Three-Minute Blood Flow Index for Assessment of Cerebrovascular Reserve

William L. Young, MD, Isak Prohovnik, PhD, James W. Correll, MD, and Noeleen Ostapkovich, REEGT

Regional cerebral blood flow studies with xenon-133 are useful in the functional assessment of cerebrovascular diseases. Conventional models for cerebral blood flow calculation employ 11 minutes of data collection. However, in many circumstances it is not possible to maintain steady-state physiologic conditions for 11 minutes. We compared a monocompartmental model that requires only 3 minutes of data collection with the bicompartamental model that requires 11 minutes of data collection. The correlation between the absolute values for global cerebral blood flow (initial slope index, intravenous method) in 72 anesthetized patients was \( r = 0.88 \); for 54 awake patients inhaling xenon-133, the correlation was \( r = 0.77 \). Cerebral blood flow was determined with intravenous xenon-133 at baseline and during a CO\(_2\) challenge in 50 patients during cerebrovascular surgery under general anesthesia. Reactivity to a 10-mm Hg rise in Paco\(_2\) was calculated in absolute terms and as a percentage change from baseline using both the 3-minute and the 11-minute models. The correlation of CO\(_2\) reactivity calculated with the two models was \( r = 0.9 \) for the absolute values and \( r = 0.8 \) for the relative change. Cerebral blood flow calculated with the two models correlated well in both awake and anesthetized patients. In addition, there was a good correlation between CO\(_2\) reactivity calculated with the two models. In situations in which physiologic conditions cannot be held stable for 11 minutes, the 3-minute initial slope index may be used to quantitatively assess cerebrovascular reserve with a CO\(_2\) challenge. 

(Stroke 1990;21:278-282)

Noninvasive techniques to measure cerebral blood flow (CBF) using xenon-133 are useful in the evaluation of ischemic cerebrovascular disease. One of the most important aspects of these techniques is their ability to quantify cerebrovascular reserve by examining the vasodilatory response to either inhaled CO\(_2\) or acetazolamide. The use of vasoactive challenges is important because first, there is a wide range of individual resting CBF values and second, a patient may have a normal resting CBF but a diminished or absent response to a vasodilator. A vasoactive challenge may be particularly useful in evaluating a patient in whom surgical revascularization is contemplated. The traditional method for computing CBF with noninvasive xenon-133 techniques involves collecting data for 11 minutes.\(^1,2\) There are many circumstances in which it may not be possible to obtain 11 minutes of data during assessment of cerebrovascular reserve, such as in uncooperative patients or in patients in whom there is considerable fluctuation in arterial blood pressure or Paco\(_2\). We have reported\(^3\) a good correlation between the initial slope index (ISI) calculated using a modification of the model proposed by Wyper et al\(^4\) (M3) and the 11-minute models described by Obrist et al\(^1\) (M1) and Prohovnik et al\(^2\) (M2). However, the ISI values were calculated in a small group of patients under general anesthesia during carotid endarterectomy, and the influence of the model on the calculation of CO\(_2\) reactivity was not addressed. We evaluate the correlation between CO\(_2\) reactivity when calculated by using both M2 and M3. In addition, we compare ISI calculated using these two models in a group of awake patients (inhalation method) and in a larger group of anesthetized patients (intravenous method).

Subjects and Methods

Data were obtained from a group of 72 anesthetized patients undergoing elective carotid endarter-
ectomy \((n=50)\) or resection of an intracranial arteriovenous malformation \((n=22)\) with intraoperative CBF monitoring. Patients received either isoflurane, halothane, fentanyl, or sufentanil in \(O_2\) and \(N_2O\). Specific anesthetic and surgical aspects of these studies are discussed elsewhere.5,6

At various times during the surgical procedure, CBF was measured by the intravenous xenon-133 technique using a Novo Cerebrograph 10a (Novo Diagnostic Systems, Bagsvaerd, Denmark), a self-contained data collection system with 10 NaI detectors encased in cylindrical lead collimators. For the carotid endarterectomy cases, the middle cerebral artery territory over each hemisphere was covered by five detectors. For the arteriovenous malformation cases, up to two detectors were placed over each hemisphere. Approximately 20 mCi of xenon-133 in sterile saline was injected intravenously for each CBF measurement, resulting in peak count rates of 200–600 cps. A small plastic catheter in the endotracheal tube sampled end-tidal gas for determination of tracer activity. The resultant air activity curve was used in deconvolution of the head curves and in correction for recirculation of the tracer. Xenon-133 clearance was recorded for 11 minutes. For environmental protection, gas exhaled by the patient was routed through an isolation valve into a xenon trap. Data were transferred to a PDP 11/73 computer for visual inspection of the individual detector head curves and their corresponding curve fits.

The CBF response to \(CO_2\) (CO\(_2\) reactivity) was assessed by measuring CBF before (baseline) and after a 10-mm Hg increase in PacO\(_2\) and was calculated as both the absolute change in mean CBF per millimeter of mercury change in PacO\(_2\) and as the percentage change in CBF from baseline per millimeter of mercury change in PacO\(_2\) for both M2 and M3. In a second group of 54 awake, ambulatory patients, CBF was measured with inhaled xenon-133 for a variety of clinical and research purposes using a Novo Cerebrograph 32c (Novo Diagnostic Systems). The protocol and equipment for inhalation studies have been described.7

Two models were used to calculate CBF. The first model is based on the standard bicompartmental model originally described by Obrist et al1 (M1), which uses an 11-minute bicompartmental analysis. An end-tidal air curve is used to reflect arterial tracer activity and as the input function in deconvolution of the head curves. The bicompartmental curve-fitting process utilizes a “start fit time” introduced to exclude artifactual data obtained during the first 60–90 seconds of data collection. M1 delays curve-fitting until the peak activity of the end-tidal air curve has decreased to 20% of its maximal value and calculates the tissue transfer function by solving for four unknowns (two rate constants and two coefficients).

M1 was modified by Risberg et al8 and Prohovnik et al. They introduced a modification of the M1 analysis that included two additional unknowns, one representing an air passage artifact and another representing arterial blood activity, so that data from the early part of the head curve can be retained. Therefore, with this modification (M2) the curve is fit using the entire head curve. The M2 model was used in this study.

Wyper et al4 described a monocompartmental calculation of CBF that required only 4 minutes of data collection (M3). As in M1 and M2, the air curve is used as the input function in deconvolution of the head curves; M3 solves for a rate constant and a coefficient. As originally described, M3 used data collected from minutes 2 through 4 of the head curve. We have modified the algorithm3 to analyze data from minutes 1 through 3 of the head curve.

After calculation of the tissue transfer function using each model, ISI was calculated. ISI as originally described by Risberg et al8 calculated the monoexponential slope of the deconvoluted clearance curve between minutes 2 and 3 of tracer washout. We employed the modified ISI calculation described by Prohovnik et al.9 The ISI that we calculated reflects clearance from both the fast and the slow compartments but is dominated by clearance from the fast compartment. The ISI that we calculated is inherently more stable, although less sensitive, than simple gray matter blood flow \((F_G)\). We constructed deconvoluted clearance curves from either M2 or M3. On these curves ISI is defined as 100 times the monoexponential slope between 0.5 and 1.5 minutes. We express ISI in milliliters per 100 g brain per minute, assuming a xenon blood-brain partition coefficient of 1.0 for the perfused tissue.

A substantial number of clearance curves in the anesthetized group yielded monoexponential solutions even with the bicompartmental model (M2). We defined a monoexponential solution as a gray matter weight \((w_g)\) value of 1. The software employed for compartmental analysis assumes a \(w_g=1.0\) when bicompartmental convergence was not achieved in 30 iterations.

For both the awake and the anesthetized groups, the mean of all the detectors was taken as global CBF. Data were analyzed using linear regression or analysis of variance (ANOVA). The threshold for significance was \(p<0.05\). All results are expressed as mean±SEM.

Results

The 72 anesthetized patients ranged in age from 20 to 88 \((\text{mean}±\text{SEM} 58±2)\) years; there were 34 men and 38 women. Their physiologic data are summarized in Table 1. The regression of ISI calculated using M3 versus that calculated using M2 is shown in Figure 1, using one baseline measurement per patient. When all intraoperative CBF measurements were combined (up to six per patient, \(n=313\)), the correlation was similar \((M3=0.83 \times M2+5.3; r=0.94, p<0.0001)\). Approximately 36% of the solutions for M2 were monoexponential. The correlation between M2 and M3 was slightly better for the 206 M2 solutions that were biexponential \((M3=0.87 \times M2+3.7; r=0.86)\) than for the 117 that were monoexponential \((M3=0.52×\).
TABLE 1. Physiologic Data for 72 Anesthetized and 54 Awake Patients Undergoing Measurement of Cerebral Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>Anesthetized</th>
<th>Awake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial blood pressure (mm Hg)</td>
<td>126±3</td>
<td>131±4</td>
</tr>
<tr>
<td>(\text{Paco}_2) (mm Hg)</td>
<td>30.2±0.6</td>
<td>*</td>
</tr>
<tr>
<td>End-tidal (\text{Paco}_2) (mm Hg)</td>
<td>24.1±0.4</td>
<td>35.6±0.6</td>
</tr>
<tr>
<td>Temperature (° C)</td>
<td>35.3±0.1</td>
<td>†</td>
</tr>
<tr>
<td>ISI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(M2) (ml/100 g/min)</td>
<td>24±1</td>
<td>44±1</td>
</tr>
<tr>
<td>(M3)</td>
<td>23±1</td>
<td>63±2</td>
</tr>
</tbody>
</table>

Data are mean±SEM. ISI, initial slope index (cerebral blood flow).
*Not measured.
†Not measured but clinically afebrile.

M2 and M3 ISI values were classified on the basis of \(w\), and subjected to ANOVA, with \(w\) (biexponential vs. monoexponential solution in the M2 analysis) as the between-group factor and model (M2 vs. M3) as the repeated measure. Among the biexponential solutions, mean M2 and M3 ISI values were 16 and 18 ml/100 g/min, respectively, significantly higher than among the monoexponential solutions, where mean M2 and M3 ISI values were 36 and 35 ml/100 g/min, respectively. However, there was no effect of biexponential vs. monoexponential solution for M2 on the difference between M2 and M3 ISI values.

The 54 awake patients were aged 21–84 (mean±SEM 56±3) years. Their physiologic data are also summarized in Table 1. The correlation between ISI calculated using M2 and M3 is shown in Figure 2, again using one baseline measurement per patient.

![Figure 1](image1.png)  
**FIGURE 1.** Correlation of cerebral blood flow (ISI CBF) calculated using M3 (3-minute model) and that calculated using M2 (11-minute model) in 72 anesthetized patients using the intravenous xenon-133 method.

![Figure 2](image2.png)  
**FIGURE 2.** Correlation of cerebral blood flow (ISI CBF) calculated using M3 (3-minute model) and that calculated using M2 (11-minute model) in 54 awake patients using the inhaled xenon-133 method.

There were no monoexponential solutions in this group.

In 50 of the anesthetized patients, absolute and relative \(\text{CO}_2\) reactivity for a mean±SEM \(\text{Paco}_2\) difference of 10.3±0.4 mm Hg calculated using the two models were nearly identical (Table 2). The correlation of absolute \(\text{CO}_2\) reactivity calculated using M2 and M3 is shown in Figure 3. For relative \(\text{CO}_2\) reactivity, the correlation was M3=1.27×M2-0.8 (\(r=0.8, p<0.0001\)).

**Table 2.** \(\text{CO}_2\) Reactivity in 50 Anesthetized Patients Undergoing Intraoperative Measurement of Cerebral Blood Flow

<table>
<thead>
<tr>
<th>Reactivity</th>
<th>M2 (11 minutes)</th>
<th>M3 (3 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute (ml/100 g/min/mm Hg)</td>
<td>1.8±0.2</td>
<td>2.0±0.2</td>
</tr>
<tr>
<td>Relative (% change/mm Hg)</td>
<td>4.5±0.3</td>
<td>5.0±0.5</td>
</tr>
</tbody>
</table>

Data are mean±SEM. Reactivity is calculated for \(\text{Paco}_2\) change of approximately 10 mm Hg.

**Discussion**

Our study demonstrates that the rapid 3-minute and the traditional 11-minute models for determination of CBF and calculation of cerebrovascular reactivity to \(\text{CO}_2\) using the intravenous xenon-133 technique yield similar results. Measurement of relative reactivity to a \(\text{CO}_2\) challenge or to acetazolamide using xenon-133 CBF techniques is a simple and cost-effective method for assessing cerebrovascular reserve; it compares favorably with the more explicit information obtained using positron emission tomography but is much more widely available. CO2 is a...
potent cerebral vasodilator that can be readily applied as an activation challenge in patients with cerebrovascular disease. A 1-mm Hg change in Paco2 leads to a 2–3% elevation in CBF in unanesthetized normal persons. In conditions where maximal vasodilation has already occurred, such as during extreme systemic hypotension, the cerebrovascular response to CO2 is blunted. With severe occlusive disease, local hypotension distal to the obstructive lesion induces a similar autoregulatory vasodilation, which reduces cerebrovascular reactivity to CO2 and probably reflects a combination of maximal vasodilation and poor collateral pathways. With alleviation of carotid stenosis or by revascularization, an improvement in CO2 reactivity can be demonstrated with xenon-133 CBF studies, and this is believed to reflect improved cerebrovascular reserve.

The previously described correlation between ISI values calculated using M2 and M3 in anesthetized patients using the intravenous xenon-133 technique appears to be equally strong in awake patients inhaling xenon-133. Under lower-flow conditions encountered during general anesthesia as a result of modest hypocapnia and hypothermia, as well as due to anesthetic effects, there is a much closer agreement between ISI values calculated using M2 and M3 than in awake, normocapnic subjects. This is to be expected because M2 reflects blood flow in both the fast- and slow-clearing compartments but M3 considers only tracer washout during the initial portion of the head curve. During anesthesia, the fact that the solutions were monoexponential instead of biexponential did not influence the difference between M2 and M3.

Since activation challenge is one of the greatest strengths of the noninvasive xenon-133 techniques for measuring CBF, it is useful to have a reliable and rapid model that accurately predicts the values obtained using the longer M2 when used to determine cerebrovascular reactivity to a CO2 challenge. In situations in which physiologic conditions cannot be held stable for 11 minutes, we conclude that the 3-minute ISI may be used to assess cerebrovascular reserve using a CO2 challenge.

**Acknowledgments**

The authors wish to thank Angela Wang for expert technical assistance; Joyce Ouchi for assistance in preparation of the manuscript; Darin Gitelman, MD, and Clarence Williams, BA, for computer assistance; T.S.T. Wang, PhD, and Philip O. Alderson, MD, for assistance with radiopharmaceuticals; and Donald O. Quest, MD, and Thomas K. Tatemichi, MD, for helpful suggestions.

**References**


**KEY WORDS** • autoregulation • cerebral blood flow • xenon
Three-minute blood flow index for assessment of cerebrovascular reserve.
W L Young, I Prohovnik, J W Correll and N Ostapkovich

Stroke. 1990;21:278-282
doi: 10.1161/01.STR.21.2.278

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/21/2/278

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/