Multiparametric cardiac $^{18}$F-FDG PET in humans: pilot comparison of FDG delivery rate with $^{82}$Rb myocardial blood flow

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Keywords: dynamic PET, kinetic modeling, myocardial blood flow, FDG delivery rate, multiparametric imaging, glucose normalization, extraction fraction correction

Abstract
Myocardial blood flow (MBF) and flow reserve are usually quantified in the clinic with positron emission tomography (PET) using a perfusion-specific radiotracer (e.g. $^{82}$Rb-chloride). However, the clinical accessibility of existing perfusion tracers remains limited. Meanwhile, $^{18}$F-fluorodeoxyglucose (FDG) is a commonly used radiotracer for PET metabolic imaging without similar limitations. In this paper, we explore the potential of $^{18}$F-FDG for myocardial perfusion imaging by comparing the myocardial FDG delivery rate $K_1$ with MBF as determined by dynamic $^{82}$Rb PET in fourteen human subjects with heart disease. Two sets of FDG $K_1$ were derived from one-hour dynamic FDG scans. One was the original FDG $K_1$ estimates and the other was the corresponding $K_1$ values that were linearly normalized for blood glucose levels. A generalized Renkin–Crone model was used to fit FDG $K_1$ with Rb MBF, which then allowed for a nonlinear extraction fraction correction for converting FDG $K_1$ to MBF. The linear correlation between FDG-derived MBF and Rb MBF was moderate ($r = 0.79$) before the glucose normalization and became much improved ($r > 0.9$) after glucose normalization. The extraction fraction of FDG was also similar to that of Rb-chloride in the myocardium. The results from this pilot study suggest that dynamic cardiac FDG-PET with tracer kinetic modeling has the potential to provide MBF in addition to its conventional use for metabolic imaging.

1. Introduction

Myocardial perfusion (blood flow) imaging with positron emission tomography (PET) has been applied in clinical cardiology to diagnose and characterize cardiovascular diseases (Kaufmann and Camici 2005, Di Carli et al 2007, Schindler et al 2010, Murthy et al 2018). Various perfusion radiotracers (e.g. $^{15}$O-water, $^{13}$N-ammonia, $^{82}$Rb-chloride, $^{11}$C-acetate) have been used (Maddahi and Packard 2014). Despite their potential, the accessibility to these flow tracers remains limited for clinical use. For example, $^{15}$O-water is the gold standard for measuring blood flow (Iida et al 1988, Danad et al 2014) but its half-life is very short (2.05 min), requiring onsite cyclotron for tracer production and is not approved for routine clinical use. $^{13}$N-ammonia (Muzik et al 1993, Slomka et al 2012) and $^{82}$Rb-chloride (Mullani et al 1983, Lortie et al 2007, El Fakhri et al 2009, Nesterov et al 2014) are the two blood flow radiotracers routinely used in clinical practice (Maddahi and Packard 2014). However, $^{13}$N-ammonia also requires an onsite or nearby cyclotron due to its short half-life of 10 min. $^{82}$Rb-chloride can be produced by a mobile generator despite its short half-life (76 s). Nevertheless, the cost of a rubidium generator is $\geq 30$ 000 for every 4–6 weeks; this is only affordable to those hospitals or centers with a high throughput of cardiac patients (Di Carli et al 2007, Maddahi 2012). $^{11}$C-acetate is another promising tracer (Sciaccia et al 2001, van den Hoff et al 2001, Timmer et al 2010) but its 20 min half-life still requires a nearby cyclotron. Together, these practical challenges limit the access to perfusion imaging by PET.
18F-fluorodeoxyglucose (FDG), which has a longer half-life of 110 min, is the most broadly used clinical PET radiotracer, mainly for metabolic imaging (Maddahi 2012). In clinical cardiology, 18F-FDG-PET is commonly used in combination with a short half-life flow tracer to evaluate flow–metabolism mismatch in the myocardium (Abraham et al 2010). Such a two-tracer PET method is the gold standard for assessing myocardial viability (Cambic et al 2008) and inflammatory conditions such as cardiac sarcoidosis (Yamagishi et al 2005). The method is not widely available in the clinic because of the limited accessibility of current flow-specific radiotracers. While the new flow tracer 18F-fluorine (Maddahi et al 2020) does not have the accessibility problem, it may result in longer clinic visit times when combined with 18F-FDG for myocardial flow–metabolism imaging because of the long half-life of the 18F isotope in the two different tracers.

The hypothesis of this study is that dynamic cardiac 18F-FDG-PET imaging as a single tracer imaging can provide myocardial blood flow (MBF) in addition to myocardial glucose metabolism by use of tracer kinetic modeling. The successful testing of this hypothesis may allow simultaneous imaging of MBF and glucose metabolism only using 18F-FDG without the need for a second flow-specific tracer. Once validated, this single-tracer (i.e. FDG) multiparametric (i.e. flow and metabolism) imaging method has the potential to enable evaluation of myocardial viability and myocardial inflammation with reduced imaging time, cost and radiation exposure as compared to the traditional two-tracer methods in clinical practice today (Di Carli et al 2007, Maddahi 2012).

The potential of 18F-FDG for blood flow imaging has been explored outside cardiac imaging. By use of tracer kinetic modeling (Carson 2005), several studies have shown that the FDG blood–tissue delivery rate $K_1$ correlates with blood flow in tumors (Tseng et al 2004, Mullani et al 2008, Bernstine et al 2011, Cochet et al 2012, Humbert et al 2018). For example, Tseng et al (Tseng et al 2004) demonstrated linear correlations between $K_1$ of 60 min dynamic FDG–PET and 15O-water blood flow in breast tumors, with a linear correlation coefficient $r = 0.62$ before neoadjuvant chemotherapy and $r = 0.81$ after the therapy. Later, (Mullani et al 2008) reported that for various types of tumors in 16 patients, regional tumor FDG $K_1$ estimated from a 2 min first-pass dynamic PET scan has a correlation $r = 0.86$ with the blood flow measured by 15O-water PET. Correlation of FDG $K_1$ to blood flow has also been reported in organs such as liver and brain (Winterdahl et al 2011, Walberer et al 2012). In pigs, hepatic FDG $K_1$ derived from a 3 min early-dynamic FDG–PET scan correlated with hepatic blood flow measured by transit time flow meters with a high correlation $r = 0.94$ (Winterdahl et al 2011). In a rat model of stroke, Walberer et al also reported that cerebral FDG $K_1$ estimated by one-hour dynamic PET data had a correlation of $r = 0.86$ with 15O-water blood flow (Walberer et al 2012). These studies support the potential use of 18F-FDG for estimating blood flow, though the usability of 18F-FDG $K_1$ likely depends on the specific tissue types; this is because FDG extraction fraction varies in different tissue and is also dependent on blood flow.

Our work is specifically focused on MBF imaging using 18F-FDG. There is no prior study yet attempting to demonstrate the effectiveness of FDG flow in the myocardium. The importance of this work relies in the possible application of myocardial FDG flow to myocardial flow–metabolism mismatch evaluation for myocardial viability and inflammation and potentially more broadly, to rest-stress perfusion imaging for diagnosis of ischemic heart disease (IHD). Toward that end, our previous work specifically evaluated the practical identifiability of myocardial FDG $K_1$ quantification under different scan durations (Zuo et al 2020). The results showed it is feasible to quantify FDG $K_1$ in the myocardium using appropriate kinetic modeling.

The purpose of this paper is to directly compare myocardial FDG $K_1$ with MBF that is determined by a flow-specific tracer in human patients with heart disease. One challenge for using FDG to assess MBF is the potential correlation of this glucose analog with blood glucose (BG) levels. As demonstrated in this paper, this may in turn compromise the performance of FDG $K_1$ for deriving MBF. To address this challenge, we also propose glucose normalization approaches to adjusting FDG $K_1$ that can reduce the effect of BG levels.

2. Methods

2.1. Dynamic 18F-FDG-PET and dynamic 82Rb PET data acquisition

Fourteen patients with IHD or suspected cardiac sarcoidosis were referred for PET myocardial viability or inflammation assessment by PET and enrolled into this study after giving informed consent. The study is approved by Institutional Review Board at the University of California, Davis. Each patient underwent a dynamic 82Rb-PET/CT scan first and then a dynamic FDG-PET/CT scan, both scans operated on a GE Discovery ST PET/CT scanner in two-dimensional mode. The time between the Rb scan and FDG scan ranges from a few minutes to one-hour, depending on the oral glucose loading procedure.

For dynamic Rb-PET imaging, patients received approximately 30 mCi 82Rb-chloride with a bolus injection. A low-dose transmission CT scan was performed at the beginning of PET scan to provide CT images for PET attenuation correction. The dynamic scan lasted for nine minutes. The acquired raw data were binned into 16 dynamic frames: $12 \times 10$ s, $2 \times 30$ s, $1 \times 60$ s, $1 \times 300$ s. Dynamic Rb-PET images were reconstructed using the
standard ordered-subset expectation-maximization algorithm. All data corrections, including normalization, dead-time correction, attenuation correction, scatter correction, and random correction, were included in the reconstruction process.

For dynamic FDG-PET imaging, patients received approximately 20 mCi $^{18}$F-FDG with a bolus injection. Data acquisition was commenced right after the FDG injection and lasted for 60 min. The acquired raw data were then binned into a total of 49 dynamic frames: $30 \times 10$ s, $10 \times 60$ s and $9 \times 300$ s. Other processing was the same as for the Rb-PET scans.

2.2. Kinetic modeling of cardiac $^{18}$F-FDG-PET data
An ellipsoidal region of interest (ROI) was manually placed in the left ventricle (LV) to extract an image-derived input function $C_{IDIF}(t)$. An additional 17 ROIs were placed within the 17 segments of myocardium according to the AHA-17 standard (Cerqueira et al., Jan 2002). These segment ROIs were combined into a global myocardial ROI and used to extract a global myocardial TAC $C_{T}(t)$ using ROI mean. Due to high noise of the dynamic data in individual segments, the analysis of this study was focused on global myocardial quantification. Based on the analysis in our previous work (Zuo et al., 2020), a reversible two-tissue compartmental model (Carson, 2005) was used to model the one-hour dynamic FDG-PET data:

\[
\frac{dC_{p}(t)}{dt} = K_{f} C_{p}(t) - (k_{2} + k_{3}) C_{t}(t) + k_{4} C_{2}(t),
\]

\[
\frac{dC_{2}(t)}{dt} = k_{3} C_{t}(t) - k_{4} C_{2}(t),
\]

where $C_{p}(t)$ is the FDG concentration in the plasma, $C_{t}(t)$ is the concentration of free FDG and $C_{2}(t)$ denotes the activity concentration of metabolized tracer in the myocardium tissue space. $K_{f}$ is the tracer delivery rate from the blood space to the tissue space with the unit ml/min/cm$^3$ (Innis et al., 2007); $k_{2}$(/min) is the rate constant of tracer exiting the tissue space; $k_{3}$ (/min) is phosphorylation rate; $k_{4}$ (/min) is the dephosphorylation rate. With $v_{b}$ denoting the fractional blood volume and $C_{wb}(t)$ denoting the activity in the whole blood, the total activity that is measured by PET is described by

\[
C_{T}(t) = (1 - v_{b})[C_{t}(t) + C_{2}(t)] + v_{b} C_{wb}(t).
\]

The unknown kinetic parameters $(v_{b}, K_{1}, k_{2}, k_{3}, k_{4})$ were estimated using nonlinear least-square curve fitting. Their initial values were set to $(0.1, 0.1, 1.0, 0.1, 0.001)$. The lower bounds were zero and the upper bounds were set to $(1.0, 2.0, 2.0, 1.0, 0.1)$ (Zuo et al., 2020).

In theory the IDIF represents the activity in the whole blood, i.e. $C_{IDIF}(t) = C_{wb}(t)$. The plasma input function $C_{p}(t)$ is related to $C_{wb}(t)$ following the model

\[
C_{p}(t) = \text{PBR}(t) \cdot C_{wb}(t),
\]

where PBR$(t)$ denotes the plasma-to-blood ratio (PBR) function. In this work, we first used PBR$(t) = 1$ by assuming the difference between $C_{p}(t)$ and $C_{wb}(t)$ is small (Gambhir et al., 1989). Unless specified otherwise, the main results of this paper were obtained with PBR$(t) = 1$. In addition, we investigated the effect of PBR correction using a recent nonlinear model (Naganawa et al., 2020),

\[
\text{PBR}(t) = 1/[0.97 - 0.06 \exp(-0.085t)].
\]

2.3. Adjustment of FDG $K_{1}$ with glucose normalization
We describe the relation between FDG $K_{1}$ and the BG level $C_{glu}$ using a linearized approximation,

\[
K_{1} \triangleq f(C_{glu}) \approx f(C_{glu,0}) + \dot{f}(C_{glu,0}) \cdot (C_{glu} - C_{glu,0}),
\]

where $f(\cdot)$ is a nonlinear function of $C_{glu}$ determined from the Renkin-Crone (RC) model and Michaelis–Menten model (Carson, 2005), see equation (19) in the appendix, $C_{glu,0}$ denotes a reference BG level and $\dot{f}(\cdot)$ is the first-order derivative of $f$. Based on the derivations in the appendix A, we have

\[
\dot{f}(C_{glu,0}) < 0.
\]

This suggests FDG $K_{1}$ is inversely correlated with the BG level,

\[
K_{1} \approx -s \cdot C_{glu} + \text{int},
\]

where $s \triangleq -\dot{f}(C_{glu,0})$ denotes the absolute slope $(s > 0)$ and $\text{int}$ is the intercept of the plot of FDG $K_{1}$ with respect to $C_{glu}$. Practically, $s$ can be estimated using a correlation analysis between the measured FDG $K_{1}$ and $C_{glu}$ data.

To reduce the dependency of FDG $K_{1}$ on $C_{glu}$, we consider $f(C_{glu,0})$ as an adjusted FDG $K_{1}$. Based on equation (6), it can be calculated using the following form
\[ K_{1,\text{adj}} = f(C_{\text{glu},0}) = K_{1} + s \cdot (C_{\text{glu}} - C_{\text{glu},0}), \]

in which the BG level of a patient is normalized and used to adjust the value of FDG \( K_{1} \) linearly. A similar linear correction was also used by (Stout et al. 1998) for reducing the effects of normal physiological concentration of plasma large neutral amino acids on the \( K_{1} \) of \(^{18}\text{F}-\text{FDG}\). As normal BG levels range between 80 and 120 mg dl\(^{-1}\), we use \( C_{\text{glu},0} = 100 \text{ mg dl}^{-1} \) in this work.

Note that equation (9) is an additive adjustment, in which \( s \) is fixed and is independent of individual patients. Alternatively, a varying \( s \), denoted as \( s' \), may be used on patient basis,

\[ s' = \frac{K_{1}}{C_{\text{glu},0}}, \]

which results in a multiplicative adjustment,

\[ K_{1,\text{adj}} = \frac{C_{\text{glu}}}{C_{\text{glu},0}} K_{1}. \]

This approach assumes the product of \( K_{1} \) and \( C_{\text{glu}} \) remains constant across different glucose levels.

2.4. Reference MBF by dynamic Rb-PET
Similar to the analysis of dynamic FDG-PET data described above, ROIs were drawn in the LV cavity and myocardium regions to extract regional TACs from the dynamic Rb-PET images. The myocardial TAC was modeled using a one-tissue compartmental model (Lortie et al. 2007) with the following expression:

\[ C_{T}(t) = (1 - v_{a}) C_{1}(t) + v_{a} C_{\text{pl}}(t), \]

where \( C_{1}(t) \) denotes the concentration of \(^{82}\text{Rb}\) in the tissue compartment with \( K_{1} \) and \( k_{2} \) now representing the rate constants of \(^{82}\text{Rb}\) transport between the plasma space and tissue space. This one-tissue model is equivalent to the two-tissue model in equation (2) with \( k_{5} = 0, k_{4} = 0 \). All the \(^{82}\text{Rb}\) kinetic parameters \( (v_{b}, K_{1}, k_{2}) \) were estimated using nonlinear least-square curve fitting in a way similar to (Zuo et al. 2020).

The estimated Rb \( K_{1} \) was then converted into MBF using the generalized RC model following Lortie’s formula for \(^{82}\text{Rb}\)-PET data (Lortie et al. 2007):

\[ K_{1,\text{RB}} = \text{MBF} \cdot \left[ 1 - a_{\text{RB}} \cdot \exp\left( - \frac{b_{\text{RB}}}{\text{MBF}} \right) \right], \]

where \( a_{\text{RB}} = 0.77 \) and \( b_{\text{RB}} = 0.63 \text{ (ml/min/cm}^{-3}\). MBF is derived from Rb \( K_{1} \) through a look-up table that is pre-generated using the model.

2.5. Extraction fraction correction (EFC) for converting FDG \( K_{1} \) to MBF
Similar to the conversion equation (13) for \(^{82}\text{Rb}\)-chloride, we can apply the generalized RC model to fit the FDG \( K_{1} \) and MBF data under the assumption that capillary recruitment is involved at higher flow (Yoshida et al. 1996) (see appendix B for further explanation),

\[ K_{1,\text{FDG}} = \text{MBF} \cdot \left[ 1 - a_{\text{FDG}} \cdot \exp\left( - \frac{b_{\text{FDG}}}{\text{MBF}} \right) \right], \]

where \( a_{\text{FDG}} \) and \( b_{\text{FDG}} \) are to be estimated from the paired data of FDG \( K_{1} \) and Rb MBF using nonlinear least-square fitting. The initial values for the two parameters \( a_{\text{FDG}} \) and \( b_{\text{FDG}} \) were both set to 0.1. Note that if \( a_{\text{FDG}} \) is fixed at 1.0, then the model is equivalent to the classic RC model without capillary recruitment.

The first-pass extraction fraction of FDG is defined by

\[ E_{\text{FDG}} \triangleq \frac{K_{1,\text{FDG}}}{\text{MBF}}. \]

Theoretically it relates to MBF following the generalized RC model, i.e.

\[ E_{\text{FDG}} = 1 - a_{\text{FDG}} \cdot \exp\left( - \frac{b_{\text{FDG}}}{\text{MBF}} \right). \]

The effect of flow-dependent FDG extraction fraction can be corrected using the inverse function of equation (14), leading to more quantitative FDG-derived MBF from FDG \( K_{1} \). Similar to \(^{82}\text{Rb}\)-chloride, the nonlinear conversion from FDG \( K_{1} \) to MBF is performed through a look-up table using equation (14) with predetermined \( a_{\text{FDG}} \) and \( b_{\text{FDG}} \). The EFC was separately performed for the original FDG \( K_{1} \) (i.e. without glucose normalization) and the adjusted FDG \( K_{1} \) (i.e. with glucose normalization).
2.6. Statistical analysis
We used the Pearson’s correlation analysis and/or the Spearman correlation when appropriate to analyze the potential correlation between FDG $K_1$ and MBF and biological variables such as age (years), body mass index (BMI) ($\text{kg m}^{-2}$), and BG level (mg dl$^{-1}$). A $p$ value $\leq 0.05$ was considered as statistically significant. All the analyses were done using MATLAB (MathWorks, MA). The Bland–Altman plot (Bland and Altman 1986) was used to quantitatively compare FDG MBF with Rb MBF. When appropriate, the estimated standard error (SE) of a parameter estimate $x$ was also reported in the format of $x \pm \text{SE}$.

3. Results

3.1. Patient characteristics
Patient characteristics are provided in table 1. Among the fourteen patients enrolled in the study, ten were diagnosed as IHD and four were diagnosed with or suspected of cardiac sarcoidosis prior to the scans. All of the patients completed the dynamic $^{82}$Rb-PET scan. Twelve patients had a dynamic FDG-PET scan of 50–60 min. Two other patients had a dynamic FDG-PET scan of only 30–40 min due to discomfort, and hence these two subjects were not included in this study.

Other characteristics of the patients, including age, sex, diabetic status, BMI, BG level (before PET imaging), and dynamic FDG-PET scan duration are also reported in table 1. Unavailable data is marked with ‘/’ in the table.

3.2. Myocardial TAC fitting and kinetics
Figure 1 (a) and (b) show an example of myocardial TAC fitting for the FDG data and Rb data, respectively. The fits demonstrated a good match between the measured time points and predicted TAC by the model in each case.

Table 1. Characteristics of the patients enrolled in the study.

| Patient | IHD | Age (years) | Sex | Diabetic | BMI | BG (mg dl$^{-1}$) | FDG Scan Time (min) |
|---------|-----|-------------|-----|----------|-----|-----------------|---------------------|
| 1       | Y   | 58          | M   | Y        | 38.6| 127             | 60                  |
| 2       | Y   | 73          | M   | N        | 24.4| 113             | 50                  |
| 3       | Y   | 61          | M   | N        | 33.9| 88              | 60                  |
| 4       | N   | 71          | F   | N        | 22.4| 116             | 60                  |
| 5       | Y   | 55          | F   | N        | 24.5| 118             | 40                  |
| 6       | N   | 37          | M   | N        | 27.4| /               | 60                  |
| 7       | Y   | 63          | M   | N        | 28.8| 105             | 60                  |
| 8       | Y   | 59          | M   | Y        | 28.3| 135             | 60                  |
| 9       | Y   | 65          | M   | Y        | 27.2| 130             | 50                  |
| 10      | N   | 81          | M   | N        | 25.8| 85              | 60                  |
| 11      | Y   | 74          | M   | N        | 28.2| 84              | 60                  |
| 12      | Y   | 83          | M   | N        | 33.6| /               | 60                  |
| 13      | Y   | 59          | M   | Y        | 35.9| 107             | 60                  |
| 14      | N   | 69          | F   | N        | 31.4| 82              | 30                  |
The estimated $^{18}$F-FDG kinetic parameters and $^{82}$Rb-chloride MBF values of all the patients are summarized in table 2. For the FDG protocol, the results of two patients were not available due to an incomplete dynamic FDG scan. The average SE values across the twelve patients are reported in table 3 for each of the FDG kinetic parameters. The result indicates that FDG $K_1$ was able to be estimated with a low SE ($<14\%$).

### Table 2. Estimates of FDG kinetics and $^{82}$Rb-chloride MBF.

| No. | $v_0$ | $K_1$ | $k_2$ | $k_3$ | $k_4$ | $v_0$ | MBF | additive | multiplicative |
|-----|-------|-------|-------|-------|-------|-------|-----|-----------|----------------|
| 1   | 0.603 | 0.138 | 0.399 | 0.021 | 0.027 | 0.446 | 0.440 | 0.293 | 0.175 |
| 2   | 0.249 | 0.440 | 1.068 | 0.129 | 0.017 | 0.374 | 0.651 | 0.515 | 0.498 |
| 3   | 0.380 | 0.675 | 2.000 | 0.176 | 0.022 | 0.389 | 0.904 | 0.607 | 0.594 |
| 4   | 0.279 | 0.681 | 2.000 | 0.061 | 0.027 | 0.304 | 1.842 | 0.773 | 0.790 |
| 5   | /     | /     | /     | /     | /     | 0.366 | 0.674 | /     | /     |
| 6   | 0.368 | 0.593 | 2.000 | 0.041 | 0.081 | 0.411 | 0.812 | /     | /     |
| 7   | 0.494 | 0.279 | 1.059 | 0.091 | 0.054 | 0.377 | 0.432 | 0.308 | 0.293 |
| 8   | 0.371 | 0.284 | 0.690 | 0.107 | 0.043 | 0.362 | 0.642 | 0.485 | 0.384 |
| 9   | 0.461 | 0.366 | 0.795 | 0.056 | 0.017 | 0.336 | 0.700 | 0.538 | 0.476 |
| 10  | 0.328 | 0.667 | 1.976 | 0.222 | 0.031 | 0.559 | 0.953 | 0.581 | 0.567 |
| 11  | 0.260 | 0.413 | 1.266 | 0.072 | 0.026 | 0.311 | 0.617 | 0.321 | 0.347 |
| 12  | 0.391 | 0.584 | 1.559 | 0.061 | 0.032 | 0.294 | 0.633 | /     | /     |
| 13  | 0.391 | 0.302 | 0.616 | 0.046 | 0.026 | 0.502 | 0.541 | 0.342 | 0.323 |
| 14  | /     | /     | /     | /     | /     | 0.428 | 1.004 | /     | /     |

### Table 3. Average standard error (SE) of the estimates of FDG kinetics.

|      | $v_0$ | $K_1$ | $k_2$ | $k_3$ | $k_4$ |
|------|-------|-------|-------|-------|-------|
| SE (%) | 3.5   | 13.8  | 15.4  | 18.4  | 19.7  |

### Table 4. Pearson’s $r$ and $p$ of FDG $K_1$ and MBF with patients’ age, BMI, and blood glucose (BG) concentration.

| Biological Variables | Age | BMI | BG |
|----------------------|-----|-----|----|
| $^{18}$F-FDG $K_1$   | $r$ | $-0.495$ | $-0.443$ | $-0.562$ |
|                      | $p$ | $0.102$ | $0.150$ | $0.091$ |
| $^{82}$Rb MBF        | $r$ | $0.237$ | $-0.365$ | $-0.076$ |
|                      | $p$ | $0.458$ | $0.055$ | $0.835$ |

The estimated $^{18}$F-FDG kinetic parameters and $^{82}$Rb-chloride MBF values of all the patients are summarized in table 2. For the FDG protocol, the results of two patients were not available due to an incomplete dynamic FDG scan. The average SE values across the twelve patients are reported in table 3 for each of the FDG kinetic parameters. The result indicates that FDG $K_1$ was able to be estimated with a low SE ($<14\%)$.

### 3.3. Correlation of FDG $K_1$ with BG and other biological variables

Table 4 summarizes the Pearson’s $r$ and $p$ values between FDG $K_1$ and the biological variables including age, BMI, and BG level. The results of MBF were also included in the table for comparison. The estimated fractional blood volume $v_0$ of FDG was not exactly equal to the $v_0$ of Rb as shown in table 2 but the two parameters were correlated with each other ($r = 0.696, p = 0.012$).

FDG $K_1$ did not correlate with age and BMI. MBF tended to inversely correlate with BMI ($r = -0.565, p = 0.055$). FDG $K_1$ tended to inversely correlate with BG ($r = -0.562, p = 0.091$) as also shown in figure 2(a), while a similar trend was not observed for MBF ($r = -0.076, p = 0.835$). The negative correlation between FDG $K_1$ and BG is in line with the derivation in equation (8).

The estimated slope $s$ between FDG $K_1$ and BG was $0.0057 \pm 0.0030$, with which the original FDG $K_1$ was then adjusted for BG levels using the additive adjustment equation (9) with a reference $C_{glu,0} = 100$ mg dl$^{-1}$. The FDG $K_1$ after the adjustment is included in table 2. The multiplicative adjustment was also implemented and the result is included in table 2 as well. Note that the adjustments were not applied if a BG value was unavailable. Therefore the two patients ($\#6$ and $\#12$) were not included in the subsequent analysis. The linear dependency of FDG $K_1$ on BG diminished with glucose normalization. Figures 2(b)–(c) show that the negative correlation was no longer existing (by the additive adjustment) or reduced (by the multiplicative adjustment) between the adjusted FDG $K_1$ and BG levels. These three sets of FDG $K_1$ were all used in the subsequent analysis.
3.4. Nonlinear conversion from FDG $K_1$ to MBF

Figure 3 shows the nonlinear association of FDG $K_1$ with MBF before and after the adjustment of FDG $K_1$ for BG. The Spearman correlation was 0.89 ($p = 0.0014$) before the adjustment and became 0.96 ($p < 0.0001$) after the additive or multiplicative adjustment. For the three cases, the data were fitted using the generalized RC model equation (14). The estimated model parameters were $a_{FDG} = 0.73 \pm 0.15$ and $b_{FDG} = 0.41 \pm 0.21$ for the approach without adjustment, $a_{FDG} = 0.80 \pm 0.10$ and $b_{FDG} = 0.63 \pm 0.11$ for the approach with the additive adjustment, and $a_{FDG} = 0.68 \pm 0.09$ and $b_{FDG} = 0.39 \pm 0.14$ for the approach with the multiplicative adjustment.

Using the fitted model for extraction fraction correction, FDG $K_1$ was converted to MBF in each case based on equation (14). Figure 4 shows the results of linear Pearson correlation between FDG-derived MBF and Rb MBF. The three correlations were statistically significant ($p < 0.01$). The correlation coefficient was moderate.
(r = 0.79) without adjusting FDG K₁ for BG, and became improved (r > 0.9) after the additive or multiplicative adjustment. Figure 5 furthers shows the Bland–Altman plots of the blood flow estimates. The differences between FDG MBF and Rb MBF were large without a glucose adjustment and became smaller with the adjustments.

Table 5 further compares the statistics (mean and standard deviation) of Rb MBF and FDG-derived MBF in the IHD group (9 patients) and non-IHD group (3 patients). The mean and standard deviation became closer to that of Rb MBF after the additive adjustment of FDG K₁ for BG in both groups.

3.5. Myocardial extraction fraction of FDG

Figure 6 shows the extraction fraction of FDG in the myocardium as a function of MBF using the FDG K₁ estimates with and without adjustment for BG levels. Both the measured $E_{FDG}$ using equation (15) and the calculated model equation (16) are shown. The theoretical extraction fraction of Rb-chloride in the myocardium (Lortie et al 2007) is also included for comparison. The results show that the relation of the extraction fraction of FDG with respect to MBF was close to that of Rb-chloride in a range of MBF between 0 and 2 ml/min/cm³. It seems that the additive adjustment approach led to a slightly better fit to the generalized RC model than the multiplicative adjustment did. Overall the FDG extraction fraction was about 60% relative to Rb MBF at 1.0 ml/min/cm³, while (Marshall et al 1998) reported an extraction fraction of 70% in rabbit heart.
3.6. Effect of the upper bound for $k_2$

As shown in table 2, some of the FDG $k_2$ estimates hit the upper bound (UB) 2.0. With a higher UB, the $k_2$ estimates can go higher, which in turn increases the $K_1$ value due to the coupling between $K_1$ and $k_2$. Figure 7(a) shows the examples with two UB values (2.0 and 4.0) for fitting a myocardial TAC. Both options fitted the TAC reasonably well. UB = 4.0 provided a lower fitting error (mainly in the early time), which however may be because of over-fitting of the noise. Figure 7(b) further shows the effect of the $k_2$ UB on the Spearman correlation of FDG $K_1$ with Rb MBF in all patients. The correlation reached the peak at UB = 2.0 and became lower at higher UB values. The use of the upper bound can be explained as adding a regularization in TAC fitting, which has the role of preventing over-fitting and stabilizing the kinetic estimation.

3.7. Effect of the PBR correction

All the results reported above were obtained with PBR(t) = 1, i.e. no PBR correction was used. The effect of using the PBR correction in equation (5) is shown in Figure 8(a). Here the FDG $K_1$ was obtained with the additive adjustment. The FDG $K_1$ with the PBR correction was related to the PBR-uncorrected $K_1$ by a scaling factor $0.911 \pm 0.002$. The result is consistent with the past studies that reported an average PBR of approximately 1.1 (see the references in (Naganawa et al 2020)), which in turn should result in a global scaling of 0.91 in the $K_1$ estimates. Figure 8(b) shows the fit of the PBR-corrected FDG $K_1$ with respect to Rb MBF using the generalized RC model. The estimated FDG extraction fraction shown in Figure 8(c) was lower when comparing to Figure 6(b). However, the resulting change (not shown) on the final FDG-derived MBF is negligible because the scaling factor was compensated in the generalized RC model.
Note that the lower FDG extraction fraction after the PBR correction may be not reflecting the ground truth because ideally the Rb data should also be corrected for PBR. However, it is practically difficult provided that there is no published model to use.

4. Discussion

In this paper, we investigated the feasibility of $^{18}$F-FDG for assessing MBF through a pilot clinical study. The FDG delivery rate $K_1$ demonstrated an inverse correlation with BG levels according to both the analytical investigation in equation (8) and patient data shown in figure 2(a). We therefore studied two glucose normalization approaches to adjusting FDG $K_1$ for removing the dependence of FDG $K_1$ on BG (figure 2). FDG $K_1$ was further compared to the Rb reference MBF for analyzing the relation between them using the generalized RC model (figure 3). The resulting EFC model was then used to convert FDG $K_1$ to MBF. The results showed that the FDG-derived MBF correlated well with Rb MBF and glucose normalization for FDG $K_1$ was important (figures 4, 5, table 5). The extraction fraction of FDG demonstrated to be close to that of Rb-chloride (figure 6). Hence, FDG $K_1$ quantification with the glucose-normalized EFC has the potential to provide MBF.

The patient study is complex to do as it consists of both a dynamic FDG-PET scan and a dynamic Rb-PET scan, making patient accrual challenging. The sample size was small in this pilot study. The range of the MBF values in this study was also limited with only one patient having a MBF > 1.0 ml/min/cm$^2$. The additive approach for glucose normalization seems slightly better than the multiplicative approach (figures 4, 6), but it remains open to further investigate the most appropriate normalization approach given the small sample size in the current study. Another limitation is the use of $^{82}$Rb-chloride which is not an ideal tracer for MBF quantification. The results mainly provided a report to warrant future studies that should have a large sample size, include hyperaemic MBF values, and potentially use a better flow tracer (e.g. $^{11}$C-butanol) for comparison. The analysis of this study was also limited to evaluation of global myocardial quantification instead of segment-level investigation to reduce the effect of noise. The noise performance of the scanner (2002 GE Discovery ST model) used in this study was far from optimal for exploring segment-based $K_1$, as indicated by the result from the previous identifiability analysis (Zuo et al. 2020).

It is worth noting that the IDIF and myocardial TAC may suffer from the spill-over effect of a large ROI. Reducing the size of the LV ROI can reduce the effect but it would increase the noise. The spill-over effect from the myocardium to the LV cavity mainly occurs in the late time of a FDG scan. It will not affect the FDG $K_1$ estimation much since the estimation of $K_1$ is more dominated by the early time points (Zuo et al. 2019). However, the spill-over may potentially lead to a bias in the $k_3$ and $k_4$ estimates, while the two kinetic parameters are not the main interest of the current study. Alternatively, the ascending aorta or arch of aorta may be used, for example, for better quantification of myocardial metabolic rate of glucose (MRGlu) (Van der Weerd et al. 2001). One of our ongoing efforts is investigating the optimal option to extract IDIF for quantification of different myocardial FDG kinetic parameters with an emphasis on FDG $K_1$.

While motion correction was not included in the study, the effect of motion was less likely to result in a significant change to the results that were based on a large ROI given the spatial resolution of the PET scanner is only about 6–8 mm. A global myocardium ROI may involve the spill-over effect from the right ventricle. With the limited temporal sampling of 10 s/frame, the kinetic model used for FDG and Rb data in this study did not explicitly include the blood fraction from the right ventricle but only the LV. The separate estimation of $v_{LV}$ and $v_{RV}$ parameters in (Zuo et al. 2020) was therefore implicitly combined into a single blood volume parameter $v_b$ in equation (3). This is not uncommon. For example, Lortie et al. also used a temporal sampling of 10 s/frame and single blood volume parameter for both $^{13}$N-ammonia and $^{82}$Rb studies. We also tested the separate modeling of $v_{LV}$ and $v_{RV}$. The estimated $v_{RV}$ (<4%) and its effect on $K_1$ were both small (results not shown). This is reasonable given that the ROI accounts for the whole myocardium which is less affected than a ROI that is solely nearby the right ventricle.

Increase of temporal sampling, for example to 5 s/frame or 2 s/frame, has the potential to improve the separation of blood fractions from the LV and right ventricle, and may lead to more robust estimation of FDG $K_1$. In particular, latest clinical PET scanners have an effective sensitivity gain of 4–25 fold and higher spatial resolution as compared to a typical conventional scanner GE Discovery 690 (see table 4 in (Wang et al. 2020)), and are remarkably better than the GE DST scanner used in this study. The EXPLORER total-body PET/CT scanner (Cherry et al. 2017, Badawi et al. 2019) has an ultrahigh sensitivity for dynamic imaging, making it more feasible to explore higher temporal resolution and even pixel-wise parametric imaging in the myocardium. Furthermore, improved dynamic image reconstruction using machine learning concepts has been developed for dynamic PET imaging, e.g. with the kernel methods (e.g. (Wang and Qi 2015, Wang 2019)) or deep neural-network methods (e.g. (Gong et al. 2019, Reader et al. 2020)) as recent examples. Thus, the progress in PET instrumentation and algorithms may provide a future opportunity to exploit higher temporal resolution, higher...
spatial resolution, and also motion-corrected segment-based quantification for a better study design for enhanced evaluations of MBF using these FDG methods.

5. Conclusion

This pilot study demonstrates that FDG delivery rate $K_1$ from a one-hour dynamic scan was closely associated with MBF in the myocardium, especially after an adjustment for BG levels. With the glucose normalization and extraction fraction correction that covert FDG $K_1$ to MBF, the FDG-derived MBF highly correlated with Rb MBF. The results also suggest FDG may have a first-pass myocardial extraction fraction similar to that of Rb-chloride. This work warrants a future, large study to further explore the potential of FDG for simultaneous imaging of MBF and glucose metabolism.

Acknowledgments

The authors thank the anonymous reviewers for their very helpful review comments. This work was supported in part by National Institutes of Health (NIH) under grant no. R21 HL131385 and American Heart Association under grant no. 15BGIA25780046. The work of JEL is also supported in part by the Harold S. Geneen Charitable Trust Awards Program and the National Center for Advancing Translational Sciences, NIH, grant number UL1 TR001860 and linked award KL2 TR001859. The authors thank Denise Caudle, Michael Rusnak, and Ben Spencer for their assistance in the dynamic PET/CT data acquisition, Diana Ramos for her efforts in patient recruitments, and the patients that agreed to participate in these studies.

Appendix

Appendix A. Linearized relation between FDG $K_1$ and BG level

The relation between FDG $K_1$ and blood flow $F$ can be described by the RC model without a specific consideration of capillary recruitment (Carson 2005),

$$K_1 = F \cdot \left[1 - \exp\left(-\frac{PS}{F}\right)\right] \equiv RC(F; PS),$$

where $P$ denotes the permeability of FDG and $S$ is the surface area of a given section of the capillary bed. Here, the RC model is also denoted as a function of $F$ and $PS$ for convenient use. Following the classic Michaelis–Menten model, the product $PS$ relates to the BG concentration $C_{glu}$ following the form (equation (11) of (Carson 2005), equation (8) of (Gjedde 1980), equation (2) of (Gjedde 1981)),

$$PS = \frac{V_m,FDG}{K_m,FDG + \frac{K_m,FDG}{K_m,glu}C_{glu}} \equiv MM(C_{glu}),$$

where $V_m$ is the maximal rate of FDG (or glucose) transfer and $K_m$ denotes the concentration of FDG (or glucose) at which the half-maximum transfer rate is reached.

Based on the above two models, FDG $K_1$ can be further expressed as a direct function of $C_{glu}$, i.e.

$$K_1 \equiv f(C_{glu}) = RC(F; MM(C_{glu})).$$

By expanding $K_1$ at a reference BG level $C_{glu,0}$ using the first-order Taylor’s expansion, we will have the following linear approximation,

$$K_1 \approx f(C_{glu,0}) + \dot{f}(C_{glu,0}) \cdot (C_{glu} - C_{glu,0}),$$

where $\dot{f}(C_{glu,0})$ is the first-order derivative of $f$ at $C_{glu,0}$,

$$\dot{f}(C_{glu,0}) = \left. \frac{\partial f}{\partial C_{glu}} \right|_{C_{glu}=C_{glu,0}}.$$

From equation (17), we have

$$\frac{\partial K_1}{\partial PS} = \frac{\partial RC(F; PS)}{\partial PS} = \exp\left(-\frac{PS}{F}\right) > 0,$$
and from equation (18), we have
\[
\frac{\partial \text{PS}}{\partial C_{\text{glu}}} = \frac{\partial \text{MM} (C_{\text{glu}})}{\partial C_{\text{glu}}} = - \frac{V_{\text{m,FDG}} \frac{K_{\text{m,FDG}}}{K_{\text{m,glu}}} C_{\text{glu}}}{(K_{\text{m,FDG}} + \frac{K_{\text{m,FDG}}}{K_{\text{m,glu}}} C_{\text{glu}})^2} < 0.
\]
(23)

Combining the above two relations together produces
\[
\hat{f} (C_{\text{glu},0}) < 0.
\]
(24)

Thus, the approximate linear relation of FDG $K_1$ with the BG level $C_{\text{glu}}$ can be re-expressed as
\[
K_1 \approx -s \cdot C_{\text{glu}} + \text{int},
\]
(25)

where the absolute slope $s$ and the intercept $\text{int}$ relate to the reference BG level $C_{\text{glu},0}$ via
\[
s = -\hat{f} (C_{\text{glu},0}) > 0, \quad \text{int} = f (C_{\text{glu},0}) + s \cdot C_{\text{glu},0}.
\]
(26)

### Appendix B. Generalized RC model for FDG

Following the hypothesis of (Yoshida et al 1996) for $^{82}$Rb and $^{13}$N-ammonia that capillary recruitment occurs at high coronary flows, we assume the PS product of FDG, is not a constant but depends on blood flow $F$ in a multicapillary system,
\[
PS' = PS + \kappa \cdot F,
\]
(27)

where $PS'$ denotes the total PS product, $PS$ is the resting PS product, and $\kappa$ is a multiplicative coefficient.

Substituting the above model into the original RC model in equation (17), we then have the following generalized Renkin-Crone (GRC) model for FDG,
\[
K_1 = F \cdot \left[ 1 - \exp \left( -\frac{PS + \kappa \cdot F}{F} \right) \right]
= F \cdot \left[ 1 - a_{\text{FDG}} \cdot \exp \left( -\frac{PS}{F} \right) \right] \triangleq \text{GRC}(F; PS),
\]
(28)

where
\[
a_{\text{FDG}} = \exp (-\kappa) > 0.
\]
(29)

The GRC model is equal to equation (14) by setting $b_{\text{FDG}} = PS$. The coefficients $a_{\text{FDG}}$ and $b_{\text{FDG}}$ will be estimated by fitting the FDG $K_1$ and MBF data.

Note that with the GRC model, we can also derive the linearized relation between FDG $K_1$ and $C_{\text{glu}}$ (equation (25)) following the derivation in appendix A for the RC model. The major change is that the term $\exp \left( -\frac{PS}{F} \right)$ in equation (22) should be replaced by $a_{\text{FDG}} \cdot \exp \left( -\frac{PS}{F} \right)$. The resulting $\frac{\partial \text{PS}}{\partial \text{PS}}$ remains positive because $a_{\text{FDG}} > 0$ as shown in equation (29).

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