Cardiac-gated parametric images from ^{82}Rb PET from dynamic frames and direct 4D reconstruction

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(Received 7 April 2017; revised 7 November 2017; accepted for publication 7 November 2017; published 30 December 2017)

Purpose: Cardiac perfusion PET data can be reconstructed as a dynamic sequence and kinetic modeling performed to quantify myocardial blood flow, or reconstructed as static gated images to quantify function. Parametric images from dynamic PET are conventionally not gated, to allow use of all events with lower noise. An alternative method for dynamic PET is to incorporate the kinetic model into the reconstruction algorithm itself, bypassing the generation of a time series of emission images and directly producing parametric images. So-called “direct reconstruction” can produce parametric images with lower noise than the conventional method because the noise distribution is more easily modeled in projection space than in image space. In this work, we develop direct reconstruction of cardiac-gated parametric images for ^{82}Rb PET with an extension of the Parametric Motion compensation OSEM List mode Algorithm for Resolution-recovery reconstruction for the one tissue model (PMOLAR-1T).

Methods: PMOLAR-1T was extended to accommodate model terms to account for spillover from the left and right ventricles into the myocardium. The algorithm was evaluated on a 4D simulated ^{82}Rb dataset, including a perfusion defect, as well as a human ^{82}Rb list mode acquisition. The simulated list mode was subsampled into replicates, each with counts comparable to one gate of a gated acquisition. Parametric images were produced by the indirect (separate reconstructions and modeling) and direct methods for each of eight low-count and eight normal-count replicates of the simulated data, and each of eight cardiac gates for the human data. For the direct method, two initialization schemes were tested: uniform initialization, and initialization with the filtered iteration 1 result of the indirect method. For the human dataset, event-by-event respiratory motion compensation was included. The indirect and direct methods were compared for the simulated dataset in terms of bias and coefficient of variation as a function of iteration.

Results: Convergence of direct reconstruction was slow with uniform initialization; lower bias was achieved in fewer iterations by initializing with the filtered indirect iteration 1 images. For most parameters and regions evaluated, the direct method achieved the same or lower absolute bias at matched iteration as the indirect method, with 23%–65% lower noise. Additionally, the direct method gave better contrast between the perfusion defect and surrounding normal tissue than the indirect method. Gated parametric images from the human dataset had comparable relative performance of indirect and direct, in terms of mean parameter values per iteration. Changes in myocardial wall thickness and blood pool size across gates were readily visible in the gated parametric images, with higher contrast between myocardium and left ventricle blood pool in parametric images than gated SUV images.

Conclusions: Direct reconstruction can produce parametric images with less noise than the indirect method, opening the potential utility of gated parametric imaging for perfusion PET. © 2017 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.12710>]

Key words: cardiac PET, direct PET reconstruction, kinetic modeling, parametric imaging

1. INTRODUCTION

In cardiac perfusion PET, kinetic modeling can be used to quantitatively assess myocardial blood flow (MBF) and myocardial flow reserve (MFR) for better assessment of patients with coronary artery disease.^{1–3} Kinetic modeling

can be done on a regional basis, or per voxel to produce parametric images. Conventionally, kinetic model fitting is performed by the “indirect method”, i.e., a series of emission time frames are reconstructed, voxel or regional time activity curves (TAC) are created, and parameters are estimated by a weighted least squares criterion. Perfusion PET can also be

used to estimate ejection fraction, which provides additional prognostic value.^{4–7} Ejection fraction is typically estimated from cardiac-gated emission images, by using later data (after ~2 min postinjection) to obtain good contrast between the myocardium and blood pool. Left ventricle volumes are determined per gate based on automated segmentation of the myocardial wall. Particularly with short-lived tracers such as ⁸²Rb, noise can be a challenge in parametric imaging. Thus, to date, cardiac gating of perfusion images for the assessment of ejection fraction is done independently of parametric imaging, i.e., data from one acquisition will be rebinned and separate gated and dynamic reconstructions performed. However, better mitigation of noise could allow cardiac gating of parametric images for simultaneous assessment of function and flow. Specifically, kinetic modeling produces images of the left and right blood pools, which could be used to assess left and right ventricle blood volumes, as well as providing flow images that are theoretically less affected by partial volume effects than standard gated emission images.

One technique for obtaining parametric images with lower noise is direct reconstruction,^{8–11} in which the kinetic model of interest is incorporated directly into the reconstruction algorithm itself. Direct reconstruction is statistically advantageous over the indirect method because noise can be more accurately modeled in projection space (as Poisson) than in image space, where the noise distribution is more complicated. Previous work on direct reconstruction for cardiac perfusion PET has shown noise reductions as compared to the indirect approach ranging from 12% to 70%, depending on count level and specific implementation, in simulated 2D¹² or 3D^{13,14} data. None of these previous studies included assessment with real data. Note that direct reconstruction naturally extends to performing cardiac-gated analysis, since it avoids the creation of gated dynamic frames, which potentially have very few counts and could have low-count biases.

Motivated by these successes and the encouraging performance of the PMOLAR-1T algorithm in brain imaging,^{15,16} we have extended PMOLAR-1T for direct reconstruction of ⁸²Rb PET by including spillover terms to account for partial volume and blood volume from the left and right ventricles into the myocardium.¹⁷ This implementation uses an analytical update in the M-step of the EM algorithm, instead of potentially more computationally demanding numerical non-linear optimization methods. We assess the performance of this algorithm in simulated and real human PET data for the purpose of cardiac-gated parametric imaging, which produces image of flow (K_1), either uncorrected or corrected for partial volume effects, as well as gated image of LV and RV blood volume. The processing of human data also included rigid event-by-event compensation for respiratory motion.

2. METHODS

2.A. Kinetic model for ⁸²Rb PET

The time-varying signal in the myocardium $C_M(t)$ (Bq/cm³) is described by the 1-tissue (1T) compartment model:^{18,19}

$$C_M(t) = C_A(t) \otimes K_1 e^{-k_2 t}, \quad (1)$$

where $C_A(t)$ is the arterial input function (Bq/ml), K_1 is the tracer influx rate constant (ml/min/cm³), k_2 is the tracer efflux rate constant (min⁻¹), and $\otimes$ is the convolution operator. To account for spillover from the left and right ventricles into the myocardium due to partial volume, cardiac motion, as well as blood volume, the PET time activity curves (TAC), $C_T(t)$, are modeled as

$$C_T(t) = (1 - V_A - V_{RV})C_M(t) + V_A C_A(t) + V_{RV} C_{RV}(t), \quad (2)$$

where V_A is the left ventricle (LV) spillover/volume fraction, V_{RV} is the right ventricle (RV) spillover fraction, and $C_{RV}(t)$ is the RV TAC. Spillover from the RV into the myocardium is minimal with the exception of the septal region, so frequently the RV term is omitted for an alternative 3-parameter model:

$$C_T(t) = (1 - V_A)C_M(t) + V_A C_A(t). \quad (3)$$

The primary parameter of interest is K_1 , which corresponds to myocardial blood flow with appropriate correction for extraction.^{20–23} The parameter k_2 is usually of little interest in ⁸²Rb studies: rubidium is trapped in viable myocardial tissue, so k_2 is small and difficult to estimate reliably with a short scan using a short-lived isotope. Also note that Eqs. (2) and (3) assume that there are no spillover effects from regions outside the myocardium, such as the lung.

2.B. Indirect parameter estimation

Emission images were reconstructed per frame using standard OSEM as implemented in MOLAR.^{24–26} Frames were generated starting 40 s postinjection (at approximate arrival of activity in the heart) with the following timing: 9 × 4 s, 3 × 10 s, 3 × 20 s, 3 × 30 s. To generate parametric images, Eq. (2) or (3) was fit to each voxel using the basis function method²⁷ with weights based on noise equivalent counts and a non-negativity constraint on all parameters.

In this implementation, the term $(1 - V_A - V_{RV})K_1$ is estimated as a lumped quantity, which we refer to as $K_{1, \text{uncorr}}$; K_1 is derived by dividing $K_{1, \text{uncorr}}$ by $1 - V_A - V_{RV}$ or $1 - V_A$ (effectively correcting K_1 for partial volume effects). While K_1 estimates will be more accurate for flow quantification, $K_{1, \text{uncorr}}$ images are less noisy and therefore might be more useful for identification of perfusion defects.

2.C. Direct parameter estimation

The direct reconstruction algorithm used in this work is an extension of PMOLAR-1T,^{15,16} to allow inclusion of the LV and RV spillover terms.¹⁷

For projection data Y_{it} along line-of-response (LOR) i at time t , the Poisson-distributed complete data space for the expectation-maximization (EM) direct reconstruction of the parameters of Eq. (2) is indexed by list mode event index (i), voxel (j), time since tracer injection (t), time of tracer delivery (τ), and linear “region” parameter (r):

$$X_{ijtr} \sim \text{Poisson}(\Delta t c_{ij} A_i N_i L_t \theta_{rj} F_{rt\tau}) \quad (4)$$

where c_{ij} is the contribution of voxel j to line-of-response (LOR) of list mode event i , Δt is the duration of a time bin (which can be greater than or equal to the list mode resolution of 1 ms), A_i is attenuation of event i , N_i is the normalization (sensitivity) factor for event i , and L_t is the decay factor at time t . The index r takes on 3 values (0,1,2) to account for the three regional contributions to the signal (myocardium, LV, and RV), such that $\theta_j = [K_{1,\text{uncorr},j}, V_{A,j}, V_{RV,j}]$ and $F_{rt\tau} = [C_A(\tau)e^{-k_{2,j}(t-\tau)}, C_A(t), C_{RV}(t)]$. This separation of the complete data space is analogous to that presented by Su et al.¹² with the addition of the right ventricle spillover term. Also, as described below, our implementation uses an analytical update for k_2 (the nonlinear parameter) rather than the basis function method employed in.¹² The corresponding complete data log-likelihood is:

$$\log f(x|\theta, k_2) = \sum_{ijtr} (x_{ijtr} \log(\Delta t c_{ij} A_i N_i L_t \theta_{rj} F_{rt\tau}) - \Delta t c_{ij} A_i N_i L_t \theta_{rj} F_{rt\tau}), \quad (5)$$

The complete data expectation at iteration n , is given by

$$E[X_{ijtr}|Y_{it}, \theta_{rj}^{(n)}, k_{2,j}^{(n)}, R_{it}, S_{it}] = \frac{y_{it} \Delta t c_{ij} A_i N_i L_t \theta_{rj}^{(n)} F_{rt\tau}^{(n)}}{\sum_{r'j't'} \Delta t c_{ij'} A_i N_i L_t \theta_{r'j'}^{(n)} F_{r't'\tau}^{(n)} + \Delta t R_{it} + \Delta t S_{it}} = M_{ijtr}^{(n)} \quad (6)$$

where y_{it} is the number of counts detected along LOR i at time t , R_{it} is the estimated randoms rate, and S_{it} is the estimated scatter rate. The quantity that the EM algorithm maximizes is the expectation of the complete data log-likelihood, conditional on the current parameter estimates in each voxel:

$$E[\log f(X|\theta, k_2)|y, \theta^{(n)}, k_2^{(n)}, R_{it}, S_{it}] = \sum_{ijtr} M_{ijtr}^{(n)} \log(\Delta t c_{ij} A_i N_i L_t \theta_{rj} F_{rt\tau}) - \Delta t c_{ij} A_i N_i L_t \theta_{rj} F_{rt\tau} \quad (7)$$

The update equations for the linear parameters obtained by maximizing (7) are:

$$\theta_{rj}^{(n+1)} = \frac{\sum_{it\tau} M_{ijtr}^{(n)}}{\Delta t \sum_{it\tau} c_{ij} A_i N_i L_t F_{rt\tau}} \quad (8)$$

Note, $F_{0r\tau}$ is dependent on the current estimate of k_2 , which is updated by

$$k_{2,j}^{(n+1)} = H^{-1} \left(\frac{\sum_{it\tau} (t-\tau) M_{ijtr}^{(n)}}{\sum_{it\tau} M_{ijtr}^{(n)}} \right). \quad (9)$$

where $H(k_{2,j})$ is identically defined as in:¹⁶

$$H(k_{2,j}) = \frac{\sum_i c_{ij} A_i N_i \sum_{t\tau} (t-\tau) L_t C_A(\tau) e^{-k_{2,j}(t-\tau)}}{\sum_i c_{ij} A_i N_i \sum_{t\tau} L_t C_A(\tau) e^{-k_{2,j}(t-\tau)}} = \frac{\sum_{t\tau} L_t (t-\tau) C_A(\tau) e^{-k_{2,j}(t-\tau)}}{\sum_{t\tau} L_t C_A(\tau) e^{-k_{2,j}(t-\tau)}} \quad (10)$$

In application to real human data, we extended this approach as outlined in¹⁵ to permit event-by-event respiratory motion correction in the direct framework. During reconstruction, each list mode event's LOR is transformed as prescribed in a pregenerated table containing estimated motion at regular time intervals (in this application, transformations were derived from an externally measured respiratory trace as described in Section 2.E). Due to the more complicated update equations of direct reconstruction compared to conventional reconstruction, where the attenuation A_i and system matrix elements c_{ij} are indexed by time to account for continuously changing position (A_{it} and c_{ijt}), it becomes necessary to modify the strategy used to estimate the sensitivity image to accommodate the time dependence; please refer to¹⁵ for a detailed derivation.

2.D. Data simulation

In order to assess bias and variability, a simulation was performed. Ground truth for the simulation was based on parametric images of the end-diastolic gate of a human ⁸²Rb scan (acquired at resting condition) acquired on the Siemens mCT. Because the subject was healthy, a perfusion defect was introduced by reducing $K_{1,\text{uncorr}}$ by 50% in ~20% of the myocardium, approximately located in the left anterior descending (LAD) artery territory (indicated by the white arrow in Fig. 1). The original parametric images (from a direct reconstruction, at six iterations/12 subsets) were smoothed with bilateral filtering (domain sigma = 2.5, range

FIG. 1. Parametric images of simulation ground truth, in short axis and masked to the heart (data simulation was based on full images before reorientation and masking). Arrow indicates region of perfusion defect. [Color figure can be viewed at wileyonlinelibrary.com]

$\sigma = 40$;²⁸) and used in conjunction with an input function and $C_{RV}(t)$ from a real human scan as input to the simulation framework in MOLAR (previously described in¹⁵). Attenuation was modeled based on the CT scan that accompanied the PET data used to generate the simulation template. Decay was simulated for the ^{82}Rb half-life (76 s). Simulated events included time-of-flight (TOF) information. Scatter, randoms, and prompt-gamma emissions were not included in the simulation. Additionally, motion was not included, as the simulation was intended to represent a single cardiac gate and assumed respiratory motion has been corrected. The simulated dataset contained approximately 170 million events over 4 min (because randoms and scatter were not included, this is equivalent to a high-count, ungated dataset). To obtain replicates at count levels comparable to a single cardiac gate in a gated reconstruction, the list mode file was downsampled by a factor of $1/8^{\text{th}}$ into “normal-count” replicates or by a factor of $1/16^{\text{th}}$ into “low-count” replicates by sequentially assigning 10 ms increments of the full-count dataset to the replicate datasets in turn.

2.E. Human data acquisition

We performed a retrospective analysis of a ^{82}Rb study of a male subject, acquired at rest on the Siemens Biograph mCT.²⁹ The 670 MBq injection was administered with the CardioGen-82 system (Bracco Diagnostics, Princeton, NJ, USA). The total acquisition contained ~184 million prompt coincident events over 4 min. The R-wave triggers from an ECG signal were recorded in the list mode data to enable retrospective cardiac gating to any number of cardiac gates.

Respiratory motion was tracked at 50 Hz with the Anzai system (Anzai Medical, Tokyo, Japan), and linearly compensated in the superior-inferior direction within the reconstruction, on an event-by-event basis (for both indirect and direct reconstruction), using an approach based on our previously published methods.^{30,31} Specifically, a respiratory-gated direct reconstruction (eight gates) was performed without respiratory motion correction, and the $K_{1,\text{uncorr}}$ images (after two iterations/15 subsets) of each gate were registered to that of the end-expiration gate, by optimizing a 3D translation transform according to the Mattes mutual information metric evaluated in a small region ($130 \times 130 \times 130 \text{ mm}^3$) around the heart (ITK, www.itk.org). The fitted superior-inferior translation transform parameters per gate were then regressed to the average Anzai amplitude for each respiratory gate (motion was insignificant in the anterior-posterior direction in this case). The resulting linear fit was used to convert the continuous Anzai amplitudes into absolute motion in physical units, which were used during reconstruction to transform each event accordingly.^{26,30}

The input function (LV TAC) and RV TAC were estimated from an ungated dynamic (indirect) reconstruction, using spherical ROIs (volume ~8 ml) placed within the LV and RV, respectively. Kinetic modeling of the clinical data was performed independently of the parameter estimation for the simulated data.

2.F. Image reconstruction

Eight replicates of the simulated dataset were reconstructed for each of the normal- and low-count levels by the indirect and direct methods (i.e., with count levels equivalent to one cardiac gate out of 8 or 16). For the human dataset, eight cardiac gates were reconstructed by the indirect and direct methods. Cardiac gating was performed by division of each ECG-detected cycle into eight gates, uniformly in time.

For the human data, corrections for random and scattered events were applied, as described in,¹⁵ with scatter estimates determined at 12 time points during the scan and interpolated for times between these points.

Two initialization schemes were tested for direct reconstructions: (a) uniformly setting all parameters to 0.1 (“uniform initialization”) and (b) setting initial estimates to the result of the indirect method after a single iteration (“alternate initialization”), where emission images were smoothed with a 3 mm FWHM Gaussian prior to model fitting (similar to the approaches tested in³²). All reconstructions used 12 subsets per iteration. Six iterations were performed for the indirect method, and 12 iterations for the direct method (simulation) and 10 iterations for the direct method (human dataset). This is fewer subsets and more iterations than conventionally used for mCT reconstructions (3 iterations/21 subsets), to allow finer tracking of convergence; in total, more subiterations were performed than are standard.

Previous implementations of direct reconstruction for cardiac PET have used either a 3-parameter model (Eq. 3),^{12,13} or have omitted spillover correction entirely (Eq. 1).¹⁴ Here, both the 4-parameter (Eq. 2) and 3-parameter models (Eq. 3) were assessed for the high-count simulated replicates. Because V_{RV} is typically close to 0 in most voxels of the myocardium, the 3-parameter model should be suitable for fitting the kinetics of the majority of the region of interest. However, without the V_{RV} term, there are voxels outside the region of interest (e.g., in the right ventricle) that cannot be adequately modeled by Eq. 3. In direct reconstruction, it is possible that poor fits, even outside the region of interest, can produce residuals that propagate bias into the region of interest.³³

For both methods, k_2 was constrained to be between 0.0001 and 0.3 min^{-1} ; all other parameters were constrained to be non-negative (indirect) or positive (direct; intrinsic to OSEM).

2.G. Quantitative analysis

For the simulated data, percent bias of each parameter was computed per voxel as

$$\% \text{ Bias}_{\theta_j} = 100 \times \frac{(\bar{\theta}_j - \theta_j)}{\theta_j} \quad (11)$$

where θ_j is the ground truth parameter value in voxel j and $\bar{\theta}_j$ is the mean parameter estimate across replicates. Voxelwise coefficient of variation (CoV) per parameter was computed across replicates as:

$$\text{CoV}_{\theta_j} = \frac{\sigma_j}{\theta_j} \quad (12)$$

where σ_j is the standard deviation across replicates at voxel j .

For simulated data, regions of interest were manually drawn for the myocardium, LV, and RV (Fig. 2). The myocardium region was split into septal and lateral halves, and voxels in the perfusion defect were assigned to a fourth region. Real data were evaluated in similarly defined regions, except without a defect region; regions were drawn from gated SUV images, reconstructed from data acquired 2–6 min postinjection. For the simulated data only, voxelwise percent bias and CoV were averaged across regions to get summary measures for each parameter. Contrast of the perfusion defect was computed as the ratio of $K_{1,\text{uncorr}}$ in the healthy myocardium of the septal region, to $K_{1,\text{uncorr}}$ in the defect region. For the human dataset, mean regional parameter estimates were computed as a function of iteration per gate.

3. RESULTS

3.A. Simulation results

3.A.1. Parametric images

Parametric images from one replicate at the normal-count level are shown in Fig. 3 for the first six iterations (see Fig. 1 for ground truth). Noise increases with iteration for all parameters and methods, but is most pronounced for the indirect method [top row in each of Figs. 3(a)–3(c)]. While the perfusion defect is readily visible in all six iterations of the $K_{1,\text{uncorr}}$ images [Fig. 3(a)] of both direct methods, noise in the later iterations of the indirect method obscures the defect. While the true $K_{1,\text{uncorr}}$ is close to 0 in the blood pools, $K_{1,\text{uncorr}}$ is still positively biased in these voxels after six iterations of direct reconstruction with the uniform initialization scheme. While the left and right blood pools are distinctly visible in the V_A and V_{RV} images [Figs. 3(b) and 3(c)] after just one iteration for the indirect and direct method with the alternate initialization scheme, even after six iterations of the direct with uniform initialization, the blood pools are not well separated. The direct method converges markedly faster with the alternate initialization scheme (based on parametric images estimated from filtered indirect reconstructions at

iteration 1), than when uniformly initializing all parametric images to 0.1.

3.A.2. Noise versus bias

Plots of regional CoV versus percent bias across the eight normal-count replicates (Fig. 4) support these observations. The increase in CoV from iteration to iteration is larger for the indirect method than the direct method with either initialization scheme. The CoV and bias of the alternate initialization are shown as open symbols in Fig. 4; the initial condition varies across the eight replicates because each replicate's initialization was based on the indirect parameter estimates from that replicate. Figures 4(a) and 4(b) show $K_{1,\text{uncorr}}$ convergence in the septal myocardium and perfusion defect, respectively. At matched bias, the direct method has lower CoV than the indirect method (by either initialization approach), for the first six iterations. For the direct method with alternate initialization, the bias in $K_{1,\text{uncorr}}$ does not change much after iteration 3. The direct method with uniform initialization takes longer to converge, with bias changing until approximately iteration 6. Both direct methods converge to similar bias. For the indirect method, $K_{1,\text{uncorr}}$ bias begins negative and becomes more positive with every iteration, continuing to increase after crossing 0, most likely a result of noise-induced bias. Figure 4(c) shows the convergence plot for V_A in the septal myocardium with a simulation ground truth average myocardial V_A of 0.39. The direct method achieves lower absolute bias than the indirect method at matched CoV, though again the alternate initialization scheme achieves lower absolute bias at earlier iteration than the uniform initialization. In this region, V_A absolute bias continues to decrease even after $K_{1,\text{uncorr}}$ bias has stabilized. The convergence of V_A in the LV and V_{RV} in the RV are shown in Figs. 4(d) and 4(e), respectively (simulated values were 0.82 and 0.50, respectively). For both, the indirect method becomes more negatively biased with each iteration. Regional bias and CoV for each parameter are summarized at iterations 2 and 4 in Table I for the high-count replicates, for the indirect method and direct method with the alternate initialization. At iteration 2, the advantage of direct over indirect is 48% for $K_{1,\text{uncorr}}$, 59% for V_A , and 55% for V_{RV} (last column of Table I, averaged over regions listed). The advantage of the direct method over the indirect method in terms of

FIG. 2. Regions used for analysis of simulation results, overlaid on $K_{1,\text{uncorr}}$ image. Green = defect; cyan = normal septal myocardium; blue = normal lateral myocardium; red = LV; magenta = RV

FIG. 3. Short axis parametric images from one replicate of the simulated data (normal-count level) by the indirect method and the direct method with two different initialization schemes, for the first six iterations (12 subsets per iteration). Images are masked to the heart. (a) $K_{1,\text{uncorr}}$. Perfusion defect is indicated in the first iteration by white arrow. (b) V_A (c) V_{RV} .

noise reduction is slightly greater but similar at iteration 4 compared to iteration 2.

Performance at different count levels of the simulation study for the indirect method and the direct method with the alternate initialization scheme is compared in Fig. S1. At approximately matched bias, the direct method had similar reduction in $K_{1,\text{uncorr}}$ CoV (noise advantage) compared to the indirect method for both count levels (25% reduction for the normal-count level; 22% for the low-count level).

3.A.3. Partial volume-corrected K_1

Figure 5(a) shows K_1 images from one replicate of simulated data, which include partial volume correction (as defined in Eq. 2). These images are more prone to outliers than $K_{1,\text{uncorr}}$, because of the possibility of dividing by a small quantity if the sum of V_A and V_{RV} is close to 1; to limit the influence of very large outliers, only voxels where $1 - V_A - V_{RV} > 0.01$ were considered. The outliers make these images less useful for assessment of flow on the voxel level. The ground truth for this parameter [shown at left in Fig. 5(a)] is not uniform outside the perfusion defect because the simulation was based on real parametric images, which were themselves affected by noise and outliers. The defect is most visible in the direct method with the alternate initialization scheme. Figures 5(b) and 5(c) demonstrate that the

performance of each method is similar between the septal and lateral regions. While at matched bias (e.g., where the curves cross the reference line at bias = 0), direct reconstruction (dark gray and black lines) has lower CoV than indirect (light gray line), indirect bias does not increase as much with iteration as direct bias. At iteration 2 of the indirect method, the mean percent bias in the septal region is -4% and in the lateral region is -2% ; the direct methods have similar magnitude bias at iteration 2 (3% in both the septal and lateral regions for the uniform initialization, 1% in both regions for the alternate initialization). Mean K_1 CoV at iteration 2 is similar between the two initialization methods for direct reconstruction, and $\sim 30\%$ lower for the direct method than the indirect (Table I).

3.A.4. Normal tissue-to-defect contrast

Because cardiac PET is used clinically to detect regions of decreased perfusion, accurate quantification of contrast between normal tissue and the perfusion defect is important. Figure 6(a) shows the contrast between average $K_{1,\text{uncorr}}$ in normal tissue of the septal myocardium and average $K_{1,\text{uncorr}}$ in the perfusion defect as a function of iteration, averaged over eight normal-count replicates. The contrast of the indirect method (light gray line) is at its greatest at the first iteration, and decreases thereafter. For the direct method with

FIG. 4. Plots of mean regional CoV versus mean regional percent bias for simulated data (normal-count replicates) for selected parameters and regions. (a) $K_{1,uncorr}$ in the septal myocardium (b) $K_{1,uncorr}$ in the defect (c) V_A in the septal myocardium (d) V_A in the left ventricle (e) V_{RV} in the right ventricle. Each symbol denotes one iteration of 12 subsets. Open symbols represent the initial condition for the Alternate Initialization. Increasing iterations lead to increasing CoV. [Color figure can be viewed at wileyonlinelibrary.com]

uniform initialization (dark gray line), the contrast is much lower than the indirect method at iteration 1, but increases with iteration to achieve the true contrast (1.96; shown as the cyan line) by iteration 10. With the alternate initialization scheme (black line), the direct method achieves the true contrast from the first iteration, and is relatively stable over iterations. Figure 6(b) shows the contrast between average K_1 in normal tissue of the septal myocardium and average K_1 in the perfusion defect for the first six iterations (excluding voxels for which $1 - V_A - V_{RV} \leq 0.01$). Because of the large positive outliers in K_1 estimates in the septal myocardium, the contrast is exaggerated by all methods. In addition, the standard deviation of the contrast estimates across eight replicates is high.

3.A.5. Three- versus four-parameter model

While the 3-parameter model is expected to provide reasonable estimates of $K_{1,uncorr}$ in the myocardium, it cannot fit the kinetics in the RV as well as the 4-parameter model; in the direct method, residuals from poor fits in the RV region can propagate to nearby voxels, causing worse bias than seen in the indirect method with the 3-parameter fit. Results of the

comparison between the 3- and 4-parameter models, i.e., with and without RV term, are shown in Fig. 7. Because V_{RV} is close to 0 in most of the myocardium, omitting the V_{RV} term from the model is not expected to greatly impact estimates of $K_{1,uncorr}$. The bias maps [Fig. 7(a)] show greater negative bias in $K_{1,uncorr}$ for the 3-parameter model [second and fourth rows of Fig. 7(a)] as compared to $K_{1,uncorr}$ estimated from the 4-parameter model [first and third rows of Fig. 7(a)], particularly for the direct method (negative bias is indicated in blue; positive bias in red). Figures 7(b) and 7(c) show CoV versus bias in $K_{1,uncorr}$ for the septal and lateral regions of the myocardium. Bias in $K_{1,uncorr}$ is similar between the 3- and 4-parameter model by the indirect method (light gray lines), and noise is similar at matched iteration. However, for the direct method, the 3-parameter model (dashed black line) has greater bias in $K_{1,uncorr}$ than the 4-parameter model (solid black line). At matched CoV of 0.35–0.37 (iteration 1 for indirect; iteration 2 for direct 3-parameter; iteration 3 for direct 4-parameter), the direct 4-parameter $K_{1,uncorr}$ estimates have the lowest bias (–5% in septal region and –3% in lateral region), followed by indirect 4-parameter (–12%; –10%), indirect 3-parameter (–16%; –11%), and direct 3-parameter (–17%; –13%).

TABLE I. Selected regional bias and CoV values for the normal-count replicate reconstructions with the 4-parameter fit. Direct reconstruction used alternate initialization method. Each iteration uses 12 subsets. % Reduction in CoV is calculated as $100 \times (\text{CoV}_{\text{indirect}} - \text{CoV}_{\text{direct}}) / \text{CoV}_{\text{indirect}}$.

Parameter	Iteration	Region	Indirect		Direct		% Reduction in CoV
			Mean % bias	Mean regional CoV	Mean % bias	Mean regional CoV	
$K_{1,\text{uncorr}}$	2	Septal Myo	−8	0.55	−6	0.29	47
		Lateral Myo	−7	0.43	−4	0.24	44
		Defect	−5	0.61	−6	0.29	52
	4	Septal Myo	−4	0.82	−5	0.41	50
		Lateral Myo	−5	0.67	−3	0.35	48
		Defect	2	0.87	−6	0.39	55
V_A	2	Septal Myo	−23	0.80	−12	0.37	54
		Lateral Myo	−24	0.73	−11	0.31	58
		Defect	−29	0.66	−18	0.26	61
		LV	−28	0.55	−14	0.21	62
	4	Septal Myo	−25	1.04	−10	0.45	57
		Lateral Myo	−27	0.97	−9	0.38	61
		Defect	−33	0.89	−16	0.32	64
		LV	−34	0.77	−12	0.27	65
V_{RV}	2	Defect	191	1.30	73	0.70	46
		RV	−9	0.80	3	0.30	63
	4	Defect	228	1.43	55	0.76	47
		RV	−16	1.05	−1.4	0.37	65
K_1	2	Septal Myo	−4	0.57	1	0.42	26
		Lateral Myo	−2	0.42	1	0.32	24
		Defect	−11	0.56	−10	0.34	39
	4	Septal Myo	0	0.91	18	0.70	23
		Lateral Myo	1	0.72	10	0.52	28
		Defect	−6	0.86	−2	0.53	38

3.B. Human data results

For the human dataset, the magnitude of respiratory motion in the superior-inferior direction was approximately 9 mm; this motion was rigidly compensated on an event-by-event basis (see Figs. S2 and S3).

3.B.1. Parametric images

Parametric images of end-diastole (gate 8) of the healthy human dataset (Fig. 8) are qualitatively similar to those obtained from the simulation (Fig. 3). As in the simulation, noise apparently increases more quickly with iteration for the indirect method than the direct method (either initialization scheme). Again, the direct method with uniform initialization converges more slowly than the direct method with the alternate initialization. The RV blood pool in the V_{RV} images is “cleaner” [Fig. 8(c)] than those from the simulation [Fig. 3(c)]. This is likely because the ground truth images used for the simulation were based on parametric images generated by direct reconstruction with uniform initialization at iteration 6, so incomplete convergence yielded parameters less realistically close to 0 in certain voxels.

3.B.2. Regional parameter estimates

The regional mean parameter estimates corresponding to the images of Fig. 8 are plotted as a function of iteration in Fig. 9 (for the septal region; other regions followed similar trends). The mean parameter estimates from the simulation [Figs. 9(a)–9(c)] had comparable means to the real parameter estimates [Figs. 9(d)–9(f)], with similar relative performance among methods. The indirect and direct parameter estimates are similar, particularly comparing values from the earlier iterations of the indirect method (light gray line) to most iterations of the direct method with the alternate initialization scheme (black line), or to the later iterations of the direct method with the uniform initialization scheme (dark gray line).

3.B.3. Ungated versus gated parametric images

Parametric images are not conventionally estimated from *cardiac-gated* data in cardiac imaging due to high noise; however, direct reconstruction can potentially improve the feasibility of this. Ungated parametric images are compared to the gated images from end-systole (Gate 4) and end-diastole (Gate 8) in Fig. 10. As expected, the ungated images

FIG. 5. (a) One replicate K_1 image (corrected for partial volume effects) from the simulation study by indirect and direct methods for the first six iterations (12 subsets per iteration). Images are shown for normal-count level, masked to the myocardium. (b–d) Mean regional CoV of K_1 versus mean percent bias of K_1 for three regions; (b) Septum, (c) Lateral wall, (d) Defect. Each symbol denotes one iteration of 12 subsets. Open symbol represents the initial condition. Increasing iterations lead to increasing CoV. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 6. Contrast of (a) $K_{1,uncorr}$ and (b) K_1 between defect and nearby healthy myocardial tissue (in the septal region) for the simulated data (normal-count level), by the indirect method and the direct method with two initialization schemes. Solid line indicates true contrast. Dashed lines represent standard deviation across eight replicates. [Color figure can be viewed at wileyonlinelibrary.com]

have lower noise, while changes in wall thickness [$K_{1,uncorr}$; first column in each of Figs. 10(a) and 10(b)] and blood pool size [V_A and V_{RV} ; second and third columns in each of Figs. 10(a) and 10(b)] can be distinguished between the two gates shown (thinner myocardial wall and larger blood pools at end-diastole). Though the direct images [Fig. 10(b)] are shown at a later iteration (4) than that for the indirect images

[Fig. 10(a); iteration 2], the direct images still appear less noisy than the indirect images.

Postfiltered parametric images and standard uptake value (SUV) images (2–6 min postinjection) by gate are shown in Fig. 11 (see Fig. S4 for images from a second scan in this subject, acquired under pharmacological stress). During systole (~Gate 4), the thickening of the myocardial wall

FIG. 7. Comparison of $K_{1,uncorr}$ from the 4- and 3-parameter models, for the indirect method and the direct method (using alternate initialization scheme), for the normal-count replicates. (a) Voxelwise bias in $K_{1,uncorr}$ masked to the myocardium. (b) and (c) Mean CoV versus mean percent bias in $K_{1,uncorr}$ for (b) septal myocardium and (c) lateral myocardium. Each symbol denotes one iteration of 12 subsets. Open symbol represents the initial condition. Increasing iterations lead to increasing CoV.

produces increased signal recovery, hence higher $K_{1,uncorr}$, whereas diastolic gates are more strongly impacted by partial volume effects. Similarly, the LV blood pool in the V_A images is smaller in the systolic gates, as is the RV blood pool in the V_{RV} images. K_1 images are noisier, but have been corrected for partial volume; the myocardial wall appears thicker particularly in the septum. The SUV images (final row) are qualitatively similar to the $K_{1,uncorr}$ images of the first row, but the scale has no direct physiological meaning. Also, the SUV images exhibit lower contrast between the myocardium and blood pool. For example, for Gate 8, the ratio of mean $K_{1,uncorr}$ in the myocardium to mean $K_{1,uncorr}$ in the LV was 30, whereas the analogous ratio for SUV was 3 (ratios were calculated from unfiltered images). Animations of parametric images over gate are given in Figs. S5 and S6 (for rest and stress studies).

Figure S7 shows the mean $K_{1,uncorr}$ and K_1 values across the entire myocardium as a function of gate, normalized to the maximum value of the eight gates, from iteration 2 results of the human dataset. Both indirect and direct K_1 values are more consistent across gates than $K_{1,uncorr}$, with direct showing less variation than indirect.

4. DISCUSSION

In this work, we have extended the direct parametric reconstruction algorithm PMOLAR-1T for cardiac perfusion

PET by including terms for LV and RV spillover into the myocardium, and characterized this algorithm with simulated and human data. Unique aspects of this work include the creation and assessment of cardiac-gated human ^{82}Rb parametric images, including rigid event-by-event respiratory motion compensation. While parametric imaging can provide quantitative estimates of MBF, in principle, cardiac-gated parametric images can provide richer information than ungated parametric images or cardiac-gated SUV images, with model output including not only partial volume-corrected images of MBF in the myocardium, but also images of the left and right ventricle blood pools.

4.A. Relative performance of direct and indirect methods

At matched iteration and roughly matched bias, the direct method (initialized from first-iteration filtered results of the indirect method), had 50%–60% lower noise than the indirect method for the parameters $K_{1,uncorr}$, V_A , and V_{RV} . For V_A and V_{RV} , bias of the direct method with the alternate initialization was lower than that of the indirect method for nearly all regions/iterations, so it was not always possible to compare at exactly matched bias. The contrast between the healthy tissue of the septal myocardium $K_{1,uncorr}$ and the simulated perfusion defect $K_{1,uncorr}$ was greatest and most stable over iterations for the direct method with the alternate

FIG. 8. Short axis parametric images from one gate (Gate 8) of the human dataset by the indirect method and the direct method with two different initialization schemes, for the first six iterations (12 subsets per iteration). (a) $K_{1, \text{uncorr}}$ (b) V_A (c) V_{RV} .

initialization scheme. While voxelwise bias and CoV could not be quantified for the human dataset (due to unknown ground truth and only a single realization), the human dataset showed similar trends in mean value per iteration and visual appearance of parametric images as in the simulated data.

For K_1 , the advantage of the direct method ($\sim 30\%$ CoV reduction), was smaller than for the other parameters and more susceptible to outliers at later iterations than indirect. The indirect method produced more negatively biased estimates of V_A and V_{RV} in the myocardial tissue [e.g., Fig. 4(c)], which helped to avoid large positive outliers in K_1 that occur when $V_A + V_{RV}$ is closer to 1. While the CoV of $K_{1, \text{uncorr}}$ and K_1 were similar for the indirect method, the direct method had higher CoV for K_1 than $K_{1, \text{uncorr}}$. The lack of increase in CoV from $K_{1, \text{uncorr}}$ to K_1 for the indirect method occurred because of a negative correlation between $K_{1, \text{uncorr}}$ and $V_A + V_{RV}$, which reduces the total variance of the final K_1 estimate (as compared to the K_1 variance if $K_{1, \text{uncorr}}$ and $V_A + V_{RV}$ were uncorrelated). On the other hand, the correlation between $K_{1, \text{uncorr}}$ and $V_A + V_{RV}$ was positive for the direct method (Fig. S6, and Table S1). Thus, while direct cardiac-gated K_1 images would be most ideal for analysis, due to removal of partial volume effects, their higher noise and sensitivity to outliers could limit their clinical utility. However, direct gated $K_{1, \text{uncorr}}$ images, albeit without partial volume

correction, do outperform cardiac-gated SUV images in terms of myocardium-to-LV signal contrast.

4.B. Regularization

Note that as in¹³ and¹² (but unlike¹⁴), we have not included spatial regularization in the reconstruction, so as not to conflate the advantages incurred by regularization with those from the direct approach, as compared to the indirect method. Further noise reduction could be attained with regularization (e.g., such as that employed in³⁴), which could help avoid outlying K_1 estimates. One disadvantage of regularization is the need to optimize one or more hyperparameters to control the amount of smoothing; however, note that direct reconstruction may offer a more convenient platform to include regularizers, since optimization of the hyperparameters would be required on a frame-by-frame basis for the indirect method. Also, anatomical priors could be used to minimize blurring of boundaries.

4.C. Convergence

Convergence was slower for the direct method than the conventional indirect algorithm, particularly when initializing the direct algorithm with uniform parametric images. The two initialization schemes tested for direct reconstruction

FIG. 9. Mean parameter estimates per iteration in the septal myocardium for (a–c) simulation and (d–f) human dataset (Gate 8). (a) and (d) show $K_{1,uncorr}$ (ml/min/g); (b) and (e) show V_A ; c and f show V_{RV} . Dashed line indicates true mean value (simulation only). [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 10. Comparison of the ungated and gated parametric images from the human dataset. (a) Indirect method; iteration 2 (12 subsets). (b) Direct method with alternate initialization; iteration 4 (12 subsets). Each of the end-diastolic and end-systolic images were reconstructed from $1/8^{\text{th}}$ of the acquired data. [Color figure can be viewed at wileyonlinelibrary.com]

(uniform or initialized to an early indirect result) appeared to converge to similar estimates for $K_{1,uncorr}$ [Figs. 4(a) and 4(b)], though additional iterations than performed here would be required to confirm this result for the parameters V_A and V_{RV} [Figs. 4(c)–4(e)]. The earlier flattening of the regional parameter estimate versus iteration curves (Fig. 9) suggests that the alternative initialization method gives faster

convergence than the uniform initialization method. No regularization was used in this work, and maximum likelihood methods are prone to over-fitting if run for many iterations. Reconstruction with the alternative initialization method can be stopped after fewer iterations than the uniform method for a given level of bias, and empirically, this achieved lower noise (Fig. 4). The disadvantage of the alternate initialization

FIG. 11. Short axis parametric images per gate from human ^{82}Rb scan (at rest), generated by the direct method (top 4 rows) and gated SUV images (bottom row). Parametric images are shown at iteration 4, using the alternate initialization scheme. SUV images (2–6 min postinjection) are shown for 2 iterations of 21 subsets. Images have been postprocessed with bilateral smoothing. [Color figure can be viewed at wileyonlinelibrary.com]

method is the requirement to perform an independent frame-based reconstruction with the associated indirect kinetic modeling.

Convergence could potentially be further enhanced by implementing a nested approach,³⁵ in which the estimation of kinetic parameters is decoupled from the tomographic update step. In this approach, each iteration of the reconstruction is comprised of a frame-based emission image estimation step, followed by multiple subiterations of voxelwise kinetic parameter estimation. Our implementation does not impose any framing on the list mode events, and emission time frame images are never stored in memory. Because the memory demands of this algorithm are already high, we opted not to include nesting with its additional storage burden. Karakatsanis et al.³⁶ evaluated such a nested approach for the generalized Patlak model (not appropriate for MBF) and found modest improvements in convergence from 10 nested iterations to 30 nested iterations, using a direct reconstruction algorithm similar to the approach presented here (except that³⁶ uses sinogram data and hence still imposes time frames).

The convergence observed for the 3- or 4-parameter direct method in this work, particularly for the parameters V_A and V_{RV} , was qualitatively slower than that observed for the parameters in the simpler 2-parameter model we employed for brain parametric imaging.¹⁵ As noted by^{32,37} in the context of direct reconstruction of Patlak parameters, parameter correlations can impede convergence of EM-based algorithms, and indeed in this application $K_{1,\text{uncorr}}$ and V_A in particular are strongly correlated (Fig. S6 and Table S1).

4.D. Low-count bias

Previous work has demonstrated that MOLAR can produce images with minimal bias, even at very low counts.³⁸ While the kinetic parameters estimated by the indirect method were not free from bias, the CoV versus bias curves of the parameters estimated by the indirect method were largely overlapping for the two count levels assessed in this work, suggesting that bias in kinetic parameters is not strictly related to the number of counts in a frame. However, fewer subsets were used than is standard practice (12 vs. 21), and the counts per subset may be the more important determining factor in low-count bias.

4.E. Stopping criterion

Without further filtering or regularization, stopping earlier than three iterations of 21 subsets when using the indirect method for this application might be beneficial. The optimal stopping iteration will depend on the particular clinical application or research question. For MBF quantification (from K_1), the indirect method can potentially give lower bias estimates at later iterations than the direct method, which was sensitive to outliers. For detection tasks (which might, for instance, require good contrast of $K_{1,\text{uncorr}}$ between healthy myocardium and defect), the direct method provides relatively stable estimates of contrast and therefore may be less sensitive to the choice of iteration number, whereas for the indirect method it would be best to use only one or two iterations with 12 subsets. Though not assessed in this work, successful LV and RV

volume estimation from V_A and V_{RV} images would likely depend on the signal-to-noise ratio of those images, which worsened more rapidly for the indirect method than the direct method.

4.F. Input function estimation

In this work, the input function was estimated from dynamic image data (indirect reconstructions), as a preprocessing step before direct reconstruction, and the same input function was used for all methods. This method has been shown to provide high quality quantitative input functions, compared to arterial samples.²⁹ However, the input function could theoretically be simultaneously estimated during direct reconstruction. Because a well-defined image region whose signal corresponds to the input function exists for cardiac imaging (i.e., the LV), it could be easier for this application than in the brain (e.g.,³⁹). Because it is preferred for the initialization of the parametric images to be based on the indirect result from an early iteration, simultaneous input function estimation would not necessarily avoid the preprocessing step, which might also be used to initialize the input function.

4.G. Value of cardiac-gated parametric images

Cardiac-gated parametric images add potential value by allowing assessment of cardiac function. The cardiac-gated V_A and V_{RV} images, especially those generated by the direct method, could be used to estimate LV and RV volumes for each gate, and therefore the ejection fraction (EF), for instance using an approach similar to that applied in ^{15}O -labeled CO blood pool imaging.⁴⁰ In,⁴⁰ LVEF was estimated by (a) setting a threshold relative to the mean ^{15}O -labeled CO blood concentration to identify the LV contour on end-diastolic and end-systolic images; (b) summing the volume of the voxels within these boundaries, corresponding to the end-diastolic (LVEDV) and end-systolic volumes (LVESV); and (c) computing $\text{LVEF} = (\text{LVEDV} - \text{LVESV})/\text{LVEDV}$. The threshold established in that study was selected to maximize the correlation with volumes measured from cardiac MR. A preliminary assessment of using gated V_A images to estimate LVEF is given in Fig. S9; for the human ^{82}Rb scan, we estimated a LVEF of 51%. Because the present study did not include a gold-standard modality for quantifying ejection fraction, we did not have a means to compare the accuracy of using gated V_A and V_{RV} images for EF estimation to that of using gated SUV images. Furthermore, we had a limited number of datasets, which all came from healthy subjects. Therefore, we leave further evaluation of LVEF measurement from the cardiac-gated parametric V_A images to future work.

5. CONCLUSION

Gated parametric imaging, including respiratory motion correction, is feasible with direct or indirect reconstruction. Direct reconstruction, using appropriate initialization scheme

and kinetic model, has advantages over indirect in terms of producing parametric images with lower bias (particularly for V_A and V_{RV}) and lower noise (roughly 50% lower noise for $K_{1,\text{uncorr}}$, V_A and V_{RV} and 30% lower for K_1). Gated parametric images provide the potential to assess myocardial blood flow and function simultaneously, with LV and RV volumes estimated from gated V_A and V_{RV} images. Future work will include assessment of ejection fraction estimation from such images.

ACKNOWLEDGMENTS

This work was supported by NIH grants 1S10OD010322-01 and F31EB018720 from the National Institute of Biomedical Imaging and Bioengineering. This publication was made possible by CTSA Grant Number UL1 TR000142 from the National Center for Advancing Translational Science (NCATS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

CONFLICT OF INTEREST

The authors have no relevant conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Fig. S1. Short axis parametric images of the unsampled (full count) simulated dataset and one replicate per count level, as generated by the (a) indirect (iteration 2) or (b) direct method (iteration 4; showing results from alternate initialization). (c,d) Plots of mean CoV versus mean percent bias in for (c) $K_{1,\text{uncorr}}$ and (d) V_A in the septal myocardium for the normal- and low-count levels. Direct reconstruction used alternate initialization. Each symbol denotes one iteration of 12 subsets. Open symbol represents the initial condition. Increasing iterations lead to increasing CoV.

Fig. S2. Linear regression between myocardium displacement in superior-inferior direction (as measured from respiratory-gated $K_{1,\text{uncorr}}$ images) and average Anzai displacements per respiratory gate, for human ^{82}Rb scan, acquired at rest. Correlation is 0.84 ($P = 0.009$); linear fit is $y = 0.0051x - 7.3$.

Fig. S3. (a) $K_{1,\text{uncorr}}$ image *without* respiratory motion compensation. (b) $K_{1,\text{uncorr}}$ image *with* motion compensation. Gate 8 (end-diastole), reconstructed by the direct method with uniform initialization (iteration 6, 12 subsets per iteration). Showing a coronal slice.

Fig. S4. Short axis parametric images per gate from human ^{82}Rb scan (*under pharmacological stress induced with 0.4 mg of regadenoson, injected over 30 s, 1 min before tracer injection*), generated by the direct method (top 4 rows) and gated SUV images (bottom row). Parametric images are shown at iteration 4, using the alternate initialization scheme. SUV images (2–6 min postinjection) are shown for two iterations of 21 subsets. Images have been postprocessed with bilateral smoothing.

Fig. S5. Postfiltered (via bilateral smoothing) gated parametric images, ^{82}Rb Rest. From left to right: $K_{1,\text{uncorr}}$; V_A ; V_{RV} ;

K_1 . Images are scaled as those in Fig. 12 of the main manuscript.

Fig. S6. Postfiltered (via bilateral smoothing) gated parametric images, ^{82}Rb Stress. From left to right: $K_{1,\text{uncorr}}$; V_A ; V_{RV} ; K_1 . Images are scaled as those in Fig. S3.

Fig. S7. Mean $K_{1,\text{uncorr}}$ and K_1 values in the myocardium, per gate, normalized to the maximum value of the eight gates, from the human dataset. The corresponding regional SUV values are indicated by the green curve. $K_{1,\text{uncorr}}$ (gray circles with solid line for indirect; black triangles with solid line for direct) varies considerably with gate, a consequence of differential impact of partial volume as the myocardium wall changes in thickness. While the direct $K_{1,\text{uncorr}}$ has greater contrast across gates for direct than indirect, indirect $K_{1,\text{uncorr}}$ is similar to SUV in terms of percent change from systole to diastole. Mean values were computed from the unfiltered images at iteration 2. The direct method used the alternate initialization scheme.

Fig. S8. Voxelwise Pearson correlation between $K_{1,\text{uncorr}}$ and $V_A + V_{RV}$ computed across eight high-count replicates. Direct method used the alternate initialization scheme.

Fig. S9. Example estimation of left ventricle ejection fraction (LVEF), using gated V_A images from a human ^{82}Rb scan (acquired at rest) to estimate the left ventricle end-systolic and end-diastolic volumes (LVESV and LVEDV). Figure shows gated V_A images overlaid with LV regions of interest. LV volumes were identified based on thresholds set for each V_A image, using Otsu thresholding within a box around the heart. The Otsu method identifies the threshold that minimizes intraclass variance, with the two classes being “background” and “LV.” The LVESV was estimated to be 102 ml; the LVEDV was estimated to be 210 ml. The LVEF, computed as $(\text{LVEDV} - \text{LVESV}) / \text{LVEDV}$, was 51%. This value is within the normal range; however, this study did not include a gold standard measurement of LVEF.

Table S1. Average Pearson correlation between $K_{1,\text{uncorr}}$ and $V_A + V_{RV}$ in the septal myocardium region. Correlations were computed voxelwise, across eight high-count replicates. Direct method used the alternate initialization scheme.