

Intraoperative ^{133}Xe Cerebral Blood Flow Measurements by Intravenous Versus Intracarotid Methods

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To document the comparability of cerebral blood flow (CBF) values determined by quantification of ^{133}Xe washout after either intravenous or intracarotid administration, 12 patients undergoing elective carotid endarterectomy anesthetized with $\text{N}_2\text{O}/\text{O}_2$ and either isoflurane or halothane were studied. Scintillation counters were placed over the middle cerebral artery territory ipsilateral to the operated carotid artery. CBF was measured by the intravenous method during dissection of the carotid sheath and was calculated as the initial slope index from head washout curves collected for 11 min after injection of 10–20 mCi ^{133}Xe in saline into a large vein. Immediately prior to carotid occlusion, CBF was determined by direct injection of 1 mCi ^{133}Xe in saline into either the internal carotid artery or the common carotid artery with the external carotid artery occluded. For the intracarotid injections, the initial slope was calculated from the 1st min of washout. Data were analyzed by linear regression and analysis of variance. Values are expressed as mean \pm SD. The mean CBF for intravenous and intracarotid methods were both $29 \pm 10 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. The correlation between CBF measured by intravenous and intracarotid methods was excellent and was described by the line $y = x + 0.6$, $r = 0.92$. We conclude that in the flow range studied, the intravenous technique may be applied to measure CBF in physiologically stable situations in which direct intracarotid injection is not feasible. (Key words: Brain; cerebral blood flow. Surgery, cerebrovascular: carotid endarterectomy. Measurement techniques: ^{133}Xe washout.)

SINCE KETY AND SCHMIDT introduced their method of quantitating cerebral blood flow (CBF) in humans,¹ a variety of elegant techniques have been developed. The most recent advances include positron emission tomography (PET)² and single-photon emission computerized tomography (SPECT).³ However, to investigate regional

cerebral tissue perfusion in humans through an intact skull during general anesthesia and surgery, diffusible tracer clearance techniques that directly record washout curves from scintillation detectors placed about the head remain the only practical method. These regional CBF techniques were first developed for direct carotid injection of radiolabeled tracers, such as ^{133}Xe , and extensive experience with this methodology to monitor cerebral hemodynamics intraoperatively has been reported.^{4–6} However, since carotid puncture is not feasible in most clinical settings, a technique was developed^{7–9} and later refined¹⁰ for the use of systemic (either intravenous or inhalation) administration of radiolabeled tracers to measure CBF. These so-called “noninvasive” techniques are standard in awake patients, and there is a good correlation between CBF determined by the inhalation and intracarotid methods.¹¹ However, there remains some debate over the correlation between direct intracarotid and systemic (*i.e.*, intravenous) tracer administration methods during general anesthesia. The objective of this investigation was to document comparability of CBF values obtained from intravenous administration of ^{133}Xe with those obtained by direct intracarotid injection.

Materials and Methods

After institutional approval and informed consent, 12 patients undergoing elective carotid endarterectomy were enrolled in the study. Anesthesia was induced with thiopental ($4 \text{ mg} \cdot \text{kg}^{-1}$), with tracheal intubation facilitated by vecuronium ($0.1 \text{ mg} \cdot \text{kg}^{-1}$) or succinylcholine ($1 \text{ mg} \cdot \text{kg}^{-1}$). Anesthesia was maintained with approximately 1 MAC of either isoflurane or halothane and 1:1 N_2O in O_2 . Monitoring included the use of a radial artery catheter for arterial blood pressure measurement and blood gas analysis, esophageal temperature probe, and a capnograph. Anesthetic agent inspired concentration was kept constant during the course of the study. Blood pressure was maintained at or slightly above the preoperative ward level with an infusion of phenylephrine, if necessary. Ventilation was controlled to maintain PaCO_2 at approximately 30–35 mmHg.

Under the supervision of one of the authors (WLY), seven patients were enrolled at the Neurological Institute of New York and received isoflurane/ N_2O , and under the supervision of another (TS), five patients were enrolled at the Rigshospitalet, Copenhagen and received

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halothane/N₂O. Identical methodology and equipment were used at both institutions.¹² The CBF device, the Novo Cerebrograph 10a* (Novo Diagnostic Systems, Bagsvaerd, Denmark) is a self-contained data collection and analysis system. In the current study, data were collected and averaged from up to five detectors placed over the middle cerebral artery territory ipsilateral to the operative site. During the period of dissection of the carotid artery, CBF was measured by the intravenous ¹³³Xe method as described previously.¹²⁻¹⁴

Approximately 10–20 mCi ¹³³Xe in sterile saline was injected intravenously for the first CBF measurement. A small plastic catheter was present in the endotracheal tube for sampling of end-tidal gas to determine tracer activity. The resultant air activity curve was used to deconvolute the head curves and to correct for recirculation of tracer. Clearance was recorded for 11 min, and CBF values were calculated from the M2 model¹⁵ (see appendix) as the initial slope index¹⁶ (see appendix). After the carotid artery was exposed, and immediately prior to carotid occlusion, remaining activity from the previous intravenous injection was recorded for a period of 5 min. Thereafter, direct intracarotid injection was performed. Depending on the surgical anatomy, approximately 1 mCi ¹³³Xe in saline was injected into either the internal carotid artery or into the common carotid artery with the external carotid artery occluded. Clearance was recorded for at least 1 min, and CBF was calculated as the initial slope, as described by Olesen *et al.*,¹⁷ fitting a monoexponential decay to activity recorded from the scalp for 60 s, beginning 3 s after attaining its peak value (approximately 90%) (see appendix).

The time between CBF measurements was approximately 30 min. Calculations for both intracarotid and intravenous CBF were performed on the same microprocessor. The reported CBF data represent the average of all detectors ipsilateral to the operative site, as previously described.^{12,14} Results were analyzed by linear regression or analysis of variance (ANOVA). In addition, we subjected the data to the analysis described by Bland and Altman.¹⁸ This method is a complement to standard correlation analysis: two different estimates of the same clinical measurement (in this case, CBF) are compared by plotting differences between the two measurements (CBF_{iv} – CBF_{ic}) against the average of the two measurements ((CBF_{iv} + CBF_{ic})/2). This analysis may be useful for examining the influence of the range of observed values on agreement between the two measurement techniques.

Results

The mean ± SD differences in PaCO₂ and mean arterial pressure between intravenous and intracarotid injection were 0.1 ± 2.4 and –3 ± 11 mmHg, respectively. Individual patient data are listed with the means and variances in table 1. A repeated-measures ANOVA, with institution as a between-subject factor and route of administration as a repeated measure, yielded no significant main effects or interactions. The correlation between mean hemispheric CBF values for the two methods was described by the equation $y = x + 0.6$, $r = 0.92$, as shown in figure 1. Using the analysis method of Bland and Altman,¹⁸ we calculated the "limits of agreement," as shown in figure 2. The mean difference in CBF values for the intracarotid

TABLE 1. Comparison of Data from Intracarotid (ic) and Intravenous (iv) CBF Determinations

Subject	Anesthesia	PaCO ₂ (mmHg)		Mean Arterial Pressure (mmHg)		CBF (ml · 100 g ⁻¹ · min ⁻¹)		Difference in CBF* (ml · 100 g ⁻¹ · min ⁻¹)	Average CBF† (ml · 100 g ⁻¹ · min ⁻¹)
		iv	ic	iv	ic	iv	ic		
1	I	41.7	43.1	74	102	37	36	1	37
2	I	38.0	35.8	102	82	24	20	4	22
3	I	41.8	39.0	102	94	36	38	–2	37
4	I	39.3	42.5	102	104	19	23	–4	21
5	I	45.0	47.0	89	87	40	37	3	38
6	I	41.0	40.7	82	86	33	25	8	29
7	I	35.3	36.3	80	91	18	20	–2	19
8	H	28.2	27.5	110	107	16	14	2	15
9	H	35.1	30.7	73	80	42	40	2	41
10	H	29.6	29.6	85	93	32	30	2	31
11	H	22.3	26.7	93	97	14	21	–7	18
12	H	32.0	30.1	73	83	40	43	–3	42
Mean		35.8	35.8	89	92	29	29	0.33	29
SD		6.7	6.8	13	9	10	10	4.06	10

Patients receiving isoflurane (I) and halothane (H) are indicated.

The last two columns of data were used to construct figure 2.

* Difference in CBF = CBF_{iv} – CBF_{ic}; note that mean and SD have not been rounded.

$$\dagger \text{Average CBF} = \frac{\text{CBF}_{iv} + \text{CBF}_{ic}}{2}$$

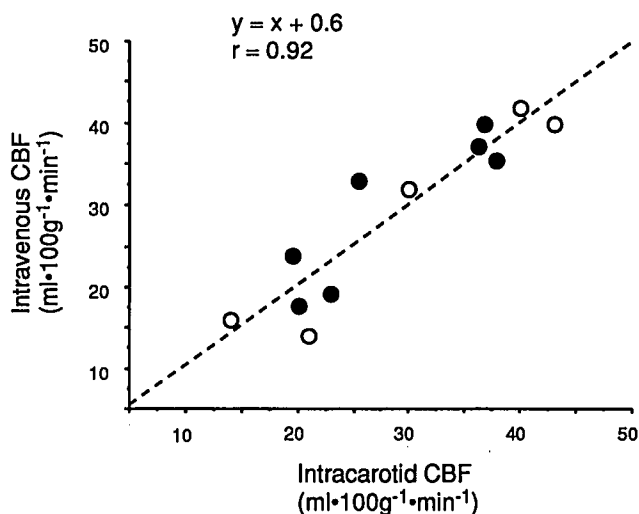


FIG. 1. Correlation of CBF determined by direct carotid injection with CBF determined by intravenous injection during carotid endarterectomy. Open circles represent patients anesthetized with halothane/N₂O, and closed circles represent patients anesthetized with isoflurane/N₂O.

and intravenous method was $0.33 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, with a standard deviation of $4.06 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. Although the sample size was small, the average difference between the intracarotid and intravenous CBF values appeared to be normally distributed. There was no apparent influence of the range of observed values or anesthetic agent on the agreement between the two methods of CBF determination. Similar analyses were performed for five individual detectors in seven patients (total $n = 35$) and resulted in similar findings, as the correlation coefficient between the intracarotid and intravenous results was $r = 0.86$ with a mean difference of $1.00 \pm 4.00 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$.

Discussion

Our study demonstrates that, in humans undergoing carotid endarterectomy during steady-state conditions, there is excellent agreement between the absolute CBF values obtained from intracarotid and intravenous administration of ¹³³Xe. The relationship between CBF values obtained by these two methods during general anesthesia for cerebrovascular surgery has not been previously described.

The noninvasive techniques have been criticized on the grounds that the influence of extracranial contamination and recirculation of tracer on measured CBF cannot be adequately determined.¹⁹ Clearly, direct carotid administration of the tracer is the model that is physiologically "cleaner," since it involves fewer assumptions and obtains data that require less mathematical manipulation. In contrast, the model involving systemic administration of tracer is more complex. When ¹³³Xe is ad-

ministered by inhalation or by intravenous injection, there is a delayed and protracted arterial input function with recirculation, and the tracer is also distributed to extracerebral tissue. Furthermore, calculation of the arterial input function is subject to error in the noninvasive estimate of arterial concentrations (*i.e.*, expired gas concentration).

Previous studies in humans that document the quantitative relationship between CBF values calculated by the noninvasive (*i.e.*, inhalation and intravenous) and direct intracarotid methods are somewhat fragmented. Meric *et al.*^{**} reported that in nine awake subjects the mean (\pm SD) ratio of CBF determined by the intravenous method to that determined by intracarotid injection was 1.06 ± 0.11 . Thomas *et al.* compared intravenous and intracarotid injection of ¹³³Xe in six patients anesthetized with halothane undergoing cerebral angiography.²⁰ They calculated gray matter flow (f_g) for the intravenous method and initial slope for the intracarotid method and found a correlation described by the line $y = x - 2.1$, $r = 0.98$. They reported a mean difference between intracarotid and intravenous methods of $0.42 \pm 4.4 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, which was similar to the results of the current study. Reivich *et al.* studied the correlation between intracarotid injection and the inhalation of ¹³³Xe and reported a similarly strong linear correlation,¹¹ but did not provide individual data points. Morawetz *et al.* studied the contribution to CBF values from extracranial circulation of ¹³³Xe during carotid endarterectomy.⁶ They performed two sets of injections prior to carotid occlusion in ten patients undergoing carotid endarterectomy. First, ¹³³Xe was injected into the common carotid artery with the external carotid *open*, and CBF was calculated. This was followed by ¹³³Xe injection into the common carotid artery with the external carotid *occluded*. Although they did not report the correlation, the means (\pm SD) with the external carotid artery open and occluded were nearly identical (37.9 ± 6.3 vs. $37.5 \pm 5.3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$).

An important caveat in using the intravenous ¹³³Xe CBF method regards the restriction of its application to the measurement of relatively steady-state phenomena. Since the intravenous method classically employs 11 min of data collection, or at best 3 min of data collection,^{21,22} its comparability during conditions of rapidly changing hemodynamic states may not be valid. For example, over the first several minutes immediately after carotid occlusion, *i.e.*, over the course of the measurement, hemispheric CBF may be dynamically changing. This is attributable to a sudden decrease in cerebral perfusion pressure distal to the occlusion and to subsequent peripheral cerebro-

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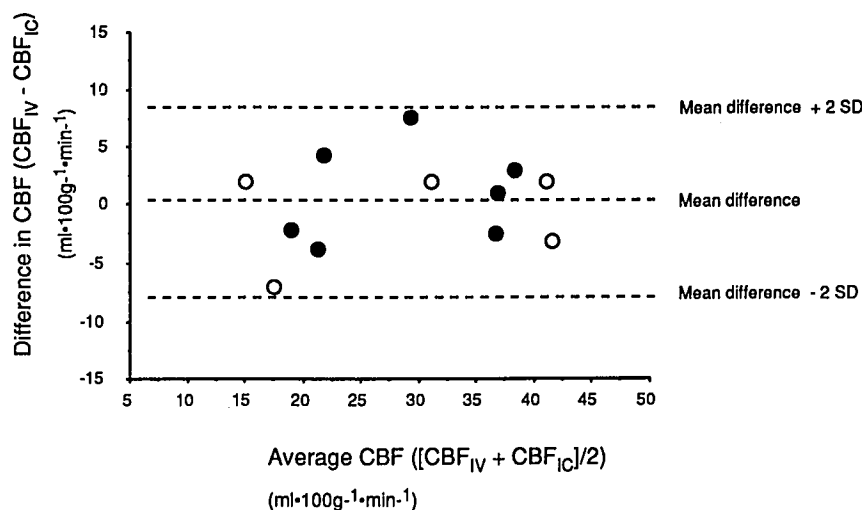


FIG. 2. Comparison of intravenous (CBF_{IV}) and intracarotid (CBF_{IC}) cerebral blood flow values. Individual patient differences between the two measurements ($CBF_{IV} - CBF_{IC}$) are plotted as a function of the average of the two measurements ($(CBF_{IV} + CBF_{IC})/2$). The mean \pm SD of the term $CBF_{IV} - CBF_{IC}$ for the 12 subjects was used to plot the calculated "limits of agreement." See text for further explanation. Open circles represent patients anesthetized with halothane/ N_2O , and closed circles represent patients anesthetized with isoflurane/ N_2O .

vascular dilation and gradual recruitment of collateral flow. By transcranial Doppler examination of the middle cerebral artery during carotid endarterectomy,⁵ this phenomenon is readily apparent after carotid artery occlusion.^{††} Under such conditions, intracarotid administration offers superior sensitivity to rapid changes. During conditions that remain stable over the course of the measurement, however, reproducible quantification of drug,¹³ Pa_{CO_2} ,¹⁴ and surgical treatment^{23,24} effects is possible with the intravenous CBF method.

There are numerous sources of variability in CBF measurements, including both error sources and true biologic variability. In the current study, biologic variability included timing effects, anesthetic differences, and any other effects due to institutional practice. Sources of measurement error included the inherent noise in Poisson-distributed radioactive decay (proportional to count rate) and errors of placement and tracer injection procedures. Since these two sources of variability are both present here, and since the data were collected without any attempt at rigorous control of institutional differences, our findings probably represent the upper limit of variability; the random measurement error in most situations will be smaller. It should be noted, however, that the excellent reliability reported here pertains to mean results of up to five individual regions supplied by the middle cerebral artery. Reliability of individual detectors is likely to be lower, because of a greater possibility of artifacts, and therefore the measurement error is likely to be greater. For mean hemispheric flow, however, since the mean difference was negligible, we conclude that, on the average,

the two methods should yield nearly identical results for a reasonably sized sample. In individual cases, the maximal error suggested by our data for a 95% confidence interval is approximately $\pm 8 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. This range may be influenced by the occurrence of monoexponential solutions in intravenous data (see appendix), for which a failure to define two compartments adds error to the intravenous initial slope index solution.²⁵ In particular, low-flow situations (e.g., under anesthesia) are likely to increase the likelihood of monoexponential solutions and therefore decrease reliability. However, this influence was not apparent in our small sample.

The range of $\pm 8 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ found here may or may not be satisfactory, depending on the nature of the question being asked by a particular study. However, this error is certain to be smaller when the other sources of variability are removed. The reproducibility of perfusion studies by any method is no better than 5–10%,^{12,25} due both to measurement error and to sensitivity to true biologic variation. Reproducibility, or reliability, determines the upper limit of validity. Considering the likely contributions in our material of small sample size and biologic variability, anesthetic agent, and the limits imposed by reproducibility, it is likely that the residual error due to differences between the methods is close to zero, even for individual cases. We conclude that there is good agreement between the two methods in the flow range examined in this study and that the intravenous technique may be applied to measure CBF in physiologically stable situations in which direct intracarotid injection is not feasible.

†† Young WL, Petty GW, unpublished data.

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Appendix

BACKGROUND

The physiologic and mathematical foundation of flow measurement by inert, diffusible tracers such as ¹³³Xe is based upon the Fick principle, which follows from the conservation of mass of an inert substance. Basic derivation from the Fick principle leads to

$$F[\text{ml} \cdot \text{min}^{-1}] = Q_b(t)[\text{mg}] / \int (C_a - C_v)dt[\text{mg} \cdot \text{ml}^{-1} \cdot \text{min}] \quad (1)$$

This equation represents a fundamental relationship used in many perfusion techniques. In this case, CBF is equal to brain residual tracer quantity divided by the integral of the arteriovenous concentration differences.

However, this equation still is insufficient since it requires determination of absolute cerebral quantities, as well as precise determination of both input and output concentration curves. These requirements, feasible in animal studies, are very difficult in humans. Further refinement of this equation consists of the introduction of terms for the blood-brain partition coefficient, which eliminates the need for determination of venous concentrations, and normalization of perfusion by tissue volume to eliminate the requirement for absolute quantity determination.

At equilibrium, venous concentrations (C_v) equal brain tissue concentrations (C_b), other than partition coefficient influence ($\lambda(b/v) = C_b/C_v$). Further, the amount of tracer in brain (Q_b) is equal to its concentration times brain (b) weight ($Q_b = C_b \cdot W_b$). Therefore, substituting in equation 1:

$$F = [C_b(t) \cdot W_b] / \int (C_a - C_b/\lambda)dt \quad (2)$$

Finally, to avoid the need for brain weight determination, we normalize flow to an arbitrary tissue weight of 100 g:

$$f[\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}] = [100 C_b(t)] / \int (C_a - C_b/\lambda)dt \quad (3)$$

This is the fundamental equation for diffusible, inert tracers. Only the arterial input function and tissue residual function need to be measured, and λ is assumed. The solution of this differential equation for a single compartment is the convolution integral:

$$C(t) = \alpha \lambda k e^{-kt} \int C_a(u) e^{k(t-u)} du \quad (4)$$

Where

- $C(t)$ = observed cerebral count rate at time t
- α = physical correction factor from tissue concentration to detector response
- λ = tissue/blood partition coefficient
- k = observed exponential clearance rate
- $C_a(u)$ = arterial input function
- t = time

Note that neither absolute tissue weight nor absolute tracer amounts (nor blood volume) appear anywhere in the equation; this convention is a fundamental advantage of diffusible tracers.

This equation applies to all administration routes, but the computational mechanics are determined by the length of measurement, the number and nature of compartments assumed, and the distinction between an instantaneous input (as in carotid administration) versus protracted and widespread input (as in systemic administration). The primary conceptual difference between systemic and intracarotid administration of ¹³³Xe are summarized in figure 3.

INTRACAROTID CBF CALCULATIONS

With direct intracarotid administration of tracer, the arterial input function is considered instantaneous, and the tracer is largely confined to relevant brain tissue. Therefore, there is no need for estimating arterial concentrations or for deconvolution, and the measurement can be performed in as little as 1 min, if only a slope analysis, rather than a compartmental solution, is required. For the current study, we calculated the initial slope as described by Olesen *et al.*¹⁷ The reader is referred to the extensive discussion in this paper for further details. Initial slope was computed as described above on the clearance curves for a period of 60 s, starting 3 s after peak counts were observed. The value was computed as

$$\text{Initial slope} = \{ \ln [H(t_1)] - \ln [H(t_2)] \} \cdot 82 \quad (5)$$

where t_1 is 3 s after peak counts, and $t_2 = t_1 + 60$ s.

The partition coefficient is assumed to be 0.82, since the initial slope reflects pure gray matter.

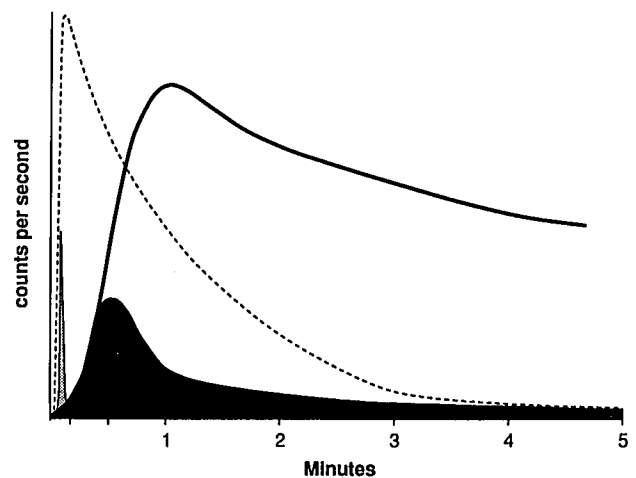


FIG. 3. Idealized input functions and washout curves recorded at the scalp obtained by intracarotid and intravenous injection of ¹³³Xe. The intracarotid head curve (dotted line) is shown with its input function (light-shaded spike), which is considered to be instantaneous and purely cerebral. The intravenous head curve (dark solid line) is accompanied by its input function (as recorded from continuous end-tidal sampling of expired ¹³³Xe), which is shared by extracerebral compartments. Note that the input function (dark-shaded curve underneath) is delayed (and smeared). This results in a slower rise and decay of head curve activity for the intravenous injection. Solutions for calculating CBF rely on deconvolution of the head curve by the delayed input function.

COMPARTMENTAL CBF CALCULATIONS

All models currently used for the calculation of CBF by systemic administration of tracer are based on the bicompartamental model originally proposed by Obrist *et al.*,¹⁰ who employed an end-tidal air curve as an estimation of arterial tracer activity and as the input function in deconvolution of the head curves. Their bicompartamental curve-fitting process involved a "start-fit time." This was introduced to exclude data obtained during the first 60–90 s of data collection, since the model could not account for these data. This model, termed M1, delays curve-fitting until the peak activity of the end-tidal air curve has decreased to 20% of its maximal value. The model calculates the tissue transfer function by solving for four unknowns (two rate constants and two weighting coefficients). A bicompartamental analysis of the data is performed, based on equation 4 above:

$$C(t) = \sum_{i=1}^2 [p_i e^{-k_i t}] \int C_a(u) e^{k_i(t-u)} du \quad (6)$$

Where

$C(t)$ = observed cerebral count rate at time t

$C_a(u)$ = the end-tidal air curve, an estimate of arterial input function

p_i = compartmental size coefficient, which includes α , λ , k , and w , separately determined for the fast-clearing (gray) and slow-clearing (white) component

k_i = clearance constant of each component

To achieve solution of even the earliest parts of the clearance curve, and to eliminate the statistical variability associated with the start-fit time, Prohovnik *et al.*¹⁵ expanded the model to include two additional linear unknowns representing tracer concentrations in air and blood compartments. Therefore, the curve-fitting procedure with this model, termed M2, is performed for the entire head curve to solve the following equation:

$$C(t) = \sum_{i=1}^2 [p_i e^{-k_i t}] \int C_a(u) e^{k_i(t-u)} du + p_3 C_{av}(t) + p_4 C_a(t) \quad (7)$$

Where

- p_3 = weighting coefficient for instantaneously exchanged ^{133}Xe in air spaces
- C_{av} = averaged air curve
- p_4 = weighting coefficient for rapidly exchanged ^{133}Xe in blood vessels
- $C_a(t)$ = end-tidal air curve, but without the lung–brain delay represented by $C_a(u)$

INITIAL SLOPE INDEX CALCULATIONS

For the intravenous data, the initial slope index was calculated from the M2 bicompartamental analysis described above. The ISI was originally proposed by Risberg *et al.*²⁶ as the monoexponential slope of the deconvoluted clearance curve between minutes 2 and 3 of tracer washout. In this study, we used the modification of the initial slope index calculation described by Prohovnik *et al.*,¹⁶ which was developed to reduce noise and increase sensitivity. The initial slope index reflects clearance from both fast and slow compartments, but is dominated by the fast compartment. Because it incorporates both compartments, it is

inherently more stable, although less sensitive, than gray matter flow.^{16,26} On the deconvoluted clearance curve, the initial slope index is defined as the monoexponential slope between 0.5 and 1.5 min. Strictly speaking, the initial slope index is a rate constant, but it can be expressed in milliliters per 100 g per minute, assuming a xenon blood–brain partition coefficient of unity for the perfused tissue, which is a mixture of gray ($\lambda = 0.82$) and white ($\lambda = 1.5$) matter. Thus,

$$\text{Initial slope index} = \{\ln [H(0.5)] - \ln [H(1.5)]\} 100 \quad (8)$$

where $H(t)$ is the deconvoluted clearance curve, or the equivalent of carotid bolus injection of ^{133}Xe into the same tissue volume.

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