Positron Imaging of Cerebral Blood Flow During Continuous Inhalation of C\textsubscript{15}O\textsubscript{2}

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SUMMARY This investigation tests the hypothesis that the normal cerebral image obtained non-invasively during continuous inhalation of C\textsubscript{15}O\textsubscript{2} is related to cerebral blood flow. Trace amounts of CO\textsubscript{2} labeled with the positron-emitting radionuclide \textsuperscript{15}O were administered to 4 normal subjects at normo- and hypocapnia and to 2 of these subjects at hypercapnia. Hypocapnia typically caused a marked decrease in cerebral \textsuperscript{15}O activity, and hypercapnia a small increase in activity. The relative difference in the change in count rate in response to hypocapnia and hypercapnia is what one would expect if the activity represented blood flow, according to a mathematical model which assumes the \textsuperscript{15}O label enters the brain as water of perfusion. The findings in this study suggest that the normal cerebral image obtained during continuous inhalation of C\textsubscript{15}O\textsubscript{2} is related to cerebral blood flow, but in a non-linear fashion, and that the technique would be more sensitive to ischemic events than to hyperemic phenomena.

METHODS

\textsuperscript{15}O is a cyclotron-produced positron-emitting radionuclide with a 2 minute half-life. Its distribution in brain can be imaged by detecting the photons released following positron emission. Positrons are positive electrons emitted in the decay of certain nuclei. Interaction of the positron with an electron leads to an annihilation process in which the masses of these particles are converted to two 511 KeV photons travelling in opposite directions. A positron imaging device detects activity on both sides of the head, and by identifying photon pairs that may arise from a single annihilation event can provide 2- and 3-dimensional images of the activity distributions with uniform resolution at all tissue depths.

Subjects and Study Protocols

Five pairs of resting (normocapnic) and hypocapnic studies were performed in 4 normal male volunteers. Two of these subjects were also studied during induced hypercapnia. End tidal CO\textsubscript{2} was monitored with a Beckman LB-2 analyzer and converted to Paco\textsubscript{2} values using the ambient barometric pressure.

In the first 3 trials hypocapnia was produced by having the subjects vigorously increase the rate and depth of ventilation over the resting study. To eliminate variable factors due to changes in respiratory dynamics the last 2 pairs of studies were done using a fixed ventilation technique, with the subject overbreathing at a constant minute volume of 24 liters. Such marked hyperventilation typically depressed Paco\textsubscript{2} below 20 mm Hg. Unlabeled 5\% CO\textsubscript{2} was then mixed in various concentrations with the in-
spired air to achieve normocapnia or the desired level of hypocapnia. Subjects could maintain relatively steady tidal volumes of 1 liter by monitoring their own inspiratory efforts on a clearly visible respirometer. A metronome was used to cue inspiration. If the inhaled air were humidified and the volunteers given a practice session they could maintain constant large minute volumes for up to an hour during normo- and hypocapnia.

Hypercapnia was produced by adding 5 or 7% CO$_2$ to the inspired air. During hypercapnia reflex respiratory drives overrode voluntary breathing patterns.

Isotope Production and Imaging Device

Oxygen-15 was produced by bombarding nitrogen with 6 MeV deuterons accelerated in the MGH cyclotron. $^{15}$O-labeled CO$_2$ was produced by passing labeled molecular oxygen over activated charcoal heated to 600°C. The gas was piped to the study area approximately 100 feet away. CO$_2$ was mixed with ambient air and delivered to the subject at a rate of 10 mCi/min. The subject inhaled the mixture through a mouthpiece attached to a one-way Hans-Rudolph valve. A noseclip prevented leakage from the nasal passages. $^{15}$O activity was continuously monitored at the cyclotron and adjacent to the mouthpiece. It was constant to ±3% during the study.

Two-dimensional imaging was done with the MGH positron camera, designed by Brownell and Burnham. It has 2 parallel detector banks, one on each side of the head. Each bank contains 127 NaI crystals viewed in a coded array of 72 photomultiplier tubes. Only events detected in coincidence are counted. Each detector on a reference side is in coincidence with 25 detectors on the opposite side. The resolution of the system is 1 cm full-width at half-maximum.

Data collection was begun after 7-10 min of continuous inhalation of C$^{15}$O$_2$. At this time constant rates of 1,000-3,000 counts per sec were achieved over the head. Typically, total head counts were greater than 100,000 per study.

Results

In 4 of the 5 pairs of studies a mean drop in Paco$_2$ of 48 ± 3% resulted in a mean fall in count rate of 24 ± 7% (table 1). In 2 subjects a mean increase in Paco$_2$ of 45% resulted in a mean increase in count rate of 8% (table 2).

Three of the volunteers experienced a drop in count rate during hyperventilation. In the fourth, during the first trial, the cerebral count rate rose despite constant measured activity at the cyclotron and at the input to the mouthpiece. This subject was studied again, 2 weeks later, using the fixed ventilation technique and showed a drop in cerebral count rate during hypocapnia that was consistent with that seen in other volunteers.

Figure 1 shows the normocapnic and hypocapnic images from the first subject. The drop in activity during hypocapnia is represented by a decrease in the brightness of this 2-dimensional cerebral image.

Discussion

In this investigation hypocapnia was associated with a marked decrease in the activity of the cerebral image during continuous inhalation of C$^{15}$O$_2$, but hypercapnia with only a small increase in activity. Three possibilities may explain these findings: 1. The count rate in the cerebral image is random and is unrelated to a meaningful physiologic parameter; 2. The count rate is related primarily to changes in metabolism or blood volume; 3. The count rate is related primarily to changes in blood flow, but in a non-linear fashion.

CO$_2$ is a potent vasoactive agent. A drop in Paco$_2$ will cause vasoconstriction in the normal brain and a decrease in CBF, whereas an increase in Paco$_2$ produces vasodilation and a rise in CBF. The determinants of this response are controversial, as is the shape of the curve relating Paco$_2$ to flow. Some investigators claim a linear relationship and others an exponential relationship when Paco$_2$ is varied from 25 to 60 mm Hg. Changes in Paco$_2$ within this range cause no consistent changes in cerebral oxygen uptake, but do proportionately alter cerebral blood volume by changing the capacitance of...
FIGURE 1. The lateral 2-D positron image obtained during continuous inhalation of C\textsuperscript{15}O\textsubscript{2} at normocapnia (left) and hypocapnia. The upper two-thirds of each image represent cerebral tissue in lateral projection, with the subject looking to the reader's left. The lower third represents facial and neck tissues. At normocapnia the cerebral tissues have much greater activity than extracranial structures; at hypocapnia the image becomes almost homogenous because of a fall in count rate over the brain. This drop in cerebral activity is thought to be due to a fall in cerebral blood flow in response to hypocapnia.

Although the number of trials in this study is too small to permit statistical analysis, the data indicate consistent trends for the changes in count rate observed during hypo- and hypercapnia in all but one of the trials. In the latter case the count rate rose over the head during hypocapnia. This rise in count rate could not be explained but was thought to be due to a change in the alveolar concentration of $^{18}$O. To remove as a variable factor the effect of change in respiratory dynamics on ventilation and cardiac output, the subject was studied again using a fixed ventilation technique (see Methods). The repeat study showed a drop in count rate during hypocapnia consistent with that seen in other volunteers. The overall findings in the 4 subjects suggest that the activity in the cerebral image is not random, but is related to a meaningful physiologic parameter.

Since hypocapnia should not affect oxygen uptake in normals, the large drop in activity that followed this fall in Paco\textsubscript{2} should not be due to such metabolic changes. Hypocapnia diminishes and hypercapnia increases blood volume; however, the tracer used in this study is readily diffusible from the intravascular space and should not be sensitive to changes in cerebral blood volume.

The count rate in this study did change typically in the direction that blood flow alters in response to hypo- and hypercapnia. The relative magnitude of the count rate response was markedly different during hypo- and hypercapnia. This difference, however, is consistent with that predicted by the mathematical model determined independently by Jones\textsuperscript{4} and Subramanyam\textsuperscript{5} and their co-workers. This model relates blood flow and relative activity levels during continuous inhalation of C\textsuperscript{15}O\textsubscript{2} under the assumption that the $^{18}$O label diffuses freely into the brain as water of perfusion ($H_2^{18}O$). The model describes the count rate as a non-linear function of cerebral blood flow (fig. 2) and indicates that for a given change in CBF the change in count rate will be greater at low flows that at high flows.

Using characteristic CO\textsubscript{2} reactivity and resting flow data the predicted mean change in count rate for these subjects can be calculated with an equation derived from the model:

$$\% \Delta CR = \left[ \frac{1 - CBF \times 34 + CBF_1 \times 34 + CBF_2}{CBF_1 \times 34 + CBF_2} \right] \times 100,$$

where $\% \Delta CR$ is the percent change in count rate over the

![Figure 2](image-url)
head between the first and second trials; CBFv and CBFs, the cerebral blood flow in cc/100 g/min during the normocapnic and hypo- or hypercapnic studies, respectively, and 34 the decay constant for 16O multiplied by 100. The formula assumes the arterial concentration of 16O does not differ from trial 1 to trial 2.

Data obtained in our laboratory with the 18Xenon inhalation method indicate that the mean change in blood flow for a 1 mm Hg change in Paco2 is 1.7 cc/100g/min. These data are from 10 normal volunteers examined in the Paco2 range 23-37 mm Hg, and are comparable to those of Grubb and co-workers, who monitored the washout of H216O following intracarotid injection in primates and found a change per mm Hg of 1.8 cc/100 g/min over a Paco2 range of 15-76 mm Hg. Assuming a resting CBF of 54 cc/100 g/min, and a CO2 reactivity of 1.7 the model predicts a drop in mean count rate of 37% and an increase of 16% for the observed mean percent alterations in Paco2 during hypo- and hypercapnia, respectively. The measured changes in mean count rate were 24% and 8%, respectively. For both the predicted and observed data the percent fall in count rate during hypcapnia is 2-3 times the percent increase during hypercapnia. That the observed difference between the hypo- and hypercapnic responses are roughly proportional to the expected may be more interesting than that the observed changes underestimate the expected. This underestimation may be due to one or more of the following considerations: The interpolated values for the resting CBF and for CO2 reactivity were obtained by other techniques; the 16O arterial concentrations may not have been constant between trials in each individual; H216O is not freely diffusible, which could cause an underestimation of flow, particularly at higher CBF values.

The large percent difference in the count rate change during hypo- compared to hypercapnia indicates that normal mean resting flow values lay near the start of the shallower part of the activity/flow curve, as predicted by the model, and suggested by Lenzi and co-workers. This investigation provides experimental support for the following concepts: 1) In normals the static, cerebral 16O image obtained during continuous inhalation of C16O2 provides normal, physiologic data. 2) The 16O activity is related to cerebral blood flow, but in a non-linear fashion. 3) The mathematical model for the relationship between count rate and flow is physiologically relevant and, 4) Normal mean flow values lay close to the start of the shallow portion of the activity/flow curve described by this model. The data suggest that this technique provides a measure of cerebral blood flow, but clinically would be more sensitive to ischemic events than to true hyperemic phenomena.

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