( \Omega \), which we define as
\[ \Omega = (\Delta D / \Delta \text{CBF} / \text{CBF}) \]
(14)
The term \( \Omega \) is a measure of the coupling between the changes in effective diffusivity of the capillary bed for oxygen delivery. If \( \Omega \) is constant over the range of \( \text{CBF} \) changes, then Eq. 14 may be substituted into Eq. 13 to yield
\[ \frac{\Delta \text{CMR}_O_2 / \text{CMR}_O_2}{\Delta \text{CBF} / \text{CBF}} = \alpha [1 - \exp\left(-D / \text{CBF}(\beta / \alpha)\right)] / \text{OEF} - 1 \]
(15)
where \( \alpha = [1 + (\Delta \text{CBF} / \text{CBF})], \beta = [1 + (\Delta \text{CBF} / \text{CBF}) / \Omega], \) and
\[ \frac{\Delta \text{OEF} / \text{OEF}}{\Delta \text{CBF} / \text{CBF}} = (1 - \exp\left(-D / \text{CBF}(\beta / \alpha)\right)) / \text{OEF} - 1 \]
(16)
Provided that \( \Delta \text{CBF} / \text{CBF}, \Omega, \) and the basal value of OEF are known, the values of \( \Delta \text{CMR}_O_2 / \text{CMR}_O_2 \) and \( \Delta \text{OEF} / \text{OEF} \) may be calculated using the above relationships. The model of Buxton and Frank (6) may be shown to be equivalent to the model proposed here at the limiting case of \( \Omega = 0 \) (see APPENDIX B), when
\[ \Omega = (\Delta D / \Delta \text{CBF} / \text{CBF}) \]
(17)
It is also useful to define a parameter that measures the coupling between changes in oxidative metabolism and perfusion, which we define as
\[ \Psi = \frac{\Delta \text{CMR}_O_2 / \text{CMR}_O_2}{\Delta \text{CBF} / \text{CBF}} \]
(18)
Depending on \( \Omega \) and the basal value of OEF, the calculated \( \Psi \) may be close to constant over the physiological range of changes in perfusion or highly nonlinear, as proposed by Buxton and Frank (6), allowing a wide range of data to be fitted. As such the model does not validate any particular reported value of \( \Psi \); only reliable experiments can do that.
Assumptions. The model for the microvascular unit, which consists of a mass of tissue irrigated by a collection of identical capillaries that are uniformly separated, has the following assumptions.
1) Within an elapsed time of \( \Delta t \) during capillary transit, the rate of oxygen loss from an infinitesimally thin element of blood can be described by a first-order rate constant \( k \), during which time the ratio \( r = C_p / C_t \) is constant. The net capillary oxygen extraction can be
described by the cumulative effect of that infinitesimally small volume of blood traversing down the capillary and can be represented by an exponential relationship between capillary extraction and perfusion (Eqs. 6 and 8).

2) Oxygen delivery can be influenced by perfusion and effective diffusivity of the capillary bed (Eq. 12). It has been demonstrated that the physiological capacity for oxygen of the capillary bed can be altered by local capillary PO2, hematocrit, and/or blood volume (9, 10, 21, 31, 32, 36, 42, 43).

3) Oxygen extraction is directly proportional to the capillary PO2 (Eq. 5). This assumed proportionality is supported by the reported low cerebral PO2 values (37–39, 41) and by a recent tracer study which showed that the majority of oxygen molecules that permeate the endothelium are metabolized (26). In this model the low cerebral PO2 is maintained over the range of autoregulation via modulation of CBF and Ω (Eq. 16).

A distribution of Ω values about a mean may arise from an ensemble of capillary transit times, lengths, or volumes, which can be a consequence of topological and/or geometric heterogeneity of the capillary network in the microvascular tissue unit (52). A range of these parameters about a mean value produces equivalent observations for the microvascular tissue unit; provided the distributions are symmetrical about the respective mean values (3, 6, 15, 16, 52).

5) Other assumptions are similar to those defined and stated previously (3, 6, 8, 15, 16, 52, 55, 60, 68). In particular, the brain is assumed to be well perfused (3, 6, 8, 15, 16, 52, 55, 60, 68) by plasma and hemoglobin, but the capillary bed has the capacity to change its local oxygen capacity (9, 10, 21, 31, 32, 36, 42, 43) by altering the number of plasmatic capillaries (1, 13, 18, 31, 50, 63, 65, 67, 69) or intracapillary stacking of erythrocytes (10, 21, 32, 36, 42, 43, 62, 67); oxygen is assumed to be carried in the blood by plasma and hemoglobin, and the exchange between these pools is extremely fast, such that the oxygen saturation curve represents the equilibrium of the exchange process (3, 6, 15, 16); the assumption of topological and geometric homogeneity of the capillary bed (3, 6, 8, 15, 16, 52, 55, 60, 68) reflects symmetrical topology and geometry of metabolism in tissue and is supported by mitochondrial aggregation around capillaries (3, 33, 68); and the assumption of the plasma pool of oxygen being well mixed (3, 6, 15, 16, 52) suggests an enhancement of oxygen transfer by an element of moving blood and indicates a steady-state picture of oxygen extraction as this element transits (3, 6).

Implications of the model for blood oxygenation level-dependent functional magnetic resonance image contrast. The experimental fractional changes in CMRO2 and CBF observed during functional activation reflect an decrease in OEF from its basal value (i.e., ΔOEF/OEF < 0), which is commensurate with an increased venous blood oxygenation (Y) in cerebral capillaries; i.e., ΔOEF/OEF = ΔY/(1 – Y) > 0, where the arterial oxygenation is assumed to be very close to 1 (see APPENDIX C). Recent advancements in fMRI have allowed the detection of changes in cerebral blood oxygenation during functional challenges with the R*2-weighted or gradient-echo image contrast (where R*2 is the apparent transverse relaxation rate of tissue water). This is the most commonly used image contrast in fMRI and has been termed blood oxygenation level dependent (BOLD) (47, 48). The BOLD fMRI image contrast relies on physiologically induced changes in the magnetic properties of blood: oxyhemoglobin is diamagnetic, and deoxyhemoglobin is paramagnetic. An increase in the physiologically induced BOLD fMRI signal (ΔS/S > 0) is consistent with a drop in venous deoxyhemoglobin concentration. Near-infrared spectrophotometry (23, 66) and intrinsic optical reflectance studies (14, 44) have shown that deoxyhemoglobin concentration decreases after stimulation onset in awake or anesthetized mammalian brains, which provides qualitative support for the BOLD fMRI hypothesis (47, 48). The physiologically induced BOLD fMRI signal change (ΔS/S) can be approximated in various ways, and a common approximation is

\[ ΔS/S = A[ΔY/(1 – Y) – (ΔCBV/CBV)λ] \]

where A is a magnetic field-dependent physiological constant and λ is a constant that modulates the blood volume component (4, 6, 22, 25, 28, 30, 47, 48, 70). To relate the change observed in BOLD fMRI studies to changes in CMRO2 and CBF, it is necessary to establish a relationship between these physiological parameters and ΔY/(1 – Y) and ΔCBV/CBV. A restatement of Eq. 13 is

\[ ΔY/(1 – Y) = 1 – γα \]

and a common expression for blood volume changes by Grubb et al. (19) is

\[ ΔCBV/CBV = α^b – 1 \]

where \( γ = (1 + (ΔCBF/CBF)λb) / b \) and \( b = 0.38 \) (from Ref. 19). There is a general agreement in the various expressions for ΔS/S (4, 6, 22, 25, 28, 30, 47, 48, 70), although there is some discrepancy about the constants. Equations 19–21 can be simplified to
ship between BOLD fMRI image contrast and CBF were examined for OEF of 0.2 and 0.4, which cover the range of basal OEF values reported in the literature for normal, adult, awake, nonstimulated human cortex (11, 12, 40, 49, 56, 59). The cases examined here are \( \Omega > 0 \) and \( \Omega = 0 \).

Figure 1 shows the effect of \( \Omega \) on \( \Psi \) for different basal OEF values. For the model of Buxton and Frank (6), where \( \Omega = 0 \), the relationship between \( \Delta \text{CBF}/\text{CBF} \) and \( \Delta \text{CMRO}_2/\text{CMRO}_2 \) is highly nonlinear, particularly at low basal values of OEF (Fig. 1, dashed curves), where large increases in CBF are needed to increase oxygen delivery. In comparison, when \( \Omega > 0 \) (Fig. 1, solid curves), the relationship between \( \Delta \text{CBF}/\text{CBF} \) and \( \Delta \text{CMRO}_2/\text{CMRO}_2 \) becomes progressively more linear because of the changing effective diffusivity of the capillary bed becoming the major factor in oxygen delivery. Most significantly, large values of \( \Psi \) are obtained at either value of OEF, whereas at higher basal OEF values, lower values of \( \Omega \) are sufficient to achieve the same \( \Psi \).

Figure 2 simulates the effects of \( \Omega \) on BOLD fMRI image contrast. Although the simulations show similar trends when \( \Omega > 0 \) and \( \Omega = 0 \), lower \( \Delta S/S \) values are obtained for higher values of \( \Omega \) because of the tighter proportionality between \( \Delta \text{CBF}/\text{CBF} \) and \( \Delta \text{CMRO}_2/\text{CMRO}_2 \). For higher values of \( \Omega \), \( \Delta S/S \) decreases above a threshold value of \( \Delta \text{CBF}/\text{CBF} \) because of the blood volume term becoming dominant (see Eq. 21). Although recent MRI studies (27) seem to suggest that the CBV contribution to the BOLD signal (see Eq. 21) may be overestimated, further testing of the predictions of the model is hampered by the limited data that exist on these relationships in vivo.

At any basal OEF, the BOLD fMRI signal is scaled by \( A \) (see Eq. 19), which is a magnetic field-dependent physiological constant (see Fig. 2 legend for details). Although the value of \( A \) may not necessarily represent in vivo values because of the complex interaction(s) between the blood water susceptibility constant (\( \Delta \chi \)) and \( R^s \) (4, 22, 28, 47, 48, 70), the relative effects of \( \Omega \) on the relationship between \( \Delta S/S \) and \( \Delta \text{CBF}/\text{CBF} \) should be independent of the specific value of \( \Omega \). Because of the complex origin of the BOLD fMRI signal, the most we can conclude from such a comparison is that trends in simulations are in general agreement with observations. Future BOLD fMRI experiments with simultaneous CBF (30), CBV (27), and CMRO2 (25) are necessary to provide better in vivo data to determine the

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Fig. 1. Calculated effects of \( \Omega \) on proportionality between \( \Delta \text{CBF}/\text{CBF} \) and \( \Delta \text{CMRO}_2/\text{CMRO}_2 \) for basal OEF values of 0.2 and 0.4. Highly nonlinear relationship between \( \Delta \text{CBF}/\text{CBF} \) and \( \Delta \text{CMRO}_2/\text{CMRO}_2 \) is observed when \( \Omega = 0 \) (dashed curves), as observed in model of Buxton and Frank (6). A linear relationship between \( \Delta \text{CBF}/\text{CBF} \) and \( \Delta \text{CMRO}_2/\text{CMRO}_2 \) is observed when \( \Omega > 0 \) (solid curves). Values of \( \Omega \) in solid curves are 0.31, 0.28, and 0.23 (\( \circ, \triangle, \text{and} \square \), respectively) in A and 0.23, 0.17, and 0.14 (\( \circ, \triangle, \text{and} \square \), respectively) in B. See Glossary for definition of abbreviations.

Fig. 2. Impact of model on BOLD fMRI image contrast simulated (using Eqs. 19–22) as follows: \( A = C_{v,\text{max}}(1 - Y_{\text{OEF}}) \text{TE} \) (4, 22, 28, 47, 48, 70), where \( (1 - Y_{\text{OEF}}) \) is arteriovenous blood oxygenation difference (i.e., blood deoxygenation) at basal OEF and \( C_{v,\text{max}} \) is equal to basal R^s, which gives rise to basal BOLD signal. \( \Delta S/S \), BOLD fMRI signal changes. Curves are simulated with \( \lambda = 1 \), \( v_{\text{max}} = 267.5B_0 \Delta \chi \) (where \( B_0 = 4 \text{ T and} \Delta \chi = 0.01 \text{ ppm} \)), \( b = 0.03 \text{,} \text{TE} = 0.03 \text{,} \text{C = 72.70, and} (1 - Y_{\text{OEF}}) \text{at} 2 \text{ different basal values of OEF (i.e., 0.2 and 0.4, which correspond to} R^s = 7.00 \times 2.33 \text{ s}^{-1} \text{and} A = 0.14 \pm 0.05 \text{ as in Ref. 30) for} \Omega > 0 \text{ (solid curves)} \text{ and} \Omega = 0 \text{ (dashed curves)} \text{ at basal OEF values of 0.2 (A) and 0.4 (B). For} \Omega > 0 \text{, reduced} \Delta S/S \text{ is due to effect of increasing} \Omega \text{ to tighten proportionality between} \Delta \text{CBF}/\text{CBF} \text{ and} \Delta \text{CMRO}_2/\text{CMRO}_2 \text{; for higher values of} \Omega \text{ there is also a tendency for} \Delta S/S \text{ to decrease above a threshold} \Delta \text{CBF}/\text{CBF} \text{. This decrease in} \Delta S/S \text{ is due to greater blood volume at higher} \Delta \text{CBF}/\text{CBF} \text{ values because of power law dependence on perfusion (see Eq. 21). See Fig. 1 legend for} \Omega \text{ values. See Glossary for definition of abbreviations.} \)
relationship between \( \text{CMR}_{\text{O}} \) and CBF with respect to BOLD fMRI image contrast. All simulations were carried out in MATLAB (Natick, MA), and values are means ± SD.

**RESULTS**

The in vivo rat and human data are fitted to determine values of \( \Psi \). Basal values of \( \Delta \text{CBF}/\text{CBF} \) and \( \Delta \text{CMR}_{\text{O}}/\text{CMR}_{\text{O}} \), at different levels of wakefulness are obtained from the literature for rats (20, 24, 45, 46, 64) and humans (29, 51, 61). In rat and human data sets the awake CBF and CMR\( \text{O}_2 \) values were used to obtain curves of \( \Delta \text{CMR}_{\text{O}}/\text{CMR}_{\text{O}} \) vs. \( \Delta \text{CBF}/\text{CBF} \), and linear regression analysis was used to obtain in vivo values of \( \Psi \) for the rat and human cortices of 0.88 ± 0.06 and 0.96 ± 0.09, respectively (\( R^2 = 0.97 \) and 0.93). Respective \( \Omega \) values are calculated with these \( \Psi \) values, with use of Eq. 23, at basal OEF of 0.2, 0.3, and 0.4.

\[
\Omega = [1 + (\Delta \text{CBF}/\text{CBF})^{-1}][\rho/\rho] - (\Delta \text{CBF}/\text{CBF})^{-1}
\]

where \( \rho = \ln (1 - \text{OEF}/\Psi) \) and \( \rho = \ln (1 - \text{OEF}) \). The result of the linear fits to the data are shown in Table 1. In Fig. 3 the in vivo data are plotted against the curve predicted with \( \Omega > 0 \) (solid curves) and \( \Omega = 0 \) (dashed curves) for three basal OEF values. The fits to the in vivo data are clearly better when \( \Omega > 0 \), showing how the flexibility in the present model allows these well-established results to be explained. In contrast, the approach of Buxton and Frank (6) cannot be extended below the awake level.

Values of \( \Psi \) have been obtained from functional activation data sets of awake humans with different stimulation paradigms (11, 12, 56, 59). In each case, a linear regression analysis is carried out for each data set to obtain an in vivo value of \( \Psi \), and the reported basal OEF value is used when an in vivo value of \( \Omega \) is calculated (using Eq. 23). For each functional data set, as shown in Table 2, the negative value(s) of oxygen utilization reported is not included in the regression analysis, and the best fits are pivoted at the origin. The cases for \( \Omega > 0 \) and \( \Omega = 0 \) are examined. The results of the linear regression analysis for each data set are shown in Table 2. Fits similar to those in Fig. 3 are made to data available for physiologically activated tissue in the awake humans. For each study the data are fit to determine a value of \( \Psi \), which leads to a value of \( \Omega \) calculated using the OEF reported in that study, as shown in Table 2. In Fig. 4, for each study the in vivo human data are plotted against the curve predicted with \( \Omega > 0 \) (solid curves) and \( \Omega = 0 \) (dashed curves) at the corresponding basal OEF value for that study. Although Fig. 4 shows that \( \Psi \) varies with different

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<th>Ref. No.</th>
<th>Anesthesia</th>
<th>( \Delta \text{CBF}, % )</th>
<th>( \Delta \text{CMR}<em>{\text{O}}/\text{CMR}</em>{\text{O}}, % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>Awake</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>45</td>
<td>Phenobarbital (50 mg/kg)</td>
<td>-21.0</td>
<td>-19.0</td>
</tr>
<tr>
<td>20</td>
<td>70% N(_2)O</td>
<td>-22.9</td>
<td>-8.0</td>
</tr>
<tr>
<td>46</td>
<td>70% N(_2)O – 1.2% halothane</td>
<td>-42.9</td>
<td>-32.4</td>
</tr>
<tr>
<td>45</td>
<td>Phenobarbital (150 mg/kg)</td>
<td>-43.0</td>
<td>-41.0</td>
</tr>
<tr>
<td>64, 24</td>
<td>( \alpha )-Chloralose (20 mg/kg)</td>
<td>-53.6</td>
<td>-70.0</td>
</tr>
<tr>
<td>45</td>
<td>Phenobarbital (250 mg/kg)</td>
<td>-57.0</td>
<td>-48.0</td>
</tr>
</tbody>
</table>

In vivo human data points in Fig. 3, D–F

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>Anesthesia</th>
<th>( \Delta \text{CBF}, % )</th>
<th>( \Delta \text{CMR}<em>{\text{O}}/\text{CMR}</em>{\text{O}}, % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>Awake</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>61</td>
<td>70% N(_2)O + thiopental</td>
<td>-16.0</td>
<td>-8.2</td>
</tr>
<tr>
<td>61</td>
<td>70% N(_2)O</td>
<td>-16.6</td>
<td>-27.8</td>
</tr>
<tr>
<td>61</td>
<td>70% N(_2)O + thiopental</td>
<td>-24.0</td>
<td>-27.9</td>
</tr>
<tr>
<td>61</td>
<td>2% Ethrane</td>
<td>-24.1</td>
<td>-39.5</td>
</tr>
<tr>
<td>61</td>
<td>0.85% Ethrane</td>
<td>-27.8</td>
<td>-30.6</td>
</tr>
<tr>
<td>61</td>
<td>13% Cyclopropane</td>
<td>-37.0</td>
<td>-31.3</td>
</tr>
<tr>
<td>51</td>
<td>Thiopental (10–55 mg/kg)</td>
<td>-48.1</td>
<td>-54.4</td>
</tr>
<tr>
<td>61</td>
<td>5% Cyclopropane</td>
<td>-51.9</td>
<td>-49.0</td>
</tr>
</tbody>
</table>

In each case, a linear regression analysis is carried out for each data set to obtain an in vivo value of \( \Psi \) from a curve of \( \Delta \text{CMR}_{\text{O}}/\text{CMR}_{\text{O}} \) vs. \( \Delta \text{CBF}/\text{CBF} \), and basal OEF values of 0.2, 0.3, and 0.4 are used to calculate in vivo values of \( \Omega \) (using Eq. 23), and mean \( \Omega \) value is shown. Raw \( \Delta \text{CBF} \) (%) and raw \( \Delta \text{CMR}_{\text{O}} \) (%) correspond to actual mean ± SD of in vivo data from rat (20, 24, 45, 46, 64) and human (29, 51, 61) cortices, whereas \( \Delta \text{CMR}_{\text{O}} \) (%) with \( \Omega > 0 \) and \( \Omega = 0 \) correspond to mean ± SD of fits with \( \Omega > 0 \) and \( \Omega = 0 \), respectively. In Fig. 3, in vivo data from rat (20, 24, 45, 46, 64) and human (29, 51, 61) cortices are shown with curves predicted with \( \Omega > 0 \) (solid curves) and \( \Omega = 0 \) (dashed curves) at basal OEF values of 0.2, 0.3, and 0.4. In each case, \( \Delta \text{CMR}_{\text{O}} \) (%) value predicted with \( \Omega > 0 \) is at least 3 times as large as value predicted with \( \Omega = 0 \). Results of a t-test (with 2 samples assuming unequal variances, 1 tail) for comparing mean values of calculated CMR\( \text{O}_2 \) (%) and raw CMR\( \text{O}_2 \) (%): * insignificantly different (\( P = 0.446 \)); † significantly different (\( P = 0.034 \)); ‡ insignificantly different (\( P = 0.326 \)); § significantly different (\( P = 0.002 \)). See Glossary for definition of abbreviations.
stimulation paradigms and laboratories, the fits to the in vivo data are clearly better when $\Omega > 0$ (solid curves) than when $\Omega = 0$ (dashed curves). However, in most of these functional studies the scatter in the data is so large that the ability to distinguish $\Omega > 0$ from $\Omega = 0$ is less conclusive than for the data obtained from variable depths of anesthesia (Fig. 3). Table 2 summarizes the results of fits when $\Omega > 0$ and $\Omega = 0$ given the data for physiologically activated tissue in awake humans. For each study, the mean value of $\Delta CMRO_2 / CMRO_2$ predicted with $\Omega > 0$ is in excellent agreement with raw in vivo observations and significantly larger than the values predicted with $\Omega = 0$ (Table 2).

### DISCUSSION

Some, but not all (56, 59), human brain functional data of PET studies have demonstrated that, during brain activation, $\Delta CBF / CBF \gg \Delta CMRO_2 / CMRO_2$ (11, 12). This has been interpreted as an uncoupling between perfusion and oxidative metabolism. Buxton and Frank (6) proposed that the greater fractional increase in CBF than in CMRO$_2$ during activation is a consequence of oxygen delivery to tissue being proportional to the capillary-tissue Po$_2$ gradient. At low basal OEF values, their model predicts a highly nonlinear relationship, with low coupling ratios between changes in

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**Table 2. Linear regression analysis and summary of fits for PET functional activation data of awake humans**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Ref.</th>
<th>$\Delta CBF$ (raw), %</th>
<th>$\Delta CMRO_2$ (raw), %</th>
<th>$\Psi$</th>
<th>OEF</th>
<th>$\Omega$</th>
<th>$R^2$</th>
<th>$\Delta CMRO_2, %$</th>
<th>$\Omega &gt; 0$</th>
<th>$\Omega = 0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>12</td>
<td>51.3 ± 13.8</td>
<td>5.0 ± 9.3</td>
<td>0.20</td>
<td>0.2</td>
<td>0.13</td>
<td>0.80</td>
<td>10.1 ± 2.5</td>
<td>3.7 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>11</td>
<td>29.4 ± 8.5</td>
<td>6.3 ± 6.4</td>
<td>0.28</td>
<td>0.2</td>
<td>0.21</td>
<td>0.75</td>
<td>8.2 ± 2.3</td>
<td>2.5 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>59</td>
<td>20.1 ± 5.7</td>
<td>8.4 ± 4.6</td>
<td>0.44</td>
<td>0.3</td>
<td>0.35</td>
<td>0.86</td>
<td>9.0 ± 2.5</td>
<td>2.8 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td>56</td>
<td>12.5 ± 6.2</td>
<td>12.2 ± 7.9</td>
<td>0.95</td>
<td>0.3</td>
<td>0.94</td>
<td>0.78</td>
<td>12.0 ± 5.9</td>
<td>1.9 ± 0.8</td>
<td></td>
</tr>
</tbody>
</table>

In each case, a linear regression analysis is carried out for each data set to obtain an in vivo value of $\Psi$ from a curve of $\Delta CMRO_2 / CMRO_2$ vs. $\Delta CBF / CBF$, and reported basal OEF value is used to calculate an in vivo value of $\Omega$ (using Eq. 23). For each functional data set, negative value(s) of $\Delta CMRO_2 / CMRO_2$ is excluded from regression analysis, and best fits are pivoted at origin. Raw $\Delta CBF$ (%) and raw $\Delta CMRO_2$ (%) correspond to actual mean ± SD of in vivo human data in each study, whereas $\Delta CMRO_2$ (%) with $\Omega > 0$ and with $\Omega = 0$ correspond to mean ± SD of fits with $\Omega > 0$ and $\Omega = 0$ in each study, respectively. In Fig. 4, human data from visual PET study of Fox et al. (12), sensory PET study of Fox and Raichle (11), sensory PET study of Seitz and Roland (59), and cognitive PET study of Roland et al. (56) are shown with curves predicted with $\Omega > 0$ (solid curves) and $\Omega = 0$ (dashed curves) at corresponding basal OEF value for that study. In each case above, $\Delta CMRO_2$ (%) value predicted with $\Omega > 0$ is at least twice as large as value predicted with $\Omega = 0$. Results of a t-test (with 2 samples assuming unequal variances, 1 tail) for comparing mean values of calculated CMRO$_2$ (%) and raw CMRO$_2$: *insignificantly different ($P = 0.979$); †significantly different ($P = 0.373$); ‡insignificantly different ($P = 0.239$); §significantly different ($P = 0.059$); ¶insignificantly different ($P = 0.430$); ††significantly different ($P = 0.028$); †‡insignificantly different ($P = 0.489$); †§significantly different ($P = 0.001$).
CMRO₂ and CBF because of the limited ability of perfusion to increase the capillary-tissue PO₂ gradient. Gjedde (15) presented a model in which oxygen delivery is limited by the maximum partial pressure difference achievable between the capillary plasma and the oxygen-consuming mitochondria. Although no specific barrier to oxygen diffusion is required in this model for a low initial OEF, the ability of CBF to increase oxygen delivery to the tissue is similarly limited (15). Here we extend this approach by considering the effect of a changing effective diffusivity of the capillary bed for oxygen. For a fixed ratio between changes in effective diffusivity of the capillary bed and perfusion, signified by a physiological parameter Ω (Eq. 14), a close-to-constant proportionality is maintained between changes in CBF and CMRO₂ throughout the physiological activity range (60). This model provides a better fit to the majority of in vivo human data of changes in CBF and CMRO₂ than does the model of Buxton and Frank (6), which is the limiting case when Ω = 0.

The effect of an increased Ω is to increase the ratio Ψ between ΔCMRO₂/CMRO₂ and ΔCBF/CBF (Fig. 1; see RESULTS). A major assumption in the model is that changes in perfusion and effective diffusivity of the capillary bed are tightly regulated and coupled to maintain a low cerebral PO₂, and as a consequence, oxygen delivery is primarily determined by the capillary PO₂. Reports of very low cerebral PO₂ (37–39, 41) suggest that the capillary-tissue PO₂ gradient is proportional to the capillary PO₂. Consistent with this view, a multiple-tracer study has shown that most of the oxygen that enters the tissue is metabolized (26). Alternatively, similar trends would be observed if the cerebral PO₂ were not negligible, provided that it was maintained at a constant and lower value than the capillary PO₂. With a constant cerebral PO₂, changes in oxygen delivery would still be determined primarily by changes in the capillary PO₂ and the coupled effective diffusivity for oxygen of the capillary bed (8, 55).

The microscopic physiological picture of this model is the ability of the capillary bed to increase effective diffusivity for oxygen, caused by the increase in capillary PO₂, hematocrit, and/or blood volume (9, 10, 21, 31, 32, 36, 42, 43) during increased brain activity. Increased CBV in the activated cortex is a well-accepted occurrence (11, 12, 56, 59) and supports the proposal of Roy and Sherrington (58) that changes in CMRO₂ and CMRGlc are regulated by alterations in CBF and CBV. During altered brain function, the swelling of capillary diameter (2, 7, 14, 44, 57, 66, 67), variation in the number of plasmatic capillaries (1, 13, 18, 31, 50, 63, 65, 67, 69), and/or intracapillary stacking of erythrocytes (10, 21, 32, 36, 42, 43, 62, 67) can contribute to the change in capillary PO₂, hematocrit, and/or blood volume. Much evidence has been presented in support of changes in the number of plasmatic capillaries (1, 13, 18, 31, 50, 63, 65, 67, 69) or intracapillary stacking of erythrocytes (10, 21, 32, 36, 42, 43, 62, 67) being critical events that can modulate oxygen delivery and demand. Because some type of capillary readjustment, with respect to capillary PO₂, hematocrit, and/or blood volume, would modify the effective diffusivity for oxygen of the capillary bed, it is not necessary to assume that there is absolutely no capillary readjustment within a microvascular tissue unit, as did Buxton and Frank (6). Although the term capillary readjustment generally reflects increases in the blood volume of the capillary bed, the term presented here suggests a modifying capillary bed with respect to capillary PO₂, hematocrit, and/or blood volume. The generally better fits obtained by the current model to in vivo data than in the case of no increase in effective diffusivity of the capillary bed suggest that one or all mechanisms may be operational in increasing this parameter in vivo.
An implication of the model of Buxton and Frank (6) is that low values of $\Psi$ should be the norm, because CMRO$_2$ is limited by the PO$_2$ gradient. However, examination of a range of PET activation data indicates that, in contrast to the results of Fox and co-workers (11, 12), the data are generally fit better with $\Omega > 0$ (Fig. 4). Furthermore, all the global measurements (Fig. 3) show very strong proportionality of CMRO$_2$ and CBF, which are in agreement with higher $\Psi$ values, such as those found by Roland and co-workers (56, 59) (Tables 1 and 2). A possible explanation for the variation in the activation data in the literature is that stimuli may only be activating a fraction of the tissue within an image voxel. Depending on the measurement methodology, the effect of this partial volume on CMRO$_2$ and CBF may be considerably different. In contrast, in the graded anesthesia studies, such partial-volume effects are reduced, because the perturbations are global. In addition, the human graded anesthesia studies were performed by arteriovenous difference methodology, for which measurements of CMRO$_2$ and CBF are relatively straightforward compared with imaging methodologies (for review, see Ref. 53). However, arteriovenous difference methods represent an average value for the entire brain, so that small regions with values of $\Psi$ that are substantially different from the mean value may have been missed. Because methodological and partial-volume differences may not account for all the variation in the human activation data, it is clearly necessary to design experiments with better sensitivity and spatial resolution to better determine the coupling between CMRO$_2$ and CBF under different states of activation and/or different stimulation paradigms.

Conclusion. Recent models of cerebral oxygen delivery (6, 15) have suggested that, at low values of OEF, oxygen delivery is limited by the inefficiency of perfusion in raising capillary PO$_2$. We have presented a model that weakens this limitation by allowing changes in the capillary effective diffusivity to oxygen with changes in perfusion. The change in capillary effective diffusivity to oxygen with respect to perfusion, i.e., $\Omega$, allows oxygen delivery to be more sensitive to changes in perfusion. An appropriate value of $\Omega$ asserts an $\sim$1:1 ratio between changes in CBF and CMRO$_2$ throughout a wide range of activity. The model of Buxton and Frank (6), in which $\Omega = 0$, is the limiting case of our model. The present model shows that when $\Omega > 0$ the limitation imposed by oxygen delivery on increases in CMRO$_2$ predicted by the model of Buxton and Frank does not hold within the physiological range. In contrast to the model of Buxton and Frank, where the data could only fit data where $\Omega = 0$, our model can fit a wide range of data, so it makes no claims to establishing the relationship between changes in CBF and CMRO$_2$; only good data can do that. The present model is able to fit all available in vivo data and depicts the transition of hemodynamic and metabolic events for a large range of physiological cases. This characteristic of the model signifies that the oxygen diffusivity properties of the capillary bed, which are adjusted with respect to perfusion, play a crucial part in regulating cerebral oxygen delivery in vivo.

APPENDIX A

Oxygen extraction by the tissue from an infinitesimally thin volume element of blood (oef) during capillary blood transit (3, 6, 15, 16, 52) over an elapsed time of $\Delta t$ can be described as

$$\text{oef}(\tau + \Delta t) = \left[ C(t) - C(t + \Delta t) \right] / C(t)$$

where $C(t)$ is the temporal profile of the changing total oxygen content of blood in transit. The loss of oxygen from the plasma component of blood during transit [C$_0$(t)] is also related to the first-order rate constant ($k$) of oxygen loss during capillary transit of blood

$$\frac{dC(t)}{dt} = -krC(t)$$

where $r = C_0/C_t$ over an elapsed time of $\Delta t$ and $k$ is related to the spatial gradients of PO$_2$ in the blood and the abluminal side of the capillary endothelium. Given that $r$ is constant over the elapsed time of $\Delta t$, it can be shown that

$$C(t + \Delta t) = C(t) \exp(-kr\Delta t)$$

where $\Delta t$ is assumed to be a fraction of the capillary transit time ($T_c$)

$$\Delta t = T_c/n$$

where $n > 1$ and is an integer [in the model of Frank and Buxton (6), $n = 1$], then for the whole transit time ($T_c$)

$$C(t) = \Pi C(t) \exp(-kr\Delta t)$$

which is equivalent to

$$C(t) = C(t) \exp(-[T_c/(n/2)] \Sigma (kr))$$

Similarly, from Eq. A1, the oxygen extraction fraction around the capillary (OEF$_c$) for $T_c$ is given by

$$\text{OEF}_c = 1 - \exp(-[T_c/(n/2)] \Sigma (kr))$$

where $T_c$ may be related to the capillary volume (CBV$_c$) and flow (CBF$_c$) by

$$T_c = \text{CBV}_c / \text{CBF}_c$$

Substitution of Eq. A8 into Eq. A7 results in

$$\text{OEF}_c = 1 - \exp(-[\text{CBV}_c / \text{CBF}_c](n/2) \Sigma (kr))$$

where the effective diffusivity for oxygen of the capillary (D$_c$) can be defined as

$$D_c = [\text{CBV}_c/(n/2)] \Sigma (kr)$$

and, by substitution, Eq. A9 becomes

$$\text{OEF}_c = 1 - \exp(-D_c/\text{CBF}_c)$$

which is equivalent to Eq. 8.

APPENDIX B

According to Buxton and Frank (6), because of a physiological perturbation, the altered OEF value is related to the basal OEF value in the following manner

$$\Delta \text{OEF} + \text{OEF} = 1 - (1 - \text{OEF})^{3\Delta \text{CBF}/\text{CBF}}$$

If the altered OEF value is related to the expression in Eq. 16 when $\Omega = 0$, then

$$1 - (1 - \text{OEF})^{3\Delta \text{CBF}/\text{CBF}}$$

$$= 1 - \exp(-D/(\Delta \text{CBF} + \text{CBF}))$$
which results in

\[ \text{OEF} = 1 - \exp(-Y/\text{DCBF}) \]  

\[(B3)\]

which is the original expression (see Eq. 10).

**APPENDIX C**

The capillary arteriovenous oxygen difference (60) is given by

\[ C_a - C_v = [\text{Hb(O}_2\text{)}]_n(1 - Y)/Y \]  

\[(C1)\]

where the arterial oxygenation is assumed to be very close to 1. Equation C1 rearranges to

\[ Y(C_a - C_v) = ([\text{Hb(tot)}] - [\text{Hb}])/(1 - Y) \]  

\[(C2)\]

where \([\text{Hb(O}_2\text{)}]_n\), \([\text{Hb}])\), and \([\text{Hb(tot)}]\) are the capillary oxy-, deoxy-, and total hemoglobin concentrations, respectively. Because

\[ C_a = [\text{Hb(tot)}] = [\text{Hb(O}_2\text{)}]_n + [\text{Hb}] \]  

\[(C3)\]

Equation C2 rearranges to

\[ 1 - C_v/C_a = 1 - Y \]  

\[(C4)\]

Because Crane (8) showed that

\[ \text{OEF} = 1 - C_v/C_a \]  

\[(C5)\]

it can be shown that

\[ \text{OEF} = 1 - Y \]  

\[(C6)\]

When fractional changes in OEF are considered due to a physiological perturbation

\[ \Delta \text{OEF}/\text{OEF} = -\Delta Y/(1 - Y) \]  

\[(C7)\]

F. Hyder acknowledges the support and advice of Drs. Kevin L. Behar, Richard P. Kennan, and Ogden A. C. Petroff. This work was supported by National Institutes of Health Grants DK-27121 (R. G. Shulman) and NS-32126 (D. L. Rothman), and by National Science Foundation Grants DBI-9730892 (F. Hyder).

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