Rapid computation of single PET scan rest-stress myocardial blood flow parametric images by table look up

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Purpose: We have recently reported a method for measuring rest-stress myocardial blood flow (MBF) using a single, relatively short, PET scan session. The method requires two IV tracer injections, one to initiate rest imaging and one at peak stress. We previously validated absolute flow quantitation in ml/min/cc for standard bull's eye, segmental analysis. In this work, we extend the method for fast computation of rest-stress MBF parametric images.

Methods: We provide an analytic solution to the single-scan rest-stress flow model which is then solved using a two-dimensional table lookup method (LM). Simulations were performed to compare the accuracy and precision of the lookup method with the original nonlinear method (NLM). Then the method was applied to 16 single scan rest/stress measurements made in 12 pigs: seven studied after infarction of the left anterior descending artery (LAD) territory, and nine imaged in the native state. Parametric maps of rest and stress MBF as well as maps of left (f_{LV}) and right (f_{RV}) ventricular spill-over fractions were generated. Regions of interest (ROIs) for 17 myocardial segments were defined in bull's eye fashion on the parametric maps. The mean of each ROI was then compared to the rest (K_{Ir}) and stress (K_{Is}) MBF estimates obtained from fitting the 17 regional TACs with the NLM.

Results: In simulation, the LM performed as well as the NLM in terms of precision and accuracy. The simulation did not show that bias was introduced by the use of a predefined two-dimensional lookup table. In experimental data, parametric maps demonstrated good statistical quality and the LM was computationally much more efficient than the original NLM. Very good agreement was obtained between the mean MBF calculated on the parametric maps for each of the 17 ROIs and the regional MBF values estimated by the NLM ($K_{Imap\ LM} = 1.019 \times K_{IROI\ NLM} + 0.019$, $R^2 = 0.986$; mean difference = 0.034 ± 0.036 mL/min/cc).

Conclusions: We developed a table lookup method for fast computation of parametric imaging of rest and stress MBF. Our results show the feasibility of obtaining good quality MBF maps using modest computational resources, thus demonstrating that the method can be applied in a clinical environment to obtain full quantitative MBF information. © 2017 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.12398]

Key words: kinetic modeling, myocardial blood flow, parametric imaging, positron emission tomography

1. INTRODUCTION

Myocardial perfusion imaging using positron emission tomography (PET) provides an accurate means for the

detection and monitoring of coronary artery disease (CAD).^{1–4} Quantitative measurements of myocardial blood flow (MBF) at rest and during stress have been successfully obtained using dynamic studies with appropriate

flow tracers and kinetic modeling.^{5–9} We previously published a nonstationary kinetic model for quantitative measurement of absolute myocardial blood flow (MBF) during a two-injection single scan rest/stress imaging session, thus obviating the need for waiting 3–5 half lives between the rest and stress scans.¹⁰ In our approach, the rest-stress scan is viewed as a single measurement in which the MBF changes as a function of time due to the introduction of a stressor. In fact, the rest MBF is assumed constant before infusion of a stressor; whereas, the stress flow prevails after the start of the infusion. Conceptually, the PET time activity curve (TAC) obtained from the two injections is treated as a single continuous entity as a single continuous input function is measured from the chamber of the left ventricle. More recently, we validated this method in a pig model¹¹ using the long half-lived ¹⁸F-Flurpiridaz flow tracer^{12–15} and adenosine as a pharmacological stressor.^{16,17} Accurate and precise rest and stress blood flow measurements were obtained in less than 15 min of PET acquisition. The validity was confirmed by comparison with microspheres and the method yielded quantitative results similar to those published using the same tracer with rest and stress scans separated by 1 h and subtraction of residual activity.¹⁵ These analyses were performed on a regional basis using TACs extracted from the 17-myocardial segment¹⁸ but the quality of the ¹⁸F-Flurpiridaz measurements suggested further developments, such as the computation of rest-stress MBF parametric maps. Compared to regions of interest (ROI) methods, parametric imaging is appealing because it has the potential to improve MBF information at the voxel level by taking full advantage of the image resolution. However, parametric imaging of compartmental models obtained by optimization using conventional nonlinear least squares methods is time consuming which

could be one of the limitations for implementation in a clinical environment.

In this work, we present an analytic solution of the nonstationary kinetic model for fast computation of parametric images of rest (K_{Ir}) and stress (K_{Is}) MBF using a table lookup method (LM). We first characterize the proposed method in a simulation study mimicking rest-stress PET measurements obtained with ¹⁸F-Flurpiridaz and compare its performance to the original nonlinear model (NLM). Then we apply the LM in ¹⁸F-Flurpiridaz rest-stress experimental measurements previously obtained in pigs for the generation of rest and stress MBF maps.

2. METHODS

2.A. Model development

2.A.1. Background

Figure 1 summarizes the single-scan method previously developed for measuring rest-stress myocardial blood flow (MBF) with a 12 min protocol for which the second tracer injection is administered midway through a 6 min adenosine infusion starting 4 min after the start of the PET acquisition. The original MGH2 nonlinear model (NLM) developed to fit the rest-stress measurements¹⁰ is described by Eqs. (1), (2), (3), (4), and (5). In these equations C_p represents the arterial concentration of the tracer (the input function) and C_{LV} and C_{RV} the PET concentrations measured in the left (LV) and right (RV) ventricular chambers. C_F represents the free and non-specifically bound radiotracer concentration and C_B the radiotracer concentration specifically and, for the study duration considered, irreversibly bound to its target. K_{Ir} and K_{Is} are the blood flow kinetic parameters and k_{2r}

FIG. 1. (a) Diagram summarizing the experimental protocol for a 12 min single scan rest-stress acquisition with the second tracer injection occurring midway through the adenosine infusion. Each tracer injection is given as a 20–30 s bolus. (b) Representation of resulting PET time activity curves in the myocardium and left ventricular chamber following this experimental protocol. [Color figure can be viewed at wileyonlinelibrary.com]

and k_{2s} the egress rate constants for the rest and stress phases respectively. The binding rate constant of the tracer for its target is modeled by k_3 and the right and left ventricular spill-over fractions to the myocardium by f_{LV} and f_{RV} . No attempt was made to correct spill-over from tissue to blood pools. Finally, *PET* is the model output describing the PET measurements for each frame i starting at time t_i and ending at t_{i+1} , with $\Delta t_i = t_{i+1} - t_i$ the frame duration. This 2-compartment model with time-varying kinetic parameters considers the blood flow transition occurring between the rest and stress phase of the exam as an abrupt change starting with the introduction of adenosine at the time T_S after the first tracer injection. In the present work, we neglect the binding rate constant k_3 as it was shown previously that fixing this parameter within a range of physiologically plausible values has a negligible effect on the estimation of the MBF parameters for ^{18}F -Flurpiridaz measurements when using less than 15 min of PET data.¹¹

$$\frac{dC_F(t)}{dt} = K_1(t)C_p(t) - [k_2(t) + k_3]C_F(t) \quad (1)$$

$$\frac{dC_B(t)}{dt} = k_3C_F(t) \quad (2)$$

$$PET_i = f_{LV}C_{LV_i} + f_{RV}C_{RV_i} + (1 - f_{LV} - f_{RV}) \frac{1}{\Delta t_i} \int_{t_i}^{t_{i+1}} C_F(t) + C_B(t) dt \quad (3)$$

$$K_1(t) = \begin{cases} K_{1r} & t < T_S \\ K_{1s} & t \geq T_S \end{cases} \quad (4)$$

$$k_2(t) = \begin{cases} k_{2r} & t < T_S \\ k_{2s} & t \geq T_S \end{cases} \quad (5)$$

2.A.2. Development of the table lookup method

The general solution for C_F , the concentration in the free compartment can then be given by Eq. (6) and the PET measurements can be described by Eq. (7) including the right and left ventricular spill-over fractions while neglecting the specific binding of Flurpiridaz.

$$C_F(t) = e^{-\int_0^t k_2(u) du} \int_0^t K_1(v)C_p(v) e^{\int_0^v k_2(y) dy} dv \quad (6)$$

$$PET_i = f_{LV}C_{LV_i} + f_{RV}C_{RV_i} + (1 - f_{LV} - f_{RV}) \frac{1}{\Delta t_i} \int_{t_i}^{t_{i+1}} C_F(t) dt \quad (7)$$

Assuming that the stress phase of the scan starts at $t = T_S$ after the first tracer injection, we differentiate two cases: (a) the rest phase for $t < T_S$ and (b) the stress phase for $t \geq T_S$.

Case 1: $0 < t < T_S$, $K_1(t) = K_{1r}$ and $k_2(t) = k_{2r}$

$$C_F(t) = K_{1r} e^{-k_{2r}t} \int_0^t C_p(v) e^{k_{2r}v} dv \quad (8)$$

Case 2: $t \geq T_S$, $K_1(t) = K_{1s}$ and $k_2(t) = k_{2s}$

$$C_F(t) = K_{1r} e^{-k_{2r}T_S} e^{-k_{2s}(t-T_S)} \int_0^{T_S} C_p(v) e^{k_{2r}v} dv + K_{1s} e^{-k_{2s}t} \int_{T_S}^t C_p(v) e^{k_{2s}v} dv \quad (9)$$

Finally, the model output presented in Eq. (7) can be formulated using a matrix representation as shown by Eq. (10). From this representation it is easily seen that the model output is linear in the MBF (K_{1r} and K_{1s}) and spill-over fraction parameters (f_{LV} and f_{RV}). The model also contains nonlinear terms (G and H) that include the egress rate constants as shown by Eqs. (11), (12), and (13). In this work, we solve the model output equation using a two-dimensional lookup table of the rest and stress egress rate constants (k_{2r} , k_{2s}). For each value of k_{2r} and k_{2s} all voxels are simultaneously fitted with linear least squares and the solution providing the lowest residual sum of square (RSS) is retained.

$$\begin{bmatrix} PET_1 \\ PET_2 \\ \vdots \\ PET_n \end{bmatrix} = K_{1r} \begin{bmatrix} G_1 \\ G_2 \\ \vdots \\ G_n \end{bmatrix} + K_{1s} \begin{bmatrix} H_1 \\ H_2 \\ \vdots \\ H_n \end{bmatrix} + f_{LV} \begin{bmatrix} C_{LV_1} \\ C_{LV_2} \\ \vdots \\ C_{LV_n} \end{bmatrix} + f_{RV} \begin{bmatrix} C_{RV_1} \\ C_{RV_2} \\ \vdots \\ C_{RV_n} \end{bmatrix} \quad (10)$$

where:

$$G_i = (1 - f_{LV} - f_{RV}) \frac{1}{\Delta t_i} \int_{t_i}^{t_{i+1}} g_i(t) dt \quad (11)$$

with:

$$g_i(t) = \begin{cases} e^{-k_{2r}t} \int_0^t C_p(v) e^{k_{2r}v} dv & t < T_S \\ e^{-k_{2r}T_S} e^{-k_{2s}(t-T_S)} \int_0^{T_S} C_p(v) e^{k_{2r}v} dv & t \geq T_S \end{cases} \quad (12)$$

and

$$H_i = (1 - f_{LV} - f_{RV}) \frac{1}{\Delta t_i} \int_{t_i}^{t_{i+1}} h_i(t) dt \quad (13)$$

with:

$$h_i(t) = \begin{cases} 0 & t < T_S \\ e^{-k_{2s}t} \int_{T_S}^t C_P(v) e^{k_{2s}v} dv & t \geq T_S \end{cases} \quad (14)$$

2.B. Simulation study

2.B.1. Generation of realistic TACs

Simulations were performed to mimic experimental time activity curves (TACs) obtained from our two injection, single scan, rest-stress myocardial blood flow method. A noiseless TAC was generated by solving the NLM equations using an input function and kinetic parameters obtained from experimental data acquired in pigs. Curves (TACs) with statistical fluctuations were generated at 10 different noise levels (1000 noise realizations for each noise level) by adding gaussian-distributed noise to the simulated noiseless TAC. The standard deviation SD of the gaussian noise was modeled as in Kamasak [Eq. (36) in Ref. (19)] and in Muzic and Christian [Eq. (10) in Ref. (20)] and is shown by Eq. (15), where y_i is the simulated noiseless PET TAC at frame i and α is a constant determining the noise level. 10 noise levels denoted as $L = [1, 2, \dots, 10]$ were simulated and corresponding to values of $\alpha = [3, 6, 9, 12, 15, 18, 21, 24, 27, 30]$ in Eq. (15). y_i is expressed in Bq/mL and Δt_i in minutes. In MATLAB, the `randn` function was used to model the gaussian noise. The first row of Table I shows the kinetic parameters used for the simulation.

$$SD = \alpha \sqrt{\frac{y_i}{\Delta t_i}} \quad (15)$$

2.B.2. Comparing LM vs. NLM methods

All simulated TACs were fitted by both the LM and the original NLM methods to compare their performance. For the LM method a two dimensional look-up table was generated for the rest and stress egress rate constants using 60 discrete values for k_{2r} (evenly spaced in the range 0–0.6 min^{−1}) and 80 discrete values for k_{2s} (evenly spaced in the range 0–0.8 min^{−1}). The upper bounds on the egress rate constants were chosen by examining the range of kinetic parameters

TABLE I. Kinetic parameters used for simulating the rest-stress TAC as well as lower and upper bounds used during the NLM fitting process.

	K_{Ir} (ml/min/cc)	k_{2r} (min ^{−1})	K_{Is} (ml/min/cc)	k_{2s} (min ^{−1})	f_{LV}	f_{RV}
Parameter	0.565	0.150	1.200	0.234	0.270	0.100
Lower bound	0	0	0	0	0	0
Upper bound	100	0.600	100	0.800	100	100

previously estimated by the NLM in 16 rest-stress studies with pigs.¹¹ For the NLM method, initial values for the kinetic parameters were randomly generated from a uniform distribution within $\pm 80\%$ the true parameter values. The lower and upper parameter bounds used for the fitting process are presented in Table I. For a fair comparison with the LM method, the upper bounds on the egress rate constant were set to 0.6 min^{−1} for k_{2r} and 0.8 min^{−1} for k_{2s} whereas large values were used for blood flow (K_{Ir} and K_{Is}) and spill-over fraction (f_{LV} and f_{RV}) parameters.

2.C. Application of the LM method to experimental measurements

2.C.1. Experimental protocol

16 single scan rest/stress ¹⁸F-Flurpiridaz measurements were made in 12 pigs (weight 49.6 $\pm$ 14.1 kg): 9 were imaged in the native state and 7 were imaged 2 to 3 weeks after infarction of the LAD territory. Full details for the two-injection, single-scan rest-stress protocol used for these studies can be found in Guehl et al. 2017.¹¹ Briefly, a 6 min adenosine infusion (140 to 250 μ g/min/kg of body weight) was started four minutes after a first ¹⁸F-Flurpiridaz injection (injected dose: 171 $\pm$ 32 MBq) and was followed by a second ¹⁸F-Flurpiridaz injection (injected dose: 226 $\pm$ 46 MBq) either 3 or 6 min after the start of the infusion. The PET scanner was started right before the first tracer injection.

2.C.2. Animal preparation and surgery

Details about the animal preparation as well as the surgery performed to induce infarction of the left anterior descending artery (LAD) have been described elsewhere.¹¹

2.C.3. Image acquisition and reconstruction

Studies were done on a Siemens Biograph PET/CT scanner. Cardiac CT and CTA were acquired prior to the PET acquisition for anatomical information. Attenuation correction of PET images was performed using the attenuation maps obtained from the CT. 3D list mode PET data were acquired during 60 min and were framed into dynamic series as previously described.¹¹ Images were reconstructed with a filtered back projection (FBP) algorithm (voxel size: 2.14 $\times$ 2.14 $\times$ 3 mm³). 12 or 14 min of data were used for data analysis, depending on the timing of the second PET injection.

2.C.4. Data analysis

All images were first transformed into a three-dimensional pig atlas developed in house²¹ and subsequently reoriented into the short axis view. Dimensions of each 3D volume were 96 $\times$ 96 $\times$ 96 (voxel size: 2.14 $\times$ 2.14 $\times$ 2.14 mm³). To obtain the measured input function, TACs were extracted by

defining a ROI of approximately $2 \times 2 \times 3 \text{ cm}^3$ in the middle of the left ventricle chamber and were corrected for the whole blood to plasma concentration ratio to obtain the model input function. Parametric maps of rest and stress MBF as well as maps of left (f_{LV}) and right (f_{RV}) ventricular spill-over fractions were then generated using the proposed LM method. As for the simulation study, the two dimensional look-up table used to analyze the experimental data contains 60 discrete values for k_{2r} (evenly spaced in the range 0–0.6 min^{-1}) and 80 discrete values for k_{2s} (evenly spaced in the range 0–0.8 min^{-1}). A threshold of 0.7 was set for f_{LV} and f_{RV} estimates to prevent unstable estimates of MBF as explained in the discussion. A 3D box with dimensions $48 \times 48 \times 52$, designed to encompass the whole heart, was defined on the atlas space prior to applying the proposed method in order to further reduce the computation time. LM was then ran slice by slice using the MATLAB R2013a (Mathworks, Natick, MA, USA) software platform and its parallel computing toolbox on 12 workers.

A myocardial mask was manually defined in the atlas template space based on the sum of the late frames of the dynamic PET images acquired in healthy pigs. The mask was then applied to the parametric maps to remove structures that are external to the myocardium. Regions of interest (ROIs) for 17 myocardial segments were defined in bull's eye fashion¹⁸ on the parametric maps. Linear regression and Bland-Altman plots were then used to compare the mean of each ROI to the K_{Ir} and K_{Is} estimates obtained from fitting the 17 regional TACs, that were extracted from the dynamic images, with the NLM.

3. RESULTS

3.A. Simulation study

Figure 2 shows representative simulated noisy rest-stress TACs at four different noise levels along with the model fits obtained with LM and NLM. The fits obtained by the two methods were indistinguishable at all noise levels. The mean and associated standard deviation of K_{Ir} and K_{Is} calculated at each noise level across the 1000 datasets using LM and NLM are shown Fig. 3. The two methods performed similarly in terms of precision and accuracy when comparing with the true simulated parameters. The comparison study did not show that bias was introduced by the use of our predefined two-dimensional lookup table (k_{2r}, k_{2s}).

3.B. Application to experimental data

Figure 4 shows a set of parametric maps, K_{Ir} , K_{Is} , f_{LV} , and f_{RV} , obtained for a healthy pig using the proposed method. All the maps generated demonstrated good statistical quality for each parameter. The f_{LV} map [Fig. 4(b) top row] showed high f_{LV} estimates mostly restricted to the left myocardium. Moreover, the maps presented higher f_{LV} in the inner part of the left myocardium (the part of the myocardium in the vicinity of the left ventricular chamber) than in the outer myocardium (the part of the myocardium proximal to the pericardium). In contrast, the f_{RV} maps showed that high f_{RV} estimates were restricted to the right myocardium and f_{RV} values were elevated in the entire right myocardium. K_I maps obtained from an injured pig scanned 3 weeks after occlusion of the LAD

FIG. 2. Representative simulated TACs (filled circles) at four different noise levels L : $L = 1$ (a); $L = 4$ (b); $L = 8$ (c); and $L = 10$ (d). LM and NLM model fits are indistinguishable (solid lines). Dashed lines represent the TACs in the left ventricular chamber. [Color figure can be viewed at wileyonlinelibrary.com]

artery are also shown Fig. 5. The blood flow maps clearly show reduction of MBF in the tissue areas fed by the LAD.

Left to right columns are short axis, horizontal long axis and vertical long axis views respectively.

In terms of computational efficiency, the LM was much faster than the original NLM. Each set of maps was obtained in 136 s whereas, several hours were required with the NLM.

Figure 6 shows the comparison between the mean MBF calculated on the parametric maps for each of the 17 ROIs and the regional MBF values estimated by the NLM. K_{I_r} and K_{I_s} obtained from all pig studies are grouped on the same graphs. The correlation and Bland-Altman plots show very good agreement ($K_{I_{map\ LM}} = 1.019 \times K_{I_{ROI\ NLM}} + 0.019$, $R^2 = 0.986$; mean difference = 0.034 ± 0.036 mL/min/cc) between K_I estimates.

4. DISCUSSION

We have presented a table lookup method (LM) designed to facilitate parametric analysis of the nonstationary MGH2 kinetic model. In a simulation study we compared the performance of the proposed method with the original NLM at different noise levels chosen to resemble those encountered in experimental measurements with ^{18}F -Flurpiridaz. The low noise levels were chosen to mimic regional TACs such as those obtained from the 17 bull's eye segments whereas the highest noise levels were intended to simulate TACs extracted

at the voxel level. The study showed that the LM method performed as well as the NLM method in terms of precision and accuracy (Fig. 3) and did not show that extra bias was introduced by the use of the two-dimensional lookup table for the predefined k_{2r} and k_{2s} set of values chosen in this work. In experimental data, the method provided good quality parametric images of the rest and stress MBF estimates and spill-over fractions. The results suggest that reasonable MBF estimates were obtained at the voxel level since very good agreement was obtained between the regional mean of the parametric images and estimates obtained from the 17 segment TACs (Fig. 6). The differences highlighted by the Bland-Altman plot are very likely due to differences in noise level between TACs extracted on a voxel by voxel basis and those extracted from the 17 segments. Moreover, f_{LV} and f_{RV} maps showed higher spill-over fractions around the blood pools which is consistent with expectation and illustrates the identifiability of the model parameters at the voxel level. f_{RV} maps showed elevated spill-over fractions in the entire right myocardium in contrast to the f_{LV} maps for which high spill-over fractions were mostly located in the inner part of the myocardial muscle. This result is very likely due to the thinner nature of the right myocardial muscle, as compared to the left myocardium, leading to more important resolution effect. The LM method was computationally much more efficient than the NLM for the generation of a set of parametric maps. Indeed, solving simultaneously for all voxels and performing

FIG. 3. Mean values of parameter estimates obtained for each noise level along with associated standard deviations. True simulated values are shown by the dashed line. Top row shows the comparison between LM (a) and NLM (b) for K_{I_r} . Bottom row shows the comparison between LM (c) and NLM (d) for K_{I_s} . [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 4. Parametric maps obtained for a control pig. (a): Resting K_{1r} (top) and stress K_{1s} (bottom) flow maps. (b): Maps of spill-over fraction from left f_{LV} (top row) and right f_{RV} (bottom row) ventricular blood pools. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 5. Parametric maps for a pig with injury to apical-septal tissue. (a): Top row shows resting (K_{1r}) flow maps and bottom row shows stress (K_{1s}) maps. (b): Maps of spill-over fraction from left f_{LV} (top row) and right f_{RV} (bottom row) ventricular blood pools. The arrows indicate location of the injury. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 6. Correlation (a) and Bland-Altman plots (b) showing the agreement between MBF estimated from the parametric maps and the 17 segment TACs. All 16 pig studies are represented. On the Bland-Altman plot, bold line is the mean difference and dashed lines are mean difference ± 1.96 standard deviations. [Color figure can be viewed at wileyonlinelibrary.com]

4800 linear least-square estimations (60 k_{2r} values times 80 k_{2s} values) slice by slice was much faster than solving with nonlinear least square for each voxel in MATLAB (Mathworks, Natick, MA, USA). In this study, we used a relatively

fine grid of (k_{2r} , k_{2s}) values. Reducing the number of elements in the look-up table would further reduce the computation time at the expense of inducing some level of bias in the estimation of the MBF parameters.

In this work, we used adenosine as a stressor and the PET measurements were made with ^{18}F -Flurpiridaz, a tracer that has previously been used to measure MBF in animal models^{11,15,22} and humans.^{23,24} However, the method can be applicable to any flow tracer and experimental setup that does not violate the model assumptions. The first assumption is that the model structure considers an abrupt change in MBF with the introduction of the stressor. This seems to be a reasonable assumption for adenosine because it is a fast-acting drug for which the hyperemia peak is reached in less than a minute.^{16,17} Moreover, we have shown that the model accurately describes the PET measurements at the adenosine doses tested (140 to 250 $\mu\text{g}/\text{min}/\text{kg}$ of body weight), which suggests that the physiological processes are correctly modeled. While there is no theoretical limitation, future experiments are needed to show that the current formulation of the LM model can be used for rest-stress measurements performed with other pharmacological stressors. Another assumption for the LM model to be valid is that the specific binding is negligible for the duration of the imaging study. For ^{18}F -Flurpiridaz, we previously demonstrated that fixing k_3 to a small value (within a range of plausible physiological values) did not significantly affect the estimations of rest and stress MBF¹¹ which allowed us to neglect this parameter in the present work. The validity of this assumption should be tested if other PET tracers are to be used with the proposed method. On a side note, for the computation of the MBF parametric maps we did set a threshold of 0.7 for the spill-over fractions since for some voxels the f_{LV} and/or f_{RV} estimates can be close to 1 or even higher and in turn lead to unstable estimates of MBF. This can be explained by several reasons: (a) some voxels can contain blood vessels or (b) be close to the blood pools and (c) the noise at the voxel level can prevent accurate estimation of these parameters for each voxel.

The use of the proposed method combined with our two-injection single-scan rest-stress protocol is attractive for clinical translation because it allows full quantitative measurements of MBF in a short period of time. This statement is especially true when comparing with the current clinical practice where, depending on the half-life of the isotope used, the rest and stress scans might need to be done on different days.

5. CONCLUSION

We developed a table lookup method that allows fast computation of rest and stress MBF parametric images using a predefined two-dimensional table of the rest and stress egress rate constant. The method did not introduce any bias on the MBF estimation as compared to the original NLM method and good quality parametric images were obtained. The agreement between the mean of parametric maps and regional estimates was very good. The use of the proposed method combined with our two-injection single-scan rest-stress protocol is theoretically applicable to any flow tracer and has the potential to greatly

streamline clinical practice while providing full quantitative MBF information.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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