Improved Method for Noninvasive Measurement of Regional Cerebral Blood Flow by $^{133}$Xenon Inhalation

Part I: Description of Method and Normal Values Obtained in Healthy Volunteers

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SUMMARY A clinical method for noninvasive measurement of regional cerebral blood flow (rCBF) and blood volume (rCBV) is described, based on Obrist's 10 minute, desaturation method after 1 minute inhalation of $^{133}$Xe. Sixteen collimated probes are placed over both hemispheres and brain stem-cerebellar regions. End-tidal $^{18}$Xe curves are used for correction of recirculation. KEV discriminators are set to record gamma and x-ray activity separately. Values are printed out automatically by a computer on a brain map. Extracerebral contamination is reduced by 1) computing curves from gamma activity, 2) applying pressure on the scalp beneath the probes, 3) 1 minute inhalation of $^{3}$Xe and recording desaturation curves for 10 minutes, thereby minimizing slow clearance from extracranial tissues. Normal values for both fast and slow compartments are reproducible and are in good agreement with the carotid injection method. The speech dominant hemisphere has higher flow than the right under conditions described. Posterior portions of the cranium over the cerebellum and brain stem appear to have higher flow gray values than the cerebral cortex. Gray matter flow decreases with advancing age.

NONINVASIVE $^{133}$Xe inhalation for measuring regional cerebral blood flow (rCBF) was first attempted by Mallett and Veall1,2 and later was improved by Obrist and coworkers.3,4 The inhalation method has the following advantages: carotid puncture is unnecessary and no premedication is required. Measurements of rCBF may be made on an outpatient basis. Flow values for both cerebral hemispheres, and probably the brain stem and cerebellum, may be measured simultaneously. Measurements may be repeated several times in the same individual with minimal patient discomfort and risk. Effects on rCBF of different types of activation may be measured such as: hyperventilation, different stages of sleep, visual, auditory, tactile and specific sensory and motor stimulation, including motor and sensory speech, moving a limb, and activation from a relaxed state to arousal.

A major disadvantage of the inhalation method has been contamination of the clearance curves by radioactivity from the scalp and extracranial sources, including the air passages and sinuses. To overcome this difficulty, Obrist et al.3 proposed a 3 compartmental analysis of the curves, in which the first compartment of flow represented the faster clearing cerebral gray matter, the second compartment of flow represented white matter and the third compartment of flow represented the much slower clearance of extracerebral tissues. While 3 compartmental analysis provided reliable measurements of gray matter, white matter and extracerebral tissue flow, the extended time interval of approximately 40 minutes required for curve fitting limited the clinical practicability of this approach.

To render the method more practical, Obrist et al.4 proposed applying 2 compartmental analysis after recording desaturation for only 10 minutes and claimed that only the first compartment would provide meaningful estimates of cerebral blood flow. Experience has shown that fitting the first 10 minutes of the clearance curve after 1 minute of inhalation minimizes the contribution of the extracerebral component of flow because of the long time required for saturation and desaturation of extracerebral tissues.

Although the fast flow compartment, which represents gray matter flow in normal brain, is of major importance, measurement of the second flow component is also of interest. The second compartment represents white matter flow in normals, but in pathological states of the brain, it may indicate changes in flow and weight of both gray and white matter.

It is possible to estimate and correct for extracerebral flow...
by the spectrum subtraction method.\(^5\)\(^-\)\(^7\) Radioactive \(^{133}\)Xe emits both X-radiation (X) at an energy level of 31 KEV and gamma radiation (\(\gamma\)) at 81 KEV. Since the X-radiation by \(^{133}\)Xe is known to have less skull and scalp penetration than \(\gamma\)-radiation, the majority of X-rays counted by external detectors placed over the skull will come from extracranial tissues, while the \(\gamma\) activity, which may be counted simultaneously, will come principally from brain and, to a much lesser extent, from extracerebral tissues. Thus, if both X and \(\gamma\) are recorded simultaneously from each probe, it should be possible to measure predominantly cerebral flow from \(\gamma\) activity, and correct for the extracerebral flow by subtracting the X curves from the \(\gamma\) counts.

Despite these technical problems encountered with the \(^{133}\)Xe inhalation method,\(^8\)\(^-\)\(^9\) several reports have appeared indicating its clinical usefulness.\(^10\)\(^-\)\(^16\)

The purpose of the present communication is to describe a modification of the \(^{133}\)Xe inhalation method for measuring regional cerebral blood flow and blood volume that has proven to be clinically useful. Normal values in 22 volunteers will also be reported.

### Methods

Xenon 133 gas is mixed with room air (5–7 mCi/L) and is inhaled for 1 minute through a close fitting transparent plastic mask. The mask holds and fitted to each patient. This ensures that there is no \(^{133}\)Xe leakage and that end-tidal gas measurements are correct. The \(^{133}\)Xe is delivered by means of the Ventil-Con closed inhalation delivery system. A Xenon-Kow permits storage of the \(^{133}\)Xe gas for 1 hour. It is fitted with horizontally moving low resistance spirometers so that breathing with the face mask in place feels natural. The entire system is shielded and a recirculating pump provides an oxygen concentration which is maintained equivalent to that of the inspired air or to a low or high oxygen mixture as desired. End-tidal Pressures are also monitored on the polygraph by means of a modified plastic nasal mask. The output from each detector is fed in parallel to discriminators adjusted to accept pulses between 67.5–94.5 KEV for \(\gamma\) activity and 23.5–38.5 KEV for X activity. The normalizing factor for each probe is determined in advance by placing a source of \(^{133}\)Xe under each detector, and \(\gamma\) and X count rates for each probe are adjusted so that they are comparable.

Printouts of \(rCBF\) values are thus derived from:

1. \(\gamma\) activity alone (\(\gamma\))
2. \(\gamma\) activity minus the X activity (\(\gamma - X\))
3. \(\gamma\) activity plus X activity (\(\gamma + X\))

It is estimated that scattered radiation from the upper air passages contributes about 6% of the radioactivity recorded from the head and, thereby, distorts the initial phase of the end-tidal curve.\(^4\) This results in overestimation of \(Kt\) or the fast component of flow if the curves are fitted during or immediately following inhalation. Obst et al. estimated that the optimal start-fit-time is when the isotope concentration in the airways has decreased by 10–20% of its maximum value.\(^4\) In the present method curve fitting begins when the end-tidal curve has declined to 20% of its maximal initial value. This usually occurs around 1.6 minutes after inhalation of \(^{133}\)Xe. End-fit-time is taken 11 minutes from the start of the 1 minute period of inhalation, except in patients with markedly reduced values, where desaturation for 14 minutes may be required.

The arterial concentration of \(^{133}\)Xe is estimated from the end-tidal \(^{133}\)Xe activity in the expired air sampled at intervals of 0.6 seconds. This estimate of the arterial concentration is used to correct for the recirculation of \(^{133}\)Xe to the head.

The end-tidal partial pressure of carbon dioxide (\(P_{\text{ECO}_2}\)) is recorded on a Grass 14 channel polygraph by means of a Goddart capnometer attached. The end-tidal \(^{133}\)Xe activity, pulse rate, blood pressure and ECG can be recorded by means of a self-inflating
finger plethysmograph fitted with a microphone to record systolic and diastolic blood pressure and pulse on the polygraph. A throat microphone is available so that the patient or volunteer can communicate when the face mask is in place.

Two compartmental analysis provides flow values and their relative weights for both slow and fast compartments are calculated by means of the basic equation of Obrist et al. with corrections made for the partition coefficient of gray and white matter if the patient's hemoglobin is not 15 gmm%. The computer program and system also provide for measurements of regional cerebral transit time following the intravenous injection of a 2 millicurie saline bolus of technetium (99mTc) into an antecubital vein. This amount is one-fourth the usual dose given for regular 99mTc brain scans. For estimation of regional transit time, the slope of the interval between the maximum and the minimum of the first derivative of the extracranially recorded isotope curves, obtained from each probe, are taken. The slope corrects for recirculation of the isotope. It is assumed that any leakage of tracer into damaged brain within the first transit time will be negligible. The calculation of rCBV is based on formulas derived from theoretical considerations discussed by Fazio et al. and Oldendorf et al. Regional CBV is then automatically calculated and printed out by the computer from the rCBF values obtained from 133Xe inhalation plus the regional transit time, based on the central blood volume principle of Zierler. A correction factor of 0.92 for the ratio of large to small vessel hematocrit is applied as recommended by Eichling et al.

The following CBF measurements are printed out by the computer using the standard formulas developed by Obrist et al. and Risberg et al.

**Flow gray (Fg)** derived from the clearance rate, \( K_1 \), of the first compartment, \( F_g = K_1 \times X_1 \times 100 \) where \( X_1 \) is the partition coefficient for 133Xe in gray matter corrected for the hemoglobin value.

**Flow white (Fw)** or "slow flow" derived from the clearance rate \( K_2 \) of the second compartment, \( F_w = K_2 \times X_2 \times 100 \), where \( X_2 \) is the partition coefficient for 133Xe in white matter corrected for the hemoglobin value.

**Mean flow (MF)** computed from \( 100 \times M \lambda (P_1 + P_2)/(P_1/K_1 + P_2/K_2) \), where \( M \lambda \) is the estimated mean partition coefficient for 133Xe in gray, white and extracerebral tissue and, \( P_1 \) and \( P_2 \) are the weighting factors (coefficients) of the first and second compartment.

**Fractional flow gray (FFg) and fractional flow white (FFw)**. \( FF_g = P_1/(P_1 + P_2) \) and \( FF_w = (1 - FF_g) \), both expressed as percentages.

**Weight gray (Wg) and weight white or "slow compartment weight" (Ww)**. \( W_g = P_1/F_g/(P_1/F_1 + P_2/F_2) \) and \( W_w = 1 - W_g \). These are the relative weights of gray and white matter (or "slow clearing tissue") expressed as percentages.

**CBF(ini)** is the sum of the products of the fractional flow (FFg and FFw) times their clearance rates (K1 and K2) for each of the two compartments i.e., \( 100 \times (FF_g \times K_1 + FF_w \times K_2) \). **ISI1.2** is a modification of the initial slope index of Risberg computed from the tangent of the desaturation curve (corrected for recirculation) at 2.5 minutes. In addition, regional cerebral blood volume (rCBV) is calculated and printed out for each head region examined as already described.

Mean hemispheric values are also calculated for each parameter. The two indices of flow ISI1.2 and CBF(ini) were included for use as an estimate of flow in grossly pathological states, such as cerebral infarction, where separation of short duration high flow gray compartments by the computer may give misleadingly high F1 values and where the partition coefficient is not known.

### Results

**Normal Values**

Values for rCBF at rest were obtained from 15 normal right-handed volunteers (9 males, 6 females) with an age range of 23 to 62 years (mean age 36.3). In addition, rCBF values were measured in 7 additional normal volunteers in quiet darkness and later during multiple psychological activation. Volunteers were a random sample of staff members and their friends known to be in good health and showing normal or superior mental performance, of different ages and habits. All measurements were made in a comfortable, supine position with the eyes open in a lighted room with the ears unplugged and minimal background noise due to the computer and intermittent conversation with the subject. All subjects were normotensive (mean MAP 96 mm Hg) and normocarbic (mean Pco2 34 mm Hg).

**Effect of Spectrum Subtraction on Flow Values**

Mean values of measurements of 14 representative areas from each hemisphere were calculated from \( \gamma + X \) curves, \( \gamma \) curves alone (\( \gamma \)) and \( X \) subtracted \( \gamma \) curves (\( \gamma - X \)) in the 15 normal volunteers and are shown in table 1. The 14 representative areas selected were from frontal, precentral, sylvian opercular, parietal, posterior temporal, inferior temporal, and occipital regions. It will be noted that \( \gamma - X \) gave slightly higher values than those derived from \( \gamma + X \) or from \( \gamma \) curves alone but these differences were generally not statistically significant. These measurements provide an index derived from the formula:

\[
F(\gamma - X) - F(\gamma) \times 100, \\
F(\gamma)
\]

which is the percentage that the blood flow values are attenuated by extracerebral flow. This index can be applied to Fg, Fw or the 2 indices of flow and has considerable usefulness in particular clinical situations where extracranial flow becomes increased, which will be discussed later. It will also be noted that spectrum subtraction produced strikingly small changes in Fw and Wg. It may be noted that the mean values of CBF(ini) correspond closely with Fg values while ISI1.2 values fall between the Fg and MF values, and it is apparent that FF1 values were remarkably constant.

**Cerebral Dominance for Speech**

As shown in table 1, (under the resting conditions cited above during intermittent conversation with the subject) Fw,
Wg, and MF values were significantly higher in the left (speech dominant) hemisphere than those from the right. Among the parameters measured, interhemispheric differences for Fw and MF were statistically significant when calculated from \( \gamma \) curves alone, while Fw, Wg and MF all showed significant increases in the left hemisphere when calculated from the \( \gamma - X \) curves. These differences also were noted when comparing regional measurements of flow values between the 2 hemispheres, which were significant for Fw and Wg in frontal, temporal and occipital regions (figs. 3 and 4).

Patterns of Flow Distribution and Interregional Variability

Table 2 summarizes results of values for mean regional 
Fg, Fw, Wg and MF calculated from the \( \gamma \) and \( \gamma - X \) curves of the 7 regions over each hemisphere as well as for the values calculated from the probes placed over the cerebellar and brain stem regions.

It may be seen that X-subtraction of the curves produced systematic increases in gray matter flow values which were greater in frontal zones (regions 1 and 8) and inferior temporal zones (regions 7 and 14). Only in the right inferior temporal region was the increase in gray matter flow produced by X-subtraction statistically significant (p < 0.05). There was little or no change in white matter flow by X-subtraction. It will also be noticed that flow values believed to come from brain stem and cerebellar gray matter were consistently the highest values for all regions examined and this difference was statistically significant.

In order to define normal patterns of flow distribution throughout each hemisphere, under the particular conditions

### Table 1: Mean rCBF Values in 15 Normal Volunteers (7 Probes Over Each Hemisphere)

<table>
<thead>
<tr>
<th></th>
<th>Fg ml/100g/min</th>
<th>Fw ml/100g/min</th>
<th>Wg %</th>
<th>MF ml/100g/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lt + Rt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Mean Regional rCBF in 15 Normal Volunteers (7 Probes Over Each Hemisphere)

<table>
<thead>
<tr>
<th>Region</th>
<th>Fg ml/100g/min</th>
<th>Fw ml/100g/min</th>
<th>Wg %</th>
<th>MF ml/100g/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M ( \gamma )</td>
<td>M ( \gamma )</td>
<td>M ( \gamma )</td>
<td>M ( \gamma )</td>
</tr>
</tbody>
</table>
of recording described, mean regional values were expressed as a percentage of the total mean values for each hemisphere (figs. 1–4). The standard deviations derived from the 7 regions were pooled and the significance of the difference of the rCBF values from the mean value expressed as 100% was calculated from the γ curves because these values showed the least variability and highest reproducibility, although rCBF calculated from γ − X and γ + X curves showed similar patterns of regional flow.

As seen in figure 1, when flow values over suboccipital portions of the cranium are excluded and regional hemispheric flow values alone considered, gray matter flow for both frontal regions, particularly from the left hemisphere, showed the highest values, but relatively high rCBF values were also seen in the right occipital and inferior-temporal regions. Both parietal regions showed lower rCBF values than the rest of the hemisphere under the recording conditions described. The right parietal rCBF values were significantly reduced below the mean (p < 0.05).

Regional hemispheric patterns for CBF(ini) are illustrated in figure 2. The CBF(ini) pattern showed excellent correlation with the regional values for Fg (r = 0.959, p < 0.01).

Figure 3 illustrates the regional flow pattern for Fw throughout the 2 hemispheres. Fw in both sylvian-opercular and posterior-temporal regions showed a tendency to be relatively highly perfused compared with both frontal regions. The distribution for gray matter weight (Wg) is shown in figure 4. Higher Wg values were found in the sylvian-opercular and posterior-temporal regions of both hemispheres. A trend for lower values for Wg was seen in frontal and precentral regions.

The regional distribution for weighted MF values was higher in the left frontal, sylvian opercular and posterior-temporal regions and in the right occipital region. Both left and right parietal regions showed low values.

As shown in table 2, flow values believed to come from the brain stem and cerebellum had consistently the highest gray matter flow values, higher than any other cerebral areas examined. The relative increase of Fg and MF was statistically significant (p < 0.05).

The interregional coefficient of variation was determined individually in each of the 15 volunteers and is shown in table 3. When γ curves alone were calculated, flow gray showed the highest interregional coefficient of variation (ICV) which averaged 12.0% under the conditions of recording with a standard deviation of 3.7%. Thus, in clinical studies in this laboratory, a coefficient of variation exceeding 12.0 ± 7.4 = 19.4% may be confidently considered abnormal (p < 0.05). These data are also taken to indicate that Fg values 24% above or below the hemispheric mean are significantly altered from the resting conditions described. Likewise, with regard to MF, 17.3% is taken to be the limit of physiological hemispheric variability, under the laboratory conditions described.

Reproducibility of the Method

In order to assess the clinical reliability and reproducibility of the method, measurements were repeated twice in 8 subjects to determine the measurement error as shown in table 4. The measurements were carried out in seriatim, the second measurement being repeated 30 minutes after the first to allow desaturation of 133Xe incurred from the first run. Residual counts from the first run were not subtracted
FIGURE 3. The cross-hatched bars indicate reduction of Fw values below mean hemispheric flow values. The solid black bars indicate increased Fw values above mean hemispheric flow values. The significant difference between homologous areas are calculated from the Fw values cited in table 2. All homologous areas showed significantly increased regional Fw values throughout the left hemisphere compared to the right.

Effect of Normal Advancing Age on rCBF Values

The effect of normal advancing age on rCBF measurements is illustrated in figures 6 and 7. There is a steadily progressive decline of all parameters of flow and gray matter weight with advancing age except for Fw which remained constant. For the entire group of 15 volunteers, including both males and females, the correlation coefficient between Fg and age was $r = 0.59 (p < 0.05)$. The regression line for Fg had a slope of $-0.53$ ml/100 gm brain/min per year. Cerebral vascular resistance (CVR), calculated from the mean arterial blood pressure (MABP) divided by mean flow values, also showed a strong correlation with age (fig. 8). The correlation coefficient was $r = 0.72 (p < 0.05)$ with a steady increase in CVR with advancing age despite the fact that none of the subjects was hypertensive, had any evidence of arteriosclerosis, nor any arteriosclerosis risk factors.

Response of rCBF to Multiple Psychophysiological Activation in Normal Subjects

Serial paired measurements of rCBF were made in 7 additional normotensive right-handed volunteers (age 26 to 63 years) under entirely different laboratory environmental circumstances to study the effect of maximal psychomotor activation by audiovisual and sensory stimulation and speech. The first run was made at rest with the eyes blindfolded and the ears plugged, with only the white noise of the computer as background. The second run was made in the maximal activated state with the blindfold and ear plugs removed, the subjects being asked to calculate and count to themselves, with music playing, the lights turned on and with normal everyday conversation and movement about the laboratory of the attending personnel. For the group of 7 normal volunteers in the quiet dark at rest, the mean left hemisphere flow gray value was 83 ml/100 gm brain/min and mean right hemispheric Fg was 85 ml/100 gm brain/min. During the second activated run, the left hemisphere mean Fg increased significantly by $+10.7\%$ and the right hemisphere mean Fg by $+2.3\%$. Regional increases were even more marked, e.g., the left parietal region increased by $+24\%$, the left temporal region by $+15\%$ and the right frontal by $+15\% (p < 0.01)$. In the normal subjects, the Fg values, believed to come from the cerebellum and brain stem, showed significant increases...
dissociation, probably indicating effects of general
arousal.22

Normal rCBV Values

For the group of 11 normal volunteers (mean age 39.4),
mean rCBV values for the brain as a whole were 3.0 ± 0.9
ml/100 gm brain/minute.

Discussion

Methodological Considerations of the Inhalation System

In the present method, rCBF values computed from γ
alone, or γ - X activity following 133Xe inhalation, were in
good agreement with those obtained from intracarotid injection of 133Xe24-26 or those obtained from 3 compartmental
analysis and desaturation of 133Xe for 40 minutes.3 The good
agreement with the intracarotid injection method achieved
with the present inhalation system is attributed to several
factors. Recirculation27 is corrected for by the use of the end-
tidal 133Xe curve, (which is in equilibrium with arterial 133Xe)
by the use of the computer program proposed by Obrist et
al.3 The brief 10 minute interval used for analysis of the
head curves derived from gamma activity minimizes con-
tamination from the slower clearing components originating
from extracerebral tissues.1 5 6 8 28

Mean values for Fg (78.2 ml/100 gm brain/min) ob-
tained in the present measurements are in good agreement
with those obtained following injection of 133Xe into the in-
ternal carotid artery, although slightly lower values were ob-
tained for Fw and MF (table 1). The present values are dis-
tinctly different from those reported from 2 compartmental
analysis by Veall and Mallett2 (60 ml/100 gm brain/min) and by Obrist et al.3 (50 ml/100 gm brain/min) from longer
clearance curves, although they are in agreement with those
obtained by the spectrum subtraction method.6 29

Contamination of the clearance of cerebral tissue by radioactivity derived from extracranial tissues during exter-
nal counting has been analyzed by another approach. After
isotope was injected into the scalp or the external carotid artery it was shown that the majority of extracerebral con-
tamination had extremely slow clearance and was largely ig-
nored by a 10 minute interval of analysis.28-30

Obrist et al.4 showed by 2 compartmental analysis that F1
(Fg) and F2 (Fw) values analyzed during a 10 minute desaturation interval yielded significantly higher measurements of both by 29% and 60% respectively, compared to those analyzed after desaturation for 41 minutes. Another important factor for minimizing extracranial contamination is the short interval of inhalation of 133Xe, such as the 1 minute interval used here. The shorter the inhalation, the less 133Xe is dispersed to extracranial tissues.4 Earlier in-
vestigators5 9 have used inhalation intervals of 2 to 5
minutes, which permits greater concentration of 133Xe in extracerebral tissues.

Another important consideration in minimizing extrac-
cranial contamination is the setting of the spectrum discrim-
inator. Almost all previous investigators have recorded both gamma and X-ray clearance together. The use of such “wide
window" settings increases the recording of both scattered radiation6 31 and that derived from extracerebral con-
tamination.

According to Potchen,6 the optimal setting of the discrim-
inator is at 75 KEV, although a small percentage of Compton scatter was still recorded. The discriminator set-
ting between 67.5 and 94.5 KEV (gamma range) used in the
present study minimizes extracerebral contamination as shown by spectrum subtraction. The present method also

<table>
<thead>
<tr>
<th>Spectrum used</th>
<th>Fγ</th>
<th>Fw</th>
<th>Wγ</th>
<th>MF</th>
<th>FP1</th>
<th>CBF (ini)</th>
<th>ISHα</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>γ</td>
<td>12.0</td>
<td>3.7</td>
<td>11.0</td>
<td>3.1</td>
<td>7.3</td>
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<td>10.5</td>
</tr>
<tr>
<td>γ - X</td>
<td>16.5</td>
<td>6.0</td>
<td>13.0</td>
<td>3.4</td>
<td>8.3</td>
<td>3.8</td>
<td>13.3</td>
</tr>
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</table>

This table shows the interregional coefficient of variation expressed as percentage of the mean of both hemispheres in normal subjects.

Table 3

<table>
<thead>
<tr>
<th>Run</th>
<th>1st</th>
<th>2nd</th>
<th>2nd - 1st (%)</th>
<th>S.D.</th>
<th>V.C. (%)</th>
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<tbody>
<tr>
<td>Fγ</td>
<td>79.0</td>
<td>77.0</td>
<td>-2.5</td>
<td>5.4</td>
<td>6.9</td>
</tr>
<tr>
<td>Fw</td>
<td>19.3</td>
<td>17.8</td>
<td>-7.8</td>
<td>1.9</td>
<td>10.4</td>
</tr>
<tr>
<td>MF</td>
<td>47.5</td>
<td>44.2</td>
<td>-6.9*</td>
<td>3.2</td>
<td>7.0</td>
</tr>
<tr>
<td>FF1</td>
<td>75.0</td>
<td>76.1</td>
<td>0.3</td>
<td>2.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Wγ</td>
<td>43.8</td>
<td>42.2</td>
<td>-3.7</td>
<td>3.0</td>
<td>6.9</td>
</tr>
<tr>
<td>CBF (ini)</td>
<td>78.2</td>
<td>75.0</td>
<td>-4.1</td>
<td>3.7</td>
<td>4.9</td>
</tr>
<tr>
<td>ISHα</td>
<td>56.7</td>
<td>56.0</td>
<td>-1.3</td>
<td>2.4</td>
<td>4.3</td>
</tr>
</tbody>
</table>

This table shows the reproducibility (measurement error) determined by serial rCBF measurements in 8 normal subjects.

Table 4

Standard deviation (S.D.) obtained from mean total blood flow difference for each patient

S.D. = \sqrt{\frac{1}{n}(1st - 2nd)^2}

*p < 0.05.

Variation coefficient (V.C.) = \frac{S.D.}{(1st + 2nd)/2} \times 100 (%).
limits extracerebral contamination by the use of a helmet, which allows each probe to be placed perpendicularly so as to compress the scalp circulation.

Clinical experience supports the conclusion that rCBF should be computed from gamma rather than X-ray curves since certain patients with high external carotid blood flow following bilateral occlusion of the internal carotid arteries or during cluster headaches and migraine attacks show ex-tracranial flow indices that more than doubled. In such patients spectrum subtraction or X-ray correction is essential. One disadvantage of spectrum subtraction is a reduction in overall count rate which accounts for the larger standard deviation for X-corrected rCBF values as displayed in table 4.

In summary, there are 5 possible explanations for the apparent lack of extracerebral contamination in the present system:

1) Brief inhalation for 1 minute minimizes applied to extracerebral tissues.
2) Two compartmental analysis during the 10 minute desaturation interval minimizes slow clearance derived from extracerebral tissues.
3) Setting the discriminator to maximize γ activity and minimize X-activity and recording X-activity simultaneously provides an index derived from the formula $F_\gamma (\gamma - X) - F_X$ which gives the percentage that flow values are attenuated by extracerebral components.
4) The probes may be adjusted in the ports of the helmet so that perpendicular application with compression of the scalp reduces extracerebral contamination, which appears to be one of the most important factors for minimizing such contamination.
5) The placement of the probes and collimation were...
selected with the aim of reducing contamination from the air passages.

Reproducibility of the System

A time interval of 30 minutes was selected before repeating the inhalation for the second run to test for reproducibility. This time interval may be criticized since it is possible that residual $^{133}$Xe may still be present in the body giving background activity, particularly in the slower clearing tissues of the extracerebral compartment. Assuming this to be so, for reasons already discussed, white matter flow values should be most affected,28 which proved to be the case as shown in table 4, where there was a reduction in the second measurement of Fw and significant reduction of MF between the two runs. Table 4 shows, however, that $\gamma - X$ curve subtraction corrected for the difference in Fw and MF between the two runs. This supports the view that $^{133}$Xe remaining in the extracerebral tissues does become a contaminant of white matter flow but can, in fact, be corrected by X-ray subtraction.

Fg and CBF(ini) also showed some decrease in the second run, suggesting that some physiological “deactivation” may have occurred between the 2 runs as the patient became more relaxed and accustomed to the procedure. This view is supported by the results of carrying out the second run during multiple psychophysiological activation after the first run was made in the resting state since flow values showed a significant increase in the second run.

The inter-test coefficient of variation obtained in the present study for all indices of rCBF calculated from $\gamma$ curves, appears to be in good agreement with those reported for the carotid bolus injection method.29, 30, 32

It is concluded that 30 minutes between measurements allows sufficient time for good reproducibility; however, a longer interval, such as 40 to 45 minutes between the two runs, is probably more desirable to allow optimal clearance of $^{133}$Xe from the slower clearing compartments of the body, although it is also possible to subtract residual activity after shorter intervals.

Regional Patterns of Cerebral Hemispheric Flow and Interregional Variation

It is now generally accepted that rCBF is not evenly distributed throughout the hemispheres during resting conditions but is influenced by various types of brain activity in normal subjects.11, 20, 22 The majority of previous reports have dealt with recording of rCBF after carotid injection of $^{133}$Xe into one hemisphere, usually the left. Both hemispheres were not examined simultaneously. For example, most authors have described higher gray matter flow values in the frontal and precentral regions and lower values in temporal and parieto-occipital regions of the left hemisphere. Ingvar et al.24 utilized the $^{133}$Xe carotid bolus technique in 7 normal volunteers and reported that the temporal region had a significantly lower cortical flow than elsewhere in the hemisphere and suggested that this was due, in part, to recirculation of $^{133}$Xe into the temporal muscle and scalp. On the other hand, Wilkinson et al.25 concluded that low values recorded from the temporal region after carotid injection represented low perfusion of the temporal cortex itself. The relatively high Fg values recorded in the inferior temporal regions after $^{133}$Xe inhalation in the present study can probably be attributed to the influence of deeper structures seen by the probes placed in this location. The relatively high perfusion values for the white matter of the sylvian-opercular and occipital temporal regions confirms previous observations reported by Wilkinson et al.26

In the measurements reported here both hemispheres were recorded simultaneously plus the flow presumed to be from the brain stem and cerebellum. These rCBF values suggest that in normal volunteers the Fg measured over the posterior fossa are consistently higher than cerebral cortical flow values and that there is a relatively higher perfusion of the frontal regions when “brain stem-cerebellar” values are high.

Values for brain tissue flow measured by probes mounted in the helmet over the posterior fossa are believed to be derived from the cerebellum and brain stem for the following reasons:

1) The probes were placed below and behind the left mastoid process beneath the line connecting the internal auditory meatus and the inion and looking slightly upward, which should record the counts derived from the cerebellum and brain stem.

2) Flows recorded from this probe position were highly reproducible. Values believed to be from gray and white matter flow and weight values were reasonable.

3) Studies in normal volunteers, where rCBF was measured at rest in a quiet, darkened room and repeated in the activated state while counting, listening to music and with the lights on, showed increased rCBF values coming from the region of the brain stem and cerebellum.

4) In patients with circulatory disturbances in the vertebral basilar system (vertebro-basilar insufficiency, embolism and migraine) flow values from the posterior fossa have shown changes which appeared consonant with the clinical status.24, 25

These points support the supposition that flow values recorded from the posterior fossa most likely represent flow in the brain stem and cerebellum.

The fact that rCBF values for Fg recorded from brain stem plus cerebellar regions were significantly higher than those recorded from anywhere else in the hemispheres, despite the fact that Fw values were the same, is of interest. The possibility that these high values are artifacts due to recording radioactivity from the nasopharynx is unlikely but cannot be entirely excluded. These observations suggest, however, that it may be possible to measure brain stem and cerebellar blood flow and to relate it to function. The high flow values obtained are consistent with the high capillary density reported for the human cerebellum. (See Letter to the Editor, p. 272.)

According to Paulson et al.,27 when using the intracarotid method, rCBF values exceeding an interregional coefficient of variation of 2 standard deviations from mean hemispheric values for rCBF, may be assumed to be significantly different from each other. In the present study, the interregional coefficient of variation was 19.4% for Fg and 17.3% for MF, which is in agreement with the carotid injection method, where 20% above or below the mean hemispheric values is considered to be significantly different.28
The Effect of Cerebral Dominance on Cerebral Blood Flow

An advantage of \(^{133}\)Xe inhalation method is that it permits measurement of rCBF of both cerebral hemispheres simultaneously. The limited data so far reported in the literature have not revealed any significant differences between the 2 hemispheres in normal volunteers.\(^{12}\) The higher values for MF and Fw in the left hemisphere reported in the present right-handed volunteers is believed to correlate with the fact that, in over 90% of right-handed people, speech and language functions are preponderantly localized to the left cerebral hemisphere. Recent morphological studies of the human brain indicate that the area of the left temporal cortex is larger than that of the right hemisphere.\(^{14}\) Psychophysiological activation in the present study, including counting, talking to the subject, and having him listen to dance music with familiar ballads, resulted in significant increases in rCBF of the left hemisphere.

Normal Aging and rCBF

In 1956 Kety reviewed limited data then available relating to effects of normal aging on CBF and metabolism.\(^{15}\) There was a sharp reduction in average CBF from childhood through adolescence; thereafter, there was a gradual but progressive decline in CBF beginning in the third decade but continuing through middle and old age. This view was contested by Shenkin and associates,\(^{42}\) who reported that normal individuals failed to show any significant reduction of CBF and metabolism with advancing age, unless they suffered from associated hypertension and arteriosclerosis. Noninvasive rCBF measurements are ideal for studying effects of normal aging. The present study demonstrates that gray matter blood flow and weight of gray matter progressively decline with advancing age. These observations correlate well with the progressive loss of cortical neurons that have been reported in normal individuals with advancing age.\(^{43}\)

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Improved Method for Noninvasive Measurement of Regional Cerebral Blood Flow by $^{133}$Xenon Inhalation

Part II: Measurements in Health and Disease

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SUMMARY The current state of the art of noninvasive measurement of regional cerebral blood flow (rCBF) by inhalation of $^{133}$Xe gas is briefly reviewed. Apparatus is now available commercially so that printouts of rCBF values for gray and white matter flow of both cerebral hemispheres, and probably the brain stem and cerebellum, are available within 30 minutes after 1 minute inhalation of 5-6 mCi of the gas mixed in air. The printout is in the form of a brain map which shows normal values. Normal values reported in volunteers are discussed and modifications of rCBF caused by normal physiological function such as sleep, attention, activation, speech, hearing, performance of tasks and the normal aging process are reviewed. Noninvasive rCBF measurements have some practical clinical and investigative applications in the evaluation of pathological states such as cerebrovascular disease, the dementias, migraine, epilepsy, narcolepsy, and head injuries. Despite certain technical limitations of the $^{133}$Xe inhalation method, which are discussed, rCBF measurements have potential for future screening of populations at risk from cerebrovascular disease, early identification of stroke-prone individuals, evaluation of methods of prevention, as well as measurement of the effects of medical and surgical treatment.

Improved Method for Noninvasive Measurement of Regional Cerebral Blood Flow by $^{133}$Xenon Inhalation

FIVE YEARS AGO, at the Eighth Princeton Conference on Cerebral Vascular Diseases, Posner outlined the requirements for an ideal technique for measuring cerebral blood flow in human subjects. These included the following criteria for the ideal technique: 1. noninvasive, 2. measure flow instantaneously, 3. be repeatable, 4. measure total and regional flow, 5. measure substrate metabolism, 6. measure intracranial, extracranial, and venous flow, 7. not require hospitalization, and 8. not entail use of radioactive materials. While some of the requirements given remain to be attained, considerable progress has been made in achieving the remainder. Measurements today can be made in a safe and reliable manner without discomfort. Apparatus is now available commercially which can be used for measurement of mean total as well as regional cerebral blood flow (rCBF) from both hemispheres, and now, probably, the brain stem, the cerebellum and both cerebral hemispheres.

measurements may be made on an in-patient or out-patient basis. The results are available within half an hour; they may be easily repeated and are reproducible so that changes in rCBF may be measured during alterations in physiological or pathological states.

The $^{133}$Xe inhalation method has the advantage of permitting estimation of extracranial as well as intracranial blood flow which is important in disorders such as migraine and occlusive disease of the internal carotid artery, where extracranial, as well as intracranial flow, are likely to be altered.

Methodological Considerations

As an indicator for measuring rCBF, $^{133}$Xe may be administered safely by inhalation of a mixture of 5-7 mCi/liter in air for 1 minute by means of a face mask. $^{133}$Xe as a radioactive indicator has many advantages: it is readily available commercially in the United States; it is relatively safe, easy to store and dispense, and requirements for its radiation safety are well established. It has a half-life of 5.3 days, is chemically inert and the partition coefficients for gray and white matter in normal brain tissues are known. When inhaled it passes rapidly from the lungs as a bolus into the arterial blood and is uniformly distributed via the heart to all parts of the brain. Measurements of regional blood flow may be made which include the brain stem, the diencephalon, the cerebellum and both cerebral hemispheres.

Values for regional blood flow are calculated by 2 compartmental analyses of the curves recorded from the head by
Improved method for noninvasive measurement of regional cerebral blood flow by 133Xenon inhalation. Part I: description of method and normal values obtained in healthy volunteers.
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