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ANNEXE 1

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THE DETERMINATION OF THE REGIONAL CEREBRAL BLOOD FLOW AND EXCHANGEABLE WATER VOLUME IN MAN, USING 15-OXYGEN AND POSITRON EMISSION TOMOGRAPHY.

GENERAL METHODOLOGICAL APPROACH
DESCRIPTION OF A MODEL
DATA FOR NUMERICAL ANALYSIS

INTRODUCTION TO AN INVESTIGATION COLLABORATIVELY UNDERTAKEN AT THE UNIVERSITY OF TEXAS, HOUSTON, AND AT THE UNIVERSITY OF LIEGE.

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CONTENT.

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General methodological approach
Description of a model
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J. C. DEPRESSEUX

1. INTRODUCTION.

1.1. The combination of the labeling of biological molecules with short-lived positron emitters and of the use of positron emission quantitative tomography (PET) opens to the non-invasive and three-dimensional determination of many physiological parameters in man.

The development of new methods in this field lies on a clear understanding of the phenomenon to be measured, on a correct structuration and parametric expression of the respective kinetics of tracers and tracees, on a proper formulation of the model and, finally, on a convergent and precise numerical analysis of the data. The obtained results should lead to a precise and accurate evaluation of parameters describing physiological and pathophysiological conditions.

The investigation of the kinetics and distribution of 15 O-labeled water within the organism is a good example of both the difficulties and the capabilities of techniques using positron-emitting radiopharmaceuticals and positron emission tomography.

1.2. The description of the kinetics of water within organs includes the quantification of convective and of diffusive flows of water and the determination of the corresponding volumes of distribution.

The only available indicator for the investigtion of the dynamic distribution of water in the human organism is presently 15O-labeled water, which has the precious advantage to be detectable by PET.

The present preliminary paper describes a method potentially leading to the determination of convective flow of water toward the brain (blood flow) and to the evaluation of the volume of distribution of water within this organ (exchangeable water volume).

2. METHODOLOGY.

2.1. Administration of $H_2{}^{15}O$.

The administration of $H_2{}^{15}O$ to the organism can be achieved in two different ways.

2.1.1. Intraarterial or intravenous injection of $H_2{}^{15}O$, directly produced as radiowater.

2.1.2. Breathing of $C^{15}O_2$, leading to an almost instantaneous transfer of more than 99% of the atoms of 15-O from $C^{15}O_2$ to $H_2{}^{15}O$ in the pulmonary capillary blood, under the catalytic action of carbonic anhydrase (1).

2.2. Kinetics of $H_2{}^{15}O$ within a tissue element.

Whatever the mode and time course of administration of radiowater, its activity within each element of tissue may be differentially described by the following equation (fig. 1) :

$$\frac{dC_{bi}(t)}{dt} = F_i\, C_a(t) - F_i\, C_{vi}(t) - C_{bi}(t)\,\lambda \qquad [1]$$

with
- subscript i identifying the tissue element under concern,
- t, the time,
- C_b, the activity of radiowater within the tissue element, per unit mass of tissue,
- C_a, the activity of radiowater, per unit volume of arterial blood,
- C_v, the activity of radiowater, per unit volume of venous blood,
- F, the blood flow perfusing the tissue element in unit volume of blood per unit mass of tissue and
- λ, the physical decay constant of 15-O. per unit of time.

The variable $C_{vi}(t)$ is not accessible to measurement, but it may be expressed using the central volume theory (2,3) :

$$C_{vi}(t) = \frac{C_{bi}(t)}{V_i} \qquad [2]$$

with V_i, the effective volume of distribution of $H_2{}^{15}O$ within the tissue element i, in unit volume of water per unit mass of tissue.

Equations [1] and [2] give :

$$\frac{dC_{bi}(t)}{dt} = F_i\, C_a(t) - \left(\frac{F_i}{V_i} + \lambda \right) C_{bi}(t) \qquad [3]$$

Equation |3| is a more general expression of the model elaborated by Kety (4) in the purpose to describe the kinetics of nitrous oxyde in the whole brain. This generalized formulation considers the local values of F_i and $C_{bi}(t)$ within tissue elements of the brain and it includes the physical decay of the tracer, occuring during the time of its tranfer through the tissue. It doesn't make any assumption about the partition of the tracer between blood and tissue.

2.3. Methodological strategies.

2.3.1. Prolegomena.

Equation 3 contains :

- 2 time-dependant variables, C_b and C_a, which are both accessible to measurement.

C_a is measured by sampling and counting of arterial blood, being cautious to avoid any time-scale shift between the sampling point and the point of input of arterial blood into the tissue element i.

C_{bi} is detected by quantified PET.

N.B. - C_a and C_b units are to be matched, by an appropriate attenuation correction of PET data and by use of calibration factors.

- C_b values are time-integrated during the collection time of PET data.

- 3 parameters, λ, F_i and V_i

λ is the physical decay constant of 15-O : 0.338 min^{-1},

F_i is the local blood flow of the tissue element i,

V_i is the effective exchangeable water volume of the tissue element i.

A MODEL OF THE KINETICS OF $H_2{}^{15}O$ WITHIN A TISSUE ELEMENT.

$$dC_{bi}(t) = F_i\, C_a(t)\, dt - \frac{F_i}{V_i}\, C_{bi}(t)\, dt - C_{bi}(t)\, dt$$

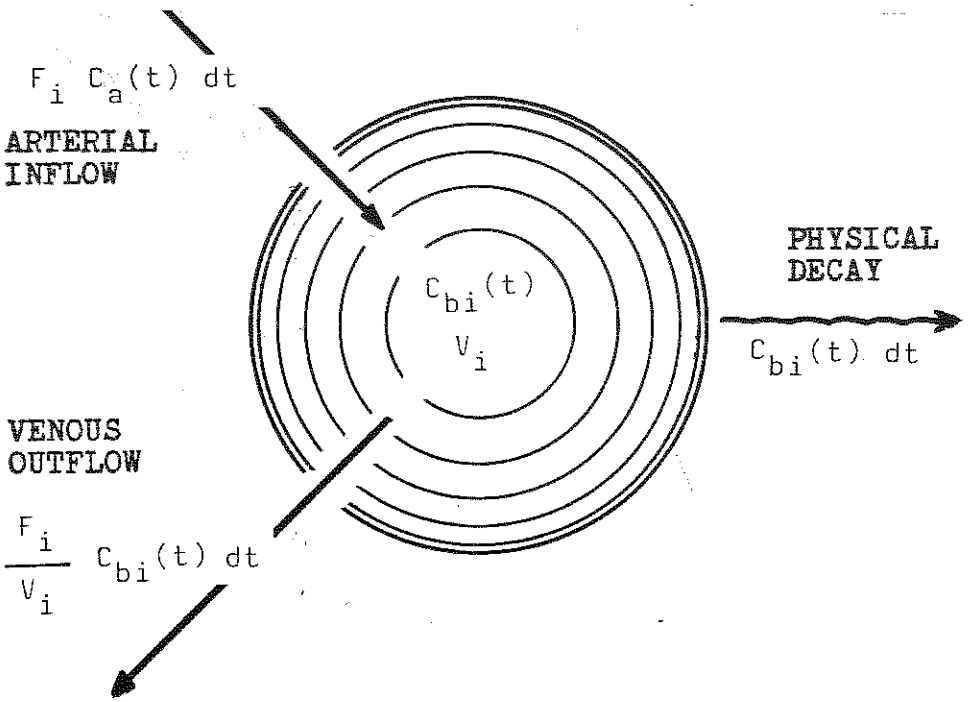

FIGURE 1.

N.B. The dependence of V_i on t, on F_i and on the local permeability x surface product of water across the capillary wall will be examined in a next mathematical development.

The review of already published methods (5-12,15) using $C^{15}O_2$ - $H_2{}^{15}O$ for the determination of cerebral blood flow reveals that F_i was always computed by a monoparametric estimation, an arbitrary value being allotted to V_i (table II).

The previously published methods lie either on the continuous inhalation of $C^{15}O_2$ and on a detection by PET after the equilibrium of activity being reached within blood and tissues (5-12), or on a bolus administration of $H_2{}^{15}O$, followed by the detection of the time course of tissular activity by a rapid sequential PET (15).

2.3.2. Equilibrium techniques.

2.3.2.1. Continuous inhalation of $C_2{}^{15}O$.

If the subject is allowed to breathe continuously a constant activity of $C^{15}O_2$, the concentration of $H_2{}^{15}O$ in the arterial blood and in the tissues raises and goes up to an equilibrium concentration after a 8-9 min time delay, t_{eq} .

2.3.2.2. Equations.

For values of $t \geq t_{eq}$, C_{aeq} and C_{beq} go up toward constant values and equation [3] simplifies to :

$$F_i \cdot C_{aeq} - \left[\frac{F_i}{V_i} + \lambda \right] \cdot C_{bieq} = 0 \qquad [4]$$

Any two-parameter analysis of the data being impossible, using this equation [4] and one set of data C_{aeq} and C_{bieq}, the authors (5-12) compute F_i by the equation :

$$F_i = \frac{\lambda}{\frac{C_{aeq}}{C_{bieq}} - \frac{1}{V_i}} \qquad [5]$$

2.3.2.3. Drawbacks of this method.

This method encounters many drawbacks, especially :

A. a sensitivity for the determination of F_i which decreases as F_i increases (table I)

B. a defavourable propagation of errors through equation [5] (13,14) (table I).

C. the impossility to assess V_i, the allotted value to V_i introduces an impossible-to-control unaccuracy in the determination of F_i.

2.3.2.4. General interest of equation [4].

Two extreme situations may be imagined, leading to two very interesting particular applications of the equilibrium model and of equation [4].

Equation [4] may be rewritten to evaluate the value of C_{bieq}:

$$C_{bieq} = \frac{F_i . C_{aeq}}{\lambda + \frac{F_i}{V_i}} \qquad [6]$$

2.3.2.4.1. If a radionuclide with a very short half-life is continuously infused into the arterial blood of a tissue element, the value of λ becomes to be high as compared with the ratio F_i/V_i and the equation |6| simplifies to :

$$C_{bieq} = \frac{F . C_{aeq}}{\lambda} \qquad [7]$$

where the value of the tissular concentration of the tracer at equilibrium, C_{bieq}, is roughly linearly proportional to F_i : the distribution of the radionuclide within the organ at equilibrium is a measurement of the corresponding distribution of regional blood flows.
Equation [7] is used for the determination of regional blood flows, using for example ^{81m}Kr.

			F_i $cm^3.min^{-1}.gr^{-1}$					RC cm^2
			0.2	0.4	0.6	0.8	I.0	
$\hat{F}_i$	SENSITVITY $gr.min.cm^{-3}$		0.98	0.48	0.29	0.19	0.13	
	RELATIVE ERROR $\Delta F_i/F_i$ (%)	HR	15.0	18.0	21.7	25.6	29.5	1.12
		MR	8.1	9.7	11.7	13.8	15.9	1.74
		LR	3.4	4.1	5.0	5.9	6.7	3.53

Table I. Estimated sensitivity and precision of the cerebral blood flow determined by the method of continuous inhalation of $C^{15}O_2$ (see 2.3.2.2.) ; F_i = cerebral blood flow ; RC = resolution cells area ; HR = high resolution ; MR = medium resolution ; LR = low res olution.
PET detection is performed with an ECAT II tomograph.

References	Allotted value to V_i in equation 5 .
Subramanyam (6)	0.85
Jones (5), Frackowiak (10),	1.0
Baron (9)	0.95

Table II. Allotted values to V_i, for computing F_i with equation 5.

The ideal tracer for such a determination should have a very short physical half-life and a great volume V_i of distribution within the organ.

For example, it is possible to compute that the ideal tracer for measuring cerebral blood flow by a continuous carotid infusion should have a physical decay constant higher than 12.18 min^{-1} (half-life, 3.4 sec), if the tracer is presumed to have a value of V_i = 0.8 $cm^3.gr^{-1}$ and if a loss of sentivity of 10% is accepted on the measurement of F_i as the cerebral blood flow goes from 0.5 to I.0 $cm^3.min^{-1}.gr^{-1}$.

2.3.2.4.2. On the contrary, with a radionuclide with a value of λ low in comparison with the ratio F_i/V_i , equation [6] describing its distribution within the tissue is :

$$\frac{C_{bieq}}{C_{aeq}} = V_i \qquad [8]$$

The distribution of the tracer indicates its regional volumes of distribution.
Equation [8] is used for the determination of the regional blood volumes, using for example ^{11}CO-tagged red blood cells.

2.3.3. Dynamic techniques.

2.3.3.1. Equations.

The differential equation [3] may be solved as follows, with initial conditions t = 0, $C_a(0) = 0$:

$$C_{bi}(t) = F_i \int_0^t e^{(\frac{F_i}{V_i} + \lambda)(t - \tau)} \cdot C_a(\tau)\, d\tau \qquad [9]$$

or

$$C_{bi}(t) = F_i \, e^{-\left(\frac{F_i}{V_i} + \lambda\right)t} * C_a(t) \qquad [10]$$

If sufficient information about the time-course of $C_{bi}(t)$ and of $C_a(t)$ is available, it is theoretically possible to derive estimations of both F_i and V_i, altogether with estimations of the errors on these two parameters.

2.3.3.2. Access to the data.

$C_a(t)$ is measured on sequential arterial blood samples (see 2.3.1.).

$C_{bi}(t)$ is detected by PET and is expressed in the same units systems as $C_a(t)$ is (see 2.3.1.) and these detected data are attributed to the different structures of the brain, according to an adequate topometry.

In fact, PET gives time-integrated values of $C_{bi}(t)$ and equation [10] should be rewritten :

$$\int_{t_j}^{t_{j+1}} C_{bi}(t) = F_i \int_{t_j}^{t_{j+1}} e^{-\left(\frac{F_i}{V_i} + \lambda\right)\tau} * C_a(\tau)\, d\tau \qquad [11]$$

2.3.3.3. Administration of $H_2{}^{15}O$.

Equations [10] and [11] may be used for the analysis of dynamic data detected during various modes of administration of the tracer :

- bolus administration, leading to a degraded δ input function.
- continuous administration, leading to a degraded rectangular-wave input funtion.
- ramp-function administration, difficultly carried out in practice.

2.3.3.4. Bolus administration of $C^{15}O_2$.

Raichle et al. (15) recently published the introductory considerations of a method using a bolus inhalation of $C^{15}O_2$ and a sequential PET detection.

The formulation of the model should be revised on two points :

- equ (2) and (4) of this paper don't take into account the physical decay of the tracer during the time of transfer of 15-O through the tissue,
- equ (3) is based on the Kety's equation, describing the volume of distribution of a tracer which instantaneously goes to equilibrium of concentration between blood and tissue.

Nonetheless, the idea to measure simultaneously the input function -$C_a(t)$- and the transfer function -$C_{bi}(t)$- of $H_2{}^{15}O$ within a tissue element after a bolus administration of the tracer could lead to interesting developments, with an appropriate reformulation of Raichle's equation, k in equation (2) becoming :

$$k = \frac{F_i}{V_i} + \lambda$$

and with a two-parameter estimation of F_i and of V_i, as we suggest in the present paper. The feasibility of this approach should be examined in a further step of this investigation.

2.3.3.5. Continuous administration of $C^{15}O_2$.

Equations [10] and [11] are suitable for a two parameter analysis of the data $C_a(t)$ and $C_{bi}(t)$ detected by PET from time 0 to equilibrium during the the continuous inhalation of $C^{15}O_2$.

This continuous administration mode was chosen because of the rather defavourable time resolution of the ECAT tomograph which is used for collecting the in vivo data.

3. NUMERICAL ANALYSIS.

Two sets of data are annexed to the present paper, in view of a preliminary study of the feasibility of the numerical analysis of the model, based on equations [10] an [11].

3.1. Annex 1 : values for $C_{bi}(t)$ are values collected from the whole head during short times of detection ; they are more suitable for testing eq [10].

3.2. Annex 2 : values for $C_{bi}(t)$ were collected on regions of interest selected on reconstructed tomograms ; they are time-integrated data, subject to be more suitably tested using equ [11] .

The points which should be investigated in a further step of the study may be pointed out as follows :
- study of the convergence of the numerical treatement of the data,
- test of the stability of the results in front of the amplitude of noise contaminating the data,
- evaluation of the propagation of errors within the computation process.

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