Abstract

The quantitative assessment of renal blood flow (RBF) would allow the understanding of the physiological basis of kidney function and the evaluation of pathophysiological events leading to vascular damage, such as renal arterial stenosis and chronic allograft nephropathy. The RBF may be quantified using PET with $H_2{}^{15}O$, although RBF studies that have been performed without theoretical evaluation, have assumed the partition coefficient of water (p ml/g) as uniform for whole region of renal tissue, and/or radioactivity from vascular space (V_A ml/ml) as negligible. The aim of this study is to develop a method to calculate parametric images of RBF (K_1, k_2) as well as V_A without fixing the p by the basis function method (BFM). The feasibility was tested in healthy subjects. A simulation study was performed to evaluate error sensitivities for possible error sources. Experimental study showed that the quantitative accuracy in the present method was consistent to nonlinear least-squares fitting, i.e., $K_{1,BFM}$=0.93$K_{1,NLF}$ -0.11 ml/min/g (r=0.80, $P<0.001$), $k_{2,BFM}$=0.96$k_{2,NLF}$–0.13 ml/min/g (r=0.77, $P<0.001$) and $V_{A,BFM}$=0.92$V_{A,NLF}$-0.00 ml/ml (r=0.97, $P<0.001$). Akaike information Criterion values from the present fitting are the smallest for all subjects except two. The quality of parametric images obtained was acceptable. The simulation study suggested that delay and dispersion time constants should be estimated within 2-sec accuracy. V_A and p cannot be neglected or fixed, and reliable measurement of even relative RBF values requires that V_A is fitted. We conclude that this study shows the feasibility of measurement of RBF using PET with $H_2{}^{15}O$.

Key words: Positron emission tomography, renal blood flow, compartment model, parametric image

Introduction

The quantitative assessment of renal blood flow (RBF) may help to understand the pathophysiological basis of kidney function and to evaluate pathophysiological events leading to vascular damage, such as renal arterial stenosis and chronic allograft nephropathy. The quantitative estimation of RBF by use of $H_2{}^{15}O$ and dynamic PET has been developed and demonstrated by Nitzsche et al [1]. The kinetic model of $H_2{}^{15}O$ has been based on the assumptions that all activity is extracted by the parenchyma, extraction is very rapid, and tubular transport has not started or is insignificant at a level that does not influence the calculation of renal blood flow [1-5]. From this assumption, region of interest (ROI) based estimation of RBF has been performed by the $H_2{}^{15}O$ dynamic PET approach [1, 3, 4]. Also, calculation of parametric RBF images has been performed [5]. However, the quantitative computation of RBF, so far, has assumed that the blood/tissue partition coefficient of water (p ml/g) was uniform for the whole region of renal tissue [3, 4], and/or that the contribution of radioactivity from vascular space was negligible [5-7]. The influence of quantitative accuracy from those assumptions is unknown.

The previous studies demonstrated to compute RBF from uptake rate (K_1 ml/min/g) [1-7]. Some studies also simultaneously compute p [6, 7], and the obtained apparent p value was ranged between 0.52 and 0.78 ml/g. From published values of water content for tissue as 76 % and for blood as 81 % [8], the p value can be physiologically determined as: p_{phys}=0.94 ml/g [9]. The extremely smaller apparent p value might be due to tissue mixture (or partial volume effect) [10, 11] because of composite structure of kidney. The effects of tissue mixture affect mostly K_1 and not clearance rate (k_2 min^{-1}). Therefore clearance rate of $H_2{}^{15}O$ (k_2 min^{-1}) multiplied by p_{phys} could be applied for the blood flow rather than K_1 ml/min/g [11], when affect of tissue mixture is not negligible, although it is unknown how the glomerular

filtration rate (GFR) additionally contribute to k_2. Thus, the influence of GFR on k_2 should be evaluated and corrected in the computation of RBF

The aim of this study was to develop a method to simultaneously calculate parametric images of K_1 and k_2 as well as the arterial blood volume (V_A ml/ml). The feasibility, in terms of quantitative accuracy and image quality on calculated images, were experimentally tested in healthy subjects. GFR was measured for each subject to investigate how much it contributes to the clearance rate (k_2 min^{-1}). A simulation study was also performed to evaluate error sensitivities for possible error sources.

Materials and methods

Theory

The present formula was characterized by simultaneously estimating multiple parameters of uptake rate constant (K_1 ml/min/g) and clearance rate constant (k_2 ml/g) as well as activity concentration in arterial vascular space (V_A ml/ml). The kinetic model for $H_2{}^{15}O$ was based on the single tissue compartment model as;

$$Ci(t) = (1 - V_A) \cdot K_1 \cdot A_w(t) \otimes e^{-k2 \cdot t} + V_A \cdot A_w(t) \qquad (1)$$

where *Ci(t)* (Bq/mL) is radioactivity concentration in a voxel of PET image, $A_w(t)$ (Bq/mL) is the arterial input function, ⊗ indicates the convolution integral..

In the present computation, we have applied a basis function method (BFM), which was introduced by Koeppe et al [12] to compute cerebral blood flow parametric image as well as the clearance rate constant simultaneously. Gunn et al [13] applied this method to parametric imaging of both binding potential and the delivery of the ligand relative to the reference region. The computation method has also been applied to myocardial blood flow studies to compute the uptake, clearance rates and blood volume [14, 15]. The BFM procedure for the present RBF computation is illustrated in Figure 1. The BFM method

enables to compute parametric images by using linear least squares together with a discrete range of basis functions as the parameter value for k_2 incorporating the nonlinearity and covering the expected physiological range. The corresponding basis functions formed as;

$$F(k_2,t) = A_w(t) \otimes e^{-k2 \cdot t} \tag{2}$$

For the physiologically reasonable range of k_2, i.e., $0 < k_2 < 15.0$ ml/min/g, 1500 discrete values for k_2 were found to be sufficient. Then Eq. (1) can then be transformed for each basis function into a linear equation as;

$$\begin{aligned} &Ci(t) = \Theta \cdot F(k_2,t) + \Psi \cdot A_w(t) \\ &\Theta = (1 - V_A) \cdot K_1 \\ &\Psi = V_A \end{aligned} \tag{3}$$

Hence for fixed values of k_2, the remaining two parameters Θ and Ψ can be estimated using given basis function by standard linear least squares, and obtained as: Θ_{k2} and Ψ_{k2}. The k_2 for which the residual sum of square;

$$s(k_2)^2 = \sum_t (Ci(t) - \Theta_{k2} \cdot F(k_2,t) - \Psi_{k2} \cdot A_w(t))^2 \tag{4}$$

is minimized is determined by a direct search and associated parameter values for this solution (K_1, k_2, V_A) are obtained.

Subjects

Six healthy human subjects (the demographics are shown in Table 1) were studied under the basal as well as under stimulation (after enalapril infusion) conditions. All subjects were non-smoking and none of them was taking any medication. All subjects gave written informed consent. The study was approved by the Ethical Committee of the Hospital District of South-Western Finland, and was conducted with the Declaration of Helsinki as revised in 1966.

PET Experiments

PET acquisition was carried out in 2D mode using the GE Advance PET scanner (GE Medical Systems, Milwaukee, Wis). After 300-sec transmission scan, two scans were undertaken with $H_2{}^{15}O$ (1.0 to 1.5 GBq) injection from cephalica vein in the right forearm. First scan was under resting conditions and the other was in stimulated conditions, namely, 20 min after 0.5 mg enalapril infusion. Scan protocol consisted of 20 frames with total of 240 sec (15 × 4 sec, and 5 × 10 sec).

During PET scanning, blood was withdrawn continuously through a catheter inserted in the left radial artery by using a peristaltic pump (Scanditronix, Uppsala, Sweden). Radioactivity concentrations in blood were measured with a BGO coincidence monitor system. The detectors had been cross-calibrated to the PET scanner *via* ion chamber [16].

Also, glomerular filtering ratio (GFR) was measured for each subject [17]. To obtain the PET equivalent flow ratio for GFR, kidney weight of 300 g and cortex ratio of 70 % were assumed [8].

Data Processing

Dynamic sinogram data were corrected for dead time in each frame in addition to detector normalization. Tomographic images were reconstructed from corrected sinogram data by the OSEM method using a Hann filter with a cut-off frequency of 4.6 mm. Attenuation correction was applied with transmission data. A reconstructed image consisted 128×128×35 matrix size with a pixel size of 4.3 mm × 4.3 mm and 4.2 mm with 20 frames.

Measured arterial blood time activity curves (TAC) were calibrated to the PET scanner and corrected for the dispersion (τ=5 and 2.5 sec for intrinsic and extrinsic, respectively) [18] and delay [19]. The corrected blood TAC was used as the input function.

A set of K_1, k_2 and V_A images were generated according to the BFM formula described above, using a set of dynamic reconstructed image and input function. Computations were programmed in C environment (gcc 3.2) on Sun workstation (Solaris 10 Sun Fire 280R) with 4 GB of memory and two Sparcv9, 900-MHz CPUs.

Data Analysis

A template of ROI was drawn on the whole region of each kidney on an image, which was obtained by summing whole frames of reconstructed dynamic image (average ROI sizes for the all subjects was 153 ± 43 cm^3). Also, a ROI was drawn on a region of high tracer accumulation on the summed image as an assumed cortical region. Functional values of K_1, k_2 and V_A were extracted from both of ROIs, i.e., for whole and cortical regions, respectively. Data were shown individually or as mean±SD. The Student's paired t-test was used for comparisons between the physiological states and $P<0.05$ was considered as significant.

The ROI for whole region was divided plane-by-plane into sub-regions of 10 pixels each. The sub-regions were created by extracting pixels firstly from horizontal then vertical directions inside the whole ROI in each slice. Each sub-region consisted of a single area with the same number of pixels. Functional values of K_1, k_2 and V_A were extracted from each sub-region. Also, tissue TACs were obtained in each sub-region from corresponding dynamic images. The three parameters of K_1, k_2 and V_A were estimated by using the Equation (1) and input function fitting to the tissue TACs by means of the nonlinear least-squares fitting method (NLF) (Gauss-Newton method). Then, functional values of K_1, k_2 and V_A from corresponding sub-regions were compared between the methods. The regression analysis was performed.

Model relevancy among introducing p and/or V_A in the computation was tested using the Akaike Information Criterion (AIC) [20]. The most appropriate model provides the

smallest AIC. The tissue TACs from above sub-regions were fitted and AICs were computed for models with three parameters of K_1, k_2 and V_A, fixing $p(=K_1/k_2)$ at 0.35 ml/g (mean value obtained in the present subjects), fixing V_A at 0 ml/ml, and fixing V_A at 0.15 ml/ml (mean value obtained in the present subjects).

Error Analyses in Simulation

Error propagation from error in input function for the present BFM formula was analyzed for two factors: delay and dispersion in arterial TAC. It is known that the measured arterial TAC is delayed and more dispersed relative to the true input TAC in the kidney because of the time and tube transit of blood through the peripheral artery and catheter tube before reaching the detector [18, 19]. Calculation of RBF, so far, employed a fixed partition coefficient: $p(=K_1/k_2)$ ml/g and/or assumed the blood volume: V_A ml/ml as negligible, throughout the whole renal region and did not estimate it regionally. BFM formulae with fixed value of p (BFM-pfix), and blood volume V_A (BFM-vfix) in addition to the present BFM formula and error in those formulae were analyzed.

A typical arterial input function obtained from the present PET study was used in the present simulation as the true input function. Applying this input function to the water kinetic model in Eq. (1), a tissue TAC was created assuming values of normal kidney tissue (K_1 = 2.0 ml/min/g, V_A=0.14 ml/g [5], and p = 0.4 ml/g (corresponding to the estimated mean in cortical regions for all subjects in this study)).

Time in input function was shifted from -4 to 4 sec to simulate the error sensitivity due to error in delay time, where a positive error represents an overcorrection of delay time. Input function was convoluted or deconvoluted with a simple exponential [18] by shifting the time constant from -4 to 4 sec to simulate the error sensitivity due to error in dispersion correction, where a negative error represents undercorrection, as described previously [18, 21].

Values of K_1 and k_2 were calculated using simulated input functions and above assumed tissue TACs based on the BFM formula. Errors in these calculated K_1 and k_2 values were presented as percentage differences from the assumed values. Then, the value of p was varied from 0.3 to 0.5 ml/g and tissue TAC was generated as above for simulating the error from the value of p in BFM-pfix formula. Also, V_A value was varied from 0.0 to 0.4 ml/ml and tissue TAC was generated for simulating the error from V_A in BFM:vfix formula. Then, K_1 and k_2 were calculated using the true input function and the created tissue TACs, assuming p = 0.4 ml/g and V_A =0.0 ml/ml in BFM-pfix and BFM-vfix formulae, respectively. Error in K_1 and k_2 values due to fixing p was presented as percent difference of K_1 and k_2 as a function of p. Error in K_1 and k_2 values due to neglecting V_A was presented as percent difference of K_1 and k_2 as a function of V_A. Also, K_1 and k_2 were computed with fixing V_A as 0.14 ml/ml in BFM-vfix formula from the set of the above created tissue TAC, in which K_1 and p were fixed to 2.0 ml/min/g and 0.4 ml/g, respectively, and V_A was varied. Percent difference of K_1 and k_2 between two conditions, i.e., the initial (K_1 = 2.0 ml/min/g and V_A = 0.14 ml/ml) and changed conditions (presented as ΔK_1 and Δk_2, respectively) was presented as a function of the percent difference of assumed V_A from 0.14 ml/ml (ΔV), to investigate the extent to watch the change of K_1 and k_2 was estimated when K_1 and k_2 was computed in BFM-vfix formula.

Results

Experiments

The relationships of the regional ROI values of K_1, k_2 and V_A between NLF and BFM are shown in Fig 2. The regression lines obtained were $K_{1,BFM}$ = 0.93 $K_{1,NLF}$ -0.11 ml/min/g (r = 0.80, $P<0.001$), $k_{2,BFM}$ = 0.96 $k_{2,NLF}$ – 0.13 ml/min/g (r = 0.77, $P<0.001$) and $V_{A,BFM}$ = 0.92 $V_{A,NLF}$ -0.00 ml/ml (r = 0.97, $P<0.001$), for K_1, k_2 and V_A, respectively, where subscripts at the

parameter show the methods to calculate parametric values, and showed that the slope were not significantly different from the unity.

The fitted curve by the present model with estimating K_1, k_2 and V_A fitted well than the other two models with fixing $p(=K_1/k_2)$ or V_A. One example of fitted curves is shown in Fig 3. Also, the Akaike Information Criterion (AIC) values from three parameters fitting are the smallest for all subjects except two values for two parameter fittings with fixing V_A in patient 2 and fixing p in patient 3, although some of AIC values are similar (Table 2). These results show the present method with three parameters fitting is feasible to compute RBF.

Quantitative values of K_1, $k_2 \cdot p_{phys}$ and V_A were obtained for whole and cortical regions (Table 3). The K_1 values were smaller than $k_2 \cdot p_{phys}$ values and the ratio between them was ranged from 0.35 to 0.45, suggesting K_1 values were underestimated than RBF due to the partial volume effect. Both K_1 and $k_2 \cdot p_{phys}$ were not significantly different between the resting and stimulating conditions after enalapril administration for whole and cortical regions, respectively, although the value of V_A became higher in stimulating than basal conditions. The GFR value obtained was 78 ± 4 ml/min, corresponding to the clearance rate of 0.37 ± 0.02 ml/min/g and to 9.6 % to the k_2 obtained for cortical region in normal condition.

K_1 and $k_2 \cdot p_{phys}$ images generated by the present method are representatively shown in Fig. 4. The image is shown in acceptable quality. The K_1 and $k_2 \cdot p_{phys}$ value is from 1.5 to 2.0 ml/min/g and 3.0 to 5.0 around cortical region, respectively, and some parts show higher value than those, respectively. The average time required to compute the parametric images was 2 min and 23 sec.

Error Analyses

The size of error introduced in both K_1 and k_2 was less than 20% for an error in the estimation of delay and in the dispersion time constant up to 2 sec (Fig. 5). The error sensitivity in K_1 and

k_2 was 40 % when the partition coefficient was 0.35 (Fig 6). The magnitude of error was remarkably enhanced when the blood volume was ignored (Fig 7a), and if the size of arterial blood volume changed to be 25 % larger, K_1 and k_2 was overestimated by 20 % (Fig 7a).

Discussion

We have presented an approach to generate quantitative K_1, k_2 and V_A images using $H_2{}^{15}O$ and PET applying BFM computation method. This article described the validity of this approach in healthy human subjects under resting and stimulating conditions. The rate constant values of K_1 and $k_2 \cdot p_{phys}$ obtained from parametric images were consistent against NFL and quality of K_1 and $k_2 \cdot p_{phys}$ images obtained was acceptable. The smaller K_1 against $k_2 \bullet p_{phys}$ values suggested that K_1 value was underestimated than absolute RBF value due to partial volume effect. The simulation showed that the delay time and dispersion time constant should be estimated within 2 sec accuracy, and V_A and p cannot be ignored/fixed to estimate the rate constants of K_1 and/or k_2. Also V_A cannot be ignored, even when only relative rate constant values are needed. These findings suggest that the present k_2 obtained BFM technique provides RBF image with reasonable accuracy and quality.

The present study experimentally computed the rate constants of K_1 and k_2, and those ratio obtained was ranged from 0.35 to 0.45 ml/g, which corresponds to the apparent kidney-blood partition coefficient. The extremely smaller apparent p value might be due to partial volume effect, as has been demonstrated in the previous brain and cardiac study [10, 11], because of composite structure in kidney, spatial resolution of reconstructed image and breathing movement of patient during the scan. When the rate constant of K_1 is underestimated due to partial volume effect, $k_2 \bullet p_{phys}$ could be applied for the RBF rather than K_1. The present study showed the smaller contribution of GFR as only 10 % to the clearance rate, $k_2 \bullet p_{phys}$ is more appropriate for RBF assessment, although further study is required how

the GFR change under stimulate conditions. The $k_2 \cdot p_{phys}$ value in cortical region obtained in the present study was 3.64 ± 2.15 ml/min/g under the normal condition and showed similar value to literature normal of 4 to 5 ml/min/g [22]. In comparison to Middlekauff et al [23-25], they applied the ROI base analysis, showing similar RBF values around 4 ml/min/g. These findings also supports to apply the $k_2 \cdot p_{phys}$ as RBF. The different values in RBF between the present results and the previous ones [3-5] might be due to the difference of approach.

The present computation for RBF applied BFM, which has two main advantages over the nonlinear NLF. One is the ability to produce a voxel-by-voxel quantitative parametric map, and the other is faster computing speed. In fact, the parametric images were obtained within reasonable time, i.e., two min and half with image size of 128 × 128 pixels with 35 slices and 22 frames. It could be further reduced by applying a threshold to omit pixel with lower values. For a clinical stand point, voxel-by-voxel analysis is preferred to ROI-based analysis because the operator can independently define ROIs to improve reproducibility, and faster computations are important for analyzing enormous datasets.

Kinetic parameters estimated by the NLF agreed well with those estimated by the BFM as shown in Fig 2. The disagreement in some rate constant values between the voxel-based (BFM) and ROI based computation methods might be due to composite structure between cortical region and surroundings or image noise. Although superior to the NLF in terms of computing speed and ability to generate parametric maps, the BFM shares the same source of errors as the NLF because they use the same model and assumption. Delay and dispersion in input function, motion of a patient during a study [26-28], and flow heterogeneity [29], are sources of error for parameters estimated by both the NLF and BFM. Selection of specific range of k_2 and the number of basis function can affect accuracy and precision of estimated parameters in neuroreceptor studies [30, 31]. However, the lower and upper limit on that range was 0 and 15 ml/min/g in the present computation with $H_2{}^{15}O$ and

this limit would be enough for the present computation. In practice, selection of wider range and/or large number of discrete values of basis function is slow and inefficient against required accuracy and precision.

The present simulation study showed that if V_A is neglected or fixed, not only the absolute rate constants, i.e. RBF value is overestimated, but estimated changes in RBF between two physiological states could be over- or underestimated. These findings suggest that V_A should be included to obtain either absolute or relative value of RBF. For p, the present simulation revealed that the error sensitivity in RBF on that value was significant. The present experimental data showed that the values of p for whole and cortical regions were 0.35 and 0.42 ml/g, respectively. If the value was fixed to 0.4 ml/g, a 40 % overestimation in RBF for regions with p of 0.35 occurred, thus, regional difference of p introduces error in quantitative RBF values. Also AIC analysis showed that introducing those extra parameters of p and V_A did not increase the AIC value against others. These findings suggest that both p and V_A need to be estimated simultaneously with quantitative RBF, especially when changes on different conditions are assessed.

The knowledge of RBF is mostly needed in determining the severity of renovascular disease. Though the degree of renal arterial stenosis is easily diagnosed, its actual effect on RBF remains difficult to quantify. In clinical work, estimates of GFR have not shown very good accuracy to a possible interventional treatment. Also, there is no good clinical method to easily measure single kidney or regional RBF. We can obtain the effective renal plasma flow (ERPF) by infusing p-aminohippuric acid and measuring their urine and plasma concentrations, but this method only gives the total ERPF for both kidneys. Alternative is magnetic resonance (MR) based method, which is problematic in patients with chronic kidney disease, because the contrast agent gadolinium is contraindicated in these subjects [32]. The present PET-related methodology may provide quantitative regional RBF, and be clinically

applicable in conditions such as chronic allograft nephropathy and acute kidney insufficiency. The procedure – as presented here – still implies a small degree of invasiveness because of blood sampling. However, many non-invasive methods for estimating input functions have been proposed [3-5, 23-25, 33, 34], and their implementation will allow to examine RBF in a fully non-invasive fashion, particularly for clinical purposes.

In conclusion, although some issues remain to be investigated, this study shows the feasibility of measurement of RBF using PET with $H_2{}^{15}O$.

Acknowledgments

The authors thank the technical staff of the Turku PET Centre for the efforts and skills dedicated to this project. This work is supported by the Hospital District of Southwest of Finland and was conducted within the "Centre of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research" supported by the Academy of Finland, University of Turku, Turku University Hospital and Abo Academy. The study was further supported by grants from the Academy of Finland (206359 to P.N.), Finnish Diabetes Foundation (P.I.), EFSD/Eli-Lilly (P.I.), Sigrid Juselius Foundation (N.K. and P.I.), and Novo Nordisk Foundation (P.N.).

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Table 1: Baseline characteristics of the present six subjects

	mean ± SD
Age	58 ± 5
P-Kreatinine umol/l	85 ± 10
eGFR ml/min	78 ± 4
Weight kg	82.8 ± 4.5
BMI	26.6 ± 2.2
BP systolic mmHg	136 ± 11
BP diastolic mmHg	82 ± 4
HR min^{-1}	57 ± 5
fP-Chol mmol/l	5.3 ± 1.0
fP-HDL mmol/l	1.5 ± 0.4
fP-Tg mmol/l	1.2 ± 0.4
fP-LDL mmol/l	3.2 ± 0.8
B-Hb g/l	144 ± 12
fP-gluk mmol/l	5.4 ± 0.4

eGFR: estimated glomerular filtration rate according to MDRD study equation

BMI: body mass index

BP: blood pressure

HR: heart rate

fP-Chol: fasting plasma total cholesterol

fP-HDL: fasting plasma high density cholesterol

fP-LDL: fasting plasm low density cholesterol

fP-Tg: fasting plasma triglyserides

B-Hb: blood haemoglobin

fP-gluk: fasting plasma glucose