The Requirement for Constant Arterial Radioactivity in the $C^{15}O_2$ Steady-State Blood-Flow Model

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This study evaluates the discrepancy between the true CBF value and the CBF value calculated according to the $C^{15}O_2$ steady-state model, for situations where the arterial input function, Ca(t), deviates considerably from its steady-state value, Ca. The fact that arterial input function and tissue O-15 concentration are not independent variables is taken into account. Inconstant or variable arterial input functions are simulated and the corresponding tissue O-15 concentrations calculated. The steady-state CBF values are evaluated for several temporal variations of Ca over the period of imaging, all derived from Ca(t) by simulation of various blood-sampling schemes, and are compared with the true CBF value. The study indicates that reliable CBF values are obtained by the $C^{15}O_2$ steady-state method even under severely impaired "unsteady-state" conditions, provided that either the true average arterial concentration over the entire scan, or the average concentration from multiple arterial samples, is used.

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Positron emission tomography (PET) is a well-recognized tool for the quantitative measurement of tissue concentrations of positron-emitting radionuclides (*1*). Whereas experience with fast dynamic PET imaging is currently being gained (*1–4*), the usually more time-consuming steady-state imaging mode offers high picture quality with maximum spatial resolution (*5,6*). One example of this approach is the measurement of regional cerebral blood flow (CBF) and oxygen metabolism by continuous administration of the short-lived radionuclide oxygen-15 in the form of $C^{15}O_2$ or $^{15}O_2$ (*7,8*). The steady-state procedure for quantitative imaging of the distribution of O-15-labeled gases was first developed by Russ et al. (*9,10*). Jones and associates (*7*) suggested a model for interpretation of these data applicable to brain studies. The limitations of this model have been discussed by several authors (*11–15*). With respect to the measurement of regional CBF, a small error in the experimental determination of the steady-state arterial O-15 concentration, Ca, translates into a substantial error in the calculated CBF value, fe (*12,15*). A prerequisite for CBF quantification is a well-stabilized supply of radionuclide from the cyclotron, held constant within 2% to 3% by means of a feedback control system. Moreover, the subject has to be maintained in a steady-state condition during the entire imaging period. Changes in the patient's respiratory pattern, caused by physical and mental stress or lack of cooperation—particularly in the case of brain tumors or in the acute stage of stroke—result in irregular tracer inhalation which, in turn, leads to fluctuations in the arterial O-15 concentration, Ca. These true fluctuations in the arterial input function, Ca(t), can no longer be treated as simple measurement errors. An error analysis of this pseudo-steady state must take into account the relationship between the input function, Ca(t), and the resulting tissue concentration, C(T) (head curve), since, according to the underlying model, any change in Ca(t) is reflected in C(T) (*16*). The information recorded by the tomo-

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graph is the time-average of C(T) over the entire scan, and its value is, therefore, dependent on the variations of the arterial input function Ca(t). The question then arises of how accurately the blood-flow value, fe, calculated according to the steady-state method under an imperfectly steady condition, reflects the true, constant CBF value, f. Since, in practice, tissue perfusion is never strictly constant, the measured CBF values represent averages over the period of observation.

The present study was carried out (a) to evaluate, by means of a computer simulation, the relationship between the pseudosteady CBF value, fe, and the true CBF value, f, for situations where the arterial input function, Ca(t), deviates considerably from its steady-state value; and (b) to devise a blood-sampling scheme for the estimation of an average arterial O-15 concentration, Ca, that would minimize the discrepancy between fe and f.

THEORY

The theory for the measurement of rCBF by means of continuous administration of short-lived radionuclides has been discussed in detail elsewhere (*8,17,18*). Its major features are summarized below in view of its application to the measurement of regional CBF by continuous inhalation of $[^{15}O]CO_2$.

Under the action of carbonic anhydrase, the O-15 label is rapidly transferred from $C^{15}O_2$ to $H_2{}^{15}O$ at the pulmonary alveolar level. The resulting circulating oxygen-15-labeled water is a diffusible tracer and its concentration C(T), in a brain-tissue element of volume V at time T after the start of $C^{15}O_2$ inhalation, is related to its arterial concentration Ca(t) by:

$$C(T) = e^{-(k+\lambda)T} \cdot p \cdot k \cdot \int_0^T Ca(t) \cdot e^{(k+\lambda)t}\, dt \quad (1)$$

Here, f is the blood flow through volume V, p the partition coefficient for water between brain tissue and blood, $k = f/p$, and λ is the physical decay constant of oxygen-15. The steady-state method takes advantage of the fact that, after a time of T = 8–12 min, the brain tissue concentration C(T) reaches a dynamic equilibrium (steady-state tissue concentration, Cb) where the washout and physical decay of $H_2{}^{15}O$ are balanced by the continuous arrival of O-15 labeled water at a steady concentration Ca in the arterial blood stream. In this condition, the steady-state regional CBF, fe, through tissue volume V, can be calculated as:

$$fe = \frac{\lambda}{\frac{Ca}{Cb} - \frac{1}{p}} \quad (2)$$

In practice, the steady-state tissue O-15 concentration, Cb, is determined by the tomograph as the time integral of the instantaneous tissue concentration C(T) over the entire scan duration from T_1 to T_2:

$$Cb = \frac{1}{T_2 - T_1} \int_{T_1}^{T_2} C(T)\, dT \quad (3)$$

Likewise, for future purposes we define the average arterial O-15 concentration, C_{ave}, over the scan interval as:

$$C_{ave} = \frac{1}{T_2 - T_1} \int_{T_1}^{T_2} Ca(t)\, dt \quad (4)$$

In practice, C_{ave} can be obtained by withdrawing an arterial sample from T_1 to T_2 at a rate proportional to $\exp(-\lambda \cdot t)$, which accounts for the physical decay of a tracer with decay constant λ.

For the following discussion and error analysis it is important to keep in mind that, according to Eqs. (1) and (3), Cb and Ca are not independent variables.

SIMULATION PROCEDURE

Basic principle. The rationale of the present simulation procedure may be summarized as follows: As demonstrated in the previous paragraph, for a given arterial tracer input function Ca(t) and a selected true regional CBF value f, the corresponding steady-state regional CBF value, fe, can be calculated and compared with f. Arterial input functions can be simulated for various pseudosteady states resembling those encountered in practice, and for a series of true regional CBF values, the corresponding steady-state regional CBF values calculated using various steady-state arterial O-15 concentrations Ca, all derived from Ca(t) by simulation of a variety of sampling schemes for arterial blood.

Arterial input function Ca(t). Two frequently encountered deviations from steady-state during $C^{15}O_2$ studies (scanning period T_1 to T_2) may be described in terms of the arterial input function as follows: (a) a continuous increase or decrease of Ca(t) over the entire scanning interval (Curve I in Fig. 1), and (b) a single positive or negative excursion of Ca(t) starting from its steady-state value at T_1 and returning to this same value at T_2 (Curve II in Fig. 1).

The following form of Ca(t) was thought to adequately simulate the above two characteristic curve shapes:

$$Ca(t) = 1 - e^{-æ \cdot t} \text{ for } 0 \le t \le T_1, \quad (5a)$$

and

$$Ca(t) = (1 - e^{-æ \cdot t}) \pm A \cdot \sin[\omega(t - T_1)] \quad (5b)$$
$$\text{for } T_1 < t \le T_2$$

The buildup constant æ was selected such that, after 10 to 12 min, more than 95% of the ideal steady-state value of Ca = 1 would be reached (for a value of æ = 0.5/min, Ca = 0.99 at t = 10 min). Appropriate selection of ω

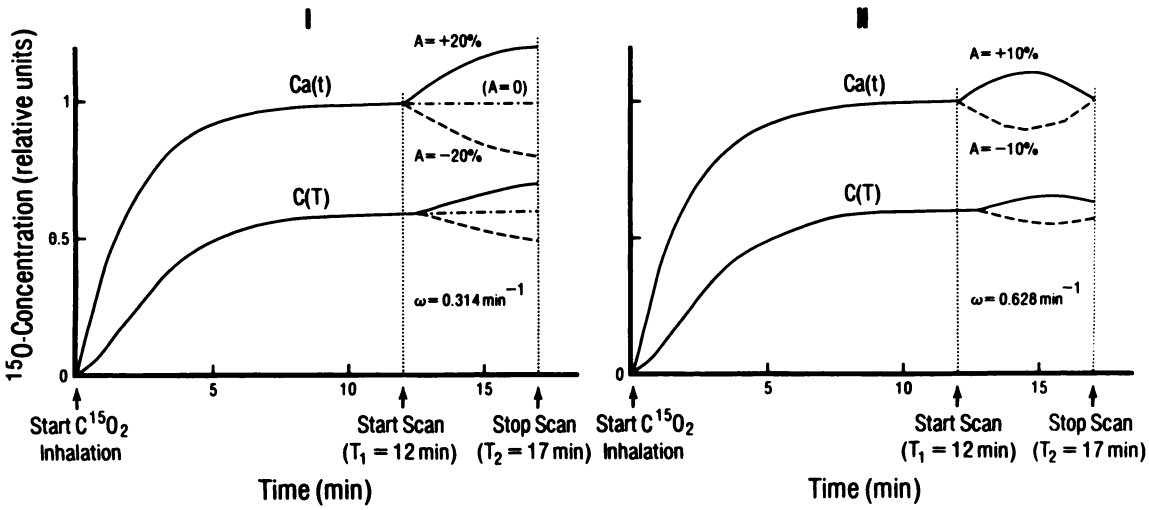

FIG. 1. Two simulated arterial input functions, Ca(t), of a $C^{15}O_2$ steady-state blood-flow study together with corresponding head curves, C(T). I: with continuously increasing (or decreasing) variation in Ca(t) with a maximum deviation of A = ±20% from the steady-state level (A = 0). II: single positive (or negative) variation, maximum deviation A = ±10%, with return to steady-state level. (Curves were calculated according to formulas 1 and 5, see text, with p = 1, æ = 0.5/min, f = 0.5/min and ω = 0.314/min or ω = 0.628/min, respectively).

allowed simulation of one or the other of the two input functions. All data were assumed to be noise-free. Error estimates for fe can be obtained for most real curve shapes of Ca(t) by appropriate interpretation and superposition of the results from these two types of variable-input functions (see Discussion).

Fixed simulation parameters. In accordance with established experimental practice, the (fictive) steady-state scan was started at T_1 = 12 min after onset of $C^{15}O_2$ inhalation, and ended at T_2 = 17 min. The tissue-blood partition coefficient for water was set to p = 1 and the buildup constant for the arterial input function to æ = 0.5/min (Eq. 5). The duration for the withdrawal of the blood samples was kept constant at 15 sec. This value has been recommended for real $C^{15}O_2$ studies (*19*) and allows one to average out fluctuations in arterial activity occurring within the respiratory cycle.

Variable simulation parameters. Two values were chosen for both the amplitude, A, and the ω, of the variation in the arterial input function Ca(t). A value of ω = 0.314/min was used to simulate a continuously increasing or decreasing input function (Curve I in Fig. 1). For the second type of variation of Ca(t) (Curve II in Fig. 1), ω was chosen as 0.628/min. For both curves, the maximum deviation from the steady-state condition (A = 0) was either A = ±10% or A = ±20%. The simulation was carried out under various sampling schemes for arterial blood.

CBF calculation. For a set of four theoretical CBF values (f = 25, 50, 75, and 100 ml/min-100 g), the steady-state blood-flow values, fe, were calculated according to Eq. (2). For the various simulated input functions Ca(t), the corresponding head curves were obtained from Eq. (1), and the steady-state tissue O-15 concentrations from Eq. (3). The arterial O-15 concentration Ca in Eq. (2) was determined in three different ways, giving rise to three steady-state CBF values as explained below.

CBF_e: here, Ca = C_{ave} as defined by Eq. (4), which is the true average arterial O-15 concentration over the entire scan.

CBF_{150}: Ca here is the average of three arterial samples, each withdrawn at a constant rate during 15 sec, at the beginning, in the middle, and at the end of the scan (150-sec intervals).

CBF_o: Ca is obtained from a single arterial sample, but instead of the average tissue O-15 concentration Cb (Eq. 3), which includes the effect of the inconstant arterial input function, the value Cb_o was used, representing the tissue O-15 concentration under ideal steady-state conditions (A = 0). This situation corresponds to previously published error analyses (*12,15*) that do not take into account the relation between arterial input function, Ca(t), and tissue concentration, C(T), and therefore evaluate only the error in CBF caused by experimental errors in the determination of Ca.

RESULTS

The error in calculated CBF is expressed as a percentage of the corresponding theoretical CBF value f (f = 25, 50, 75, 100 ml/min-100 g). Figure 2 shows the error in the three calculated flow values as a function of the theoretical flow value, f, for the two types of incon-

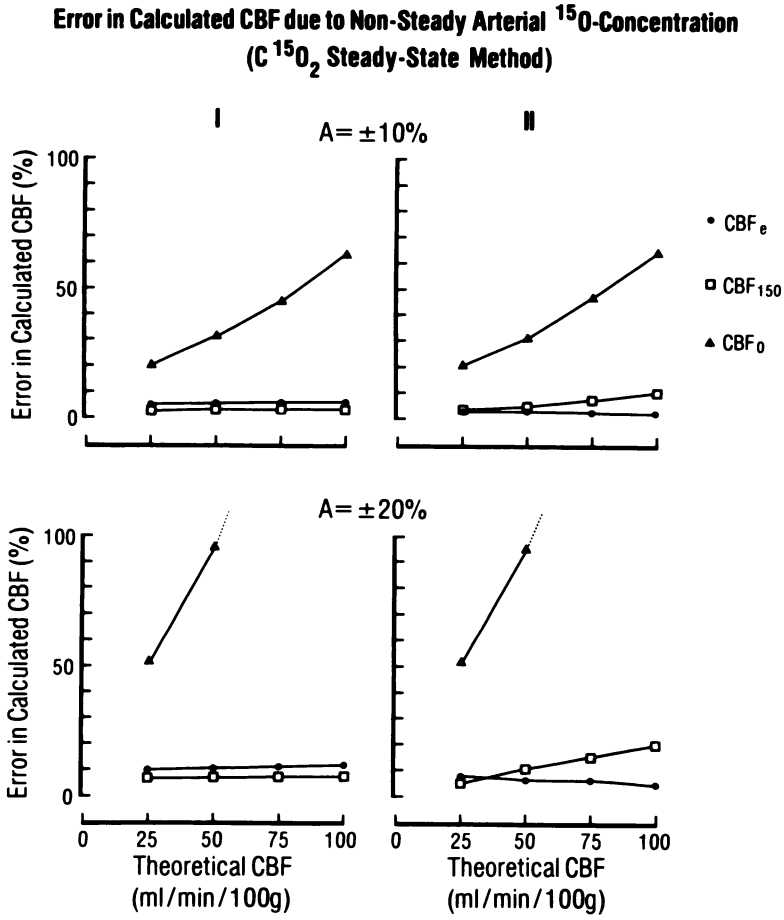

FIG. 2. Error in CBF as calculated by the $C^{15}O_2$ steady-state method using various arterial-blood sampling schemes, plotted as a function of theoretical CBF, for two types (I and II) of inconstant arterial input function (see Fig. 1), with maximum deviations from steady state of A = ±10% and A = ±20%, respectively (see Table 1 for definition of symbols).

stant arterial input functions (I and II) with amplitudes of maximum deviation from steady state being A = ±10% and A = ±20%, respectively. For CBF_e and CBF_{150}, the errors for positive and negative variations of equal amplitude in Ca(t) were averaged, since their magnitudes were similar. For CBF_0, the errors for positive and negative values of A differed greatly and the largest error was therefore plotted. For the three depicted situations, the error was largest for CBF_0, in agreement with previously published data (*12,15*) where Ca and Cb were treated as independent variables. There is a marked flow dependence, with the error increasing rapidly for larger flow values. For both types of inconstant arterial input functions (Curves I and II) with A = ±10%, the continuous sampling (CBF_e) or averaging of several blood samples (CBF_{150}) gave errors in calculated CBF between 1% and 10% only, with little or no flow dependence. For a variation of Curve type I with A = ±20%, the averaging of three blood samples (CBF_{150}) as well as use of the average arterial O-15 concentration (CBF_e) gave an approximately 10% error in calculated CBF, with practically no flow dependence. For Curve type II with A = ±20%, continuous sampling (CBF_e) gave errors around 5%, with no significant flow dependence. With three arterial samples (CBF_{150}), a flow-dependent error resulted, ranging from 5% to 21%.

Table 1 summarizes the results of the simulation study. It shows the maximum errors of the three different CBF calculations for a flow range from 0 to 100 ml/min-100 g and the two types of pseudosteady states (Fig. 1). It is obvious that single arterial sampling gives by far the largest error (CBF_0). The best result is obtained by using the average arterial concentration over the entire scan (CBF_e). Sampling at the beginning, in the middle, and at the end of the scan comes next in accuracy. Both for continuous withdrawal (CBF_e) or averaging of arterial samples (CBF_{150}), the error in calculated CBF is roughly proportional to the amplitude of the variation, ranging from 6% to 10% for A = ±10% and from 14 to 21% for A = ±20%. For single sampling (CBF_0), the relation between the error in calculated CBF and A becomes exponential.

DISCUSSION

The high sensitivity of the $C^{15}O_2$ steady-state CBF method to experimental errors in the determination of the steady-state arterial O-15 concentration, Ca, is well recognized (*12,15*). A proper blood-sampling procedure limits this experimental error in Ca to a few percent. This is essential, since a small experimental error in Ca results in a strongly flow-dependent error in CBF that is several

TABLE 1. MAXIMUM ERROR (%) IN CALCULATED CBF VALUES FOR TWO TYPICAL PSEUDOSTEADY-STATES, WITH MAXIMUM DEVIATIONS FROM STEADY STATE OF A = ±10% AND A = ±20%, RESPECTIVELY (CURVES I AND II) AND BLOOD FLOWS BETWEEN 0 AND 100 ml/min-100 g

Method of CBF-calculation	Maximum error (%) in calculated CBF	
	A = ±10%	A = ±20%
CBF_e*	6	14
CBF_{150}†	10	21
CBF_o‡	64	370

* Blood flow calculated using a single arterial sample withdrawn at an exponentially decreasing rate over the entire scan (C_{ave}).

† Blood flow calculated using the average of three samples withdrawn for 15 sec at the beginning, middle, and end of scan.

‡ Blood flow calculated using a single arterial sample withdrawn over 15 sec at any time during the scan, but neglecting the relationship between input function and head curve in the error calculation.

times larger (CBF_o in Fig. 2). This first source of error in the determination of the steady-state CBF value, fe, has to be distinguished clearly from a second source, which is related to true fluctuations observed in Ca due to irregular $C^{15}O_2$ inhalation by the patient. In this case, an error analysis of the steady-state CBF value, fe, has to take into account the relationship between the arterial input function, Ca(t), and the tissue O-15 concentration C(T) (Eq. 1). The present simulation study indicates that the error in fe, caused by quite considerable (≥10%) true deviations of Ca from its steady-state value, can be kept within acceptable limits (~10%) by choosing an adequate blood-sampling strategy. As is to be expected under an inconstant "steady-state" condition, a single arterial sample withdrawn uniformly over 15 sec leads to large errors in calculated CBF. However, a single arterial sample withdrawn over the entire scan period at an exponentially decreasing rate drastically reduces the error in calculated blood flow (CBF_e). From a practical point of view, the use of as few samples as possible looks attractive and causes less blood loss from the patient. On the other hand, if a single sample should be lost accidentally, the study cannot be evaluated at all. An alternative approach, therefore, has been simulated: it consists of withdrawal of several arterial samples at constant intervals throughout the entire scan and use of their arithmetic mean for CBF calculation. The blood-sampling scheme simulated here uses samples at the beginning, middle, and end of the scan (CBF_{150}). For slow fluctuations in Ca(t) with amplitudes no larger than 10%, three-point sampling (beginning, middle, end) is adequate (CBF_{150}). Obviously, since the exact shape of the variation in Ca(t) cannot be predicted, sampling as frequently as is practically possible will give the best result if the multiple sampling scheme is selected.

With respect to continuously increasing or decreasing arterial O-15 levels during the scan, we note that, due to the particular mathematical form of the steady-state CBF equation (Eq. 2), for a given amplitude A, the error in calculated blood flow is always larger for negative variations in Ca, since Ca/Cb approaches the value of 1/p (Eq. 2). The two curves studied here represent two particularly critical types of inconstant arterial input functions as far as the error in cerebral blood flow, calculated according to the steady-state method, is concerned. Curves with positive as well as negative variations during the imaging period give a smaller error in calculated CBF due to a certain degree of cancellation that exists in this case. Rough error estimates for CBF in most real situations, therefore, may be obtained by appropriate superposition of the present results.

In conclusion, the results of the present simulation study indicate that reliable CBF values can be obtained by means of the $C^{15}O_2$ steady-state method even under far from steady-state conditions provided that, instead of a single short arterial sample, one uses either the true average arterial concentration over the entire scan period or the average concentration from multiple arterial samples. Although variations of arterial blood activity can, and should, be kept minimal by a properly devised method, the results of this study help to assess the reliability of CBF measurements by the $C^{15}O_2$ steady-state method in a more precise manner.

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