Concordance of Inhalation rCBFs with Clinical Evidence of Cerebral Ischemia

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SUMMARY Using the 133-Xenon inhalation technique, cerebral blood flow (CBF) and hemispheric blood flow (HBF) were determined serially in 45 patients with acute stroke undergoing pharmacologic trials and in 8 transient ischemic attacks (TIA) scheduled for superficial temporal-middle cerebral artery anastomoses. Both patient populations had lower blood flow than a control group of similar ages. Patients in both populations with lateralized clinical signs demonstrated an asymmetry in HBF which corresponded to their clinical signs. In the stroke population, the trend we expected over time toward development of asymmetrical HBF as the non-infarcted hemisphere recovered from diaschisis did not appear.

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the 133-Xenon intracarotid (IC) injection technique using either stochastic analysis or the widely used initial slope of the clearance curve. In the inhalation technique, the analog of the IC injection technique’s initial slope is the ISI, which is stable and, as we demonstrate, insensitive to the model used in its calculation.

In this study, we use the ISI to characterize rCBF by the inhalation technique in a series of controls with no evident neurological problems, patients who recently had a stroke, and patients with transient ischemic attacks (TIAs) attributed to a lateralized hemodynamic deficit.

To the extent that our measures of CBF and HBF replicate prior findings concerning blood flow in the ischemic brain, the following results ought to occur: (1) overall, the average ISI for patients with cortical and non-cortical stroke in the acute phase (less than or equal to 8 days) should be less than for the controls; and (2) in the first month, an overall plurality of lower ISI’s should be in the infarcted rather than the non-infarcted hemisphere of unilateral cortical patients and 3) initially, the acute cortical stroke population should show no systematic side-to-side differences but within one month lower values should prevail more often on the infarcted than on the non-infarcted side. Finally, for the selected TIA patients we studied, lower ISI should occur more often in the involved than the non-involved hemisphere.

Materials and Methods

Subjects

Informed consent was obtained for all flow studies of subjects in the 3 groups constituted as follows:

1) Controls. Seventeen persons (10 females aged 46 to 80 with a mean of 64 years and 7 males aged 47 to 67 with a mean of 55 years for an overall mean of 59 years) were selected for rCBF measurement at entry and then weekly for the next month. Not all scheduled flow studies were performed, however, and there was a tendency for patients with low initial neurological scores (determined from a standardized form) to have a smaller number of studies because of early death, deteriorating status, or complicating circumstances.

2) TIA Patients. Eight patients with TIA attributable to a unilateral flow deficit (1 female, 7 male; aged 47 to 70, with a mean of 55 years) were selected for rCBF studies. All were without a recent stroke, were scheduled for superficial temporal artery-middle cerebral artery anastomoses, and had angiographic studies supportive of a hemodynamic cause. Each patient had at least one flow study before surgery and one or two additional studies in the 8 weeks following surgery.

Clinical Determinations of Laterality

1) Stroke Patients. A clearly stated decision in the discharge summary was required of the attending neurologist in order to accept that stroke was unilateral and to determine the side of the brain in which the pathology was believed to have occurred. The stroke was considered to be “cortical” unless a diagnosis of a subcortical or brainstem infarct was clearly stated. A stroke was labelled “non-unilateral” when mixed symptoms precluded an unambiguous assignment of laterality.

2) Patients with TIA. Each patient had a unilateral arterial obstruction determined by angiogram and in 6/8 patients a flow deficit on nuclear brain scan. The history and clinical findings were uniformly consistent with this except for one patient with a history of bilateral symptoms.

Laboratory Procedures

The laboratory procedures followed those of the Obrist et al. one minute inhalation technique.
cept that the patient breathed the radioactive gas indicator mixture for 70 to 80 seconds and data were collected for exactly 11 min after the start of indicator administration. Cerebral activity was monitored by 7 pairs of 1/2" X 1/2" NaI (TI) scintillation detectors held in a bilateral parallel array against the subject's head. In a small number of studies 6 or 8 pairs of detectors were used, according to the availability of detectors. Detector thresholds for counting were set at about 20 keV.

The experimental environment was quiet and well-lit. The subject was instructed to lie quietly and relax. During the test the operator spoke to the patient in order to reassure him about the routineness of the procedure.

The 2-compartment, 4-parameter model of Obrist et al. 18 served as the mathematical model of washout in the brain. Automated procedures were used to infer the parameters from a knowledge of the indicator input function and the tissue clearance curve. A combination of the methods of least squares and maximum likelihood was used in an iterative algorithm. 2 If the solution did not converge for the 4-parameter fit, a reduced 3-parameter model was used. 3 This rule was founded on our experience with the 2-compartment, 4-parameter model of Obrist et al. 18 but the fit time in calculating the ISI starts at 2 min and 45 sec, rather than at 2 min after the onset of tracer administration. The extra delay accommodates our administration times, which are typically longer than those of others.

A flow study was considered valid only if there was no major departure from the inhalation laboratory protocol, a peak rate of greater than or equal to 15,000 CPM in a detector was achieved, and at least one set of ISIs from a contralateral probe pair was available. These criteria were met in more than 87% of all 356 flow studies attempted.

Data Analyses

Comparison of Patients with Stroke and Controls. The average of ISI values from all probes in a flow study was used as an index of cerebral blood flow. Similarly, to characterize a patient with several flow studies during a period of time, the grand average of all ISI values in that period was obtained. These values were used to compare patients with acute stroke (less than or equal to 8 days from onset) and the control group in an F-test of the null hypothesis after multiple regression adjustment for effects of age differences between the two groups. 4 No adjustment was made for the control group's negligible differences in ISI values between the sexes.

Concordance with Clinical Laterality in Cortical Stroke Patients. Hemispheric asymmetry for a patient in any period of time was defined as the occurrence of a plurality of probe pairs with the lower ISI value for the left hemisphere (Left Hemisphere Asymmetry-LHA) or for the right hemisphere (RHA). For patients with unilateral cortical stroke, asymmetry was based on the first 31 days after the onset of stroke and this was used to test concordance with clinical laterality. Agreement or disagreement between blood flow asymmetry and clinical laterality for patients with cortical stroke was scored, respectively, as a success (+) or failure (−) in a Wilcoxon non-parametric rank sign test. 5 We ranked the importance of a success or failure according to the strength of the evidence for asymmetry as determined by the product of 2 factors: a) the absolute asymmetry, measured by the absolute value of the difference between the proportion of probe pairs with a lower ISI on the right versus the proportion with a lower value on the left; b) the square root of the number of probe pairs (fig. 2). This weighting of the evidence for asymmetry for a given patient is proportional to the z-value (uncorrected for continuity) which one would obtain if a sign test were applied to the set of probe pairs for that patient. Thus, the ranks for the Wilcoxon test are determined by the order of the strength of the individual patient's evidence for asymmetry as indicated by his sign test z-value.

For patients with TIA, a similar Wilcoxon test of rCBF concordance with clinical laterality was performed. For these patients, LHAs and RHAs were defined in terms of the combined results of all flow studies performed before and after surgery.

Development of Blood Flow Asymmetry Corresponding to the Infarcted Hemisphere of Cortical Stroke Patients. According to a previous study, 6 asymmetry corresponding to the infarcted hemisphere should progress from low to high during the first 31 days after the

![Figure 1. rCBF initial slope indexes calculated from both 3 and 4 parameter estimates for 3,368 washout curves.](http://stroke.ahajournals.org/DownloadedFrom)
onset of cortical stroke. We designed a formal test of that assertion as follows:

1) For each flow, the proportion of probe pairs with lower ISIs in the infarcted hemisphere minus the proportion with lower ISIs in the contralateral hemisphere was determined; this measured ipsilateral asymmetry (IA) on a given day.

2) For each patient with unilateral cortical stroke with 2 or more flows in the first 31 days, the least squares slope of IA as a function of days post stroke was determined (fig. 3); a positive slope was deemed a success (+), since this agrees with the expectation of a progressively greater asymmetry corresponding to the infarcted side; a negative slope was scored a failure (−).

3) A Wilcoxon rank sign test of successes and failures was performed, with ranks based on the strength of evidence for ipsilateral progression; the strength of evidence was determined by the product of a) the absolute value of the slope of IA and b) the square root of the variation in flow study days, i.e., the square root of the sum of squared deviations of flow study days about their mean.

Other Analyses. Other multiple regression or Wilcoxon-type analyses were similar to those in the foregoing descriptions of the principal analyses. For example, concordance for patients with non-cortical, clinically unilateral stroke was examined. Such subsidiary analyses will be mentioned as appropriate in connection with the principal results and discussion.

Results

Valid rCBF’s were obtained from 17 of the 20 controls and from 40 of the 46 patients with stroke. For 37 of the patients with stroke, valid flows included those obtained during the acute post-stroke phase (less than or equal to 8 days). The average time post-stroke for an acute phase blood flow study was 3.3 days. All 8 of the patients with TIA had valid rCBFs.

The most common laboratory occurrence serving to invalidate a probe-pair was radiation due to leakage around the face mask appearing in one of the probes after the start-fit time of the flow study, as evidenced by high-frequency transients in the clearance curve of the head probe (c.f. ref. 36). At times, this leakage was intense enough to invalidate all probes in a flow study. The next most common occurrence invalidating a probe-pair was lack of cerebral uptake sufficient to attain 15,000 CPM in one of the clearance curves at start-fit time, either because lung function was too poor, and/or CBF too low. The most common reason for invalidating an entire study was that none of the probe pairs in the study passed the 15,000 CPM criterion. Other occurrences invalidating an entire study included operator errors in handling magnetic storage media, and system failure due to power outages or computer failure.

Average ISI values in the groups of patients generally agreed with the expected pattern (table 1). After adjustment for minor effects of age differences, the stroke and TIA groups averaged substantially lower than the controls. Patients with non-unilateral stroke seemed to be an exception, but reliability in the slight excess of their mean ISI over that of controls...
TABLE 1. Average ISI Values for Control, Acute Stroke* and TIA Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical Laterality</th>
<th>Number of Patients</th>
<th>Mean Age (years)</th>
<th>Average No. of rCBFs/Patient</th>
<th>Average ISI* Adjusted for Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>None</td>
<td>17</td>
<td>60</td>
<td>1.5</td>
<td>0.3571</td>
</tr>
<tr>
<td>Non-Unilateral Stroke</td>
<td>None</td>
<td>2</td>
<td>58</td>
<td>1.5</td>
<td>0.3750</td>
</tr>
<tr>
<td>Unilateral Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>14</td>
<td>65</td>
<td>2.1</td>
<td>0.2960</td>
<td>0.3131</td>
</tr>
<tr>
<td>Right</td>
<td>12</td>
<td>58</td>
<td>2.6</td>
<td>0.3123</td>
<td>0.3311</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>62</td>
<td>2.4</td>
<td>0.3035</td>
<td>0.3032</td>
</tr>
<tr>
<td>Non-Cortical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>6</td>
<td>68</td>
<td>2.8</td>
<td>0.3074</td>
<td>0.3056</td>
</tr>
<tr>
<td>Right</td>
<td>3</td>
<td>61</td>
<td>2.0</td>
<td>0.3515</td>
<td>0.3514</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>65</td>
<td>2.6</td>
<td>0.3221</td>
<td>0.3209</td>
</tr>
<tr>
<td>TIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>6</td>
<td>57</td>
<td>2.7</td>
<td>0.2886</td>
<td>0.2896</td>
</tr>
<tr>
<td>Right</td>
<td>2</td>
<td>51</td>
<td>3.0</td>
<td>0.3092</td>
<td>0.3119</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>55</td>
<td>2.8</td>
<td>0.2937</td>
<td>0.2951</td>
</tr>
</tbody>
</table>

*The acute phase is defined as the first 8 days following onset of stroke. ISI averages for individual patients (see Materials and Methods) were used to obtain the observed and age-adjusted averages reported in this table.

**Adjusted for age by multiple regression.**

should be discounted because of the small number (N = 2) of patients in this sub-group. The age-adjusted grand average ISI for all 37 patients with acute phase stroke was 0.3114 as compared to 0.3574 for the group of 17 controls. The difference, as tested against the null hypothesis by partial regression analysis with adjustment for age, was highly significant (F = 11.75, with 1 and 58 d.f.; p less than 0.005). This conforms with the expected lower blood flow in the ischemic brain. The age-adjusted average ISI of 0.2951 for patients with TIA was even lower than the average for the patients with acute stroke. Thus, despite the small number of patients with TIA available for study, their average ISI was also significantly lower than controls (p less than 0.05).

The next test centered upon rCBF concordance with clinical laterality. Flow was asymmetrically lower in the hemisphere contralateral to clinical symptoms in 19 cases and the asymmetry was discordant in 5 patients with unilateral cortical stroke who were tested (table 2). This approximately 4 to 1 ratio was accentuated by a consistent tendency for disagreements to occur only when the evidence for asymmetry, as expressed by Wilcoxon ranks, was relatively weak. The resulting ratio of the totals of positive and negative Wilcoxon ranks was 263 to 37, more than 7 to 1 in favor of concordance (p less than 0.001). This significant relationship between rCBF and clinical laterality was evident regardless of whether the left or right hemisphere of the brain had been affected.

While rCBF concordance with clinical laterality in patients with non-cortical stroke was not one of our *a priori* expectations, we nevertheless performed an additional Wilcoxon test based on the data from 9 patients with unilateral non-cortical stroke. Since none of these patients had fewer than 3 rCBF studies (20 or 21 probe pairs), we were fortunate in having such a relatively reliable basis for ranking the evidence for rCBF asymmetry. The ratio of positive to negative rank totals was 41 to 4, over 10 to 1, thus indicating significant concordance in this sub-group of stroke patients (p less than 0.02).

TABLE 2. rCBF Concordance with Clinical Laterality in Cortical Stroke Patients

<table>
<thead>
<tr>
<th>Clinical Laterality</th>
<th>Hemispheric Flow Asymmetry</th>
<th>Number of Patients</th>
<th>Absolute Asymmetry Average</th>
<th>Average Number of Probe Pairs/Patient</th>
<th>Total of Wilcoxon Ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>Agreement (+)</td>
<td>8</td>
<td>.4881</td>
<td>26</td>
<td>+137</td>
</tr>
<tr>
<td></td>
<td>Disagreement (−)</td>
<td>3</td>
<td>.1429</td>
<td>12</td>
<td>−12</td>
</tr>
<tr>
<td>Right</td>
<td>Agreement (+)</td>
<td>11</td>
<td>.2864</td>
<td>29</td>
<td>+126</td>
</tr>
<tr>
<td></td>
<td>Disagreement (−)</td>
<td>2</td>
<td>.3704</td>
<td>17</td>
<td>−25</td>
</tr>
<tr>
<td>Total</td>
<td>Agreement (+)</td>
<td>19</td>
<td>.3714</td>
<td>28</td>
<td>+2631</td>
</tr>
<tr>
<td></td>
<td>Disagreement (−)</td>
<td>5</td>
<td>.2339</td>
<td>14</td>
<td>−37</td>
</tr>
</tbody>
</table>

*Based on all flow studies during the first 31 days after the onset of stroke.

†Excludes three patients with no flow asymmetry, and includes one patient whose first valid flow study time was greater than 8 days post-stroke.

‡Significant concordance; one-tailed p is less than 0.001.
TABLE 3 *rCBF Concordance with Clinical Laterality in TIA Patients*

<table>
<thead>
<tr>
<th>Clinical Laterality</th>
<th>Hemispheric Flow Asymmetry*</th>
<th>Number of Patients</th>
<th>Absolute Symmetry Average*</th>
<th>Average Number of Probe Pairs/ Patient*</th>
<th>Total of Wilcoxon Ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>Agreement (+)</td>
<td>5</td>
<td>.5357</td>
<td>19.2</td>
<td>+ 26</td>
</tr>
<tr>
<td></td>
<td>Disagreement (—)</td>
<td>1</td>
<td>.0769</td>
<td>13.0</td>
<td>— 1</td>
</tr>
<tr>
<td>Right</td>
<td>Agreement (+)</td>
<td>2</td>
<td>.4806</td>
<td>20.5</td>
<td>+ 9</td>
</tr>
<tr>
<td></td>
<td>Disagreement (—)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>Agreement (+)</td>
<td>7</td>
<td>.5208</td>
<td>19.6</td>
<td>+ 35†</td>
</tr>
<tr>
<td></td>
<td>Disagreement (—)</td>
<td>1</td>
<td>.0769</td>
<td>13.0</td>
<td>— 1</td>
</tr>
</tbody>
</table>

*Based on all flow studies before and after surgery.
†Significant concordance; one-tailed p is less than 0.02.

For patients with TIA, the test of concordance in laterality led to the same conclusion as for patients with stroke (table 3). The ratio of agreements to disagreements was 7 to 1. Moreover, the sole disagreement occurred in the case of a patient who exhibited the weakest evidence of asymmetry, i.e., with a Wilcoxon rank of 1. The resulting ratio of 35 to 1 in positive versus negative Wilcoxon rank totals strongly supports the contention that the rCBF is sensitive to hemispheric ischemia even in patients with TIA, who were asymptomatic at the time of the rCBF measurement.

The last principal test considered whether ipsilateral asymmetry typically develops in patients with cortical stroke during the first 31 days after the onset of stroke. There were 23 patients with cortical stroke with the 2 or more flows required in the computation of a least squares slope (table 4). Contrary to expectations, the slope of the relationship between asymmetry and time was predominantly negative by a ratio of 14 to 9. Unlike the previous tests of concordance, scores of one sign were not confined to cases with the weakest evidence. In fact, although in the majority, negative slopes averaged less in absolute value than the positive ones. This led to a ratio of 164 to 112, less than 1.5 to 1, of Wilcoxon rank totals, against the development of ipsilateral asymmetry. Thus, there was no significant agreement of this test with predicted behavior (p greater than 0.70) and it left open the question of whether, and to what extent, the development of ipsilateral asymmetry over time, as measured by the inhalation technique ISI, was characteristic of this disease process.

**Discussion**

The accuracy of the inhalation method, when used for measuring blood flow per unit weight of tissue perfused in the ischemic brain, is largely unknown and for several reasons it cannot be inferred from the success of the method in measuring focal rCBF in normal tissue. In the present study a standardized array of contralateral pairs of probes has produced ISI values which are definitely associated with clinical manifestations of ischemic strokes and transient ischemic attacks.

Some of the factors that might be expected to dilute the precision of the method were partly offset by the pairwise comparison of ISIs for contralateral probes, which especially helps to balance for variations in regional structure and in the perfused volume of tissue substrate viewed. Moreover, by combining the paired contralateral observations for an entire array of probes, statistical precision is gained through sacrificing possible focality of a higher, i.e. more focal, order than hemispheric.

No corrections in the ISI were made for CO₂ reactivity. This is because the CO₂ reactivity of infarcted brains is different from that of controls. A standard correction for changes in hematocrit would be unreliable because the blood:brain partition coefficient for Xenon in infarcted, possibly edematous,

**TABLE 4 Development of Ipsilateral Asymmetry in Cortical Stroke Patients***

<table>
<thead>
<tr>
<th>Clinical Laterality</th>
<th>Ipsilateral Asymmetry Slope</th>
<th>Number of Patients*</th>
<th>Average Absolute Slope (IA units/day)</th>
<th>Average Number Flows/Patient</th>
<th>Total of Wilcoxon Ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>+</td>
<td>4</td>
<td>.1824</td>
<td>3.5</td>
<td>+ 43.5</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>7</td>
<td>.0533</td>
<td>4.0</td>
<td>— 69.0</td>
</tr>
<tr>
<td>Right</td>
<td>+</td>
<td>5</td>
<td>.0763</td>
<td>4.0</td>
<td>+ 68.5</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>7</td>
<td>.0823</td>
<td>4.1</td>
<td>— 95.0</td>
</tr>
<tr>
<td>Total</td>
<td>+</td>
<td>9</td>
<td>.1235</td>
<td>3.8</td>
<td>+ 112.0</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>14</td>
<td>.0678</td>
<td>4.1</td>
<td>— 164.0†</td>
</tr>
</tbody>
</table>

*Includes only cortical stroke patients with greater than or equal to 2 flows during the first 31 days after the onset of stroke. Excludes one patient with slope = 0.
†Not significant; one-tailed p is greater than 0.70.
tissue may vary unpredictably.\textsuperscript{44} While this might account for some differences between patients and controls, it does not affect comparisons of HBF, since the non-infarcted hemisphere serves as the control for the infarcted hemisphere.

Another possibility is that certain probes in the array might yield characteristically low or high counts. This would not necessarily translate into biased ISI values, since the latter is an estimate of a relative slope. But it is conceivable that some probes might yield ISI values which are differentially biased in comparison to other probes. This would be especially evident in repeated testing of individuals with a given array of probes. Such a bias would operate to produce greater concordance with either left or right clinical laterality, depending on the direction of the bias. However, there was no evidence of such a tendency among patients with stroke or TIA in any of our analyses (tables 2, 3, 4). As additional reassurance, we found no suggestion of left or right laterality in the control group.

Clinically, misdiagnoses and errors in assigning laterality may have occurred. Without such precise diagnostic aids as CT scans, an error rate of about 6% in diagnoses of ischemic strokes could have been expected.\textsuperscript{44} Also, while laterality is not likely to be mistaken by an attending neurologist, the possibility of a clinical laterality error cannot be dismissed. It is reasonable to expect that such errors, made without knowledge of the blood flow measurements, would not be associated with ISI laterality and would be positively associated, if at all, with the average level of ISI values. Consequently, the reduction of clinical errors by more precise diagnostic aids would be expected to produce an even stronger association with laterality and an even greater reduction in average levels of ISI values for patients with ischemic stroke and TIA than those which we have reported.

The evidence that the inhalation technique is sensitive to hemispheric differences received additional confirmation from the experience of one of the patients with cortical stroke. This patient was the most discordant cortical case, with unambiguous clinical evidence of a right hemispheric stroke and a clear left hemispheric deficit in ISI values. A brain scan performed 15 days post-stroke showed an area of increased uptake in the left cerebral hemisphere, indicating pathology correlated with blood flow in the month post-stroke but not correlated with the neurological examination.

In light of our consistent finding that the inhalation technique was sensitive to ischemic infarct, it came as a surprise that stroke patients' natural histories showed no consistent trend toward asymmetry as previously reported.\textsuperscript{8} In fact, 14 of the 23 patients demonstrated a trend toward resolution of asymmetrical flow. Conceivably, this unexpected phenomenon could be the result of treatment. However, this possibility is not supported by a preliminary analysis which revealed no difference in laterality for either the first acute flow or the first 31 days of flow for the Pavabid versus placebo groups. Nor is it supported by subsequent analyses in which we found no suggestive differences in the levels of ISI values among the combinations of dextran and Pavabid versus placebo groups.

Large slopes of both signs showed a variability in post-stroke recovery of flow which has not previously been reported. This variability may be meaningless noise, or it may represent a true phenomenon of variability revealed by the inhalation technique's sensitivity to hemispheric differences. A third explanation may be that the hydrogen clearance technique, as described by Meyer et al,\textsuperscript{8} includes appropriately weighted hyperemic tissue compartments in its estimates of HBF while the inhalation technique does not. Clarification of these issues would require more clinical studies of the pathophysiology of acute stroke, with the inhalation technique as a uniquely appropriate tool for repeated rCBF studies of each subject.

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