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Quantitative Measurement of Renal Plasma Flow by Positron Emission Tomography with Oxygen-15 Water

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INABA, T., YAMASHITA, M., KAWASE, Y., NAKAHASHI, H. and WATANABE, H. *Quantitative Measurement of Renal Plasma Flow by Positron Emission Tomography with Oxygen-15 Water*. Tohoku J. Exp. Med., 1989, **159** (4), 283-289 —— We successfully determined renal plasma flow in the human kidney by means of positron emission tomography (PET) with oxygen-15 water using a one compartment model. ———— positron emission tomography ; renal plasma flow

There are a few clinical methods to measure renal blood flow non-invasively and quantitatively. The clearance method, using para-amino hippuric acid, is very available for routine study but it cannot give regional renal blood flow. Renal blood flow can also be measured by ultrasonic Doppler method but difficult problems are left for quantitative analysis. On the other hand, positron emission tomography is now a very useful technique for quantitative analysis of the biochemical and physiological function in the brain and the heart (Ginsberg et al. 1982, 1984 ; Bergmann et al. 1984 ; Raichle et al. 1984). We applied PET to the kidneys and successfully determined renal blood flow and renal plasma flow with oxygen-15 water using a one compartment model.

MATERIALS and METHODS

A positron emission tomography (PET) system using a whole body collimator (HEADTOME III SET-120W, Shimadzu Co., Kyoto) and a cyclotron with a gas purifying system (BC-1710, Japan Steel Works, Muroran) were used in the study. The performance characteristics of the PET system in this study were as follows : an image resolution of 8.2 mm in full width at half-maximum (FWHM), and a slice thickness of 11-13 mm FWHM. The matrix size of the image was 128×128 with 2-mm pixel size. The slice interval of the planes was 15 mm.

An ionic ^{68}Ge-^{68}Ga generator (New England Nuclear Co., Boston, MA, USA) was used with 2 ml of 1 N HCL to eluate the ^{68}Ga (Yamashita et al. 1988).

Eight normal subjects (7 males (20-74, with an average age of 41.0 years) and one 55 year old female) were studied. The scan position for each subject was determined using

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ultrasonotomography. After positioning of the kidneys, a transmission scan was performed using an external ^{68}Ge ring source. About 10–20 mCi of $C^{15}O$ gas was administrated by a single inhalation method. About 10 mCi of $H_2{}^{15}O$ and 3–7 mCi of ^{68}Ga-EDTA were administrated by intravenous bolus injection. Arterial blood samples were obtained from the brachial artery 2 and 3 min after the injection of each tracer. They were measured by a gamma-scintillation counter. Emission data was collected simultaneously for 3 slices (1.5 cm width/slice) by initial twelve 5 sec scans followed by eight 30 sec scans. Regions of interest (ROI) were placed on the aorta and the parenchymal portion of the kidney and time-activity curves (TAC) were then obtained. The region of interest shape was a rectangle 6×6 mm in the center of the aorta. The TAC of the aorta was corrected by the counter data obtained from the arterial blood samples. Physical decay of O-15 (halflife 123 sec) and Ga-68 (68 min) was also corrected every 2.5 sec.

Preliminary experiment

A preliminary experiment was carried out prior to the clinical trials in order to determine how water content would be washed out from the human kidney. A catheter for angiography was inserted into the right renal artery of a 71 year old male. After a transmission scan, approximately 0.5 mCi of $H_2{}^{15}O$ was injected as rapidly as possible and TAC of the right kidney was obtained. A total of twelve 5 sec scans of the right kidney were obtained. ROI were placed on the whole parenchymal portion of the kidney. The resulting TAC is shown in Fig. 1. The results indicated that water injected into the kidney was washed out approximately monoexponentially.

Theory

Based on the results of the preliminary experiment, a one compartment model can be used for the analysis of renal blood flow (RBF). The input function to the kidney ($Ca(t)$) can be thought of as the TAC of the aorta. $H_2{}^{15}O$ flows into the kidney by RBF (F) with the activity $Ca(t)$ (Fig. 2). The radioactivity in the kidney ($Ct(t)$) is washed out by RBF (F). The radioactivity derived from urine can be considered to be negligible, because the

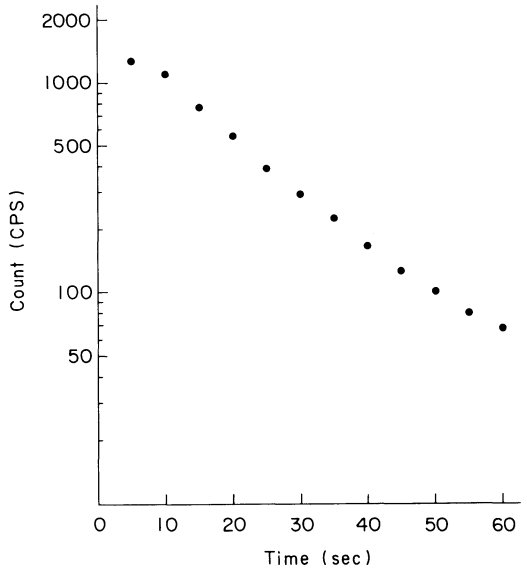

Fig. 1. Time-activity curve after bolus injection of $H_2{}^{15}O$ into the right renal artery.

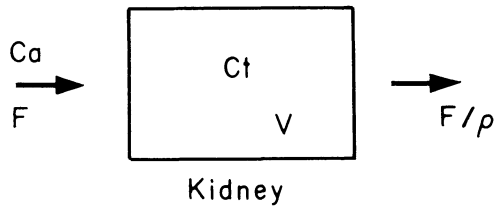

Fig. 2. One compartment H_2O model for the kidney
Ca, radioactivity of $H_2{}^{15}O$ in the arterial blood; Ct, radioactivity of $H_2{}^{15}O$ in the kidney; F, renal blood flow (RBF); V, volume of the kidney; ρ, constant.

RBF is much larger than the urinary flow under normal physiological conditions (Ganong 1973). The differential equation is expressed as

$$\frac{dCt}{dt}=\frac{F}{V}Ca-\frac{F}{\rho V}Ct, \tag{1}$$

where V is the volume of the kidney and ρ is a constant. Equation (1) is solved as

$$Ct=\frac{F}{V}\int_0^t e^{-\frac{F}{\rho V}(t-x)}\cdot Ca(x)dx=Ca(t)*\rho ke^{-kt}, \tag{2}$$

where $k=F/\rho V$. The asterisk denotes the convolution integral.

Integrating both sides of equation (2) for time duration (t_i, t_{i+1}; $i=0, 1, \ldots, 19$) gives

$$\int_{t_i}^{t_{i+1}} Ctdt=\int_{t_i}^{t_{i+1}} Ca(t)*\rho ke^{-kt}\ dt. \tag{3}$$

The left side of equation (3) is given by a measured PET image accumulated during (t_i, t_{i+1}) and the right side is calculated using the TAC of the aorta ($Ca(t)$) for a given ρ and RBF. Comparing both sides of equation (3) for given ρ and RBF values, ρ and RBF can be determined by the least-square fitting method.

On the other hand, glomerular filtration rate (GFR) can be obtained by dynamic $C^{15}O$ and ^{68}Ga-EDTA studies using PET with an accumulation model for ^{68}Ga-EDTA (Yamashita et al. 1988). The renal TAC of ^{68}Ga-EDTA includes both the accumulation and blood circulation processes, where the blood volume cannot be negligible. The blood volume was estimated by CO study and the blood activity evaluated from the blood volume was subtracted from the measured renal activity to obtain a real accumulation curve of EDTA. GFR can be obtained as a real accumulation of EDTA divided by the time integral of the activity in the aorta.

Results

A typical series of PET images (first 16 images) of the aorta and the kidneys after intravenous bolus injection of $H_2{}^{15}O$ is shown in Fig. 3. The TAC of the aorta, shown in Fig. 4, was almost stable 2 min after the start of the PET scan. The TAC of the right kidney in the same case, measured by PET, and the TAC of the kidney calculated using the least-square fitting method are shown in Fig. 5. Both are quite similar to each other and thus RBF and ρ can be determined. Renal plasma flow (RPF) was calculated as RPF = RBF · (1 − Ht), where Ht was systemic hematocrit. RPF, GFR and constant ρ for the 8 subjects (15 kidneys) are shown in Table 1. The RPF and GFR values were 90 to 288 ml/min/100 g

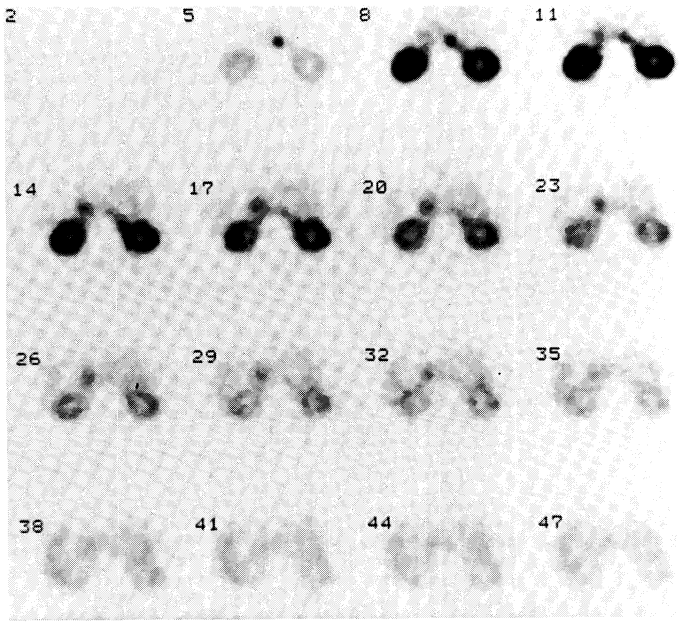

Fig. 3. A typical series of PET images of the aorta and the kidneys after bolus injection of $H_2{}^{15}O$.
The first 16 images are shown.

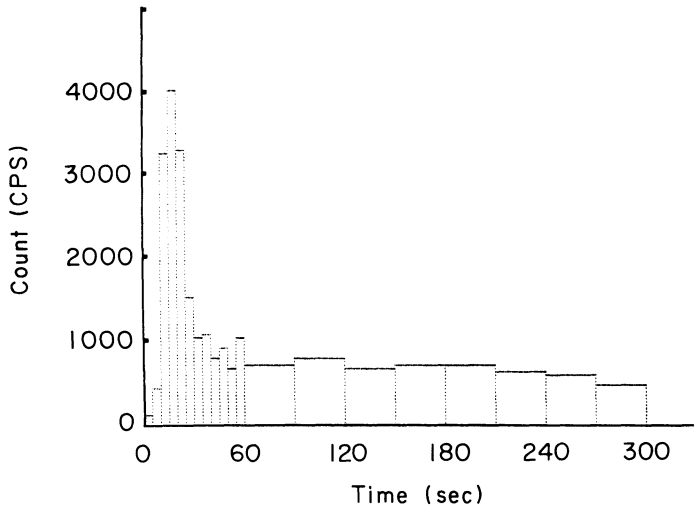

Fig. 4. A typical time-activity curve (TAC) of the aorta measured by PET after bolus injection of $H_2{}^{15}O$.

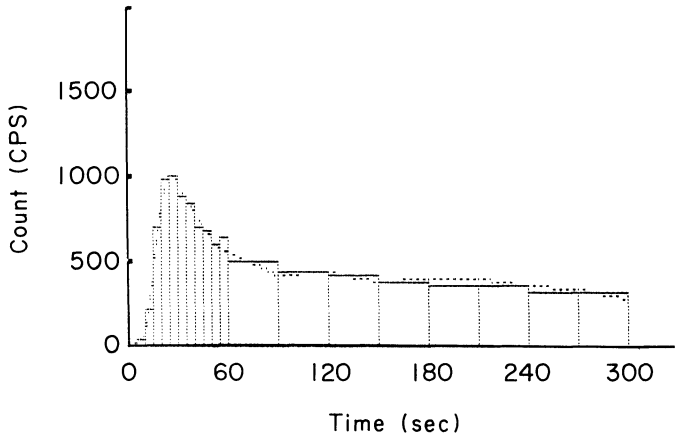

Fig. 5. Typical time-activity curves (TAC) of the kidney. Histogram and dotted line denote the TAC measured by PET and the TAC calculated using a one compartment model and the least-square fitting method, respectively. Both are quite similar to each other.

kidney (171 ± 61 ml/min/100 g kidney) and 21.3 to 58.4 ml/min/100 g kidney (38.2 ± 10.9 ml/min/100 g kidney), respectively. Good correlation between RPF (Y) and GFR (X) was observed as demonstrated in Fig. 6 ($Y = -32 + 5.31X$; $r = 0.961$).

TABLE 1. *Renal plasma flow, glomerular filtration rate and constant* ρ

Case	Side	RPF (ml/min/100 g)	GFR (ml/min/100 g)	ρ
1	R	90	22.6	.54
	L	91	21.3	.56
2	R	105	28.4	.59
	L	120	31.3	.62
3	R	116	29.5	.51
	L	120	29.8	.54
4	R	181	40.0	.74
	L	153	39.8	.73
5	R	198	46.6	.66
	L	229	44.8	.66
6	R	201	39.5	.78
	L	192	35.5	.73
7	R	233	51.2	.68
8	R	288	58.4	.73
	L	248	54.7	.84

R, right kidney; L, left kidney; RPF, renal plasma flow; GFR, glomerular filtration rate; ρ, constant.

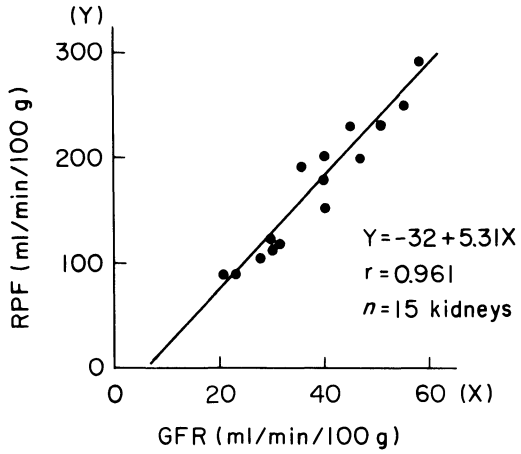

Fig. 6. Correlation between RPF and GFR measured by PET with $H_2{}^{15}O$ and ^{68}Ga-EDTA, respectively.

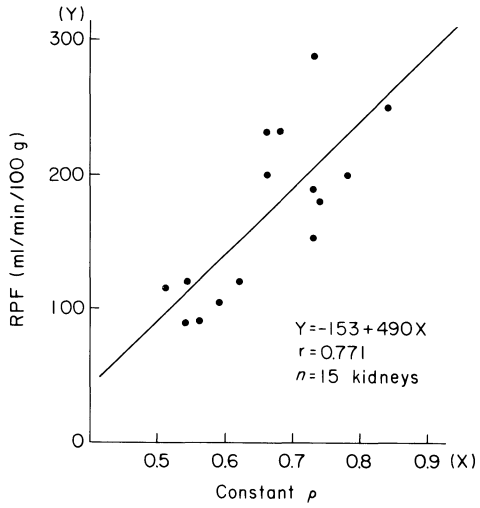

Fig. 7. Correlation between RPF and constant ρ in the kidney.

The constant ρ (X) was distributed from 0.51 to 0.84 (0.66 ± 0.10) and showed some correlation with RPF (Y) as shown in Fig. 7 ($Y = -153 + 490X$; $r = 0.771$).

Discussion

No reports have been published on quantitative analysis of RBF using PET. In addition, it has not been clarified how water in the kidney is washed out nephrologically. Our preliminary experiment indicated that water in the kidney was washed out appoximately by monoexponential function like those in the brain and the heart. The radioactivity in the urine is considered to be negligible

compared with that of the parenchymal portion of the kidney, because urinary flow is only about 1% of GFR under normal physiological conditions (Ganong 1973). Based on these results, we used a one compartment H_2O model for the kidney and could measure RBF and RPF. As the RBF and RPF values were reasonable compared to the GFR values, it could be said that PET studies were quite valuable for the quantitative measurement of RBF and RPF.

Although the physiological significance of constant ρ is not clear, it is not the renal tissue/blood partition coefficient of water but a function of several physiological parameters (blood flow, blood volume and so on) in the kidney, because our results indicate that it is correlated with renal plasma flow and blood volume (unpublished data).

In this study, we placed the ROI on the whole parenchymal portion of the kidney. but it must be discussed in the future whether PET can detect the difference between the cortical and medullary blood flow.

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