A Model for Regional Cerebral Oxygen Distribution During Continuous Inhalation of $^{15}O_2$, $C^{15}O$, and $C^{15}O_2$

Rajeshwari Subramanyam, Nathaniel M. Alpert, Bernard Hoop, Jr., Gordon L. Brownell, and Juan M. Taveras

Massachusetts General Hospital, Boston, Massachusetts

Equilibrium positron brain scans were obtained during continuous inhalation of $C^{15}O$, $C^{15}O_2$, and $^{15}O_2$. Inhalation of $C^{15}O$ labels hemoglobin, whereas $C^{15}O_2$ instantaneously labels stable water to $H_2{}^{15}O$. During the continuous inhalation of $^{15}O_2$, body tissues extract it from the blood in proportion to local metabolism and ultimately convert it to water of metabolism. After 6–8 min of inhalation, a steady-state equilibrium is established in which the inflow of tracer is balanced by its disappearance due to radioactive decay ($T_{1/2}$ = 2 min) and biologic removal. Mathematical models of the steady-state distributions of $C^{15}O$, $C^{15}O_2/H_2{}^{15}O$, and $^{15}O/H_2{}^{15}O$ are derived.

The major results are: a) The steady-state distribution of $C^{15}O$ is insensitive to variations in blood flow and essentially measures blood volume. b) The distribution of $H_2{}^{15}O$ during inhalation of $C^{15}O_2$ is dependent, though nonlinearly, on blood flow. c) The distribution of $H_2{}^{15}O$ during inhalation of $^{15}O_2$ depends linearly on the oxygen extraction fraction and nonlinearly on blood flow. d) The dependence on blood flow in the $^{15}O_2$ steady-state image can be removed by the division, point by point, of the $^{15}O_2$ image by the $C^{15}O_2$ image.

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There has been continuing interest in techniques for the in vivo measurement of parameters related to regional circulation and metabolism. Of the several methods available for determination of regional cerebral blood flow (rCBF) the most widely used is a modification of the Kety-Schmidt method (*1–3*). This technique involves an injection of radioactive tracer into an internal carotid artery, followed by extracranial monitoring of its clearance rate. Saline solutions of Xe-133, Kr-85 and $H_2{}^{15}O$ in blood are the most frequently used tracers for rCBF measurements (*4–7*). Studies of metabolism have been carried out with intra-arterial administration of O-15-labeled oxyhemoglobin to estimate regional oxygen utilization rates (*8*).

The need to puncture the internal carotid artery for injections has limited the wide application of this technique, and general interest has shifted to less drastic methods of administering the radioactive tracer (*9–12*). Ter-Pogossian and coworkers have attempted the measurement of parameters related to rCBF and oxygen metabolism by monitoring the clearance rate of activity following a single breath of $^{15}O_2$ (*13*). Recently, Jones and coworkers (*14,15*) have described a new noninvasive method for visualization of regional cerebral oxygen extraction and regional cerebral blood flow. In their method, continuous inhalation of O-15-labeled gases establishes a dynamic equilibrium in which the inflow of the tracer is balanced by its physical decay and its removal due to biologic transport. The short

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For reprints contact: R. Subramanyam, Boston University School of Medicine, Dept. of Radiation Physics, 80 East Concord St., Boston, MA 02118.

physical half-life of O-15 (123 sec) enables steady-state conditions to be established within 6–8 min. Oxygen-15 decays by positron emission, resulting in the subsequent emission of two 511-keV annihilation photons (*16*). External detection of the annihilation radiation permits scintigrams to be obtained during the steady-state conditions described above. Regional variations of the count density in these scintigrams reflect the effects of underlying dynamic processes.

Preliminary equilibrium-imaging studies by Jones and coworkers, by Hoop and coworkers (*17*) and by Subramanyam (*18*) have stimulated an interest in the quantitative interpretation of such data. This paper describes simple mathematical models of the steady-state distribution of O-15-labeled gases in terms of blood flow, O_2 utilization, tracer distribution volumes, and physical decay constant. Using these models, the feasibility of qualitative visualization and quantitative measurements of rCBF and oxygen extraction fraction are shown. The results of some preliminary studies for qualitative visualization of rCBF and the distribution of oxygen extraction fraction are presented.

Mathematical model. Radioactive oxygen-15 can be administered in the form of three gases: molecular oxygen ($^{15}O_2$), carbon dioxide ($C^{15}O_2$), and carbon monoxide ($C^{15}O$). During inhalation these compounds diffuse out of the pulmonary alveoli into the blood of the pulmonary capillaries, respectively labeling oxyhemoglobin and water, and forming labeled carboxyhemoglobin. The circulating blood carries the activity to the various organs throughout the body in proportion to their blood flow.

Models for the kinetics of the O-15-label during continuous inhalation of each compound will be developed separately. The following assumptions are made for all three compounds:

1. Brain is a homogeneous steady-state system; that is, blood flow, blood volume, and O_2 utilization rate are constant over the period of measurement.

2. Arterial input of blood is constant, and during continuous inhalation of a constant concentration of gaseous radioactivity, the specific activity of the blood is gradually raised to a steady-state value. Initially, the activity carried to and deposited in various organs is not constant but increases with the rising arterial activity. In addition to the continuous fresh supply, recirculation causes some activity to return to the organ. Following a period of inhalation extending over several half-lives of the tracer, the total arterial activity due to the continuous supply and recirculation reaches a constant value. During the imaging of equilibrium scintigrams, the constancy of input arterial concentration is a perfectly reasonable assumption.

The brain is represented by a single compartment in the cases of $C^{15}O$ and $C^{15}O_2$ inhalation. However, for $^{15}O_2$ the system is modeled as two compartments: one as the cerebral blood pool and the other as the tissue-water pool of the brain. Admittedly, this is an oversimplified representation of the cerebral system, but it represents a first step in understanding the complex underlying dynamic processes.

$C^{15}O$ inhalation. Due to a strong chemical affinity between CO and hemoglobin (Hb), CO is neither released appreciably in the tissues nor exchanged with oxygen in the lungs. Hb $C^{15}O$ is essentially a nondiffusible vascular tracer.

Figure 1 shows a compartment of volume V_{co} with a radioactive tracer entering at a rate of $C_{co}F$, where C_{co} represents the arterial concentration (mCi/ml) of $C^{15}O$ and F the blood flow (ml/min). Under the usual compartmental assumptions, the tracer disappearing from the compartment by radioactive decay and biologic transport is proportional to the amount of tracer present, Q_{co}. The rate of accumulation of tracer is given by the differential equation,

$$\frac{dQ_{CO}}{dt} = C_{CO}F - (\lambda + F/V_{CO})Q_{CO} \qquad (1)$$

where $\lambda = 0.34\ min^{-1}$ is the physical decay constant for O-15. Since carboxyhemoglobin is a nondiffusible tracer, the volume V_{co} can be associated with the blood volume.

After prolonged inhalation of the radioactive gas, a steady state is reached such that the regional counting rates remain constant. That is, as $t \rightarrow \infty$, $dQ_{co}/dt \rightarrow O$ and Q_{co} is given by

$$Q_{CO} = \frac{C_{CO}\,F}{(\lambda + F/V_{CO})} = (C_{CO}V_{CO}f_1)/(\lambda + f_1), \quad (2)$$

where $f_1 = F/V_{co}\ (min^{-1})$.

$C^{15}O_2$ inhalation. On inhalation of CO_2, water in blood is labeled with oxygen-15 by the in vivo exchange between CO_2 and water:

$$C^{15}O_2 + H_2O \rightleftharpoons H_2C^{15}O_3 \rightleftharpoons H_2{}^{15}O + CO_2.$$

The labeled water, being essentially a diffusible

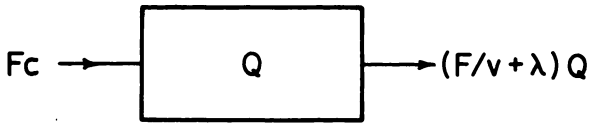

FIG. 1. Single compartment of volume V(ml) at equilibrium with inflow rate (CF) equal to outflow rate ($\lambda + F/V$)Q, where C represents arterial concentration (mCi/ml) of tracer and F the blood flow (ml/min). Q represents amount of tracer in compartment, which corresponds to blood-pool activity during inhalation of $C^{15}O$ and water-pool activity during inhalation of $C^{15}O_2$.

tracer, is rapidly taken up by cerebral tissue. Under continuous administration of $C^{15}O_2$, the cerebral water-pool activity equilibrates with the activity of the total-body water pool. With similar reasoning, as in the case of $C^{15}O$ inhalation, the total activity Q_{H_2O} in the compartment obeys the differential equation:

$$\frac{dQ_{H_2O}}{dt} = C_{H_2O}F - (\lambda + F/pV)Q_{H_2O}, \quad (3)$$

where C_{H_2O} = arterial $H_2{}^{15}O$ concentration (mCi per ml), V = volume of brain tissue (ml), and p represents the brain/blood partition coefficient. At steady-state equilibrium, when $t \to \infty$, $dQ_{H_2O}/dt \to 0$ and

$$Q_{H_2O} = (C_{H_2O}pVf_2)/(\lambda + f_2), \quad (4)$$

where $f_2 = F/pV$ (min^{-1}).

$^{15}O_2$ inhalation. During inhalation of $^{15}O_2$, the label is transferred to hemoglobin to form $Hb^{15}O_2$. The blood carries the labeled oxyhemoglobin to various organs where oxygen-15 diffuses into the tissues. It combines with hydrogen ions to form O-15-labeled water of metabolism which also circulates along with oxyhemoglobin. During continuous inhalation, as the arterial concentration of $^{15}O_2$ approaches a steady state, $H_2{}^{15}O$ concentration also becomes constant. Hence, the input radioactivity to any organ consists of two parts: (a) labeled oxyhemoglobin and (b) labeled water. The signal registered by an external detector would be proportional to the sum of the activities of these two components.

Figure 2 shows a highly simplified diagram of the kinetics of the O-15-label in the brain. The system is modeled as two compartments, one being the brain's blood pool, the other its tissue water pool. This model does not account for the kinetics of the label while it is participating in the metabolic process that ultimately converts O_2 to H_2O. It is also assumed that the $^{15}O_2$ present in the tissue as dissolved O_2 is negligible compared with that labeling the red cells.

Let Q_{O_2} and $Q^*_{H_2O}$ represent the quantities of O-15-tracer as $^{15}O_2$ and $H_2{}^{15}O$, respectively. Then, under the usual assumptions for compartmental modeling, their rates of accumulation are given by:

$$\frac{dQ_{O_2}}{dt} = C_{O_2}F - B - (\lambda + F/V_{O_2})Q_{O_2}, \quad (5)$$

and

$$\frac{dQ^*_{H_2O}}{dt} = C^*_{H_2O}F + B - (\lambda + F/pV)Q^*_{H_2O}, \quad (6)$$

where

C_{O_2} = arterial $^{15}O_2$ concentration (mCi/ml),
$C^*_{H_2O}$ = arterial $H_2{}^{15}O$ concentration (mCi/ml),
V_{O_2} = volume of distribution for $^{15}O_2$ (approximately the vascular volume),

and F, p, and V are as defined before.

The quantity B represents the rate at which $^{15}O_2$ metabolizes to H_2O. It can be expressed as

$$B = C_{O_2}F\,(C_A - C_V)/C_A \text{ (mCi/min)},$$

where C_A and C_V represent the arterial and venous concentrations of O_2, respectively. The quantity $(C_A - C_V)/C_A$ represents the fraction of O_2 extracted from that which is available for metabolism.

At steady state $dQ_{O_2}/dt \to 0$, $dQ^*_{H_2O}/dt \to 0$ and the amount of tracer observable, $Q = Q_{O_2} + Q^*_{H_2O}$, is given by

$$Q = \frac{C_{O_2}F - B}{\lambda + F/V_{O_2}} + \frac{C^*_{H_2O}F}{\lambda + F/pV} + \frac{C_{O_2}F}{\lambda + F/pV}\left(\frac{C_A - C_V}{C_A}\right). \quad (7)$$

Discussion of the model. For each tracer at t = 0, Q = 0 and dQ/dt = CF—that is, the amount of tracer in brain at the beginning of inhalation is

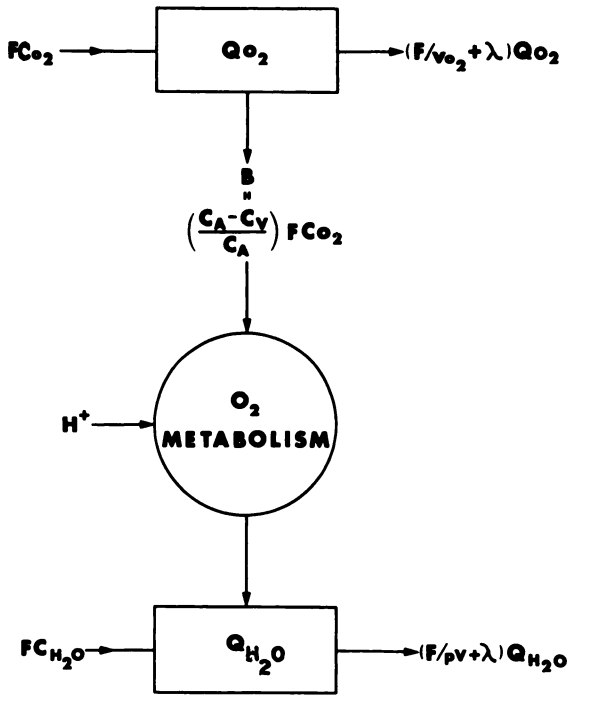

FIG. 2. Conversion of $Hb^{15}O_2$ to $H_2{}^{15}O$ during $^{15}O_2$ respiration is modeled as a two-compartment system. Q_{O_2} and Q_{H_2O} represent $^{15}O_2$ and $H_2{}^{15}O$ activity, respectively. $B = FC_{O_2}(C_A - C_V)/C_A$ is the O_2 metabolism rate, where C_A and C_V are the arterial and venous O_2 concentrations.

zero and the rate of its increase is the rate of entrance of the tracer.

After 6–8 min inhalation of the radioactive gas, a dynamic equilibrium is established between incoming tracer and tracer disappearing by radioactive decay and biologic removal. An imaging device viewing this activity will record constant local counting rates. The short physical half-life of O-15 and the details of the mathematical model permit extraction of information about the underlying dynamic processes. Increased local intensities typically reflect increased biologic turnover. Multiple views of the activity distributions can be obtained during the steady state, thus permitting transverse-section reconstruction, if desired.

$C^{15}O$ and $C^{15}O_2$ inhalation. Equilibrium scintigrams obtained during inhalation of $C^{15}O$ and $C^{15}O_2$ have activity distributions given by the relation $Q = CF/(\lambda + F/V)$. The activities for the two compounds differ because of their different volumes of distribution, V_{co} and V (see Eqn 2 and 4). $C^{15}O$ is confined to the cerebral vascular pool, which is about 3% of total tissue volume. On the other hand, labeled water perfuses both the intra- and the extracellular water pools of the brain and occupies almost 80% of the total tissue volume. For a normal adult, the cerebral tissue volume is about 1500 ml (*19*). Hence, V_{H_2O} and V_{co} are in the ratio 1200/45.

In the case of a tracer with $\lambda << F/V$, the disappearance of the tracer from the compartment is primarily due to biologic washout, and the loss due to physical decay is negligible. In such a case $F/V + \lambda \approx F/V$ and $Q \approx CV$. Equivalently, it may be stated that with continuous infusion of a tracer whose physical decay constant is negligible compared with the washout constant, the total activity reaches a constant value with a concentration equal to that of arterial blood. This is approximately the case for $C^{15}O$ because the physical decay constant 0.34 min^{-1} of ^{15}O is negligible in comparison to the average washout constant, $F/V \approx 13$/min. The steady-state activity distribution is then insensitive to regional variations in flow and the tracer essentially outlines the cerebral intravascular pool.

For a tracer with a short half-life, $\lambda >> F/V$ and $Q \approx CF$, implying that, at equilibrium, the disappearance of the tracer from any region is primarily due to its physical decay. The steady-state image will then give a static representation of cerebral perfusion.

The situation for continuous inhalation of $C^{15}O_2$ represents an intermediate case. Equation 4 shows that the activity distribution in a $C^{15}O_2$-$H_2{}^{15}O$ image is a function of blood flow, tissue-water volume, and the physical decay constant of O-15. Figure 3 plots the predicted counting rate as a function of cerebral blood flow. The steady-state image provides the possibility of determining absolute values of regional blood flow. The externally recorded counting rate, N, can be expressed as

$$gN = \frac{C_{H_2O}pVf_2}{\lambda + f_2},$$

where g is the geometric sensitivity of the detector. Solving for F/V results in the relation

$$\frac{F}{V} = \frac{\lambda}{(C_{H_2O}V/gN) - p^{-1}}.$$

The quantity p has been determined (*7*), and both C_{H_2O} and g are easily measured. The tissue volume, V, is not usually known for a two-dimensional projection, but can be obtained by means of three-dimensional reconstruction.

$^{15}O_2$ inhalation. According to Eqn 7, the activity distribution in an equilibrium image obtained during $^{15}O_2$ inhalation has contributions from three components. The first term in Eqn 7 represents the O-15 activity present as dissolved oxygen in red cells and tissues. Part of the O-15 activity supplied to the brain diffuses into the tissues to form water of metabolism, which is represented by the third term. In addition, the recirculating water also contributes to the signal; this is represented by the second term. Estimates of these components for a typical case ($F = 0.6$ ml/min and $B = 0.04$ mCi/min) give the

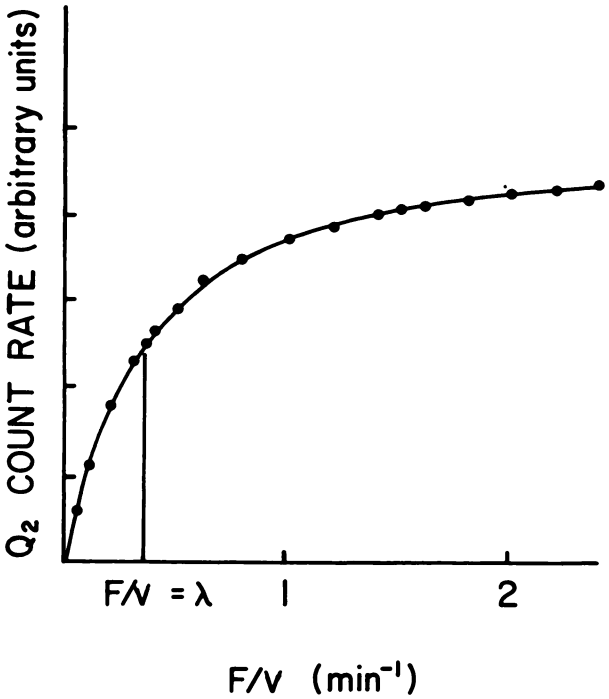

FIG. 3. At equilibrium, variation of activity Q_2 or count rate as function of blood flow.

FIG. 4. Left lateral views of distribution of radioactivity at equilibrium during continuous inhalation of $^{15}O_2$, $C^{15}O_2$, and $C^{15}O$.

contributions to the total signal to be 6.5% for $^{15}O_2$ activity, 29% for recirculating water, and 64.25% for oxygen utilization rate.

The predominant contribution to the local count density in an O-15 equilibrium scintigram is due to the continuous generation of water of metabolism. There is also a significant contribution from recirculating water activity. As can be seen from Eqn 7, these contributions are functions of flow and the physical decay constant of the radioactive label. These last two factors pose considerable difficulties in the interpretation of variations in count densities in an O-15 equilibrium scintigram. However, if this dependence could be reduced or eliminated, the scintigram would be easier to interpret and would be of greater clinical significance. Fortunately, a $C^{15}O_2$-$H_2{}^{15}O$ image provides such a possibility.

Since the contribution due to O-15 red-cell activity is negligible, Eqn 7 reduces to

$$Q \simeq \frac{F}{\lambda + F/pV}\left[C^*_{H_2O} + C_{O_2}\left(\frac{C_A - C_V}{C_A}\right)\right]. \quad (8)$$

A $C^{15}O_2$-$H_2{}^{15}O$ image has an activity distribution given by

$$Q_{H_2O} = C_{H_2O}F(\lambda + F/pV). \quad (9)$$

Division of Eq. (8) by Eq. (9) yields

$$\frac{Q}{Q_{H_2O}} = \frac{1}{C_{H_2O}}\left[C^*_{H_2O} + C_{O_2}\left(\frac{C_A - C_V}{C_A}\right)\right]. \quad (10)$$

Equivalently, division of a $^{15}O_2$ equilibrium scintigram, element by element, by the corresponding $C^{15}O_2$ scintigram results in a scintigram with the density distribution given by Eqn 10. Such an image will reflect regional oxygen extraction fractions $E = (C_A - C_V)/C_A$. C_{O_2}, C_{H_2O}, and $C^*_{H_2O}$ can be determined by withdrawing arterial blood samples at equilibrium, thus permitting the calculation of the absolute values of regional oxygen extraction fractions.

Preliminary studies and results. Preliminary studies were carried out in human volunteers to test the feasibility of obtaining distinctively different distributions of activity in brain following inhalation of $^{15}O_2$, $C^{15}O_2$, and $C^{15}O$.

Instrumentation and techniques. Oxygen-15 is produced by the $^{13}N(d, n)\ ^{15}O$ reaction, using deuteron irradiation of gaseous nitrogen containing 2–3% oxygen (*20*). The recoil O-15 atom scavenged by carrier oxygen is extracted as $^{15}O_2$, which is then passed over charcoal furnaces heated to suitable temperatures for conversion to $C^{15}O_2$ and $C^{15}O$. The production of these compounds is described in detail elsewhere (*21*).

The labeled gaseous compounds are supplied at the rate of 0.5 l/min, containing 1 mCi. The radioactive gas mixed with room air was inhaled through a one-way Rubin valve and a mouthpiece. Leaks through nose were prevented by clamping the nostrils. The exhaled radioactive gas was exhausted to waste. Imaging was carried out with the subject supine, using the M.G.H. positron camera (*22*).

After continuous inhalation of the radioactive gas for 6–8 min, lateral and anterio-posterior equilibrium scintigrams were obtained for each labeled gas. All images were stored in a minicomputer for subsequent processing and display.

RESULTS

The lateral views of the steady-state distribution of radioactivity during continuous inhalation of $^{15}O_2$, $C^{15}O_2$, and $C^{15}O$ for a normal subject are shown in Fig. 4. The $C^{15}O$ image clearly outlines the cerebral vascular pool. The $^{15}O_2$ and $C^{15}O_2$ images have a diffuse distribution of activity and do not provide much anatomic information except for the central region, where decreased activities probably correspond with white matter, which is known to have less blood flow and oxygen metabolism than the surrounding gray matter.

The $^{15}O_2$ and $C^{15}O_2$ images for a normal subject, and the resultant image obtained by dividing the $^{15}O_2$ image by $C^{15}O_2$ image, are shown in Fig. 5. The quotient image reflects regional oxygen extraction fraction. In the absence of arterial blood samples,

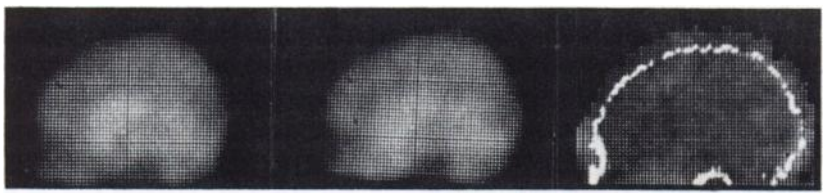

FIG. 5. Left lateral view images of distribution of radioactivity at equilibrium during continuous inhalation of $^{15}O_2$, and $C^{15}O_2$, and a quotient image, reflecting O_2 extraction fraction (E), obtained by dividing $^{15}O_2$ image by that of $C^{15}O_2$.

the absolute values or extraction fractions could not be determined.

CONCLUSIONS

We have studied the possible usefulness of O-15-labeled gaseous compounds for cerebral function studies. Simple mathematical equations have been developed to aid the understanding of the distribution of activity in terms of flow, volume of distribution of tracer, physical decay constant, and metabolic rate during continuous inhalation of O-15-labeled gases.

At equilibrium, the activity deposited is the balance between inflow and its loss due to physical decay and biologic washout. The activity distribution in a $C^{15}O_2$ image is a function of blood flow, whereas a $^{15}O_2$ image predominantly reflects oxygen metabolism. An attractive feature of this technique is that it permits formation of an image reflecting oxygen extraction either as two-dimensional projection or as a transverse-section reconstruction.

We emphasize that the models presented in this paper are highly simplified, using only one or two compartments to explain complex dynamic phenomena. It would be naïve, therefore, to expect these models to describe the processes of blood flow and oxygen metabolism perfectly. Nevertheless, it is expected that they will be useful for interpreting in-vivo data in many practical situations.

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