Brain Oxygen Utilization Measured with Oxygen-15 Radiotracers and Positron Emission Tomography: Generation of Metabolic Images

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We recently described a PET method for the measurement of local brain tissue oxygen extraction (E) and the local cerebral metabolic rate for oxygen ($CMRO_2$) using ^{15}O-labeled radiotracers. The equation for the calculation of E from measured PET data is mathematically complex and its direct application in the generation of PET images of either E or the $CMRO_2$ on a pixel-by-pixel basis is computationally burdensome. We describe a simplification of this equation which permits the efficient generation of quantitative images.

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We recently described and validated a technique for the measurement of regional cerebral oxygen extraction (E) and regional cerebral metabolic rate for oxygen ($CMRO_2$) with positron emission tomography (PET) and oxygen-15- (^{15}O) labeled radiotracers (*1*). The technique uses data from an i.v. injection of ^{15}O-labeled water for regional cerebral blood flow (rCBF) (*2,3*), a brief inhalation of ^{15}O-labeled CO for cerebral blood volume (CBV) (*4*), and a brief inhalation of ^{15}O-labeled oxygen for the final calculation of E and $CMRO_2$. The local oxygen extraction is obtained from the following equation:

$$E = \frac{PET_{obs} - f\int_{t_1}^{t_2} C_{art}^{H_2O}(t) * \exp(-ft/\lambda)dt - R\text{-}CBV\int_{t_1}^{t_2} C_{art}^{O_2}(t)\,dt}{f\int_{t_1}^{t_2} C_{art}^{O_2}(t) * \exp(-ft/\lambda)dt - 0.835\text{-}R\text{-}CBV\int_{t_1}^{t_2} C_{art}^{O_2}(t)\,dt} \quad (1)$$

where f is cerebral blood flow; PET_{obs} is the regional, decay-corrected tissue counts collected over the scan time, t_1 to 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 (*4,5*).

The direct application of this equation, which includes numerical integration of two convolution operations, to PET images on a pixel-by-pixel basis is cumbersome and time-consuming because of the large amount of spatial data to be analyzed (e.g., a scan obtained with the PETT VI tomograph (*6*) yields seven slices containing approximately 10,000 to 14,000 pixels from brain tissue). Although Eq. (1) could be applied to tissue-count data obtained from regions of interest containing many pixels, this would not provide metabolic images. In this regard it should be pointed out that images obtained following the inhalation of $O^{15}O$ alone cannot be used as qualitative metabolic maps of local brain metabolism in the same manner one might use an image produced by the i.v. bolus injection of $H_2{}^{15}O$ for the measurement of blood flow (*2,3*) or the inhalation of $C^{15}O$ for the measurement of local blood volume (*4*). In these latter two examples the "raw" images provide an accurate, qualitative visual representation of the measurement of interest (i.e., either blood flow or volume). However, in the case of an inhalation of $O^{15}O$, the resulting unprocessed image reflects a complex summation of contributions from labeled water of metabolism, unmetabolized $O^{15}O$ bound to hemoglobin, and recirculating ^{15}O-labeled water of metabolism. Thus, the creation of a processed metabolic image is an essential step in the analysis of data.

We wish to describe an approach to the evaluation of Eq. (1) which greatly reduces the computation required to convert images of local tissue counts to PET metabolic maps of E and $CMRO_2$. This approach was prompted by our observation that, using the PET adaptation of the Kety autoradiographic method to measure CBF with $H_2{}^{15}O$, there is a near-linear relationship between local blood flow and tissue counts (*2*). In fact, we

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found that the flow could be expressed as a function of counts using a second-order polynomial with a high degree of accuracy (*3*). This approach greatly facilitated the generation of flow images from regional count data.

We have implemented a similar technique to evaluate the two terms in Eq. (1) involving convolution operations. The first such term, in the denominator of Eq. (1), equals the local tissue counts, C_{100}, that would result if there were 100% extraction of arterial $O^{15}O$, i.e.,

$$C_{100} = f \int_{t_1}^{t_2} C_{art}^{O_2}(t) * \exp(-ft/\lambda)\, dt. \quad (2)$$

This expression is identical in form to the operational equation of the PET/autoradiographic method for rCBF measurement (*2*). For any given arterial time-activity curve, $C_{art}^{O_2}(t)$, this relationship between local flow, f, and tissue counts, C_{100}, can be very accurately described by a second-order polynomial. Thus, we express C_{100} as a function of flow,

$$C_{100} = a_1 f^2 + a_2 f. \quad (3)$$

The parameters a_1 and a_2 are obtained by least squares fit to C_{100} and f pairs generated by evaluating Eq. (2) for ten flow values ranging from 10 to 100 ml/(min·100 g).

The local tissue counts due to recirculating water of metabolism, C_{recirc}, are given by the second term in the numerator of Eq. (1) as

$$C_{recirc} = f \int_{t_1}^{t_2} C_{art}^{H_2O}(t) * \exp(-ft/\lambda)\, dt. \quad (4)$$

This relationship can similarly be fit to a second order polynomial,

$$C_{recirc} = a_3 f^2 + a_4 f. \quad (5)$$

Alternatively, we have noted that the arterial time-activity curve for recirculating water of metabolism, $C_{art}^{H_2O}(t)$, can be described by a linear function, using a single measurement of $C_{art}^{H_2O}$ obtained at the end of the scan (*1*). The resulting linear equation for $C_{art}^{H_2O}(t)$ could be inserted into Eq. (4) and the integrations performed analytically. However, the expression thus obtained for C_{recirc} would be more complex than that in Eq. (5).

Finally, the integral of $C_{art}^{O_2}(t)$, which appears in both of the blood volume correction terms in Eq. (1), need only be evaluated once and then multiplied by the appropriate constants (i.e., R in the numerator term, to yield the constant I_1, and 0.835·R in the denominator term, to yield the constant I_2). Thus, Eq. (1) for the evaluation of E reduces to

$$E = \frac{PET_{obs} - f(a_1 \cdot f + a_2) - CBV \cdot I_1}{f(a_3 \cdot f + a_4) - CBV \cdot I_2}. \quad (6)$$

The parameters of this equation (a_1, a_2, a_3, a_4, I_1, I_2) need only be evaluated once for a given $O^{15}O$ study. As Eq. (6) involves only 12 arithmetic operations, it can easily be applied to PET images on a pixel-by-pixel basis. With the Perkin-Elmer 3240 computer, this takes less than 15 sec for a study consisting of seven slices.

We assessed the error in the calculation of E that results from our simplification of Eq. (1). We used ^{15}O arterial time-activity curves obtained during studies in humans to generate the parameters for Eqs. (3) and (5) and simulated a wide variety of combinations of local flow [range 10–90 ml/(min·100 g)], blood volume (range 2–6 ml/100 g), and oxygen extraction (range 0.1–0.6). The error in E due to the use of the polynomial approximations of Eq. (6), rather than the original operational equation, Eq. (1), was, in all cases, less than 1%.

We note that the above simplification of our equation for the calculation of regional oxygen extraction is a specific example of a more general problem in the analysis of PET data. With the development of complex tracer kinetic models for PET, solution of the operational equations relating PET measurements of local radioactivity to the physiologic variable of interest may be computationally burdensome. The polynomial approximation presented here reduced computational time for an operational equation [Eq. (1)] that is explicit for the physiologic variable of interest. However, in more complex models (*7*), it may not be possible to express the desired variable explicitly as a function of measurable data and, thus, iterative techniques must be used. As such techniques are typically very time-consuming, additional strategies will be needed to efficiently generate physiologic or metabolic images from the measurements of local radioactivity provided by PET (*8*).

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REFERENCES

1. Mintun MA, Raichle ME, Martin WRW, et al: Brain oxygen utilization measured with O-15 radiotracers and positron emission tomography. *J Nucl Med* 25:177–187, 1984
2. Herscovitch P, Markham, J, Raichle ME: Brain blood flow measured with intravenous $H_2{}^{15}O$. I. Theory and error analysis. *J Nucl Med* 24:782–789, 1983
3. Raichle ME, Martin WRW, Herscovitch P, et al: Brain blood flow measured with intravenous $H_2{}^{15}O$. II. Implementation and validation. *J Nucl Med* 24:790–798, 1983
4. Grubb RJ Jr, Raichle ME, Higgins CS, et al: Measurement of regional cerebral blood volume by emission tomography. *Ann Neurol* 4:322–328, 1978
5. Lammertsma AA, Brooks DJ, Beaney RP, et al: In vivo measurement of regional cerebral haematocrit using positron emission tomography. *J Cereb Blood Flow Metabol* 4:317–322, 1984
6. Ter-Pogossian MM, Ficke DC, Hood JT, et al: PETT VI: A positron emission tomograph utilizing cesium fluoride scintillation detectors. *J Comput Assist Tomogr* 6: 125–133, 1982
7. Mintun MA, Raichle ME, Kilbourn MR, et al: A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann Neurol* 15:217–227, 1984
8. Blomqvist G: On the construction of functional maps in positron emission tomography. *J Cereb Blood Flow Metabol* 4:629–632, 1984