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Quantification of regional myocardial oxygen metabolism in normal pigs using positron emission tomography with injectable $^{15}\text{O-O}_2$

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Abstract

Purpose Although $^{15}\text{O-O}_2$ gas inhalation can provide a reliable and accurate myocardial metabolic rate for oxygen by PET, the spillover from gas volume in the lung distorts the images. Recently, we developed an injectable method in which blood takes up $^{15}\text{O-O}_2$ from an artificial lung, and this made it possible to estimate oxygen metabolism without the inhalation protocol. In the present study, we evaluated the effectiveness of the injectable $^{15}\text{O-O}_2$ system in porcine hearts.

Methods PET scans were performed after bolus injection and continuous infusion of injectable $^{15}\text{O-O}_2$ via a shunt between the femoral artery and the vein in normal pigs. The injection method was compared to the inhalation method. The oxygen extraction fraction (OEF) in the lateral walls of the heart was calculated by a compartmental model in view of the spillover and partial volume effect.

Results A significant decrease of lung radioactivity in PET images was observed compared to the continuous inhalation

of $^{15}\text{O-O}_2$ gas. Furthermore, the injectable $^{15}\text{O-O}_2$ system provides a measurement of OEF in lateral walls of the heart that is similar to the continuous-inhalation method (0.71 ± 0.036 and 0.72 ± 0.020 for the bolus-injection and continuous-infusion methods, respectively).

Conclusion These results indicate that injectable $^{15}\text{O-O}_2$ has the potential to evaluate myocardial oxygen metabolism.

Keywords Myocardial oxygen metabolism · PET · Pig · OEF · Injectable $^{15}\text{O-O}_2$

Introduction

In the myocardium, fatty acid or glucose is used to produce energy by aerobic metabolism. Oxygen is one of the most important substrates closely related to the aerobic metabolism in the TCA cycle; thus, oxygen metabolism should be a direct reflection of myocardial metabolism of these substrates. Therefore, there has been considerable interest in the development of a method to quantify oxygen metabolism in the myocardium.

Recently, ^{11}C -acetate has been used for this purpose [1–5]. ^{11}C -acetate is taken up by the mitochondria and metabolically converted into acetyl-CoA. It then enters the TCA cycle and is transformed to ^{11}C - CO_2 , which is cleared rapidly from the myocardium. Thus, the clearance pharmacokinetics reflects oxygen metabolism in the myocardium. However, the quantification of oxygen metabolism using ^{11}C -acetate is quite difficult because of various intermediary compounds.

The use of $^{15}\text{O-O}_2$ gas inhalation and PET scanning can provide a quantitative myocardial metabolic rate for oxygen (MMRO₂) [6, 7]. The tracer kinetic model used is based on that originally proposed to describe the behavior of $^{15}\text{O-O}_2$ in brain tissue [8, 9]. However, the direct translation of the

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compartmental model for the brain to the heart is not permitted, because subtraction for spillover from gas volume in addition to that from the blood pool is needed. A previous study demonstrated that the gas volume can be accurately estimated from the transmission scan data; thus, this technique did not require additional emission scanning for estimating the quantitative gas volume images [6, 7]. However, gaseous radioactivity in the lung during the inhalation of $^{15}\text{O-O}_2$ gas is too high in comparison to other regions. Subtraction for this contribution is straightforward and accurate using the transmission scan-derived gaseous volume images, but the lung radioactivity degraded image quality in the estimated MMRO₂ images.

As an alternative to gas inhalation, we recently developed a method to prepare an injectable form of $^{15}\text{O-O}_2$. This was accomplished by exposing pre-collected blood to $^{15}\text{O-O}_2$ gas using a small artificial lung system resulting in a maximum yield of 130 MBq/ml. We demonstrated that cerebral oxygen metabolism could be estimated in normal and ischemic rats using injectable $^{15}\text{O-O}_2$ [10–12]. This technique has the potential of avoiding the inhalation protocol.

The aim of the present study was therefore to test the feasibility of using the injectable $^{15}\text{O-O}_2$ oxygen system for estimating myocardial oxygen metabolism in pigs. The injection method was compared to the inhalation method to determine if the injection method resulted in a reduction of lung radioactivity, an improved image quality, a more accurate estimate of myocardial oxygen metabolism, and an improved signal-to-noise ratio.

Materials and methods

Theory

$^{15}\text{O-Oxygen}$ was administered by IV injection or inhalation and was carried as $^{15}\text{O-hemoglobin}$ by blood to peripheral tissues including the myocardium, where it was converted to $^{15}\text{O-water}$ ($^{15}\text{O-H}_2\text{O}_{\text{met}}$) through aerobic metabolism. The increased distribution volume of $^{15}\text{O-H}_2\text{O}_{\text{met}}$, represented by the exchangeable water space of tissue, causes delayed removal of radioactivity. This allows the definition of an appropriate model and equations to be derived for the calculation of a regional myocardial metabolic rate for oxygen (rMMOR₂) and regional oxygen extraction fraction (rOEF). Previous studies demonstrated that these calculations were similar to those used for estimating cerebral blood flow and oxygen metabolism and require the measurement of regional myocardial blood flow (rMBF) and a correction for spillover of activity from the vascular pools and the pulmonary alveoli [6, 7]. rMBF was measured by the $^{15}\text{O-H}_2\text{O}$ injection technique [13]. Activity in the vascular

pools of the heart chambers and the lung was evaluated with a conventional measurement of blood volume using $^{15}\text{O-CO}$, and activity in the pulmonary alveoli was evaluated with an unconventional and indirect measurement of gas volume obtained from the transmission scan. Furthermore, the existence of recirculating $^{15}\text{O-H}_2\text{O}_{\text{met}}$ in the blood freely accessible to the myocardium was taken into consideration.

The differential equation describing the myocardial kinetics after administration of $^{15}\text{O-O}_2$ can be written as follows:

$$\frac{dC^{\text{myo}}(t)}{dt} = \text{OEF} \cdot f \cdot A_0(t) + f \cdot A_w(t) - \left(\frac{f}{p} + \lambda\right) C^{\text{myo}}(t) \quad (1)$$

where $C^{\text{myo}}(t)$ designates the true radioactivity concentration in the myocardium at time t , f is myocardial blood flow, $A_0(t)$ is the $^{15}\text{O-O}_2$ radioactivity concentration in arterial blood, $A_w(t)$ is the $^{15}\text{O-H}_2\text{O}$ radioactivity concentration in arterial blood, p is the myocardium/blood partition coefficient of water, and λ is the physical decay constant of O-15.

Solving Eq. (1) in terms of $C^{\text{myo}}(t)$ gives:

$$C^{\text{myo}}(t) = \text{OEF} \cdot f \cdot A_0(t) * e^{-\left(\frac{f}{p} + \lambda\right)t} + f \cdot A_w(t) * e^{-\left(\frac{f}{p} + \lambda\right)t} \quad (2)$$

where the asterisk denotes the convolution integral. During steady-state conditions under the continuous administration of $^{15}\text{O-O}_2$, the following relationship holds:

$$C^{\text{myo}} = \frac{\text{OEF} \cdot f \cdot A_0 + f \cdot A_w}{\left(\frac{f}{p} + \lambda\right)} \quad (3)$$

In the actual PET studies, the spillover from vascular pools and pulmonary alveoli and the partial volume effect should be taken into consideration [14]. Then, the measured radioactivity concentration in the region of interest (ROI) in the myocardium ($R^{\text{myo}}(t)$) can be expressed as:

$$R^{\text{myo}}(t) = \alpha \cdot C^{\text{myo}}(t) + (V_B^{\text{myo}} \cdot A_A(t) - \alpha \cdot F_{\text{vein}} \cdot \text{OEF} \cdot A_0(t) - \alpha \cdot F_{\text{vein}} \cdot A_w(t)) + V_G^{\text{myo}} \cdot C_{\text{gas}}(t) \quad (4)$$

where α denotes the myocardial tissue fraction, V_B^{myo} is the myocardial blood volume, $A_A(t)$ is the total O-15 radioactivity concentration in arterial blood, F_{vein} is the microscopic venous blood volume, V_G^{myo} is the gas volume in the myocardial ROI and $C_{\text{gas}}(t)$ is the O-15 radioactivity concentration in V_G^{myo} .

With the bolus injection or infusion methods using an artificial lung system, the radioactivity in the pulmonary alveoli is expected to be negligible in comparison with the inhalation method. Thus, Eq. (4) can be converted to:

$$R^{myo}(t) = \alpha \cdot C^{myo}(t) + (V_B^{myo} \cdot A_v(t) - \alpha \cdot F_{vein} \cdot OEF \cdot A_o(t) - \alpha \cdot F_{vein} \cdot A_w(t)) \quad (5)$$

Subjects

In this study, four healthy miniature pigs (22–30 kg) were used. The pigs were anesthetized by IM injection of ketamine and xylazine followed by continuous infusion of propofol (5 mg/kg/h). The animals were then placed in the supine position on the bed of the PET scanner. All experimental procedures were approved by the local animal welfare committee.

Injectable ¹⁵O₂ preparation

In the “injection” study, injectable ¹⁵O₂ was used. Injectable ¹⁵O₂ was prepared as described previously [10–12]. In brief, part of an infusion line kit (Terumo Corporation, Tokyo, Japan) and an artificial lung 18 cm in length (Senko Medical Instrument Mfg Co. Ltd., Tokyo, Japan) were connected using silicone tubing to make a closed system. Then, venous blood collected from a pig, which was used in the following PET studies, was added to the system and circulated (100 ml/min) by a peristaltic pump, followed by introduction of ¹⁵O₂ gas (~7,000 MBq/min/433 ml) into the artificial lung for 15 min to prepare injectable ¹⁵O₂ (5.6–60.7 MBq/ml).

In the “continuous infusion” study, the left femoral artery and right femoral vein were both cannulated. The two cannulas from the artery and the vein were connected to the opposite sides of an artificial lung to create a femoral shunt. The blood flow in the shunt was aided by a peristaltic pump (30–50 ml/min). ¹⁵O₂ gas (~7,000 MBq/min/433 ml) was continuously introduced into the artificial lung.

PET protocol (Fig. 1)

The PET scanner was an ECAT EXACT HR (CTI/Siemens) [15], which has an imaging field of view (FOV) of 55 cm in diameter and 15 cm in axial length. The spatial resolution of the scanner is 5.8 mm in full width at half maximum at the center of the FOV.

After obtaining a 20-min transmission scan for attenuation correction and gas volume estimation, the blood pool image was obtained with a 4-min PET scan after the pigs inhaled 2.7 GBq ¹⁵O-CO for 30 s. Arterial blood samples were taken every minute during the ¹⁵O-CO scanning, and

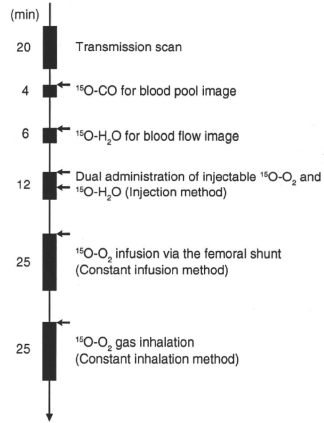


Fig. 1 Outline of the PET imaging study. The interval between scans was more than 15 min to allow for physical decay of O-15 radioactivity to background levels

the radioactivity concentration in the whole blood was measured with a NaI well-type scintillation counter calibrated against the PET scanner. Subsequently, ¹⁵O-water was injected into the right femoral vein for 30 s at an infusion rate of 10 ml/min (injected radioactivity was about 1.11 GBq). Immediately after injection of ¹⁵O-water, 26 dynamic frames (12×5 s, 8×15 s and 6×30 s) of PET data were acquired for 6 min.

Furthermore, two PET scans were successively performed after the IV injection of ¹⁵O₂ (5.6–60.7 MBq/ml) for 30 s at an injection rate of 20–80 ml/min for the “injection” study, and by the continuous ¹⁵O₂ gas infusion through the artificial lung in the femoral shunt for the “continuous infusion” study. In the “injection” study, 52 dynamic frames (12×5 s, 8×15 s, 6×30 s, 12×5 s, 8×15 s and 6×30 s) of PET data were acquired for 12 min, and 1.11 GBq of ¹⁵O-water was injected IV for 30 s at 10 ml/min starting at 6 min after the administration of IV ¹⁵O₂ according to the dual administration protocol we developed previously [16]. In the “continuous infusion” study, 26 dynamic frames (10×30 s, 5×60 s, 1×600 s and 10×30 s) were acquired for 25 min, and the 600-s frame was used for steady-state analysis.

Another PET scan was performed by ¹⁵O₂ gas inhalation in one of the four pigs in the same protocol as the “continuous infusion” study. This was the “continuous inhalation” study. The interval between scans was more

than 15 min to allow for physical decay of O-15 radioactivity to background levels. All acquisitions were obtained in the two-dimensional mode (septa extended).

Data analysis

A filtered back-projection algorithm with a 6-mm Gaussian filter was used for image reconstruction. The reconstructed images had a matrix size of $128 \times 128 \times 47$ and a voxel size of $1.84 \times 1.84 \times 3.38$ mm, and all image data sets were resliced into short-axis images across the left ventricle [13].

Myocardial blood flow

rMBF was calculated from the injection of $^{15}\text{O}\text{-H}_2\text{O}$ by fitting the myocardial and arterial time-activity curve data to a single-tissue-compartment model that implemented corrections for partial-volume effects by introducing the tissue fraction. In addition, the model was corrected for spillover from the left ventricular (LV) chamber into the myocardial ROI by introducing the arterial blood volume [13]. In these experiments, the time-activity curves generated from large ROIs placed in the LV chamber were used as the input function.

Regional oxygen extraction fraction

In the “injection” study, rOEF was calculated according to Eqs. (2) and (5). In these formulations, F_{vein} was assumed to be 0.10 ml/g tissue and p was fixed at 0.90 ml/g. The blood volume image obtained from the $^{15}\text{O}\text{-CO}$ scan was used for the determination of V_B^{mpo} . The value of $A_i(t)$ was obtained from the LV radioactivity concentration measured from the PET data set with small LV ROIs to minimize spillover from the myocardium. The calculation for the estimation of recirculating $^{15}\text{O}\text{-H}_2\text{O}$ was performed as previously described [16]. For the “continuous infusion” and “continuous inhalation” studies, in which a 600-s frame was regarded as steady-state, Eqs. (3) and (5) or Eqs. (3) and (4) were used for calculating rOEF, respectively.

Results

Table 1 summarizes the conditions of animals during the PET studies. The parameters were all within the physiologic range.

Table 1 Physiological parameters of pigs during the PET studies

	pH	pCO ₂ (mmHg)	pO ₂ (mmHg)	tHb (g/dl)	O ₂ Sat (%)	HR (bpm)	BP (mmHg)	
							Diastolic	Systolic
Average	7.46	40.3	125.8	12.8	97.7	85	97.8	125.2
SD	0.032	2.51	16.69	1.30	1.83	19.5	10.4	19.3

Figure 2 demonstrates the dynamic images obtained in the “injection”, “continuous infusion”, and “continuous inhalation” studies. With the injection and continuous-infusion methods, the right ventricle on the left side and the vena cava on the lower side were well delineated, whereas the left ventricle was moderately shown on the right side. The 16th frame (600–1,200 s after the initiation), which was used for steady-state analysis with the continuous-infusion method, was visibly distinct compared with all of the frames obtained with the injection method. However, with the continuous-inhalation method, neither ventricle could be depicted because of high radioactivity in the lung on the right and lower-side images.

The radioactivity in the blood pool obtained by $^{15}\text{O}\text{-CO}$ PET (Fig. 3g) and the gaseous volume estimated by inverse transmission data (Fig. 3h) were subtracted from the raw PET images (16th frame) with the continuous-inhalation and continuous-infusion methods, respectively (Fig. 3c and f). Both methods clearly delineated the myocardium after subtraction in comparison to the blood flow image (Fig. 3i). However, the continuous-inhalation method showed salient radioactivity on the lateral wall (Fig. 3c), whereas the continuous-infusion method showed only modest radioactivity in the myocardium (Fig. 3f). It is also notable that there was considerable radioactivity in the right ventricle with the continuous-infusion method even after the subtraction (Fig. 3f).

To further examine the differences between the continuous-infusion and continuous-inhalation methods, time-radioactivity curves during the PET scans were taken from four ROIs: the left ventricle (LV), right ventricle (RV), myocardium (Myo), and lung (Fig. 4). At the steady-state frame (600–1,200 s), the continuous-infusion method showed higher radioactivity in the RV and LV than in the myocardium (Fig. 4a), whereas the radioactivity of these regions was similar with the continuous-inhalation method (Fig. 4b). The radioactivity in LV was about two-thirds of that in RV in Fig. 4a, indicating that measurable radioactivity was excreted through the lung even after the femoral administration of $^{15}\text{O}\text{-O}_2$. The lung excretion was also observed on the blood-subtracted image (Fig. 3e). Actually, there was significant radioactivity in the lung (Fig. 4a), although that was the lowest among the four ROIs. In contrast, the radioactivity in the myocardium was the lowest among the four ROIs with the continuous-inhalation method

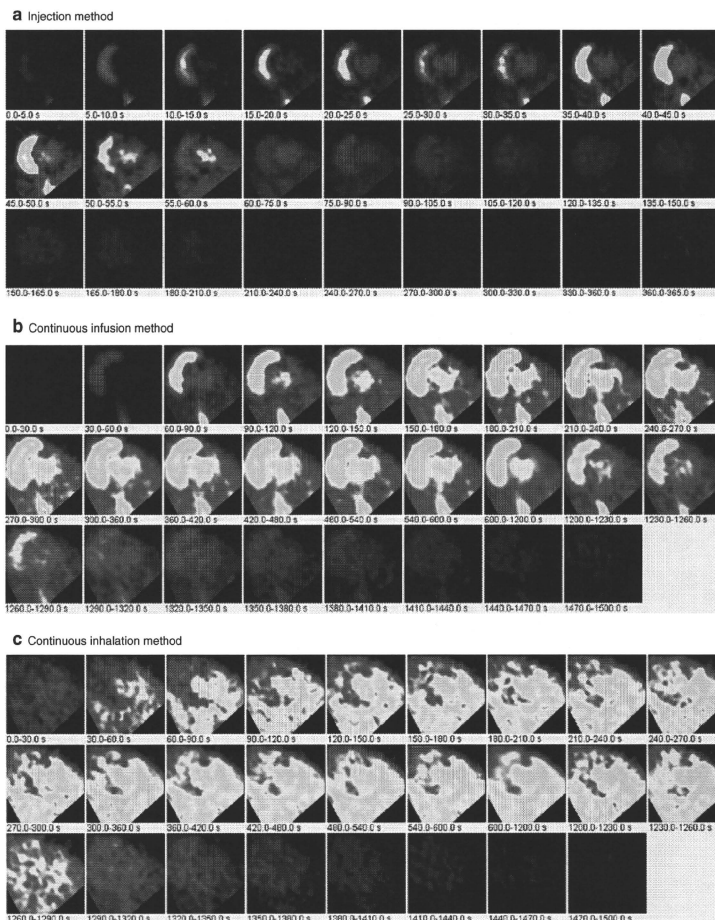


Fig. 2 PET images obtained in (a) the injection method, (b) the continuous-infusion method with injectable $^{15}\text{O}-\text{O}_2$, and (c) the continuous-inhalation method with $^{15}\text{O}-\text{O}_2$ gas

(Fig. 4b). The heart-to-lung radioactivity ratios were calculated from Fig. 4 for the quantitative estimation of image quality; the continuous-infusion method provided a ratio of 1.38 ± 0.24 , whereas the ratio was less than one with the continuous-inhalation method.

Table 2 shows the quantitative OEF values in the lateral wall obtained by the injection, continuous-infusion, and

continuous-inhalation methods. These OEF values were consistent among the three methods.

Figure 5 represents the noise equivalent counts (NEC) standardized by the total counts detected by the PET scanner. Although the injection method tended to show rather high values, there was no significant difference between the values obtained by the injection and

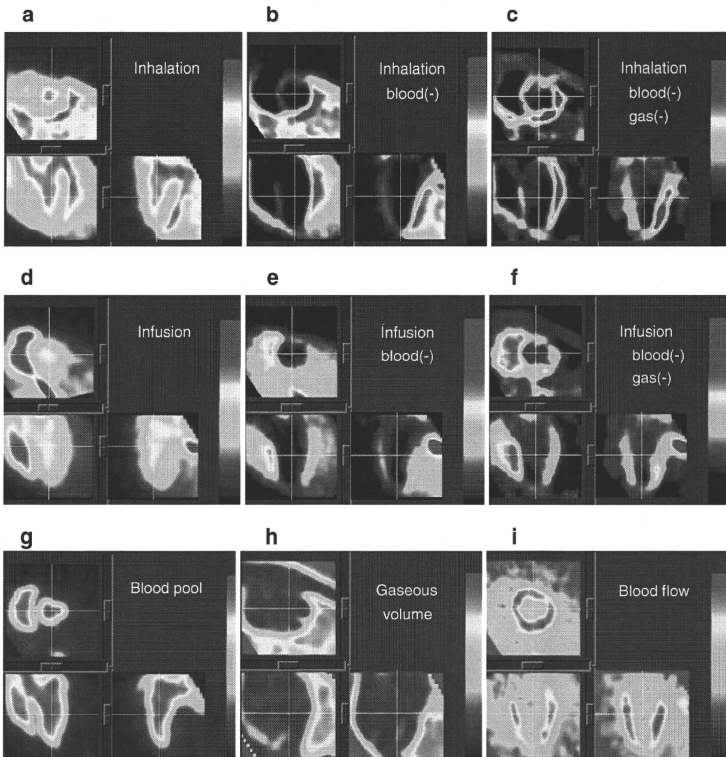


Fig. 3 PET images obtained in the study are shown. The 16th frame (steady-state frames) of the continuous-inhalation method and the continuous-infusion method are shown in (a) and (d), respectively. The ‘blood-subtracted’ images shown in (b) and (e) were created by

subtraction of the blood-pool image by $^{15}\text{O}\text{-CO}$ (g) from (a) and (d). The ‘blood- and gas-subtracted’ images shown in (c) and (f) were created by the successive subtraction of the gaseous image (h) from (b) and (e). The myocardial blood flow image is also shown in (i)

continuous-infusion methods as determined by a Mann Whitney *U*-test.

Discussion

In previous studies, we showed the usefulness of the injectable $^{15}\text{O}\text{-O}_2$ system for estimating cerebral oxygen metabolism in small animals such as rats under normal or ischemic conditions [10–12]. Injectable $^{15}\text{O}\text{-O}_2$ replaced the inhalation protocol and radioactive $^{15}\text{O}\text{-O}_2$ was administered via the tail vein. Thus, injectable $^{15}\text{O}\text{-O}_2$ could abolish the artifact from the high radioactivity in the

inhalation tube that distorts the PET images, especially in small animals. We considered that the concept could also be utilized in the hearts of large animals. Therefore, in the present study, we tested the feasibility of an injectable $^{15}\text{O}\text{-O}_2$ system for estimating myocardial oxygen metabolism in normal pigs. In addition, since a shunt between the femoral artery and vein can be created in pigs but not in small animals, continuous infusion via the femoral shunt was also performed to achieve a constant and reliable delivery of radioactivity to the heart.

Dynamic PET scans showed a large difference in the radioactivity distribution among the three methods. Since the labeling efficiency to prepare injectable $^{15}\text{O}\text{-O}_2$ was

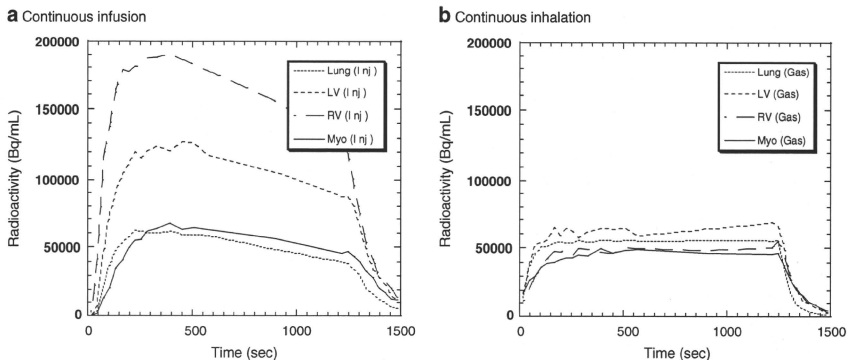


Fig. 4 Time-activity curves from the left ventricle (*LV*), the right ventricle (*RV*), the myocardium (lateral wall, *Myo*) and a lung region with the continuous-infusion method (a) and the continuous-inhalation

method (b). The supply of radioactivity was started at time 0 s and stopped at 1,200 s. The 16th frame for the steady-state analysis was 600–1,200 s

lower with pig blood (ca. 61 MBq/ml at most) than with the blood of rats and humans (130 MBq/ml), the injection method provided rather obscure images. With the injection and continuous-infusion methods, the radioactivity in the lung was dramatically reduced in comparison to the continuous-inhalation method, since the heart-to-lung ratio with the continuous-infusion method was about 40% higher than with the continuous-inhalation method. This finding suggested that the two methods that inject radioactivity via a vein are more useful for analyzing myocardial oxygen metabolism in pigs than the continuous-inhalation method. However, a distinct difference between radioactivity of the right and left ventricles was observed in the images and time-radioactivity curves after venous administration of ¹⁵O-O₂, indicating a certain degree of excretion of the radioactivity by the lung. Therefore, the spillover from the pulmonary alveoli to the myocardium could not be omitted in the two methods with venous administration, and Eq. (4)

was used for the OEF analysis, although the radioactivity in the lung was lower than that in the myocardium.

On the other hand, with the continuous-inhalation method, the radioactivity of the lung was in between the radioactivity in the RV and LV. This is curious because O-15 radioactivity was supplied from the inhalation tube and transferred from the lung to blood so that the radioactivity in the lung should have been the highest among the four ROIs. This may have been caused, in part, by inhomogeneous distribution of the radioactivity in the lung due to its structure in comparison with the myocardium and ventricles, and/or by artifacts from the lung to other

Table 2 OEF estimated by the three methods using injectable ¹⁵O-O₂ or ¹⁵O-O₂ gas

	OEF		
	Injection	Infusion	Inhalation
Pig. 1	0.70	0.72	
Pig. 2	0.67	0.72	
Pig. 3	0.71	0.74	
Pig. 4	0.76	0.69	0.72
Average	0.71	0.72	0.72
SD	0.036	0.020	

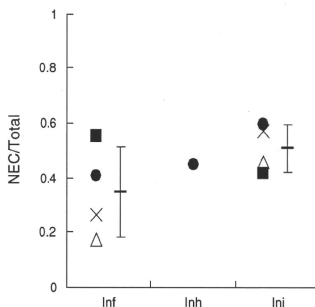


Fig. 5 The ratio of noise equivalent counts (*NEC*) to total counts in the total field of view of the PET scanner obtained with the continuous-infusion method (*Inf*), the continuous-inhalation method (*Inh*) and the injection method (*Inj*)

tissues. In any case, it is notable that the radioactivity in the myocardium was the lowest with the continuous-inhalation method, leading to difficulty in analyzing myocardial oxygen metabolism.

The OEF values in lateral walls were calculated to compare the ability of the three methods to determine myocardial oxygen metabolism by using the blood flow derived from the dual-administration protocol with the injection method and the single-administration protocol with the two continuous methods. There was no difference in the blood flow between the two protocols. Consequently, the three methods provided the same OEF value of about 0.7 and this is a physiological value in normal pigs, as was previously demonstrated [17, 18]. We have demonstrated the potential of the injectable $^{15}\text{O}-\text{O}_2$ system for the estimation of physiological cerebral oxygen metabolism in rats and monkeys during early and late ischemia, hypertension, and ischemia plus hypertension [10–12, 19]. Therefore, we believe that the injection and continuous-infusion methods provide a physiological OEF in the myocardium. Nevertheless, we recognize the necessity to evaluate the reliability and usefulness of the injectable $^{15}\text{O}-\text{O}_2$ method in myocardial applications. Further studies using pathophysiological animal models are required in the future, such as myocardial ischemia, hypoxia, and heart failure. On the other hand, since MMRO_2 is basically regarded as the product of MBF and OEF, the results indicated that these three methods were equivalent in their ability to quantify MMRO_2 in normal pigs, at least in the lateral wall. Although the images after the subtraction of spillovers from blood and gas showed different contrast between the continuous-infusion and continuous-inhalation methods, the ability of these two methods to measure OEF and MMRO_2 in the lateral walls was equivalent.

We did not evaluate myocardial oxygen metabolism in other heart regions since the radioactivity in the right ventricle could not be removed due to a significant difference of radioactivity between the ventricles with the continuous-infusion method. The injection method might be able to evaluate oxygen metabolism in other regions besides the lateral wall, although this was not evaluated in this study due to the low radioactivity of injectable $^{15}\text{O}-\text{O}_2$ as described above. In the injection method, O-15 radioactivity was delivered from the femoral vein to RV, the lung, LV, and finally the myocardium. Thus, when the LV and myocardial activity reach a maximum, the RV activity is expected to be low. The later frames of the dynamic PET images with the injection method might avoid the high RV activity and delineate the myocardium and LV more clearly. With accurate anatomical information by gated PET/CT, the injection method will provide oxygen metabolism in other heart regions. In addition, the injection method has a benefit in that it is noninvasive and shortens the acquisition time in

comparison with the continuous-infusion method. Future studies are needed to determine whether the injectable $^{15}\text{O}-\text{O}_2$ system can be used in other heart regions.

With the injection method, the ratio of noise equivalent counts (NEC) to total counts tended to be the higher, probably because of the absence of high radioactivity adjacent to the PET scanner. Nevertheless, the continuous-infusion method did not show this tendency. This may be because tubes for the input to the artificial lung were positioned at the femoral shunt and the output to the drain of O-15 gas was positioned alongside the PET scanner, resulting in an increase of random counts during the study. Also, it is notable that the value with the continuous-inhalation method was not small, which suggests that the inhalation protocol itself did not worsen the results, but rather the high radioactivity in the lung might affect the analysis. In any case, if more care is given to shielding of the radioactivity in tubes and/or for arrangement of instruments in the PET room, a higher value of NEC/total counts will be obtained with the injectable $^{15}\text{O}-\text{O}_2$ system.

The declining slope delineated in the time-activity curves with the continuous-infusion method requires some explanation. Since the flow rate of O-15 gas supply to the artificial lung positioned at the femoral shunt was maintained constant during the PET scan, it is possible that a decrease of labeling efficiency of the artificial lung occurred due to the deposition of any components of blood. The blood of rats or humans was negligibly deposited in the artificial lung during circulation at the same rate for at least 30 min in our other experiments, so that this problem may be specific for pigs. It is unclear which component in pig blood was exactly involved in the deposition and three of four pigs did not show a declining slope of the time-activity curve.

In practice, in routine studies on myocardial oxygen metabolism using large animals such as pigs, the continuous-inhalation method with $^{15}\text{O}-\text{O}_2$ gas may be easier to perform for the following reasons: (1) the intubation tube used for gas anesthesia prior to the PET scan can also be used for $^{15}\text{O}-\text{O}_2$ gas inhalation; (2) catheterization of the femoral artery and vein to create the femoral shunt for the continuous-infusion method may be troublesome; and (3) the injection of $^{15}\text{O}-\text{O}_2$ requires an artificial lung, preparation time, and blood taken from the same animal prior to the PET scan. However, the injection of $^{15}\text{O}-\text{O}_2$ has a substantial advantage over the continuous-inhalation method in that there is reduced radioactivity in the lung and clearer images of the heart are obtained. Therefore, the method for estimating myocardial oxygen metabolism should be selected depending on the objectives of the study and the surgical procedures. Furthermore, since radioactivity administered into the femoral vein is partially excreted into expired air, the injectable $^{15}\text{O}-\text{O}_2$ system might be used for evaluating pulmonary function in the future.

Conclusion

In this study, we tested the feasibility of using an injectable ^{15}O - O_2 system to estimate myocardial oxygen metabolism in pigs. Both the bolus-injection and continuous-infusion methods reduced the radioactivity in the lung and provided similar OEF values in the lateral walls of the heart. These findings indicate that the injectable ^{15}O - O_2 system has the potential to evaluate myocardial oxygen metabolism.

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3-Tesla Magnetic Resonance Angiographic Assessment of a Tissue-Engineered Small-Caliber Vascular Graft Implanted in a Rat

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Abstract: In the development of small-caliber vascular grafts (diameter; less than 3 mm), animal implantation studies have been mostly performed by using rat abdominal aortas, and their certain patency must evaluate with sacrificing every observation periods, which is both labor-intensive and time-consuming when performing a large number of experiments. This study is the first to demonstrate the application of 3-Tesla contrast-free time-of-flight magnetic resonance angiography (TOF-MRA) in the continuous assessment of the status of a tissue-engineered vascular graft in rat. As a model graft, a single connective tubular tissue (diameter; 1.5 mm), prepared by embedding the silicone rod (diameter; 1.5 mm) into a subcutaneous pouch of a rat for 2 weeks an *in vivo* tissue-engineering, was used. The graft was implanted in the abdominal aorta (diameter; 1.3 mm) of the rat by end-to-end anastomosis. Repeated TOF-MRA imaging of the graft obtained over a 3-month follow-up period after implantation made it possible to evaluate the patency of the graft, both simply and noninvasively. It also permitted visualization of the connected abdominal aorta and renal and common iliac arteries having smaller caliber (diameter; less than 1 mm). In addition, the degree of the stenosis or aneurysm could also be detected. 3-Tesla MRA allowed the simplified and noninvasive assessment of the status on the vascular graft, including the formation of a stenosis or aneurysm, in the same rat at different times, which will be contributing to enhance the development of tissue-engineered vascular grafts even with small caliber. © 2009 Wiley Periodicals, Inc. *J Biomed Mater Res Part B: Appl Biomater* 92B: 156–160, 2010

Keywords: small-caliber vascular grafts; magnetic resonance angiography; animal implantation; biotube; tissue engineering

INTRODUCTION

Small-caliber arterial substitutes are needed for cardiac and peripheral revascularization procedures. For such small artery bypass grafting procedures, autologous arterial (e.g., internal thoracic artery and radial artery) or venous (e.g., saphenous vein) grafts still remain the most ideal vascular substitutes.^{1,2} However, many patients do not have a vessel suitable for use owing to the poor quality, inadequate size or

length, or previous harvest of such vessels. Moreover, a second surgical procedure is required to initially obtain the necessary vessel. Vascular prostheses, such as expanded polytetrafluoroethylene (ePTFE) and poly(ethylene terephthalate) (Dacron) grafts, have been used clinically for reconstructing arteries.³ However, small-caliber (<6 mm) arterial substitutes have generally proved inadequate largely because of the formation of thromboses and intimal hyperplasia.^{4,5}

Many design criteria have been proposed for the development of functional small-caliber arterial replacement grafts.^{5–11} All most of all artificial vascular grafts (inner diameter, 1.5–3.0 mm) have been employed for transplantation

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to rat abdominal aortas as an *in vivo* model.⁶⁻⁸ Graft patency has been evaluated during the follow-up period by angiography⁸ or by direct inspection at the time of removal for histological evaluation.^{6,7} However, angiography requires cannulation of the carotid artery,⁸ and a midline laparotomy is needed for direct inspection.^{6,7} As a consequence, these methods are complex and invasive. Therefore, it is difficult to evaluate graft patency repeatedly in the same rat. Although, graft patency has also been evaluated by palpating the femoral pulse,⁷ this method is subjective and uncertain.

The current imaging systems, including fluorescence antibody method, single photon emission computed tomography (SPECT),¹² laser doppler system,¹³ or high-resolution ultrasound¹⁴ for blood flow imaging in addition to magnetic resonance angiography (MRA), are powerful tool in tissue engineering field. However, it is considered that no imaging systems except for MRA fit for evaluation of the status of implanted small-caliber vascular grafts.

In clinical practice, MRI has been used as a noninvasive evaluation method for the assessment of brain blood vessels and peripheral arteries and also been widely used in preclinical research on experimental small rodents.¹⁵⁻¹⁸ The studies have typically been aimed at understanding the patho-physiological status and evaluating the efficacy/side effects of newly developed treatments, such as pharmaceutical and regenerative medicine.

Our purpose in this study was to evaluate the status of a tissue-engineered vascular graft with inner diameter of 1.5 mm, clinically, repeatedly, and noninvasively in a rat implantation model. To this end, 3-Tesla contrast-free time-of-flight magnetic resonance angiography (TOF-MRA) was applied.

MATERIALS AND METHODS

Preparation and Implantation of the Connective Tubular Tissue

All animal experiments were conducted in accordance with local regulations, complying with the Principles of Laboratory Animal Care (formulated by the National Society for Medical Research) and the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 86-23, revised 1985). The research protocol (No. 8050) was approved by the ethics committee of the National Cardiovascular Center Research Institute.

The connective tubular tissue was prepared by *in vivo* tissue engineering according to the previous reported method.⁹ Briefly, a silicone rod (diameter, 1.5 mm; length, 10 mm; Tigers Polymer, Osaka, Japan) was used as a mold. One adult female Wistar rat (weight; 300 g) was anesthetized with 1.5% isoflurane (vol/vol air). The mold was placed in a dorsal subcutaneous pouch, and after 2 weeks, the implant was removed. The tubular tissue was obtained from the implant after trimming the peripheral tissues and pulling out the rod. The tube thus obtained was treated by coating with Argatroban (1 mg/graft; Mitsubishi

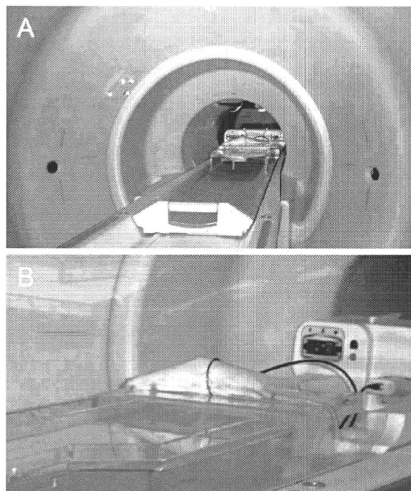


Figure 1. Experimental setup in MR imaging on a human whole-body 3T-MR scanner (GE Healthcare). (A). The coil was placed at the center of the gantry and its turn axis had perpendicular alignment to the static magnetic field (B). Rat's abdomen was positioned inside the coil along the craniocaudal direction. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Chemical Co., Tokyo, Japan) to make it antithrombogenic. It was then implanted to the infrarenal abdominal aorta of the same rat using an end-to-end anastomosis under microscopic guidance and sutured using 12 interrupted 10-0 nylon stitches [Figure 1(A)]. Patency was examined at the time of surgery by direct inspection. The wound was closed with 4-0 silk sutures. Thereafter, the rat had free access to standard food and water. Graft status was evaluated at 2, 36, and 78 days after transplantation by contrast-free TOF-MRA under anesthesia induced by an intramuscular injection of pentobarbital (40 mg/kg).

MR Data Acquisition

A human whole-body 3-Tesla magnetic resonance imaging (MRI) scanner (Signa, GE Healthcare, Milwaukee, WI) was employed in this study (Figure 1). The gradient coil system was capable of providing a maximum gradient amplitude of 40 mT/m. All sequence programs employed in this study were designed for clinical studies. A developed single-turn surface coil of 62 mm diameter was used for MR imaging [Figure 1(B)]. Contrast-free TOF-MRA was performed using a three-dimensional flow-compensated fast spoiled gradient recalled (3D-FSPGR) sequence [repetition

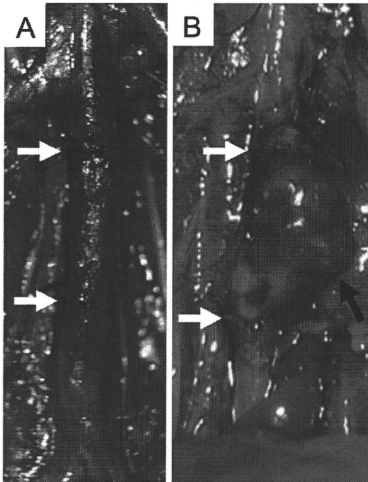


Figure 2. (A) The tubular connective tissue vascular graft (diameter, 1.5 mm) after autoimplantation in the rat infrarenal abdominal aorta (diameter, 1.3 mm) performed by end-to-end anastomosis under microscopic guidance using 12 interrupted stitches of 10-0 nylon suture. (B) The tubular connective tissue formed an aneurysm (max diameter, 3.0 mm) at 78 days after autoimplantation. White arrows indicate the proximal and distal anastomosis regions. Black arrow indicates the aneurysm. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

time (TR) = 21 ms, echo time (TE) = 5.4 ms (out of phase), flip angle (FA) = 15°, slice thickness = 0.4 mm, field of view (FOV) = 80 mm × 60 mm, matrix = 288 × 192, locs per slab = 128, the number of excitations (NEX) = 1, scanning time = 5 min 58 s]. For suppressing venous signals, a region of 40-mm thickness on the caudal side of the measured slab was saturated. The measured voxel size in TOF-MRA was 0.278 × 0.291 × 0.400 mm. The image reconstruction was zero-filled to a matrix size of 512 × 512 and the voxel size was 0.156 × 0.156 × 0.400 mm. MR angiograms were analyzed by generating the partial maximum intensity projection (pMIP) with a commercial software package (AZE, Tokyo, Japan). Our previous report on TOF-MRA was shown detail in rat.¹³

RESULTS

The tubular connective tissue with a diameter of 1.5 mm was autoimplanted successfully into the 1.3 mm diameter abdominal aorta of the rat by end-to-end anastomosis [Figure 2(A)]. After suturing with 12 interrupted stitches, there was little bleeding from either of the sites of anastomosis, indicated by the arrows in Figure 2(A). The patency

of the graft was recognized directly by the satisfactory pulsation at the graft and distal side of the aorta.

3-Tesla contrast-free TOF-MRA of the rat was performed at 2 days after implantation [Figure 3(A)] to evaluate the status of the graft. The measurement time was ~6 min and no contrast medium was needed. The MRA distinctly visualized the patent graft connected to the abdominal aorta together with renal arteries and common iliac arteries of 0.7 and 0.8 mm diameter, respectively. Spatial resolution in the MRA was less than several hundred microns. A mechanical stenotic lesion, which may have been due to the anastomosis, was observed in both anastomosis regions. At 36 days after implantation, little stenosis and no aneurysmal dilation of the graft were observed [Figure 3(B)]. At 78 days after implantation, the maximum diameter of the aneurysm formed at the graft was 3.0 mm [Figure 3(C)]. The shape of the aneurysm was very close to that observed macroscopically [Figure 2(B)]. Therefore, the status of the graft could be precisely determined, repeatedly, and noninvasively.

DISCUSSION

This study is the first to demonstrate the application of MRA to the evaluation of the status of a small-caliber arti-

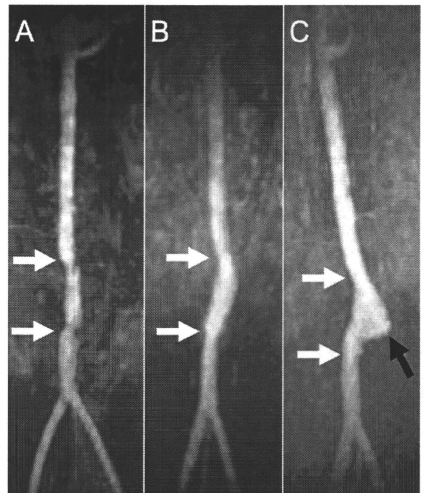


Figure 3. 3-Tesla contrast-free TOF-MRA images of the rat abdominal aorta at 2 (A), 36 (B), and 78 (C) days after autoimplantation of the biotube vascular graft. White arrows indicate the proximal and distal anastomosis regions of the abdominal aorta. A stenotic lesion was visible in the anastomosis regions at 2 days. An aneurysm formation in the graft was visible at 78 days (black arrow indicates the aneurysm).

ficial vascular graft implanted in the abdominal aorta of a rat. In the development of small-caliber vascular grafts as a preclinical study, *in vivo* evaluation is needed. Implantation studies have been performed mostly by using the abdominal aorta of rats.⁶⁻⁸ Their certain patency must evaluate with sacrificing every observation periods, which is both labor-intensive and time-consuming when performing a large number of experiments. Since some rats survive with no symptoms after graft occlusion, assessment of the occlusion of an abdominal aorta after graft implantation is not possible solely on the basis of the rat's appearance. On the other hand, some researchers have evaluated graft patency by palpating the femoral pulse⁷; however, this method is prone to subjectivity and uncertainty. Therefore, evaluation of graft patency should be performed by direct inspection under laparotomy. On the other hand, even in histological observations, the evaluation of the degree of graft stenosis is very difficult.

In this study, MRI images of a reasonable quality were obtained from a rat using a human whole-body MRI scanner at 3-Tesla. Contrast-free TOF-MRA was able to depict the implanted graft with a diameter of ~ 1.5 mm, connected to the abdominal aorta with a diameter of ~ 1.3 mm, and also revealed arteries with diameters of less than 1 mm, such as the renal, common iliac, and tail arteries. In addition, an evaluation of the graft status, including the stenosis, was also feasible due to the high resolution and reasonable contrast. As indicated in Figure 3(A), the mechanical stenosis was clearly indicated at both sites of anastomosis. Furthermore, the aneurysm formation was clearly observed [Figure 3(C)]. Since the observation by MRA is simple and noninvasive, assessment of the status of small-caliber vascular grafts could be performed in the same rat at different times. The repeatable MRA observation in a single rat enabled correct assessment of the graft status over the follow-up period. Such repeatability will reduce the variation in results stemming from individual difference in experimental animals.

As a model graft for implantation in this study, the tubular connective tissue was used. The tissue was prepared similar to biotubes.⁹ Biotubes are autologous prosthetic tubular tissues prepared by in-body tissue architecture technology. The biotube, obtained from rats by embedding the silicone rods (diameter; 3 mm) into their subcutaneous pouches for 4 weeks, had several 10 μ m in thickness, about 500 gf in maximum load at rupture, and about 1000 mmHg in burst pressure.¹⁹ This technology, a novel and practical concept in regenerative medicine, is based on the phenomenon of tissue encapsulation of foreign materials *in vivo*, and it can be used to develop autologous tissues of the desired shape, depending on the mold design.⁹⁻¹¹ Using this technology, several types of tissues, including "biotubes" as vascular tissues,⁹⁻¹¹ "biovalves" as tri-leaflet heart valve-shaped tissues,^{20,21} and "biocovered stents" as hybrid IVR devices,²² have been developed. In this study, by shortening of the encapsulation period weak and ununi-

form wall structure was prepared particularly for observation of the variety of vascular graft fate. As expected, normal, stenosis, or aneurysm models were appropriately obtained in one rat.

The assessment of graft status using MR imaging does, however, have limitations. When using certain materials for artificial grafts (e.g., ePTFE and Dacron), MR imaging might be difficult owing to graft artifacts. Furthermore, such as ultrasound and/or digital subtraction angiography, it is difficult to evaluate blood stream by 3D evaluation. The TOF-MRA is more appropriate for the evaluation of tissue-engineered vascular grafts. The signal-to-noise ratio in image quality on TOF-MRA is strongly dependent on the static field strength and the coil design. Further study should be needed in developing coil. We hope that others who study at understanding the patho-physiological status and evaluating the efficacy/side effects of newly developed treatments, such as pharmaceutical and regenerative medicine.

CONCLUSIONS

Contrast-free TOF-MRA with 3-Tesla allowed an assessment of tissue-engineered small-caliber vascular graft status in the rat systemic arterial circulation. As the protocol used in this study is simple and noninvasive, it is useful for the longitudinal evaluation of graft status in the rat; this will contribute to enhancing the development of tissue-engineered small-caliber vascular grafts, particularly in the field of regenerative medicine.

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Development of motion correction technique for cardiac ^{15}O -water PET study using an optical motion tracking system

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Abstract

Objective Cardiac ^{15}O -water PET studies provide an accurate quantitation of regional myocardial blood flow (rMBF). We developed a motion correction system using an optical motion-tracking device to detect a subject's global movement for cardiac study.

Methods PET studies were carried out on a cardiac phantom and a healthy volunteer at rest. The three-dimensional locations of the markers attached to the subjects during scans were measured using an optical motion-tracking system. In the phantom study, we performed a transmission scan and seven ^{18}F emission scans of a baseline and with artificial misalignment of shifts and rotations. The correlation coefficients between the baseline and the other images before and after the corrections for the misalignment were calculated. In the human study, we performed a ^{15}O -water dynamic scan with a transmission and axially 30 mm-shifted transmission scans. Motion of the subject was estimated by the information from the

system, and was corrected on each sinogram using attenuation maps realigned to dynamic frames. Reconstructed dynamic images were then realigned to the transmission data. We calculated rMBF values for nine segments and myocardial images from the emission images, which were reconstructed with the first attenuation map (reference) and with the misaligned attenuation map before and after our corrections.

Results In the phantom study, the correlation coefficients were improved from 0.929 ± 0.022 to 0.987 ± 0.010 (mean \pm SD) after the corrections. In the human study, the global and cyclic movements were detected. The cyclic movement due to respiration was smoothed by frame-averaging, and reasonable information of the global movement was obtained. The rMBF value (mean \pm SD) was 0.94 ± 0.12 mL/min/g for the reference. The rMBF values using the misaligned attenuation map changed from 1.03 ± 0.21 to 0.93 ± 0.11 mL/min/g after the correction, and spurious defects in myocardial images were also recovered.

Conclusions Our technique provided reasonable information for correcting the global movement of the subject. It was shown that this system was applicable to detect and correct subject movement in cardiac PET studies at rest.

Keywords Myocardial blood flow · PET · Motion correction · Attenuation correction · ^{15}O -labeled water

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Introduction

Motion of a patient during a positron emission tomography (PET) scan can cause deterioration in image quality and quantitative accuracy. Several techniques have been

proposed for motion compensation in neuroimaging [1–7]. In cardiac PET studies, effects of wall contractile and respiratory motion can be smoothed in the temporary sampled PET images, but global movement of the patients during the relatively long scanning period is still a significant source of errors [8–11].

It was shown that misalignment by a 20-mm shift in the lateral/septal direction between transmission and ^{18}F -fluorodeoxyglucose (^{18}F -FDG) emission scans caused a 30% change in regional activity in cardiac ^{18}F -FDG PET [8]. To align two ^{18}F -FDG emission images acquired on different days, Bacharach et al. [11] proposed a registration technique based on the rigid body model using the transmission images by assuming no misregistration between transmission and emission data sets.

Cardiac ^{15}O -water PET studies provide quantitative information with regard to the viabilities of myocardium using the myocardial blood flow (MBF), coronary flow reserve, and perfusable tissue index [12–19]. Naum et al. [20] demonstrated that the movement occurred during dynamic scans with cycling. They proposed a method to correct for the motion during a single dynamic scan, and among different sessions, by aligning the dynamic frames of ^{15}O -water images using two external radioactive markers placed on the back of a subject. Although their technique did not provide correction for misalignment between transmission and emission data, reasonable improvement in calculated MBF values was demonstrated.

Correcting the misalignment between the transmission and emission data is a challenging task because the image contrast of transmission images differs from that of emission images. The distribution of ^{15}O -water also varies dramatically in regions of the right and left ventricles, myocardium, and other organs over time. Additionally, the image quality of PET with ^{15}O -water is worse than that with other radioligands due to the short half life of ^{15}O , which makes image registration difficult.

In this paper, we describe a novel approach using an optical motion-tracking system for detecting the subject's global movement during the relatively long study period, as an extension of the early studies of Watabe et al. [4]. The proposed technique provided correction for misalignment between dynamic emission sinograms, and also provided accurate attenuation correction, in which misalignment between attenuation map and each emission sinogram was corrected in the reconstruction stage.

First, the inherent accuracy of our system was evaluated. Then, the system was validated on a cardiac phantom study for artificial misalignment between an attenuation map and emission data. Correction for global movement obtained by monitoring the locations of external markers on chest skin was validated in a ^{15}O -water cardiac PET study in a healthy volunteer at rest.

Materials and methods

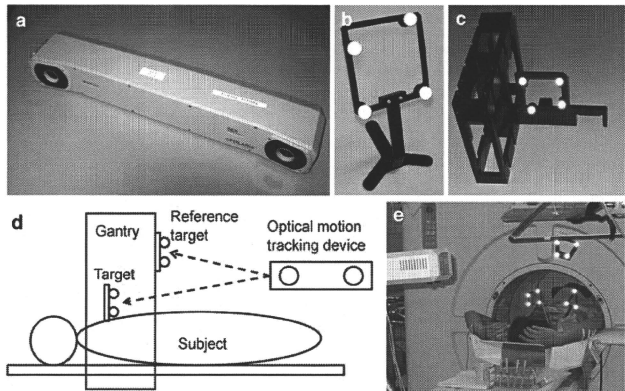
Hardware-based position monitoring system

To detect motion of a subject, we adopted an optical motion-tracking device in which targets attached to the chest skin are monitored. The motion compensation approach using an optical motion-tracking system has been previously validated in brain PET studies [3–7]. We applied this approach to the cardiac PET studies. Figure 1a shows an optical motion-tracking system, POLARIS (Northern Digital Inc., Canada). The POLARIS has two charge-coupled-device cameras, and provides the 3D position of a target. The three-dimensional position is measured in the form of 6 degrees of freedom: three rotational angles, and three translational directions. The manufacturer reports that the accuracy of the rotational angle and translation are better than 0.3° and 0.5 mm, respectively. Figure 1b shows a target with four infrared-reflective markers and supporting post. The target and supporting post made of carbon resin were pinned with two fluoroplastic screws. Figure 1c shows the position calibration tool used to convert the locations of subject positions in the POLARIS coordinate into PET coordinates. Figure 1d represents the schematic diagram of our system. Locations of targets attached to the chest skin of the subject and the gantry of a PET scanner were measured with the POLARIS. The target on the gantry of the PET scanner was used as a reference in order to convert the subject's positions from the POLARIS coordinate to the PET coordinate. Figure 1e shows an example of the experimental setup with a healthy volunteer in the cardiac PET study. Two targets were attached to the chest skin of the subject. Three legs of the supporting post were attached to the skin of the subject using surgical tape. The axial field-of-view (FOV) of the PET scanner used in the human study, HEADTOME-V tomography (SHIMADZU Corp., Kyoto, Japan), was 200 mm, and the gantry diameter was 850 mm [21]. The geometries of targets attached to the thoracic surface were $85 \times 85 \text{ mm}^2$ (the left-hand target in Fig. 1e, target 1) and $65 \times 90 \text{ mm}^2$ (the right-hand target in the Fig. 1e). The heights of supporting posts for target 1 and target 2 were 50 and 42 mm, respectively. We calculated the subject's positions in the PET coordinate by measuring the locations of the target with four infrared-reflective markers (the primary target). Another target was used as a reserve in cases when the primary target was hidden from the FOV of the POLARIS.

Motion correction

The rigid motion correction technique employed is an extension of the previous work for brain PET studies by

Fig. 1 Our motion correction system. **a** Optical motion-tracking device. **b** Target consists of infrared-reflective markers with supporting post. **c** Position calibration tool with a target. **d** Schematic diagram of the system. Locations of the targets on the subject and the gantry were measured with the optical motion-tracking device. **e** An example of the experimental configuration



Watabe et al. [4]. We consider four coordinates: the POLARIS C_S , a target on a PET gantry for reference C_G , a target attached on a subject C_T , and the PET scanner C_P . By measuring the location and orientation of each target attached to the subject and the gantry using the POLARIS, we obtained a 4×4 transformation matrixes, $T_{T \rightarrow S}$ from C_T to C_S , and $T_{G \rightarrow S}$ from C_G to C_S , respectively. Motion matrix $M_{P_1 \rightarrow P_2}$ from a position $P_1 = P(t_1)$ to another position $P_2 = P(t_2)$ in the PET coordinate is written as follows [4]:

$$M_{P_1 \rightarrow P_2} = T_{G \rightarrow P} T_{G \rightarrow S}^{-1} T_{T_1 \rightarrow S} T_{T_2 \rightarrow S}^{-1} T_{G \rightarrow S} T_{G \rightarrow P}^{-1} \quad (1)$$

where T_1 and T_2 are positions in target coordinates corresponding to positions P_1 and P_2 in the PET coordinate. $T_{G \rightarrow P}$ is the matrix to transform a position from the gantry coordinate to the PET coordinate. The matrix is given by the following equation:

$$T_{G \rightarrow P} = T_{S \rightarrow P} T_{G \rightarrow S} \quad (2)$$

$T_{S \rightarrow P}$ is the matrix which relates the POLARIS and PET coordinates and is obtained by position calibration.

The point source was embedded in a given position of a target, which is fixed on the calibration tool shown in Fig. 1c. By measuring the position of the point source using the POLARIS, the position $P_S = (x_s, y_s, z_s)$ of the point source in the POLARIS coordinate is calculated using the known position $P_T = (x_T, y_T, z_T)$ in the target coordinate and $T_{T \rightarrow S}$, as $P_S = T_{T \rightarrow S} P_T$. The position $P_P = (x_p, y_p, z_p)$ in the PET coordinate is also obtained from the reconstructed emission image. By changing the position of the target, in which the point source is embedded, $T_{S \rightarrow P}$ is calculated using the least-squared-fit between the pairs of P_{SS} and P_{Ps} . The PET coordinate was

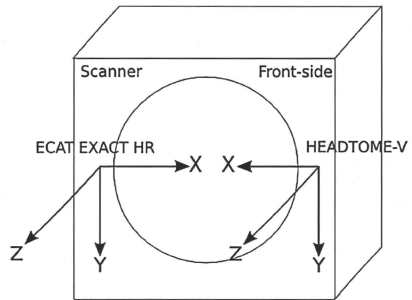


Fig. 2 PET coordinates defined by position calibrations

defined by the position calibration as shown in Fig. 2. The positions of subjects in the PET coordinate will be discussed in the following.

To correct a subject's movements during a dynamic acquisition of an emission scan with multiple frames, we estimated the heart locations from the locations of the target, which are measured by the POLARIS. The displacement of the COG of the heart's position from during the transmission scan to during each dynamic frame of the emission scan is given by

$$\begin{aligned} H^F - H^{TCT} &= \frac{1}{L} \sum_1^F H(t) - \frac{1}{N} \sum_1^{TCT} H(t) \\ &= \frac{1}{L} \sum_1^F [P(t) + \Delta(t)] - \frac{1}{N} \sum_1^{TCT} [P(t) + \Delta(t)] \end{aligned} \quad (3)$$

where H^{TCT} and H^{F} are the averaged COGs of the heart positions during the transmission and the dynamic frame, $H(t)$ and $P(t)$ are the COGs of positions of the heart and the target at time t , $\Delta(t)$ is a term representing a non-rigid relation for positions at time t between the heart and the target, L and N are the numbers of measurements of the target's positions by the POLARIS during acquisition of the dynamic frame and the transmission scan, respectively. For motion correction, we assumed the rigid body model, in which the target and the COG of the heart's position have linear movement at least in the FOV of a PET scanner, that is, we assumed that summations of $\Delta(t)$ for the transmission scan and the dynamic frame equal to zero. The procedures of our motion-correction technique are as follows: (1) An attenuation map is aligned to the coordinate of a dynamic frame of an emission scan using the motion matrix in Eq. 1, in which P_1 and P_2 are $\Sigma^{\text{TCT}}P(t)/N$ and $\Sigma^{\text{F}}P(t)/L$ in Eq. 3. (2) The attenuation map is then converted to its sinogram by forward projection. (3) Each sinogram of the dynamic frames is reconstructed with the realigned attenuation sinogram. (4) The emission image is aligned to the transmission coordinate with the inverse matrix of the motion matrix. (5) Last, procedures from 1 through 4 are repeated for all dynamic frames of the emission data.

Position calibrations

Position calibrations were performed on two PET scanners to obtain a matrix $T_{G \rightarrow P}$ in Eq. 2, which transforms the subject's positions from a gantry coordinate to a PET coordinate. For ECAT EXACT HR tomography (CTI/Siemens, Knoxville, TN, USA) [22] used in a cardiac phantom study, ten emission scans were performed, each displaying different positions of a radioactivity point source of ^{18}F solution, using the calibration tool in Fig. 1b. For the PET scanner used in a healthy volunteer study, 14 emission scans were performed with the ^{18}F solution point source and calibration tool.

The accuracy of the calibrations was evaluated from $T_{G \rightarrow S}$ and $T_{S \rightarrow P}$ in Eq. 2. The accuracy of $T_{G \rightarrow S}$ part was evaluated by determining the standard deviation (SD) of rotational angles and translations calculated from position data of the gantry, because $T_{G \rightarrow S}$ depends on only the accuracy of the measurements in regard to the POLARIS. To evaluate the accuracy of $T_{S \rightarrow P}$ part, we calculated errors between a position of a point source P_P , and the approximation position using $T_{S \rightarrow P}$, $P_X = T_{S \rightarrow P}P_S$:

$$e(i, k) = P_X(i, k) - P_P(i, k) \quad (4)$$

$$\text{RMSE}(i) = \sqrt{\sum_{k=X, Y, Z} |P_X(i, k) - P_P(i, k)|^2} \quad (5)$$

($k = X, Y, Z$ and $i = 1, \dots, N$)

where $e(i, k)$ is the approximation error of a point source in the i th position for each direction, X, Y , and Z are orthogonal axes in Fig. 2, $\text{RMSE}(i)$ is the root mean square error, and N is the number of positions of a point source.

Phantom study

To validate our correction technique for the misregistration between the attenuation map and emission data, we performed PET scans using a cardiac phantom (KYOTO KAGAKU co., LTD, Kyoto, Japan, type HL-D) and the ECAT EXACT HR tomography. The phantom mimics the human thoracic region and has cardiac and liver inserts. The insert can be filled with radioisotope solution. The myocardium and liver inserts were filled with the ^{18}F solution of relative activities of 1 and 4. A target (without the supporting port) for the POLARIS was attached to the phantom using polyethylene cross tape. Then, we performed a 1,000-s transmission scan for attenuation corrections. After the transmission scan, seven ^{18}F emission scans were performed with a set of single frame data for 180 s. The first scan was the baseline (scan #1), in which there was no misalignment to the transmission. For the following three emission scans (scan #2–4), the phantom was moved in the X, Y , and Z directions. For the other three scans, the phantom was rotated about the X, Y , and Z axes (scan #5–7). The phantom's positions were measured with the POLARIS.

The reconstructed images before and after the correction were obtained using an FBP (filtered back-projection) algorithm with a Gaussian filter of 6 mm FWHM (full-width at half-maximum). The matrix size and voxel size of images were $128 \times 128 \times 47$ and $4.4 \times 4.4 \times 3.1 \text{ mm}^3$, respectively. All emission data were corrected for physical decay of ^{18}F with base time as the start of the first emission scan, and all of the emission images were reoriented to the short axis using a transformation matrix.

To evaluate the effects of the corrections, we calculated correlation coefficients for myocardial regions between the baseline and misaligned emission images, both before and after the corrections.

Human study

A cardiac ^{15}O -water PET study was performed on a healthy volunteer (male, 32 years old) using the HEADTOME-V tomography in order to validate use of the external markers on the chest skin and also to evaluate the effects of the global movement on the quantification of MBF by artificial misalignment between attenuation and emission data. The healthy volunteer gave written informed consent according to a protocol approved by the Ethical Committee and

Internal Review Board of Osaka University. The PET study consisted of a 20-min transmission scan, an 8-min ^{15}O -CO emission scan for blood pool imaging, a 6-min ^{15}O -water emission scan with 26 dynamic frames (12×5 , 8×15 and 6×30 s), and a second 20-min transmission scan. All scans were acquired in a 2D acquisition mode. The radioactivity of inhaled ^{15}O -CO gas was 3.2 GBq. ^{15}O -water was injected via the left brachial vein; activity was 1.1 GBq for 40 s. All scans were performed without pharmacological stress. To investigate the accuracy of the POLARIS for tracking the locations of the target attached to the thorax skin of the subject, the couch of the PET scanner was moved +30 mm along the axial direction before the second transmission scan, corresponding to the Z direction in Fig. 2, with the subject lying on the couch. It was expected that the shift in the +Z direction caused the artificial deterioration of image quality and quantitative accuracy in especially the anterior and lateral regions. The subject's positions during the scans were monitored by the POLARIS, at a frequency of one sample per second.

The reconstructed images for the four cases were obtained using an FBP algorithm with a Gaussian filter of 9 mm FWHM. The matrix and voxel sizes of the reconstructed images were $128 \times 128 \times 63$ and $2.03 \times 2.03 \times 3.13$ mm³. No scatter correction was performed during the image reconstruction stage.

Regional MBF values were estimated for four cases. Case 1: the first attenuation map and emission data, case 2: the first attenuation map and emission data with correction for the subject's motions, case 3: the second attenuation map and the emission data, case 4: the second attenuation map and the emission data after the correction for the subject's motions and the 30-mm-shifted misalignment. Differences in the MBF values for cases 1 and 2 were considered to indicate effects from the correction for the frame-averaged motion if the subject's motion was small. Differences in MBF values for cases 1 and 3 could indicate errors in the quantification of MBF caused by the artificial misalignment between the second attenuation map and the emission data. The lack of any difference in MBF values for cases 1 and 4 indicated that our technique tracked the shift of the target on the thorax skin accurately and corrected the misalignment. In order to generate cases 2 and 4, the positions P_1 and P_2^j in Eq. 1 were calculated as averaged COGs of the subject's positions during the first and second transmission scans and the j th dynamic frame of ^{15}O -water or C^{15}O emission scan. Using Eq. 1 with P_1 and $\{P_2^j\}$, we performed frame-by-frame motion corrections for all dynamic frames of emission data. Due to the fact that the PET scanner did not provide a dynamic transmission scan, we assumed that the subject did not move during the transmission scan.

For quantification of MBF, we employed a compartment analysis model proposed by Iida et al. [13], which provided corrections for spillover from a left ventricle and partial volume effect and generated a MBF value in units of mL/min/g of perfusable tissue. All transmission and emission images were reoriented to the short axis. To calculate tissue time activity curves, regions of interest (ROIs) were drawn in nine myocardial regions: apical, mid-anterior, mid-lateral, mid-posterior, mid-septal, basal-anterior, basal-lateral, basal-posterior, and basal-septal regions. To avoid spillover effects from the right ventricle, the sizes of ROIs in septal regions were smaller than those in other regions. Another ROI was drawn on the left ventricle in order to estimate the arterial input function [19]. These ROIs were manually and independently drawn for the four cases. In addition, to validate the consistency between the quantitative results of MBF values and the quality of the images, we calculated the build-up and washout phase images [23] for the four cases. The build-up and washout phase images were obtained by subtracting a blood pool image from summed images of early (0–180 s) and later (180–360 s) frames of a ^{15}O -water image.

We evaluated the magnitude of the subject's motions in the PET coordinate during each scan. We defined position P_1 in Eq. 1 as the position at the start of the first transmission scan, and position P_2 as the position at an arbitrary time during a transmission or an emission scan. The rotational angles and translations for arbitrary times were obtained using Eq. 1. We represented motion during a scan in the form of mean \pm SD for each rotational angle and translation.

Results

Position calibrations

Table 1 shows the inherent accuracy of our system in the two PET scanners. Values of SDs for rotations and translations obtained from $T_{G \rightarrow S}$ data were very small. Table 1 also shows the approximation errors (mean \pm SD) occurred while transforming the positions of a point source from the POLARIS coordinate to the PET coordinate using $T_{S \rightarrow P}$. There was no bias in any direction in either scanner. Each value of RMSE was smaller than the spatial resolution of the corresponding scanner [21, 22].

Cardiac phantom study

Table 2 lists the observed misalignment from the reference position of the phantom in the transmission scan and the correlation coefficients between the reference image and the misaligned images before and after the corrections (mean \pm SD; 0.929 ± 0.022 and 0.987 ± 0.010). The