CHAPTER 3

Parametric images of myocardial viability using a single $^{15}$O-H$_2$O PET/CT scan


Hendrik J. Harms
Stefan de Haan
Paul Knaapen
Cornelis P. Allaart
Adriaan A. Lammertsma
Mark Lubberink
ABSTRACT

Perfusable tissue index (PTI) is a marker of myocardial viability and requires acquisition of transmission, $^{15}$O-CO, and $^{15}$O-H$_2$O scans. The aim of this study was to generate parametric PTI images from a $^{15}$O-H$_2$O PET/CT scan without an additional $^{15}$O-CO scan.

Methods: Data from 20 patients undergoing both $^{15}$O-H$_2$O and $^{15}$O-CO scans were used, assessing correlation between PTI based on $^{15}$O-CO (PTI$_{CO}$) and on fitted blood volume fractions (PTI$_{Vb}$). In addition, parametric PTI$_{Vb}$ images of 10 patients undergoing $^{15}$O-H$_2$O PET/CT scans were generated using basis-function methods and compared with PTI$_{Vb}$ obtained using nonlinear regression. Simulations were performed to study the effects of noise on PTI$_{Vb}$.

Results: Correlation between PTI$_{CO}$ and PTI$_{Vb}$ was high ($r^2 = 0.73$). Parametric PTI$_{Vb}$ correlated well with PTI$_{Vb}$ obtained using nonlinear regression ($r^2 = 0.91$). Simulations showed low sensitivity to noise (coefficient of variation, <10% at 20% noise).

Conclusion: Parametric PTI images can be generated from a single $^{15}$O-H$_2$O PET/CT scan.

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.

PET using $^{15}$O-H$_2$O is considered to be the gold standard for measuring myocardial blood flow (MBF). In addition, the combination of $^{15}$O-H$_2$O MBF and $^{15}$O-CO blood volume scans enables the calculation of perfusable tissue index (PTI), a validated marker of myocardial viability. PTI is defined as the ratio of water perfusable and anatomic tissue fractions (PTFs and ATFs, respectively). PTI$_{Vb}$ is, together with MBF, obtained from a $^{15}$O-H$_2$O scan, whereas ATF is calculated by subtracting a normalized $^{15}$O-CO blood-pool image from a transmission image. The $^{15}$O-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 $^{68}$Ge 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, 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, 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) have enable accurate calculation of MBF at a voxel level, resulting in parametric MBF images of diagnostic quality. When calculating MBF images, additional images of PTF, arterial and right-ventricular blood volume ($V_a$ and $V_{RV}$, 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 inter-scan 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 $^{15}$O-H$_2$O PET/CT scan without an additional $^{15}$O-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 $^{15}$O-H$_2$O and $^{15}$O-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 $^{15}$O-H$_2$O PET/CT scans. The study was approved by the 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. 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 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.

### 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. Traditional ATF (g·mL$^{-1}$) images were constructed as described elsewhere; 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·g$^{-1}$·min$^{-1}$), PTF (g·mL$^{-1}$), and VA and VRV (both dimensionless) were obtained using nonlinear regression (NLR) of the single-tissue-compartment model, with corrections for spillover and partial-volume effects:

$$ C_A(t) = \text{PTF} \times \text{MBF} \times C_{A0}(t) \otimes e^{\frac{-\text{MBF}}{V_A}} + V_A \times C_A(t) + V_R \times C_{RV}(t) \quad \text{Eq. 1} $$

where $V_A$ represents arterial blood volume and left-ventricular spillover fraction, $V_R$ 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 (PTI$_{CO}$) and PTI$_{th}$ was calculated using

$$ \text{PTI}_{CO} = \frac{\text{PTF}}{\text{ATF}} = \frac{\text{PTF}}{1.06 \times (T_{\text{transmission}} - \text{CO})} \quad \text{Eq. 2} $$

$$ \text{PTI}_{th} = \frac{\text{PTF}}{1.06 \times (T_{\text{transmission}} - V_R - V_t)} \quad \text{Eq. 3} $$

in which $T_{\text{transmission}}$ (dimensionless) is the normalized transmission scan, CO is the normalized $^{15}$O-CO concentration, and 1.06 represents the density of blood. Correlation and agreement of PTI$_{th}$ and PTI$_{CO}$ 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 of Equation 1, as described previously. Attenuation-correction images based on the LD CT scan were normalized, and parametric images of $V_A$ and $V_R$ were subtracted to obtain parametric ATF$_{th}$ (ATFs based on fitted blood volume fractions) images. PTI$_{th}$ images were then calculated as the ratio of PTF and ATF$_{th}$ 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 PTI$_{th}$ was compared with PTI$_{th}$ 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 image on the PET/CT scanner. Tissue time–activity curves $C_{\text{norm}}(t)$ were generated for MBF of 1 mL·g$^{-1}$·min$^{-1}$ and PTI$_{th}$ levels of 0.5 and 1.0, which represent (nontransmural) scar and healthy tissue, respectively. $T_{\text{transmission}}$ was fixed to 1 and considered to be noise-free. Different levels of gaussian noise were added to $C_{\text{norm}}(t)$ (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, $V_A$, $V_R$, 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 $C_{\text{norm}}(t)$. Average PTI$_{th}$ values, together with corresponding bias and coefficient of variation (COV), were calculated for each combination of noise level and PTI$_{th}$.

### RESULTS

**Validation of PTI$_{th}$**

Figures 1A and 1B show short-axis blood volume and ATF images, respectively, obtained from a $^{15}$O-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 $\text{PTI}_{\text{CO}}$ and $\text{PTI}_{\text{Vb}}$. 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 ($P < 0.001$).

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.

Figure 2: Correlation between segmental PTI, obtained using stand-alone PET scanner, based on fitted $^{15}$O-H$_2$O blood volume fraction and $^{15}$O-CO blood volume images with corresponding Bland–Altman plot (B).

Figure 3: Parametric PTI$_{\text{Vb}}$ image obtained using PET/CT scanner (A) and corresponding DCE MR image (B) of typical patient with myocardial infarction, indicated by reduced PTI$_{\text{Vb}}$ and hyperenhancement in DCE MR image. Arrows indicate myocardial infarction.
**Table 1: COV (%) and Relative Bias (%) Derived from Simulations (n = 1,000 for Each Condition) of Scar and Healthy (PTI = 0.5 and 1.0, Respectively) Tissue**

<table>
<thead>
<tr>
<th>Method</th>
<th>Scar ROI</th>
<th>Scar Voxel</th>
<th>Healthy ROI</th>
<th>Healthy Voxel</th>
</tr>
</thead>
<tbody>
<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.

**Figure 4:** Correlation between average segmental PTI and PTI obtained using NLR (PTINLR) of segmental time–activity curves (A), with corresponding Bland–Altman plot (B) obtained using PET/CT scanner.

**Simulations**

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 $^{15}$O-H$_2$O PET/CT scan was developed and evaluated. This method makes use of fitted blood volume fractions derived from the $^{15}$O-H$_2$O scan itself rather than using an (additional) $^{15}$O-CO scan.

The slope of the linear fit between PTICO and PTI$_{VB}$ was 0.90 and significantly lower than 1. This may be due to the fact that the V$_{RV}$ represents only spillover from the right ventricle but not the actual venous blood volume fraction (V$_{V}$) of the myocardium. Actual V$_{V}$ in myocardial tissue is approximately 10%,$^{18}$ and consequently ATF$_{VB}$ is 10% higher than ATF based on $^{15}$O-CO, leading to values 10% lower for PTI$_{VB}$ than for PTI$_{CO}$ (i.e., slope of linear fit, 0.90). This overestimation due to V$_{V}$ is, however, also seen in PTF because the model used for kinetic analysis of $^{15}$O-H$_2$O data cannot distinguish venous blood from tissue (concentrations are similar). In PTI$_{CO}$, V$_{V}$ is included in PTF but not in ATF—possibly becoming a source of error during PTI$_{CO}$ measurements because of the large spread of venous blood volumes (average V$_{V}$ of 0.093 ± 0.103 mL·g$^{-1}$) ($^{19}$). Because V$_{V}$ is included in both PTF and ATF$_{VB}$, PTI$_{VB}$ should be less sensitive to changes in V$_{V}$.

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 $^{15}$O-H$_2$O 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 $^{68}$Ge sources, as is common in stand-alone PET scanners, reduces the risk of patient motion between scans, improving reliability and image quality of parametric PTI$_{VB}$ images. Using a slowrespiration–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 $^{15}$O-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, PTI$_{VB}$ could be calculated with high accuracy and precision (COV, 10%, no significant
bias). Furthermore, flow heterogeneity, a possible source of bias in PTI,\textsuperscript{20} is expected to be much smaller in individual voxels (4 x 4 x 4 mm), reducing possible bias when using parametric PTI images.

Thresholds used for generating parametric images were chosen empirically, based on previous results.\textsuperscript{17} Further studies are needed to optimize these thresholds. Furthermore, it could be of interest to directly compare parametric PTI\textsubscript{Vb} and PTI\textsubscript{CO} images on a clinical PET/CT scanner.

**CONCLUSION**

The proposed method enables calculation of parametric PTI\textsubscript{Vb} images based solely on a single myocardial \textsuperscript{15}O-H\textsubscript{2}O 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.

**ACKNOWLEDGEMENTS**

We thank Suzette van Balen, Judith van Es, Amina Elouahmani, Femke Jongisma, Nazerah Sais, and Annemiek Stekema for scanning patients; Dr. Gert Luurtsema, Robert Schuit, Kevin Takkenkamp, and Henri Greuter for production of \textsuperscript{15}O-H\textsubscript{2}O; and Dr. Marc Huisman for helpful comments on the manuscript. This work was supported financially by Philips Healthcare.

**REFERENCES**


