Brief Inhalation Method To Measure Cerebral Oxygen Extraction Fraction with PET: Accuracy Determination Under Pathologic Conditions

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The initial validation of the brief inhalation method to measure cerebral oxygen extraction fraction (OEF) with positron emission tomography (PET) was performed in non-human primates with predominantly normal cerebral oxygen metabolism ($CMRO_2$). Sensitivity analysis by computer simulation, however, indicated that this method may be subject to increasing error as $CMRO_2$ decreases. Accuracy of the method under pathologic conditions of reduced $CMRO_2$ has not been determined. Since reduced $CMRO_2$ values are observed frequently in newborn infants and in regions of ischemia and infarction in adults, we determined the accuracy of the brief inhalation method in non-human primates by comparing OEF measured with PET to OEF measured by arteriovenous oxygen difference ($A\text{-}VO_2$) under pathologic conditions of reduced $CMRO_2$ (0.27-2.68 ml $100g^{-1}$ min^{-1}). A regression equation of OEF (PET) = 1.07 × OEF ($A\text{-}VO_2$) + 0.017 ($r = 0.99$, $n = 12$) was obtained. The absolute error in oxygen extraction measured with PET was small (mean 0.03 ± 0.04, range −0.03 to 0.12) and was independent of cerebral blood flow, cerebral blood volume, $CMRO_2$, or OEF. The percent error was higher (19 ± 37), particularly when OEF is below 0.15. These data indicate that the brief inhalation method can be used for measurement of cerebral oxygen extraction and cerebral oxygen metabolism under pathologic conditions of reduced cerebral oxygen metabolism, with these limitations borne in mind.

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The brief inhalation method to measure cerebral oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen consumption ($CMRO_2$) with positron emission tomography (PET) and ^{15}O-radiotracers has been applied extensively in humans to study cerebral oxidative metabolism at rest, during physiologic cortical activation, and in pathologic processes such as ischemia (*1,2*). The initial description of the method by Mintun and colleagues included validation by comparison with residue detection of ^{15}O-oxyhemoglobin injected into the carotid artery of non-human primates sedated with 70% nitrous oxide (*3*). OEF was varied over a wide range (0.08-0.58) by manipulating the inspired carbon dioxide tension to change cerebral blood flow (CBF). Linear regression analysis of the 22 pairs of extraction values resulted in the equation OEF(PET) = 1.035 × OEF (TRUE) − 0.018 ($r^2 = 0.96$). $CMRO_2$ was 1.4-5.8 ml $100g^{-1}$ min^{-1}. Only 2 of 22 values were <2 ml $100g^{-1}$ min^{-1} and only 4 were below 2.5 ml $100g^{-1}$ min^{-1}. No data regarding the accuracy of the method under pathologic conditions was provided. Sensitivity analysis by computer simulation indicated that the method may be subject to increasing error as $CMRO_2$ decreases due to propagation of errors in the measurement of the intravascular ^{15}O-oxyhemoglobin, CBF or observed PET counts. Furthermore, the analysis suggested that additional compartmental modelling of the intravascular ^{15}O-oxyhemoglobin compartment to account for delayed mixing caused by slow red blood cell transit might be necessary under conditions of reduced $CMRO_2$. Since reduced $CMRO_2$ values measured by this method are observed frequently in regions of ischemia and infarction in adults and have recently been observed by us in newborn infants (*4*), we have now determined the accuracy of the brief inhalation method under pathologic conditions of reduced $CMRO_2$. In this study, we compared OEF measured by the brief inhalation method to OEF calculated from arteriovenous oxygen difference ($A\text{-}VO_2$) at $CMRO_2$ of 0.27-2.68.

MATERIALS AND METHODS

Animal Preparation

Measurements were performed in two adult macaques (Macaca nemestrina) and two adult baboons (Papio anubis). On the morning of the experiment, each animal was anesthetized with ketamine 25 mg/kg i.m., given atropine 0.04 mg/kg i.m., intubated with a soft-cuffed endothracheal tube and ventilated with 70% N_2O/30% O_2. Peripheral venous and arterial catheters were placed to permit administration of $H_2{}^{15}O$ for CBF measurements, drug administration and arterial blood sampling. Via femoral

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vein catheterization, a catheter was positioned in the jugular bulb under fluoroscopic control to permit cerebral venous blood sampling. In two animals, an ascending aortic arch catheter was placed via femoral artery catheterization to allow continuous sodium cyanide infusion.

PET Measurements

Measurements of CBF, CBV, OEF and $CMRO_2$ were performed on the PETT VI tomograph in the low-resolution mode, using a reconstructed resolution of 18 mm, FWHM (*5*). This tomograph collects seven parallel slices, 14.4 mm apart. The head of the animal was immobilized with a head holder and the position of the seven slices was recorded on a lateral skull radiograph with the aid of a plastic plate with seven radiopaque lines. A transmission scan with a $^{68}Ge/^{68}Ga$ ring source was performed on all animals to allow subsequent individual attenuation correction of emission scans. CBF was calculated from a 40-sec emission scan after bolus intravenous injection of ^{15}O-labeled water (*6,8*). CBV was measured by a 5-min emission scan begun 2 min after brief ventilation with ^{15}O-labeled carbon monoxide (*7,8*). OEF was measured by a 40-sec emission scan after brief ventilation with ^{15}O-labeled oxygen and using the previously collected CBF and CBV data (*3,8*). The method is based on a two-compartment model that describes the fate of ^{15}O-oxygen following inhalation (Fig. 1). Oxygen-15-oxygen is extracted from the arterial blood by the brain tissue and is converted immediately to ^{15}O-labeled water of metabolism which subsequently washes out of the brain. Labeled recirculating water of metabolism, produced by both the brain and the rest of the body, is delivered to brain tissue via its arterial input. Thus, the tracer kinetic model incorporates the various sources of ^{15}O following inhalation of ^{15}O-oxygen, i.e., ^{15}O-oxygen in the incoming arterial blood; ^{15}O-water of metabolism in the brain; unextracted ^{15}O-oxygen in the cerebral venous circulation; and the recirculating ^{15}O-water of metabolism. The model uses data from an intravenous injection of ^{15}O labeled water for calculation of CBF, and data from brief inhalation of ^{15}O-labeled carbon monoxide for calculation of CBV. The latter is used to correct for unextracted intravascular ^{15}O-oxygen. The local oxygen extraction is obtained from the following equation:

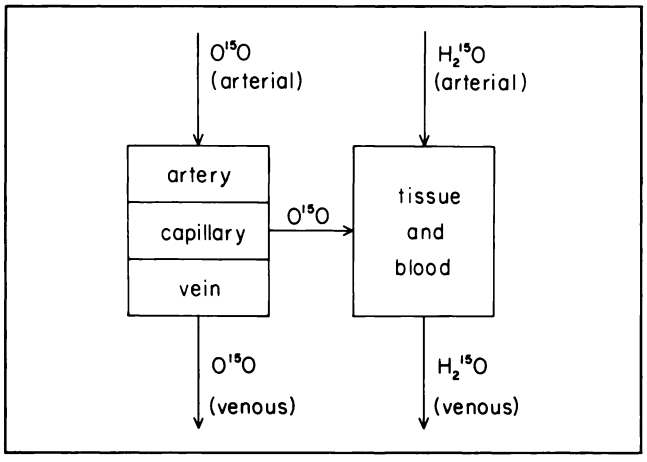

FIGURE 1. Two-compartment model that describes the behavior of two ^{15}O-radiotracers, $O^{15}O$, and $H_2{}^{15}O$. Left compartment represents $O^{15}O$ in vascular spaces; right compartment represents water of metabolism, $H_2{}^{15}O$, in tissue and blood spaces. Each compartment has a separate entrance and exit of tracer, interacting with each other only through extraction of $O^{15}O$ from vascular space and subsequent conversion to water of metabolism (reproduced with permission from Mintun et al. *J Nucl Med* 1984;25:177).

$$E = \frac{PET_{obs} - f\int_{t_1}^{t_2} C_{art}^{H_2O}(t)*\exp(-ft/\lambda)dt - R\cdot CBV\int_{t_1}^{t_2} C_{art}^{O_2}(t)dt}{f\int_{t_1}^{t_2} C_{art}^{O_2}(t)*\exp(-ft/\lambda)dt - 0.835\cdot R\cdot CBV\int_{t_1}^{t_2} C_{art}^{O_2}(t)dt},$$

where f is cerebral blood flow; PET_{obs} is the regional, decay-corrected tissue counts collected over the scan time, t_1 and t_2, following ^{15}O-oxygen inhalation; $C_{art}^{O_2}(t)$ and $C_{art}^{H_2O}(t)$ are the time-dependent concentrations of $O^{15}O$ and $H_2{}^{15}O$, respectively, in arterial blood (cps/ml); λ is the equilibrium brain: blood partition coefficient for water (ml/g); and R is the ratio of small vessel to large vessel hematocrit used in the calculation of CBV.

To implement this technique, a 40-sec emission scan is obtained following the brief inhalation of ^{15}O-oxygen. Arterial blood samples are drawn every 3-5 sec, corrected for physical decay and an arterial input function curve is constructed. At the end of the scan, an arterial blood sample is drawn; and following centrifugation, the plasma supernatant is removed, weighed and radioactivity measured to determine the recirculating water component. $CMRO_2$ is calculated as the product of CBF, OEF and arterial oxygen content, as previously described (*3,8*).

Arteriovenous Measurements

Blood samples for pH, pCO_2, pO_2, hematocrit, hemoglobin concentration and oxygen content were drawn anaerobically into 1-cc tuberculin syringes. pO_2, pCO_2, and pH were measured using an Instrument Laboratories pH and blood gas analyzer (IL 1306). Hemoglobin, arterial and venous oxygen contents were measured using an IL Co-Oximeter 282. Hematocrit was measured by microcentrifugation. Whole-brain oxygen extraction was calculated from the arterial (CaO_2) and jugular bulb (CvO_2) oxygen contents as OEF (A-VO_2) = (CaO_2 - CvO_2)/CaO_2.

Experimental Design

CBF, $CMRO_2$ and OEF were varied in different animals as follows. In two animals, barbiturate coma was produced with a constant methohexital infusion of approximately 1 mg/kg/min. Cerebral oxidative metabolism was suppressed in one animal by infusing sodium cyanide continuously into the ascending aorta [0.05 mg/kg/min of a 1.85% sodium cyanide solution (*9*)]. One animal was maintained in barbiturate coma and $CMRO_2$ was further suppressed with sodium cyanide. CBF was reduced in one animal by decreasing the pCO_2. After a steady-state of >30 min for these various conditions, PET measurements of CBF, CBV, OEF, and $CMRO_2$ were performed. CaO_2, CvO_2, and OEF(A-VO_2), were measured immediately before and after the complete set of PET scans. Only those experiments for which OEF (A-VO_2) remained constant, indicating steady-state during the PET measurements, were used in the data analysis.

Data Analysis

Because of the size of the primate brain (100-150 g) only one slice, corresponding to the cerebral hemispheres as identified from the skull x-ray, was used for the data analysis. Whole-brain CBF, CBV, OEF and $CMRO_2$ measured with PET were calculated from an irregular region outlining the cerebral hemispheres and excluding the sagittal sinus. The mean vascular red blood cell

TABLE 1
Oxygen Extraction Fraction (OEF) and $CMRO_2$ Measured with PET and Measured by Arteriovenous Difference ($A\text{-}VO_2$)

		PET Measurements				$A\text{-}VO_2$ Measurements			
		CBF*	CBV†	OEF	$CMRO_2$‡	OEF	$CMRO_2$§	pCO_2	Experimental condition
m238	1	79.5	3.4	0.08	0.95	0.06	0.68	17	Cyanide
	2	51.8	3.2	0.14	0.99	0.11	0.77	17	
	3	39.3	3.6	0.12	0.65	0.11	0.59	18	
m242	1	70.3	4.1	0.12	1.67	0.06	0.80	48	Methohexital, cyanide
	2	67.0	4.6	0.09	1.14	0.06	0.76	32	
	3	70.2	6.1	0.02	0.27	0.05	0.62	27	
	4	36.8	4.0	0.10	0.54	0.08	0.42	21	
m246	1	20.3	2.6	0.66	2.43	0.67	2.44	20	Methohexital
	2	16.8	2.2	0.78	2.33	0.66	1.97	22	
m247	1	38.5	2.7	0.43	2.51	0.40	2.32	34	
	2	41.4	3.0	0.43	2.68	0.36	2.24	34	Methohexital
	3	17.5	2.0	0.62	1.62	0.56	1.46	32	

* CBF = ml $100g^{-1}$ min^{-1}
† CBV = ml $100g^{-1}$
‡ $CMRO_2$ = ml $100g^{-1}$ min^{-1}
§ $CMRO_2$ = CBF (PET) × OEF ($A\text{-}VO_2$) × CaO_2 (ml $100g^{-1}$ min^{-1})

transit time ($\bar{t}$) was calculated from the ratio of whole brain CBV to CBF (CBV/CBF).

A second value for $CMRO_2$ was calculated from the product of OEF ($A\text{-}VO_2$), CBF (PET) and CaO_2.

RESULTS

Twelve sets of paired, steady-state PET and arteriovenous measurements were obtained from four animals (Table 1). The range of $CMRO_2$ measured with PET was 0.27 to 2.68 ml $100g^{-1}$ min^{-1}, the range of CBF was 16.8 to 79.5 ml $100g^{-1}$ min^{-1} and the range of CBV was 2.2-6.1 ml $100g^{-1}$. The range of OEF measured with PET was 0.02 to 0.78. In all animals, OEF was uniform throughout the whole brain. Linear regression analysis demonstrated the relationship OEF (PET) = 1.07 × OEF ($A\text{-}VO_2$) + 0.017 (r = 0.99) (Fig. 2). The absolute OEF (PET) error, calculated as the difference between OEF (PET) and OEF ($A\text{-}VO_2$), was small (mean 0.03 ± 0.04, range = 0.03 to 0.12). These small absolute errors produced much larger mean percentage errors (19 ± 37), especially at OEF below 0.15. Neither the absolute nor the percent OEF error was correlated with the baseline OEF value as measured with PET [p = 0.07, r = 0.54 (absolute OEF error), p = 0.68, r = 0.13 (percent OEF error)]. Furthermore, the absolute OEF error was not correlated with CBF, CBV, $\bar{t}$(CBV/CBF), and $CMRO_2$ as measured with PET [(p > 0.05: r = 0.36 (CBF), r = 0.58 (CBV), r = −0.15 ($\bar{t}$, CBV/CBF), and r = 0.55 ($CMRO_2$)]. Similarly, the absolute $CMRO_2$ (PET) error (mean 0.22 ± 0.28; range −0.35 to 0.87) was not correlated with CBF, CBV, $\bar{t}$(CBV/CBF), or $CMRO_2$ as measured with PET [(p > 0.05: r = 0.17 (CBF), r = 0.25 (CBV), r = −0.36 ($\bar{t}$, CBV/CBF), and r = 0.38 ($CMRO_2$)]. Linear regression analysis demonstrated the relationship $CMRO_2$ (PET) = 1.02 × $CMRO_2$ ($A\text{-}VO_2$) + 0.20 (r = 0.94).

DISCUSSION

The initial experimental validation of the bolus inhalation method to measure OEF with PET was carried out in primates at $CMRO_2$ of 1.4-5.8 ml $100g^{-1}$ min^{-1}. Only 2 of 22 values were <2.0 ml $100g^{-1}$ min^{-1} and only 4 were less than 2.5 ml $100g^{-1}$ min^{-1} (Mintun MA, personal communication). In this report, we have extended the validation to demonstrate the accuracy of this method under pathologic conditions of severely reduced cerebral oxygen metabolism.

In this study, OEF (PET) was slightly higher than OEF ($A\text{-}VO_2$). We believe this is due in part to venous blood with low oxygen extraction from extracranial tissue such

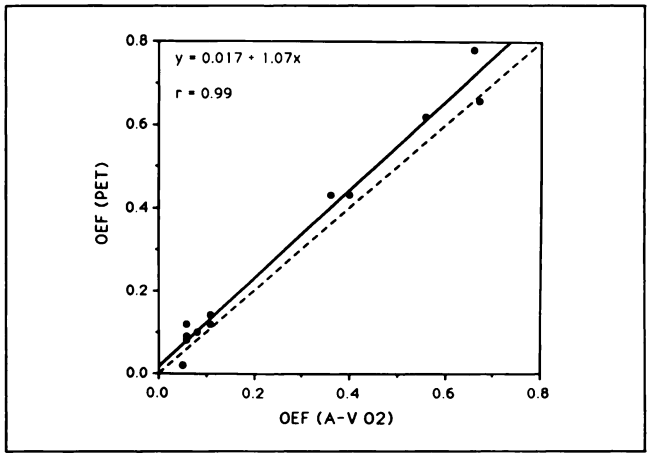

FIGURE 2. Comparison of OEF measured with PET and brief inhalation of ^{15}O-oxygen and OEF measured by arteriovenous oxygen difference. Twelve measurements were obtained in four animals. Linear regression analysis resulted in equation OEF (PET) = 1.07 × OEF($A\text{-}VO_2$) + 0.017 (r = 0.99, solid line). Dashed line is line of identity.

as scalp entering the jugular vein. Jugular venous blood may received as much as 5% to 7% of its blood from extracranial sources (*10*).

The effect of partial volume averaging on the measurements of CBF, CBV and OEF in these experiments needs to be considered. We employed a large irregular region outlining both cerebral hemispheres for the data analysis, since this approximates best the whole brain value obtained by arteriovenous oxygen difference. All images showed a homogeneous value for OEF throughout the slice indicating that partial volume effect from relatively high CBV in the scalp and skull did not cause artifically low OEF at the brain surface. Furthermore, since OEF (PET) reflects the ratio obtained with $O^{15}O$ and $H_2{}^{15}O$, it is insensitive to partial volume effects that effect both these tracers equally (*11*).

Although the absolute OEF error was small, the percent OEF error was larger, especially when OEF was below 0.15. Since $CMRO_2$ measured by PET is a product of CBF, OEF and CaO_2, it is affected by factors other than the accuracy of OEF measurement. At high CBF, a small absolute error in OEF will produce a larger absolute error in $CMRO_2$; whereas at low CBF, the same error in OEF will produce a proportionately smaller absolute error in $CMRO_2$. Data from the present study also indicate that accuracy of OEF (PET) was independent of CBF, CBV or mean red blood cell vascular transit time ($\bar{t}$). Thus, although the method used to correct for intravascular ^{15}O represents an approximation, the data in this study indicate the method is accurate when $\bar{t}$ is prolonged.

In summary, the brief inhalation method to measure OEF with PET has been demonstrated to have small absolute errors under pathologic conditions with $CMRO_2$ as low as 0.27 and CBF of 16 ml $100g^{-1}$ min^{-1}. Additional compartmental modeling of the intravascular compartment to account for slow red blood cell transit ($\bar{t}$) does not appear necessary for situations similar to those of the study. The percent error is higher particularly when OEF is low and CBF is high. We conclude the method can be applied appropriately to measure cerebral oxidative metabolism in situations where CBF and $CMRO_2$ are reduced, if these limitations in accuracy are borne in mind.

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