Parametric Images of Myocardial Viability Using a Single 15O-H2O PET/CT Scan

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Perfusable tissue index (PTI) is a marker of myocardial viability and requires acquisition of transmission, 15O-CO, and 15O-H2O scans. The aim of this study was to generate parametric PTI images from a 15O-H2O PET/CT scan without an additional 15O-CO scan. Methods: Data from 20 patients undergoing both 15O-H2O and 15O-CO scans were used, assessing correlation between PTI based on 15O-CO (PTICO) and on fitted blood volume fractions (PTIVb). In addition, parametric PTIVb images of 10 patients undergoing 15O-H2O PET/CT scans were generated using basis-function methods and compared with PTICO obtained using nonlinear regression. Simulations were performed to study the effects of noise on PTIVb. Results: Correlation between PTICO and PTIVb was high (r² = 0.73). Parametric PTIVb correlated well with PTICO obtained using nonlinear regression (r² = 0.91). Simulations showed low sensitivity to noise (coefficient of variation < 10% at 20% noise). Conclusion: Parametric PTI images can be generated from a single 15O-H2O PET/CT scan.

Key Words: myocardial viability; PET/CT; parametric images

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Detection of viable myocardium in patients with coronary artery disease is of great clinical importance. In contrast to nonviable myocardium, viable hibernating myocardium is capable of regaining contractility after revascularization, leading to improved cardiac function and associated patient prognosis (1).

PET using 15O-H2O (2,3) is considered to be the gold standard for measuring myocardial blood flow (MBF). In addition, the combination of 15O-H2O MBF and 15O-CO blood volume scans enables the calculation of perfusible tissue index (PTI), a validated marker of myocardial viability (4–10). PTI is defined as the ratio of water perfusible and anatomic tissue fractions (PTFs and ATFs, respectively). PTF is, together with MBF, obtained from a 15O-H2O scan, whereas ATF is calculated by subtracting a normalized 15O-CO blood-pool image from a transmission image. The 15O-CO scan has no clinical use other than measuring blood volume. It prolongs overall study duration and thereby increases risk of patient motion during a study. On stand-alone PET scanners, acquisition of transmission scans using 68Ge sources takes about 10 min, further prolonging study duration. Furthermore, for these scanners it was not possible to generate parametric MBF or PTF images of reasonable quality (11), ruling out parametric PTI images as well. These factors have limited the use of PTI in routine clinical practice.

Introduction of hybrid PET/CT scanners in cardiac PET (12,13), using low-dose (LD) CT for attenuation correction, reduces overall scan time and thus risk of patient motion between emission and transmission scans. Furthermore, improvements in detector efficiency and implementation of basis-function methods (BFM) (11,14) have enabled accurate calculation of MBF at a voxel level, resulting in parametric MBF images of diagnostic quality (15). When calculating MBF images, additional images of PTF, arterial and right-ventricular blood volume (VA and VRV (16), respectively), and spillover fractions are also obtained. Because all these images are calculated from the same dynamic scan, by definition, they do not suffer from interscan patient motion. Consequently, using blood volume fraction images and fast LD CT scans should enable generation of parametric PTI images of diagnostic quality.

The aim of this study was to develop and validate a method for generation of parametric PTI images based on a 15O-H2O PET/CT scan without an additional 15O-CO blood-pool scan.

MATERIALS AND METHODS

Patient Data

Existing data from 20 patients (mean age, 61 y; age range, 34–83 y; 13 men, 7 women) with known or suspected ischemic cardiomyopathy, who had undergone both 15O-H2O and 15O-CO scans on a stand-alone PET scanner, were used. In addition, 10 patients (mean age, 66 y; age range, 55–80 y; 5 men, 5 women) with ischemic cardiomyopathy (ejection fraction < 35%) underwent 15O-H2O PET/CT scans. The study was approved by the

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institutional Medical Ethics Review Committee, and all participants gave written informed consent.

Image Acquisition
Stand-Alone PET. Both $^{15}$O-CO and $^{15}$O-H$_2$O scans were obtained in 2-dimensional acquisition mode using an ECAT EXACT HR+ scanner (Siemens/CTI) according to a protocol that has been described previously (9).

PET/CT. $^{15}$O-H$_2$O scans were acquired using a Gemini TF-64 PET/CT scanner (Philips Healthcare). $^{15}$O-H$_2$O (370 MBq) was administered intravenously, simultaneously starting with a 6-min list-mode emission scan. This PET scan was followed immediately by a slow non–cardiac or respiration-gated LD CT scan (17) to ensure that conditions for this scan were comparable to those for the transmission scan of the stand-alone PET studies. Images were reconstructed into 22 frames of increasing duration, as described previously (17).

Validation of PTI Based on Fitted Blood Volume Fractions (PTIVb)
Arterial and venous time–activity curves ($C_A(t)$ and $C_{RV}(t)$, respectively) were obtained as described previously (17). Traditional ATF ($g\cdot mL^{-1}$) images were constructed as described elsewhere (9); these were rotated to obtain short-axis images of the heart. Sixteen myocardial-segment volumes of interest were drawn manually on ATF images according to the 17-segment model of the American Heart Association, excluding the apex. This volume-of-interest template was projected onto both short-axis transmission and emission scans. Segment time–activity curves were extracted, and MBF ($mL/min/g$), PTF ($g\cdot mL^{-1}$), and $V_A$ and $V_{RV}$ (both dimensionless) were obtained using nonlinear regression (NLR) of the single-tissue-compartment model, with corrections for spillover and partial-volume effects (3,16):

$$C_T(t) = PTF \times MBF \times C_A(t) \otimes \frac{\text{spillover}}{VT} + V_A \times C_A(t) + V_{RV} \times C_{RV}(t),$$

Eq. 1

where $V_A$ represents arterial blood volume and left-ventricular spillover fraction, $V_{RV}$ right-ventricular spillover fraction, and $V_T$ the partition coefficient of water (which was fixed to 0.91 $mL/g^{-1}$). Finally, PTI based on $^{15}$O-CO (PTICO) and PTIVb was calculated using

$$PTICO = \frac{PTF}{ATF} = \frac{PTF}{1.06 \times (Tx_{norm} - CO)},$$

Eq. 2

$$PTIVb = \frac{PTF}{1.06 \times (Tx_{norm} - V_A - V_{RV})},$$

Eq. 3

in which $Tx_{norm}$ (dimensionless) is the normalized transmission scan (9), CO is the normalized $^{15}$O-CO concentration, and 1.06 represents the density of blood. Correlation and agreement of PTIVb and PTICO were assessed using both linear regression with zero intercept and Bland–Altman analysis.

Parametric PET/CT Images
Parametric images were generated using a BFM implementation (11,14,15) of Equation 1, as described previously (17). Attenuation-correction images based on the LD CT scan were normalized, and parametric images of $V_A$ and $V_{RV}$ were subtracted to obtain parametric ATFVb (ATFs based on fitted blood volume fractions) images. PTIVb images were then calculated as the ratio of PTF and ATFCO images. ATF and PTF of voxels with a total blood volume fraction above 0.75, an ATF below 0.25, or a PTF below 0.1 were set to 0 to avoid noise-induced high PTI levels in blood vessels or outside the heart. Average segmental PTIVb was compared with PTIVb calculated from segmental time–activity curves using linear regression with zero intercept, intraclass correlation coefficient (ICC), and Bland–Altman analysis.

Simulations
Simulations were performed for both BFM and NLR using $C_A(t)$ and $C_{RV}(t)$ of a randomly selected patient imaged on the PET/CT scanner. Tissue time–activity curves $C_{tissue}(t)$ were generated for MBF of 1 $mL/min/g$ and PTIVb levels of 0.5 and 1.0, which represent (nontransmural) scar and healthy tissue, respectively. $Tx_{norm}$ was fixed to 1 and considered to be noise-free. Different levels of gaussian noise were added to $C_{tissue}(t)$ (4% and 20%), representing segmental and voxel noise levels, respectively. Lower noise (1%) was added to $C_A(t)$ and $C_{RV}(t)$, as these time–activity curves are based on large volumes of interest. Next, MBF, $V_A$, $V_{RV}$, and PTF were obtained using both NLR and BFM. This process was repeated 1,000 times for each combination of noise on $C_A(t)$, $C_{RV}(t)$, and $C_{tissue}(t)$. Average PTIVb values, together with corresponding bias and coefficient of variation (COV), were calculated for each combination of noise level and PTIVb.

![FIGURE 1. Example of short-axis fractional blood volume (A and C) and ATF (B and D) images obtained from $^{15}$O-CO (A and B) and fitted blood volume fraction (C and D) images of same patient. Images were obtained using stand-alone PET scanner and 10-mm gaussian filter. Also shown is example of short-axis fractional blood volume (E) and ATF (F) images obtained using clinical PET/CT scanner and fitted blood volume fraction images.](http://example.com/figure1)
RESULTS

Validation of PTIVb

Figures 1A and 1B show short-axis blood volume and ATF images, respectively, obtained from a 15O-CO scan acquired on the stand-alone PET scanner. For the same patient and scanner, corresponding images based on fitted blood volume fraction images are shown in Figures 1C and 1D. Finally, blood volume and ATF images based on fitted blood volume fraction images for another patient acquired on the PET/CT scanner are shown in Figures 1E and 1F, respectively. Figure 2 shows correlation and agreement between PTICO and PTIVb. Correlation and agreement were high ($r^2 = 0.73$; ICC = 0.86). The slope of the linear regression was 0.90, which was significantly different from 1 ($P < 0.001$).

Parametric PET/CT Images

A parametric PTIVb image of a typical patient with a known myocardial infarction can be seen in Figure 3. This patient also underwent delayed contrast-enhanced (DCE) MRI, and the corresponding DCE MR image is shown for illustration. Correlation and agreement of PTIVb obtained using NLR on segmental time–activity curves and directly from parametric images were high ($r^2 = 0.91$; ICC = 0.95), as shown in Figure 4. The slope of the linear regression between both parameters was not significantly different from 1 ($P > 0.05$).

Simulations

Table 1 Results of the simulations are summarized in Table 1. Accuracy and precision of both NLR and BFM were high, with no significant bias and a COV less than 10%, even at high noise levels.

DISCUSSION

In the present study, a method for generating parametric PTI images from a single 15O-H2O PET/CT scan was developed and evaluated. This method makes use of fitted blood volume fractions derived from the 15O-H2O scan itself rather than using an (additional) 15O-CO scan.

The slope of the linear fit between PTICO and PTIVb was 0.90 and significantly lower than 1. This may be due to the fact that the VRV represents only spillover from the right ventricle but not the actual venous blood volume fraction (VV) of the myocardium. Actual VV in myocardial tissue is approximately 10% (18), and consequently ATFVb is 10% higher than ATF based on 15O-CO, leading to values 10% lower for PTIVb than for PTICO (i.e., slope of linear fit, 0.90). This overestimation due to VV is, however, also seen in PTF because the model used for kinetic analysis of 15O-H2O data cannot distinguish venous blood from tissue (concentrations are similar). In PTICO, VV is included in PTF but not in ATF—possibly becoming a source of error during PTICO measurements because of the large spread of venous blood volumes (average VV of 0.093 ± 0.103 mL·g⁻¹) (19). Because VV is included in both PTF and ATFVb, PTIVb should be less sensitive to changes in VV.

Using a clinical PET/CT scanner, the proposed method resulted in parametric PTI images of diagnostic quality, enabling simultaneous imaging of myocardial viability and perfusion based solely on a 6-min 15O-H2O scan, followed by a short (<1 min) LD CT scan. The use of a fast LD CT instead of a (longer) transmission scan based on 68Ge sources, as is common in stand-alone PET scanners, reduces the risk...
of patient motion between scans, improving reliability and image quality of parametric PTIVb images. Using a slow-respiration–averaged LD CT scan ensures that the transmission scans are obtained under the same conditions (i.e., normal breathing) as traditional transmission scans. Image quality was further improved by scanning in 3-dimensional mode, because noise-equivalent count rates in 3-dimensional mode are typically 3–5 times higher than rates in 2-dimensional mode. Even in 3-dimensional acquisition mode, however, the need for an additional 15O-CO scan could still hamper accurate parametric images in some patients because of mismatch between scans. The method described here overcomes this issue.

Simulations showed that even at noise levels typically seen in voxel time–activity curves, PTIVb could be calculated with high accuracy and precision (COV, 10%, no significant bias). Furthermore, flow heterogeneity, a possible source of bias in PTI (20), is expected to be much smaller in individual voxels (4 × 4 × 4 mm), reducing possible bias when using parametric PTI images.

Thresholds used for generating parametric PTIVb images were chosen empirically, based on previous results (17). Further studies are needed to optimize these thresholds. Furthermore, it could be of interest to directly compare parametric PTIVb and PTICO images on a clinical PET/CT scanner.

### TABLE 1

<table>
<thead>
<tr>
<th>Method</th>
<th>COV (%)</th>
<th>Relative Bias (%)</th>
<th>Scar</th>
<th>Healthy</th>
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<tbody>
<tr>
<td></td>
<td>ROI</td>
<td>Voxel</td>
<td>ROI</td>
<td>Voxel</td>
</tr>
<tr>
<td>NLR</td>
<td>1.44</td>
<td>7.05</td>
<td>1.60</td>
<td>8.82</td>
</tr>
<tr>
<td></td>
<td>-0.04</td>
<td>-0.82</td>
<td>-0.10</td>
<td>-0.33</td>
</tr>
<tr>
<td>BFM</td>
<td>2.16</td>
<td>10.43</td>
<td>1.77</td>
<td>8.88</td>
</tr>
<tr>
<td></td>
<td>0.09</td>
<td>1.14</td>
<td>-0.12</td>
<td>-0.36</td>
</tr>
</tbody>
</table>

ROI and voxel noise levels were 4% and 20%, respectively.

### CONCLUSION

The proposed method enables calculation of parametric PTIVb images based solely on a single myocardial 15O-H2O scan and an LD CT scan. This method reduces scan duration, radiation dose, and risk of patient motion between scans and enables simultaneous and quantitative assessment of both myocardial perfusion and viability with a 10-min scanning protocol.

### DISCLOSURE STATEMENT

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734.

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