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Optimization of a Model Corrected Blood Input Function from Dynamic FDG-PET Images of Small Animal Heart *In Vivo*

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Abstract

Quantitative evaluation of dynamic Positron Emission Tomography (PET) of mouse heart *in vivo* is challenging due to the small size of the heart and limited intrinsic spatial resolution of the PET scanner. Here, we optimized a compartment model which can simultaneously correct for spill over and partial volume effects for both blood pool and the myocardium, compute kinetic rate parameters and generate model corrected blood input function (MCBIF) from ordered subset expectation maximization – maximum a posteriori (OSEM-MAP) cardiac and respiratory gated ^{18}F -FDG PET images of mouse heart with attenuation correction *in vivo*, without any invasive blood sampling. Arterial blood samples were collected from a single mouse to indicate the feasibility of the proposed method. In order to establish statistical significance, venous blood samples from $n=6$ mice were obtained at 2 late time points, when SP contamination from the tissue to the blood is maximum. We observed that correct bounds and initial guesses for the PV and SP coefficients accurately model the wash-in and wash-out dynamics of the tracer from mouse blood. The residual plot indicated an average difference of about 1.7% between the blood samples and MCBIF. The downstream rate of myocardial FDG influx constant, K_i ($0.15 \pm 0.03 \text{ min}^{-1}$), compared well with K_i obtained from arterial blood samples ($P=0.716$). In conclusion, the proposed methodology is not only quantitative but also reproducible.

Index Terms

Tracer Kinetic Modeling; FDG-PET; Cardiac and Respiratory Gating; OSEM-MAP; Blood Input Function; Small Animals

I. Introduction

Tracer kinetic modeling is commonly used for quantitative evaluation of dynamic PET data. The estimation of kinetic rate constants requires an accurate knowledge of the blood input function. However, quantitation of dynamic PET data of the mouse heart *in vivo* is challenging due to the small size of the heart and the limited intrinsic spatial resolution of the PET scanner [1], [2]. As a result, the image-derived blood input function (IDIF), which is the same as blood pool (BP) time activity curve (TAC), is susceptible to partial volume (PV) effect and spill-over (SP) radioactivity [3] from the surrounding myocardium tissue and vice versa. Also, cardiac and respiratory motion can cause further cross contamination between BP and myocardium by blurring the images. Although invasive arterial blood sampling is the gold standard for measuring the blood input function [4], it requires extensive animal handling. Hybrid imaging method is another technique which is a combination of the image-derived approach at the early time points and blood sampling at

the late time points in a dynamic PET scan [5]. Factor Analysis is an image-derived approach which lacks the ability to account for the significant SP into the blood from the surrounding left ventricle (LV) and the right ventricle (RV) at the early time points [6]. Earlier work by El Fakhri et al [7] also accounted for blood volume contribution from both the RV and LV into the tissue, but did not account for SP contamination from the tissue to the blood in a factor analysis approach to measure myocardial perfusion using ^{82}Rb PET in a 2-compartment kinetic model.

The effect of iterative OSEM-MAP reconstruction algorithm on IDIF has been reported by Stout et al [8] and more recently by Shogi et al [9]. The authors reported significant SP contamination from the tissue to the blood especially at the late time points, in spite of using iterative algorithm. In an earlier work from our laboratory, we established the significance of cardiac gating and OSEM-MAP reconstruction algorithm in reducing SP contamination in IDIF [10]. Recent work by Fang et al concluded that a compartment model corrected blood input function when applied to IDIFs obtained from high-resolution images with less severe PV recovery and SP contamination, may result in an improved estimate of the downstream FDG influx constant [11]. The combined effect of resolution and model correction with correct bounds for PV recovery and SP contamination on the estimation of input function and FDG influx constant, has not been shown to-date. In this study, we optimized a compartment model which can simultaneously account for SP and PV effects for both BP and the myocardial tissue, compute kinetic rate parameters and generate model corrected blood input function (MCBIF) from OSEM-MAP cardiac and respiratory gated ^{18}F -FDG PET images of the mouse heart with attenuation correction *in vivo*, without the need for any invasive blood sampling. We validate our methodology by blood sampling and also measure the downstream rate of myocardial FDG uptake. We compare our results with the usual method of performing FBP reconstruction without gating [11].

II. Materials And Methods

All experiments were performed in compliance with the Guide for the Care and Use of Laboratory Animals, published by the National Institutes of Health and was conducted under protocols approved by the Institutional Animal Care and Use Committee at the University of Virginia.

A. Imaging Protocols

Following the protocol in [12], the animals were fasted overnight with only access to water. PET scans were performed between 9 a.m. and 5 p.m. on anesthetized animals. We used a similar imaging protocol as described in [10] except for using a different anesthesia and respiratory gating in addition to cardiac gating. Briefly, $n=6$ adult C57BL/6 male mice (9 to 10 weeks of age) obtained from Charles River, with ECG surface electrodes (Blue Sensor, Ambu Inc., Glen Burnie, MD) and a respiratory pillow attached to their limbs and chests respectively, were imaged using a microPET Focus-F120 scanner (Siemens, Inc.) under sevoflurane anesthesia [13]. Transmission scan using Co57 point source was done for attenuation correction prior to FDG administration. 60 minute dynamic PET scan was performed under 2 to 2.5% sevoflurane anesthesia in oxygen, which was initiated few seconds before the administration of 29.6 MBq ^{18}F -FDG for 30 seconds via a tail-vein catheter to capture the initial time points. A small-animal gating and monitoring system (Small Animal Instruments, Inc., model 1025L for PET) was used for continuously monitoring heart rate, respiration, and core body temperature. Cardiac gate signals generated at the end-expiration phase of the respiratory cycle, using the small animal gating system, were used to trigger the PET scanner. The time stamped list mode PET data was then retrospectively arranged into 23 time bins and 3 cardiac phases per time bin [14]. The list

mode data sorted into 23 time bins: frames $\times$ time in seconds (11×8 s, 1×12 s, 2×60 s, 1×180 s, and 8×400 s) [10], [15], [16]. and 3 cardiac gates was reconstructed using OSEM-MAP algorithm, and also into 23 time bins without gates using FBP algorithm [17]. An OSEM-MAP (FastMAP) version 2.4 was used for reconstruction and the parameters were 12 OSEM3D subsets with 2 OSEM3D iterations, 18 MAP iterations, span 3, ring difference 47 and image resolution 1.438 mm. The reconstructed image consisted of 95 slices with 128×128 pixels and an in-plane voxel resolution of $0.4 \text{ mm} \times 0.4 \text{ mm}$, corresponding to a zoom factor of 2.164 and slice thickness of 0.8 mm.

B. Arterial and Venous Blood Sampling

To validate the MCBIF, arterial blood samples (15 to 20 μL per sample) over the whole scan duration were obtained from one mouse. Arterial blood sampling in a mouse was performed by a surgical method: Prior to surgery, anesthesia was induced with 3% Isoflurane in Oxygen (0.5–0.8 L/min) and maintained at 1.5%–2.5% Isoflurane. Surgery was performed on a thermostatically controlled operating table ($37\text{--}39^\circ\text{C}$). Hair from the surgery area was removed and cleaned with alcohol. An incision was made in the neck and the carotid artery exposed by blunt dissection. A catheter was formed from PE-50 tubing with the end stretched and placed in the carotid artery. The artery was tied off above the insertion site with 7-0 Prolene and temporarily occluded distal to the insertion site using clamps or pressure from an untied ligature. The catheter was ligated in place with prolene in three places and all clamps removed. The incision was closed with prolene suture. Seventeen blood samples ($<30 \mu\text{L}$ each) were taken over the course of the scan by the following schedule: 3 blood samples were taken at 20, 40 and 60 seconds during tail-vein injection of FDG, then every minute up to 10 minutes and then 1 sample was taken every 10 minutes until the 60 minute mark. Blood draws are followed by flushing the catheter with a small volume of heparinized saline. Blood loss volume was replaced with an equal volume of sterile saline at the end of the first 10 min period. Each whole-blood sample is weighed and its FDG activity measured in a gamma counter (2480 Wizard, Perkin Elmer Inc.). Since arterial blood sampling was very challenging we resorted to venous blood samples from the tail-vein, at 43 and 56 minutes post FDG administration in $n=6$ mice, when the SP from the tissue to the blood is expected to be maximum [8]. Also, Fang et al [11] showed earlier that arterial blood is well approximated by venous blood at late time points.

C. Recovery Coefficient (RC) Measurements

A Jaszczak Micro Deluxe hot rod phantom scan (Data Spectrum Inc.) filled uniformly with about 14.9 MBq FDG was imaged in list mode format for 20 minutes. Co-57 scan for performed for attenuation correction. The list mode data corrected for attenuation was reconstructed with OSEM-MAP and FBP algorithms (Fig.1). The ratio of the measured average concentration to the known concentration determined the recovery coefficient (RC) for each of the rod sizes ranging from 1.2 mm to 4.8 mm. The initial guesses and bounds for the PV averaging coefficients (r_m , r_b) used in the kinetic model were derived from the RC plot. The dimensions of the myocardial wall (0.9 ± 0.1 mm) and LV (3.3 ± 0.2 mm) in mice were based on previous MRI measurements (unpublished work). These dimensions are consistent with published work using ultrasound in mice of similar age and strain [22].

D. Kinetic Modeling

Regions of interest (ROI) in the region corresponding to the left ventricle BP and the myocardium were drawn on short-axis slices in the last frame and the last gate of the dynamic image data and time activity curves (TAC) generated for the whole scan duration of 60 minutes. The blood pool ROIs were round shape of diameter approximately 1.6 mm

located in the middle of the LV cavity, and the myocardium ROIs were donut shape of inner diameter ~3.2 mm and outer diameter ~5.6 mm drawn along the LV wall.

Following a general approach of a 3-compartment kinetic model in [11] and [18] (Fig. 2), the differential equations for FDG kinetics can be written as:

$$dC_e/dt = K_1 C_a(t) - (k_2 + k_3) C_e(t) + k_4 C_m(t) \quad (1)$$

$$dC_m/dt = k_3 C_e(t) - k_4 C_m(t) \quad (2)$$

The three compartments shown in figure 2 can be described as follows: $C_a(t)$ is the FDG concentration in the vascular space, $C_e(t)$ is the concentration of FDG in the interstitial and cellular spaces and $C_m(t)$ is the FDG concentration within the cell of the phosphorylated FDG-6-Phosphate. K_1 and k_2 are the forward and reverse rate constants respectively between the first 2 compartments. k_3 and k_4 are the rates of phosphorylation and de-phosphorylation between compartments 2 and 3. $C_e(t)$ and $C_m(t)$ can be solved in terms of $C_a(t)$ and the rate constants, K_1 – k_4 :

$$C_T(t) = \frac{K_1}{a_1 - a_2} \cdot [(k_3 + k_4 - a_1)e^{-a_1 t} + (a_2 - k_3 - k_4)e^{-a_2 t}] \otimes C_a(t) \quad (3)$$

Where

$$a_{2,1} = (1/2) * (k_2 + k_3 + k_4 \pm \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}) \quad (4)$$

and

$$C_T(t) = C_e(t) + C_m(t) \quad (5)$$

is the net myocardium tissue concentration (Fig. 1). Assuming the rate of de-phosphorylation, $k_4 = 0$, the net myocardial FDG influx constant, K_i , can be written as:

$$K_i = (K_1 \cdot k_3) / (k_2 + k_3) \quad (6)$$

In a situation where there is no PV or SP, when a region of interest is drawn within the cavity of the left ventricle, the IDIF would equal the whole-blood time activity curve $C_a(t)$. However, due to SP and PV effects, the model equation for an image-derived time activity curve from the blood pool can be written in terms of fraction of the tissue concentration in the blood compartment and partial recovery of radioactivity concentration from the blood as [11]:

$$Model_{IDIF,i} = \frac{\int_{t_b^i}^{t_e^i} [S_{mb}(C_T(t)) + r_b C_a] dt}{t_e^i - t_b^i} \quad (7)$$

and similarly for the myocardium tissue, one can write the model equation as:

$$Model_{myo,i} = \frac{\int_{t_b^i}^{t_e^i} [r_m C_T(t) + S_{bm} C_a] dt}{t_e^i - t_b^i} \quad (8)$$

where, r_m , r_b , are the recovery coefficients (accounting for PV effect) for the myocardium and blood pool respectively. S_{bm} , S_{mb} are the SP coefficients from the blood pool to the myocardium and vice versa respectively. t_b^i and t_e^i are the beginning and end times respectively for frame i in a dynamic PET scan. The model equation for the blood input function can be written as [19]:

$$C_a(t) = (A_1(t - \tau) - A_2 - A_3)e^{L_1(t-\tau)} + A_2e^{L_2(t-\tau)} + A_3e^{L_3(t-\tau)} \quad (9)$$

where, each of the terms determines the amplitude, shape and wash-out of the tracer over time. The model equations can be fitted to the blood (PET_{IDIF}) and myocardium (PET_{myo}) TACs obtained from OSEM-MAP cardiac and respiratory gated PET images with attenuation correction by substituting (3) and (9) in (7) and (8), as indicated below:

$$O(p) = \sum_{i=1}^n [(Model_{IDIF,i} - PET_{IDIF,i})^2 + (Model_{myo,i} - PET_{myo,i})^2] \quad (10)$$

The fit was performed by minimizing the objective function (10), in the MATLAB R2010b programming environment using the function “fmincon”, which is based on an interior-reflective Newton method. Both image-derived and model TAC’s were equally weighted. There is not much of a difference between these two sets since both image-derived TACs are susceptible to PV and SP effects, and both model TACs include PV recovery and SP contamination. The initial guesses and bounds for all the parameters used in the optimization routine are shown in Table I. Minimization of (10) results in simultaneous estimation of the blood input function, and compartment model parameters K_1-k_4 and hence K_i along with the SP and PV coefficients (S_{mb} , r_b , S_{bm} , r_m).

The general formalism described above is following [11] and [18], however the main difference lies in choosing correct PV bounds for the myocardium and the blood pool, based on the reconstruction algorithm (Fig. 1), in eq 10, as opposed to arbitrary bounds used in [11]. The difference also lies in using IDIF from high resolution gated images as opposed to the normal method of relying on IDIFs from FBP un-gated images [11].

III. Results

Fig. 1 shows a plot of the RC obtained using OSEM-MAP and FBP reconstruction algorithms as a function of the rod size. The plot indicates that OSEM-MAP results in improved PV recovery as compared to FBP over the entire range. The initial guess values and the bounds used in the optimization routine for the two different algorithms were determined from this plot.

Representative results of comparison between TACs derived from dynamic gated PET images (Fig. 3A–D) (PET IDIF and PET myo TAC) and model corrected output time activity curves obtained (Model blood and Model myo) of mouse left ventricle BP and myocardium respectively, are shown in Fig. 3E. Arterial blood samples collected over the whole scan duration for one mouse compared with the MCBIFs applied to the IDIFs obtained from OSEM-MAP gated image and from FBP un-gated image are shown in Fig.

3F. The figure indicates that, in this animal, MCBIF from OSEM-MAP gated image matches late time points better than FBP un-gated image.

A residual plot of MCBIF applied to OSEM-MAP gated images, when compared to the two late venous blood samples obtained from $n=6$ mice, is shown in Fig. 4. The analysis reveals an average difference of 0.017 MBq/cm^3 . The precision (standard deviation of differences) was calculated to be 0.13 MBq/cm^3 . The figure also shows the analysis obtained from FBP un-gated images. An average difference of 0.28 MBq/cm^3 and precision of 0.33 MBq/cm^3 were obtained from FBP un-gated data sets. The residual plot exhibits the quantitative accuracy and repetitive behavior of MCBIF when applied to OSEM-MAP gated images.

The PV and SP factors, along with the net myocardial FDG influx constant K_i generated by minimization, are shown in Table II. $K_i = 0.15 \pm 0.03$, shown in Table II, agrees with that obtained from arterial blood sampling, $K_i = 0.14 \pm 0.06$ [11]. A student t-test revealed a P value equal to 0.716, indicating no statistically significant difference. Also, the downstream K_i has a lower standard deviation ($\sim 20\%$) as compared to a standard deviation of $\sim 52\%$ reported in [11] obtained from un-gated FBP images.

IV. Discussion

Compartment model has long been regarded as a reliable way of analyzing dynamic PET images, and the accurate knowledge of blood input function is crucial to tracer kinetic modeling [20], [21]. However, including the procedure of acquiring arterial blood samples in routine PET procedure is not practical due to the invasive blood sampling surgery preparation, limited blood volume and extensive radioactivity measurement efforts. Although there are automated procedures for sampling blood using beta-microprobes in small animals [23], [24] an alternative methodology without invasive blood sampling is highly desired. Obtaining image-derived blood input function from dynamic PET images is the simplest way, but SP and PV effect makes it unreliable [8]. In this study we proposed a reliable and practical method, which can simultaneously correct for the SP and PV effects and generate kinetic rate constants without any invasive blood sampling.

A recent study by Shogi et al indicated that IDIFs obtained from high-resolution images still have about 15–20% SP contamination in them [9]. We showed, for the first time, that model correction on high resolution FDG PET gated images with correct PV bounds, models the wash-in and wash-out dynamics of the tracer from mouse blood, without the need for any blood sampling (eq 10) as opposed to [11]. Our study compares the gold standard blood input function obtained by arterial blood sampling from a single mouse and model corrected estimate of blood input function, for validation purposes only. Since the arterial blood samples are well approximated by venous blood at the late time points [11], we established statistical significance by sampling blood from the tail-vein at 43 min and 56 min, with same time points on MCBIF in $n=6$ mice. The residual plot indicates that MCBIF applied to OSEM-MAP gated images are repeatable compared to that obtained from FBP un-gated images. The downstream rate of myocardial FDG influx, K_i is accurate and precise as indicated in the results section.

The kinetic model proposed in this study may also be adapted to different PET tracers such as ^{13}N -ammonia for measuring myocardial perfusion or ^{11}C -acetate for measuring flow and oxygen consumption in vivo [25]. The kinetic rate constants and compartments can be adjusted to adapt to different metabolic processes for different tracers, while the form of the equations of model corrected image-derived heart ventricle and image-derived tissue time activity would have a similar form. Also, the initial values and optimization bounds should be modified when switching to other tracers or animal models. In addition, blood samples

from a number of experimental subjects may be necessary to validate model output estimates. Nevertheless, application of this technique to other scanners and isotopes would require careful validation since positron range and depth of interaction will be different for other isotopes and scanners.

V. Conclusion

MCBIF applied to OSEM-MAP gated images correctly accounts for the shape, wash-in and wash-out dynamics of FDG from mouse blood without the need of any invasive blood sampling. Lower SP of radioactivity from the myocardium to the BP and higher PV recovery from OSEM-MAP gated images lead to improved MCBIF estimate as compared to that obtained from un-gated FBP images in a dynamic PET scan of the mouse heart.

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Fig. 1. Plot of RC with different rod sizes using OSEM-MAP (dash line with diamonds) and FBP reconstruction algorithm (dotted line with open squares).

Fig. 2.

Three compartment FDG model. Block diagram indicating the rate constants, k_1 – k_4 , between the 3 compartments of the FDG kinetic model.

Fig. 3. (A–D) Select coronal dynamic end-diastolic PET images at 0, 0.5, 2 and 56 minutes fused with transmission images. A–D respectively stands for pre, early time points and a late time point. (E–F) Representative estimated results of mouse model correction. (E) Representative image-derived time activity curves of BP (squares) and myocardium (open circles) obtained from OSEM-MAP cardiac and respiratory gated images shown above and model estimated BP (line) and myocardium (dash line) time activity curves are shown here. (F) MCBIF applied to the IDIF obtained from OSEM-MAP gated image (solid line) and FBP ungated image (dashed line), compared to the arterial blood samples (open triangles) obtained during the scan time of 60 minutes.

Fig. 4. Residual plot shows the difference between MCBIF applied to OSEM-MAP cardiac and respiratory gated images (diamonds) and FBP un-gated images (open squares), when compared to the 2 late venous blood samples obtained at 43 and 56 minutes post FDG administration.

TABLE I

INITIAL GUESS VALUES AND BOUNDS FOR PARAMETERS USED IN THE OPTIMIZATION ROUTINE APPLIED TO OSEM-MAP GATED IMAGES

Parameter	K_1 (l/min)	K_2 (l/min)	K_3 (l/min)	K_4 (l/min)	S_{mb}	r_b	r_m	S_{hm}	A_1 (MBq/min/mL)	A_2 (MBq/mL)	A_3 (MBq/mL)	L_1 (l/min)	L_2 (l/min)	L_3 (l/min)	τ_{0min}
Initial value	0.01	0.01	0.001	0.001	0.5	0.75	0.3	0.5	111	0.296	0.259	-27	-0.55	0.04	0.15
Upper bound	1	1	1	0.001	1	0.9	0.4	1	500	500	100	0	0	0	0.5
Lower bound	0	0	0	0	0	0.6	0.15	0	0	0	0	-200	-10	-10	0

TABLE II

SP, PV FACTORS, AND FDG INFLUX CONSTANT GENERATED BY MODEL CORRECTION ON OSEM-MAP GATED IMAGES IN N=6 MICE. ALL THE VALUES ARE MEAN $\pm$ STANDARD DEVIATION

r_m	r_b	S_{bm}	S_{mb}	Ki
0.30 $\pm$ 0.01	0.73 $\pm$ 0.04	0.21 $\pm$ 0.03	0.12 $\pm$ 0.01	0.15 $\pm$ 0.03