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# Evaluation of the hemodynamics of the femoral head compared with the ilium, femoral neck and femoral intertrochanteric region in healthy adults: measurement with positron emission tomography (PET)

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***Objective:*** Non-traumatic osteonecrosis of the femoral head (ONF) is considered to be a disease that occurs primarily due to ischemia of the femoral head, while its etiology and pathology are not fully understood. It is therefore necessary to identify the characteristics of the hemodynamics of the femoral head. In this study, the hemodynamics in the ilium and proximal regions of the femur, including the femoral head, was investigated using positron emission tomography (PET). ***Methods:*** The subjects of this study consisted of 8 hip joints of four healthy male adults and 3 hip joints on the contralateral side of a femoral neck fracture, avulsion fracture of the greater trochanter and coxarthrosis (1 case each, all females) for a total of 11 hip joints of 7 subjects. The ages of the subjects ranged from 25 to 87 years (average age: 54 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 determined to be 9.1 ± 4.8 m*l*/min/100 g in the ilium and among proximal regions of the femur (femoral head, neck and intertrochanteric region), 1.8 ± 0.7 m*l*/min/100 g in the femoral head, 2.1 ± 0.6 m*l*/min/100 g in the femoral neck, and 2.6 ± 0.7 m*l*/min/100 g in the intertrochanteric region. In addition, blood volume was 4.7 ± 1.3 m*l*/100 g in the ilium, and among proximal regions of the femur, 1.1 ± 0.5 m*l*/100 g in the femoral head, 2.1 ± 0.7 m*l*/100 g in the femoral neck, and 2.6 ± 0.9 m*l*/100 g in the intertrochanteric region. The results showed that both blood flow and volume were lowest in the femoral head. Blood flow and volume were significantly lower in the proximal regions of the femur (femoral head, neck and intertrochanteric region) than in the ilium ($p < 0.01$). ***Conclusion:*** The present study demonstrated that the femoral head is in a hypoemic state as compared with other osseous tissue, indicating that even the slightest exacerbation of hemodynamics in the femoral head can trigger an ischemic condition culminating in ONF.

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

## INTRODUCTION

NON-TRAUMATIC OSTEONECROSIS of the femoral head (ONF) is a disease that occurs primarily due to ischemia of the femoral head. Its etiology and pathology are still not fully understood. It is therefore important to identify its characteristics by measuring hemodynamics at the site of occurrence, namely the femoral head, in order to determine the pathology of ONF.

The hydrogen washout method[1] and microsphere method[2] have conventionally been used to measure bone hemodynamics. However, the specimens on which these methods can be used are limited due to problems with the measurement technique and invasiveness. It was therefore considered to be necessary to establish a safe and

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accurate measurement method for determining bone hemodynamics in the body.

We therefore attempted to evaluate hemodynamics of the femoral head by focusing on positron emission tomography (PET), a kind of nuclear imaging diagnostic procedure, that has been used for measurement of hemodynamics in tissues such as the brain[3] and liver.[4] PET has been one of the most effective methods to measure the hemodynamics in the femoral head.[5]

In this study, the blood flow and volume in the ilium and proximal regions of the femur (femoral head, neck and intertrochanteric region) were examined in the same subjects by means of PET to clarify the characteristics of hemodynamics in the femoral head.

## SUBJECTS AND METHODS

The subjects of this study consisted of 8 hip joints of four healthy male adults and 3 hip joints on the contralateral healthy side of a femoral neck fracture, avulsion fracture of the greater trochanter and coxarthrosis (1 case each, all females) for a total of 11 hip joints of 7 subjects. The ages of the subjects ranged from 25 to 87 years (average age: 54 years). The hip joints examined in the study were confirmed to be free of abnormalities by X-ray examinations. The subjects defined had no significant medical problems or abnormalities of their complete blood counts.

The protocol was approved by the Ethics Committee, Kyoto Prefectural University of Medicine.

An SET-140W system (Shimadzu Corp., Kyoto, Japan) and a baby cyclotron BC-1710 equipped with an automatic gas synthesizer (Japan Steel Works, Japan) were used for the whole-body PET system.[5]

The nuclide used was $^{15}O$ (half life, T1/2 = 2.1 min). [$^{15}O$]Oxygen was produced by the irradiation of 0.5% oxygen in nitrogen with 10 MeV deuterons from a cyclotron at 30 $\mu$A for 3 min, then $H_2{}^{15}O$ was synthesized by recoil reaction, and $C^{15}O$ was synthesized with a gas synthesizer. The full width at half maximum (FWHM) of this PET system is 6.0 mm, and it can scan 13 mm-thick axial slices.

PET images were obtained from axial sections of a total of seven slices having a thickness of 13 mm centered on a line that connected the upper ends of both greater trochanters. The first slice from the head side was designated as the ilium, the fourth slice serving as the reference plane was designated as the femoral head, the sixth slice was designated as the femoral neck, and the seventh slice was designated as containing the femoral intertrochanteric region (Fig. 1-1). Region of interest (ROI) was determined on the area within the respective bone marrow by comparing preliminary obtained CT images and the PET cross-sectional images (Fig. 1-2).

In the present study, blood flow was measured with the single-compartment model by means of the $H_2{}^{15}O$ dynamic study method and blood volume was measured by the $^{15}O$-labeled carbon monoxide bolus inhalation method.[5]

*Blood flow.* 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), after the i.v. bolus injection of [$H_2{}^{15}O$]water (740 MBq/5 m*l*) into the right forearm. At the same time, 2 m*l* 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-$\gamma$, Packard Japan, Tokyo). The connections were analyzed by non-linear regression analysis, and the input function Ca was determined.

In the present study, blood flow was measured with the single-compartment model. Ct is the radioactive concentration in bone tissue, F is the blood flow in the bone tissue. $\rho$ is the distribution coefficient of the tracer for bone tissue and blood and the distribution coefficient was chosen to be 0.90 because it is consistent with values reported in the literature for tissues such as brain.[6] Time delay between the femoral head and the sample site exists in this study. The delay is overcome by fitting the input curve, corrected for dispersion, into the measured tissue time-activity.[7]

When the definite integral is obtained for the time range between ti and ti + 1, the following equation can be obtained:

$$\int_{ti}^{ti+1} Ctdt = F\int_{ti}^{ti+1} Ca * \exp(-F \cdot t/\rho)dt.$$

The left side is measurable by the [$H_2{}^{15}O$]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 determined by using a non-linear least squares method.

*Blood volume.* Blood volume was measured by a $^{15}O$-labeled carbon monoxide bolus inhalation method. After performing a transmission scanning, 2 m*l* 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. In the present study, hematocrit values of arteries and bone marrow were assumed to be constant.

$$V = Ct/Ca \ (ml/100 \ g)$$

To compare the two groups at each site of blood flow and blood volume, the Wilcoxon signed-ranks test was used. P values less than 0.05 were considered to indicate statistically significant differences. Summary statistics are expressed as median ± SD. Linear regression analysis was used to evaluate the correlation between the different sites of blood flow and blood volume. Correlation in the

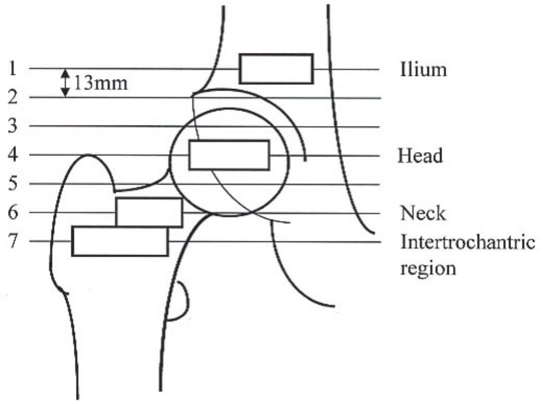


**Fig. 1-1** Schema of ilium and proximal femur (femoral head, femoral neck and intertrochanteric region) showing the levels of bone examined by PET. PET images were obtained from axial sections of a total of seven slices having a thickness of 13 mm centered on a line that connected the upper ends of both greater trochanters. Region of interest (ROI) was determined on the area within the respective bone marrow of the ilium and proximal femur (femoral head, neck and intertrochanteric region) by comparing preliminary CT images and the PET cross-sectional images.

results was evaluated by Pearson's correlation coefficient test. P values less than 0.05 were considered to indicate statistical significance.

## RESULTS

*Blood flow*

Blood flow was 9.1 ± 4.5 m*l*/min/100 g (range 3.24–19.62 m*l*/min/100 g) in the ilium, and among the proximal regions of the femur (femoral head, neck and intertrochanteric region), 1.8 ± 0.7 m*l*/min/100 g (range 0.40–2.88 m*l*/min/100 g) in the femoral head, 2.1 ± 0.6 m*l*/min/100 g (range 1.33–3.65 m*l*/min/100 g) in the femoral neck, and 2.5 ± 0.7 m*l*/min/100 g (range 1.64–3.71 m*l*/min/100 g) in the intertrochanteric region (Fig. 2). Among the proximal regions of the femur, blood flow in the femoral head was the lowest and increased distally. A significant difference was observed between blood flow in the femoral head and blood flow in the intertrochanteric region ($p < 0.05$). Blood flow was significantly lower as compared with the ilium for all proximal regions of the femur ($p < 0.01$), with blood flow in the femoral head being only one-fifth of that of the ilium.

*Blood volume*

Blood volume was 4.7 ± 1.3 m*l*/100 g (range 2.75–6.38 m*l*/100 g) in the ilium and among the proximal regions of the femur (femoral head, neck and intertrochanteric region), 1.1 ± 0.5 m*l*/100 g (range 0.23–1.99 m*l*/100 g) in the femoral head, 2.1 ± 0.7 m*l*/100 g (range 0.99–3.16 m*l*/100 g) in the femoral neck, and 2.6 ± 0.9 m*l*/100 g (range 1.31–3.97 m*l*/100 g) in the intertrochanteric region (Fig. 3). Blood volume in the proximal regions of the femur increased in the order of the femoral head, femoral neck and intertrochanteric region in the same manner as blood flow, and significant differences were observed among the blood volumes except between the femoral neck and intertrochanteric region ($p < 0.01$). Blood volume in the ilium was significantly greater than blood volume of all three proximal regions of the femur ($p < 0.01$). Blood volume in the femoral head was only 1/2 that in the ilium.

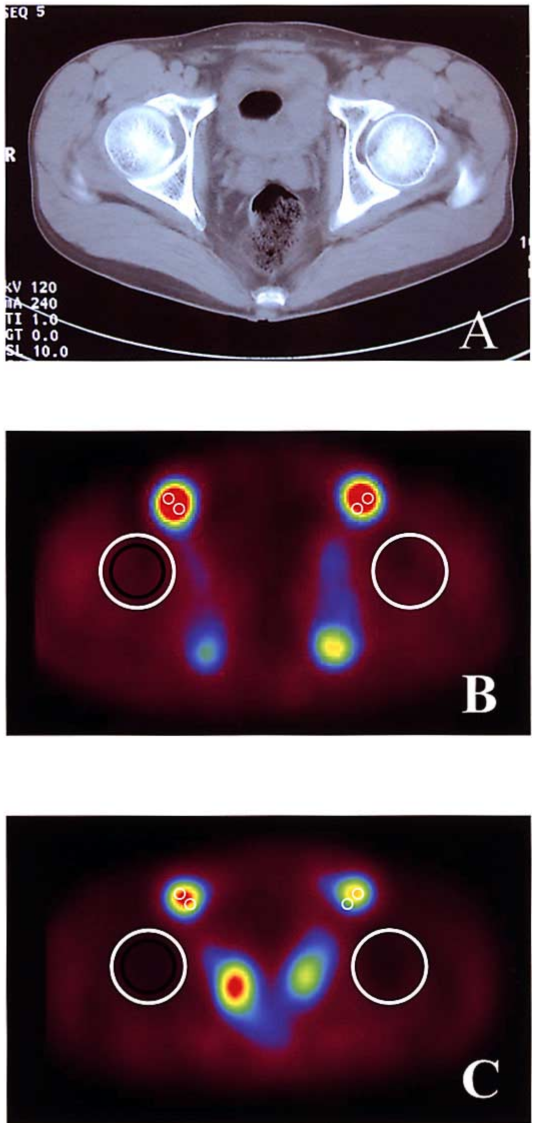


**Fig. 1-2** Images from CT and PET. A, CT image. B, PET image of blood flow, 2 min after the bolus injection of [$^{15}$O] water. C, PET image of blood volume. CT and PET images were overlapped on the monitor. Then by using the femoral artery on the CT image as a guide, the femoral head on the CT image was traced on the PET image, and region of interest (ROI: *black circle*) was determined on the area corresponding to the femoral head.

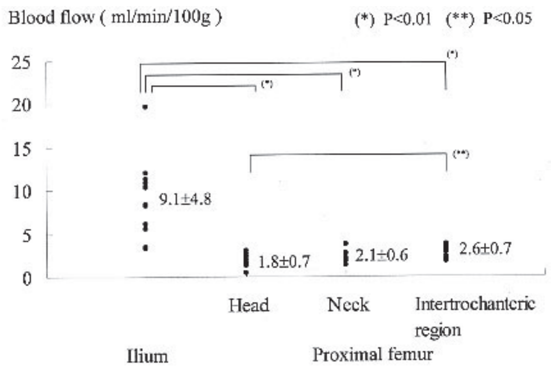


**Fig. 2** Blood flow in the ilium and proximal femur (femoral head, neck and intertrochanteric region). The blood flow in the proximal femur was significantly lower than that in the ilium ($p < 0.01$). The blood flow in the femoral head was the lowest among those in three different sites in the proximal femur, and there was a significant difference in blood flow between the femoral head and the intertrochanteric region ($p < 0.05$).

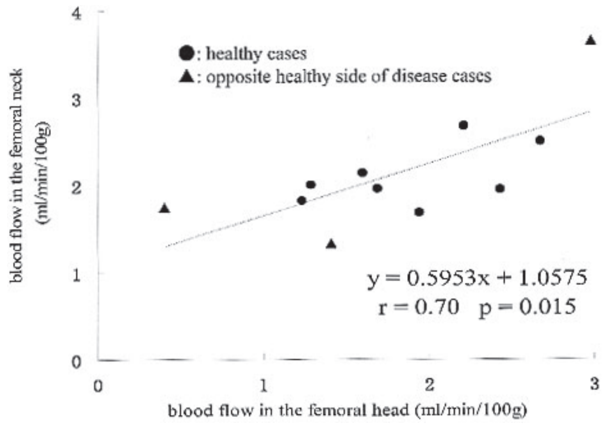


**Fig. 4** Correlation between the blood flow in the femoral head and neck. On the *y*-axis, blood flow in the femoral neck is shown (m*l*/min/100 g), and on the *x*-axis, that in the femoral head is depicted (m*l*/min/100 g). A correlation was noted between the blood flows in the femoral head and neck ($r = 0.70$, $p = 0.015$).

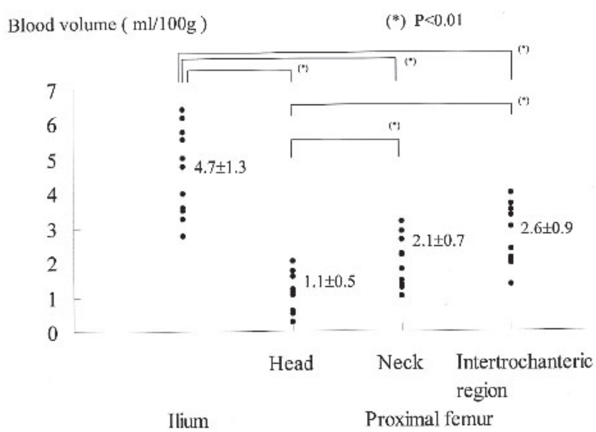


**Fig. 3** Blood volume in the ilium and proximal femur (femoral head, neck and intertrochanteric region). The blood volume in the proximal femur was significantly lower than that in the ilium ($p < 0.01$). Comparing the blood volume in three sites of the proximal femur, the blood volume in the femoral head was lower than that in the femoral neck ($p < 0.01$) and in the intertrochanteric region ($p < 0.05$).

*Correlation of blood flow and blood volume between the different sites*

No correlations were observed in blood flow with the exception of a positive correlation between the femoral head and femoral neck ($r = 0.70$, $p = 0.015$) (Fig. 4).

In an analysis of the correlation of blood volume between the ilium and the three proximal regions of the femur, positive correlations were observed between the ilium and femoral head yielding values of $r = 0.78$ and $p = 0.012$ and between the ilium and intertrochanteric region yielding values of $r = 0.68$ and $p = 0.023$. In the proximal regions of the femur, positive correlations were observed between the femoral head and intertrochanteric region ($r = 0.73$, $p = 0.011$) (Fig. 5).

## DISCUSSION

Recent prospective and animal studies using MRI have clearly demonstrated that ONF is an acute ischemic disease that constitutes a single episode.[8–11] Although various theories have been proposed regarding the mechanism underlying the occurrence of ischemia of the femoral head, including impaired blood flow based on anatomical characteristics,[12] thrombus formation in nutritive vessels,[13] fat embolism,[14] fibrinolysis abnormalities[15] and angitis,[16] the details of that mechanism are not fully understood. An understanding of the hemodynamics of the femoral head is essential for elucidating the pathology of ONF. Since there are no methods for quantitatively measuring the blood flow of osseous tissue that are not invasive with respect to the measurement site, there are few reports of studies conducted on humans.

We previously attempted to quantitatively measure bone hemodynamics (blood flow, blood volume) of the femoral head by applying the PET technique to osseous tissue, and PET was clearly demonstrated to be an effective measuring technique for assessing bone hemodynamics in the femoral head, which is thought to be in a hypoemic state.[5] As a result of using this technique, new findings were obtained, namely that although blood flow decreases with aging, blood volume increases, and the femoral head becomes ischemic.

Even in the same osseous tissue, bone characteristics can vary depending on location. Osseous blood flow and volume may differ between cortical and cancellous bone, and even in the same cancellous bone, parameters may differ between yellow and red marrow. In this study, the characteristics of the hemodynamics of the femoral head were objectively elucidated by measuring blood flow and volume in the bone marrow of proximal regions of the

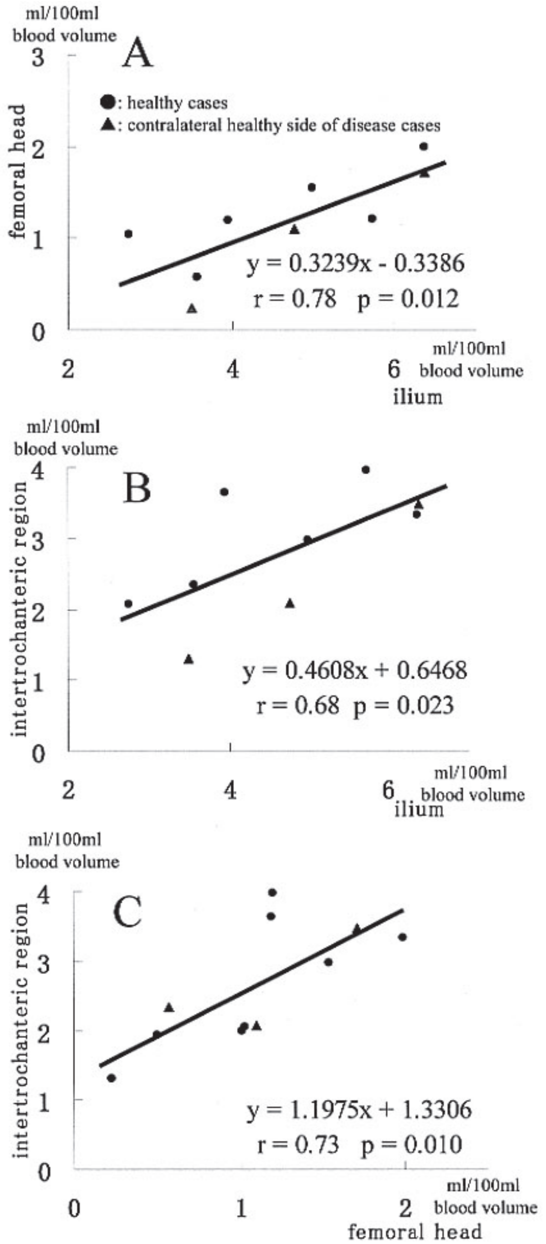


**Fig. 5** Correlation between the blood volumes at the different sites. A: On the *y*-axis, blood volume in the femoral head is shown (m*l*/100 g), and on the *x*-axis, that of the ilium is depicted (m*l*/100 g). A significant correlation was observed between blood volume in the ilium and in femoral head (r = 0.78, p = 0.012). B: Intertrochanteric region and ilium (r = 0.68, p = 0.023). C: Intertrochanteric region and femoral head (r = 0.73, p = 0.011).

femur in addition to the femoral head as well as cancellous bone of the ilium within the same individuals using PET.

The subjects of this study involved 3 hip joints on the contralateral healthy side of a femoral fracture, an avulsion fracture of the greater trochanter and a coxarthrosis. These hip joints were confirmed to be free of abnormalities by X-ray examinations. These subjects were examined after their ADL recovered to the normal level, and therefore there is no possibility that blood flow in bone tissue was influenced by the ability to walk.

As a result, hemodynamics was determined to be quite different between the ilium and proximal regions of the femur. One of the characteristics of the proximal regions of the femur was considerably lower blood flow and blood volume as compared with the ilium. Blood flow of the ilium has been reported by Kahn et al. to be 11.1 ± 2.2 m*l*/min/100 g as determined by PET with [$^{15}$O]water.[17] Although there are differences attributable to age of the subjects and the site where blood flow is measured in the ilium, this value is considered to closely approximate the results of this study.

With PET, lower resolution or smaller ROI resulted in a greater partial volume effect. In the previous study, the ROI was drawn as large as possible by taking into account the partial volume effect, comprising the entire marrow of the femoral head. Consequently, blood flow and volume in the femoral head were 3.52 ± 1.2 m*l*/min/100 g and 3.00 ± 1.27 m*l*/100 g, respectively.[5] In the present study, blood flow and volume in the femoral head were 1.8 ± 0.7 m*l*/min/100 g and 1.1 ± 0.5 m*l*/100 g. Compared to the previous study, both blood flow and volume were lower for the present study. Depending on the ROI setting, blood flow and volume in the femoral head might possibly be affected by surrounding soft tissues. Use of PET equipment with an FWHM of 6.0 mm in this study thus allowed establishment of an ROI inside the marrow with less impact from the partial volume effect compared to the previous study with an FWHM of 8.2 mm. When measuring blood flow and volume in the femoral head, consideration of partial volume effect and setting of an appropriate ROI are very important.

Furthermore, when investigating intraosseous circulation using the present method, blood flow measurements are affected by the blood partition coefficient for water and the delay time between osseous tissue and measurement site. Blood volume measurements are also affected by hematocrit levels in tissue. The details of blood flow and volume in osseous tissue have not yet been fully elucidated, and because osseous measurements are assessed based on values in other organs such as brain or liver, further investigation of blood flow and volume in osseous tissue is warranted.

As a result of analyzing three sites (femoral head, femoral neck and intertrochanteric region) located at proximal regions of the femur, the femoral head was found to exhibit the lowest values for both blood flow and volume, and those values were determined to increase moving distally from the femoral head to the femoral intertrochanteric region. The femoral head has been thought to lack blood flow in comparison with the femoral neck and femoral intertrochanteric region due to the anatomical characteristic of the periphery being covered with articular cartilage that prevents the entrance of blood vessels.

The results of actual measurements support this contention and have suggested that the hemodynamics of the femoral head is vulnerable to the ischemic state having the potential for escalating into necrosis even in the presence of only a slight exacerbation of hemodynamics that would only have a minimal effect on other proximal regions of the femur.

In the present study, both blood flow and volume were measured in osseous tissue, including the venous sinus. The results showed that blood flow in the femoral head exhibited a positive correlation only to that in the femoral neck. Blood flow is affected by not only arterial blood flow, but also capillary permeability and surface area.[18] Because blood flow was measured in the bone marrow of the proximal femur within the same individuals in this study, it was assumed that blood flow in the femoral head and neck is equally affected by capillary permeability and surface area. The present results agree with the anatomical features: blood flow in the femoral head depends on nutritive vessels from the femoral neck and all of these arteries are merely terminal arteries and lack anastomoses.[19–21] Furthermore, the present study confirmed a positive correlation between blood flow in the femoral head and that in the ilium and intertrochanteric region. Blood volume in the marrow exhibited a correlation to blood volume in not only the same bone, but also other bones. The development of capillary beds including the venous sinus of the bone marrow is stipulated for each individual regardless the site of the osseous tissue.

As the present study examined only 11 hip joints from 7 individuals, further investigations of the same points in a larger subject population are needed. In addition, cases of ONF were not included in the subjects of this study. Future studies on the correlation between hemodynamics of the femoral head and the occurrence of ONF in the form of prospective studies using PET will not only make it possible to significantly contribute to elucidation of the cause of ONF, but also make it possible to predict the risk of ONF and potentially lead to its prevention.

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