Critical Appraisal of Cerebral Blood Flow Measured from Brain Stem and Cerebellar Regions After \(^{133}\)Xe Inhalation in Humans

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SUMMARY Validity of regional cerebral blood flow (rCBF) measurements recorded over the human posterior fossa after \(^{133}\)Xe inhalation was tested. Recording of counts from both brain stem and cerebellum (BSC) was reproducible and contamination by counts derived from surrounding anatomical structures was low and no greater than that found over hemispheres. BSC values were \(F_1 = 99 \pm 19\) ml/100g brain/min, \(F_2 = 17 \pm 4\) in reasonable agreement with data reported from experimental animals. BSC flow values showed significant correlation with the state of awareness as judged by clinical and EEG evaluation with lowest \(F_1\) values in semicoma and step increases in stupor, non-REM sleep, drowsiness, rest, activation, REM sleep and highest values during focal and generalized epileptic seizures.

DEVELOPMENT of the \(^{133}\)Xe inhalation method has made possible reproducible measurements of regional cerebral blood flow (rCBF) of both cerebral hemispheres in humans in a noninvasive manner, with results that compare favorably with the intracarotid injection method. The \(^{133}\)Xe gas is inhaled from a facemask for one minute, rather than injected as a bolus via the carotid artery. After inhalation, the \(^{133}\)Xe enters the circulation through the lung and, after passing through the heart, is distributed in the arterial blood to both the verteobasilar and carotid arterial systems simultaneously, so that the entire brain is perfused with \(^{133}\)Xe.

Theoretically, this should make possible measurements of rCBF in those regions of the brain supplied by the verteobasilar arterial distribution, such as the brain stem, diencephalon and cerebellar regions.

It has been reported that counts recorded from probes placed over the posterior fossa and directed toward the brain stem-cerebellar regions are comparable to those recorded from probes placed over the hemispheres in the distribution of the carotid artery. Unlike the carotid bolus method, they should not be influenced by anomalies of the circle of Willis. The results of \(^{133}\)Xe inhalation measurements of rCBF of the hind-brain have been reported to give values for gray matter that are slightly higher than mean values from the cerebral hemispheres although white matter flow values were the same. These results were in agreement with values reported in man or the primates. Results of measurements of blood flow of the brain stem and cerebellar regions were correlated with the clinical and electroencephalographic assessment of different states of consciousness and brain activity in patients and volunteers.

Methods

One hundred and twenty measurements of rCBF were recorded from probes placed in both lateral suboccipital regions over the posterior fossa and directed toward the brain stem and cerebellar hemispheres in 74 patients and volunteers. Measurements were made after one minute inhalation of a mixture of 5–7 mCi/1 of \(^{133}\)Xe in air delivered by means of a Ventil-Con system. This gave an average peak counting rate of 28,000 cpm for the head curves. The experimental design and the informed consent for these procedures was approved by the institutional review boards for Baylor College of Medicine, University of Texas in Houston, and the Veterans Administration and the Methodist Hospitals.
The recording system consisted of 16 sodium iodide crystal detectors mounted in a lead-lined motorcycle helmet. The use of the helmet assured reproducibility of probe placement, reduced unwanted counts derived from extracephalic portions of the patient's body and from the xenon delivery system. It has also been shown to reduce radiation derived from the scalp circulation by allowing the probes to exert light pressure on the extracranial tissues.

Two types of cylindrical collimators were used: the hemispheric probes were fitted with 26 mm long collimators (19 mm in diameter), while for the probes directed at brain stem and cerebellar areas, 40 mm long collimators (13 mm in diameter) were used in order to reduce the optical circle of resolution for deep structures. Each probe was tuned to record separately both the gamma emission (67.5 to 94.5 KEV) and the characteristic x radiation (23.5 to 38.5 KEV). This allowed estimation of x-rays derived from extracephalic portions of the patient's body and from the xenon delivery system. It has also been shown to reduce radiation derived from the scalp circulation by allowing the probes to exert light pressure on the extracranial tissues.

Computation of rCBF values including correction for recirculation by means of the end-tidal air curve, was performed by a PDP11-05 mini-processor with a program modified after Obrist's "short" 10 minute bicompartamental analysis of the desaturation curves. The computer terminal provided a hard-copy printout of CBF initial (CBF lnl); flow of gray matter (F1; flow of "white" matter (F2); and relative weights of "gray" and "white" matter (W1, W2, respectively). An initial slope index (ISI) was also calculated, similar to the one proposed by Risberg.

Blood pressure, pulse rate, respiratory rate, end-tidal CO2 (Peco2), end-tidal O2 (Peo2), digital temperature, electroencephalogram, facial electromyogram and electrooculogram were recorded concurrently on a polygraph.

Results and Comment

Anatomical and Physical Measurements Testing the Feasibility of Recording Counts Derived from Brain Stem and Cerebellar Structures

Anatomical Measurements

Two probes were placed extracranially in both lateral suboccipital regions and were directed so as to converge toward the cerebellar hemispheres and the brain stem. Each probe was placed at the midpoint of the 2 straight lines connecting the apex of each mastoid process to the occipital tuberosity. The probes were projected on a plan elevated 25° above the orbito-meatal line.

Anatomical measurements were made both from the human skull obtained postmortem and from computer-assisted tomograms of the head made in the same plane of section as the probes. These measurements revealed that the center of the truncated cone of resolution of the probes was directed through the cerebellum at the level of the dentate nucleus and toward the brain stem at the level of the origin of the eighth cranial nerve. Figure 1 illustrates the anatomical relationships drawn from 2 anatomical sections 5 mm above and 5 mm below the center of the cone of resolution.

Physical Measurements of Radioisotope Counts

The corresponding isocount lines, also displayed in figure 1, were drawn from measurements made within a water-filled human skull obtained at postmortem, using a point source of 133Xe and the 2 40 mm collimated probes mounted in the usual position over the posterior fossa. These measurements showed that the cerebellar hemisphere lay between the 100% isocount line, arbitrarily set at the inner table of the occipital bone and the 25% isocount line, while the brain stem lay between the 25% and the 10% lines.

Measurement Error Introduced by Counts Derived from Nasopharynx, Sphenoidal Sinus, Venous Sinuses and Extracranial Tissues

Contamination from Nasopharynx and Sphenoidal Sinus

These 2 structures may be considered to be major sources of potential contamination of the desaturation curves derived from cerebellum and brain stem. As shown in figure 2, the plane of projection of the probes was directed above the nasopharynx and was shielded from it by the intervening presence of the bone of the clivus, which should minimize unwanted counts from the nasopharynx and sphenoid sinus.

The percentage of these unwanted counts, compared to the average counting rates recorded by probes placed over the brain stem-cerebellar area, was estimated in a healthy volunteer, by injecting doses of 20 ml of 5–7 mCi/l of 133Xe by means of a syringe, into the mouth and nasopharynx while the subject was holding his breath for one minute. The counts recorded from the brain stem-cerebellar probes were 4.75% of the normal count rate recorded using standard inhalation of the same concentration of 133Xe over the same interval of time. Over the hemispheres the counts recorded were found to be 4.85% for the mean of all hemispheric probes.

For purposes of comparison, to see what the counting rate and shape of the curve would be, if the probes placed over the suboccipital bone were heavily contaminated by counts derived from the air passages, the counting rate and the shape of the "desaturation" curves were recorded from a probe placed over the ventral part of the larynx with a piece of the human calvarium obtained at necropsy intervening. The probe was directed through the larynx and to the soft tissues of the neck during standard inhalation of 133Xe. This recording obtained in a healthy volunteer is shown in figure 3. The curve recorded over the larynx was found to be comparable in shape to the end-tidal air curve and, unlike the brain stem-cerebellar curve, was almost devoid of any tissue component. In addition, the maximum count rate was found to be 10 times higher despite the intervening piece of calvarium overlying the larynx and standard probes and collimation over the brain stem-cerebellar area.
Confirmation of the low contamination of clearance curves recorded over the posterior fossa from the nasopharynx and sphenoid sinus was obtained by measurements made in 3 otherwise healthy volunteers who had been laryngectomized 2-11 years earlier for carcinoma in the larynx.* For these volunteers there was no communication between the tracheal stoma, low in the neck, and the nasopharynx. The $^{133}$Xe was administered by a small mask or tube fitted at the edges with a tightly fitting inflated rubber cuff, which was compressed against the neck around the stoma and sealed with vaseline. In these patients, as a group, the shape, counting characteristics of the recorded curves and resulting flow and weight values for gray and white matter were similar to those recorded in normal subjects via the nasopharynx by the use of a face mask (differences in Fj compared to 10 normal volunteers = < 3%). Figure 4 (a and b) illustrates results from one of the volunteers. Since there is little or no possibility of nasopharyngeal or sinus contamination in these laryngectomized volunteers, these experiments confirmed that the curves recorded by the brain stem-cerebellar probes were not greatly distorted by counts derived from these structures.

Contamination of Counts from the Scalp and Muscles of the Neck

The percentage of contamination derived from the scalp and neck muscles was measured by the proportion of short penetration x-ray counts, which are principally derived from these structures, compared to the amount of gamma counts derived from both cerebral and extracranial structures and recorded by the same probe. Of a total of 32 measurements, the mean percentage of x-ray counts was 16% for brain stem-cerebellar areas and was 21% for the mean of the hemispheric probes.

In addition, it has been shown previously* that the measured flow values calculated from the gamma activity alone and from the gamma minus-x, which corrects for scalp circulation,16 were not significantly different for both hemispheric and brain stem-cerebellar regions. This provides confirmatory evidence that contamination of counts by extracranial flow is no greater in the brain stem-cerebellar area than over the hemispheres.

Contamination of Counts from the Venous Sinuses

The possible contamination of the clearance curves by counts derived from the venous blood of the torcular and venous sinuses of the posterior fossa was

*Dr. Dan Kelly referred these patients for study from the Institute of Speech and Hearing of the University of Texas in Houston.
SHAPE OF BRAINSTEM-CEREBELLAR CLEARANCE CURVES COMPARED TO END-TIDAL AIR CURVE AND TO END-TIDAL CURVE RECORDED FROM PROBE PLACED PERCUTANEOUSLY OVER VENTRAL LARYNGEAL REGION (35y/o MALE VOLUNTEER STEADY STATE)

Figure 3. $^{133}$Xe inhalation curve artificially created by placing a probe over the larynx separated by a piece of the bony calvarium to show the effect of contamination by the airways (broken line). The counting rate is about ten times higher than in the normal brain stem-cerebellar area (solid line) and the shape of the curve is comparable to that of the end-tidal curve recorded from the facemask (dotted line).

minimized by placing the probes inferior and lateral to the suboccipital region and also by reducing the width of the cone of resolution of the probes by using 40 mm collimators.

The effects of contamination of the curves by counts derived from subtentorial venous blood was investigated by placing one of the probes over the midline directly above and directed toward the sagittal sinus. Resulting curves were then compared to those recorded by the adjacent parasagittal parietal probe (fig. 5). The difference of the 2 curves were not statistically significant ($\Delta$counts = 2%, $\Delta F_1$ = 6.8%), which is most likely due to the fact that cerebral venous blood has comparable clearance curves to cerebral tissue.

Values of Regional Brain Stem Versus Cerebellar Flow Measurements

Two patients have been studied with unilateral or bilateral extensive removal or absence of the cerebellum with normal brain stem function. Patient 1, a 21-year-old female, who had undergone left suboccipital craniectomy 4 years earlier for a large 5 cm acoustic neuroma in the cerebellar-pontine angle, gave us the opportunity to compare regional flow values obtained in the presence of a normal right cerebellar hemisphere with surgical excision of most of the left cerebellar hemisphere at the time of removal of the tumor. Computerized tomograms showed enlargement of the fourth ventricle with cystic atrophy of the left cerebellar hemisphere.

Comparison of Head Curves Recorded Over Brain Stem-Cerebellar Region and End-Tidal Air Curves in a Laryngectomized Volunteer (58 y/o Female) With Those Obtained in a Normal Volunteer (54 y/o Female) After $^{133}$Xe Inhalation

On the side of the excised cerebellum, the counting rate of the desaturation curve was 37% below that of the normal side. The calculated flow values were $F_1$ = 102 ml/100 g/min for the normal side, and $F_2$ = 143 ml/100 g/min for the left side which was considered to be a measurement of almost pure brain stem flow. Patient 2, a 28-year-old female, had a large...
Carbon Dioxide Reactivity in Brain Stem-Cerebellar Area

Regional cerebrovascular reactivity to hyper- and hypocarbia was measured in 13 volunteers after inhalation of 5% CO₂ via the face-mask or during voluntary hyperventilation. Administration of 5% CO₂ in air by inhalation in 8 normal volunteers produced a 25% increase in brain stem-cerebellar F₁ values for a mean change in PecO₂ of 9 mm Hg (39 to 48 mm Hg). Mean hemispheric F₁ increased by 31%. Reduction of PecO₂ by 9 mm (38-27 mm Hg) was carried out in 10 normal volunteers by increasing the volume of respiratory exchange without tachypnea. Relaxed and slow voluntary hyperventilation was carried out in this manner to avoid activation of the brain stem structures by the effect of marked respiratory effort. This produced a 24% reduction in brain stem-cerebellar F₁ values and a 37% reduction in mean hemispheric flow values. Thus, brain stem-cerebellar flow changes seem comparable to mean hemispheric flow changes in vasodilator and vasoconstrictor responses to hypo- and hypercapnia.

Reproducibility of Brain Stem-Cerebellar Blood Flow Measurements

The reproducibility of BSC flow values was calculated in a group of 24 volunteers with 2 consecutive measurements made at intervals of 30 minutes. Percent change for F₁ values from 1st to 2nd measurement was −5.6%. The reliability coefficient for the two measurements was r = 0.76, (p < 0.001), which is comparable to the same calculation made for hemispheric probes in the same group.

Brain Stem and Cerebellar Flow Values Obtained in Animals with Different Techniques

Table 2 compares the brain stem-cerebellar flow values obtained in human subjects with the few available reports of possibly comparable measurements made in lower animals utilizing the autoradiographic technique in the cat and the indicator fractionation method in the gerbil. The mean values for the cat brain stem-cerebellar regions were calculated from the reported values of Landau et al. using the ¹³¹I labelled fluorocarbon autoradiographic technique. While comparison of different lower animals with man has obvious limitations, the mean values were calculated from data published for the reticular formation, cerebellar nuclei, cerebellar cortex and inferior colliculi as 97 ml/100g/min for F₁ and 24 ml/100g/min for F₂ in 10 awake cats. Likewise, the calculated values derived from the data of Reivich et al. using the ¹⁴C-labelled antipyrine autoradiographic technique were 101ml/100g/min for F₁ and 24 ml/100g/min for F₂ in 6 awake cats. Van Uittert and Levy, utilizing the ¹⁴C-butanol fractionation technique, reported total flow values of 93 ml/100g/min for the cerebellum and 114 ml/100g/min for the brain stem in awake gerbils.

Effects of Changes in State of Consciousness and Brain Activity on Brain Stem-Cerebellar Flow

One hundred and twenty measurements were recorded over the brain stem-cerebellar area in 74 patients and volunteers under different levels of consciousness and brain activity and the results are displayed in table 3. For purpose of statistical analysis,
TABLE 2  Comparison Between Brain Stem and Cerebellar Flow Values Measured in Man With $^{133}$ Xe Inhalation, to Cats (Autoradiography), and Gerbils (14c Butanol Indicator-Fractionation) in ml/100g/min

<table>
<thead>
<tr>
<th>Authors</th>
<th>Methods</th>
<th>Species</th>
<th>Anatomical structures</th>
<th>Mean $F_t$</th>
<th>Mean $F_{r}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>$^{133}$Xe inhalation</td>
<td>Man (n = 50)</td>
<td>Cerebellum and brain stem</td>
<td>99</td>
<td>17</td>
</tr>
<tr>
<td>Landau (et al)</td>
<td>Autoradiography</td>
<td>Cats (n = 10)</td>
<td>Brain stem Inf. Colliculli: Reticular f.:</td>
<td>180</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cerebellum Nuclei: Cortex: White m.:</td>
<td>97*</td>
<td>24</td>
</tr>
<tr>
<td>Reivich (et al)</td>
<td>Autoradiography</td>
<td>Cats (n = 6)</td>
<td>Brain stem Inf. Colliculli: Reticular f.:</td>
<td>174</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>14c-Antipyrine</td>
<td></td>
<td>Cerebellum Nuclei: Cortex: White m.:</td>
<td>101*</td>
<td>24</td>
</tr>
<tr>
<td>Van Uitert and Levy</td>
<td>14c-Butanol</td>
<td>Gerbils (n = 10)</td>
<td>Brain stem (total flow):</td>
<td>114</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cerebellum (total flow):</td>
<td>93</td>
<td>NE</td>
</tr>
</tbody>
</table>

NE = Not examined.
*Calculated from published data (7, 8).

the state of awareness and/or brain activity were arbitrarily graded I-X as judged by the clinical and EEG evaluation of the patients or to the standard stages of sleep classified from the literature. Mean arterial blood pressure, respiratory rate and $P_{ECO_2}$ were not markedly different among the different groups. However, $F_t$ values corrected for differences in $P_{ECO_2}$ are also provided for purposes of comparison. The correction factor used was ± 2.5% flow change for each ± 1 mmHg deviation from the normal $P_{ECO_2}$ of 38 mm Hg. Flow values for $F_t$ of the brain stem-cerebellar area, $P_{ECO_2}$ corrected values, differences from normal values expressed in percent and hemispheric mean value for $F_t$ are also in table 3.

All the start fit times (SFT) selected by the computer for computation of flow values (according to Obrist's 20% criterion for determination of SFT) were found to be in the range of 42 to 72 seconds after the peak of the end-tidal air curve, which appeared entirely satisfactory. This is mentioned because rapid

TABLE 3  Relationship of State of Awareness and/or Brain Activity to Brain Stem - Cerebellar (BSC) Mean $F_t$ Values in Patients and Volunteers ($N = 74$)

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Graded state of awareness and/or brain activity</th>
<th>Mean BSC $F_t$ ± 5% (ml/100g/min)</th>
<th>$F_t$ Values corrected to $P_{ECO_2}$ 38 mm Hg (1)</th>
<th>Δ% Compared to normal controls</th>
<th>Mean hemispheric $F_t$ (ml/100g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I Semicoma, massive left cerebral infarction and herniation</td>
<td>44 ± 6</td>
<td>56 ± 10</td>
<td>56 ± 10</td>
<td>90 ± 13</td>
</tr>
<tr>
<td>2</td>
<td>II Stupor, with cerebrovascular diseases</td>
<td>69 ± 4</td>
<td>76 ± 10</td>
<td>76 ± 10</td>
<td>100 ± 13</td>
</tr>
<tr>
<td>7</td>
<td>III Sleep stages I-II, normals with EEG</td>
<td>79 ± 14</td>
<td>79 ± 10</td>
<td>79 ± 10</td>
<td>100 ± 13</td>
</tr>
<tr>
<td>5</td>
<td>IV Drowsy with SAH</td>
<td>95 ± 15</td>
<td>96 ± 10</td>
<td>96 ± 10</td>
<td>100 ± 13</td>
</tr>
<tr>
<td>14</td>
<td>V rest, quiet darkness, ear plugs</td>
<td>98 ± 20</td>
<td>98 ± 10</td>
<td>98 ± 10</td>
<td>100 ± 13</td>
</tr>
<tr>
<td>20</td>
<td>VI Steady state, lights on, no ear plugs</td>
<td>100 ± 23</td>
<td>100 ± 10</td>
<td>100 ± 10</td>
<td>100 ± 13</td>
</tr>
<tr>
<td>14</td>
<td>VII Activation, music, talking, watching</td>
<td>114 ± 18</td>
<td>114 ± 10</td>
<td>114 ± 10</td>
<td>114 ± 10</td>
</tr>
<tr>
<td>2</td>
<td>VII REM-Sleep, narcoleptic with EEG, EOG, EMG</td>
<td>126 ± 5</td>
<td>126 ± 10</td>
<td>126 ± 10</td>
<td>126 ± 10</td>
</tr>
<tr>
<td>8</td>
<td>IX Focal seizures, focal spikes on EEG during rCBF</td>
<td>143 ± 11</td>
<td>143 ± 10</td>
<td>143 ± 10</td>
<td>143 ± 10</td>
</tr>
<tr>
<td>1</td>
<td>X Generalized seizures, generalized spikes on EEG during rCBF</td>
<td>184 ± 18</td>
<td>184 ± 10</td>
<td>184 ± 10</td>
<td>184 ± 10</td>
</tr>
<tr>
<td>74</td>
<td>Correlation of flow values, with grades I-X</td>
<td>$r_t = .72, p &lt; .001$</td>
<td>$r_t = .62, p &lt; .001$</td>
<td>$r_t = .52, p &lt; .001$</td>
<td>$t = 8.88^*$</td>
</tr>
</tbody>
</table>

*Flow values from BSC area result in a significantly higher correlation than mean flow values from hemispheres ($t = 2.49, p < 0.01$; one tailed test) (1) ± 2.5% per mm Hg $P_{ECO_2}$. 
desaturation of $^{133}$Xe end-tidal air curves, such as may be seen in tachypneic patients or during too rapid voluntary hyperventilation, may result in displacement of the SFT too far to the left with overestimation of computed flow values for $F_1$, although ISI$_2$, mean flow and $F_2$ are not affected.

The patients with acute disorders of the level of consciousness (graded I, II and IV) had generalized slowing of the electroencephalogram and had normal arterial filling of the vertebrobasilar system confirmed by diagnostic arteriography made before the rCBF determination. One additional patient, in a chronic apallic state, was recorded 3 weeks after self-administered overdose of opiates with cardio-pulmonary arrest, resuscitation within a few minutes and subsequent anoxic encephalopathy. In this patient, brain stem function was preserved as judged by normal spontaneous respiration and $CO_2$ responsiveness and the relative preservation of brain stem reflexes, with normal chewing, coughing, sucking and corneal reflexes and a decorticate response to pain. BSC flow was found in the low normal range ($F_1 = 92$ ml/100g/min) but mean hemispheric $F_1$ and $W_1$ were reduced (mean hemispheric $F_1 = 63$ ml/100g/min, $W_1 = 34\%$) as might be expected from his decorticate state. Since the brain stem function was considered to be relatively well preserved in this patient and the damage appeared to involve cerebral cortex with extremely low voltage theta activity in the EEG, he was not included with the graded groups.

The two groups of volunteers who were recorded during sleep had simultaneous sleep laboratory EEG recording, which showed typical stage 1 and 2 (graded III) and REM sleep patterns (graded VIII). The volunteers recorded at rest (graded V) were recorded in quiet darkness wearing ear plugs and showed normal alpha activity in the EEG. The volunteers recorded in the steady state (graded VI) are the same as presented in Table III, under normal laboratory conditions with the lights turned on, with and without the improved lead shielding. This group showed predominant beta activity in the EEG with some alpha activity. The activation study (graded VIII) consisted of standard counting, brief conversation, listening to music and watching activity in the laboratory. This group showed suppression of alpha activity with diffuse low voltage beta activity.

Eight patients with seizures, who showed focal spike discharges during the CBF measurements, were classified as grade IX. Six of them had psychomotor seizures, one had absence attacks and the other had focal and generalized seizures by history. The single patient recorded during frequent brief generalized myoclonic seizures (graded X) had Creutzfeldt-Jakob disease confirmed by cortical biopsy. In this patient the EEG was also recorded concurrently and showed generalized bursts of spike activity during the seizures. Based on the graded classification system, brain stem $F_1$ flow values are significantly related to state of awareness and/or brain activity ($r_a = 0.72, t = 8.88$, $p < 0.001$). Comparable results were found with $P_{ECO_2}$ corrected values ($r_a = 0.62, t = 6.17$, $p < 0.001$). Although hemispheric flow gray values are similarly related ($r_a = 0.52, t = 5.15$, $p < 0.001$), comparison of the 2 relationships suggests that the flow values for the brain stem regions are significantly more indicative of the state of awareness and/or behavioral activity than the mean hemispheric values ($t = 2.49, p < 0.01$, one tailed test).

**Discussion**

Theoretical and practical aspects of recording counts derived from the brain stem and from the cerebellar hemispheres have been presented and reviewed. There appears to be little doubt that counts derived from the cerebellar hemispheres are easily recorded by probes placed over the suboccipital region: however, the recording of sufficient counts derived from the brain stem might be questioned. The brain stem was found to lie between 40 and 70 mm from the tip of the suboccipital probe. At this distance there may be considerable loss of counts due to tissue absorption of gamma rays. The half tissue absorption for gamma rays, generated from $^{133}$Xe, has been measured to be about 40 mm. The isocount lines obtained in water confirm this phenomenon and show that between 25 to 10% of the gamma rays derived from the brain stem reach the crystal of the probe.

However, there is a progressive increase in the volume of the cone of resolution obtained with a cylindrical collimator with each progressive increase in depth, so that the loss of counts due to the inverse square law is compensated for by these added gamma counts, although lower energy activity (such as x-rays) will be absorbed to a greater extent. For the brain stem, this compensation is probably not complete, since the brain stem does not fill the entire volume of the cone of resolution. However, due to the "look-through" phenomenon the high flows derived from the gray matter of brain-stem, such as the inferior colliculus, tend to overshadow the low flow values of white matter origin. Taking into account these factors, the ratio of the counts reaching the probe is estimated by geometric reconstruction to be between 1:1 and 1:2 for the brain stem to the cerebellum, if the brain stem is considered as a cylinder and the field of resolution of the collimator as a truncated cone. The loss of spatial resolution with depth, therefore, makes it advisable to consider the regional flow values to be derived from 2 tissue compartments: a rapidly clearing tissue ($F_1$) which includes the cerebellar cortex and nuclei, the brain stem reticular formation and the brain stem nuclei; and a slower clearing tissue ($F_2$) composed mainly of white matter of both brain stem and cerebellum.

An important factor to be considered is the potential contamination of curves recorded from brain stem and cerebellum by counts derived from non-brain tissues and airways. To evaluate this question of nasopharyngeal and air sinus contamination of counts, ideal studies were made possible by three laryngectomized volunteers in whom nasopharyngeal contamination may be excluded.
APPRAISAL OF INHALATION METHOD/7uge et al.

Three cases demonstrated that in practice, nasopharyngeal contamination of counts derived from venous blood appears to be of little importance as judged by the probe over the sagittal sinus.

As judged by the percentage of x-ray to gamma counts, there is less extracranial tissue contamination recorded from the suboccipital probes than from standard hemispheric probe placement. It appears probable that an important factor responsible for this is that the two posteriorly placed probes exert optimum pressure on the upper neck and scalp tissues in the recumbent position adopted for these measurements. An additional consideration is that low flow values in the range of $6.7 \pm 1$ and $14.1 \pm 4$ ml/100g/min have been reported for the cranial muscles of anesthetized dogs by the use of the microspheres technique.\(^{19}\) Such low flows should not introduce many counts derived from the extracranial component of the desaturation curves and certainly should not influence the fast component of these curves. From these considerations, it is concluded that contamination of the counting rates derived from the brain stem-cerebellar tissues by counts derived from nasopharyngeal air and from the venous sinuses and circulation of the scalp and neck muscles does not significantly distort the brain stem-cerebellar values of flow and is no greater than the contamination that occurs when the probes are placed in the conventional areas overlying both hemispheres.

There is, nevertheless, a close temporal correspondence of portions of the saturation and early desaturation brainstem-cerebellar curves, which begin to undergo a precipitous decline at the same time as the air curve, so that the 2 are overlapping for a few seconds after the inhalation stops. Since the appearance of this "peak" cannot be attributed to the radioactivity from the air passages, as shown by laryngectomized patients, it is considered most likely to be due to the early passage of isotope through the basilar artery and its rich superficial branches overlying the brain stem and cerebellum. Because of the start fit time beginning after 80% desaturation of the air curve, distortion of the initial part of the desaturation curve has been shown to be excluded from the analysis,\(^{28, 31}\) so that overestimation of flow due to the basilar arterial "spike" is unlikely.

The reactivity of brain stem-cerebellar flow values to hyper- and hypocarbia was found to be comparable to the hemispheric flow changes, which may be taken as additional evidence that cerebral gray and white matter are the main constituents of the tissue flows measured in the brain stem-cerebellar area, since the blood flow of extracranial structures, such as the scalp and muscles of the neck, should show little or no reaction to changes in $\text{Paco}_2$.\(^{17}\)

Measurements made in otherwise unselected volunteers showed that careful shielding of the lateral aspect of the probes and of the helmet considerably improves the agreement of flow values derived from homologous areas of both sides of the head, particularly for mean flow, flow of white matter and relative weight of gray matter. This is considered to be due to reduction of scattered radiation from non-cephalic parts of the body and from the xenon delivery system, which in this laboratory is placed on the right side of the patient.

Comparison of flow values obtained here by the inhalation method in volunteers agrees well with the values reported in the literature using the autoradiographic techniques in animals for measurement of brain stem and cerebellar regions. The slightly lower values found here for the slow component are not surprising since in the model of computation used for deriving the flow values, $F_i$ is a compromise between clearance of white matter and extracranial tissue.

Testing of the reproducibility for $F_i$ in 24 patients measured twice after an interval of 30 minutes showed that the reproducibility coefficient for BSC areas was comparable to that found with standard hemispheric probe placements.

The fact that differences in flow values for the brain stem-cerebellar region correlate well with the clinical and electroencephalographic assessment of the state of consciousness is adduced to lend additional validity to these measurements, since it is unlikely that flow values that are heavily contaminated by counts derived from the airways and scalp would show such correlation.

These changes in regional cerebral blood flow that correlated with different states of consciousness and/or behavioral activity cannot be ascribed to changes in MABP, $\text{Paco}_2$, occlusion of the vertebro-basilar arterial blood supply or to computational errors related to the start fit time. Stepwise increases in brain stem-cerebellar flow correlated with progressive increases in brain function and are thought to be related to resultant local increases in brain stem and cerebellar metabolism.

The fact that BSC flow values correlate statistically better with the state of consciousness than mean hemispheric values is attributed in part to foci of reactive hyperemia in the semi-comatose patient with embolism to the left carotid artery and by the presence of arterial spasm in the carotid territory in 3 of 5 of the drowsy patients with subarachnoid hemorrhage. In contrast, in the chronic apallic state illustrated by the patient with anoxic encephalopathy, with clinically preserved brain stem function, BSC-$F_i$ values were found to be low-normal while mean hemispheric $F_i$ and $W_i$ values were reduced. These observations suggest that different etiologies of unresponsiveness may be investigated by this technique. Comparison of BSC flow values with mean hemispheric flow was also of interest in REM sleep, where mean hemispheric $F_i$ was only slightly increased compared to that found in the steady state, but BSC-$F_i$ values were markedly elevated, as might be expected from animal models.\(^{28}\) The relationship between BSC-$F_i$ flow values and levels of consciousness and/or brain activity appears to be linear as shown in figure 6.

The relative importance of cerebellum versus brain stem as tissue determinants for changes in local blood flow measured by these probes is difficult to establish. Animal studies have shown that the brainstem nuclei,
such as the inferior colliculi and reticular formation, have high blood flow relative to cerebellum and are more involved with levels of brain activity. It is possible that higher flow in the brain stem structures dominates the observed changes in BSC flow. This view is supported by the fact that relatively high BSC flows were measured in patients with unilateral or bilateral extensive removal or absence of the cerebellum with normal brain stem function. This view is also in accordance with measurements made with $^{14}$C-butanol in gerbils, indicating a higher flow for brain stem compared to cerebellum and in stable xenon clearance measured in the baboon by CT scan (unpublished observations). This interpretation has been further confirmed in the baboon where barbiturate anesthesia has been shown (by both aortic intubation and tracheostomy) to reduce brain stem-cerebellar flow. 20 Comparable flow values were also observed in the baboon with changes in the state of consciousness, under deep anesthesia, light anesthesia and wakefulness.

The changes in BSC flow obtained during sleep stages I and II compared to REM stage sleep are also in accordance with previous studies in man and in animals which implicates reticular formation of brain stem to regulation of blood flow during sleep.

In conclusion, regional measurements of brain stem-cerebellar flow made for the first time in man after $^{133}$Xe inhalation appear to provide reliable quantitative data that may prove useful in clinical investigations of cerebral function in health and disease.

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Recovery of Brain Mitochondrial Function in the Rat after Complete and Incomplete Cerebral Ischemia

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SUMMARY Respiratory function was evaluated in brain mitochondria prepared from rats subjected to either complete compression ischemia or pronounced incomplete hypotensive ischemia of 30 min duration, and from animals allowed a 30 min recirculation period following 30 min of ischemia. Oxygen utilization rates in the mitochondrial preparations were measured with an oxygen electrode in a closed and stirred chamber with glutamate plus malate or with succinate as substrates.

After 30 min of ischemia there was a decrease in respiratory control ratio (RCR), in state 3 respiratory activity and maximal phosphorylation rate whether ischemia was complete or incomplete. After recirculation following complete ischemia, mitochondria showed extensive functional recovery with normalization of RCR, as well as of state 3 and maximal phosphorylation rates. Following incomplete ischemia, there was a suggestive further deterioration of mitochondrial function. Addition of Mg++ did not reverse the pattern of respiratory inhibition. The results are in agreement with previous communications from this laboratory, demonstrating a nearly complete recovery of cerebral energy state upon recirculation after an equivalent period of complete compression ischemia but not after pronounced, incomplete hypotensive ischemia. The persistence of mitochondrial dysfunction following recirculation after incomplete ischemia indicates that a mitochondrial damage could be a primary factor for the deficient recovery of the cerebral energy state. Events during the initial recirculation period may be at least partly responsible for failure of energy metabolism.

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AS A RESULT OF experimental work during the last few years, earlier opinions concerning the sensitivity of cerebral tissue to anoxia and ischemia have changed. Thus, although integrated brain function does not return, extensive recovery of neurophysiological parameters, such as spontaneous electrocortical activity and evoked response, as well as of cerebral energy metabolism, has been shown to be possible even after periods of complete cerebral ischemia of 60 min duration in the cat and monkey.14-1 In these experiments barbiturate anesthesia was used. In lightly anesthetized (70% N2O) rats a virtually complete recovery of cerebral energy state was found during recirculation after 30 min period of complete compression ischemia.5,6 However, no comparable recovery occurred during recirculation after a similar period of severe, incomplete hypotensive ischemia.5,7 In the latter type of ischemia, protection was afforded by barbiturate anesthesia.7 These results indicate that transient incomplete ischemia is more deleterious for brain tissue than complete cessation of cerebral blood flow. The pathophysiological mechanisms responsible for this difference are poorly understood. Histopathological investigations have demonstrated that mitochondrial alterations are the first sign of cell damage in brain anoxia-ischemia.5-6 However, mitochondrial function, as evaluated from the respiratory activity of isolated brain mitochondria, has been found relatively resistant to ischemia.10-12 There is no information about the recovery of mitochondrial respiratory function upon recirculation following ischemic periods known to cause significant depression of respiratory rates.

The present investigation was undertaken to evaluate mitochondrial function in brain tissue after a 30 min period of complete and incomplete ischemia, as well as during recirculation.

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Critical appraisal of cerebral blood flow measured from brain stem and cerebellar regions after 133 Xe inhalation in humans.

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