Myocardial O2 supply and O2 utilization of the right ventricle in pulmonary arterial hypertension
Wong, Y.Y.

2012

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain.
• You may freely distribute the URL identifying the publication in the public portal.

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:
vuresearchportal.ub@vu.nl

Download date: 19. Apr. 2022
MYOCARDIAL OXYGEN EXTRACTION FRACTION MEASURED USING BOLUS INHALATION OF $^{15}$O-OXYGEN GAS AND DYNAMIC POSITRON EMISSION TOMOGRAPHY

Mark Lubberink, Yeun Ying Wong, Pieter G Raijmakers, Robert C Schuit, Gert Luurtsema, Ronald Boellaard, Paul Knaapen, Anton Vonk-Noordegraaf, Adriaan A Lammertsma

ABSTRACT

Introduction
The aim of this study was to determine accuracy of oxygen extraction fraction (OEF) measurements using a dynamic scan protocol following bolus inhalation of $^{15}$O$_2$. The method of analysis was optimised by investigating potential re-use of myocardial blood flow (MBF), perfusable tissue fraction (PTF), and blood and lung spill-over factors derived from separate $^{15}$O-water and $[^{15}O]$CO scans.

Methods
Simulations were performed to assess accuracy and precision of OEF for a variety of models in which different parameters from $^{15}$O-water and $[^{15}O]$CO scans were re-used. Reproducibility was assessed in eight patients who underwent one 10 min dynamic scan after bolus injection of 1.1 GBq $^{15}$O-water, two 10 min dynamic scans after bolus inhalation of 1.4 GBq $^{15}$O$_2$, and a 6 min static scan after bolus inhalation of 0.8 GBq $[^{15}O]$CO for ROI definition.

Results
Simulations showed that accuracy and precision were lowest when all parameters were determined from the $[^{15}O]$O$_2$ scan. Optimal accuracy and precision of OEF was obtained when fixing MBF, PTF and blood spill-over to values derived from a $^{15}$O-water and estimating spill-over from the pulmonary gas volume using an attenuation map. This was confirmed in the patient study, showing an OEF test-retest variability of 13% for whole myocardium. Correction of spill-over from pulmonary gas volume requires correction of the lung time-activity curve for pulmonary blood volume, which could equally well be obtained from a $^{15}$O-water rather than $[^{15}O]$CO scan.

Conclusion
Measurement of OEF is possible using bolus inhalation of $[^{15}O]$O$_2$ and a dynamic scan protocol, with optimal accuracy and precision when other relevant parameters, such as MBF, are derived from an additional $^{15}$O-water scan.
INTRODUCTION

Oxygen extraction fraction (OEF; an overview of abbreviations is given in Supplemental Table S3.1) is an important parameter in describing myocardial function. Oxygen delivery to the healthy myocardium is regulated by varying myocardial blood flow (MBF) in response to changes in oxygen demand. In diseased myocardium, however, this relationship may be disturbed and measurement of myocardial oxygen consumption could provide additional information, as oxygen supply to the heart may also be moderated by changes in OEF.

Measurement of regional myocardial oxygen consumption has previously been described using steady-state or autoradiographic methods and applying continuous inhalation of $^{15}$O$_2$ oxygen gas. Apart from the $^{15}$O$_2$ scan, this protocol requires additional $^{15}$O-water and $^{15}$O-CO scans to measure MBF and blood volume, respectively. Many current low-energy proton cyclotrons, however, cannot provide a steady-state delivery of $^{15}$O$_2$ to the patient. The availability of a bolus inhalation protocol would enable more widespread use of $^{15}$O$_2$ gas measurements. Such a protocol has previously been described for cerebral oxygen consumption, but its use for myocardial imaging has not been described and presents a number of additional challenges, mainly because of increased scatter and image noise, and the presence of large amounts of radioactivity in the lungs during the bolus inhalation period. The measured radioactivity concentration in the myocardial wall is affected both by the limited spatial resolution of PET relative to the thickness of the myocardium and by spill-over from the left- and right ventricular cavities as well as from the lung. As blood volume and spill-over factors can be determined directly from a dynamic $^{15}$O-water scan or even from the $^{15}$O$_2$ scan itself, it may be possible to obtain OEF from a smaller number of scans. Furthermore, since the total injected amount of activity in a dynamic protocol is considerably smaller than that in a steady-state protocol, a noticeable reduction in radiation burden to the patient can be achieved, especially if the $^{15}$O-CO scan can be omitted.

The aim of the present study was to establish the optimal method for analysing dynamic PET scans after bolus inhalation of $^{15}$O$_2$, especially in relation to possibly re-using parameters derived from $^{15}$O-water and/or $^{15}$O-CO scans. To this end, accuracy and precision of various OEF measures, derived from a dynamic scanning protocol, were assessed using both simulations and a test-retest study.

METHODS

Subjects

Scan data from 8 patients (age 45 ± 12 years) included in a clinical study on pulmonary hypertension was used in the present study. None of the patients had a documented history of cardiovascular disease. The clinical study had been approved by the Medical Ethics Review Committee of the VU University Medical Center and all patients gave their informed consent prior to inclusion.

Gas tracer production and administration

Gas tracer production and gas delivery system (GDS) have been described in detail elsewhere. After tracer production, $^{15}$O-labelled gases were collected in an empty rubber balloon within
a sealed Perspex container and allowed to decay to the prescribed dose. Administration to the patient took place by forcing air into the Perspex container, which directed the $^{15}$O-labelled gas from the balloon into the patient’s nasal oxygen catheter (Unomedical, Denmark). Previous studies have shown that approximately 20% of the measured dose in the GDS is actually administered to the patient.\(^5\)

**Scanning procedure**

Each patient underwent one 10 min dynamic emission scan after bolus injection of 1.1 GBq $^{15}$O-water, two 10 min dynamic emission scans after bolus inhalation of approximately 1.4 GBq $[^{15}\text{O}]\text{O}_2$, and a 6 min static emission scan starting 1 min after bolus inhalation of approximately 0.8 GBq $[^{15}\text{O}]\text{C}^{15}\text{O}$. After each scan, radioactivity was allowed to decay for 10 min before start of the next scan. Dynamic scans consisted of 40 frames with frame durations increasing from 5 s during the first minute to 30 s at the end of the scan. Scans were acquired on an ECAT EXACT HR+ scanner (Siemens, Knoxville, TN, USA) in 2D acquisition mode.\(^6\) Five blood samples were taken from the radial artery during both $^{15}$O scans for measuring $[^{15}\text{O}]\text{O}_2$ and re-circulating $^{15}$O-water contributions to the total blood radioactivity concentration. An additional blood sample was taken for measurement of blood oxygen content. An 80 million counts (10-15 min) transmission scan, obtained using rotating $^{68}$Ge rod sources, was performed before the $^{15}$O-water scan and was used for attenuation correction of all subsequent scans. Prior to the $[^{15}\text{O}]\text{CO}$ scan, a short 5 min transmission scan was performed to verify patient positioning. Dynamic images were reconstructed using filtered back projection applying a Hanning filter with a cut-off at 0.5 of the Nyquist frequency. $[^{15}\text{O}]\text{CO}$, attenuation images ($\mu$-maps) and summed $^{15}$O-water and $[^{15}\text{O}]\text{O}_2$ images were reconstructed using ordered subsets estimation maximization with 2 iterations and 16 subsets. The summed images were used for verification of ROI positioning.

**Region of interest (ROI) definition**

For ROI definition, an anatomical tissue fraction (ATF) image was calculated by subtracting the $[^{15}\text{O}]\text{CO}$ image, normalized to the $\mu$-value in the left ventricle, from the corresponding $\mu$-map.\(^7\) This procedure results in an image that only shows the myocardial wall (i.e. extravascular tissue). Anterior, posterior, lateral and septal ROIs were defined on apical, basal and mid short-axis slices of the ATF images, and subsequently transferred to all other scans, which had undergone the same short-axis transformation. Similar ROIs were placed over the right ventricular wall, which was possible because these patients had an enlarged right ventricle with right ventricular wall thickness comparable to that of the left ventricle. ROI positioning was verified on the summed images. For both $^{15}$O-water and $[^{15}\text{O}]\text{O}_2$, a 1 cm diameter circular ROI was drawn over the ascending aorta in approximately 10 consecutive image planes in the frame where the first pass of the bolus was best seen. This ROI was transferred to all dynamic frames to create an arterial whole blood time-activity curve (TAC) $C_A(t)$. In addition, an ROI was drawn in three image planes in the right ventricular cavity and transferred to all dynamic frames to create the right ventricular AC $C_{RV}(t)$. Similarly, a large circular ROI was drawn in three planes in the lungs to create a lung TAC $C_L(t)$.
Input functions

Applying a plasma to whole blood ratio of 1.12 for $^{15}$O-water, and with plasma containing only recirculating $^{15}$O-water, the absolute $[^{15}\text{O}]\text{O}_2$ activity concentration $C_A^\text{O}(t)$ in blood was calculated for each of the five measured samples as:

$$C_A^\text{O}(t) = C_A^\text{wb}(t) - 1.12 \cdot C_A^\text{pl}(t) \quad (3.1)$$

Here, $C_A^\text{wb}(t)$ and $C_A^\text{pl}(t)$ are radioactivity concentrations in whole blood and plasma samples, respectively. Division of both sides of the equation with $C_A^\text{wb}$ gives:

$$\frac{C_A^\text{O}(t)}{C_A^\text{wb}(t)} = 1 - 1.12 \frac{C_A^\text{pl}(t)}{C_A^\text{wb}(t)} \quad (3.2)$$

A sigmoid function was fit to the right side of equation (2) and evaluated at all frame midpoints times. Multiplication of the measured arterial blood TAC $C_A^\text{O}(t)$ with this fit function yielded the $^{15}$O$_2$ input curve $C_A^\text{O}(t)$. The (recirculating) $^{15}$O-water input curve $C_A^\text{W}(t)$ was then evaluated at all frame midpoints by fitting the solution of a two compartment model to the five measured data points $C_A^\text{W}(t)$, using a simplified version of the model suggested by Kudomi et al., assuming a constant production rate of $^{15}$O-water:

$$C_A^\text{W}(t) = \phi C_A^\text{O}(t) \otimes e^{-\theta t} \quad (3.3)$$

In equation 3, $\phi$ and $\theta$ describe the average rate of conversion of $[^{15}\text{O}]\text{O}_2$ into $^{15}$O-water and the clearance rate of $^{15}$O-water from blood, respectively.

Data analysis

Myocardial perfusion model

Kinetics of $^{15}$O-water in the heart were described by the standard single tissue compartment model, applying corrections for left- and right-ventricular spill-over fractions $V_a$ and $V_{RV}$, respectively, and for perfusable tissue fraction $\alpha$, which has the following solution:

$$C_{\text{myo}}^\text{PET}(t) = \alpha F C_A^\text{O}(t) \otimes e^{-\frac{F}{V_T} t} + V_A C_A^\text{O}(t) + V_{RV} C_{RV}^\text{W}(t) \quad (3.4)$$

Here, $F$ is myocardial blood flow and $C_{\text{myo}}^\text{PET}(t)$ is the radioactivity concentration in the myocardium as measured by PET.

Oxygen extraction fraction model

The kinetics of $[^{15}\text{O}]\text{O}_2$ in the heart can be described by:

$$\frac{dC_{\text{myo}}(t)}{dt} = EFC_A^\text{O}(t) + Fc_A^\text{W}(t) - \frac{F}{V_T} C_{\text{myo}}(t) \quad (3.5)$$

The first term on the right hand side describes the extraction of oxygen which is assumed to be instantaneously converted into water in the myocardium. The second term represents uptake of recirculating water and the last term clearance of water from the myocardium. Here, $C_{\text{myo}}(t)$ is the radioactivity concentration in the myocardial wall and $E$ is oxygen extraction fraction. The solution of this differential equation is written as follows:

$$C_{\text{myo}}(t) = EFC_A^\text{O}(t) \otimes e^{-\frac{F}{V_T} t} + Fc_A^\text{W}(t) \otimes e^{-\frac{F}{V_T} t} \quad (3.6)$$
In addition to spill-over from the ventricles, spill-over from activity in the lungs $C_L(t)$ must be taken into account. Furthermore, a term must be added accounting for the venous blood concentration of $[^{15}\text{O}]/_{2}$ due to its incomplete extraction. This results in the following total PET signal:

$$C_{\text{mvo}}^{\text{PET}}(t) = \alpha F C_A(t) \odot \frac{1}{1 + e^{-t/\tau}} + \alpha F C_L(t) \odot \frac{1}{1 + e^{-t/\tau}} + \alpha V_v(1 - e^{-t}) C_A(t) + V_L C_L(t) + V_{rv} C_{rv}(t)$$ (3.7)

In equation 3.7, $V_v$ is the venous blood volume in the myocardial wall, which has been estimated at 0.1 ml/g. If $F$ and $\alpha$ are known, this equation can be solved by direct matrix inversion or by a non-negative linear least squares fit to prevent noise-induced negative parameter values.

**Lung spill-over** As suggested previously, spill-over from gas radioactivity in the lungs can be corrected for using the $\mu$-map to determine $V_G$:

$$V_G = 1 - \frac{V_{\text{air}}}{V_{lv}}$$ (3.8)

Since this implicitly corrects only for spill-over due to radioactivity in the gas volume in the lungs, not the total lung activity $C_L(t)$ but the time-activity curve of the gas volume $C_G(t)$ should be used in equation 3.7:

$$C_G(t) = \frac{\lambda^G}{C^G(t) - \lambda^G C^V(t)}$$ (3.9)

Here, $V_b^L$ and $V_g^L$ are the fractional blood and gas volume in the lungs, respectively. The pulmonary blood volume can either be determined from the $C^{15}$O scan:

$$\lambda^B = \frac{C^L}{C^G}$$ (3.10)

or using the spill-over parameters as determined in the $^{18}$O-water scan. Then, the gas volume $TAC C_G(t)$ is calculated as:

$$C_G(t) = \frac{C_G(t) - V_A C_A(t) - V_{rv} C_{rv}(t)}{V_G}$$ (3.11)

Here, $V_A^L$ and $V_{rv}^L$ are arterial and pulmonary circulation blood volumes, respectively, in the lung. In both cases, instead of using $V_G$ as based on the $\mu$-map, $V_v(t)$ can be included as a fit parameter in solving equation 3.7.

**Parameter estimation**

A number of different approaches in fitting equation 3.7 to the PET data were investigated in terms of re-using parameters previously determined from $^{15}$O-water and/or $[^{15}\text{O}]/_{2}$ scans (Table 3.1). Model 1, which is essentially the model used by Iida et al. for the steady state method, re-uses MBF and PTF from the $^{18}$O-water scan and uses blood volume and gas spill-over as determined from $[^{15}\text{O}]/_{2}$ scan and $\mu$-map (equations 3.8 and 3.10). Models 2 and 3 re-use MBF, PTF, $V_A^L$ and $V_{rv}^L$ from the $^{18}$O-water scan, and include $V_G$ as determined from the $\mu$-map, with lung blood volume either based on the $[^{15}\text{O}]/_{2}$ scan (equation 3.9 and 3.10; model 2) or the $^{18}$O-water scan (equation 3.11; model 3). Models 4 and 5 are similar to models 2 and 3, but now $V_v$ is estimated as a fit parameter in equation 3.7, i.e. in the operational equation for the $[^{15}\text{O}]/_{2}$ scan. Models 6 and 7 re-use MBF and PTF, or only MBF, respectively, from the $^{18}$O-water scan. In model
MYOCARDIAL OEF AND DYNAMIC [15O]2-GAS PET

All parameters were determined from the [15O]O2 and [15O]CO scans, applying boundaries at ±10% (F) or ±25% (α, VA, VRV) from the results of the 15O-water scan. This would allow for compensation for inaccurate ROI placement due to small patient movements between scans, or for small physiological changes between scans. In model 9, all parameters were determined from the [15O]O2 and [15O]CO scans without any information from the 15O-water scan. Model 9 would allow measurement of all parameters without an additional 15O-water scan, whereas models 3 and 5 would obviate the need for an additional [15O]CO scan. For models 8 and 9, parameters were estimated using non-linear regression of equation 3.7. In approaches 1 - 7, which are essentially linear problems since MBF is re-used from the results of the 15O-water scan, parameters were estimated using non-negative least squares. All linear models were evaluated with (1 - 7) and without (1' - 7') accounting for venous [15O]O2 due to incomplete extraction of [15O]O2. Only a limited number of these models, chosen based on the results of the simulation study, was used for analysis of patient data.

Simulations

[15O]O-water and [15O]O2 TACs (n=1000) were calculated according to equations 3.4 and 3.7, with randomly chosen parameters 0.3 < MBF < 5 ml g⁻¹ min⁻¹, 0.3 < OEF < 1, 0.1 < VA < 0.3, 0.1 < VRV < 0.3 or VRV = 0, 0.3 < PTF < 1.0, and 0.15 < VL < 0.25. For each [15O]O-water and [15O]O2 TAC generated, normally distributed noise was added corresponding to typical noise levels found in segmental TACs in patients (average SD 10% and 20% in the last 20 frames for [15O]O-water and [15O]O2, respectively). Parameters used for generating [15O]O-water and [15O]O2 TACs were either identical, assuming both no physiological changes between scans and no patient movements, or were varied with randomly distributed changes with a standard deviation of 5% (F, PTF) or 10% (VA, VRV, VL). Simulated TACs were analysed according to the approaches described above and correlation and agreement between true and simulated OEF were addressed using linear regression and Bland-Altman plots. In addition, accuracy and precision of OEF for typical parameter values found in left (LVW) and right (RVW) ventricular walls, and septum were estimated using

### Table 3.1 Parameter estimation

<table>
<thead>
<tr>
<th>Model</th>
<th>OEF</th>
<th>MBF</th>
<th>α</th>
<th>VA</th>
<th>VRV</th>
<th>V̅L/V̅L</th>
<th>Nr*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>[15O]O2</td>
<td>[15O]-water</td>
<td>[15O]-water</td>
<td>[15O]-water</td>
<td>[15O]-water</td>
<td>C15O/μ-map</td>
<td>1</td>
</tr>
</tbody>
</table>


*Number of parameters to be estimated from [15O]O2 scan

**5 parameters estimated within limits from results of [15O]O-water scan
simulations of 100 noisy TACs with MBF=1, OEF=0.6, $V_A=0.25$, $V_L=0.2$, and $V_{RV}=0.15$ or $V_{RV}=0$; or MBF=0.5, OEF=0.6, $V_A=0.1$, $V_{RV}=0.2$, and $V_L=0.2$, respectively.

**Test-retest study**

The level of agreement between test and retest values was assessed using the intra-class correlation coefficient (ICC) with a 2-way random model with absolute agreement. In addition, Bland-Altman analysis was used, plotting the percentage difference between two measured values against the mean of both. Systematic bias and a possible dependency of agreement on absolute values of extraction fraction were assessed by linear regression. In addition, the repeatability coefficient was calculated as the standard deviation of the mean relative difference between test and retest OEF values.

**RESULTS**

Figure 3.1 shows $C_{AV}(t)/C_{AW}(t)$, the fit used to determine the $^{15}$O$_2$ input curve, and the compartment model fit used to estimate the $^{15}$O-water water input curve, for a typical patient during inhalation of $^{15}$O$_2$. Clearly, the compartment model of equation 3 gave a good description of the measured activity concentrations of $^{15}$O-water.

Results of the simulations are shown in Figure 3.2 and Figures S3.1 and S3.2. In the simulations, both models 2 and 3 and models 4 and 5 were indistinguishable from each other since no $^{15}$O$^2$CO

---

Figure 3.1 Ascending aorta, right ventricle and lung time-activity curves (A), ratio of $^{15}$O$_2$ to whole blood concentrations (B), compartment model fit of $^{15}$O-water radioactivity concentration in blood (C), and resulting $^{15}$O$_2$ and $^{15}$O-water input functions (D) for a typical patient during $^{15}$O$_2$ inhalation.
scan was simulated and identical lung blood volumes were used, so only values for models 2 and 4 are reported. Clearly, re-use of parameters from the 15O-water scan led to more robust values of OEF, whereas determining all parameters from the 15O-scans gave the least robust results, as seen in Figure 3.2. As shown in Figure 3.2 and Figure S3.1, omission of a correction for venous [15O]O2 (due to limited extraction of [15O]O2) in models 2', 3' and 4' leads to a positive bias in OEF. This bias is inversely proportional to OEF itself, increasing to around 25% for OEF values of 0.3 and therefore these models were excluded from further evaluation. Furthermore, as shown in Figure S3.2, the impact of movements or small physiological changes on the accuracy of OEF measurements is still smaller for model 2 (and 3-5, data not shown), which re-uses parameters from the 15O-water scan, than for model 8, which allows for some variation of these parameters. Models 2 and 4, which differ only in the way of determining lung spill-over (from μ-map or as fit parameter, respectively) performed equally well in the simulation study.

Based on the results of the simulations, only models 1-5 were used for analysis of patient data, all including a correction for non-complete extraction of [15O]O2. Figure 3.3 shows test-retest variability of OEF values using these five models. Intraclass correlation coefficients are given in Table 3.2. The best reproducibility was found for models 2 and 3, which re-use MBF, PTF,
VA and $V_{uv}$ from the $^{15}$O-water scan and which use a lung spill-over factor determined from the μ-map. Variability in OEF determined using models 4 or 5, which include $V_L$ as a fit parameter, was slightly larger than for models 2 or 3, especially in the LVW. Correlation and Bland Altman plots of model 3 are shown in Figure 3.4.

The mean test-retest variability for individual myocardial segments was 27% using models 2 and 3, compared to 13% for the whole myocardium. The repeatability coefficient for the whole myocardium was 29% using models 2 and 3. Figure 3.5 shows mean OEF values, obtained with models 1 - 5, for the present patient population.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Av myocard</td>
<td>0.96</td>
<td>0.75</td>
<td>0.70</td>
<td>0.68</td>
<td>0.66</td>
</tr>
<tr>
<td>LVW+Septum</td>
<td>0.76</td>
<td>0.85</td>
<td>0.84</td>
<td>0.84</td>
<td>0.72</td>
</tr>
<tr>
<td>LVW</td>
<td>0.99</td>
<td>0.75</td>
<td>0.80</td>
<td>0.71</td>
<td>0.14</td>
</tr>
<tr>
<td>RVW</td>
<td>0.63</td>
<td>0.54</td>
<td>0.57</td>
<td>0.54</td>
<td>0.58</td>
</tr>
<tr>
<td>Septum</td>
<td>0.87</td>
<td>0.70</td>
<td>0.72</td>
<td>0.78</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**Table 3.2** Intraclass correlation coefficients.

---

$V_A$ and $V_{uv}$ from the $^{15}$O-water scan and which use a lung spill-over factor determined from the μ-map. Variability in OEF determined using models 4 or 5, which include $V_L$ as a fit parameter, was slightly larger than for models 2 or 3, especially in the LVW. Correlation and Bland Altman plots of model 3 are shown in Figure 3.4.

The mean test-retest variability for individual myocardial segments was 27% using models 2 and 3, compared to 13% for the whole myocardium. The repeatability coefficient for the whole myocardium was 29% using models 2 and 3. Figure 3.5 shows mean OEF values, obtained with models 1 - 5, for the present patient population.
DISCUSSION

The present study describes a method for measuring OEF using dynamic PET scans after bolus inhalation of $^{[15\text{O}]}\text{O}_2$. Re-using MBF, PTF and blood spill-over fractions estimated from an additional $^{[15\text{O}]}$-water scan, with lung spill-over estimated using a $\mu$-map, yielded optimal precision and accuracy, with a test-retest variability of 13% and a repeatability coefficient of 29% for whole myocardium with slightly larger values for left- and right-ventricular free walls and septum. These values cannot be compared with steady-state OEF values, since no test-retest studies in patients have been reported for this method. Although the present variability is larger than reported repeatability coefficient values of around 20% for e.g. $^{[15\text{O}]}$-water tumour perfusion measurements $^{10}$, or proliferation measurements using $^{[18\text{F}]}\text{FLT}$, $^{14}$ it is acceptable for inter-group comparisons. On a myocardial segment basis, however, test-retest variability increases to 27%. Moreover, in many cases model fits of single segments resulted in physiologically meaningless values of OEF>1 or OEF close to zero. Therefore, measurement of OEF using the present method is limited to larger ROIs such as the whole left- or right-ventricular wall or septum. On the other hand, if with the latest generation PET-CT scanners a similar improvement in $^{[15\text{O}]}\text{O}_2$ image quality can be achieved as for $^{[15\text{O}]}$-water, $^{11}$ improved quantification in individual myocardial segments may become feasible using these newer PET systems, possibly even only based on a single $^{[15\text{O}]}\text{O}_2$ scan. A limitation of the present work is that it is based on a small patient group. There is a need for larger studies in different patient populations to confirm the presented results, ideally in comparison to the steady-state method.

There were no significant differences in OEF values between the various methods, except for model 1 (Figure 3.5). Model 1 provided much lower OEF values than the other models. Mean (± SD) values of OEF in left ventricle and septum for models 2 - 4 (e.g. 0.66 ± 0.12 and 0.68 ± 0.11 for models 2 and 3, respectively) were not significantly different from those reported previously (0.60 ± 0.1) for healthy volunteers using the steady state method. $^{1}$ Since the results of the steady-state method corresponded well with invasive measurements, $^{2}$ and possibly a slightly higher OEF could be expected in the present patient group, the lower OEF results of model 1 (0.51 ± 0.23) are physiologically not very plausible. The much larger range of OEF values found with model 1 also explains the high ICC values for this model, which erroneously suggest good reproducibility. Probably, even small differences in ROI positioning between $^{[15\text{O}]}\text{CO}$ and $^{[15\text{O}]}\text{O}_2$ scans cause large errors in patient studies when using this method.

Methods that fit for lung spill-over $V_L$ show poorer reproducibility than methods that use a lung spill-over factor determined from the $\mu$-map. Models 6 and 7, which also include blood spill-over as fit parameters, showed very poor accuracy (Figures 3.2 and 3.3) in the simulations and were not evaluated in the clinical study. The similar shape of the lung, arterial blood, and right-ventricular TACs, as clearly shown in Figure 3.1A, along with the relatively high noise level of myocardial TACs, makes them effectively indistinguishable in the fit procedure, which also affects the accuracy and precision of the other parameters.

Model 3 allows for measurements of OEF based only on $^{[15\text{O}]}\text{O}_2$ and $^{[15\text{O}]}$-water scans, obviating the need for an additional $^{[15\text{O}]}\text{CO}$ scan. In the present study, the $^{[15\text{O}]}\text{CO}$ images were used to create an ATF image, on which ROIs were defined. In principle, parametric MBF or PTF images could be used for ROI definition instead. Although it was not possible to construct parametric MBF and PTF images of sufficient image quality using the 2D PET data in the present study, state-of-the-art PET-CT scanners with much improved scan statistics do
allow for generation of good quality parametric images and [¹⁵O]CO scans will no longer be needed for delineation of myocardial segments. Apart from increasing patient comfort because of the shorter duration of the total procedure, this also decreases the possibility of errors due to patient movement between the different scans. In addition, the major part of the total radiation dose is due to the [¹⁵O]CO scan. Although the availability of OEF measurements using PET may be expanded using the current method because it obviates the need of a [¹⁵O]CO scan, uses a standard PET cyclotron, and results in reduced radiation dose, feasibility of routine clinical use is dependent on improved automation of data analysis and the availability of a gas administration system.

The total effective dose to the patient in a continuous infusion/inhalation protocol consisting of [¹⁵O]-water, [¹⁵O]O₂ and [¹⁵O]CO scans has been reported to be 10.5 mSv. Omission of the [¹⁵O]CO scan and using bolus administrations of 1.1 GBq [¹⁵O]-water and 1.4 GBq [¹⁵O]O₂, followed by dynamic scanning, leads to a considerable reduction in effective dose to approximately 2 mSv. Using the latest generation PET-CT scanners, absorbed doses could be reduced further due to the possibility of using smaller amounts of radioactivity.

**Conclusion**
Measurement of OEF is possible using a dynamic scan protocol after bolus inhalation of [¹⁵O]O₂ when MBF, PTF and blood spill-over factors are derived from an additional [¹⁵O]-water scan and spill-over from pulmonary gas volume is estimated from an attenuation map, with correction for pulmonary blood volume based on the [¹⁵O]-water scan. Omission of a [¹⁵O]CO blood volume scan reduces the risk of errors due to patient movement between scans. The proposed method results in a significant reduction in radiation burden to the patient compared to a continuous infusion/inhalation protocol, and leads to improved feasibility of oxygen consumption measurements using [¹⁵O]O₂ and PET.

**ACKNOWLEDGEMENTS**
The authors would like to thank Suzette van Balen and Femke Jongsma for performing the scans and Kevin Takkenkamp and Henri Greuter for producing [¹⁵O]-labelled tracers.
REFERENCE LIST


**SUPPLEMENTARY DATA**

### Table S3.1 Glossary of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>OEF, E</td>
<td>Oxygen extraction fraction</td>
</tr>
<tr>
<td>MBF, F</td>
<td>Myocardial blood flow</td>
</tr>
<tr>
<td>PTF, α</td>
<td>Per fusable tissue fraction</td>
</tr>
<tr>
<td>$C_a^{\text{O}}(t)$</td>
<td>Arterial $^{15}$O$_2$ activity concentration</td>
</tr>
<tr>
<td>$C_a^{\text{H}}(t)$</td>
<td>Arterial $^{15}$O-water activity concentration</td>
</tr>
<tr>
<td>$C_a^{\text{wb}}(t)$, $C_a(t)$</td>
<td>Arterial whole blood activity concentration</td>
</tr>
<tr>
<td>$C_a^{\text{p}}(t)$</td>
<td>Arterial plasma activity concentration</td>
</tr>
<tr>
<td>$C_v(t)$</td>
<td>Right ventricle activity concentration</td>
</tr>
<tr>
<td>$C_l(t)$</td>
<td>Lung activity concentration</td>
</tr>
<tr>
<td>$V_v$</td>
<td>Activity concentration in lung gas volume</td>
</tr>
<tr>
<td>$V_d$</td>
<td>Distribution volume (partition coefficient of water)</td>
</tr>
<tr>
<td>$V_s$</td>
<td>Fractional arterial blood volume and spill-over fraction</td>
</tr>
<tr>
<td>$V_{iv}$</td>
<td>Right ventricle spill-over fraction</td>
</tr>
<tr>
<td>$V_v$</td>
<td>Fractional venous blood volume</td>
</tr>
<tr>
<td>$V_l$</td>
<td>Lung spill-over fraction (fit parameter)</td>
</tr>
<tr>
<td>$V_g$</td>
<td>Gas spill-over fraction (from μ-map)</td>
</tr>
<tr>
<td>$V_a^{\text{L}}$</td>
<td>Fractional arterial lung blood volume (from $^{18}$O-water scan)</td>
</tr>
<tr>
<td>$V_{iv}^{\text{L}}$</td>
<td>Fractional pulmonary circulation lung blood volume (from $^{18}$O-water scan)</td>
</tr>
<tr>
<td>$V_c^{\text{L}}$</td>
<td>Fractional total lung blood volume (from $^{15}$O-CO scan)</td>
</tr>
<tr>
<td>$V_v^{\text{L}}$</td>
<td>Fractional lung gas volume</td>
</tr>
<tr>
<td>$C_l^{\text{CO}}$</td>
<td>Lung activity concentration in $^{15}$O-CO image</td>
</tr>
<tr>
<td>$C_v^{\text{CO}}$</td>
<td>Left ventricle activity concentration in $^{15}$O-CO image</td>
</tr>
</tbody>
</table>

---

**Figure S3.1** Simulation study: percentage deviation between fitted and simulated OEF values for models 2 (A) and 2’ (B).
Figure S3.2 Simulation study: percentage deviation between fitted and simulated OEF values for models 2 (A) and 8 (B), in case of small movements between $^{18}$O-water and $[^{18}O]O_2$ scans.