IV. 1 Assessment of Cerebral Blood Flow and Oxygen Metabolism in Human
—— Validation of Techniques and Preliminary Results

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INTRODUCTION

Functional level of organs can be assessed in vivo using positron emission
tomograph (PET or ECAT) and labelled radio-pharmaceuticals. Substrates like
glucose are carried via blood vessels to tissues and it is well known that blood
flow is normally adjusted to the rate of tissue metabolism.\(^1\) Discrepancy
between flow and metabolism may be seen in some deteriorated conditions like
infarct brain\(^2\) or tumour tissues\(^3\). Therefore measurement of both blood flow
and tissue metabolism is useful to evaluate activity or condition of tissues.

We started in the last April to measure regional cerebral blood flow
(rCBF), oxygen extraction fraction (rOFF) and oxygen consumption (rCMRO\(_2\))
applying 15O-0 steady-state method developed by Jones et al.\(^4\). This article
describes accuracy and error assessment of the technique and results of some
stimulation studies.

PRINCIPLES

rCBF measurement

15O labelled CO2 is inhaled by subjects at constant level. 15O is
transferred from C\(^{15}\)O\(_2\) to H\(_2\)\(^{15}\)O by carbonic anhydrase in the lung then
transported to the brain via blood flow. Amount of radioactivity accumulates in
the tissue directly correlates to CBF. According to the Fick's principle
changes in the brain per unit time is difference between inflow of the isotope
through blood flow and tissue wash-out of the activity via veins as well as
physical decay of the radioisotope (\(\lambda = 0.341/min\)) and is written as follows\(^5\):

\[
\Delta C_t = F \cdot C_a^C \cdot C_f \cdot E^C / V - (C_t^C \cdot \lambda + C_t^C / V \cdot F)
\]  

(1)

where F is flow per V volume of the brain, \(C_a^C\), \(C_t^C\) are arterial and tissue
concentration of H\(_2\)\(^{15}\)O respectively, \(C_f\) is calibration factor between well
counter and ECAT and \(E^C\) is extraction ratio of H\(_2\)\(^{15}\)O in the tissue (Fig. 1). At
equilibrium changes in the brain activity is null and H\(_2\)O extraction in the
tissue is almost 100 % then
\[ r_{\text{CBF}} = \frac{F/V}{\lambda/(C_a^O \cdot C_f/C_t^O - 1)} \]  \hspace{1cm} (2)

**rCMRO\textsubscript{2} measurement**

15-\textsubscript{O} labelled \textsubscript{O} inhaled produces oxy-hemoglobin in the lung and transferred to the brain where \textsubscript{15}O is converted to \textsubscript{H}_2\textsubscript{15}O through electron transport system in mitochondria. At equilibrium input via blood flow is again equal to the output through physical decay of the isotope and washout:

\[ F \cdot C_a^O \cdot C_f \cdot E^O/V = C_t^O \cdot \lambda + C_t^O/V \cdot F - F \cdot C_a^h \cdot C_f/V \]  \hspace{1cm} (3)

where \textsubscript{E} is oxygen extraction fraction (OEF) and \textsubscript{C} \textsubscript{a}, \textsubscript{C} \textsubscript{t}, \textsubscript{C} \textsubscript{h} are arterial and tissue concentration of \textsubscript{15}O\textsubscript{2} and arterial concentration of recirculating \textsubscript{H}_2\textsubscript{15}O respectively. Solving equation (1) and (3) rOEF is calculated. Regional oxygen consumption is then calculated using arterial oxygen content, \textsubscript{A}o:

\[ r_{\text{CMRO2}} = r_{\text{CBF}} \cdot r_{\text{OEF}} \cdot \text{A}_o \]

Oxygen extraction and consumption calculated above are much affected by regional blood volume (rCBV), i.e. the values are always over-estimated in the region with increased blood volume. Then \textsubscript{11}CO gas study is needed for CBV evaluation. Simplified gas study principles are summarized in Table 1.

**METHODS**

Bombarding nitrogen gas with 18 MeV neutrons, oxygen-15 is produced and transported continuously to the ECAT room. After checking its purity the gas is introduced to patients' face mask at constant level between 8-12 mCi/min for \textsubscript{15}O\textsubscript{2} study and 12-18 mCi/min for \textsubscript{15}O\textsubscript{2} study. From six to eight minutes inhalation is usually enough to get to equilibrium in brain count and then ECAT scan is started. Arterial blood samples are taken by femoral artery punctures in the early studies or through a radial artery canula. Regional CBF, OEF and CMRO\textsubscript{2} are calculated by solving above equations at pixel level. The resolution of the machine is 18 mm at FWHM both axial and trans-axial direction.

Eight normal subjects, 6 men and 2 women, are studied for the analysis. Among them one is left-handed. The mean age of them is 44±11 y.o. between 25 to 58 y.o.

**RESULTS**

(1) **Assessment of the technical errors**

Fig. 2 shows data of gas radioactivity transported and total brain count during a scan of a typical case. Fluctuations of radioactivities according to time seem permissible. Radioactive decay of a blood sample are plotted in Fig. 3. The curve has two component, the half life of the fast one is 2 min and of
slow one is 20 minutes which corresponds contaminated 11-CO₂. The contamination
in the early case is calculated to be 0.005 % (left figure) and in the late one
after increasing thickness of the target is 0.001 % (right figure of Fig. 3).

Blood samples are taken in the middle of each scan. Fluctuations of blood
count (cpm/g, decay corrected) is analysed in table 2. The mean standard
deviation of the fluctuation is 5 to 7 %.

(2) Normal values

Normal values for the three parameter measured in the temporal lobe near
insula at OM + 40 to 60 mm planes are shown in Table 3. The mean values in the
temporal grey matter near insula are 49 ml/100 g/min, 3.9 ml/100g/min, 0.39 for
rCBF, rCMRO₂ and rOEF respectively and difference between right and left
hemisphere is not obvious (left/right ratio is 0.9 in rCBF). The anterior
posterior ratio in rCBF of grey matter is 0.95 ± 0.25 ranging from 0.68 to 1.40.
A typical functional images are shown in Fig. 4.

(3) Activation study

Fig. 5 shows effects of hearing stimulation. The subject inhaled C¹⁵O₂
continuously for about 35 minutes while CBF studies are done before and within
vocal music stimulation. Activation of left temporal lobe corresponding hering
center is obvious.

DISCUSSION

Positron tomographs in state-of-art are not so suitable to follow rapid
wash-out of radioisotopes in tissues that the method to measure blood flow using
continuous inhalation of 15-0 labelled CO₂ and O₂ was developed.⁴) It has
advantages of being possible to measure both flow and oxygen consumption.

Error factors including simplifications of the model are evaluated by
Lammertsma et al. (6). In this paper we only discuss technical factors that
affect the reproducibility of the results.

(1) Break down of the steady-state

The steady-state requires constant input of radioactive gases to patients
and unchanging brain condition from start of inhalation to the end of
examination. Radioactive gas transportation is usually constant as long as
cyclotron operates without any failure. But brain radioactivity sometimes
fluctuate probably due to unstable respiration which may reflect anxiety of
patients. We use anesthetic gas mask to pass strict radioisotope regulations.
This may give stress to some patients.

(2) Blood count measurement

Because of short-half life of 15-0, the error in time for decay correction
of blood count is crucial. According to Lammertsma's simulation⁶) permissible
time error for decay correction is about 5 seconds in order to keep error level
of calculated CBF less than 3 %. We first considered 99.5 % purity of 15-0 gas
and less than 0.5% contamination of $^{11}\text{CO}_2$ is enough. It does not affect much on the brain count; actually it just decreases decay constant of 15-0 but not significantly. But because blood is counted usually around 8 minutes after withdrawal from vessel, a little contamination of 11-C significantly increases blood 15-0 count. For example on the condition that blood radioactivity contains 0.5% or 1.0% 11-C and is counted at 8 minutes after arterial sampling, decay corrected blood count shall be overestimated 5 or 11% of true value respectively. Then calculated cortical CBF values may underestimate 15 to 20% respectively.6) We modified the target later and 11-C contamination reduced to 0.1% (Fig. 3).

Fluctuation of blood count of the same subjects analysed in Table 2. The average s.d. of the change is 5.5% for $^{15}\text{O}_2$ study and simulation shows the value may result 15% error in cortical CBF. The actual mean CBF value obtained from normals is 49±8 ml/100g/min. The percent s.d. is 16% and almost same as predicted.

(3) Results of human studies

Because of contamination of grey and white matter true grey value is difficult to be obtained. We selected temporal pole-insular complex as the region of grey matter. Normal values are calculated as 49 ml/100g/min, 3.9 ml/100g/min and 0.39 for rCBF, rCMRO$_2$ and rOEF respectively. The values are quite agreeable in rCBF with those reported for the English but slightly higher in rCMRO$_2$ and rOEF.

Short life of 15-0 is suitable for repeated studies. The time needed to get to reequilibrium in the stimulated brain region is not clear so that the method is so far useful to see stimulated pattern in the brain qualitatively.

References

Table 1. Flow chart of gas study principle

\[ C^{15}_a \xrightarrow{\text{O}_2 \text{ Extraction (OEF)}} \xrightarrow{\text{OEF-CBV corrected}} \text{CBV corrected} \]

\[ C^{15}_a \xrightarrow{\text{Blood Flow (CBF)}} \xrightarrow{\text{O}_2 \text{ consumption (CMRO}_2\text{)}} \text{CMRO}_2 \]

\[ C^{15}_a \xrightarrow{\text{Blood volume (CBV)}} \]

\[ \text{Start} \rightarrow \text{s-1} \rightarrow \text{s-2} \rightarrow \text{s-3} \rightarrow \text{End} \]

Total brain count

\[ ^{15} \text{O - Gas radioactivity} \]

Time (min)
Fig. 3.

Table 2.

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<td>mean</td>
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Table 3.

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n=R