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Functional Cerebral Blood Flow Images by Positron Emission Tomography

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Abstract

In this study functional cerebral blood flow images (CBF) were generated using positron emission tomography (PET) for three different protocols. In the first protocol, $C^{15}O_2$ was inhaled by the patient for length of time 2.0 min (activity 6MBq/ml). In the second protocol, $H_2{}^{15}O$ was infused to the patient (2000 GBq/ml). In the third protocol a bolus of water was injected over a short time 5.0 sec (5000 GBq/ml).

For each of these protocols, the optimum integral time for CBF images was evaluated. Thereafter, comparison between the three different protocols was made on the basis of relative error on CBF.

Dynamic and integral analysis based on the Kety Model were applied to a dynamic sequences of positron emission tomographic scans collected during and following the administration of tracer. The dynamic analysis was used to correct continuously monitored arterial whole-blood activity for delay and dispersion relative to tissue scans. An integral analysis, including correction for this delay and dispersion was then used to calculate CBF on a pixel –by- pixel basis. Three computer programmers (TRACRS, MODELS and TURBCBF) were used to calculate CBF and generate functional CBF images.

From these different dynamic studies, the calculations predict that, the statistical errors in CBF, delay and dispersion in the case of the third protocol were small compared with the first protocol. Also the effect of varying scanning time on relative error of CBF were investigated for the three different protocols.

*This study was carried at Hammersmith Hospital MRC unit, Nuclear Medicine Department(2019), U.K

Introduction

The positron emission tomography (PET) is powerful research tool of great value to clinical physiologist. In its use to elucidate various aspects of regional cerebral function.

Recently, the PET technique developed as a result of three main contributing factors, first, the advantage of using positron-emitting isotopes to study the internal structures of the body, second, the successful use of image reconstruction technique in computer-aided transmission tomography provided the impetus for applying these some methods to the reconstruction of high resolution images of radionuclides distributed inside the brain, third, the introduction of methods for the rapid labeling of metabolic traces with suitable short-lived positron emitting isotopes end the development of theoretical models for describing the cerebral metabolic events made the quantitation of regional metabolism and regional cerebral blood flow (rCBF) possible. Today, in the early 1980s, PET has emerged as an enormously powerful clinical research tool for the study of normal and abnormal brain functions as well as physiological correlates of mental events.

In this paper we have to investigate the measurement of CBF and generating optimum quantitative CBF images by using PET and ^{15}O labeled water and CO_2. Three different protocols have been performed on the patient to produce an optimum integral time for scanning and from this, optimum quantitative CBF images. In the first protocol, the patient inhaled constant supply of $C^{15}O_2$ for images.In the first protocol, the patient inhaled constant supply of $C^{15}O_2$ for period of time 2.0 min at activity rate 6MBq/ml, in the second protocol $H_2{}^{15}O$ was infused to the patient at activity rate 6MBq/ml, in the second protocol $H_2{}^{15}O$was infused to the patient at activity rate 2.2×10^{3}GBq/ml,inthe third protocol bolus of $H_2{}^{15}O$. was injected with total activity 2.2×10^{5} GBq based on the criteria of the kety kinetic model for traces dynamic and integral analysis to the dynamic sequences of PET scan collected during and following the administration of tracer were used to correct arterial whole blood curves (input function) for delay and dispersion relative to tissue scan.

Three computer programmers (TRACERS, MODELS and TURBOCBF) were used in our mathematical calculations to find out an optimum time and quantitative CBF images.

Compartmental model used:

Most kinetic models commonly in use in nuclear medicine are compartmental models with first-order rate constant, describing the flux of material between compartments[2].Consider the simple two-compartment model illustrated in Figure 1.1

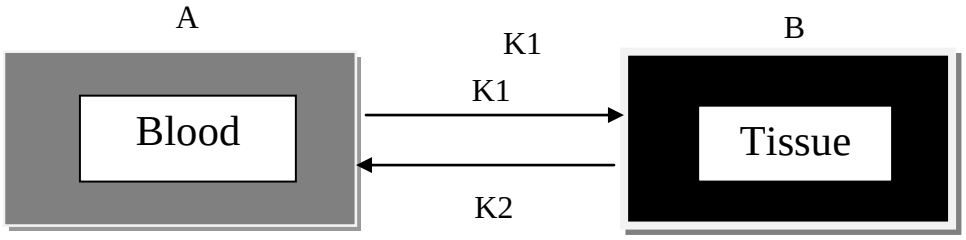

Fig 1.1 Transport between two compartments, A and B is described by rate constantsK_1 and K_2

If tracer is present in compartment A (blood) with a concentration defined byA(t), then the rate of change in concentration B(tissue) is described by:

dB(t) /dt = flux into B - flux out of B (1)

Because first order kinetics apply, the flux into B is simply K_1 A(t) and the flux out of B is K_2 B(t); therefore:

$$dB(t)/dt = K_1 A(t) - K_2 B(t) \quad (2)$$

This first order ordinary differential equation with constant coefficient is a typical example of the mathematical equations used to define tracer models. This time course of the tracer in the delivery compartment (usually the blood) A(t) is the input function, while the rate constants K_1 and K_2 are model parameters.

These two parameters can be estimated numerically with technique known as non-linear regression analysis.

The input function A(t) is usually measured by well counter, tissue activity B(t) is determined from the images.

Kety blood flow model:

All practical of H_2O technique for CBF measurement are based on the Kety blood flow model, which is described by the following differential equation[4]**:**

$$dCt(t)/dt = F\,Ca(t) - (F/Vd + \lambda)\,Ct(t) \quad (3)$$

where Ct(t) is regional tissue concentration of $H_2{}^{15}O$, Ca (t) is arterial whole-blood concentrationof $H_2{}^{15}O$, F is regional CBF (ml/min), Vd is volume of distribution of $H_2{}^{15}O$ (ml/ml) andλ is the decay constant of ^{15}O.

The main assumptions in eq (3) are that:

Water is freely diffusible, and this is not strictly true[7],resulting in possible underestimation of regional CBF[6] .The exact error in CBF will depend on the particular implementation of the model and on the actual value of CBF. The contribution to the signal in the region of interest (ROI) a rising from arterial activity is negligible[2],the venous and tissue concentration are negligible different[3] ,both F and Vd are constant during the measurement period.

The solution of eq(3) for Ct(0) = 0.0 is given by

$$Ct(t) = K_1\, c(t') * e^{-k2(t-t')}d't \quad (4)$$

Where $K_1 = F$, $K_2 = F/Vd + \lambda$

*Is mathematical convolution symbol.

The experimental protocols:

Six dynamic measurements were performed on the patient, two studies using $C^{15}O_2$ inhalation labeled with O^{15}, activity was 6.0 MBq/ml, and flow rate 500 ml/min, two studies using $H_2{}^{15}O$infusion with activity 2.2×10^3GBq/ml (volume 10 ml, infusion time 1 min.) and the other two studies were bolus injection of $H_2{}^{15}O$ (volume 10 ml, infusion time 10 sec.) with total activity 2.2×10^5GBq.

Measurement of activity for cerebral tissue and arterial blood:

The cerebral tissue time - activity curves were measured using the ECAT 931-08/12 PET scanner. Following acquisition of transmission scan of average count density 1.6×10^6 counts/plane[5] , for the purpose of attenuation correction. Sequential dynamic scans (frames) were collected over period 3.5 min. (for each study) according to the following protocols:

1 (background) frame of 30 sec, 4 of 5 sec and 16 of 10 sec. for water infusion the protocol: 1 (background) frame of 30sec, 12 of 5 sec and 12 of 10 sec. For bolus injection: 1 (background) frame of 30 sec, 30 of 2 sec and 12 of 10 sec.

For the third protocol the patient inhaled a constants supply of $C^{15}O_2$ for a period of

2min. beginning at the start of the second frame.

Arterial whole-blood time activity curves where measured on the six studies using an on-line detection system[8] . Blood was withdrawn continuously through a radial artery cannula at speed 5ml/min using polyethene tubing (length 65 cm from cannula to scintillation crystal) with an internal diameter of 1 mm and a wall thickness of 0.5 mm, total length of 7.5 cm of catheter tubing was positioned within a 4 mm-deep circular groove (diameter 2.1cm) of a plastic scintillation crystal (diameter 3.8 cm, thickness 8 mm) surround by lead housing. The attached photomultiplier tube was connected to a quad scaler, which in turn was linked to the scanner computer (Micro VaxII.DEC). The sensitivity of this blood monitoring system was 30 counts / sec/kBq/ml. Computer clock time and accumulated counts were recorded every seconds. For each study blood withdrawal was started first andscanning commenced when all tubing component were filled with blood[8]. Ahalf minute after end of scanning, a 2 ml calibration sample was collected through a three- way tap positioned directly behind the plastic scintillator, butin front of the peristalic pump. Following the collection of this calibrationsample, the whole blood circuit (including cannula) was flushed withheparenised saline.

All emission scans were reconstructed using a Hanning filter with a cut-offfrequency of 0.5 of maximum. This resulted in spatial of 8.4 x 6.6 mm fullwidth at half-maximum at the centre of the field of view.

After reconstruction, the dynamic images were transferred to a workstation(model 3/60).

Whole-brain ROIs were defined on planes 6-10 of the 15 collected planes. Then, before implemented any computer code to find out the CBF, it wasnecessary to correct for delay and dispersion, because in practice the timecourse of the arterial concentration Ca(t) arriving in brain can not beaccurately measured from the usual sampling site, the measured arterial bloodcurve from the radial artery will be delayed and dispersed compared to thecerebral arterial curve.

The dispersion in brachial vessels, radial artery, cannula and tubing can in practice be described by a single exponential[9] given by this equation:

$$Cm(t+ d) = p\ Ca(t) * \exp [- (p +\lambda)] \quad (5)$$

This equation described the relation between the measured arterial blood (Cm) and actual arterial blood concentration (Ca) , where d is the delay of the measured arterial blood curve and p is the time constant of single-exponential dispersion . By using Laplace transform with eqs(5) and (4) it is possible to drive an expression

between the PET signal and the measured blood curve[5]

$$\int_{T1}^{T2} Ct(t)dt=(k_1/pk_2)[p+\lambda \int_{T1+d}^{T2+d} Cm(t)dt+(k_2 -p-\lambda)\int_{T1+d}^{T2+d} Cm(t)*\exp(-k_2t)dt \quad (6)$$

Where k_1 = F and k_2 - F/Vd +λ T_1 is start time frame and T_2 is end time frame.

By performing multiple scans and monitoring arterial concentration Ca, it is possible to solve eq(6) for k_1 and k_2 using standard non-linear least-square fitting procedures assuming constant value for Vd (0.95 ml).

Blood calibration factor :

The calibration factor was obtained from the calibration sample (measured in well counter cross-calibrated against the PET scanner) collected 1.5 min after the end of inhalation of CO_2. The last half minute of the blood curve before withdrawal of the calibration sample was fitted to a single exponential.

The calibration sample was then calculated from the interpolated value of thisexponential curve[5] of the time of sampling and the sample well counter value.

Computational implementation:

Three computer programs have been involved in dealing with mathematicalmodel to find out the CBF and functional CBF images.

1- TRACERS program, this program will do the following:

* Taken the sample blood data as input data from the files created byVAX-II computer connected directly with Pet and well counter.
* Creates the region of interest (ROI) curves for the whole brain.

2- MODEL, is a general purpose program and will do the following:

* Taken the blood curves and tissue curves created by the previousprogram as input data.
* Solved a set of equations related to the kinetic models to evaluate k_l,vd, d,p and blood calibration factor.
* Comparing the model solution with experimental data.
* Adjusting the kinetic model parameters using non-linear regression fitting technique to find out the best fit.

3- TURBOCBF, this program was used to produce normalized blood flowfrom add images, also produces a linear flow images with pixel graylevel of a 256. The input data for this program were: delay, dispersion,blood calibration factor , scale factor (from Vax-II format to Sun format)and integral time.

Approachto find an optimum functional CBF images:

After reconstruction of dynamic images for the six dynamic studies, all datarelated to these images were transferred to workstation (model 3/60, Sun computer) . Thereafter, the optimum integral time was obtained according tothe following sequence:

TRACERSandMODELS programs were implemented to compute the model parameters.

TURBOCBF was implemented for different integral times (1 min, 2 min, 3min, etc.) and for each integral time the relationship between cerebral tissuecounts and CBFwas drawn, also the relationship between the counts andnoise level and CBF and error propagation corresponded to these CBF werealso drawn.

For different integral times and different CBF the relationship between CBFand relative error % on CBF was drawn. From these curves it is easy to pickup the less error % and thereat, the integral time corresponded to that error ispick up and will be considered as optimum time. The number of frames corresponded to that optimum time were picked upfromthe dynamic files and then all these frames were added andreconstructed using VAX-II program.

TURBOCBF program was loaded with the new data (optimum integral timeand Vax-Sun scale factor) and by creating look-up table for CBF and integraltissue counts, functional CBF images corresponding to that optimum timecan be evaluated..

Results

As a result of combination of dynamic and integral methods for generating anoptimum functional CBF images by performing three dynamic studies on thepatient, different curves and data from the implementation of the three computer codes(MODELS, TRACERS and TURBOCBF) have beenobtained. Figure 1A shown the arterial whole-blood curve (input function)for dynamic study no.1 ($C^{15}O_2$, inhalation for2 min, withdrawal time forblood sample 9.78 sec). Figure 1B shown the average whole-brain tissuetime-activity curve (dotted) together with the curve corresponding to the bestfit for delay (d), dispersion (p), volume distribution (Vd) and CBF. Figure1C gives the relationship between the scanning time in sec. And relative errorpercent on CBF for different values of CBF from 0.3 up to 0.9, we have chosen one value for CBF (0.6 ml/min) and we have done our analysis on this value for all dynamic studies. In this dynamic study, the optimum integral time for this study was 210.0 sec which is corresponding to 36.9% relative error on CBF and the optimum functional CBF

images corresponded to this time was shown in Fig-A Figure 2A shown the arterial whole blood curve for dynamic study no.2 (water infusion), this input function seemingly less noisy compared with the first study, Fig 2B indicates the same relation as Fig 1B. For this study the withdrawal time 11.61 sec and optimum integral time was 200 sec, relative error on CBF42.3% and functional CBF images corresponded to this time shown in Fig-B.

Fig 3A shows the arterial whole blood curve for dynamic study no. 3 (bolus injection, withdrawal time 8.06 sec). For this dynamic study the curve (Fig 3C) indicates that , the optimum integral time 150 sec and the relative error was 45.91% Table I gives all fitted values for the average whole-brain ROI (plane 6-10) for all three dynamic studies.

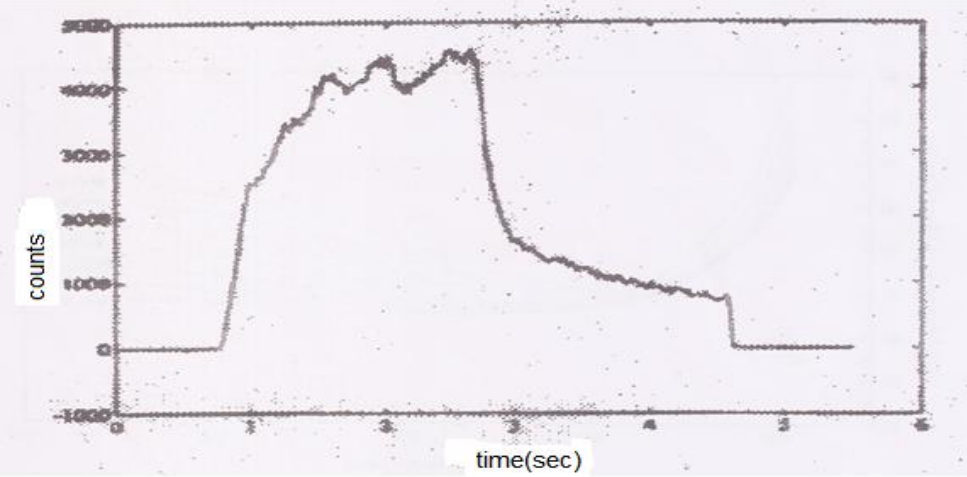

Fig.1A The arterial whole-blood time activity curve for dynamic study no1

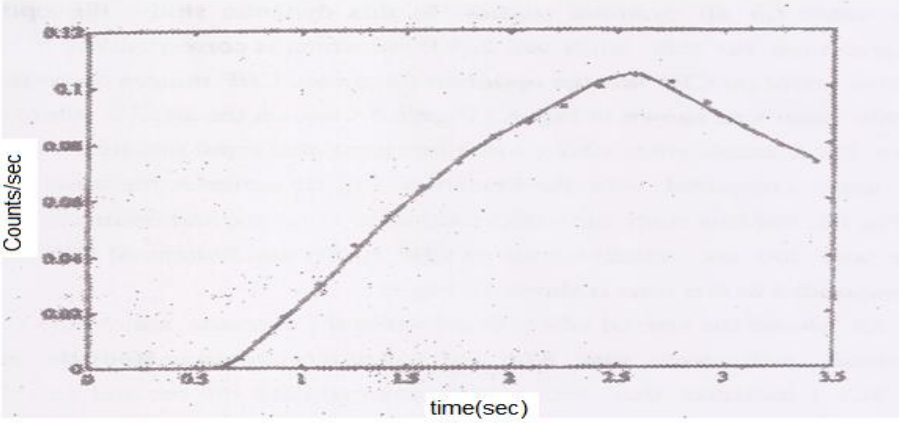

Fig.1B Cerebral tissue time-activity curve for whole brain region of interest

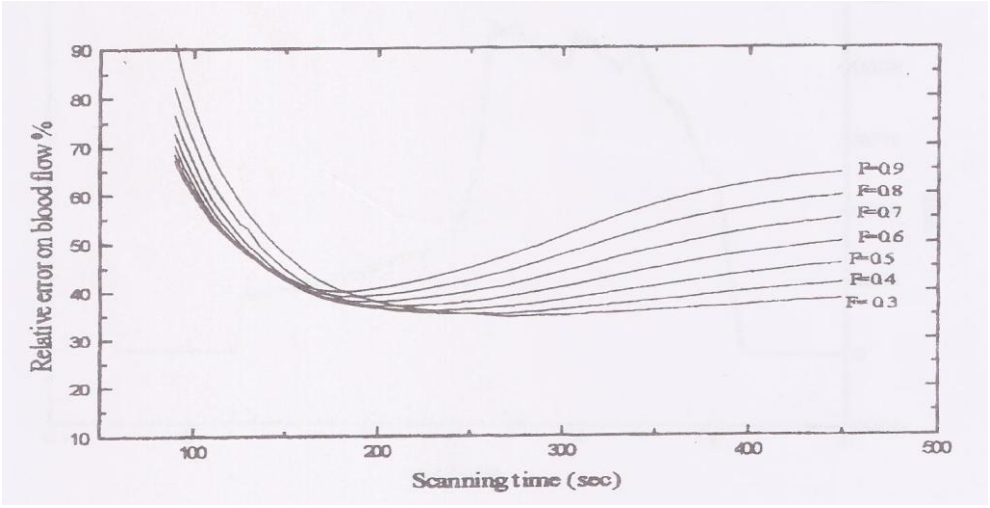

Fig.1C Relative error on CBF vs. integral scanning time for different values of CBF for dynamic study no1

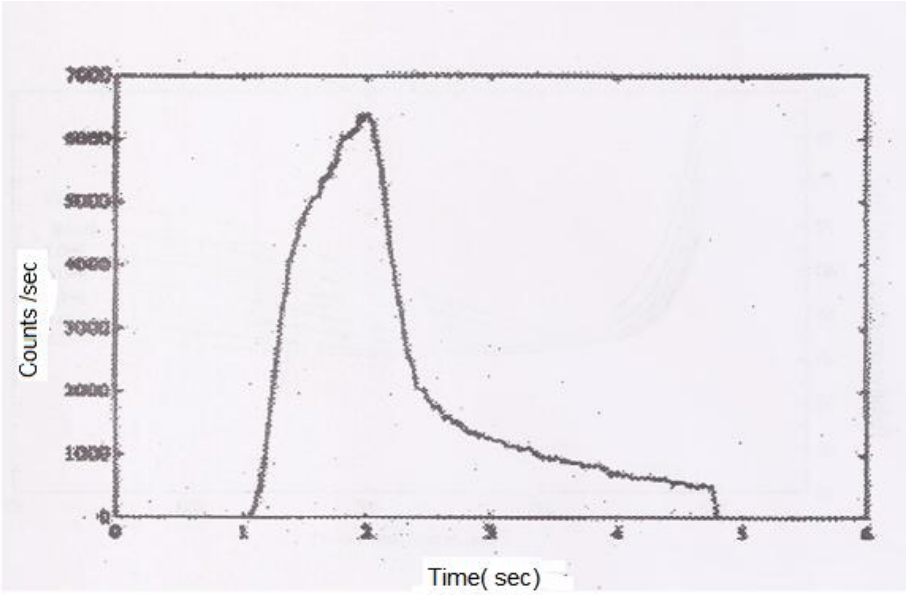

Fig.2A The arterial whole-blood time activity curve for dynamic study no2

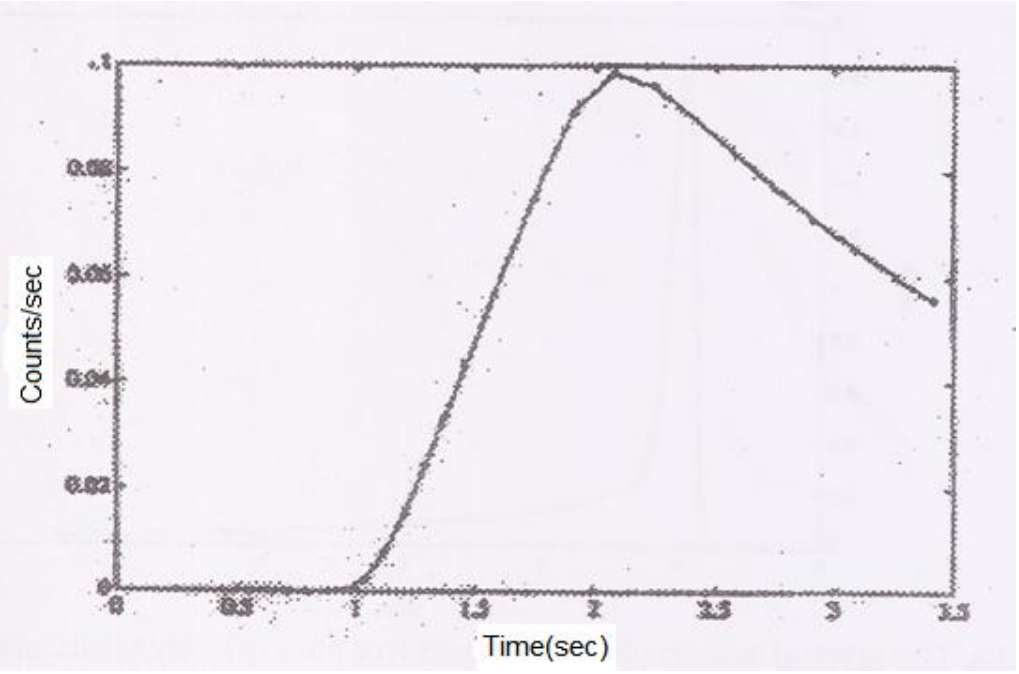

Fig.2B Cerebral tissue time-activity curve for whole brain region of interest

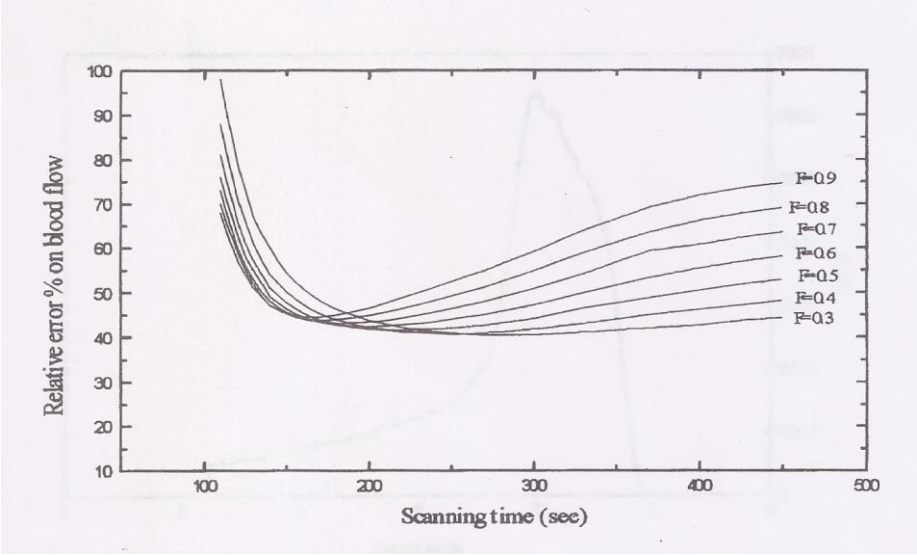

Fig.2C Relative error on CBF vs. integral scanning time for different values of CBF for dynamic study no2

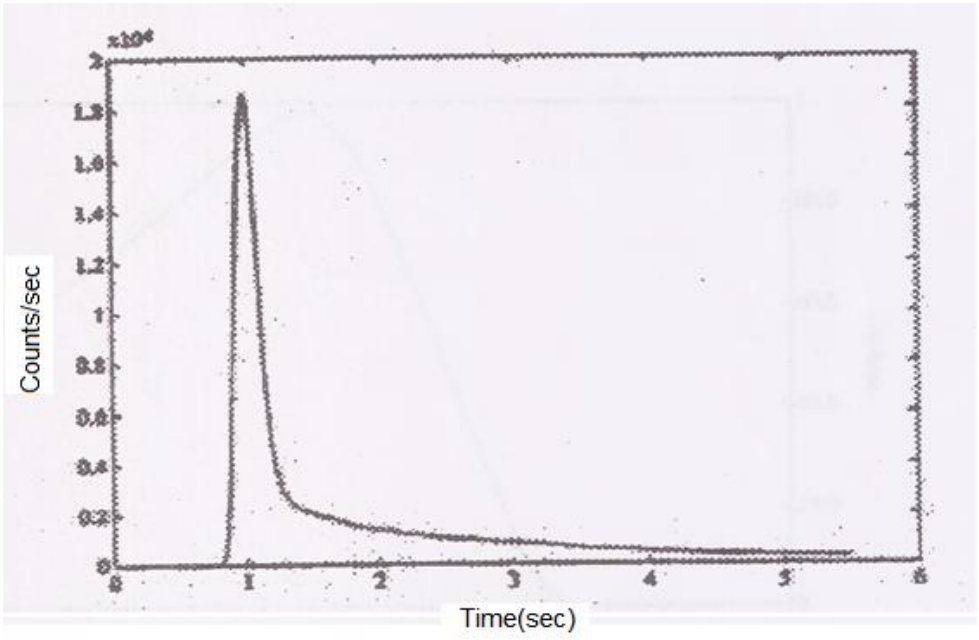

Fig.3A The arterial whole-blood time activity curve for dynamic study no3

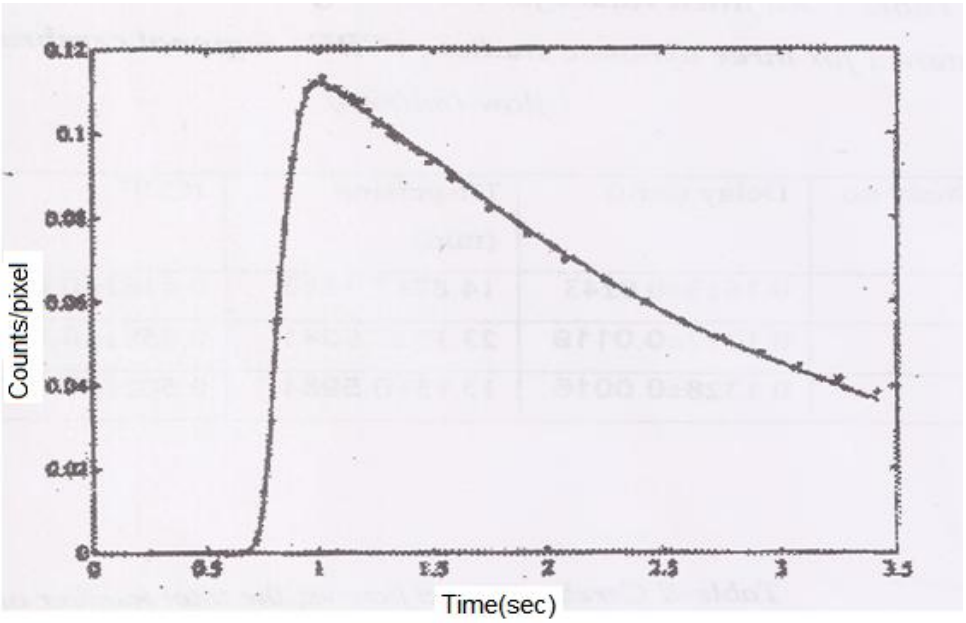

Fig3B Cerebral tissue time-activity curve for whole brain region of interest

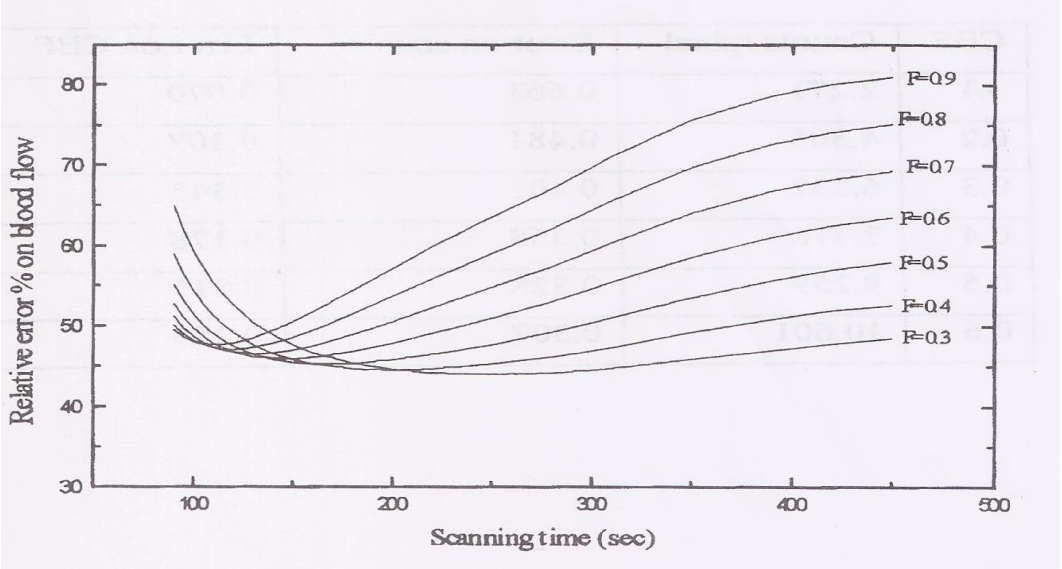

Fig.3C Relative error on CBF vs. integral scanning time for different values of CBF for dynamic study no3

Discussion

From the combination of dynamic and integral methods throughout the six dynamic studies

performed on the patient, it can be seen that, from the model fitting (Table- I) for the three different protocols, the error propagation on CBF in the third protocol (study no.3) was less compared to the first protocol (study no.1). This result might be recommended that the third protocol (water injection) was superior for generating functional CBF images. On the other hand, the results obtained from the dynamic integral for the third protocol shown that, the relative error on CBF corresponded to the optimum integral time was 45%, while the relative error on CBF for the first protocol was 36%, this discrepancy might be due to two reasons:

1- Errors due to arterial blood sampling.

* The noise level on tissue counts corresponded to the optimum integral time for the third protocol was large (30%) compared to the noise level in the first protocol (22%).

* The sensitivity of CBF to the volume distribution of water (Vd) in the third protocol might be more than in the first protocol

Investigation of errors

The CBF and functional CBF images which we have obtained from the six dynamic studies carried out at Hammersmith Hospital, PET unit were optimum for the time being, but the studies on the quantitative CBF images should be extended to overcome the errors which affected the CBF images. Some of these errors we will mention below

In our continuous withdrawal system, the external dispersion was caused by the long

distance (40 cm) between the catheter and the detector. With respect to this error a short distance tubing might be better also increasing withdrawal speed of blood sampling from 5 ml/min up to 20 ml/min, this will reduce the dispersion up 1.0 sec[8]

2- Errors due dispersion correction.

In our study a fixed value for dispersion (10.0 sec) was used, this value was previously determined experimentally by Lammertsma[9]. This timeconstant might have the following ambiguities: (a) the external dispersion in the tube system depends not only on the withdrawal speed but also on another hemorrheological factors such as the heamatocrit[8].

(b) the internal dispersion will be dependent on each patient.

3- Error due to delay between blood curve and tissue curve.

Another practical problem that might degrade the quality of measured input function (blood curve) is the ambiguity of the relative axis between Ca(t) and Ct(t). In our study, the time delay was 9.0 sec as the result of the measurement, any error in the measurement of delay even a few second will affect the CBF.

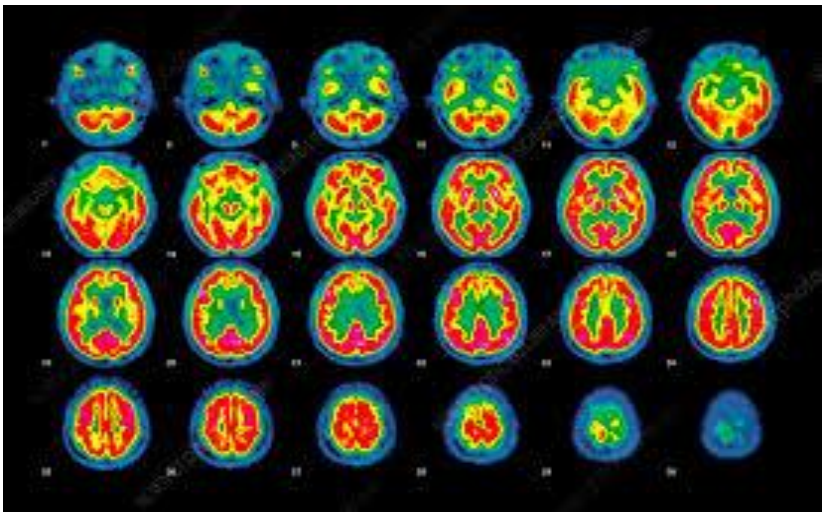

Fig-A an optimum functional images of regional cerebral blood flow corresponding to dynamic study no.1

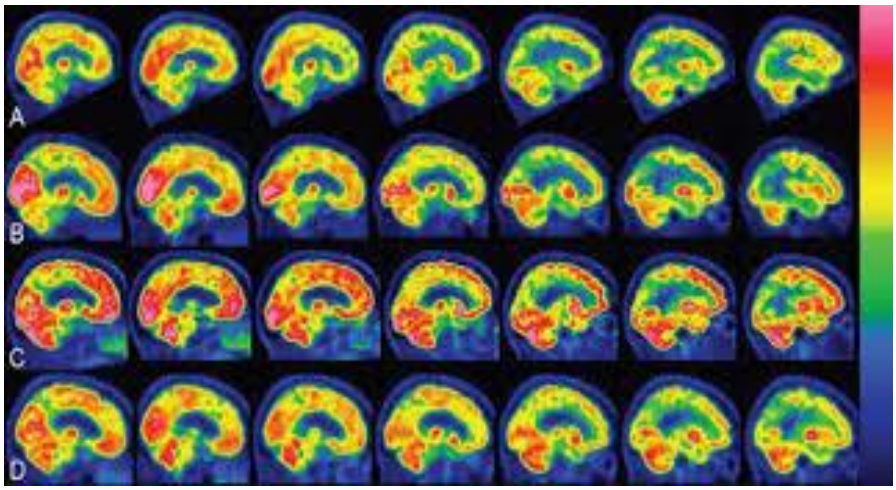

Fig-B an optimum functional images of regional cerebral blood flow corresponding to dynamic study no.2

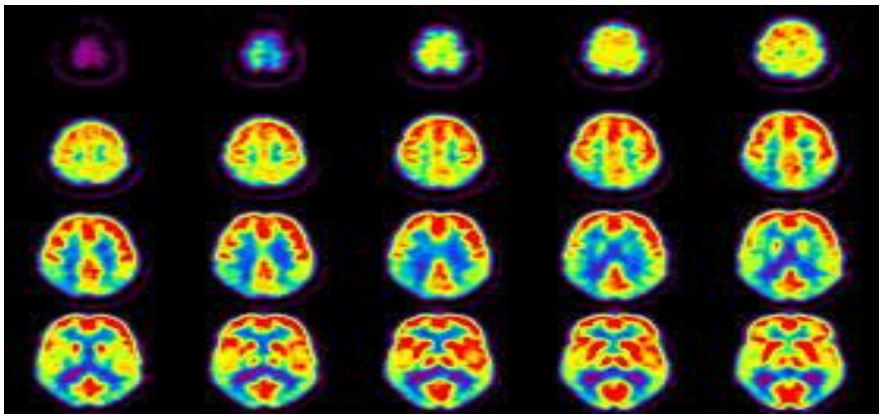

Fig-C an optimum functional images of regional cerebral blood flow corresponding to dynamic study no.3

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