Estimation of arterial input by a noninvasive image derived method in brain H$_2^{15}$O PET study: confirmation of arterial location using MR angiography

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Abstract

A noninvasive method to estimate input function directly from H$_2^{15}$O brain PET data for measurement of cerebral blood flow (CBF) was proposed in this study. The image derived input function (IDIF) method extracted the time-activity curves (TAC) of the major cerebral arteries at the skull base from the dynamic PET data. The extracted primordial IDIF showed almost the same radioactivity as the arterial input function (AIF) from sampled blood at the plateau part in the later phase, but significantly lower radioactivity in the initial arterial phase compared with that of AIF-TAC. To correct the initial part of the IDIF, a dispersion function was applied and two constants for the correction were determined by fitting with the individual AIF in 15 patients with unilateral arterial stenoocclusive lesions. The area under the curves (AUC) from the two input functions showed good agreement with the mean AUC$_{IDIF}$/AUC$_{AIF}$ ratio of 0.92 ± 0.09. The final products of CBF and arterial-to-capillary vascular volume ($V_0$) obtained from the IDIF and AIF showed no difference, and had with high correlation coefficients.

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Introduction

Positron emission tomography (PET) with H215O is the standard and most reliable approach for quantitative measurement of cerebral blood flow (CBF). However, it requires blood sampling from an arterial line, which is an invasive procedure with cannulation in the brachial artery or the radial artery, to estimate the arterial input function (AIF). It does not necessarily represent the precise AIF of the major cerebral arteries, and usually the arterial time-activity curve (TAC) from the sampled blood data needs further corrections of delay and dispersion to estimate the brain AIF (Kanno et al 1987, Toussaint and Meyer 1996). The image derived input function (IDIF) method would also need appropriate correction for well known effects of partial volume, spill-out and spill-in; however, if the AIF can be estimated from dynamic PET data, it would reduce the invasiveness to patients of the PET scans while also eliminating complicated handling procedures and reducing practitioners’ radiation exposure (Zanotti-Fregonara et al 2011). Furthermore, the time difference between the arterial blood sampling site and the major cerebral arteries may induce an estimation error compared with the corrected IDIF obtained from the TAC of the local arteries.

There are several methods to estimate AIF noninvasively other than the IDIF; however, they are tracer specific due to differences in tracer kinetics and amount of radio-metabolites produced in the body (Zanotti-Fregonara et al 2011). Although a number of studies tried to establish IDIF methods, only a few studies showed effective ways for brain 15O-PET. Iida et al (1998) developed the IDIF method using the large vessels for the TAC from a dual PET system; this method requires a specific imaging modality to define regions of interest (ROI) on the aorta or the heart to estimate the AIF. Treyer et al (2003) reported a method based on the wash out rate of a tracer, although it employs scaling based on a standard input curve that neglects individual differences in physiology and uncontrolled timing variability of tracer introduction. Iguchi et al (2013) used a semi-automated MR-guided technique to estimate AIF noninvasively for 15O2 and C15O2 PET by applying the recovery coefficient correction. Kudomi et al (2016) proposed a method using multiple tissue curves from brain dynamic PET images with rate constant parameters. Recently, more sophisticated methods were developed by co-registration of PET and MR angiography images (Fung et al 2013, Su et al 2013, 2016), although the method requires individual MRI scans.

Our purpose was to develop a suitable noninvasive method of extracting the input function directly from a brain H215O dynamic PET study, and to apply the method for evaluation of hemodynamics in patients with cerebrovascular disease (CVD). The arterial TAC from IDIF was corrected for dispersion, as well as possible spill-out and partial volume effect (PVE) simultaneously using a dispersion function to obtain brain hemodynamic parameters. The extracting method of arterial IDIF was confirmed with reference to MR angiography for precise location of arteries at the skull base.

Material and methods

Subjects

Thirty-three patients (16 males and 17 females, 46.3 ± 20.8 y.o.) with cerebrovascular disease were included in the study. Fifteen patients had unilateral stenosis or occlusions in
the internal carotid artery (ICA), the common carotid artery (CCA), or the middle cerebral artery (MCA). Two patients had bilateral stenosis in the ICA, and the other 16 patients had moyamoya disease caused by occlusive lesions in the Willis ring. They underwent a $^{15}$O-PET study to evaluate their hemodynamic status before further treatment was considered. They also underwent MRI scans (Discovery 750, GE Healthcare, Milwaukee, WI, USA) to co-register the PET and MR images and to confirm the precise location of ROIs and volume of interest (VOI). The $^{15}$O-PET study for CVD patients to evaluate hemodynamic parameters was approved by the Ethics Committee of the University of Fukui, Faculty of Medical Sciences, and written informed consent was obtained from each patient. This study was designed retrospectively to improve the accuracy of the hemodynamic PET parameters using the $^{15}$O-PET data.

**PET data acquisition**

A whole-body PET scanner (Advance, GE Medical Systems, Milwaukee, WI, USA) was used for PET data acquisition. The scanner permits simultaneous acquisition of 35 image slices in 2D mode with an interslice spacing of 4.25 mm (DeGrado et al 1994). Brain H$_2^{15}$O PET data of the CVD patients with arterial blood sampling were used in the study. The details of PET scans were described in the previous papers (Okazawa et al 2007, Isozaki et al 2011). In brief, 3 min dynamic PET acquisition with a bolus injection of 555 MBq $^{15}$O-water was performed to calculate CBF (ml/100 g/min) and arterial-to-capillary blood volume ($V_0$: ml/100 g) images. Each dynamic scan consisted of frames of 2 s $\times$ 30, 10 s $\times$ 6, and 20 s $\times$ 3. An arterial line was obtained from the brachial artery, and arterial blood radioactivity during H$_2^{15}$O scans was counted continuously at a constant rate of 7 ml min$^{-1}$ using an automatic arterial blood sampling system (ABSS) with a positron radioactivity counter (Apollomec Co. Ltd, Kobe, Japan) and a mini-pump (AC-2120, Atto Co., Tokyo, Japan). After 2 min continuous blood sampling with the ABSS, manual blood sampling (0.5 ml) was performed every 20 s during the remaining scan time. Radioactivity of the ABSS was calibrated with the manually sampled blood at 2 min after tracer administration. Decay of the radioactivity from dynamic PET acquisition and blood data was corrected to the starting point of each scan. The arterial TAC obtained from ABSS was corrected for dispersion of the external tube (Okazawa et al 2002). Although C$^{15}$O and $^{15}$O$_2$ PET scans were also performed in the $^{15}$O-PET study, these data were not used in the present study.

**Estimation of IDIF**

The 12 slices at the skull base in the average images of the initial 10 frames were used for extraction of the internal carotid artery (ICA). The most intense 30 voxels in radioactivity of the 12 slices were extracted to evaluate only voxels inside the bilateral ICA. To confirm the position of the arterial VOI mask, 3D time-of-flight MRA (TOF-MRA) images were used for co-registration of individual patient’s PET and MRI (Su et al 2013). By applying the VOI mask on the dynamic PET data, slice-by-slice average ICA counts of each frame were obtained. The primordial IDIF ($C_{PI}(t)$) were generated from the maximum counts of the slice-wise mean obtained above.

After the delay and dispersion correction of the TAC from ABSS ($C_A(t)$) (Okazawa et al 2002), it was used for correction of the initial phase of $C_{PL}(t)$, in which a double exponential function was applied. In brief, the initial phase of the $C_{PL}(t)$ can be represented as

$$C_{PL}(t) = C_A(t) \otimes d(t),$$

(1)
where \( C_{Pl}(t) \) and \( C_A(t) \) are the initial phases of \( C_{Pl}(t) \) and \( C_A(t) \), respectively (Iida et al 1986, Meyer 1989). \( \otimes \) represents the convolution and \( d(t) \) is the dispersion function. \( d(t) \) can be expressed by the following double-exponential equation (Yeung et al 1992, Vafaee et al 1996):

\[
d(t) = \frac{a}{\tau_1} e^{-\frac{t}{\tau_1}} + \frac{1-a}{\tau_2} e^{-\frac{t}{\tau_2}},
\]

where \( \tau_1, \tau_2 \) are the dispersion time constants and \( a \) is the amplitude factor of the first term. The \( C_A(t) \) can be estimated from the following equation using Laplace transforms of equation (1):

\[
C_A(t) = \frac{\tau_1 + \tau_2}{a(\tau_2 - \tau_1) + \tau_1} C_{Pl}(t) + \frac{\tau_1 \tau_2}{a(\tau_2 - \tau_1) + \tau_1} \left( \frac{dC_{Pl}}{dt} \right)
\]

(3)

\[
C_A(t) = AC_{Pl}(t) + B \left( \frac{dC_{Pl}}{dt} \right)
\]

(4)

With fixed values of \( \tau_1, \tau_2 \) and \( a \), the terms \( \frac{\tau_1 + \tau_2}{a(\tau_2 - \tau_1) + \tau_1} \) and \( \frac{\tau_1 \tau_2}{a(\tau_2 - \tau_1) + \tau_1} \) can be substituted by constants \( A \) and \( B \). In equation (4), \( C_A(t) \) and \( C_{Pl}(t) \) are the known quantities, and the two unknown constants \( A \) and \( B \) can be determined using regression analysis. To determine the optimal constants of \( A \) and \( B \), the normal sides of the 15 patients with unilateral stenoocclusive ICA lesions were analyzed, and the mean values of \( A \) and \( B \) from this analysis were used as the fixed constants for all patients. The \( C(t) \) was obtained from the \( C_{Pl}(t) \) with dispersion and PVE correction in the initial part, followed by the maximal counts of the slice-wise means in the VOI mask in the later plateau phase. The initial part of an arterial curve was determined as the period from the beginning of the tracer injection to the point that arterial radioactivity settled into a plateau level after the washout phase. In most patients, the first 45 s could be applied for the initial phase except for a few cases who took a long time up to a steady level.

To compare the difference of the two input functions, AUCs of AIF (\( C_A(t) \)) and IDIF (\( C_I(t) \)) were calculated because the values of hemodynamic parameters are closely correlated with the area under the curve (AUC) of the input function (Jochimsen et al 2016). The ratios of the two curves (\( r \text{AUC} = \text{AUC}_{\text{IDIF}}/\text{AUC}_{\text{AIF}} \)) were also calculated.

The pixelwise delay correction method in our previous study was used for the regional delay and dispersion correction (Islam et al 2017), and AIF and IDIF thus obtained were used for further steps of hemodynamic parameter estimation. In the method, the least-square fitting was applied for delay estimation between regional brain tissue TACs and arterial input curves (Iida et al 1986; Islam et al 2017).

Calculation of regional CBF and \( V_0 \)

CBF and \( V_0 \) images were calculated from brain PET data with AIF (\( C_A(t) \)) and IDIF (\( C_I(t) \)) using a one-tissue compartment model (1-TCM) by applying a weighted integration method as described elsewhere (Ohta et al 1992, 1996). In brief, the model for the 1-TCM can be represented by the following equation:

\[
\frac{dM_e(t)}{dt} = K_1 C_A(t) - k_2 M_e(t),
\]

(5)

where \( M_e(t) \) (Bq/100 g) is the radioactivity in the brain tissue and \( C_A(t) \) (Bq ml\(^{-1}\)) is the delay and dispersion corrected input function from \( C_A(t) \) for AIF images and \( C_I(t) \) for IDIF images. \( K_1 \) (ml/100 g/min) and \( k_2 \) (1 min\(^{-1}\)) are the rate constants for influx and outflux of the tracer, respectively, and \( K_1 \) apparently represents regional CBF. The equation is solved as equation (6).
\[ M_r(t) = K_1 C_a(t) \otimes e^{-k_2 t} \]  

(6)

Including the radioactivity in the intravascular spaces, total radioactivity in the brain is expressed as

\[ M(t) = K_1 C_a(t) \otimes e^{-k_2 t} + V_0 C_a(t), \]  

(7)

where \( M(t) \) (Bq/100g) is the regional PET count, and \( V_0 \) (ml/100g) is the arterial-to-capillary vascular volume (Ohta et al 1996). Equation (7) can be integrated after weighting with three different weights of \( w_i(t) \) \((i = 1-3)\) as below:

\[ \int_0^T w_1(t)M(t)\,dt = K_1 \int_0^T w_i(t)C_a(t) \otimes e^{-k_2 t}\,dt + V_0 \int_0^T w_i(t)C_a(t)\,dt \]  

(8)

Here, \( K_1, k_2 \) and \( V_0 \) can be calculated from measured \( M(t) \) and \( C_a(t) \) using the weighted integration method (Ohta et al 1992, 1996). In brief, equation (9) is obtained by rearranging three equations of equation (8) to eliminate the \( V_0 \) term, where \( K_1 \) is canceled, and various \( k_2 \) values can be estimated from the right-hand side ratio using the table look-up method.

\[
\frac{\int_0^T w_3(t)C_a(t)\,dt \cdot \int_0^T w_1(t)M(t)\,dt - \int_0^T w_1(t)C_a(t)\,dt \cdot \int_0^T w_3(t)M(t)\,dt}{\int_0^T w_3(t)C_a(t)\,dt \cdot \int_0^T w_2(t)M(t)\,dt - \int_0^T w_2(t)C_a(t)\,dt \cdot \int_0^T w_3(t)M(t)\,dt} \\
= \frac{K_1 \left[ \int_0^T w_3(t)C_a(t)\,dt \cdot \int_0^T w_1(t)C_a(t) \otimes e^{-k_2 t}\,dt \right.}{\left. - \int_0^T w_1(t)C_a(t) \cdot \int_0^T w_3(t)C_a(t) \otimes e^{-k_2 t}\,dt \right.} \\
- \frac{K_1 \left[ \int_0^T w_3(t)C_a(t)\,dt \cdot \int_0^T w_2(t)C_a(t) \otimes e^{-k_2 t}\,dt \right.}{\left. - \int_0^T w_2(t)C_a(t) \cdot \int_0^T w_3(t)C_a(t) \otimes e^{-k_2 t}\,dt \right.}
\]  

(9)

The \( K_1 \) values can be estimated either from the numerator or denominator by substituting the \( k_2 \) values in equation (9). The same weighting functions of \( w_i(t) \) to \( w_3(t) \) were used as in the original papers (Ohta et al 1992, 1996). Finally, the parameter \( V_0 \) can be obtained from \( K_1 \) and \( k_2 \) using equation (8).

**Statistical analysis**

CBF and \( V_0 \) images calculated from the \( C_A(t) \) and \( C_t(t) \) were then compared by scatter plots for pixelwise comparison of AIF and IDIF. Bland–Altman plots (Bland and Altman 1986) were applied to observe relationships and bias distribution of CBF and \( V_0 \) pixel values from the two methods. To compare the regional values, 30 circular ROIs 10 mm in diameter were set in the MCA territory of each hemisphere and applied to all parametric images of individual subjects (figure 1). Repeated measures analysis of variance (ANOVA) with a post-hoc test (paired \( t \)-test) was applied to analyze the difference in cortical CBF and \( V_0 \) values between the AIF and IDIF methods, as well as between the ipsilateral and contralateral hemispheres. \( P < 0.05 \) was considered to be statistically significant.

**Results**

Representative 3D views from the TOF-MRA image of a CVD patient are shown in figures 2(a)–(c). Arterial high radioactivity from the average image of the initial ten frames of PET data was superimposed on the MRI. The extracted primordial IDIF \( (C_{PI}(t)) \) showed lower
counts in the initial phase compared with the TAC from the ABSS; however, they had almost equal count level in the later phase of about 45 s and beyond (figure 2(d)).

TACs of $C_{PI}(t)$, $C_I(t)$, and $C_A(t)$ from a representative case are shown in figure 3. The $C_I(t)$ seems to fit closely with the $C_A(t)$ from visual inspection. $A$ and $B$ in equation (4) were
estimated from the 15 patients with unilateral CVD and the means of the constants from them were \( A = 3.5 \pm 0.6 \) and \( B = 3.0 \pm 2.7 \). These constants were used for all patients’ \( C_p(t) \) correction, and the mean of rAUC of all patients was 0.92 \( \pm 0.09 \).

Pixelwise comparisons of CBF and \( V_0 \) images from a representative case by using AIF and IDIF are shown in figure 4. CBF and \( V_0 \) pixel values showed good agreement for pixels all over the brain with excellent correlations (\( r^2 > 0.99 \)).

Figure 5 shows Bland–Altman plots for CBF and \( V_0 \) from the same images as in figure 4. In CBF image, the mean of global bias was very small (0.2 ml/min/100 g) and there was no tendency of biases in small and large CBF. On the other hand, \( V_0 \) tended to show smaller values than \( V_0 \) in the high \( V_0 \) region although most pixels were within a small range of difference.

Comparison of the cortical CBF and \( V_0 \) values from AIF and IDIF is shown in table 1. The mean values of CBF and \( V_0 \) obtained from AIF and IDIF were similar for each hemisphere (3% and 2% difference, respectively) and there were no significant differences (\( p > 0.05 \), paired \( t \)-test), but there were significant differences between the two hemispheres on both images (table 1). Plots of regional values for individual parameters showed close correlation between images from AIF and IDIF, and the correlation coefficients were 0.91 \( \pm 0.09 \) and 0.89 \( \pm 0.13 \) for the ipsi- and contra-lateral CBF and 0.96 \( \pm 0.02 \) for \( V_0 \) of both sides, respectively.

**Discussion**

In the present \( H_2^{15}O \) brain PET study, regional values of CBF and \( V_0 \) from the IDIF were very close to those from the conventional AIF method with blood sampling. After delay and dispersion correction, the AIF and IDIF showed similar TACs which were acceptable even after using fixed constants determined from the normal sides of the 15 unilateral CVD patients for
dispersion correction. Pixelwise analysis also showed close correlation between the methods for both CBF and \( V_0 \). These results indicate that arterial blood sampling may be replaced by the IDIF, a less invasive and more patient-friendly method requiring only dynamic brain PET images.

For the detection of arterial ROI through which blood is supplied into the brain, the initial frames of slices at the skull base were used. Images of the initial frames of brain PET data usually show the major arteries better than in the later phase where the radioactivity in the brain reaches a steady state (Zanotti-Fregonara et al. 2011). It is difficult to extract good arterial

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**Table 1.** Comparison of regional CBF and \( V_0 \) values between AIF and IDIF.

|            | Ipsilateral | Contra-lateral |
|------------|-------------|----------------|
| **CBF**    | 49.2 ± 6.6\(^a\) | 54.2 ± 5.5     |
| **\( V_0 \)** | 0.97 ± 0.43\(^b\) | 1.11 ± 0.56    |
| **CBF**    | 50.7 ± 9.0\(^a\) | 55.7 ± 8.2     |
| **\( V_0 \)** | 0.99 ± 0.35\(^a\) | 1.10 ± 0.45    |
| **Correlation coefficients** | 0.91 ± 0.09 | 0.96 ± 0.02 |

Note: mean values were obtained from ROIs on MCA territory of CBF (ml/100 g/min) and \( V_0 \) (ml/100 g) images. Correlation coefficients between AIF and IDIF were calculated from individual regional ROI values on MCA territory and averaged for all patients.

\(^a P < 0.01, ^b P < 0.05\) comparing between the ipsi- and contra-lateral hemispheres.
TACs from a single specified slice level because of differences in the arterial shape and various TACs that depend on patient physiology. The ROI obtained from initial frames of multiple slices can reliably extract the high activity voxels in the ICA, and this can be confirmed by MRA co-registration. Since the method for generating VOI masks proposed in this study successfully detected the ICA location in all patients, it can be applied to H$_2^{15}$O PET study without MRA images if a patient does not have MRI.

The extracted primordial IDIF ($C_{PI}(t)$) showed very close radioactivity to arterial TAC in the later phase; however, it was significantly lower in the initial arterial phase as shown in figure 2. After appropriate cross-calibration between the PET scanner and well counter, the counts should be identical in the plateau phase except for the effects of PVE. However, high radioactivity in a small structure is affected not only by the PVE, but also by spill-in/spill-out effects. All the correction and filtering processes are used to obtain a better quality image from PET data, but they reduce pixel counts especially in the pixels with high activity at a transient condition (Iriarte et al 2016). Retrieval of the original counts at a transient condition in the major arteries may be possible using artery enhancement filters and by applying special post processing steps, in which the counts at major arteries would not be reduced, but the process would be methodologically challenging and complex (Zanotti-Fregonara et al 2011, Fung et al 2013, Su et al 2013, 2016).

We proposed an alternative approach by assuming that the dispersion function might correct both arterial dispersion and PVE of IDIF to estimate the initial part of AIF correctly. Co-registration of TOF-MRA directly revealed that the described method of the ICA VOI reliably extracted $C_{PI}(t)$ from the brain PET data. The primordial $C_{I}(t)$ obtained from the ICA VOI mask using multiple slices at the skull base could estimate a stable arterial radioactivity close to the real count in the later phase, although the initial arterial phase should be corrected for the underestimation. Using the 15 patients’ normal side ICA-TACs, constants of $A (3.5 \pm 0.6)$ and $B (3.0 \pm 2.7)$ for the double exponential dispersion function were determined and these constants provided acceptable results of IDIF correction. The mean of rAUC was small enough and corrected IDIF provided similar CBF and $V_0$ with very close values to the conventional method. The constants of the dispersion function might be suitable for PET data. 

Figure 5. Bland–Altman plots for relationships of parametric images from AIF and IDIF. CBF images showed a good correlation in a wide range from small to large CBF values; however, $V_0$ from the IDIF method ($V_{IDIF}$) tended to show small values in the large $V_0$ regions compared with that from AIF ($V_{AIF}$). Solid lines show the means of differences and dotted lines show $\pm 1.96$ SD.
of similar image quality with similar resolution; however, since the constants include factors of PVE as well, dispersion constants should be determined for each PET system. Because IDIF without any correction underestimated arterial input significantly (figure 3, gray line), CBF and \( V_0 \) images calculated from this uncorrected IDIF is not reliable. IDIF correction for dispersion and PVE should be needed for any PET data system. The double exponential function employed here seems appropriate because it provided a similar TAC to AIF and close regional values in parametric images. This new method without arterial blood sampling is less invasive and more patient-friendly, and requires only dynamic PET data. Another advantage of the IDIF method is that it does not require cross-calibration between the PET scanner and a well-counter, which will reduce errors in the process of blood sample counting.

**Conclusion**

The present study showed that the arterial input function was estimated by the image based method with similar quality to arterial blood sampling. The regional CBF and \( V_0 \) values calculated from the IDIF by the new method showed very close values from the conventional AIF method. The present IDIF method will be useful in clinical settings because of its less invasive nature.

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**References**

Bland J M and Altman D G 1986 Statistical methods for assessing agreement between two methods of clinical measurement *Lancet* **327** 307–10

DeGrado T R, Turkington T G, Williams J J, Stearns C W, Hoffman J M and Coleman R E 1994 Performance characteristics of a whole-body PET scanner *J. Nucl. Med.* **35** 1398–06

Fung E K and Carson R E 2013 Cerebral blood flow with \( ^{15} \)O-water PET studies using an image-derived input function and MR-defined carotid centerlines *Phys. Med. Biol.* **58** 1903–23

Iguchi S, Hori Y, Moriguchi T, Morita N, Yamamoto A, Koshino K, Kawashima H, Zeniya T, Enmi J and Iida H 2013 Verification of a semi-automated MRI-guided technique for non-invasive determination of the arterial input function in \( ^{15} \)O-labeled gaseous PET *Nucl. Instrum. Methods Phys. Res. A** **702** 111–3

Iida H, Miura S, Shoji Y, Ogawa T, Kado H, Narita Y, Hatazawa J, Eberl S, Kanno I and Uemura K 1998 Noninvasive quantitation of cerebral blood flow using oxygen-15- water and a dual-PET system *J. Nucl. Med.* **39** 1789–98

Iida H, Kanno I, Miura S, Murakami M, Takahashi K and Uemura K 1986 Error analysis of a quantitative cerebral blood flow measurement using \( H_2^{15} \)O autoradiography and positron emission tomography, with respect to the dispersion of the input function *J. Cereb. Blood Flow Metab.* **6** 536–45

Iriarte A, Marabini R, Matej S, Sorzano C O and Lewitt R M 2016 System models for PET statistical iterative reconstruction: a review *Comput. Med. Imaging Graph.* **48** 30–48

Islam M M, Tsujikawa T, Mori T, Kiyono Y and Okazawa H 2017 Pixel-by-pixel precise delay correction for measurement of cerebral hemodynamic parameters in \( H_2^{15} \)O PET study *Ann. Nucl. Med.* **31** 283–94
Isozaki M, Kiyono Y, Arai Y, Kudo T, Morì T, Maruyama R, Kikuta K and Okazawa H 2011 Feasibility of 62Cu-ATSM PET for evaluation of brain ischemia and misery perfusion in patients with cerebrovascular disease Eur. J. Nucl. Med. Mol. Imaging 38 1075–82.

Jochimsen T H et al 2016 Fully automated calculation of imagederived input function in simultaneous PET/MRI in a sheep model Eur. J. Nucl. Med. Mol. Imaging 3 2

Kanno I, Iida H, Miura S, Murakami M, Takahashi K, Sasaki H, Inugami A, Shishido F and Uemura K 1987 A system for cerebral blood flow measurement using an H215O autoradiographic method and positron emission tomography J. Cereb. Blood Flow Metab. 7 143–53

Kudomi N, Maeda Y, Yamamoto Y and Nishiyama Y 2016 Reconstruction of an input function from a dynamic PET water image using multiple tissue curves Phys. Med. Biol. 61 5755–67

Meyer E 1989 Simultaneous correction for tracer arrival delay and dispersion in CBF measurements by the H215O autoradiographic method and dynamic PET J. Nucl. Med. 30 1069–78

Ohta S, Meyer E, Fujita H, Reutens D C, Evans A and Gjedde A 1996 Cerebral [15O]water clearance in humans determined by PET: I. Theory and normal values J. Cereb. Blood Flow Metab. 16 765–80

Ohta S, Meyer E, Thompson C J and Gjedde A 1992 Oxygen consumption of the living human brain measured after a single inhalation of positron emitting oxygen J. Cereb. Blood Flow Metab. 12 179–92

Okazawa H, Kishibe Y, Sugimoto K, Takahashi M and Yamauchi H 2002 Delay and dispersion correction for a new coincidental radioactivity detector, pico-count, in quantitative PET studies Brain Imaging Using PET ed M Senda et al (New York: Academic) pp 15–21

Okazawa H, Tsuchida T, Kobayashi M, Arai Y, Pagani M, Isozaki M and Yonekura Y 2007 Can reductions in baseline CBF and vasoreactivity detect misery perfusion in chronic cerebrovascular disease? Eur. J. Nucl. Med. Mol. Imaging 34 121–9

Su Y, Arbelaez A M, Benzinger T L S, Snyder A Z, Vlassenko A G, Mintun M A and Raichle M E 2013 Noninvasive estimation of the arterial input function in positron emission tomography imaging of cerebral blood flow J. Cereb. Blood Flow Metab. 33 115–21

Tsou S, Vlassenko A G, Couture L E, Benzinger T L S, Snyder A Z, Derdeyn C P and Raichle M E 2016 Quantitative hemodynamic PET imaging using image-derived arterial input function and a PET/ MR hybrid scanner J. Cereb. Blood Flow Metab. 37 1435–46

Toussaint P J and Meyer E 1996 A sensitivity analysis of model parameters in dynamic blood flow studies using H215O and PET Quantification of Brain Function Using PET ed R Myers et al (New York: Academic) pp 196–200

Treyer V, Jobin M, Burger C, Teneggi V and Buck A 2003 Quantitative cerebral H215O perfusion PET without arterial blood sampling, a method based on washout rate Eur. J. Nucl. Med. Mol. Imaging 30 572–80

Vafaee M, Murase K, Gjedde A and Meyer E 1996 Dispersion correction for automatic sampling of O-15-labeled H2O and red blood cells Quantification of Brain Function Using PET ed R Myers et al (New York: Academic) pp 72–5

Yeung I W T, Lee T Y, Del Maestro R F, Kozak R, Bennett J D and Brown T 1992 An absorptiometry method for the determination of arterial blood concentration of injected iodinated contrast agent Phys. Med. Biol. 37 1741–58

Zanotti-Fregonara P, Chen K, Liow J S, Fujita M and Innis R B 2011 Image-derived input function for brain PET studies: many challenges and few opportunities J. Cereb. Blood Flow Metab. 31 1986–98