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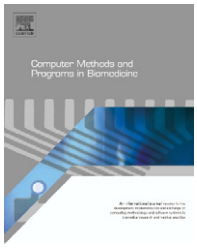

A novel blood-cell-two-compartment model for transferring a whole blood time activity curve to plasma in rodents

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ABSTRACT

The term input function usually refers to the tracer plasma time activity curve (pTAC), which is necessary for quantitative positron emission tomography (PET) studies. The purpose of this study was to acquire the pTAC by independent component analysis (ICA) estimation from the whole blood time activity curve (wTAC) using a novel method, namely the FDG blood-cell-two-compartment model (BCM). This approach was compared to a number of published models, including linear haematocrit (HCT) correction, non-linear HCT correction and two-exponential correction. The results of this study show that the normalized root mean square error (NRMSE) and the error of the area under curve (EAUC) for the BCM estimate of the pTAC were the smallest. Compartmental and graphic analyses were used to estimate the metabolic rate of the FDG (MR_{FDG}). The percentage error for the MR_{FDG} (PE_{MRFDG}) was estimated from the BCM corrected pTAC and this was also the smallest. It is concluded that the BCM is a better choice when transferring wTAC into pTAC for quantification.

1. Introduction

Positron emission tomography (PET) combined with tracer kinetic modeling is an excellent tool for quantification of parameters of interest. For instance, after venous injection of FDG, the local metabolic rate of glucose can be accurately quantified. The arterial tracer plasma time activity curve (pTAC) is referred to as an input function because it records the delivery of the tracer to all tissues. In addition, the arterial pTAC is necessary for rate constant calculations where it serves as an input for the tracer kinetic model. Therefore, an accurate determination of the pTAC is important when carrying out kinetic modeling. The gold standard for pTAC determination is arterial blood sampling [1,2]. This technique relies on arterial cannulation and frequent blood sampling, but is uncomfortable due to the need for arterial puncture. The arterialized venous method [3] uses a heated limb to abate the invasion but still has several drawbacks including repeated radiation exposure of the blood sampler, frequent sampling, and centrifugation. All of these affect the accuracy of the pTAC due to gross error. Furthermore, there is relatively large blood loss, which may affect the physiological parameters. These problems have led several groups to investigate alternative methods. The alternatives include the following:

(1) A population-based pTAC, which is generated by averaging the pTACs from a sample population. After taking one or two blood samples from an individual, the estimated pTAC

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can be obtained by scaling the population-based pTAC using the actual arterial plasma activity [4,5,14]. However, the quantitation error may become larger due to the different physiological states of the individuals as well as the protocol itself.

(2) Positron-emitting nuclides emit positrons that traveling with a finite range before undergoing annihilation. Thus, it is possible to detect the positron before annihilation. Two β-sensitive probes are used to directly measure the whole blood time activity curve (wTAC) [6,7]. One is inserted into the artery directly, and the other is inserted close to the artery in order to detect accumulated tracer in the surrounding tissue. After correction for tracer sticking and dispersion relative to the probe using a one-compartment model, the wTAC is determined by subtracting the surrounding tissue signal from the arterial signal. This approach has several disadvantages, including invasiveness due to surgical insertion and the large number of annihilation photons that need to be counted.

(3) In another method, catheters are inserted into an artery and vein. Using the catheters, a fraction of whole blood flow is shifted outside the body through an arteriovenous shunt system [7,8]. The wTAC can be derived from a coincidence probe or β-sensitive probe in the arteriovenous shunt system. The disadvantages of this method include invasive surgery to create the arteriovenous shunt and adhesion of the tracer to the catheters, which will affect accuracy.

(4) A further method involves correction for the partial volume effect and the spillover effect with dynamic images. Here, the image-based wTAC is determined from the region of interest (ROI) within the blood pool [7,9]. This method is noninvasive and simpler.

(5) Factor analysis (FA) and independent component analysis (ICA) can also be used to segment the blood pool from the dynamic images. The wTAC may be derived from an average of the segmented blood pool [7,10,11,12]. This method is most attractive because it is noninvasive, involves a simpler protocol than manual blood sampling, β-sensitive probes, and an arteriovenous shunt system and has a higher precision than the ROI method.

It is important to transfer the wTAC to pTAC accurately because most of the methods described above only produce the wTAC. The purpose of this study is to acquire the tracer pTAC from the ICA-estimated wTAC using a novel method, the FDG blood-cell-two-compartment model (BCM) and to compare the results with the published models, namely the linear haematocrit (HCT) correction [12], the non-linear HCT correction [9], and the two-exponential correction [1,6,8,13].

2. Materials and methods

2.1. Data acquisition and preprocessing

Imaging coverage from the brain to the heart apex was performed using a micro PET R4® (Concorde Microsystems, now Siemens). After a transmission scan using a ^{68}Ge rod source for attenuation correction, a dynamic PET image was acquired at rest for 3600 s. This produced 31 time frames (6 images of 10 s, 6 images of 30 s, 6 images of 60 s, 5 images of 120 s, 8 images of 300 s) after a bolus injection of 18F-FDG. The transaxial images were reconstructed using the filtered backprojection (FBP) method to give a $256 \times 256 \times 63 \times 31$ four-dimensional matrix with a pixel size of 0.423 mm × 0.423 mm × 1.121 mm. Arterial blood samples were taken at 0, 8, 15, 30, 45, 60, 120, 180, 300, 450, 600, 900, 1500, 2100, 2700 and 3600 s. After spinning for 5 min in a centrifuge, 40 μL of plasma from each sample was counted in a gamma counter. The HCT was obtained by linear HCT correction. Two groups of normal adult male Sprague–Dawley rats (SD rats) weighing 350–450 g were used in this study (Group 1: $n = 3$ and Group 2: $n = 3$).

2.2. ICA-estimated wTAC by Su's method

Su et al. proposed a method to extract the image-derived wTAC from dynamic PET images using ICA [12]. Dynamic PET images are treated as mixed signal that is the spatial distribution of several tissues. ICA can estimate the tissues that are spatially statistically independent. After the ICA estimation, the cardiac blood pool is segmented into a dynamic component image. The mask of the cardiac blood pool ICA image is then determined using the Gaussian fitting method and the image dilation method. The wTAC is also corrected for the partial volume and any spillover effect.

2.3. WTAC and pTAC processing

Both the image-derived wTAC and the manually sampled pTAC are discrete points with different time intervals. When calculating the tracer kinetic model, the wTAC and pTAC need to have the same time intervals so that they are available at any arbitrary time point due to convolution and numerical integration of differential equations. The wTAC and pTAC are linearly interpolated using the post injection time to time of peak in the curve and are fitted using three exponentials from the time of the peak to the end time [3,5]. These equations are

$$C(t) = m \times t \quad 0 \le t < \text{time to peak} \tag{1}$$

$$C(t) = \sum_{i=1}^{3} A_i \, e^{-\lambda_i t} \quad t \ge \text{time to peak} \tag{2}$$

where $C(t)$ is the radiotracer concentration at time t and m is the fitted parameter for the linear interpolation. A_i, and λ_i are fitting parameters for the two-exponential correction.

2.4. Transferring wTAC to pTAC

Four methods of transferring wTAC to pTAC are available; our proposed method named FDG BCM, linear HCT correction as proposed by Su et al. [12], non-linear HCT correction as proposed by Wahl et al. [9], and two-exponential correction as proposed by Lammertsma et al. [1]. All four methods were evaluated in this study.