Automatic 3D registration of dynamic stress and rest ^{82}Rb and flurpiridaz F 18 myocardial perfusion PET data for patient motion detection and correction

Jonghye Woo, Balaji Tamarappoo, Damini Dey, and Ryo Nakazato

Departments of Imaging and Medicine, Cedars-Sinai Medical Center, Los Angeles, California 90048

Ludovic Le Meunier

Siemens Healthcare Molecular Imaging, Knoxville, Tennessee 37932

Amit Ramesh

Departments of Imaging and Medicine, Cedars-Sinai Medical Center, Los Angeles, California 90048

Joel Lazewatsky

Lantheus Medical Imaging, North Billerica, Massachusetts 01862

Guido Germano, Daniel S. Berman, and Piotr J. Slomka^{a)}

Departments of Imaging and Medicine, Cedars-Sinai Medical Center, Los Angeles, California 90048

and Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California 90024

(Received 1 March 2011; revised 6 October 2011; accepted for publication 11 October 2011; published 31 October 2011)

Purpose: The authors aimed to develop an image-based registration scheme to detect and correct patient motion in stress and rest cardiac positron emission tomography (PET)/CT images. The patient motion correction was of primary interest and the effects of patient motion with the use of flurpiridaz F 18 and ^{82}Rb were demonstrated.

Methods: The authors evaluated stress/rest PET myocardial perfusion imaging datasets in 30 patients (60 datasets in total, 21 male and 9 female) using a new perfusion agent (flurpiridaz F 18) ($n = 16$) and ^{82}Rb ($n = 14$), acquired on a Siemens Biograph-64 scanner in list mode. Stress and rest images were reconstructed into 4 (^{82}Rb) or 10 (flurpiridaz F 18) dynamic frames (60 s each) using standard reconstruction (2D attenuation weighted ordered subsets expectation maximization). Patient motion correction was achieved by an image-based registration scheme optimizing a cost function using modified normalized cross-correlation that combined global and local features. For comparison, visual scoring of motion was performed on the scale of 0 to 2 (no motion, moderate motion, and large motion) by two experienced observers.

Results: The proposed registration technique had a 93% success rate in removing left ventricular motion, as visually assessed. The maximum detected motion extent for stress and rest were 5.2 mm and 4.9 mm for flurpiridaz F 18 perfusion and 3.0 mm and 4.3 mm for ^{82}Rb perfusion studies, respectively. Motion extent (maximum frame-to-frame displacement) obtained for stress and rest were $(2.2 \pm 1.1, 1.4 \pm 0.7, 1.9 \pm 1.3)$ mm and $(2.0 \pm 1.1, 1.2 \pm 0.9, 1.9 \pm 0.9)$ mm for flurpiridaz F 18 perfusion studies and $(1.9 \pm 0.7, 0.7 \pm 0.6, 1.3 \pm 0.6)$ mm and $(2.0 \pm 0.9, 0.6 \pm 0.4, 1.2 \pm 1.2)$ mm for ^{82}Rb perfusion studies, respectively. A visually detectable patient motion threshold was established to be ≥ 2.2 mm, corresponding to visual user scores of 1 and 2. After motion correction, the average increases in contrast-to-noise ratio (CNR) from all frames for larger than the motion threshold were 16.2% in stress flurpiridaz F 18 and 12.2% in rest flurpiridaz F 18 studies. The average increases in CNR were 4.6% in stress ^{82}Rb studies and 4.3% in rest ^{82}Rb studies.

Conclusions: Fully automatic motion correction of dynamic PET frames can be performed accurately, potentially allowing improved image quantification of cardiac PET data. © 2011 American Association of Physicists in Medicine. [DOI: 10.1118/1.3656951]

Key words: motion correction and detection, image registration, flurpiridaz F 18, cardiac PET myocardial perfusion imaging

I. INTRODUCTION

Coronary artery disease (CAD) is the major cause of death in the industrial world. Noninvasive cardiac imaging allows the diagnosis and management of patients with known or

suspected CAD. In particular, myocardial perfusion imaging by positron emission tomography (PET) plays a crucial role and has demonstrated ability to accurately detect CAD.^{1,2} PET offers functional information and the ability to detect myocardial ischemia with low radiation burden and high

spatial resolution (4–7 mm).^{3–8} Typically, myocardial perfusion PET is performed with Rb-82 agent or if cyclotron is present at the site with ¹³N-ammonia agent. In addition, a new ¹⁸F based agent for PET myocardial perfusion imaging (flurpiridaz F 18) has been developed recently⁹ and showed excellent image quality in phase I clinical trials.¹⁰ Myocardial extraction of this tracer exhibits a linear relationship with blood flow, suggesting that it may therefore be more sensitive than ⁸²Rb for detecting CAD and for measuring absolute myocardial blood flow.^{11,12}

One of the factors affecting final image quality of myocardial perfusion PET is patient motion during image acquisition, causing spatial blurring and artifacts, and therefore leading to spurious perfusion defects.^{13,14} This is due to the fact that static perfusion images are acquired during a period of several minutes (up to 15 min) with potential patient motion during that time. In SPECT imaging, which requires a similar amount of time, Mukherjee *et al.*¹⁴ found that 23% of 66 patients had sustained motion (>4 min) between 3–6 mm, 5% had sustained motion larger than 6 mm during emission imaging. In addition, Wheat and Currie¹⁵ analyzed 800 studies of which 36% contained visually detectable motion. Patient motion of that magnitude is therefore also likely to occur and affect image quality of the high-resolution PET.

Image registration techniques have been used to correct respiratory motion artifacts in cardiac PET.^{4,6,8,13,14,16–18} In related studies, there have been previous reports to mitigate respiratory motion with gated acquisition of both CT and PET datasets.^{5,6} Respiratory motion was corrected using simultaneous PET imaging and tagged-MRI with Harmonic phase (HARP) based motion tracking.¹⁹ In cardiac PET imaging, respiratory gating schemes have been attempted in real-time⁴ or list-mode^{5,6} with rigid-body spatial transformations.⁵ In addition, PET respiratory motion correction with optical flow based approach^{11,15} or regularized registration based approach¹⁸ was proposed. There are only a few reports on patient motion correction in cardiac PET.^{20,21} Turkington *et al.*²⁰ proposed the use of cross-correlation based rigid registration of cardiac PET images to cardiac templates in order to correct patient motion. Naum *et al.*²¹ used external radioactive skin markers to detect and correct motion.

In general, image registration is often posed as an optimization problem with a cost function consisting of data similarity and regularization. The cost function evaluates the similarity between source and target frames and is minimized (or maximized) by the optimization procedure. The most common similarity measures include sum of squared differences (SSD), normalized cross-correlation (NCC),²² and information-theoretic measures such as mutual information (MI).²³ SSD and NCC are well-suited for same-modality registration whereas MI is most often used for multimodal registration.²⁴ The similarity measure should guarantee a single maximum/minimum when the two volumes are perfectly aligned. Often, image intensities alone are insufficient and therefore additional information needs to be incorporated such as regional information obtained from the segmentation of

anatomic structures.²⁵ This is of particular importance in cardiac PET where the image characteristics are highly variable from patient to patient due to frequently very large perfusion defects.

In this feasibility study, we employ image registration algorithms to (1) evaluate the amount of patient motion occurring during cardiac PET scan, (2) develop an image-based patient motion detection and correction method for stress and rest cardiac PET images, and (3) assess the effect of proposed the motion correction method on image quality. The algorithm aims to correct patient motion rather than the cyclical respiratory or cardiac motion, which is a separate problem tackled in other studies.^{4–6,13,14,16,18,19} The patient motion correction mechanism hinges on the rigid registration method using NCC that involves automatic selection of the 3D target reference frame, followed by consecutive registrations of each frame with the target frame. This is because the effective PET image resolution and noise limits the application of deformable registration for nonlinear corrections. To provide robust motion correction results, we define modified NCC incorporating weighting function using a bilateral filter. A novel rigid registration scheme using modified NCC that combines both global and local regions with adaptive weights allows us to robustly establish the correspondence even in the presence of the poor count statistics and dynamic characteristics tracer uptake throughout the heart.

We test this new method on studies acquired with standard Rb-82 tracer as well as with flurpiridaz F 18, a new tracer with high image resolution, especially in conjunction with high resolution PET detectors.²⁶ Therefore, accurate patient motion correction during a patient scan may be of particular importance for this tracer.

Although PET spatial resolution is high due to the new developments in imaging techniques, image quality of individual time frames is still poor due to count limitations and noise. To provide adequate image statistics, we use 1 min frames dynamic frame for patient motion correction which have higher image quality than the shorter image frame typically used for kinetic modeling.²⁷

II. MATERIALS AND METHODS

II.A. Description of algorithm

In this section, we describe our proposed method. The problem can be considered as the same-modality intrasubject rigid registration. NCC is adopted as our similarity measure since it allows for affine dependency²⁸ of the count values between source and target frames. NCC is a statistical similarity measure that relies on the mean and variance of local 3D window in the image and has been widely used as a comparison criterion for image registration.²⁸ Our method incorporates spatial and geometric image features and evaluates them in an iterative fashion optimizing frame-to-frame image similarity. The cost function for the registration is based on NCC that combines global and local features. In addition, we devise an adaptive scheme to address the potential count variability during contrast agent

uptake by incorporating bilateral filter weights when calculating NCC. The proposed motion correction algorithm consists of the following two steps: (1) an automated method for best target (reference) frame selection for the motion correction and (2) subsequent 3D frame-to-frame registration of all frames to the selected target frame. The flowchart of the proposed patient motion correction method is illustrated in Fig. 1.

II.A.1. Modified normalized cross-correlation

Let $\mathcal{S}(x, t) : \Omega \subset \mathbb{R}^3 \times \mathbb{R}^+ \rightarrow \mathbb{R}^+$ denote the space-time acquisition of the frames and $\mathcal{T}(x) : \Omega \subset \mathbb{R}^3 \rightarrow \mathbb{R}^+$ denote a target frame selected from $\mathcal{S}(x, t)$. We estimate a rigid transformation $T_\Theta(\cdot)$ composed of six parameters $\Theta = (t_x, t_y, t_z, \theta_x, \theta_y, \theta_z)$ describing translations and rotations in the x, y, and z axes, respectively. The NCC is a similarity measure defined as

$$\text{NCC}(\mathcal{S}, \mathcal{T}; T_\Theta, c) = \frac{\sum_{x \in \mathcal{N}_c} (\mathcal{S}(T_\Theta(x), t) - \mu(T_\Theta(c))) \cdot (\mathcal{T}(x) - \gamma(c))}{\sqrt{\sum_{x \in \mathcal{N}_c} (\mathcal{S}(T_\Theta(x), t) - \mu(T_\Theta(c)))^2 \cdot \sum_{x \in \mathcal{N}_c} (\mathcal{T}(x) - \gamma(c))^2}}, \quad (1)$$

where $\mathcal{N}_c$ is the local 3D window centered at pixel c and $\mu(c)$ and $\gamma(c)$ are the mean value of each window, respectively.

Since 1-min frames of PET images are of poorer image quality as compared to full static images and the image in each frame may change during tracer uptake, we adopt a modified NCC measure. The weighted window coefficient, which is similar to the work by Heo *et al.*,²⁹ incorporates the geometric distance as well as the count difference to have smoothed yet edge-preserving property using bilateral filter.³⁰ In general, the bilateral filter is used to suppress noise. However, in contrast to the isotropic Gaussian filter, the bilateral filter incorporates both geometric and intensity distances to

preserve edges. In this work, we adopt bilateral filter coefficients to remove noise and keep the edges, thereby providing accurate correspondence between the frames. Local window $\mathcal{N}_c$ centered at pixel c has different weights given by,

$$w(x) = \exp\left(-\frac{\|c - x\|^2}{2\sigma_{pos}^2} - \frac{\|\mathcal{I}(c) - \mathcal{I}(x)\|^2}{2\sigma_{cnt}^2}\right), \quad (2)$$

where x denotes the pixel coordinate within the local window $\mathcal{N}_c$, $\|\cdot\|$ represents the Euclidean distance, $\mathcal{I}(x)$

(a)

(b)

FIG. 1. Overview of proposed motion correction method. The first row shows sequence of steps. Second row shows the resulting images after motion correction is applied.

represents the count value at the image location x , and σ_{pos} and σ_{cnt} denote, respectively, the geometric distance and count difference standard deviations. The weights are further renormalized to have an average value of 1 within the window. In our implementation, we used 2 mm for both σ_{pos} and σ_{cnt} similar to the image resolution (2.673 mm $\times$ 2.673 mm $\times$ 2 mm), providing accurate registration results.

The weighted mean $m(c)$ of each window can then be defined as

$$m(c) = \frac{\sum_{x \in \mathcal{N}_c} w(x) \mathcal{I}(x)}{Z(c)}, \quad (3)$$

where $\mathcal{N}_c$ denotes local window centered at pixel c , $w(x)$ denotes a weight function for the center pixel c defined in Eq. (2), and $Z(c)$ represents the normalization constant.

Modified NCC incorporating the weight function using bilateral filter can then be given by

$$\text{mNCC}(\mathcal{S}, \mathcal{T}; \mathcal{T}_\Theta, c) = \frac{\sum_{x \in \mathcal{N}_c} (w_S(x) \mathcal{S}(T_\Theta(x), t) - \hat{\mu}(T_\Theta(c))) \cdot (w_T(x) \mathcal{T}(x) - \hat{\gamma}(c))}{\sqrt{\sum_{x \in \mathcal{N}_c} (w_S(x) \mathcal{S}(T_\Theta(x), t) - \hat{\mu}(T_\Theta(c)))^2 \cdot \sum_{x \in \mathcal{N}_c} (w_T(x) \mathcal{T}(x) - \hat{\gamma}(c))^2}}, \quad (4)$$

where $w_S(x)$ and $w_T(x)$ denote weighting functions defined on frames $\mathcal{S}(x, t)$ and $\mathcal{T}(x)$, respectively, $\hat{\mu}(\cdot)$ and $\hat{\gamma}(\cdot)$ are the weighted means calculated on frames $\mathcal{S}(x, t)$ and $\mathcal{T}(x)$, respectively.

II.A.2. Automatic target frame selection

In order to correct for motion, we need to objectively select a target (reference) frame to which all other frames are registered. Ideally, the target frame should be spatially centered with respect to the motion of the myocardium. Therefore, we define the target frame as the one for which the sum of global mNCCs (computed between the candidate frame and all remaining frames) is maximal. The target frame is therefore given by

$$j^* = \arg \max_{j \in \{1, 2, \dots, N\}} \sum_{i=1, i \neq j}^N \text{mNCC}(\mathcal{S}(x, i), \mathcal{S}(x, j)) \quad \text{and} \quad (5)$$

$$\mathcal{T}(x) = \mathcal{S}(x, j^*),$$

where N and j^* denote total number of frames and target frame number, respectively.

II.A.3. Registration based on global and local mNCC

The most prominently visible structure in cardiac PET images is the myocardium and its neighborhood, and therefore, we incorporated these regions as presegmented region of interests (ROIs) in the registration method. To delineate and localize these ROIs, we used an automated PET segmentation algorithm previously developed by our group,^{31,32} which performs segmentation of the left ventricular (LV) myocardium. We used a bounding box containing the segmented myocardium as an image mask for the local mNCC computation. Since the segmentation algorithm provides the contour for the first frame only, a 5-mm 3D margin was applied around the bounding box to accommodate for motion.

Local mNCC computation is restricted to the bounding box encompassing the LV obtained from the segmentation

algorithm, which helps emphasize the myocardium and the local neighborhood during registration. However, segmentation failures and low counts in the myocardium could affect registration if they were solely based on the local mNCC. To remedy this, we combine both the local mNCC and the global mNCC computed over the entire image in the cost function. The final combined cost function is therefore defined as

$$E = \frac{1}{|\Omega|} \int_{\Omega} (1 - \alpha) \text{mNCC}_g + \alpha \text{mNCC}_l dx, \quad (6)$$

where mNCC_g and mNCC_l denote global and local mNCC, respectively, and the parameter $\alpha \in [0, 1]$ is a weighting factor. Inspired by the work of Yi and Soatto,³³ we model α as a function of local mNCC to accommodate the local context in an adaptive manner. This alleviates potential problems that may direct the registration towards irrelevant anatomical structures when using global mNCC only. Since each frame has nonnegative count values and the mNCC value is bounded between -1 and 1 , we model $\alpha = (\text{mNCC}_l + 1)/2$. Substituting this into Eq. (6) yields

$$E = \frac{1}{|\Omega|} \int_{\Omega} \frac{1 - \text{mNCC}_l}{2} \cdot \text{mNCC}_g + \frac{\text{mNCC}_l + 1}{2} \cdot \text{mNCC}_l dx, \quad (7)$$

The underlying mechanism is that a large mNCC_l (close to 1) makes the local mNCC the main contributor, whereas a small mNCC_l (close to -1) suggests that the result is primarily determined by the global mNCC. This allows avoiding local minima.

II.A.4. Optimization

The optimal values for the six parameters Θ_i ($i = 1, 2, \dots, 6$) that minimize the cost function are obtained by solving the Euler–Lagrange equations, and a gradient descent method is performed.²⁸ We use negative of the Eq. (7) to minimize the

cost function. Parameterizing the descent direction by an artificial time $t \geq 0$, the derivation of the Euler–Lagrange equations is given below:

$$\frac{\partial \Theta_i}{\partial t} = -\frac{\partial E}{\partial \Theta_i} (i = 1, 2, \dots, 6), \quad (8)$$

where the variation of E is given by

$$\begin{aligned} \frac{\partial E}{\partial \Theta_i} = & \frac{1 - \text{mNCC}_l}{2} \cdot \frac{\partial \text{mNCC}_g}{\partial \Theta_i} \\ & + \left(\frac{1}{2} + \text{mNCC}_l - \frac{\text{mNCC}_g}{2} \right) \cdot \frac{\partial \text{mNCC}_l}{\partial \Theta_i} \\ & \times (i = 1, 2, \dots, 6). \end{aligned} \quad (9)$$

Derivation details of NCC are detailed by Hermosillo *et al.*²⁸ Additionally, to improve the computational efficiency and robustness of the optimization process, we employed a coarse-to-fine multiresolution scheme (two levels). In our implementation, we use C++ with an open source library, insight segmentation and registration toolkit (ITK).³⁴

II.B. Validation

II.B.1. Patient data

The validation of the motion correction algorithm was performed as a retrospective analysis of patients who underwent stress–rest PET/CT with ^{82}Rb for clinical reasons or who participated in an ongoing phase 2 flurpiridaz F 18 clinical study. Motion detection and correction were performed and validated for both types of data. This study was conducted according to the guidelines of the Cedars-Sinai Medical Center Institutional Review Board. All patients provided written consent for use of their data. Table I shows the patient characteristics.

II.B.2. Imaging protocols

II.B.2.a. ^{82}Rb perfusion protocol. The study population consisted of 14 patients (10 males, 4 females) who underwent stress–rest ^{82}Rb PET/CT scanning, with a mean age of 68 ± 15 yr and a mean body weight of 83 ± 26 kg (Table I). Patients were instructed to continue breathing normally throughout the duration of the scan as reported in previous studies.³⁵ Prior to PET image acquisition, a 2.8-s CT topo-

gram with 120 kVp was performed for CT-based attenuation correction. Rest PET images were acquired for 6 min starting at the injection time. Typically, the injected dose was 25 mCi of ^{82}Rb for patients under 90 kg, 40 mCi for patients between 91 and 113 kg, and 50 mCi for patients over 113 kg. Patients underwent a vasodilator stress scan 10 min after completion of rest ^{82}Rb scan. For vasodilator stress, adenosine was infused at $140 \mu\text{g/kg/min}$ for 7 min and ^{82}Rb was injected 1.5 min after adenosine infusion.

II.B.2.b. Flurpiridaz F 18 perfusion protocols. Flurpiridaz F 18 perfusion imaging at rest and stress was performed in 16 patients (13 males, 3 females) undergoing stress–rest myocardial perfusion imaging, with a mean age 59.4 ± 16.4 yr, and mean weight 85 ± 14 kg (Table I). Rest perfusion images were acquired immediately upon infusion of 2.3–4.5 mCi of flurpiridaz F 18. Images were acquired for 15 min followed by a 30 min interval between rest and stress for adenosine and a 60 min interval for exercise stress. Stress testing was performed with a symptom-limited Bruce treadmill exercise protocol or adenosine challenge, as described previously.³⁶ At near-maximal exercise, 6.4–9.6 mCi of flurpiridaz F 18 was injected intravenously. For treadmill stress, exercise continued for 1–2 min after flurpiridaz F 18 dose administration. Flurpiridaz F 18 perfusion PET acquisition started 25 min after termination of exercise. For vasodilator stress, adenosine was infused at $140 \mu\text{g/kg/min}$ for 6 min. At the end of the third minute, flurpiridaz F 18 was injected and myocardial imaging was started immediately. Twelve lead electrocardiography (ECG) were monitored continuously during stress testing.

II.B.3. PET acquisition and reconstruction

II.B.3.a. PET system. All images were acquired on a Siemens Biograph-64 TruePoint PET/CT with TrueV option. Images were acquired in 3D and list mode. This 3D system consists of a 64-slice CT and a PET scanner with 4 rings of lutetium oxyorthosilicate (LSO) detectors with detector element dimensions of $4 \text{ mm} \times 4 \text{ mm} \times 20 \text{ mm}$.³⁷ The image resolution was $2.673 \text{ mm} \times 2.673 \text{ mm} \times 2 \text{ mm}$. The PET axial and transaxial FOV were 216 mm and 605 mm, respectively. The coincidence time window and the energy window were respectively 4.5 ns and 425–650 keV. The 3D datasets are rebinned in 2D using the Fourier rebinning technique.³⁸ The scatter correction is done with a single scatter simulation.³⁹ The random events are corrected using a delayed window.⁴⁰ For ^{82}Rb PET, images were reconstructed with 2D-attenuation weighted ordered subsets expectation maximization (2D-AWOSEM),⁴¹ with Gaussian filtering [2 iterations, 21 subsets, full width half maximum (FWHM) of 10 mm], and attenuation and scatter correction. Four stress and four rest dynamic frames (each 1 min in duration) were reconstructed from the list mode data after a 2 min delay to allow for the blood clearance from the blood pool. For flurpiridaz F 18, attenuation correction was used and iterative reconstruction was performed with a Gaussian filter (2 iterations, 21 subsets, FWHM 4 mm). One minute dynamic images (rest, adenosine and exercise) were reconstructed from 15 min list mode acquisition. Since the rest acquisition

TABLE I. Patient characteristics.

	Flurpiridaz F 18	^{82}Rb
Number of patients	16	14
Male	14	8
Age	59 ± 16	62 ± 15
Body weight	85 ± 14 (kg)	83 ± 26 (kg)
BMI	28.2 ± 4.8	25.3 ± 6.5
Exercise stress	8	0
Adenosine stress	8	14
Dose injected (rest)	3.1 ± 0.8 (mCi)	28.3 ± 6.0 (mCi)
Dose injected (Stress)	8.3 ± 0.8 (mCi)	28.3 ± 6.0 (mCi)

TABLE II. Patient motion extent during cardiac PET.

	Motion extent between any 2 frames (mm)		
	X axis	Y axis	Z axis
Stress (flurpiridaz F 18)	2.2 ± 1.1	1.4 ± 0.7	1.9 ± 1.3
Rest (flurpiridaz F 18)	2.0 ± 1.1	1.2 ± 0.9	1.9 ± 1.0
Stress (^{82}Rb)	1.9 ± 0.7	0.7 ± 0.6	1.3 ± 0.6
Rest (^{82}Rb)	2.0 ± 0.9	0.6 ± 0.4	1.2 ± 1.2

and adenosine stress acquisition started at the injection time, the first 5 min of the list mode file were ignored to allow for blood clearance. For exercise stress images, there was no need to skip the first 5 min of the list mode file because the acquisition started about 25 min after the injection, which occurred when the patients were on the treadmill. Original transverse orientation was used for all reconstructions.

II.B.4. Evaluation of registration algorithm

In this section, we describe a series of experiments to assess the performance of the proposed approach including quantitative analysis of image quality, simulated motion correction, qualitative visual assessment, and motion detection.

II.B.4.a. Quantitative analysis of uncorrected and corrected images. We measured the amount of corrected motion for each registration parameter (translations only) by calculating motion extent (maximum frame-to-frame displacement) from the source frame to target frame.

We computed maximal radial myocardial counts before and after correction to show the effect of the correction. We also calculated the contrast (CONT) between the blood pool and the myocardial wall, and the contrast-to-noise ratio (CNR), defined by

$$\text{CONT} = \frac{\mu_w}{\mu_b} \quad \text{and} \quad \text{CNR} = \frac{\mu_w - \mu_b}{\sigma_b}, \quad (10)$$

where μ_w and μ_b denote mean counts in myocardial wall and blood pool, respectively, and σ_b represents the root mean square of the noise as defined by the standard deviation of the counts in the blood pool region.

II.B.4.b. Simulated motion test. To test the reproducibility of the motion correction, we performed multiple registrations from different initial positions, by simulating motion ranging from -10 mm to $+10$ mm in steps of 5 mm in x, y, and z directions (125 combinations in total per dataset). As a reference standard, we selected four datasets (two normal and two abnormal datasets) without motion as assessed visually. The known displacements we introduced were considered the ground truth. The range of the initial positions was selected to represent patient motion that could be encountered in clinical practice. The mean error was subsequently defined as the mean of absolute differences from the original position to the registered result for each x, y, and z directions.

II.B.4.c. Qualitative visual assessment. For comparison, visual scoring of the motion magnitude was performed on a scale of 0 to 2 (no motion, moderate motion, and large motion) by two experienced observers using fusion display in Cedars-Sinai QPS software²⁵ with multiplanar display and LV contour overlaid on the images. Results were compared to the visual motion scoring by two observers before and after motion correction. Scores of 1 and 2 were grouped together and considered as the evidence of motion, while score 0 was considered as no motion. In addition, Cohen κ -coefficients⁴² with linear weight were applied to compare the difference of visual scoring between two observers.

FIG. 2. Average 3D motion extent with different protocols. The motion extent averaged across all subjects (y axis) is plotted with respect to the different protocols (x axis). The error bar represents the standard deviation of the motion extent averaged across all subjects. The scanning time of flurpiridaz F 18 and ^{82}Rb perfusion studies is 10 min and 4 min, respectively.

FIG. 3. Average RMS motion extent versus scanning time. (a) Average RMS motion extent from all axes (y axis) is plotted using flurpiridaz F 18 perfusion studies with respect to scanning time (10 min) and (b) average RMS motion extent from all axes is plotted using ^{82}Rb perfusion studies with respect to scanning time (4 min).

II.B.4.d. Motion detection. Detection of significant patient motion in a cardiac PET dataset may be an important quality control step before subsequent analysis of PET studies. In order to establish a quantitatively visually detectable motion threshold, we compared motion extent obtained from the automatic registration to the visual scores from the experts. Receiver operator characteristics (ROC) analysis⁴³ was used to determine the optimal motion extent threshold based on the visual scores and motion extent. After setting a range of threshold values, a classification table was built for each threshold value. Each point produces a point in the ROC curve where each point is a pair of sensitivity and 1-specificity values. The pair that produces the best classification accuracy was the motion threshold. This motion extent threshold was subsequently used to find the agreement between the visual and automatic method.

III. RESULTS

The computations were performed on a standard personal computer with an Intel dual-core processor, a clock speed of 2.5 GHz and 4 GB memory. The mean computation time for the registration of all frames was 58 ± 6 s and 17 ± 3 s for flurpiridaz F 18 and ^{82}Rb perfusion studies, respectively. Hence, the approximate average computation time for each frame was 8.6 s.

III.A. Quantitative analysis of uncorrected and corrected images

The motion extent averaged across all subjects is shown in Table II and Fig. 2, in which the scanning time of flurpiridaz F 18 and ^{82}Rb perfusion studies is 10 min and 4 min, respectively. Motion extent in the x and z axes was bigger

FIG. 4. Examples of motion effect for flurpiridaz F 18 studies: (a) a patient with minimum motion (motion range is 1.0 mm), (b) a patient with average motion (motion range is 3.8 mm), and (c) a patient with maximum motion (motion range is 5.2 mm). White outline illustrates the LV contour automatically derived from the first frame.

TABLE III. Effect of motion correction on count statistics. CONT -contrast, CNR-contrast to noise ration

Count Statistics	Before correction (mean $\pm$ SD)	After correction (mean $\pm$ SD)	Change (%) (p value)
Stress flurpiridaz F 18	38779 $\pm$ 19683	41152 $\pm$ 22105	6.1 ($p = 0.04$)
Rest flurpiridaz F 18	7698 $\pm$ 1784	7823 $\pm$ 1609	1.6 ($p = 0.13$)
Stress ^{82}Rb	159476 $\pm$ 47049	161845 $\pm$ 48272	1.5 ($p = 0.03$)
Rest ^{82}Rb	95690 $\pm$ 26312	97150 $\pm$ 26930	1.5 ($p = 0.04$)
CONT stress flurpiridaz F 18	2.13 $\pm$ 0.46	2.23 $\pm$ 0.39	4.7 ($p = 0.09$)
CONT rest flurpiridaz F 18	1.93 $\pm$ 0.49	1.98 $\pm$ 0.44	2.6 ($p = 0.24$)
CONT stress ^{82}Rb	1.44 $\pm$ 0.07	1.44 $\pm$ 0.04	0 ($p = 0.61$)
CONT rest ^{82}Rb	1.53 $\pm$ 0.13	1.54 $\pm$ 0.11	0.7 ($p = 0.31$)
CNR stress flurpiridaz F 18	1.48 $\pm$ 0.31	1.72 $\pm$ 0.19	16.2 ($p = 0.03$)
CNR rest flurpiridaz F 18	1.36 $\pm$ 0.78	1.53 $\pm$ 0.74	12.5 ($p = 0.03$)
CNR stress ^{82}Rb	1.44 $\pm$ 0.32	1.50 $\pm$ 0.21	4.2 ($p = 0.38$)
CNR rest ^{82}Rb	1.77 $\pm$ 0.20	1.85 $\pm$ 0.17	4.5 ($p = 0.06$)

than motion extent in the y axis. The amount of motion was related to scanning time. Thus, the motion extent for flurpiridaz F 18 perfusion studies was larger than the motion extent for ^{82}Rb perfusion studies. Figure 3 illustrates the average root-mean-square (RMS) motion extent versus time. Average RMS motion extent of each time frame is given by

$$\text{Average RMS} = \frac{1}{N} \sum_{i=1}^N \sqrt{\frac{mx_i^2 + my_i^2 + mz_i^2}{3}}, \quad (11)$$

where N denotes number of subjects and mx , my , and mz represent motion extent of each time frame in x, y, and z axes, respectively.

In both protocols, generally more motion was observed in the beginning and at the end of the acquisition, probably due to the definition of the reference frame as spatially most central with respect to motion. The motion extent in two subjects during stress and three subjects during rest were larger than 2 voxels (≥ 4 mm) and ten subjects at stress and nine subjects at rest were larger than 1 voxel (≥ 2 mm) in flurpiridaz F 18 perfusion studies. In ^{82}Rb perfusion studies, no study had a motion extent larger than 2 voxels (≥ 4 mm), and six stress studies and eight rest studies had motion extent larger than 1 voxel (≥ 2 mm). Figure 4 illustrates the motion effect for flurpiridaz F 18, in which a patient with minimum

motion is shown in (a), a patient with average motion is shown in (b), and a patient with maximum motion is shown in (c). Our results indicate that patient motion during cardiac PET is similar for stress and rest. This finding is similar to the work of Mukherjee *et al.*¹⁴ in which stress and rest images do not show any significant differences in body motion. The visually detectable patient motion threshold was found to be 2.2 mm by comparison of visual qualitative scores with quantitative values.

The maximal radial LV counts were measured across all the frames within the fixed myocardium contour, which was derived from the first frame. Table III summarizes the count statistics, CONT and CNR before and after motion correction. Count statistics varied partly because count changes nonuniformly during tracer uptake and the contour were fixed across the frames. The myocardium moves around the contour from the reference frame due to patient motion, and therefore the maximal radial LV counts (polar map counts) that are detected within the stationary reference contour are changing. Increases in mean polar map counts due to motion correction in cases above the motion threshold (2.2 mm) were 6.1% ($p = 0.09$) and 1.6% ($p = 0.19$) in stress and rest flurpiridaz F 18 perfusion studies and 1.5% ($p = 0.09$) and 1.5% ($p = 0.08$) in stress and rest ^{82}Rb perfusion studies, respectively. It was observed that the increases in the average CONT measure due to motion correction were 4.6% ($p = 0.13$) and 2.5% ($p = 0.28$) for stress and rest flurpiridaz F 18 perfusion studies and 0.5% ($p = 0.65$) and 0.5% ($p = 0.35$) in stress and rest ^{82}Rb perfusion studies, respectively. Additionally, it was observed that the increase in the average CNR measure was 16.2% ($p = 0.07$) and 12.2% ($p = 0.07$) in stress and rest flurpiridaz F 18 perfusion studies and 4.6% ($p = 0.43$) and 4.3% ($p = 0.10$) in stress and rest ^{82}Rb perfusion studies, respectively.

III.B. Simulated motion

We tested the performance of the proposed approach with different levels of simulated motion. In this test, the ground truth is the original image frame position and the algorithm is applied to images with known amounts of simulated translations. Figure 5 illustrates that the proposed approach could

FIG. 5. Registration errors after motion correction of simulated motion. Translational errors are shown in four datasets.

FIG. 6. Images before and after correction for simulated motion in a flurpiridaz F 18 study. The first row shows frame 3, frame 9, and summed image before motion correction by introducing 6 mm to the odd number frame and -6 mm to the even number frame in z direction. The second row shows frame 3, frame 9, and summed image after motion correction. Images show that motion correction improves image quality (reduced blurring and higher contrast) compared with the summed image before motion correction.

correct large motion extent with an error <0.3 mm. Figures 6 and 7 illustrate how myocardial movement in flurpiridaz F 18 and ^{82}Rb perfusion PET studies can cause spatial blurring

in the summed image. The total magnitude of simulated motion in the z direction was 12 mm in both cases. The dataset shown in these figures had no motion and we provided

FIG. 7. Examples of registration results using simulated motion in ^{82}Rb perfusion study. The first row shows frame 1, frame 3, and summed image before motion correction by introducing 6 mm and -6 mm in z direction. The second row shows frame 1, frame 3, and summed image after motion correction. Images show that motion correction has better image quality (reduced blurring and higher contrast) compared with the summed image before motion correction.

FIG. 8. Two examples of registration results in stress flurpiridaz F 18 perfusion study. The first row shows short axis, long axis, vertical axis, and summed image of short axis before motion correction (motion extent in x, y, and z axes is 4.4 mm, 2.3 mm, and 0.8 mm, respectively). The increases of CNR and CONT were 22% and 8%, respectively. The second row shows short axis, long axis, vertical axis, and summed image of short axis after motion correction (motion extent in x, y, and z axes is 4.9 mm, 2.1 mm, and 5.2 mm, respectively). The increases of CNR and CONT were 42% and 16%, respectively, showing that motion correction has better image quality compared with the summed image before motion correction.

translations of 6 mm to the odd number frame and -6 mm to the even number frame in the z direction by translating the volume. The last columns in Figs. 6 and 7 demonstrate the improvement in image quality in flurpiridaz F 18 and ^{82}Rb perfusion PET studies after correction of simulated motion.

III.C. Qualitative visual assessment

Motion (visual scores of 1 and 2) was found by the user in $n = 31$ and $n = 32$ cases and no motion (visual score of 0) was found in $n = 29$ and $n = 28$ cases by the two observers, respectively. Using the visually detectable motion threshold of 2.2 mm, the agreement in automated detection of motion with the two visual observers was 74% and 75%, respec-

tively. Figure 8 shows a representative case, with motion extent greater than 4 mm with blurring of the summed image.

Tables IV and V show visual motion scores assessed by two visual observers before and after motion correction. Visual motion scores of 1 or 2 were improved to a score of 0 when reassessed after motion correction, in 93% of patients. To test the difference of visual scoring between the two observers, agreement and kappa statistics were calculated. Analysis with respect to the visual score (score 0 to 2) between two observers revealed an exact agreement of 86% (kappa = 0.56) as shown in Fig. 9(a). Similarly, analysis with respect to the visual score (motion or no motion) between the two observers revealed an exact agreement of

TABLE IV. Visual motion detection before and after motion correction in flurpiridaz F 18 studies.

	Observer 1				Observer 2			
	Stress before motion correction	Rest before motion correction	Stress after motion correction	Rest after motion correction	Stress before motion correction	Rest before motion correction	Stress after motion correction	Rest after motion correction
Subject 1	2 ^a	2	0	0	1	0	1	0
Subject 2	1	0	0	0	1	0	0	0
Subject 3	1	0	0	0	0	0	0	0
Subject 4	0	0	0	0	0	1	0	0
Subject 5	1	1	0	0	1	0	0	1
Subject 6	0	1	0	0	0	0	0	0
Subject 7	1	1	0	0	1	1	0	0
Subject 8	2	0	0	0	2	1	0	0
Subject 9	2	1	0	1	2	0	0	0
Subject 10	2	0	0	0	2	0	0	0
Subject 11	2	0	0	0	0	0	0	0
Subject 12	1	0	0	0	1	0	0	0
Subject 13	2	0	0	0	1	0	0	0
Subject 14	1	0	0	0	2	2	0	1
Subject 15	2	0	0	0	1	0	0	0
Subject 16	1	1	0	0	1	2	0	0

^a2, large motion (black); 1, moderate motion (gray); and 0, no motion (white).

85% ($\kappa = 0.63$) as shown in Fig. 9(b). The κ -coefficients for the agreement between the two observers show that it is within moderate agreement.

IV. DISCUSSION

In this study, we developed an image-based motion correction using a fully automated registration method and applied it to myocardial perfusion PET data obtained with two different imaging protocols. There are three principal contributions in our work. First and foremost, by using the fully automated approach, we were able to minimize the

effect of patient motion, leading to increases in polar map counts, contrast, and signal-to-noise for the myocardium. Contrast and contrast-to-noise ratio improved both in flurpiridaz F 18 and ⁸²Rb perfusion studies. Second, we defined a visually detectable patient motion threshold, by comparison of visual assessment of motion with the motion extent found by the algorithm, which may enable a practical method for quality control of cardiac PET studies for patient motion. Finally, we demonstrated that the amount of patient motion during cardiac PET is similar in stress and rest scans, at least within the resolution of the PET imaging system and for the adenosine or exercise stress protocols. Studies with other

TABLE V. Visual motion detection before and after motion correction before and after motion correction in ⁸²Rb studies.

	Observer 1				Observer 2			
	Stress before motion correction	Rest before motion correction	Stress after motion correction	Rest after motion correction	Stress before motion correction	Rest before motion correction	Stress after motion correction	Rest after motion correction
Subject 1	1 ^a	0	0	0	1	0	0	0
Subject 2	1	0	0	0	2	0	0	0
Subject 3	2	2	0	0	1	1	0	0
Subject 4	0	0	0	0	1	2	0	0
Subject 5	1	0	0	0	1	0	0	0
Subject 6	0	0	0	0	2	0	0	0
Subject 7	2	0	0	0	2	0	0	0
Subject 8	0	0	0	0	1	0	0	0
Subject 9	2	1	0	0	2	0	0	0
Subject 10	0	0	0	0	0	0	0	0
Subject 11	0	0	1	0	0	0	1	0
Subject 12	1	0	0	0	2	0	0	0
Subject 13	1	0	0	0	1	2	0	0
Subject 14	0	0	0	0	0	1	0	0

^a2: large motion (black); 1: moderate motion (gray); and 0: no motion (white).

FIG. 9. Comparison of visual score agreement with respect to the (a) visual score (score 0 to 2) and (b) visual score (motion and no motion) between two observers. Hatched regions indicate exact agreement.

stress protocols and other imaging modalities may have different findings.

This is the first attempt to optimize reconstruction myocardial perfusion flurpiridaz F 18 images with respect to patient motion. Image resolution is not optimal with ^{82}Rb because positrons must travel a relatively long distance in the body (average range 4 mm) before annihilation and emission of the photons that are detected by the PET camera. Greater improvements in spatial resolution and contrast resolution are possible with an ^{18}F -labeled tracer such as flurpiridaz F 18, as its positron range is much shorter (0.54 mm) and its half-life much longer than ^{82}Rb (110 min versus 1.3 min). Improvement in image quality was observed after motion correction with both ^{82}Rb and flurpiridaz F 18 PET images, with results more pronounced for the flurpiridaz F 18 tracer reflecting its higher image resolution. Therefore, the motion correction may be of particular importance for this tracer. We detect motion with respect to a central frame, and thus the maximum motion between any 2 frames may be larger. Motion as small as $1/2$ pixel can reduce the maximum value within the myocardial contour (as typically used in creation of polar map for perfusion analysis) due to a partial volume effect, consequently affecting the quantitative perfusion analysis. The analysis of subtle changes between stress and rest myocardial perfusion PET may be affected by changes as small as 5%–10% in the reduction of the apparent maximal activity.¹

In this study, we developed a modified NCC. PET images suffer from poor image quality, and the counts may change nonuniformly during tracer uptake. Consequently, the traditional similarity measures such as NCC or MI may not be suitable. The modified NCC as proposed here can circumvent possible bias from noise or differences in intensities.

For the reconstruction method, we used 21 subsets, which corresponded to a number of maximum likelihood equivalent iterations (defined as the product of the number of iterations and the number of subsets) of 42. This partially compensates for the low number of iterations in OSEM as described in Hudson and Larkin.⁴⁴ Van der Weerd *et al.*⁴⁵ showed that using OSEM with only 24-emission-equivalent iterations resulted in only minor underestimations of ^{18}F -FDG uptake ($\sim 2\%$), compared with FBP, for most regions. Larger underestimations ($\sim 10\%$ on average, with a maximum of $\sim 20\%$) were observed in regions with low uptake. The impact of these underestima-

tions on the quality of clinical evaluation of myocardial ^{18}F -FDG studies was assessed and found to be insignificant. We also chose to keep the number of iterations low and stopped before full convergence to limit the variance in the final image (which increases with the number of iterations). There could be potential differences between the level of counts between Van der Weerd *et al.*⁴⁵ and our work. Since we reconstructed 1-min frames, which are much shorter than a full 6–10 min acquisition, this is a legitimate concern. However, Van der Weerd *et al.*⁴⁵ used a 2D system with three rings of detectors while we used a full 3D system with four rings of detectors which lead to a much higher sensitivity (almost a factor 10 between the 2 systems HR+ sensitivity $2\text{D}(3\text{D}) = 1357(6650)$ cps/MBq, Biograph 4-ring sensitivity $= 6362 \times 1.8 = 11451$ cps/MBq).^{46,47} With the level of activity injected in the ^{82}Rb and flurpiridaz F 18 studies and with a significant sensitivity increase in our PET system, the level of counts in our work was similar to the one in Van der Weerd *et al.*⁴⁵ Previously, for dynamic studies with shorter time frames (5–10 s), only filtered backprojection techniques were typically applied⁴⁸ due to noise considerations.^{49,50} However, in this study, we have used much longer 1-min frames with high sensitivity system.

This study has several potentially limiting factors. In addition to patient movement, there may be other factors including cardiac motion, respiratory motion, and misalignment between PET and CT for some or all of the frames, which may potentially result in further errors with attenuation correction. Further improvement in image quality could be potentially demonstrated if attenuation correction were reapplied to motion-corrected image frames. However, such frame-by-frame realignment and attenuation correction cannot currently be performed within vendor reconstruction software. In general, separate acquisition of CT maps and PET on a PET/CT scanner is a limitation since misregistration may occur and affect the quality of the correction of the real time motion correction. In the future, simultaneous acquisition systems such as PET/MR⁵¹ may potentially resolve this issue. However, the current cost of such systems is prohibitive for clinical applications. In this work, we only considered a motion correction method and did not address further attenuation correction problems as in Bai and Brady.¹⁸ Additionally, there is also a trade-off between the frame time (temporal resolution) and image quality. Therefore, the application of this algorithm to shorter time frames such as used in kinetic modeling needs to be evaluated. Potentially different reconstruction techniques may need to be used in such cases as previously discussed. However, this work focused on motion correction for the purposes of creating the summed perfusion images. In this application, we employed rigid rather than nonlinear registration to compensate for patient motion. However, the proposed approach is not bound to a specific transformation model, allowing us to capture more detailed motion using affine registration or deformable registration with the same cost function, if required. Nevertheless, the effective PET image resolution and noise limitations may limit the amount of nonlinear motion that could be assessed by such methods. Furthermore, deformable registration could introduce errors in the actual perfusion signal, which would

eliminate any benefit of this correction. We used a trilinear interpolation method in this work. In general, the choice of different interpolation methods could affect the results (e.g., image resolution). However, we tried third order BSpline interpolation, and results were similar to those using trilinear interpolation method. This is likely due to the fact that effective PET resolution is not high enough compared to the pixel size to show much difference as visually assessed. Nevertheless, given that subvoxel motion was detected, it is possible that trilinear interpolation slightly affects the image quality. We found that the agreement between motion classified as above or below the threshold and visual assessment was moderate, 74%–75%. However, note that the motion detection threshold may not be optimal, and further evaluation of optimal motion detection threshold may be required. Finally, the validation of the ultimate utility for the proposed motion correction will require comparison with invasive angiography in order to evaluate its potential impact on improving diagnostic accuracy.

V. CONCLUSION

A method for automated image-based motion correction using rigid registration is presented to correct patient motion in cardiac PET. We demonstrated that this approach is accurate, robust, and agrees with expert visual evaluation. We also demonstrated that motion correction for cardiac PET improves image quality quantitatively, and therefore has the potential to improve the diagnostic value of cardiac PET with both ^{82}Rb and flurpiridaz F 18.

ACKNOWLEDGMENTS

This research was supported in part by grant R01HL089765-01 from the National Heart, Lung, and Blood Institute/National Institutes of Health (NHLBI/NIH) (PI: Piotr Slomka). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NHLBI. The authors would like to thank Mark Hyun for his assistance in manual visual scoring and Arpine Oganyan for editing and proof-reading the text.

^{a)}Author to whom correspondence should be addressed. Electronic mail: Piotr.Slomka@cshs.org; Telephone: 310-243-4348; Fax: 310-243-0173.

¹P. J. Slomka, L. Le Meunier, S. W. Hayes, W. Acampa, M. Oba, G. G. Haemer, D. S. Berman, and G. Germano, "Comparison of myocardial perfusion ^{82}Rb PET performed with CT- and transmission CT-based attenuation correction," *J. Nucl. Med.* **49**, 1992–1998 (2008).

²T. M. Bateman, G. V. Heller, A. I. McGhie, J. D. Friedman, J. A. Case, J. R. Bryngelson, G. K. Hertenstein, K. L. Moutray, K. Reid, and S. J. Cullom, "Diagnostic accuracy of rest/stress ECG-gated ^{82}Rb myocardial perfusion PET: Comparison with ECG-gated $^{99\text{m}}\text{Tc}$ sestamibi SPECT," *J. Nucl. Cardiol.* **13**, 24–33 (2006).

³D. S. Berman, A. Abidov, R. Hachamovitch, J. K. Min, P. J. Slomka, G. Germano, and L. J. Shaw, "Comparative roles of cardiac CT and nuclear cardiology in assessment of the patient with suspected coronary artery disease," *J. Invasive Cardiol.* **21**, 352–358 (2009).

⁴G. J. Klein, B. W. Reutter, M. H. Ho, J. H. Reed, and R. H. Huesman, "Real-time system for respiratory-cardiac gating in positron tomography," *IEEE Trans. Nucl. Sci.* **45**, 2139–2143 (1998).

⁵L. Livieratos, K. Rajappan, L. Stegger, K. Schafers, D. L. Bailey, and P. G. Camici, "Respiratory gating of cardiac PET data in list-mode acquisition," *Eur. J. Nucl. Med. Mol. Imaging* **33**, 584–588 (2006).

⁶L. Livieratos, L. Stegger, P. M. Bloomfield, K. Schafers, D. L. Bailey, and P. G. Camici, "Rigid-body transformation of list-mode projection data for respiratory motion correction in cardiac PET," *Phys. Med. Biol.* **50**, 3313–3322 (2005).

⁷D. S. Berman, R. Hachamovitch, L. J. Shaw, J. D. Friedman, S. W. Hayes, L. E. Thomson, D. S. Fieno, G. Germano, N. D. Wong, X. Kang, and A. Rozanski, "Roles of nuclear cardiology, cardiac computed tomography, and cardiac magnetic resonance: Noninvasive risk stratification and a conceptual framework for the selection of noninvasive imaging tests in patients with known or suspected coronary artery disease," *J. Nucl. Med.* **47**, 1107–1118 (2006).

⁸R. G. Wells, T. D. Ruddy, R. A. DeKemp, J. N. DaSilva, and R. S. Beanlands, "Single-phase CT aligned to gated PET for respiratory motion correction in cardiac PET/CT," *J. Nucl. Med.* **51**, 1182–1190 (2010).

⁹H. M. Sherif, S. G. Nekolla, A. Saraste, S. Reder, M. Yu, S. Robinson, and M. Schwaiger, "Simplified quantification of myocardial flow reserve with flurpiridaz F 18: Validation with microspheres in a pig model," *J. Nucl. Med.* **52**, 617–624 (2011).

¹⁰J. Maddahi, J. Czernin, J. Lazewatsky, S. C. Huang, M. Dahlbom, H. Schelbert, R. Sparks, A. Ehlgren, P. Crane, Q. Zhu, M. Devine, and M. Phelps, "Phase I, first-in-human study of BMS747158, a novel ^{18}F -labeled tracer for myocardial perfusion PET: Dosimetry, biodistribution, safety, and imaging characteristics after a single injection at rest," *J. Nucl. Med.* **52**, 1490–1498 (2011).

¹¹M. C. Huisman, T. Higuchi, S. Reder, S. G. Nekolla, T. Poethko, H. J. Wester, S. I. Ziegler, D. S. Casebier, S. P. Robinson, and M. Schwaiger, "Initial characterization of an ^{18}F -labeled myocardial perfusion tracer," *J. Nucl. Med.* **49**, 630–636 (2008).

¹²S. G. Nekolla, S. Reder, A. Saraste, T. Higuchi, G. Dzewas, A. Preissel, M. Huisman, T. Poethko, T. Schuster, M. Yu, S. Robinson, D. Casebier, J. Henke, H. J. Wester, and M. Schwaiger, "Evaluation of the novel myocardial perfusion positron-emission tomography tracer ^{18}F -BMS-747158-02: Comparison to ^{13}N -ammonia and validation with microspheres in a pig model," *Circulation* **119**, 2333–2342 (2009).

¹³M. Dawood, F. Buther, X. Jiang, and K. P. Schafers, "Respiratory motion correction in 3-D PET data with advanced optical flow algorithms," *IEEE Trans. Med. Imaging* **27**, 1164–1175 (2008).

¹⁴J. M. Mukherjee, K. L. Johnson, J. E. McNamara, and M. A. King, "Quantitative study of rigid-body and respiratory motion of patients undergoing stress and rest cardiac SPECT imaging," *IEEE Trans. Nucl. Sci.* **57**, 1105–1115 (2010).

¹⁵J. M. Wheat and G. M. Currie, "Incidence and characterization of patient motion in myocardial perfusion SPECT: Part 1," *J. Nucl. Med. Technol.* **32**, 60–65 (2004).

¹⁶M. Dawood, T. Kusters, M. Fieseler, F. Buther, X. Jiang, F. Wubbeling, and K. P. Schafers, "Motion correction in respiratory gated cardiac PET/CT using multi-scale optical flow," *Med. Image. Comput. Comput. Assist. Interv.* **11**, 155–162 (2008).

¹⁷M. Marinelli, A. Martinez-Moller, B. Jensen, V. Positano, S. Weismuller, N. Navab, L. Landini, M. Schwaiger, and S. G. Nekolla, "Registration of myocardial PET and SPECT for viability assessment using mutual information," *Med. Phys.* **37**, 2414–2424 (2010).

¹⁸W. Bai and M. Brady, "Motion correction and attenuation correction for respiratory gated PET images," *IEEE Trans. Med. Imaging* **30**, 351–365 (2011).

¹⁹B. Guerin, S. Cho, S. Y. Chun, X. Zhu, N. M. Alpert, G. El Fakhri, T. Reese, and C. Catana, "Nonrigid PET motion compensation in the lower abdomen using simultaneous tagged-MRI and PET imaging," *Med. Phys.* **38**, 3025–3038 (2011).

²⁰T. G. Turkington, T. R. DeGrado, M. W. Hanson, and R. E. Coleman, "Alignment of dynamic cardiac PET images for correction of motion," *IEEE Trans. Nucl. Sci.* **44**, 235–242 (1997).

²¹A. Naum, M. S. Laaksonen, H. Tuunanen, V. Oikonen, M. Teras, J. Kempainen, M. J. Jarvisalo, P. Nuutila, and J. Knuuti, "Motion detection and correction for dynamic (15)O-water myocardial perfusion PET studies," *Eur. J. Nucl. Med. Mol. Imaging* **32**, 1378–1383 (2005).

²²D. L. Collins and A. C. Evans, "Animal: Validation and applications of nonlinear registration-based segmentation," *Int. J. Pattern Recognit. Artif. Intell.* **11**, 1271–1294 (1997).

²³F. Maes, A. Collignon, D. Vandermeulen, G. Marchal, and P. Suetens, "Multimodality image registration by maximization of mutual information," *IEEE Trans. Med. Imaging* **16**, 187–198 (1997).

- ²⁴J. P. Pluim, J. B. Maintz, and M. A. Viergever, "Mutual-information-based registration of medical images: A survey," *IEEE Trans. Med. Imaging* **22**, 986–1004 (2003).
- ²⁵J. Woo, P. J. Slomka, D. Dey, V. Y. Cheng, B. W. Hong, A. Ramesh, D. S. Berman, R. P. Karlsberg, C. C. Kuo, and G. Germano, "Geometric feature-based multimodal image registration of contrast-enhanced cardiac CT with gated myocardial perfusion SPECT," *Med. Phys.* **36**, 5467–5479 (2009).
- ²⁶L. Le Meunier, P. J. Slomka, D. Dey, A. Ramesh, L. E. Thomson, S. W. Hayes, J. D. Friedman, V. Cheng, G. Germano, and D. S. Berman, "Enhanced definition PET for cardiac imaging," *J. Nucl. Cardiol.* **17**, 414–426 (2010).
- ²⁷T. Kokki, H. T. Sipila, M. Teras, T. Noponen, N. Durand-Schaefer, R. Klen, and J. Knuuti, "Dual gated PET/CT imaging of small targets of the heart: Method description and testing with a dynamic heart phantom," *J. Nucl. Cardiol.* **17**, 71–84 (2010).
- ²⁸G. Hermosillo, C. Chef'd'Hotel, and O. Faugeras, "Variational methods for multimodal image matching," *Int. J. Comput. Vis.* **50**, 329–343 (2002).
- ²⁹Y. S. Heo, K. M. Lee, and S. U. Lee, "Illumination and camera invariant stereo matching," in *IEEE Conference on Computer Vision and Pattern Recognition* (Anchorage, Alaska, 2008).
- ³⁰C. Tomasi and R. Manduchi, "Bilateral filtering for gray and color images," in *Sixth International Conference on Computer Vision* (Bombay, India, 1998).
- ³¹G. Germano, J. Erel, H. Lewin, P. Kavanagh, and D. Berman, "Automatic quantitation of regional myocardial wall motion and thickening from gated technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography," *J. Am. Coll. Cardiol.* **30**, 1360–1367 (1997).
- ³²P. Slomka, S. Dorbala, D. Berman, J. Gerlach, G. Germano, and M. DiCarli, "Automated quantification and normal limits for myocardial perfusion stress/rest Rb-82 PET/CT," *J. Nucl. Med.* **50**, 216 (2009).
- ³³Z. Yi and S. Soatto, "Nonrigid registration combining global and local statistics," in *IEEE Conference on Computer Vision and Pattern Recognition* (Miami, FL, 2009).
- ³⁴L. Ibanez, W. Schroeder, L. Ng, and J. Cates, *The ITK Software Guide*, 2nd edition (Kitware, Inc., Clifton Park, NY, 2005).
- ³⁵M. F. Di Carli, S. Dorbala, J. Meserve, G. El Fakhri, A. Sitek, and S. C. Moore, "Clinical myocardial perfusion PET/CT," *J. Nucl. Med.* **48**, 783–793 (2007).
- ³⁶D. S. Berman, A. Abidov, X. Kang, S. W. Hayes, J. D. Friedman, M. G. Sciammarella, I. Cohen, J. Gerlach, P. B. Waechter, G. Germano, and R. Hachamovitch, "Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation," *J. Nucl. Cardiol.* **11**, 414–423 (2004).
- ³⁷C. Jonsson, R. Odh, P. O. Schnell, and S. A. Larsson, "A comparison of the imaging properties of a 3- and 4-ring biograph PET scanner using a novel extended NEMA phantom," *IEEE Nucl. Sci. Symp. Conf. Rec.* **4**, 2865–2867 (2007).
- ³⁸M. Defrise, P. E. Kinahan, D. W. Townsend, C. Michel, M. Sibomana, and D. F. Newport, "Exact and approximate rebinning algorithms for 3-D PET data," *IEEE Trans. Med. Imaging* **16**, 145–158 (1997).
- ³⁹C. Watson, "New, faster, image-based scatter correction for 3D PET," *IEEE Trans. Nucl. Sci.* **47**, 1587–1594 (2000).
- ⁴⁰M. E. Casey and E. J. Hoffman, "Quantitation in positron emission computed tomography: 7. A technique to reduce noise in accidental coincidence measurements and coincidence efficiency calibration," *J. Comput. Assist. Tomogr.* **10**, 845–850 (1986).
- ⁴¹C. Comtat, P. Kinahan, M. Defrise, C. Michel, and D. Townsend, "Fast reconstruction of 3D PET data with accurate statistical modeling," *IEEE Trans. Nucl. Sci.* **45**, 1083–1089 (1998).
- ⁴²J. Cohen, "A coefficient of agreement for nominal scales," *Educ. Psychol. Meas.* **20**, 37–46 (1960).
- ⁴³L. E. Moses, D. Shapiro, and B. Littenberg, "Combining independent studies of a diagnostic test into a summary ROC curve: Data analytic approaches and some additional considerations," *Stat. Med.* **12**, 1293–1316 (1993).
- ⁴⁴H. M. Hudson and R. S. Larkin, "Accelerated image reconstruction using ordered subsets of projection data," *IEEE Trans. Med. Imaging* **13**, 601–609 (1994).
- ⁴⁵A. P. van der Weerd, R. Boellaard, P. Knaapen, C. A. Visser, A. A. Lam-mertsma, and F. C. Visser, "Postinjection transmission scanning in myocardial ¹⁸F-FDG PET studies using both filtered backprojection and iterative reconstruction," *J. Nucl. Med.* **45**, 169–175 (2004).
- ⁴⁶H. Herzog, L. Tellmann, C. Hocke, U. Pietrzyk, M. E. Casey, and T. Kuwert, "NEMA NU2-2001 guided performance evaluation of four Siemens ECAT PET scanners," *IEEE Trans. Nucl. Sci.* **51**, 2662–2669 (2004).
- ⁴⁷B. W. Jakoby, Y. Bercier, C. C. Watson, V. Rappoport, J. Young, B. Bendriem, and D. W. Townsend, "Physical Performance and Clinical Workflow of a new LSO HI-REZ PET/CT Scanner," in *IEEE Nuclear Science Symposium Conference Record* (San Diego, CA, 2006).
- ⁴⁸S. J. Park-Holohan, M. C. Asselin, D. R. Turton, S. L. Williams, S. P. Hume, P. G. Camici, and O. E. Rimoldi, "Quantification of [¹¹C] GB67 binding to cardiac 1-adrenoceptors with positron emission tomography: Validation in pigs," *Eur. J. Nucl. Med. Mol. Imaging* **35**, 1624–1635 (2008).
- ⁴⁹M. D. Walker, M. C. Asselin, P. J. Julyan, M. Feldmann, P. S. Talbot, T. Jones, and J. C. Matthews, "Bias in iterative reconstruction of low-statistics PET data: Benefits of a resolution model," *Phys. Med. Biol.* **56**, 931–949 (2011).
- ⁵⁰G. Wang and J. Qi, "Analysis of penalized likelihood image reconstruction for dynamic PET quantification," *IEEE Trans. Med. Imaging* **28**, 608–620 (2009).
- ⁵¹B. J. Pichler, M. S. Judenhofer, C. Catana, J. H. Walton, M. Kneilling, R. E. Nutt, S. B. Siegel, C. D. Claussen, and S. R. Cherry, "Performance test of an LSO-APD detector in a 7-T MRI scanner for simultaneous PET/MRI," *J. Nucl. Med.* **47**, 639–647 (2006).