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Measurement of brain oxygen utilization with radioactive oxygen-15: experimental verification

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RAICHLE, M. E., R. L. GRUBB, JR., J. O. EICHLING, AND M. M. TER-POGOSSIAN. *Measurement of brain oxygen utilization with radioactive oxygen-15: experimental verification.* J. Appl. Physiol. 40(4): 638–640. 1976.—This study was designed to provide direct experimental evidence in support of the method employing radioactive ^{15}O-tagged hemoglobin for the in vivo and regional measurement of the cerebral oxygen utilization rate ($CMRO_2$). This was accomplished by simultaneously measuring in vivo the mean $CMRO_2$ in monkeys and human beings by the ^{15}O method and a direct appeal to the Fick principle using measured arteriovenous oxygen differences of brain. The correlation between the 2 methods was excellent, with a correlation coefficient of 0.90 ($P < 0.001$) in monkeys and 0.88 ($P < 0.001$) in human beings.

human; *Macaca mulatta;* cerebral blood flow

IN 1970 TER-POGOSSIAN, EICHLING, and their colleagues (2, 9) introduced the first and only method for the in vivo determination of regional cerebral oxygen utilization in man. The method employs oxyhemoglobin labeled with the cyclotron-produced radioisotope ^{15}O. This tracer is rapidly injected into the internal carotid artery of the patient under study. This injection is followed by the injection of blood labeled with ^{15}O-labeled water. After each injection the time course of the radioactive label is followed by an array of collimated scintillation detectors placed over the patient's head. The data collected subsequent to injection of the [^{15}O]oxyhemoglobin reflect the arrival of the labeled oxygen in the tissue, its partial conversion to water of metabolism, and the clearance of labeled water from the tissue. The ratio of the amount of labeled water formed to the amount of oxygen perfusing the tissues is a measure of the regional fractional utilization of oxygen. The data collected subsequent to the injection of [^{15}O]water are used to calculate the regional blood flow. The product, regional fractional utilization of oxygen × regional blood flow × arterial oxygen content, gives a measure of the regional oxygen utilization rate. The degree of regionality achieved depends on the detection system employed.

Although data accumulated with this technique (1, 9) have generally agreed well with previously reported values for brain oxygen metabolism, no direct comparison has been reported between established methods for the in vivo estimation of whole brain oxygen utilization using the arteriovenous oxygen difference of brain, and the ^{15}O method. This brief report details such a comparison in monkeys and human subjects.

METHODS

Animal studies. The animal studies were performed on 5 adult rhesus monkeys *(Macaca mulatta).* To facilitate the injection of radioisotopes into the internal carotid artery, the right external carotid artery was ligated at its origin from the common carotid artery at least 2 weeks prior to experimentation.

For the cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) measurements, the monkeys were anesthetized with phencyclidine (2 mg/kg), paralyzed with gallamine triethiodide, intubated with a cuffed endotracheal tube, and passively ventilated on 100% oxygen with use of an animal respirator (Harvard Apparatus Co.). A catheter (1.4 mm OD) was then inserted into a femoral artery and its tip positioned in the right carotid artery under fluoroscopic control. A second catheter (1.4 mm OD) was inserted into the femoral vein and its tip positioned in the right jugular bulb. To prevent clotting in these catheters all animals were anticoagulated with heparin. The end-tidal P_{CO_2}, arterial blood pressure, and rectal temperature were continuously monitored. Rectal temperature was maintained between 37°C and 39°C with a heating pad. Arterial and cerebral venous (jugular bulb) pH, P_{O_2}, P_{CO_2}, and oxygen content were measured before and after each injection of radioisotope. The oxygen content of all blood samples was determined by an oxygen galvanic cell method (Lexington Instruments Corp.).

In each animal, CBF and $CMRO_2$ were measured at several different levels of arterial carbon dioxide tension (Pa_{CO_2}). The Pa_{CO_2} was lowered by passive hyperventilation and raised by passive hypoventilation (Pa_{CO_2} range: 19–47 mmHg). A 0.25-ml sample of the animal's blood containing the appropriate tracer was injected into the carotid artery for each measurement.

Human studies. Eight adult patients undergoing diagnostic carotid angiography for suspected or overt disease of the brain were studied. Informed consent was obtained in each case. A short catheter was placed into the internal carotid artery for the injection of radioisotopes and angiographic contrast material, and for the sample of arterial blood. A second short catheter was placed into the internal jugular vein and its tip positioned in the jugular bulb. A 1.5-ml sample of the patient's blood containing the appropriate radiopharmaceutical was injected into the internal carotid artery for each measurement.

Radioisotope preparation and detection. The preparation of the radiopharmaceuticals ^{15}O-labeled oxyhemoglobin and ^{15}O-labeled water is described elsewhere (10).

In monkeys the tracers were monitored by means of a single 3″ × 2″ NaI(Tl) scintillation detector appropriately collimated and positioned to insure uniform detection of the brain. In human beings the tracers were monitored by 13 5 cm × 5 cm NaI(Tl) detectors appropriately collimated and positioned to view 13 regions of the injected cerebral hemisphere. The details of data processing are described elsewhere (3).

Data analysis. The CBF was determined by utilizing the height/area residue detection (11) of the bolus of [^{15}O]water injected into the internal carotid artery. The time-activity curve for the washout of $H_2{}^{15}O$ from the brain was used to

calculate the water mean transit time ($\bar{t}_{H_2O}$), which is defined as

$$\bar{t} = \frac{\int_0^\infty q(t)dt}{q_0}$$

where $q(t)$ is the radioactivity level in the region under study as a function of time, and q_0 is the dose of radioactivity in the injected bolus. The computed value of $\bar{t}_{H_2O}$ was combined with the central volume principle (7, 11)

$$\bar{t} = V/F$$

where F is the volumetric flow rate of vascular fluid and V is the volume of distribution of the tracer, and the mean equilibrium brain-blood partition coefficient of water (λ_{H_2O}) to yield the CBF in ml/100 g·min^{-1}

$$CBF = \frac{\lambda_{H_2O} \times 100}{\bar{t}}$$

A value of 0.95 ml/g was used for λ_{H_2O}. In the studies on human beings the data from all 13 detectors were averaged to obtain a mean hemispheric CBF.

The $CMRO_2$ was calculated in two ways. First, the fraction of ^{15}O-labeled oxygen extracted by the brain during a single capillary transit (E_{O_2}) was determined from the externally detected time-activity curve produced by the injection of [^{15}O]-oxyhemoglobin (Fig. 1). This time-activity curve is interpreted as follows: the maximum value reached by the curve (A, Fig. 1) is proportional to the amount of oxygen perfusing the tissues viewed by the detector. This peak is followed by a rapid drop in activity (clearance half-time, $t_{\frac{1}{2}}$ = 1.3 s; Fig. 1) followed by a much slower egress of the ^{15}O label (clearance half-time, $t_{\frac{1}{2}}$ = 66 s; Fig. 1). In effect the injected bolus divides into two fractions: a nonextracted fraction representing hemoglobin-bound ^{15}O not utilized by the tissues, which remains confined to the vascular volume of the brain and clears from brain as a vascular tracer, and an extracted fraction which equilibrates with the tissue and is rapidly utilized and converted to water. The slower phase of the time-activity curve shown in Fig. 1 represents the washout of this water. E_{O_2} is measured by graphically extrapolating the relatively slow clearance of the ^{15}O-labeled water from brain tissue back to the maximum of the perfusion peak and computing the ratio

$$E_{O_2} = B/A,$$

as shown in Fig. 1. In the studies of human beings the data from all 13 detectors were averaged to obtain a mean hemispheric E_{O_2}. The mean $CMRO_2$ by this method ($CMR^{15}O_2$) was then calculated by computing the product of CBF, E_{O_2}, and the measured arterial oxygen content.

Second, the mean $CMRO_2$ was calculated in a conventional manner by combining the CBF and the measured brain arteriovenous oxygen content difference ($CMRO_2$ (Fick)).

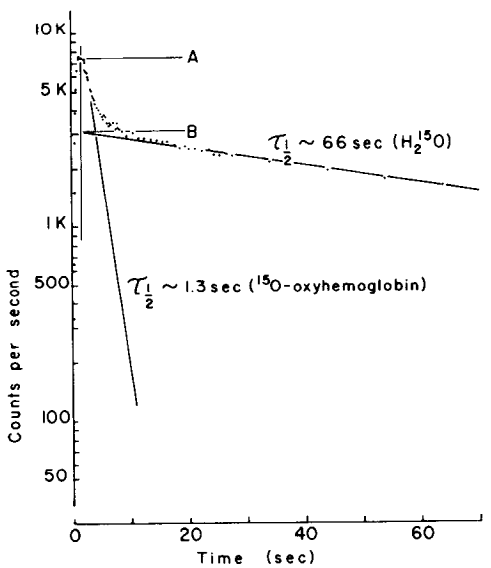

FIG. 1. Semilogarithmic recording obtained subsequent to the intracarotid injection of [^{15}O]oxyhemoglobin. The clearance curve can be resolved into 2 components, a fast component (half-time, $t_{\frac{1}{2}}$ ~ 1.3 s) representing the passage of nonextracted [^{15}O]oxyhemoglobin through the brain vasculature and a slow component ($t_{\frac{1}{2}}$ ~ 66 s) representing the washout of [^{15}O]water of metabolism. Graphic extrapolation of the relatively slow clearance of labeled tissue water back to the maximum of the perfusion peak allows the calculation of the fraction of oxygen extracted by the brain: E_{O_2} = B/A.

RESULTS

Twenty-nine paired measurements were made in five monkeys. The correlation between the 2 methods was excellent

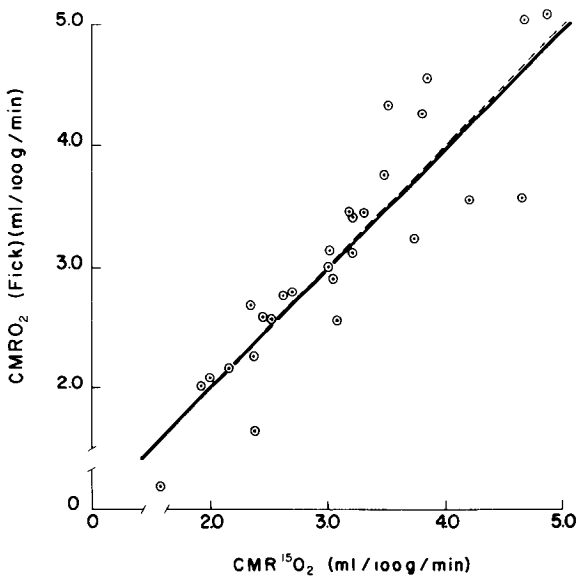

FIG. 2. Comparison of 2 methods of measuring the relative mean cerebral metabolic rate for oxygen ($CMRO_2$) in rhesus monkeys. *Abscissa:* rates as measured by the ^{15}O method ($CMR^{15}O_2$). *Ordinate:* rates as measured by direct appeal to the Fick principle. The unweighted linear regression line fitted to the data is the solid line, and the line of identity is the broken line. The correlation coefficient between the 2 methods is 0.90.

TABLE 1. *Patient data*

Patient No.	Diagnosis	CBF, ml/100 g per min	Pa_{CO_2}, mmHg	$CMR^{15}O_2$, ml/100 g per min	$CMRo_2$ (Fick), ml/100 g per min
1	Leigh's encephalopathy	32	22	3.09	2.79
2	Presenile dementia	29	45	2.39	2.30
		29	45	2.49	2.43
3	Subarachnoid hemorrhage	49	42	2.75	2.89
		46	41	2.60	2.71
4	Cerebral infarction	33	37	2.33	2.71
5	Cerebral infarction	25	40	1.81	1.76
6	Post-op cerebral A-V malformation	44	42	1.74	2.21
7	Subarachnoid hemorrhage	40	33	3.36	3.20
8	Subarachnoid hemorrhage	32	38	2.57	2.54

CBF, cerebral blood flow; Pa_{CO_2}, arterial carbon dioxide tension; $CMRo_2$, cerebral metabolic rate for oxygen.

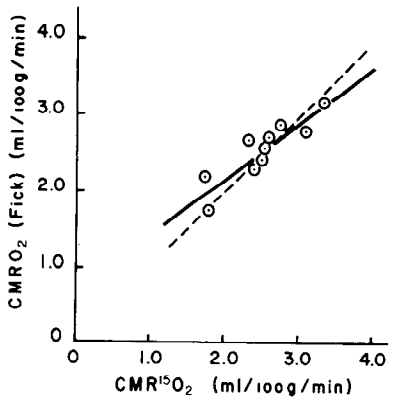

FIG. 3. Comparison of 2 methods of measuring the relative mean cerebral metabolic rate for oxygen ($CMRO_2$) in selected human beings. The details of the figure are similar to Fig. 2. The correlation coefficient between the two methods is 0.88.

(Fig. 2), with the regression line $CMR^{15}O_2$ = 1.02 $CMRO_2$ (Fick) − 0.023 yielding a correlation coefficient of 0.90 ($P < 0.001$).

Ten paired measurements of the mean $CMRO_2$ were made in eight patients (Table 1). The correlation between the 2 methods was excellent (Fig. 3), with the regression line $CMR^{15}O_2$ = 1.10 $CMRO_2$ (Fick) − 0.29 yielding a correlation coefficient of 0.88 ($P < 0.001$).

DISCUSSION

The theoretical aspects of the ^{15}O method for the measurement of the $CMRO_2$ have been previously presented in detail (2, 9). The present study complements this earlier work by now providing direct experimental evidence in support of the ^{15}O method. The correlation between the $CMRO_2$ as simultaneously measured by the ^{15}O method and a standard Fick method is excellent in both monkeys and man.

The ^{15}O method has two major advantages over standard methods of measuring $CMRO_2$ employing a direct appeal to the Fick principle. First and most obvious, it permits the in vivo measurement of regional oxygen metabolism ($rCMRO_2$) when combined with a properly designed radiation detection system. Measurements of $rCMRO_2$ can be particularly important when studying areas of potential acute injury to brain tissue where measurements of regional cerebral blood flow (rCBF) alone cannot be reliably used to draw inferences about regional metabolism (6). Discrepancies between rCBF and $rCMRO_2$ in areas of acute brain injury should not be too surprising when it is realized that a variety of nonphysiologic factors within the cranial vault and brain tissue itself can influence rCBF as well as $rCMRO_2$ under these circumstances (6). Furthermore, when ^{133}Xe is employed for the measurement of rCBF in human beings with various diseases, as is usually the case in most laboratories, additional discrepancies can be anticipated between rCBF and $rCMRO_2$. This results from the fact that the accurate measurement of rCBF depends on a precise knowledge of the equilibrium partition coefficient of the diffusible tracer employed (3). Because the partition coefficient of ^{133}Xe depends on the tissue lipid content, it is subject to marked uncertainty in cases of cerebral pathology (5). ^{15}O-labeled water, which we employ for the measurement of rCBF, is not subject to this constraint because its partition coefficient is independent of tissue lipid content. Second, the ^{15}O technique eliminates errors in the measurement of the $CMRO_2$ due to uncertainties in the measurement of the oxygen content of cerebral venous blood. Although blood obtained from the jugular bulb in primates, including man, is primarily derived from brain tissue, contamination from extracerebral tissue may be as high as 7% (8). Additionally, the oxygen content of the jugular bulb venous blood may vary significantly between the right and left sides in man due to variations in areas of brain drained by each bulb as well as the existence of focal pathological changes (4). As a result, venous samples from one jugular bulb may not always be representative of the whole brain or the homolateral cerebral hemisphere.

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