Reduced Scanning-Time with a Dual-Injection Protocol for Dynamic Whole-Body PET

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***Abstract*–Dynamic whole-body (DWB) PET data for irreversible tracers, such as [^{18}F]-FDG, can be obtained with conventional PET scanners using multi-bed multi-pass data acquisition protocols, providing parametric images, which are more informative than standard SUV images. The drawback is a relatively long scanning time. Recently, a dual injection protocol with a reduced scanning time was proposed for a total-body PET scanner (Wu et al., JNM 2022). We developed a dual-injection protocol for a conventional PET scanner with multi-bed multi-pass acquisition. The input function is derived from the heart or aorta, and fitted with an analytical function, with the 1st part being obtained after the 2nd injection. Two different models were used for fitting the time-activity curves: standard compartmental modelling (CM) and a combination of CM and Patlak analysis. We have evaluated the protocol using computer simulations, and investigated the effect of different injection fractions, injection time-points, scan start-times as well as different values of blood volume (V_b) and tracer non-irreversibility (k_4). Our results showed that the injection fraction and time point for the 2nd injection had minor impact on the estimated parameters. While a late scan start time as well as non-zero V_b or k_4 values could result in bias. Both bias and variance were lower with the combined model as compared to the standard model. Also, the parameter estimation was not very sensitive to errors in injection fraction with the combined model. In conclusion, we found that the proposed protocol is feasible for obtaining dynamic whole-body PET data with irreversible tracers, using the multi-bed multi-pass acquisition protocol, while still measuring individual AIFs.**

I. Introduction

UNLESS a total-body PET scanner, with a long axial field-of-view (FOV) [1], is available, dynamic whole-body (DWB) PET scans are performed with multi-bed multi-pass (MB-MP) acquisition [2]. Using kinetic analysis, parametric images can then be derived. For irreversible tracers, such as [^{18}F]FDG, Patlak analysis [3] is typically used, and the parameters obtained represent irreversible uptake rate, (K_i) and volume of distribution plus blood volume (V_d+V_b). The drawbacks of dynamic imaging include the long scanning time and the requirement of an arterial input function (AIF). If the data acquisition starts at the time of injection of the tracer, an image derived input function (IDIF) can be obtained. When using Patlak analysis, the early part of the tissue time-activity curves (TACs) is not needed, suggesting that the data acquisition could start some time after the injection. However, that means missing the early part of the IDIF.

A relative Patlak approach was presented, which simply ignores the initial part of the AIF, and can be useful if absolute values are not required [4]. Several scanning protocols with a late-start time have also been proposed in combination with a population-based input function [5]-[7]. These allow for absolute quantification but may suffer from limited accuracy. A dual injection strategy was proposed for quantification of reversible tracers in brain PET studies using a reference region model [8]. Recently, Wu et al. proposed a dual-injection protocol for FDG studies with a long axial FOV PET scanner [9].

In this paper, we propose a dual-injection protocol for irreversible tracer studies with a conventional PET scanner and MB-MP data acquisition. We present an evaluation base on computer simulations, looking at various factors affecting the quantification.

II. Methods

A. Protocol

The tracer dose is divided into two injections, the first one containing the main part of the dose. The proposed protocol is illustrated in Fig. 1 and can be described as follows:

1) The first injection is administered.
2) The scanning starts 30 min later with 4 scans over 6 bed-positions with 35 s per bed-position.
3) A second injection is then administered, and dynamic acquisition is performed over the heart region with 10-20 s time frames for 2 min.
4) Finally, another 4 multi-bed scans are performed.

We assume that the two injections are identical apart from activity and that the injection fractions are known. Various alternative versions of this protocol will be investigated as described below.

B. Data generation

The AIF was generated based on an analytical function proposed by Feng et al. [10]. The activity concentration in plasma, C_p, at time t was given by:

$$C_p(t) = f_1 C_i(t) + f_2 C_i(t - \Delta t) \quad (1)$$

with

$$C_i(t) = (A_1 t - A_2 - A_3)e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t}$$

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where f_1 and f_2 are the injection fractions for the 1st and 2nd injection, respectively (f_1+f_2=1), Δt is time delay between the two injections, and A_1-A_3 and λ_1-λ_3 are the parameters of the Feng-function. In the simulations below, we used the following parameter values: A_1=23 Bq/mL/min, A_2=0.6 Bq/mL, A_3=0.57 Bq/mL, λ_1=4.1 min^{-1}, λ_2=0.12 min^{-1}, λ_3=0.01 min^{-1}.

The activity concentration in tissue as a function of time was generated with a 2-tissue compartment (2-TC) model (Fig. 2a) as follows:

$$C_T(t) = V_b C_p(t) + (1 - V_b) C_p(t) \otimes F(t; K_1, k_2, k_3, k_4)$$

where V_b is the fractional blood volume and $F(\cdot)$ is the impulse response function of the model. In most of the simulations below we used the following parameter values: K_1=0.1 mL/min/mL, k_2=0.2 min^{-1}, k_3=0.07 min^{-1}, k_4=0-0.014 min^{-1}, V_b=0-0.2.

Normally distributed noise was added to the data, with a standard deviation of $S_i = c\sqrt{a_i/\Delta t_i}$, where c is a scaling factor, a_i is the activity concentration in frame i, and Δt_i is the length of the time-frame. For the AIF we used c=0.01, and for the tissue TACs c=0.03. All time frames were 35 s long, apart from those of the dynamic scans, which were 10-20 s.

C. Data analysis

The IDIF was estimated by fitting (1) to the sampled noisy AIF data. The injection fractions were assumed to be known (from well-counter measurements).

For the fitting of the tissue TACs, based on the fitted input function, we have investigated two different methods:

1) A standard irreversible 2-TC model, with 3 rate-constants (Fig. 2b). From these, we derived the output parameters: $K_i = K_1 k_3/(k_2 + k_3)$, and $V_d = K_1 k_2/(k_2 + k_3)^2$.
2) A combination of Patlak analysis and compartmental modelling (CM), similar to [8]. The Patlak model was applied to the data corresponding to the 1st injection, while CM was used for the 2nd injection data, with an uncoupled 2-TC model (Fig. 2c). Three parameters were used: K_i, V_d and K_1' with $k_2' = K_1'/V_d$, where $K_1' = K_1 k_2/(k_2 + k_3)$ and $k_2' = k_2 + k_3$.

The blood volume (V_b) was not explicitly included in the models. We therefore assumed it would be incorporated into the estimated V_d values, which would thereby correspond to the Patlak intercept (V_d+V_b).

D. Evaluation

We have evaluated the effect of the following factors on the quantification: 2nd injection fraction (5, 10, 20%), time-point for injection-2 (37, 44, 51 min), start of scan after injection-1 (15, 30, 45 min), blood volume (0-20%), "de-phosphorylation" rate (k_4) (0-20% of k_3), and injection-fraction error (0-50%). Ten noise realizations were performed in each experiment, and the mean and SD of K_i and V_d were calculated.

III. Results

Figure 3 shows two examples of simulated and fitted AIFs. In one case, there is a good agreement between the simulated and fitted curves, while, in the other case some discrepancy can be seen around 5-10 min p.i. Figure 4 shows examples of simulated tissue TACs for two noise-levels, fitted with the two models. Slightly different fits can be obtained with the different models, showing that they are not equivalent.

Figure 5 shows the estimated K_i and V_d values for different injection protocols with the two models. The 2nd injection fraction does not have a significant impact on the estimated parameters, within the range 5-20%. The 2nd injection time point has a small effect on the estimated parameters when the standard model is used, but not when the combi model is used. The scan start time has only a small effect on the estimated parameters up to 30 min p.i., but >10% bias in K_i is obtained with a 45-min start time with both models.

Figure 6 shows the effect of non-zero V_b and k_4. Both situations lead to bias. The blood volume, V_b, was not explicitly included in the models, which were designed for irreversible tracers, i.e. k_4=0. With V_b=20% the K_i bias was ~20%, while with a k_4-value equal to 20% of k_3, it was >40%.
Further simulations showed (data not shown) that bias and variance are lower with the combi model than with the standard model in various situations. Also, with the combi model, the parameter estimation was not sensitive to errors of up to 50% in injection fraction.

IV. Discussion & Conclusions

We have performed simulations to evaluate a dual-injection protocol for acquiring dynamic whole-body data for irreversible tracers with a multi-bed multi-pass scan. We implemented two different models for fitting the tissue TACs.

Our results show that the injection fraction and time point for the 2nd injection have minor impact on the estimated parameters, while a scan start time > 30 min can lead to bias in the estimated parameters. Non-zero V_b and k_4 values also leads to bias. Both bias and variance were lower with the combi model compared to the standard model. Furthermore, the combi model was less sensitive to errors in injection fraction.

The overall conclusion is that the proposed dual-injection protocol with a reduced scanning time is feasible for obtaining dynamic whole-body PET data with irreversible tracers, using the multi-bed multi-pass acquisition protocol, while still measuring individual AIFs.

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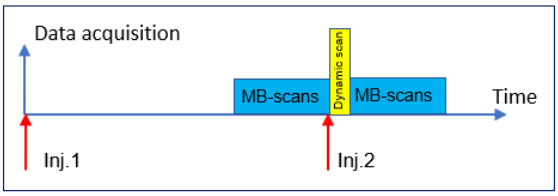

Fig. 1. Dual-injection protocol with a series of multi-bed (MB) scans, starting some time after the 1st injection, a short dynamic acquisition directly after the 2nd injection, and then another series of MB-scans.

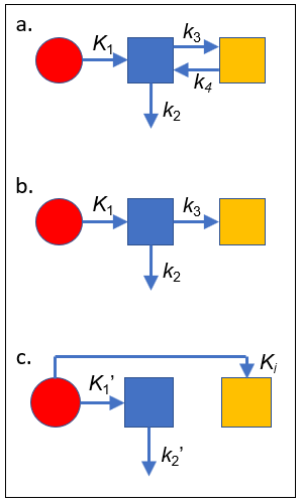

Fig. 2. Compartment models used, including a) reversible 2-TC model, b) irreversible 2-TC model, and c) uncoupled irreversible 2-TC model.

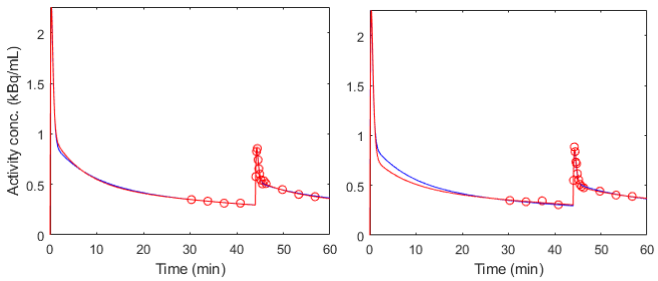

Fig. 3. Simulated AIFs, including true curves (blue), sampled values (circles) and fitted curves (red) for 20% 2nd inj. protocol, with good (left) and less good (right) agreement.

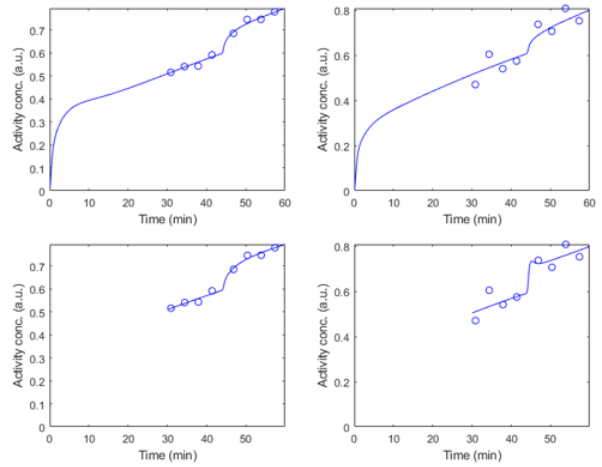

Fig. 4. Simulated TACs (20% 2nd inj.) fitted with the standard (top row) and the combi method (bottom row) for low (left column) and high (right column) noise-levels. Circles are data samples, solid lines fitted curves and dashed lines true curves.

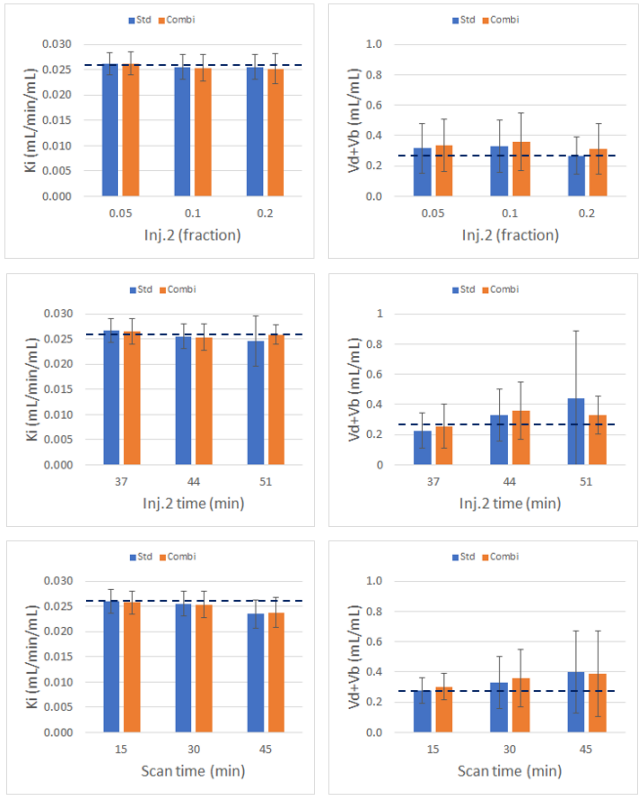

Fig. 5. Estimated K_i (left) and (V_d+V_b) values (right column) for standard (blue) and combi (red bars) models, as a function of injection -2 fraction (top), injection-2 time-point (middle) and scan start time (bottom row). The dashed horizontal lines indicate true values.

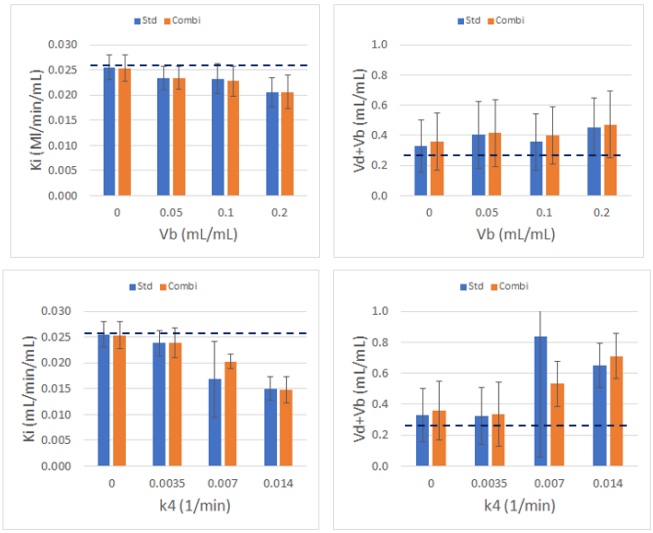

Fig. 6. Estimated K_i (left) and (V_d+V_b) values (right column) for standard (blue) and combi (red bars) models, as a function of blood volume (V_b) (top) and un-trapping rate (k_4) (bottom row). The dashed horizontal lines indicate true values.