

Blood flow and blood volume in the femoral heads of healthy adults according to age: Measurement with positron emission tomography (PET)

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Objective: To deepen understanding of hemodynamics in the femoral head, i.e., the essential factor in clarifying pathogenesis of hip disorders, this study examined blood flow and blood volume in the femoral heads of healthy adults, and their changes with age, by using positron emission tomography (PET).

Methods: In 16 healthy adult males (age: 20–78 years old, mean age: 42 years), blood flow was measured by means of the $H_2^{15}O$ dynamic study method, and blood volume was measured by means of the ^{15}O -labeled carbon monoxide bolus inhalation method.

Results: Blood flow was 1.68–6.47 ml/min/100 g (mean \pm SD: 3.52 ± 1.2), and blood volume was 1.67–6.03 ml/100 g (mean \pm SD: 3.00 ± 1.27). Blood flow significantly decreased ($p < 0.01$) with age, and blood volume significantly increased ($p < 0.05$).

Conclusion: PET was useful in the measurement of blood flow and blood volume in the femoral heads. With age, physiological hemodynamic changes also increased in femoral heads.

Key words: positron emission tomography, blood flow, blood volume, femoral head

INTRODUCTION

UNDERSTANDING the hemodynamics of the femoral head is essential in studies on the process of development of hip diseases such as osteonecrosis of the femoral head, but to date, hemodynamic studies have been conducted mainly on animals,^{1–7} because there has been no established method to quantitatively and non-invasively monitor blood flow in a specific portion of bone tissue, and it has also been quite difficult to measure another important parameter of hemodynamics, i.e., blood volume.

On the other hand, positron emission tomography (PET), i.e., a new measurement method with positron, has attracted attention as a means of quantifying the blood flow and blood volume in a target organ. PET is expected to be

useful in monitoring the hemodynamics of bones,^{8–10} but PET has not yet been applied to human femoral heads.

As a step towards the establishment of PET as a means of clinical examination for hip disorders, we examined blood flow and blood volume in the femoral heads of healthy adult male volunteers and their changes with age by means of PET.

SUBJECTS AND METHODS

Sixteen healthy male volunteers were examined. Their ages ranged between 20 and 78 years old (mean: 42 years, Table 1). All subjects submitted informed consent according to the Helsinki declaration, and this study was approved by the Ethical Committee for the Study of Human Subjects in Kyoto Prefectural University of Medicine.

This study used a SET-120W PET system equipped with a whole-body collimator (Shimadzu, Corp., Kyoto, Japan) and a baby cyclotron BC-1710 with an automatic gas synthesizer (Japan Steel Works, Japan). The nuclide used was ^{15}O (half life, $T_{1/2} = 2.1$ min). [^{15}O]oxygen was

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produced by the irradiation of 0.5% oxygen in nitrogen with 10 MeV deuterons from a cyclotron at 30 μ A for 3 min, then H₂¹⁵O was synthesized by recoil reaction, and C¹⁵O was synthesized with the gas synthesizer. The full width at half maximum (FWHM) of this PET system is 8.2 mm, and it can scan 15 mm-thick axial slices.

Before starting PET, a CT scan was performed, and the image on the line connecting the tops of the right and left greater trochanters was obtained (Fig. 1A). The CT image and PET image were overlapped on a computer monitor, then by using the femoral artery on the CT images as a guide, the position of the femoral head was traced on the PET image (Fig. 1B), and the region of interest (ROI) was determined in the area corresponding to the femoral head.

In PET, immediately after the i.v. bolus injection of [H₂¹⁵O]water (740 MBq/5 ml) into the right forearm, PET images were obtained by the dynamic study method where 10 sec scanning was performed 6 times and one min scanning was performed 4 times (total 10 times). At the same time, 2 ml arterial blood was collected from the left cubital artery at 5, 10, 15, 20, 25, 30, 35, 120, 180 and 240 sec after starting the scanning (total 10 times), and the radioactive concentration in the blood was measured with a gamma-scintillation counter (MINAXI- γ , Packard Japan, Tokyo). Blood sampling was not performed between 35 and 120 sec, because in a preliminary study on the same volunteers, the activity peak of blood samples was found to be before 35 sec regardless of the age. The concentrations were analyzed by non-linear regression analysis, and the input function, Ca, for the equations shown in Figure 2 was determined.

In the present study, blood flow was measured with the single-compartment model¹¹ (Fig. 2). In brief, the time-activity curve showing the changes in the tracer level in the arterial blood was made by means of the radioactive concentration in the arterial blood, i.e., the input function Ca. Delay of the time when blood was sampled in the forearm from the time when PET data were obtained on the femoral head was programed in this PET system. Ct is the radioactive concentration in bone tissue, F is the blood flow in the bone tissue, and ρ is the distribution coefficient of the tracer for bone tissue and blood. With these parameters, dynamics of the tracer can be expressed. If the tracer is not attenuated with time, the relationship between them can be expressed as equation 1 in Figure 2 according to Fick's principle. From this equation, equation 2 in Figure 2 is obtained. When the definite integral is obtained for the time range between t_i and t_{i+1}, the following equation can be obtained.

$$\int_{t_i}^{t_{i+1}} Ct dt = F \int_{t_i}^{t_{i+1}} Ca \cdot \text{Exp}(-F \cdot t/\rho) dt.$$

The left side is measurable by the [H₂¹⁵O]water dynamic study method. The right side is theoretically obtained by using the radioactive concentration in the arterial blood as the input function Ca. Blood flow F is then

Table 1 Blood flow and blood volume in the femoral heads

Case No.	Age (years old)	Blood flow (ml/min/100 g)		Blood volume (ml/100 g)	
		Left	Right	Left	Right
1	20	3.83	5.40	2.60	3.50
2	20	6.47	5.83	1.97	2.26
3	21	3.24	3.03	1.87	2.06
4	23	5.86	4.51	3.26	2.35
5	24	3.95	3.77	2.79	3.40
6	26	2.32	2.47	2.67	2.47
7	28	2.11	2.47	2.16	1.91
8	34	5.28	3.46	3.32	2.40
9	35	3.14	4.57	4.44	1.77
10	44	2.74	3.04	1.67	1.67
11	45	2.91	2.76	4.72	1.72
12	50	4.36	4.71	4.10	3.50
13	72	4.22	3.46	2.03	5.80
14	73	1.68	2.40	6.03	5.10
15	76	2.11	2.64	5.30	2.34
16	78	1.84	2.01	2.14	2.77

determined by inserting different F and ρ values at successive approximations and by using a non-linear least squares method. The approximation is automatically done in the program of this PET system.

Blood volume was measured by an ¹⁵O-labeled carbon monoxide bolus inhalation method. In this method, red blood cells (RBC) were labeled with C¹⁵O-Hb and the blood volume was measured when the labeled RBC was thought to have reached equilibrium^{12,13} at 2.5 min according to the preliminary data. After performing a transmission scanning, C¹⁵O (2 GBq) was inhaled with a mask, then 180 sec scanning was performed when the labeled RBC was thought to have reached equilibrium. At the mid-point of scanning, 2 ml arterial blood was collected from the left cubital artery, and the radioactivity concentration was measured in a gamma-scintillation counter.

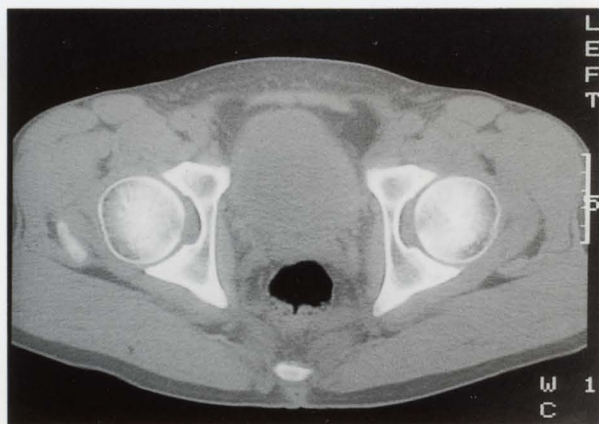
Blood volume (V) was calculated with the following equation where Ct is the radioactive concentration in the femoral head measured by PET, and Ca is the radioactive concentration in the arterial blood.

$$V = Ct/Ca \text{ (ml/100 ml)}$$

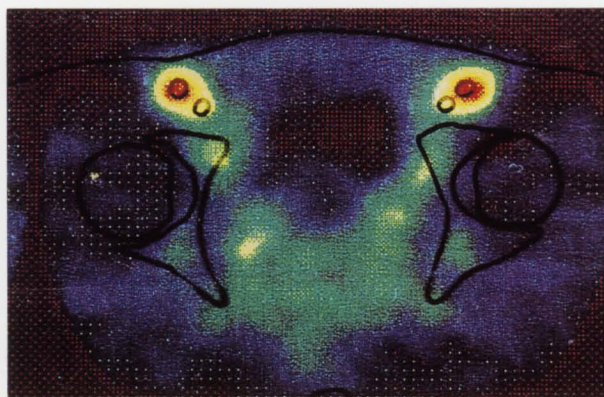
Correlation in the results was evaluated by linear regression analysis. P values were obtained by means of Student's t-test, and p value less than 0.05 was considered statistically significant.

RESULTS

Blood flow. Data were obtained from the 32 ROI in the 32 hip joints of 16 subjects, and blood flow ranged between 1.68 and 6.47 ml/min/100 g (mean \pm SD: 3.52 \pm 1.2 ml/min/100 g, Table 1).



A



B

Fig. 1 A 28 years old male. A. CT image. B. PET image 2 min after the bolus injection of $[H_2^{15}O]$ water (740 MBq/5 ml). CT and PET images were overlapped on the monitor, then by using the femoral artery on the CT image as a guide, the femoral head on the CT image was traced on the PET image, and region of interest (ROI) was determined on the area corresponding to the femoral head.

Blood volume. Data were obtained from the 32 ROI in the 32 hip joints of 16 subjects, and blood volume ranged between 1.67 and 6.03 ml/100 g (mean \pm SD: 3.00 ± 1.27 ml/100 g, Table 1).

Relationship between age and blood flow or blood volume. According to age, blood flow in the femoral head ranged between 2.11 and 6.47 ml/min/100 g in the 20 s ($n = 14$, mean: 3.95 ml/min/100 g), 3.14 and 5.28 ml/min/100 g in the 30 s ($n = 4$, mean: 4.11 ml/min/100 g), 2.74 and 3.04 ml/min/100 g in the 40 s ($n = 4$, mean: 2.86 ml/min/100 g), 4.36 and 4.71 ml/min/100 g in the 50 s ($n = 2$, mean: 4.54 ml/min/100 g), and 1.68 and 4.22 ml/min/100 g in the 70 s ($n = 8$, mean: 2.55 ml/min/100 g). As shown in Figure 3, blood flow decreased with age, and there was a negative correlation ($r = -0.500$, $p < 0.01$).

The blood volume ranged between 1.87 and 3.50 ml/100 g in the 20 s ($n = 14$, mean: 2.52 ml/100 g), 1.77 and 4.44 ml/100 g in the 30 s ($n = 4$, mean: 2.98 ml/100 g), 1.67

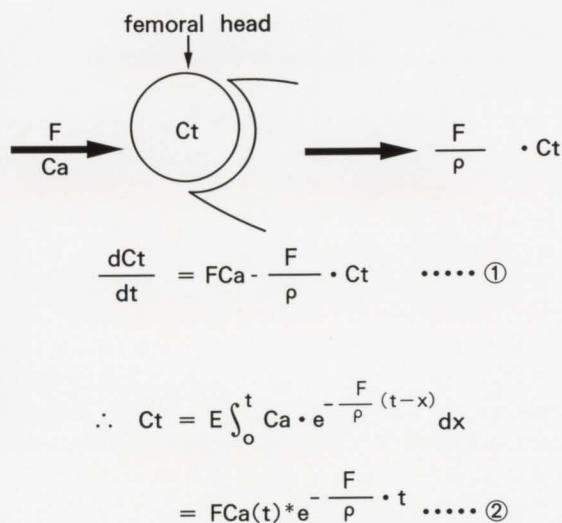


Fig. 2 One-compartment model in the $H_2^{15}O$ dynamic study method. Ca: radioactive concentration in the arterial blood. Ct: radioactive concentration in bone tissue. F: blood flow in the bone tissue. p : distribution coefficient of $H_2^{15}O$ between the bone tissue and the blood.

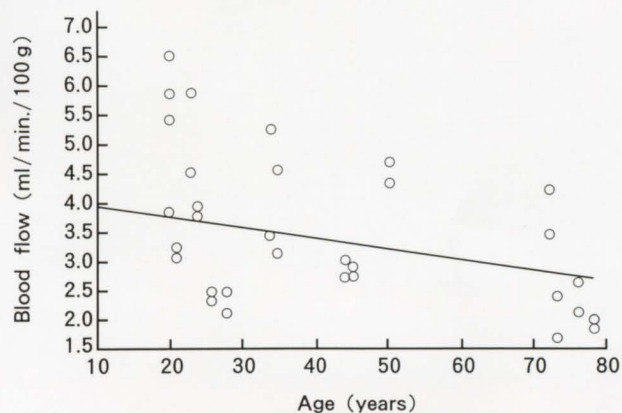


Fig. 3 Bone blood flow and age. There was a negative correlation ($r = -0.500$, linear regression test: $p < 0.01$).

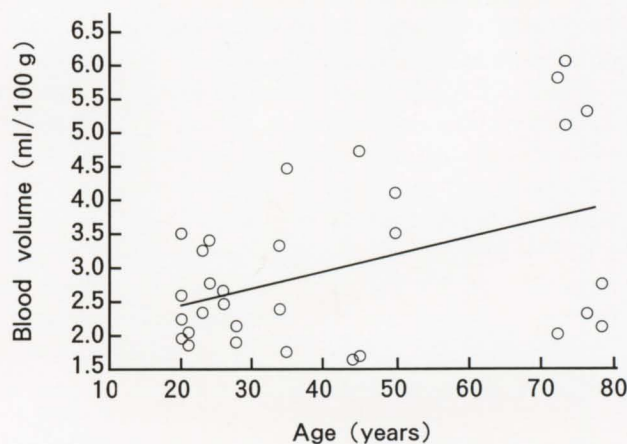


Fig. 4 Bone blood volume and age. There was a positive correlation ($r = 0.436$, linear regression test: $p < 0.05$).

and 4.72 ml/100 g in the 40 s (n = 4, mean: 2.45 ml/100 g), 3.50 and 4.10 ml/100 g in the 50 s (n = 2, mean: 3.80 ml/100 g), and 2.03 and 6.03 ml/100 g in the 70 s (n = 8, mean: 3.94 ml/100 g). As shown in Figure 4, the blood volume increased with age ($r = 0.436$, $p < 0.05$).

DISCUSSION

In PET, substances (water and gas) are labeled with a radioisotope which radiates positrons such as ^{11}C , ^{13}N , ^{18}F , and ^{15}O , and these substances can be safely administered to human subjects. PET depicts radioactivity distribution in the body as a transverse scanning image, and it also measures the radioactivity concentration in any specific area. Because PET detects and visualizes 2 γ -rays which radiate to make a 180° angle, the sensitivity and resolution are highly reproducible regardless of the location of the target area. The distinct feature of PET is that physiological blood flow and blood volume can be measured without causing tissue damages to the measurement site. We used ^{15}O in the present study, because oxygen is a constitutive element of the body, and distributable to any part of it. In addition, the half life of ^{15}O is very short, i.e., 2 min, so that ^{15}O has very limited effects on the human body.

For determination of the ROI, the position of the femoral head in CT images was traced on the PET image, and the ROI was determined in the area corresponding to the femoral head. The results showed that mean blood flow on the femoral head was 3.52 ± 1.2 ml/min/100 g which is quite compatible with the blood flow in bone (3 ml/min/100 g) as described by Guyton,¹⁴ and the flow was lower than in the other organs, i.e., brain: 50 ml/min/100 g, heart: 70 ml/min/100 g, kidney: 360 ml/min/100 g, and liver: 95 ml/min/100 g.¹⁴ Nevertheless, our individual data varied over a relatively wide range. Possible explanations for this are (i) a CT image was superimposed to a PET image on a computer monitor in order to determine the ROI, and (ii) there could be the effects of partial volume and scatter at a low radioactive concentration. These technical points need to be examined and improvements made in future studies.

Blood volume is another essential parameter in the clarification of hemodynamics, but it has not been measured in the femoral head because of a technical difficulty. The present PET study for the first time demonstrated the blood volume in the human femoral head, and it was 3.00 ± 1.27 ml/100 g. This level was approximately 60% of the cerebral blood volume.¹³ The above mentioned technical points concerning blood flow would also affect the measurement of blood volume, and they also need to be examined for blood volume.

In regard to the effects of age, MacPherson et al.³ investigated total bone blood flow in rats by the microsphere method, and reported that blood flow within the long bones decreased with age. In the present study, blood flow

in the human femoral head significantly decreased with age, whereas blood volume significantly increased although PET images themselves were almost the same regardless of the age of volunteers, and one of them is shown in Figure 1. Our findings indicate that with age the femoral head much more easily develops a congestive condition, and this condition could lead to a lower blood turnover within the femoral head. The findings of this study are quite interesting from the viewpoint of pathogenesis of osteonecrosis in the femoral head. It has been suggested that several factors are involved in the occurrence of osteonecrosis of the femoral head,^{15,16} and the mean age of disease onset is the 50s.¹⁶ Our subjects were healthy volunteers, but the blood flow and blood volume in the femoral heads were lower than in the other organs, and with age changed. These levels changed towards a congestive condition. This suggests that ischemic changes could occur easier under this specific hemodynamic condition in the femoral head. Future PET studies should depict the pathogenesis of ischemic diseases in femoral heads more clearly from the hemodynamic viewpoint.

In the present study, PET was useful in the measurement of blood flow and blood volume in femoral heads *in vivo*, even though several technical points remained to be examined. PET would be a useful method in hemodynamic evaluation of the femoral head, and in studies on the pathogenesis of hip disorders.

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