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Statistical method for the estimation of cerebral blood flow using the Kety–Schmidt technique

J. N. S. MATTHEWS*, D. S. F. MATTHEWS† and J. A. EYRE†
*Department of Statistics, University of Newcastle, Newcastle upon Tyne NE1 7RU, U.K., and †Department of Child Health, University of Newcastle, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, U.K.

A B S T R A C T

The Kety–Schmidt technique for the measurement of cerebral blood flow (CBF) has been in use for many years, but efficient statistical methods for producing estimates of CBF have received little attention. This paper proposes simple statistical models for this problem and explores their properties using data from a recent study of severe head injury in children. The method, which can readily be implemented on a personal computer, allows the uncertainty in the estimate of CBF to be quantified.

INTRODUCTION

Kety and Schmidt [1,2] described a method for the measurement of cerebral blood flow (CBF) based on the introduction of a low proportion (5–10%) of nitrous oxide (N_2O) into the subject's inhalation mixture. The method uses the observation that the arterial N_2O concentration rises to a saturation level (A) faster than does the N_2O concentration in the venous drainage of the brain (see Figure 1). Other physiologically inert tracers can be used, but our experience is restricted to N_2O and terminology consistent with this will be used throughout.

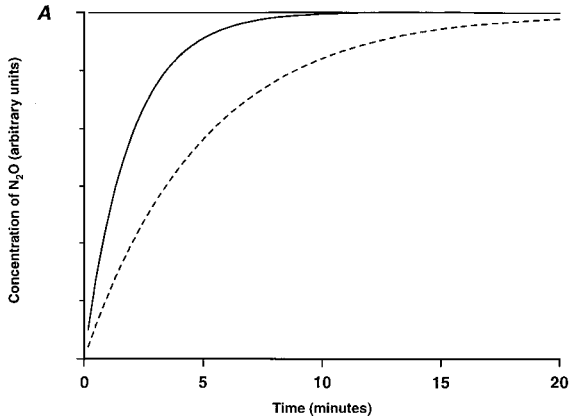

Figure 1 Examples of cerebral saturation curves: arterial (solid) and venous (broken)

The CBF is obtained by applying Fick's principle to the difference between the arterial and venous concentrations t min after the introduction of N_2O. If $C_a(t)$ and $C_v(t)$ denote the arterial and venous concentrations respectively, then it can be shown [2] that the CBF is given by:

$$\mathrm{CBF} = 100 \times \frac{\lambda C_v(t_{\mathrm{eq}})}{\int_0^{t_{\mathrm{eq}}} C_a(u) - C_v(u)\,du} \qquad (1)$$

where λ is the blood:brain partition coefficient, and the factor of 100 is required to give the conventional units of $\mathrm{ml \cdot 100\ g^{-1} \cdot min^{-1}}$. The upper limit t_{eq} is the time by which the arterial, venous and cerebral tissue concentrations of N_2O have reached saturation.

The method introduced by Kety and Schmidt has been scrutinized for more than half a century by many

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Correspondence: Professor J. N. S. Matthews (e-mail j.n.s.matthews@newcastle.ac.uk).

investigators (see, for example, [3–8]). It is accepted to be the reference method for the measurement of average levels of CBF, and is widely used both in experimental settings [9–12] and in clinical applications in severely ill patients [13–17]. Its validity rests on two key assumptions, namely: (1) that the venous samples, usually taken from one internal jugular vein, represent the venous drainage of the whole brain, and (2) that the concentration of the tracer in all brain tissue is the same as that in mixed cerebral venous blood at the beginning and end of blood sampling. It has been argued that, in practical applications of the technique, the latter condition is usually not satisfied, and a correction for this problem has been suggested [6].

In practice, the method can be implemented at the bedside by measuring the concentration of N_2O in samples taken intermittently from a peripheral arterial line and from a line placed in a superior jugular venous bulb [13,18]. This type of arrangement also facilitates sampling of arterio–venous differences in important brain metabolites, such as glucose and lactate, and has the advantage that these will arise from the same distribution within the brain as is used to determine the CBF [13].

While some of the mathematical properties of the processes underlying the Kety–Schmidt technique have received attention [6,19], the statistical aspects of the estimation of CBF from data generated by this technique have been almost completely neglected. The present paper presents an efficient statistical method for estimating CBF that can easily be implemented on a personal computer and which also allows the error in the estimate to be quantified. This paper assumes that the Kety–Schmidt technique is used in its saturation mode, but the ideas can be readily adapted to the desaturation mode.

In the next section the disadvantages of an *ad hoc* approach are explained, and the ideas behind the use of a statistical model are presented; in the following section two models are introduced and are illustrated and compared using data from 109 determinations of CBF obtained in the course of a study of severe head injury in children [20,21]; the penultimate section discusses the estimation of error; and some general comments are given in the final section.

MODEL-BASED APPROACH

An *ad hoc* approach to the analysis might start from a plot of the data as shown in Figure 2. The area under each curve could be calculated by a simple numerical method, such as the trapezium rule, and the CBF would be obtained by dividing the difference between the areas into some estimate of $C_v(t_{eq})$. This approach was advocated with $t_{eq} = 10$ min [2], and these authors also suggested assessing the stability of the estimate of CBF

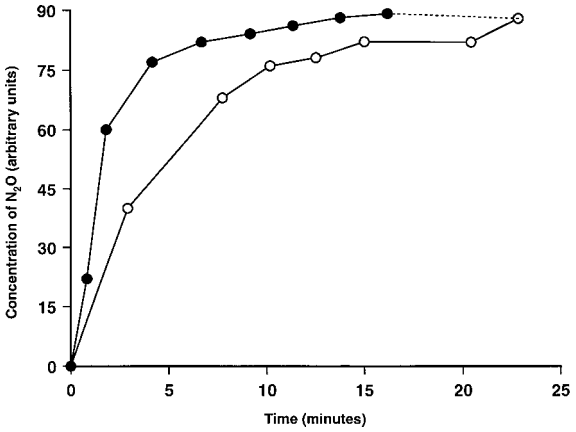

Figure 2 **Data from a determination of CBF: arterial (●) and venous (○) samples**

by repeating these calculations for an increasing sequence of values of $t_{eq} \leqslant 10$. Some investigators (e.g. [14]) state that they have used essentially this approach, while many others are not explicit on this point; it is surmised that something like this technique is widely used. An exception is [15], in which the authors 'fit a curve and integrate to infinity', but details are not given.

The *ad hoc* method has at least four statistical disadvantages. (1) If a single observation from the venous curve is used to estimate $C_v(t_{eq})$, then the error on this one observation becomes an important component of the error in the estimate of CBF. (2) The method ignores the fact that $C_a(t)$ and $C_v(t)$ are most likely to be smooth curves and the observed concentrations will be subject to error. So, for example, it would be quite possible to observe venous N_2O concentrations that exceed earlier arterial concentrations, and for the sequence of observations from the venous or arterial lines not to increase monotonically with time. (3) Unless simultaneous arterial and venous samples are available, some extrapolation is needed to allow calculation of the integrals of the arterial and venous curves over the same interval. (4) The error in the estimate of CBF is not quantified. There are also substantial difficulties in the choice of t_{eq}, but many of these are essentially non-statistical and have received attention elsewhere [3,4,6]. Consideration of these and their statistical implications will be deferred until the next section.

An alternative approach is to try to identify mathematical functions, $f_a(t)$ and $f_v(t)$, defined in terms of a few parameters, that provide good approximations for the curves $C_a(t)$ and $C_v(t)$, and then the CBF can be estimated by substituting $f_a(t)$ and $f_v(t)$ into eqn. (1). There are some general features that any such functions should have, including the following: (a) $f_a(0) = f_v(0) = 0$ (initial N_2O concentration is zero); (b) $f_a(t), f_v(t)$ must increase as t increases, both reaching the same maximum value A; and (c) $0 \leqslant f_v(t) \leqslant f_a(t)$, i.e. the arterial con-

centration is always at least as high as the venous concentration. The choice of the precise form of $f_a(t), f_v(t)$ will be discussed in the next section.

If the observed N_2O concentrations obtained from the arterial line are written as $y_a(1), \ldots, y_a(n_a)$, where n_a samples are taken from the arterial line, at times $t_a(1), \ldots, t_a(n_a)$, then a statistical model for the observed concentrations is $y_a(i) = C_a[t_a(i)] + \varepsilon_a(i); i = 1, \ldots, n_a$; where ε values are errors. A similar model, with subscripts v in place of a, applies to the venous data. The main sources of error are: (i) imprecise measurement of the N_2O concentration, (ii) incomplete mixing of the N_2O in the breathing mixture, and (iii) biological variation in the rate at which the N_2O is absorbed. Each source has different implications for the form of the error structure assumed for the ε values. It may be that source (ii) produces ε values with S.D.s that decrease with time. As successive measurements are from the same patient, source (iii) could induce dependence between the ε values. However, source (i) will probably be the dominant source of error, and a constant S.D. is likely to be appropriate here, so we assume that the ε values are independent with constant S.D. (σ). Moreover, practical constraints mean that both n_a and n_v are likely to be less than 10, so in any case the dataset is too small to allow detailed examination of the more complicated structures mentioned for (ii) and (iii). It follows that the parameters defining $f_a(t), f_v(t)$ can be estimated by ordinary least-squares.

CHOICE AND ASSESSMENT OF MODELS

The conditions (a)–(c) listed above do not characterize particular functions $f_a(t)$ and $f_v(t)$, and a wide choice remains to be made in the light of further practical and theoretical considerations. Notice should be taken of any theoretical guidance in the literature that can inform the choice, but it is also necessary to assess how well any proposed model fits data obtained from the Kety–Schmidt technique. Moreover, as practical constraints on the implementation of the method mean that, generally, n_a and n_v are both $\leqslant 10$, models should not be too elaborate and contain more parameters than can sensibly be estimated from such limited data.

Modelling $C_a(t)$

There appears to be little discussion in the literature of the functional form of the arterial curve. One model proposes a sum of exponentials [6]. As this use of exponential functions is consistent with the general functional forms relevant to the uptake of inert gases [19], we will use:

$$f_a(t) = A(1 - e^{-k_a t}) \quad (2)$$

In a simulation model [6], a second exponential term was envisaged, but we will restrict attention to the form in eqn. (2) provided that it fits our data.

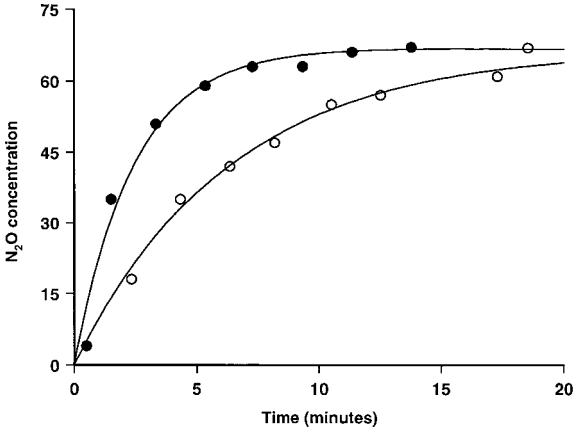

Figure 3 Arterial (●) and venous (○) samples and fitted curves from model I

Modelling $C_v(t)$

Given the choice in eqn. (2), an analogous choice for the venous curve is:

$$f_v(t) = A(1 - e^{-k_v t}) \quad (3)$$

Eqns. (2) and (3) will be referred to as model I.

While model I is our primary model for the N_2O concentration curves, it is certainly not the only model that satisfies conditions (a)–(c). It is therefore useful to have an alternative model to which the fit of model I can be compared and which will also allow some assessment of the dependence of the estimates of CBF on the assumed model. Kety [19] provides an extensive discussion of the application of compartmental modelling of the diffusion of inert gas in tissue. If the brain is taken as a single compartment, then the venous concentration of an inert gas is related to the arterial concentration by:

$$C_v(t) = k_v e^{-k_v t} \int_0^t C_a(u) e^{k_v u} du$$

Substituting from eqn. (2) for $C_a(t)$ into this integral suggests the alternative form:

$$f_v(t) = A\left(1 - \frac{k_v e^{-k_a t} - k_a e^{-k_a t}}{k_v - k_a}\right) \quad (4)$$

Eqns. (2) and (4) will be referred to as model II. Although a single-compartment model for the brain is questionable [6], eqns. (2) and (4) obey conditions (a)–(c), and model II provides a useful comparison for model I.

Choice of t_{eq}

Eqn. (1) is valid only if the cerebral tissue is in diffusion equilibrium with its blood supply by t_{eq}. The adequacy of the value of 10 min chosen by the originators of the

Table I Estimates of CBF and their ratios

	CBF ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)				
Model	Minimum	Lower quartile	Median	Upper quartile	Maximum
I	11.6	31.9	39.9	59.8	179.7
II	12.5	35.0	45.0	68.9	146.6
Ratio I/II	0.62	0.86	0.90	0.93	1.31

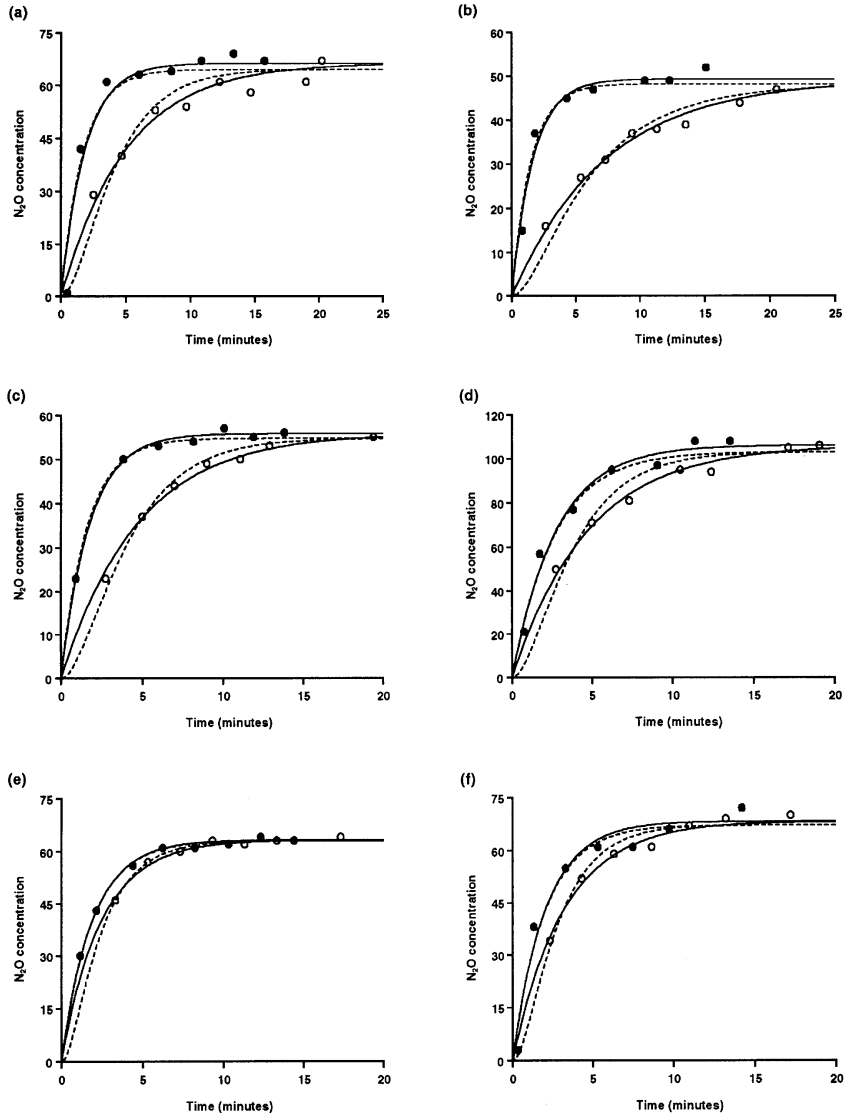

Figure 4 Arterial (●) and venous (○) samples and fitted curves for model I (solid lines) and model II (broken lines)
The CBFs under model I are below the lower quartile (a and b), between the lower and upper quartiles (c and d), and above the upper quartile (e and f).

technique has been questioned [3], and an improved method to calculate CBF, based on 'extrapolation to infinity', or $t_{eq} = \infty$, was proposed. This is clearly not practical with an *ad hoc* method, but need not present difficulties for one based on a statistical model, such as the ones above or that which was implicit in the method suggested by Lassen and Munck [3].

Substituting the formulae for $f_a(t)$ and $f_v(t)$ into eqn. (1) with $t_{eq} = \infty$ gives:

Model I:

$$\text{CBF} = 100 \times \lambda k_a k_v/(k_a - k_v)\ \text{ml} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1} \quad (5\text{I})$$

Model II:

$$\text{CBF} = 100 \times \lambda k_v\ \text{ml} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1} \quad (5\text{II})$$

Table 2 Estimates of CBF and its standard error and residual standard deviation for determinations shown in Figure 4

Determinations were based on model I or model II, as indicated.

	Model I	Model II	Model I	Model II
Panel in Figure 4...	(a)	(a)	(b)	(b)
CBF ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	31.7	37.1	17.6	18.7
S.E. of CBF	6.7	10.2	1.5	2.2
σ	5.11	6.03	2.21	3.09
Panel in Figure 4...	(c)	(c)	(d)	(d)
CBF ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	34.4	36.0	51.2	71.2
S.E. of CBF	1.8	2.7	8.5	22.2
σ	1.04	1.53	3.91	5.93
Panel in Figure 4...	(e)	(e)	(f)	(f)
CBF ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	179.7	137.4	86.5	104.0
S.E. of CBF	30.1	14.8	27.5	35.8
σ	0.92	0.81	3.73	3.97

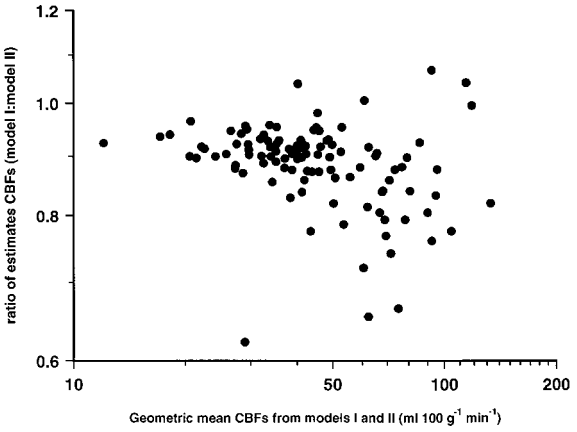

Figure 5 Comparison of CBF determinations from models I and II

It should be emphasized that the device of using $t_{eq} = \infty$ overcomes errors due to an inadequate measurement period only if the functions $f_a(t)$ and $f_v(t)$ adequately represent $C_a(t)$ and $C_v(t)$ not only over the period of data collection but also for all later times. The adequacy over the former period can be checked by assessing how well the models fit the observed data, but there is no easy way to assess the adequacy of the model over the latter period. One approach to the problem [6] is to postulate a plausible underlying model and use this to quantify the size of possible errors, such as those due to a second cerebral compartment. We do not pursue this matter further.

The CBF is estimated by fitting either model I or model II to the data and substituting the estimates obtained for k_a and k_v into eqn. (5I) or (5II). Note that the estimate of CBF should not depend on the amount of tracer used, and this explains why A does not appear in eqns. (5I) and (5II).

Figure 3 shows the curves for model I fitted to some data by least squares: the values obtained for the parameters are 66.82 (A), 0.412 (k_a) and 0.157 (k_v), and therefore the estimate of CBF is $100 \times 0.412 \times 0.157/(0.412 - 0.157) = 25.4$ $ml \cdot 100\ g^{-1} \cdot min^{-1}$ (provided we take the partition coefficient, λ, to be equal to 1).

Data and model assessment

The performance of models I and II can be assessed using data from 109 determinations of CBF obtained from 18 patients in a study of severe head injury in children [20,21], using methods of data collection and measurement of N_2O concentration described previously [18]. We are presently concerned only with the assessment of models I and II for the estimation of CBF, so issues associated with repeated determinations on a patient will be ignored.

The number of arterial samples available for a determination ranged from four to eight, with only 13 CBF estimates being based on fewer than seven samples. The number of venous samples ranged from two to eight, with six CBF estimates having fewer than six samples and 22 having fewer than seven. The distribution of the CBFs is shown in Table 1. Figure 4 shows the fit of models I and II to data from six patients, two randomly chosen from below, two from between and two from above the quartiles of CBF according to model I; the derived CBFs and some related quantities are given in Table 2.

Figure 4 shows that both models offer a good fit to the data. In most cases model I fits better, in terms of both visual inspection and lower residual variation as measured by σ (see Table 2). Inspection of a larger number of plots confirms that both models generally offer good fits to the data, with model I usually being superior. The ratio of the

estimate of σ from model I to that from model II ranges from 0.59 to 1.38 (median 0.85; upper and lower quartiles of 0.74 and 0.93 respectively). Note that σ is measured on the scale of N_2O concentration, so cannot be compared directly between patients.

If fits of models I and II are compared [22], no evidence that model II is superior is found. The statistic C derived in section 4 of [22] was significant at the 5% level for only eight out of 109 cases; given the number of tests performed, this is consistent with model II offering no improvement in fit. A normal plot of the ordered C values confirmed this.

While it appears clear that model I offers a better fit, it is instructive to assess the influence of the choice of model on the CBF values obtained. If the different models give similar CBFs, then the user may have more confidence in the values obtained. If this is the case, the ratios of the CBF value obtained from model I to that obtained from model II should be close to 1; these ratios are plotted in Figure 5 against their geometric mean.

Model II yields CBFs that are on average 10% higher than those obtained from model I, but, apart from this bias, there is good agreement for slower blood flows. Agreement is less good for higher CBFs, but, as will be seen in the next section, the uncertainty in any CBF determination increases as the CBF increases, and the discrepancy shown in Figure 5 probably reveals the difficulty in measuring CBF in these cases rather than any model-dependence in the estimates.

QUANTIFYING THE ERROR IN CBF

If we assume that the errors ε have a normal distribution, then statistical theory allows the standard errors and correlations of the fitted parameters to be estimated. From these, it is possible to infer an approximate value for the standard error of the estimate of CBF; some details are given in the Appendix. If we assume that model I provides a good model for the data, then this standard error will measure the uncertainty in our estimate of CBF due to errors in the measurement of N_2O concentration. The standard errors of the CBFs derived from Figure 4 are given in Table 2.

The accuracy of the various approximations involved was assessed in a small simulation study and was found to be satisfactory, provided that the CBF was not too large. For flows below about 70 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ the standard error can reasonably be used to construct confidence intervals in the usual way. For example, for the case illustrated in Figure 4(c), a 95% confidence interval is $(34.4 \pm 1.96 \times 1.8) = 30.9, 37.9\ ml \cdot 100\ g^{-1} \cdot min^{-1}$.

However, from Table 2 it can be seen that that the standard errors increase as the CBF increases and by considering, for example, Figures 4(b) and 4(e), it is easy to appreciate why this is so. In the former, where the CBF is low, the curves are well separated and errors in the data points will lead to only a small change in the area between them. In the latter, where the CBF is high, errors in the data points could lead to very large proportionate changes in the estimated area, and hence in the estimate of the CBF. Although increasing imprecision with increasing CBF is thus inevitable, the methods of calculating standard errors and confidence intervals are themselves flawed for larger CBFs, making matters worse and leading to absurd results, such as the two determinations in the present study with confidence intervals of (−74.0, 314) from a CBF of 120 and (−61.0, 298) from a CBF of 118 (all with units of $ml \cdot 100\ g^{-1} \cdot min^{-1}$).

An alternative approach is to construct confidence intervals using a method known as profile likelihood, which is outlined briefly in the Appendix. This method gives intervals that cannot be negative and may be skewed (that is, the estimate of CBF is not in the middle of the interval). In extreme examples, such as those at the end of the last paragraph, the curves are so close that coincident curves are compatible with the data and the profile likelihood method will provide only a lower boundary for the CBF, the upper limit being effectively infinite. Although physiologically absurd, this is not statistically unreasonable, given that the venous and arterial curves differ by amounts that are similar to the noise in the data. For the above examples the intervals are therefore (46.0, ∞) and (47.0, ∞) respectively. Fortunately, from a clinical point of view, the precise value of CBF in cases where the CBF is large may not be of crucial importance, but at least the method provides a lower limit.

DISCUSSION

Model I provides a coherent approach to the analysis of data generated by the Kety–Schmidt technique for the estimation of CBF. In addition to overcoming the problems with *ad hoc* methods mentioned above, the error in the estimate and confidence intervals based on this model can be obtained. Part of our assessment of the method rested on data obtained in a study in which N_2O was used as the tracer, so strictly our methods apply only when this tracer is used. However, we see no reason why the model should not provide a good fit when other tracers, such as argon, ^{85}Kr or ^{133}Xe, are used.

Model II does not appear to offer as good a fit to our data as model I. Moreover, the use of bi-exponential functions for $f_a(t)$ and $f_v(t)$ did not improve the fit of the model (results not shown).

As was observed in the section on quantifying error, larger standard errors and wider confidence intervals accompany larger values of CBF. The Kety–Schmidt technique would appear to be well equipped to dis-

tinguish between cerebral ischaemia and hyperaemia. It can provide precise estimates of CBF in ischaemia, but is less able to do so when the CBF is high. However, once it has been established that hyperaemia is present, there is less clinical importance attached to the exact value of the CBF.

Model I can be fitted when as few as four N_2O concentrations have been obtained, although our experience suggests that at least six, and preferably seven or eight, samples from each of the venous and arterial lines are needed for good estimation of CBF. While it is unwise to attempt to estimate CBF from fewer than 12 data points, it may in practice be impossible to collect this many samples, yet an estimate of CBF would be clinically valuable. In these circumstances our method could be applied, but caution is required for at least two reasons: (i) there may be too few points for the data themselves to confirm that the model fits, and (ii) fewer data mean less precise estimation, regardless of the statistical technique used. With regard to the first problem, the analyst must fall back on the general performance of the model, which this study suggests is good. It is important with regard to the second problem to quantify the amount of information that is available by calculating a standard error and confidence interval.

The determinations of N_2O concentration are necessarily made repeatedly on the same individual, and this may lead to the error terms $\varepsilon_a(i)$ and $\varepsilon_v(i)$ being dependent. We have not pursued this aspect of the model for several reasons. The estimates obtained by assuming independence will still be accurate, although in theory it is possible that the estimate of error will not be correct. However, with the number of determinations of the concentration of the marker that it is feasible to make in practice, it would be impossible to estimate the degree of dependence between the errors with worthwhile precision, and any attempt to do is likely to lead to estimates that have a greater mean square error than those presented in this paper.

Programs for a personal computer that fit model I and calculate the quantities described in this paper are available from URL:
http://cs.portlandpress.com/cs/097/cs0970485add.htm

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APPENDIX

If we assume normal errors then, when model I is fitted, we obtain not only estimates of A, k_a and k_v, but also their standard errors and related quantities. We estimate CBF using eqn. (5I) (see the main text) and the δ-method approximates its standard error by:

$$\frac{100\lambda}{(k_a-k_v)^2}\sqrt{\sigma_a{}^2 k_v{}^4+\sigma_v{}^2 k_a{}^4-2\rho\sigma_v\sigma_a k_a{}^2 k_v{}^2} \quad \text{(A 1)}$$

where σ_a and σ_v are, respectively, the standard errors of the estimates of k_a and k_v, and ρ is their correlation.

For high CBFs (in practice higher than about 70λ ml·100 g^{-1}·min^{-1}), when k_a and k_v are of similar size, this approximation breaks down, and a profile likelihood confidence interval for CBF is to be preferred. This is most easily done by working with the parameter $\delta = k_v{}^{-1}-k_a{}^{-1} = 100\lambda/\text{CBF}$; inverting the limits for the confidence interval for δ and multiplying by 100λ gives the interval for CBF. If we write $\hat{\delta}$ for 100λ times the reciprocal of the estimated CBF, the 95 % limits for δ are found by solving $\ell(\delta) = \ell(\hat{\delta})-\frac{1}{2}\times 3.84$ separately for $\delta<\hat{\delta}$ and for $\delta>\hat{\delta}$, where

$$\ell(\delta) = \max_{k_a}\ell[k_a, k_a/(1+\delta k_a)] \quad \text{(A 2)}$$

and

$$\ell(k_a,k_v) = -\tfrac{1}{2}(n_a+n_v)\log\left\{\sum_i y_a{}^2(i) + \sum_i y_v{}^2(i) - \frac{\left[\sum_i y_a(i)\,q_{ai}+\sum_i y_v(i)\,q_{vi}\right]^2}{\sum_i q_{ai}{}^2+\sum_i q_{vi}{}^2}\right\} \quad \text{(A 3)}$$

where $q_{ai} = 1-\exp[-k_a t_a(i)]$ and q_{vi} is defined similarly.

If the CBF is large, then it is possible that $\ell(0) > \ell(\hat{\delta})-\frac{1}{2}\times 3.84$, so no solution for $\delta < \hat{\delta}$ can be found, and in this case we take zero as the lower boundary on the interval for δ, and the upper boundary of the interval for CBF becomes infinite.

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