Parametric images of myocardial viability using a single $^{[15]O}H_2O$ PET/CT scan

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This research was originally published in JNM. Hendrik J. Harms, Stefan de Haan, Paul Knaapen, Cornelis P. Allaart, Adriaan A. Lammertsma and Mark Lubberink. Parametric images of myocardial viability using a single $^{[15]O}H_2O$ PET/CT scan. JNM. 2011;52:745-749. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.
Abstract

Perfusable tissue index (PTI) is a marker of myocardial viability and requires acquisition of transmission, $[{^{15}}O]CO$ and $[{^{15}}O]H_2O$ scans. The aim of this study was to generate parametric PTI images from a $[{^{15}}O]H_2O$ PET/CT scan without an additional $[{^{15}}O]CO$ scan.

Methods: Data from 20 patients undergoing both $[{^{15}}O]H_2O$ 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 $[{^{15}}O]-H_2O$ PET/CT scans were generated using basis-function methods and compared with PTI$_{Vb}$ obtained using non-linear 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 non-linear 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$_2O$ PET/CT scan.
5.1 Introduction

Detection of viable myocardium in patients with coronary artery disease (CAD) 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 (164).

PET using $^{15}\text{O}H_2\text{O}$ (10, 11) is considered to be the gold standard for measuring myocardial blood flow (MBF). In addition, combination of $^{15}\text{O}H_2\text{O}$ MBF and $^{15}\text{O}CO$ blood volume scans enables calculation of perfusable tissue index (PTI), a validated marker of myocardial viability (11, 109–112, 114, 115). PTI is defined as the ratio of water perfusable (PTF) and anatomical (ATF) tissue fractions. Both PTF and MBF are obtained from a $^{15}\text{O}H_2\text{O}$ scan, whilst ATF is calculated by subtracting a normalized $^{15}\text{O}CO$ blood pool image from a transmission image. The $^{15}\text{O}CO$ 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 $^{68}\text{Ge}$ sources takes about 10 minutes, further prolonging study duration. Furthermore, for these scanners it was not possible to generate parametric MBF or PTF images of reasonable quality (131), ruling out parametric PTI images as well. These factors have limited the routine clinical use of PTI.

Introduction of hybrid PET/CT scanners in cardiac PET (7, 74), utilizing low-dose CT (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 (131, 132) have enabled accurate calculation of MBF at a voxel level, resulting in parametric MBF images of diagnostic quality (81). When calculating MBF images, additional images of PTF, arterial ($V_A$) and right-ventricular ($V_{RV}$, (107)) blood volume and spill-over fractions are also obtained. Since 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 $^{15}\text{O}H_2\text{O}$ PET/CT scan without an additional $^{15}\text{O}CO$ blood pool scan.

5.2 Materials and methods

5.2.1 Patient data

Existing data from 20 patients (age 61, range 34–83, 13 men) with known or suspected ischemic cardiomyopathy, who had undergone both $^{15}\text{O}H_2\text{O}$ and $^{15}\text{O}CO$ scans on a stand-alone PET scanner, were used. In addition, 10 pa-
tients (age 66, range 55–80, 5 men) with ischemic cardiomyopathy (ejection fraction $< 35\%$) underwent $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CT scans. The study was approved by the institutional Medical Ethics Review Committee, and all participants gave written informed consent.

5.2.2 Image acquisition

Stand-alone PET

Both $[^{15}\text{O}]\text{CO}$ and $[^{15}\text{O}]\text{H}_2\text{O}$ scans were performed in 2-dimensional acquisition mode using an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN, USA) according to a protocol that has been described previously (112).

PET/CT

$[^{15}\text{O}]\text{H}_2\text{O}$ scans were acquired using a Gemini TF-64 PET/CT scanner (Philips Healthcare, Best, The Netherlands). 370 MBq $[^{15}\text{O}]\text{H}_2\text{O}$ was administered intravenously, simultaneously starting a 6 min list mode emission scan. This PET scan was followed immediately by a slow non cardiac or respiratory gated LD-CT scan (96) to ensure comparable conditions as for the transmission scan of the stand-alone PET studies. Images were reconstructed into 22 frames of increasing duration as described previously (96).

5.2.3 Validation of PTI$_V_b$

Blood time-activity curves were obtained as described previously (96). Traditional ATF (g mL$^{-1}$) images were constructed as described elsewhere (112). These images were rotated in order to obtain short-axis images of the heart. Sixteen myocardial segment volumes of interest (VOIs) were drawn manually on ATF images according to the 17-segment model of the American Heart Association, excluding apex. This VOI template was projected onto both short-axis transmission and emission scans. Segment TACs were extracted and MBF (mL g$^{-1}$ min$^{-1}$), PTF (g mL$^{-1}$), V$_A$ and V$_RV$ (both dimensionless) were obtained using non-linear regression (NLR) of the single tissue compartment model with corrections for spill-over and partial volume effects (11,107):

\[
C_T(t) = PTF \cdot MBF \cdot C_A(t) \otimes e^{-\frac{MBF}{VT}t} + V_A \cdot C_A(t) + V_{RV} \cdot C_{RV}(t) \tag{5.1}
\]

where $V_A$ represents arterial blood volume and left ventricular spill-over fraction, $V_{RV}$ right ventricular spill-over fraction and $V_T$ the partition coefficient of water which was fixed to 0.91 mL g$^{-1}$. Finally, PTI$_{CO}$ and PTI$_{V_b}$ were calculated using

\[
PTI_{CO} = \frac{PTF}{ATF} = \frac{PTF}{1.06 \cdot (T_{x_{norm}} - CO)} \tag{5.2}
\]

\[
PTI_{V_b} = \frac{PTF}{1.06 \cdot (T_{x_{norm}} - V_A - V_{RV})} \tag{5.3}
\]
5.2. Materials and methods

Figure 5.1. Example of short-axis fractional blood volume (A, C) and ATF (B, D) images obtained from \[^{15}\text{O}]\text{CO} (A, B) and fitted blood volume fraction (C, D) images of the same patient. Images were obtained using a stand-alone PET scanner and were filtered using a 10 mm Gaussian filter. Also shown is an example of short-axis fractional blood volume (E) and ATF (F) images obtained using a clinical PET/CT scanner and fitted blood volume fraction images.

in which \( T_{\text{norm}} \) (dimensionless) is the normalized transmission scan (112), \( \text{CO} \) the normalized \[^{15}\text{O}]\text{CO} \) concentration and 1.06 represents the density of blood. Correlation and agreement of \( \text{PTI}_{\text{Vb}} \) and \( \text{PTI}_{\text{CO}} \) were assessed using both linear regression with zero intercept and Bland-Altman analysis.

5.2.4 Parametric PET/CT images

Parametric images were generated using a basis function method (BFM) implementation (81, 131, 132) of equation 5.1 as described previously (96). 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 \( \text{ATF}_{\text{Vb}} \) images. \( \text{PTI}_{\text{Vb}} \) images were then calculated as the ratio of \( \text{PTF} \) and \( \text{ATF}_{\text{Vb}} \) images. \( \text{ATF} \) and \( \text{PTF} \) of voxels with a total blood volume fraction above 0.75, an \( \text{ATF} \) below 0.25 or a \( \text{PTF} \) below 0.1 were set to 0 to avoid noise induced high PTI levels in blood vessels or outside the heart. Average segmental \( \text{PTI}_{\text{Vb}} \) was compared with \( \text{PTI}_{\text{Vb}} \) calculated from segmental TACs using linear regression with zero intercept as well as ICC and Bland-Altman analysis.
Chapter 5. Generation of parametric PTI images

5.2.5 Simulations

Simulations were performed for both BFM and NLR using $C_A(t)$ and $C_{RV}(t)$ of a randomly selected patient scanned on the PET/CT. Tissue TACs $C_{Tissue}(t)$ were generated for MBF of 1 mL g$^{-1}$ min$^{-1}$ and PTI$V_b$ levels of 0.5 and 1.0, which represent (nontransmural) scar and healthy tissue, respectively. $T_x$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 TACs are based on large VOIs. Next, MBF, $V_A$, $V_{RV}$ and PTF were obtained using both NLR and BFM. This process was repeated 1000 times for each combination of noise on $C_A(t)$, $C_{RV}(t)$ and $C_{Tissue}(t)$. Average PTI$V_b$ values, together with corresponding bias and coefficient of variation (COV), were calculated for each combination of noise level and PTI$V_b$.

5.3 Results

5.3.1 Validation of PTI$V_b$

Figures 5.1A and 5.1B 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 5.1C and 5.1D. 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 5.1E and 5.1F, respectively. Figure 5.3 shows correlation and agreement between PTI$V_b$ and...
5.3. Results

PTI<sub>Vb</sub>. 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).

5.3.2 Parametric PET/CT images

A parametric PTI<sub>Vb</sub> image of a typical patient with a known myocardial infarct can be seen in Figure 5.2. This patient also underwent delayed contrast enhanced (DCE) MRI and the corresponding DCE-MRI image is shown for illustration. Correlation and agreement of PTI<sub>Vb</sub> obtained using NLR on segmental TACs and directly from parametric images were very high (r^2=0.91, ICC=0.95), as shown in Figure 5.4. The slope of the linear regression between both parameters was not significantly different from 1 (p>0.05).

5.3.3 Simulations

Results of the simulations are summarised in Table 5.1. Accuracy and precision of both NLR and BFM were high with no significant bias and a coefficient of variation < 10% even at very high noise levels.

<table>
<thead>
<tr>
<th></th>
<th>Scar ROI</th>
<th>Scar Voxel</th>
<th>Healthy ROI</th>
<th>Healthy Voxel</th>
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<td>7.05</td>
<td>1.60</td>
<td>8.82</td>
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<tr>
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<td>-0.82</td>
<td>-0.10</td>
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<tr>
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<td>1.77</td>
<td>8.88</td>
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<tr>
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<td>3.14</td>
<td>-0.12</td>
<td>-0.56</td>
</tr>
</tbody>
</table>

Figure 5.3. Correlation between segmental PTI, obtained using a stand-alone PET scanner, based on fitted $^{15}$O<sub>H2O</sub> blood volume fraction and $^{15}$O<sub>CO</sub> blood volume images (A) with corresponding Bland-Altman plot (B).
5.4 Discussion

In the present study, a method for generating parametric PTI images from a single $^{15}$O$\text{H}_2\text{O}$ PET/CT scan was developed and evaluated. This method makes use of fitted blood volume fractions derived from the $^{15}$O$\text{H}_2\text{O}$ scan itself rather than using an (additional) $^{15}$O$\text{CO}$ scan. The slope of the linear fit between PTI$_{\text{CO}}$ and PTI$_{\text{VB}}$ was 0.90 and significantly lower than 1. This may be due to the fact that the right ventricular blood volume fraction only represents spill-over 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% (165) and consequently ATF$_{\text{VB}}$ is 10% higher than ATF$_{\text{CO}}$, leading to 10% lower PTI$_{\text{VB}}$ values compared to PTI$_{\text{CO}}$ (i.e. slope of linear fit of 0.90). This overestimation due to $V_V$ is, however, also seen in PTF since the model used for kinetic analysis of $^{15}$O$\text{H}_2\text{O}$ data cannot distinguish venous blood from tissue (concentrations are similar). In PTI$_{\text{CO}}$, $V_V$ is included in PTF but not in ATF. Due to the large spread of venous blood volumes (average $V_V$ of 0.093 ± 0.103 mL/1g) (166) this may become a source of error during PTI$_{\text{CO}}$ measurements. As $V_V$ is included in both PTF and ATF$_{\text{VB}}$, PTI$_{\text{VB}}$ 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$\text{H}_2\text{O}$ 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$_{\text{VB}}$ images. Using a slow respiration averaged LD-CT ensures that the transmission scans are performed under the same conditions (i.e. normal breathing) as traditional transmission scans. Image quality was further improved by scanning in 3D mode, as noise equivalent count (NEC) rates in 3D mode are typically 3 to 5 times higher than in 2D mode. Even in 3D acquisition mode, however, the need for an additional $^{15}$O$\text{CO}$ scan still hamper accurate parametric images in some patients due to mismatch between scans. The method described here overcomes this issue.

Simulations showed that even at noise levels typically seen in voxel TACs,
PTI\textsubscript{Vb} could be calculated with high accuracy and precision (CoV < 10\%, no significant bias). Furthermore, flow heterogeneity, a possible source of bias in PTI (116), is expected to be much smaller in individual voxels (4x4x4 mm), reducing possible bias when using parametric PTI images.

Thresholds used for generating parametric images were chosen empirically, based on previous results (96). 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.

5.5 Conclusion

The proposed method enables calculation of parametric PTI\textsubscript{Vb} images based solely on a single myocardial \textsuperscript{15}O\textsubscript{2}O scan and a low-dose CT scan. This 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 minutes scanning protocol.

Acknowledgements

The authors would like to thank Suzette van Balen, Judith van Es, Amina Elouahmani, Femke Jongsma, Nazerah Sais and Annemiek Stiekema for scanning patients, dr. Gert Luurtsema, Robert Schuit, Kevin Takkenkamp and Henri Greuter for production of \textsuperscript{15}O\textsubscript{2}O and dr. Marc Huisman for helpful comments on the manuscript. This work was supported financially by Philips Healthcare.