Cerebral Blood Volume is Increased in Dogs during Administration of Nitrous Oxide or Isoflurane

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Positron emission tomography was used to study the effects of nitrous oxide (N₂O) and isoflurane on regional cerebral blood volume (rCBV) in dogs during normocapnia and hypocapnia. Regional cerebral blood volume was measured serially during the administration of 50% N₂O to a background anesthetic of fentanyl in normocapnic (group 1) and hypocapnic (Paco₂ 25 mmHg; group 2) dogs. In each group, after 15 min of N₂O administration accompanied by rCBV measurement, elimination of N₂O with 100% O₂ was continued for 15 min. This was followed by introduction of 2% isoflurane (no N₂O), again accompanied by serial measurements of rCBV. In the normocapnic animals, the addition of 50% N₂O caused an 11% increase in rCBV (6.1 ± 1.4 to 6.8 ± 1.0 ml/100 g, P < 0.02) while 2% isoflurane caused a 35% increase (6.1 ± 1.3 to 8.9 ± 1.7 ml/100 g, P < 0.02). The initial induction of hypocapnia during administration of fentanyl in group 2 animals was associated with a 17% decrease in rCBV. In the hypocapnic dogs, there was no change in rCBV when N₂O was introduced; however, an increase of 15% occurred following the administration of isoflurane (5.0 ± 0.6 to 4.5 ± 0.7 ml/100 g, P < 0.02). Isoflurane, even during hypocapnia, may increase cerebral blood volume which in some circumstances may lead to an increase in ICP. (Key words: Anesthetics, gases; nitrous oxide. Anesthetics, volatile; isoflurane. Brain; blood volume; intracranial pressure. Surgery; neurologic.)

Cerebral blood volume (CBV) is an important determinant of intracranial pressure and cerebral hemodynamics. Volatile anesthetics like halothane have been avoided by some anesthesiologists during treatment of patients with raised ICP because they are cerebral vasodilators. Until the advent of accurate methods for measuring CBV,¹ the vasodilatory effects of a drug were most commonly evaluated by measuring its effect on cerebral blood flow (CBF). Although there is a correlation between CBV and CBF when CBF is increased by hypercapnia,² in some other conditions no such relationship holds. Thus, when cerebral perfusion pressure is reduced either by ischemia³ or by raised ICP,⁴ CBV has been shown to increase, despite decreased or constant CBF.

Although some human studies suggest that isoflurane and nitrous oxide (when used with other drugs) may increase ICP less than does halothane,⁵-⁷ recent observations suggest that these agents may not be innocuous in patients with raised ICP.⁸,⁹ Therefore, in this study, we have used the direct measurement of CBV by positron emission tomography (PET) to evaluate the changes in rCBV produced by nitrous oxide and isoflurane.

Methods and Materials

Ten mongrel dogs (18–25 kg) were studied. The experimental protocol was approved by the Montreal Neurological Institute Animal Care Committee.

General Procedure

General anesthesia was induced with thiopental, 7 mg·kg⁻¹, and fentanyl citrate, 12 μg·kg⁻¹, both administered intravenously. Following intubation of the trachea, ventilation with oxygen was controlled using a Bird Mark 4 + 8 ventilator (Bird Corp., Palm Springs, CA) set to function in a volume-limited mode. A circle circuit with a variable bypass of the soda lime CO₂ absorber was used to vary the inspired CO₂ and, consequently, the PaCO₂ to the desired level. The protocol was executed so as to produce minimal tactile and auditory stimulation. All incisions were performed after local infiltration with 0.25% bupivacaine. Sedation was provided with a fentanyl infusion, 2.4 μg·kg⁻¹·h⁻¹. Muscle relaxation was provided with pancuronium bromide (0.2 mg·kg⁻¹ at induction, continuous infusion of 0.1 mg·kg⁻¹·h⁻¹). The femoral artery was cannulated with a 16-gauge catheter for blood radioactivity and blood gas determination and measurement of arterial pressure (strain gauge transducer, Bentley-Trantec® Model 800, Bentley Lab. Inc., Irvine, CA). The femoral vein was cannulated with a 16-gauge catheter for fluid and drug administration. Temperature was monitored with a rectal thermistor probe using a 43 TD Tele-Thermometer® (Yellow Springs Instrument Inc., Yellow Springs, Ohio), and maintained at 38 ± 1°C by heat lamps or ice packs. Mean arterial pressure, referenced to the external auditory meatus, was determined by

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Received from the Department of Neuroanaesthesia and Neuroimaging, Montreal Neurological Institute and Hospital, McGill University, Montreal, Canada. Accepted for publication May 27, 1987. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, 1986. Supported in part by the Canadian Anaesthetist's Society Research Award.

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electronic integration of the transducer signal using a Siemens Sirecust® 300 System (Siemens AG, Erlangen, West Germany). Arterial blood gases were serially measured during the procedure, using a Corning 165/2 pH/blood gas analyzer (Corning Medical, Boston, Mass). End-tidal concentrations of isoflurane were monitored continuously when appropriate with an infrared isoflurane monitor (model AAM 222, Puritan-Bennett Corp., Lenexa, KS).

**Measurement of Regional CBV (rcBV)**

The measurement of regional CBV (rcBV) was performed with a Therascan® 3128 positron emission tomography (PET) scanner (Atomic Energy of Canada, Ltd., Ottawa).

Regional CBV was determined by tomographically measuring the radiation emitted from a region of interest in the brain while simultaneously measuring the radioactivity in arterial blood.1 Brain radioactivity measurements were performed with the PET scanner. Blood 11CO radioactivity was assayed in a well counter (Model 810c, Baird Atomic Inc., Cambridge, MA) and corrected for physical decay. These determinations allow(rcBV) in the brain to be calculated with the formula presented in the Appendix.

Following production in the radiochemistry laboratory as previously described,10 the 11C carbon monoxide (11CO) was administered directly into the endotracheal tube through which ventilation was being provided. For each experiment, 11CO was delivered at a rate of 50 mCi·min⁻¹ for approximately 5 min per subject on three occasions 1 h apart to maintain sufficient cerebral activity for effective imaging. The specific activity of the radioactive gas was 1000–2000 Ci/mmol; the 11CO was, therefore, administered in trace quantities of approximately 33 micromoles/min. The average total coincidence rate at the start of scanning was 50,000 counts sec⁻¹ for all three slices. Following an equilibration period of 4 min after the start of 11CO administration, imaging was begun on the first scan of the protocol. Tissue radioactivity data (PET scan) was collected for 5-min periods (high resolution mode). Scanning was performed during the washin of nitrous oxide and isoflurane. The rcBV values are reported at times that represent the midpoint (2.5 min) in the data collection. The radioactivity determinations in two blood samples taken 1.5 and 3.5 min after the start of each scan were averaged to provide the blood radioactivity value for that scan.

**Experimental Protocol**

The effects of nitrous oxide and isoflurane on rcBV were studied by subjecting each animal to a pre-defined anesthetic sequence. Measurements of mean arterial pressure (MAP) and rcBV were performed 90 min after tracheal intubation. This gave sufficient time to allow stabilization of conditions following transfer of the animal from the laboratory and positioning in the PET scanner. In the scan room, quiet conditions were maintained and stimulation of the animal was minimized. The animals were then divided into two groups. In group 1 (n = 6), ventilation was adjusted to maintain normocapnia throughout the study, while, in group 2 (n = 4), after making measurements at normocapnia, hypocapnia (P<sub>CO₂</sub> 25–30 mmHg) was induced before N₂O and isoflurane were introduced. After obtaining measurements with fentanyl alone, nitrous oxide (50%) was introduced into the anesthesia circuit. rCBV and the other variables were measured at 5, 10, and 15 min after the introduction of N₂O. Nitrous oxide was then eliminated by ventilation with 100% oxygen for the next 15 min, and the measurements repeated. Isoflurane was then added to the anesthesia circuit from a calibrated vaporizer in concentrations sufficient to achieve a stable end-tidal concentration of 2% after 15–30 min exposure. Regional cerebral blood volume was measured at 5, 10, 15, 20, 30, and 60 min after the introduction of isoflurane. A phenylephrine infusion was used to maintain mean arterial pressures at pre-isoflurane levels.

During the final portion of the sequence for the group 2 animals, isoflurane was eliminated by ventilation with oxygen until the end-tidal concentration was less than 0.25%, at which time a final measurement of rcBV was performed.

**Image Selection and Calculation of rcBV**

In one representative animal, coronal sections of the brain in situ in the skull were obtained post-mortem to relate the brain anatomy to the external landmarks on the skull. Animals were positioned prone so that the center coronal slice was obtained 4.0 cm rostral to the occipital protuberance.

From the 11CO PET images, circular regions of interest (ROI), 1.5 cm in diameter (area 1.8 sq cm), were chosen to correspond to regions of interest (ROI) in brain approximately located over the caudate, thalamus/hippocampus, and rostral cerebellum in the rostral, middle, and caudal PET slices, respectively. The resolution of the scanner is such that regions chosen in this way include both gray and white matter, and probably represent whole brain more than the specific structures mentioned above. Values for rcBV in the three ROIs were averaged to provide a single value of rcBV for each experimental condition. Inspection of values in the three ROIs chosen did not reveal any obvious dif-
ferences in behavior among the regions during the experimental protocol. These regions were chosen by examining the coronal cross-sectional anatomy in a representative animal. In addition, a cerebral blood flow scan performed with the $^{18}$CO-4CO$_2$ method in one animal was used to locate the canine brain in relation to the large vessels at the base of the skull. The regions of interest were chosen sufficiently far from the vessels at the base of the brain that the interference from these vessels on rCBV measurements was minimal. This was confirmed by mathematical modeling using the tissue concentrations obtained from the vessel-rich regions during one representative experiment. Time-activity curves were then generated for $^{18}$C radioactivity in the region of interest in each of the three slices.

**DATA ANALYSIS**

Comparisons of rCBV values with control levels were performed at sample times that we felt represented equilibrium conditions.

Within each experimental group (1 and 2), the anesthetic sequence was analyzed in two parts. The rCBV measurements obtained after 15 min of 50% N$_2$O administration were compared by paired t test to the preceding values obtained during the fentanyl infusion alone (columns 2 and 1, respectively, in both tables 1 and 2). Observations made following washout of nitrous oxide were considered to be a separate independent data point. The values obtained after 30 and 60 min of isoflurane administration were averaged for each animal, and compared to the values obtained with the fentanyl infusion alone (after nitrous oxide washout) (columns 4 and 3, respectively, in both tables 1 and 2) by paired t tests.

In addition to the above, in group 2, rCBV with fentanyl at normocapnia was compared to rCBV with fentanyl at hypcapnia by paired t test. All values in the text are expressed as mean ± SD. P < 0.05 was used to designate statistical significance.

**RESULTS**

**PHYSIOLOGICAL STATE OF THE ANIMALS**

In both groups, the PaCO$_2$ and the mean blood pressure (mean BP) were unchanged during the anesthetic sequences (tables 1, 2). The stability of rCBV during hyperventilation was confirmed in the group 2 sequence, since the rCBV which was determined at the end of the study after washout of isoflurane was similar to that obtained during the previous measurement performed with fentanyl alone (3.8 ± 0.6, 3.9 ± 0.6, both values in ml·100 g$^{-1}$).

**EFFECT OF NITROUS OXIDE ON rCBV**

In normocapnic animals (group 1), the introduction of 50% N$_2$O was associated with an 11% increase in mean rCBV (P < 0.02, table 1, fig. 1). In contrast, in group 2 (hypocapnic animals), no significant change in rCBV was observed (table 2, fig. 1) when 50% N$_2$O was introduced.

**EFFECT OF ISOFLURANE ON rCBV**

In the normocarbic animals (group 1), introduction of 2% isoflurane caused an increase in rCBV. With isoflurane at equilibrium (average of 30- and 60-min values) the rise was 31% (P < 0.02, table 1, fig. 2).

In the hypocarbic animals (group 2), rCBV increased 15% with the introduction of 2% isoflurane (average of 30- and 60-min values) (P < 0.02, table 2, fig. 2). Washout of isoflurane to end-tidal values of 0.24 ± 0.7% was

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### Table 1. Physiologic Variables in Group 1 Studies (n = 6)

<table>
<thead>
<tr>
<th></th>
<th>1 Fentanyl</th>
<th>2 N$_2$O 50%</th>
<th>t(Test 1 Vs. 2)</th>
<th>3 Fentanyl</th>
<th>4 Iso 2%</th>
<th>t(Test 3 Vs. 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBV (ml/100 g)</td>
<td>6.1 ± 1.4</td>
<td>6.8 ± 1.0</td>
<td>P &lt; .02</td>
<td>6.1 ± 1.3</td>
<td>8.0 ± 1.7</td>
<td>P &lt; .02</td>
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<td>MAP (mmHg)</td>
<td>114 ± 22</td>
<td>125 ± 23</td>
<td>NS</td>
<td>117 ± 19</td>
<td>115 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO$_2$ (mmHg)</td>
<td>30 ± 3</td>
<td>40 ± 4</td>
<td>NS</td>
<td>41 ± 6</td>
<td>40 ± 5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Mean values ± standard deviation.

### Table 2. Physiologic Variables in Group 2 Studies (n = 4)

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<th>2 N$_2$O 50%</th>
<th>t(Test 1 Vs. 2)</th>
<th>3 Fentanyl</th>
<th>4 Iso 2%</th>
<th>t(Test 3 Vs. 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBV (ml/100 g)</td>
<td>3.6 ± .5</td>
<td>3.5 ± .4</td>
<td>NS</td>
<td>3.9 ± .6</td>
<td>4.5 ± .7</td>
<td>P &lt; .02</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>132 ± 9</td>
<td>140 ± 15</td>
<td>NS</td>
<td>136 ± 26</td>
<td>137 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO$_2$ (mmHg)</td>
<td>25 ± 2</td>
<td>24 ± 2</td>
<td>NS</td>
<td>23 ± 3</td>
<td>23 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3 Fentanyl</td>
<td>4 Iso 2%</td>
<td>t(Test 3 Vs. 4)</td>
<td>5.2 ± 11.5</td>
<td>5.2 ± 12.5</td>
<td>P &lt; .02</td>
</tr>
<tr>
<td>rCBV (ml/100 g)</td>
<td>3.6 ± .5</td>
<td>3.5 ± .4</td>
<td>NS</td>
<td>3.9 ± .6</td>
<td>4.5 ± .7</td>
<td>P &lt; .02</td>
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<tr>
<td>MAP (mmHg)</td>
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<td>NS</td>
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<tr>
<td>PaCO$_2$ (mmHg)</td>
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<td>24 ± 2</td>
<td>NS</td>
<td>23 ± 3</td>
<td>23 ± 2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Mean values ± standard deviation.
associated with a significant decrease in rCBV from 4.5 ± 0.7 to 3.8 ± 0.6 ml/100 g (P < 0.02).

EFFECT OF HYPOCAPNIA ON rCBV

In the group 2 animals, the initial reduction in PaCO₂ from 41 mmHg to 24 mmHg during induction of hypcapnia resulted in a 17% decrease in rCBV from 4.7 ± 0.5 ml to 3.9 ± 0.6 ml·100 g⁻¹ (P < 0.02).

Discussion

CEREBRAL BLOOD FLOW, CEREBRAL BLOOD VOLUME, AND ICP

As one of the three principal constituents of the contents of the skull, the cerebral blood volume plays an important role in cerebral hemodynamics and intracranial pressure. Grubb et al. demonstrated that, when CBF is changed by altering PaCO₂, there is a positive correlation between CBV and CBF². Note that, in this study in monkeys,² arterial pressure was allowed to increase as PaCO₂ was varied from less than 40 mmHg to 80 mmHg. It is not unexpected that such conditions would lead to increased CBV, since mean arterial pressure increased during vasodilation. It is not known whether CBV increases when a cerebral vasodilator is administered while arterial pressure is kept constant. When local CBF is increased by a rise in local metabolic activity provoked by tremor,¹⁰ no correlation with CBV is observed. When cerebral perfusion pressure is reduced by either vascular obstruction³ or by intracranial hypertension,⁴ cerebral vasodilation increases CBV while CBF either remains constant or decreases. Hence, although CBV and ICP are positively correlated,¹⁰ CBF and CBV are positively correlated only during certain conditions.

This study demonstrates clearly that, in the dog, nitrous oxide causes a significant increase in CBV under normocapnic conditions, and that this increase does not occur when the animals are first rendered hypocapnic.

In the normocapnic dog, exposure to 60–70% N₂O under conditions of light anesthesia has been associated with 44–200% increases in CBF.¹³,¹⁴ If CBV is correlated with CBF during N₂O administration in the same way as during hypercarbia,² CBV would be expected to increase 15–30%. The administration of barbiturate (done in our study) has been shown to abolish or reduce the increase in CBF in the dog¹⁴ even 45–60 min after administration. Thus, at normocapnia, the 11% increase in CBV observed in our study is consistent with what would be predicted from the previous CBF studies mentioned above. We are not aware of any previous demonstration that hypcapnia prevents the CBV increase associated with N₂O administration.

Under both normocapnic and hypocapnic conditions, the introduction of 2% isoflurane was associated with a significant increase in rCBV. The increase in rCBV observed in this study (31% at 2.0% isoflurane) was larger than the 9–11% increase observed by Artru¹⁵ following administration of 1.4% isoflurane. Part of the differ-

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Fig. 1. Mean values (±SEM) of serial rCBV measurements made during the introduction of 50% N₂O. The equilibrium rCBV value (15 min, *) was statically significantly different (P < .02) from control (0 min) in the normocapnic (■), but not in the hypocapnic (○), animals.

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Fig. 2. Mean values (±SEM) of serial rCBV measurements made during the introduction of 2% isoflurane. The equilibrium rCBV value [30 = (•) and 60 = (••) min values averaged] was statistically significantly different (P < .02) from control (0 min) in both the normocapnic (■) and the hypocapnic (○) animals. Numbers in parentheses are the mean values of the end-tidal isoflurane concentration recorded at each respective rCBV measurement.
ence may be due to the administration of higher concentrations of isoflurane in our study. In addition, there are major methodological differences between the two studies (see Appendix). Unfortunately, technical difficulties prevented us from measuring CBF and ICP concurrently with CBV and, therefore, we cannot comment on the CBF-CBV-ICP relationship. If the relationship between CBF and CBV is the same with isoflurane (induced changes in CBF) as it is with P_{aCO_2} (CBV = 0.8 CBF\textsuperscript{20-26}),\textsuperscript{2} we would anticipate an increase of at least 10% since CBV increased by 32% during 1.4% isoflurane anesthesia in the dog.\textsuperscript{16}

In three studies of animals with intracranial mass lesions,\textsuperscript{17-19} no differences were found between the rise in intracranial pressure produced by halothane, enflurane, or isoflurane. In humans patients with brain tumors, significant increases in intracranial pressure were observed in some patients, despite the minimal increase in CBV observed with isoflurane anesthesia in humans.\textsuperscript{20} To explain this paradox, Artur\textsuperscript{15} has speculated that the vascular effects of volatile agents may differ and that, although the effect of isoflurane on cerebral resistance vessels may be small, producing little change in CBF, the drug may dilate conductance or capacitance vessels. The ensuing increase in CBV would be independently responsible for an increase in ICP. It is to be noted that, in the dog, increases in CBV were observed at concentrations greater than 1 MAC concentrations\textsuperscript{16} of isoflurane and, therefore, the statements above concerning the paradoxical observation of an increase in ICP despite an unchanging CBF do not apply to this species.

MAC was not determined in this study; 2% end-tidal concentrations of isoflurane were chosen because isoflurane MAC in dogs has been determined to be 1.28%,\textsuperscript{21} and a common concentration for clinical use of a volatile agent alone is 1.5 MAC.

In this study, blood pressure was maintained with phenylephrine when isoflurane was introduced. This was based on indirect evidence in humans\textsuperscript{22} that cerebral autoregulation is maintained with isoflurane in concentrations up to 1.5 MAC. Also, in cats anesthetized with 1.6% isoflurane +70% N\textsubscript{2}O, autoregulation was better maintained than with an equivalent concentration of halothane +70% N\textsubscript{2}O.\textsuperscript{23}

A critical assumption in this study was the selection of a value of 0.69 for r, the ratio of the cerebral-to-large vessel hematocrit. This value was determined for humans\textsuperscript{24} and, although r has not been determined for the dog, 0.69 agrees well with values determined for the cat (0.62\textsuperscript{25}) and the rat (0.69 - 0.84\textsuperscript{26}). There may be two types of error if the value of 0.69 is inappropriate. First, if the true value is different but constant, there will be a systematic error that will not affect the relative changes in rCBV that occurred with the anesthetic sequence. Second, and more seriously, if r was changed by the anesthetic sequence, then changes observed in "rCBV" may be due, in part, to changes in cerebral hematocrit. Sakai et al.\textsuperscript{27} have reported that cerebral hematocrit fell when cerebral blood flow was increased by 5% \textsubscript{a}CO\textsubscript{2} inhalation in humans. In their study, when P_{aCO_2} increased from 40 to 46 mmHg, the cerebral/central hematocrit ratio decreased from 75.9 to 72.4 (P < .05). If these results apply to hypocarbia conditions in dogs, then our methods of calculating rCBV would lead us to underestimate the decrease in rCBV with hypocapnia by approximately 13%. Similarly, if isoflurane increased CBF, the effect of a decrease in cerebral hematocrit (and r) would lead us to underestimate an increase in rCBV.

Since ICP was not measured in this study, we can only speculate on the physiological significance of the observed changes in rCBV (31% increase in the normocarbic group). In a previous study in dogs with normal intracranial compliance, Ravussin et al.\textsuperscript{10} demonstrated that a 27% increase in rCBV produced by rapid infusion of mannitol caused a significant increase in ICP. If similar changes occur in human subjects (brain mass of a young adult male is approximately 1400 g, rCBV approximately 5 ml/100 g), the resultant increase in total cranial blood volume would be 22 ml, a physiologically important increase. Even the smaller increase observed under hypocarbia conditions (11% increase, table 2) would be approximately 7.7 ml, an amount that could cause an important rise in intracranial pressure in patients with decreased intracranial compliance.\textsuperscript{28} However, it is important to recall that this study was done with conditions that should give normal or increased intracranial compliance. If the CBV increase was in low pressure, capacitance vessels, then it is possible that these increases would not occur in the presence of intracranial hypertension.

In summary, both nitrous oxide and isoflurane increase cerebral blood volume in normocapnic dogs. Prior induction of hypocapnia prevented the increase in CBV with \textsubscript{a}N\textsubscript{2}O and blunted the increase with isoflurane. The increase of rCBV associated with 2% isoflurane (31%) was larger than had been previously observed (10%) with 1.4% isoflurane.\textsuperscript{14}

Appendix

Measurement of Cerebral Blood Volume by Positron Emission Tomography (PET)

Indicator-dilution techniques for measuring tissue blood volume can be divided into two general classes: 1) those that calculate blood volume from measurements of flow and transit time, and 2) those that measure tissue and blood radioactivity
rCBV increases with N2O and isoflurane

Levels. It is to the latter techniques the PET has been applied and to which the present discussion is limited.

In these methods, a trace quantity of an isotope which does not leave the vascular space is introduced into the blood stream and allowed to equilibrate throughout the blood volume. The tissue and blood radioactivity levels are then measured simultaneously and used to calculate the tissue blood volume (see equation 1 below).

Accurate quantitative methods for obtaining tissue radioactivity measurements have awaited the development of techniques that provide for: 1) exclusion of radioactivity originating from sites outside the tissue or region in question, and 2) the detection of a constant major fraction of the radiation emitted from the tissue or region. Risberg et al. measured CBV by labelling either hemoglobin (14C) or albumin (31I) and then positioning a collimated gamma counter across the biparietal diameter of the skull. Despite the surgical removal of the muscle and soft tissue overlying the skull, they estimated that 30% of the radiation detected by the counter originated from extracranial sources. Since only a single detector was used, the total tissue radioactivity level could not be estimated, and only values relative to some initial condition could be calculated.

Measurement of cerebral blood volume by PET fulfills the requirements outlined above, and allows the quantitative regional determination of CBV. A comprehensive review of the study of cerebral function by PET has been published, the following discussion will be limited to aspects that pertain to the measurement of CBV.

Positron emission tomography is a radiation detection technique that produces tomographic delineation of local tissue radioactivity levels derived from injection or inhalation of radioactive tracers. The radiation detected is in the form of two 511 keV photons (gamma radiation), which are emitted during the annihilation of a positron with an electron. The positron-emitting isotopes commonly used in CBV measurement are carbon-11 and oxygen-15, which, when incorporated into 11CO and 15O, respectively, bind to the red blood cells.

High detection efficiency is provided by the scanner's array of bismuth germanate detectors, arranged in two rings of 64 detectors each. Since photons produced during positron annihilation are emitted 180° apart, an electronic form of collimation can be used. This collimation is achieved by recording an event sensed by a detector only if there is a coincidence (within 9 nanoseconds) event in one of the opposing detectors. In this way, the only radiation recorded is that emitted from within the tissue slice in the scanner.

Since the spatial definition of the technique is not infinite, a point source of radioactivity is 'seen' by the scanner as a sphere. In other words, for a point source, the scanner's representation of radiation intensity versus position in any dimension (x, y, or z) is in the form of a curve whose maximum is located at the source (the point-spread function). The resolution of the scanner may be defined by the width of the point-spread function at one-half of the maximum radioactivity level recorded. This parameter has dimensions in millimeters an is referred to as full width half maximum (FWHM). The resolution of the scanner depends largely on the size and number of detectors used and the movements of the gantry during scanning. The resolution (FWHM) of the Therascan 3128 PET Scanner used in this study (high resolution mode) was 12 mm. This scanner is capable of generating 5 12-mm-thick images per gantry position.

Image reconstruction is accomplished by a mathematical algorithm similar to those used for x-ray transmission computed tomography (x-ray CT). The resultant image is composed of the tissue radioactivity concentrations in counts·sec⁻¹·volume⁻¹. The cerebral blood volume within a region of interest selected by visual inspection of the scan may be calculated from:

\[ rCBV = \frac{C_T(T)}{C_B(T)} \times r \times d \times \text{cal}, \]

where \( C_T(T) \) is the local tissue radioactivity concentration in region i measured at time T with PET (counts·sec⁻¹·ml⁻¹) and \( C_B(T) \) is the venous blood radioactivity concentration measured at time T. The term \( r \) represents the ratio of cerebral hematoctrit to central venous hematoctrit (taken in this study to be 0.69±4), while d is the density of cerebral tissue (1.04 g·ml⁻¹). 31 "cal" is the calibration factor which links the well counter to the PET scanner. Computer averaging techniques allow the calculation of average \( C_T \) values for any selected region of interest.

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