The Effect of Age on Blood Flow in the Proximal Femur in Man

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Blood flow in the proximal femur was measured in 45 healthy male and female adults by means of a Xe-133 washout method. On the basis of a two-compartment exponential model, blood flow was calculated assuming that the compartments were hematopoietic (red) marrow and nonhematopoietic tissues of bone. Between the ages of 20 and 55 the bone perfusion was 8.3 ± 1.4 (1 s.d.) ml/100g/min, decreasing thereafter in older patients. During the same period the red-marrow blood flow (RMBF) decreased linearly: RMBF(ml/100g/min) = −0.14 × age + 24.5. The nonhematopoietic bone perfusion changed like the bone perfusion.

The fractional masses of red marrow and nonhematopoietic tissues of bone in the greater trochanteric region of the femur were determined morphometrically from the bone biopsies of seven adult cadavers. They agreed with the values estimated by the Xe-133 washout method. The blood-flow values will be used as reference values for the Xe-133 bone circulation method.

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There are few quantitative measurements of the blood flow in the human skeleton (*1–3*). The fraction of cardiac output going to the skeleton, and the mean skeletal blood flow, has been measured recently (*1,2*). The distribution of blood flow between red marrow and bone is not known. We have found no reports of noninvasive measurements of the blood flow in red marrow.

Age-induced changes in skeletal blood flow are poorly known in man. In animal experiments, a diminution of blood flow has been observed (*4–6*). The relationship between the distribution of red marrow in the skeleton and skeletal blood flow with age has not been studied. On the basis of F-18 and Fe-52 scans in humans, Van Dyke (*7*) suggests that there is a relationship between skeletal blood flow and erythropoietic marrow.

The human proximal femur contains hematopoietic marrow until the age of about 55 (*8*), and it fulfills the requirements presented for a Xe-133 measurement of bone circulation (*9*). The Xe-133 method permits an investigation of blood flow in red marrow and in nonhematopoietic tissues of bone, and the mean blood flow in bone at different ages can be obtained. The present study shows that blood flow in the proximal part of the femur in healthy persons decreases with advancing age.

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MATERIALS AND METHODS

Patients. Patients with no history of skeletal or hematological disease, having given informed consent, were chosen for bone circulation measurements. The group included 26 males and 19 females, with ages between 22 and 81 yr (mean age 46.1 ± 17.1, s.d.). Weights and heights were measured.

Blood-flow measurements. These used a Xe-133 washout method (*9*). The patients were rested 30 min before the study. A dose of about 1.08 mCi (40 MBq) of Xe-133 in physiological saline was injected rapidly into the antecubital vein. A single NaI(Tl) scintillation probe carrying a small-aperture lead collimator was tightly pressed against the greater trochanteric area of the femur (Fig. 1).

Theoretical basis for the calculation of blood flow. The curves for the next 30 min of Xe-133 washout from the

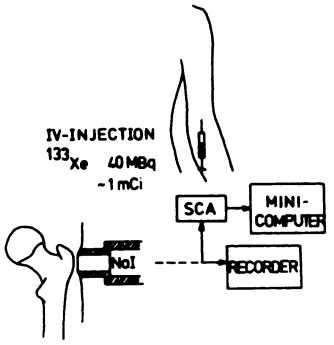

FIG. 1. Arrangements for measurement.

bone were analyzed on a two-compartment basis. Previously we have proposed (*9–11*) that the rapidly falling segment of the curve is caused by the disappearance of xenon from red marrow, and the slowly falling segment by the elimination of xenon from the nonhematopoietic tissues of bone. Nonhematopoietic tissue of bone implies bone without red marrow, i.e., mostly solid bone substance and intraosseous fat.

The mean bone perfusion F was calculated from

$$F(ml/100g/min) = w_1(m)f_1 + w_2(m)f_2, \quad (1)$$

where $w_1(m)$ and $w_2(m)$ are the fractional weights of red marrow and nonhematopoietic tissue in the total mass of bone (*12*). They can be calculated from

$$w_i(m) = \frac{A_i/f_i}{A_1/f_1 + A_2/f_2} \quad (i = 1,2) \quad (2)$$

if the Xe-133 bone washout curve C(t) is expressed as

$$C(t) = A_1 \exp(-k_1 t) + A_2 \exp(-k_2 t). \quad (3)$$

Here A_1 and A_2 describe the initial quantities of xenon in Compartments 1 and 2 at $t = 0$. f_1 and f_2 are the compartmental blood perfusion rates, and can be expressed as

$$f_i(ml/100g/min) = \lambda_i k_i \quad (i = 1,2), \quad (4)$$

where k_1 and k_2 are the slopes of the compartmental activities on a semilogarithmic scale. They can be calculated from the half-times $t_{1/2}$ of the compartmental activity: $k = \ln 2/t_{1/2}$. The Xe-133 partition coefficients for the two bone compartments are $\lambda_1 = 0.95$ ml/g and $\lambda_2 = 0.049 \times \text{age} + 3.11$ (*13*).

The fraction $w_i(F)$ of the skeletal blood flow going through Compartment 1 or 2 (*12*), was calculated from

$$w_i(F) = A_i/(A_1 + A_2) \quad (i = 1,2). \quad (5)$$

The patient's bone blood perfusion was also calculated as units of perfusion per unit body weight and per unit surface area.

The total flow through the skeleton and the fraction of cardiac output to the skeleton were estimated using the assumptions that skeletal weight is approximately 15% of the body weight (*14*) and that the blood flow in the proximal femur can be regarded as representative of the whole skeleton. Since we did not measure the patient's actual cardiac output, we have estimated it. J. T. Kuikka and E. Länsimies in our laboratory have gathered their own and other representative values (*15,16*) for cardiac output as a function of age. Table 1 summarizes these findings. Since the mean age of our patients was 46.1 yr, the various methods gave the following values for a standard man (surface area 1.73 m^2): 5500, 5700, and 6400 ml/min. The mean of these values, 5900 ml/min, was used in our calculations.

Xe-133 recirculation. The effect of arterial recirculation of xenon on the results for compartmental perfusion and mean bone perfusion was estimated by the method of Veall and Mallett (*17*). The activity in the expired air was recorded with a scintillation detector placed on the expiration tubing 10 cm from the breathing mask. The expired-air curve was analyzed and yielded three exponential components. The washout rate of the second component was assumed to correspond to the washout rate k_b of Xe-133 from arterial blood (*17*). The concentration of Xe-133 in the *i*th compartment can be obtained (*18*) from

$$c_i(t) = c_i(0)\exp(-k_i t) + \lambda_i c_a(0)[k_i/(k_b - k_i)] \times [\exp(-k_i t) - \exp(-k_b t)], \quad (6)$$

where $c_a(0)$ is the blood concentration at $t = 0$.

The measured washout curve $c_i(t)$ is derived from the true exponential washout represented by the first term and from the recirculation of the tracer represented by the second term. Since rapid injection was used, we can assume (*18*) that $c_i(0) = \lambda_i c_a(0)$ at $t = 0$. The slowly falling segment was first corrected for recirculation. The uncorrected rapidly falling segment was obtained by subtracting the corrected segment from the measured

TABLE 1. CARDIAC INDEX (l/min-m^2) WITH AGE, OBTAINED BY VARIOUS METHODS

Method	Number of patients	Age range	Cardiac index (l/min-m^2)
Dye dilution	82 males	12–82	−0.027 × age + 4.4
Fick principle	42 males	20–83	−0.020 × age + 4.2
Radiocardiography	69 males	6–78	−0.025 × age + 4.8
Radiocardiography	79 females	6–73	−0.018 × age + 4.3

points on the washout curve. After correction for recirculation of the rapid segment, the bone washout curve was reanalyzed on a two-compartment basis and the flow values for the compartments were derived.

Morphometric determination of bone-tissue components. From seven patients who died suddenly of a nonhematological disease, histological specimens were taken from the cancellous midportion of the greater trochanter and were fixed in 10% neutral buffered formalin. The specimen was decalcified by 5% aqueous nitric acid for 16 hr, then embedded in paraffin (*19*). Sections 6 μm thick were stained with the van Gieson hematoxylin method.

In the morphometric analysis, a point-counting method was used (*20*). The Weibel multipurpose graticule with 42 points was inserted into the projection head of a semiautomatic sampling microscope.* Using a magnification of 86×, 700–1000 points per specimen were counted with the systematic field-sampling technique. The number of points falling on different bone-tissue compartments, (P_i), and the total number of points counted on the reference area, (P_T), were registered. The volumetric fraction V_{Vi} (cm^3/cm^3) of a tissue compartment i was calculated from the formula (*20*): $V_{Vi} = P_i/P_T$. The bone tissue was divided into three compartments: (1) hematopoietic bone marrow (V_{VH}), (2) nonhematopoietic tissue of bone marrow (V_{VF}) consisting mainly of intraosseous fat, and (3) bone trabeculae (V_{VB}).

Since the volumetric fractions of red marrow, intraosseous fat, and bone trabeculae are known, and the densities of the compartments are 1.028, 0.91, and 2.2 g/cm^3, respectively (*14*), the fraction (g/g) of hematopoietic tissue in the bone will be $m_{VH}/m_T = 1.028\ V_{VH}/(1.028\ V_{VH} + 0.91\ V_{VF} + 2.2\ V_{VB})$. This fraction should equal the $w_1(m)$ obtained from the analysis of the bone washout curves (Eq. 2).

RESULTS

The mean perfusion in proximal femur is shown as a function of age in Fig. 2. Blood flow was constant, 8.3 ± 1.4 (1 s.d.) ml/100g/min, between the ages of 20 and 55. The 95% confidence limits for the flow were 5.5 and 11.1 ml/100g/min. After approximately age 55, blood flow begins to decrease. It may be estimated from Fig. 2 that at age 80 the blood flow in the proximal femur is approximately half that in a middle-aged person. There was no statistical difference in bone perfusion between males and females.

The red-marrow blood flow (RMBF) decreased linearly with age (Fig. 3). Between the ages of 20 and 55 the correlation can be expressed as RMBF (ml/100g/min) = $-0.14 \times$ age + 24.5 ($r = 0.41$, $p < 0.05$). Five patients under the age of 55 did not have a rapid component in the washout curve. In two patients over the age of 55, the curves were biexponential, indicating the existence of hematopoiesis in the proximal femur.

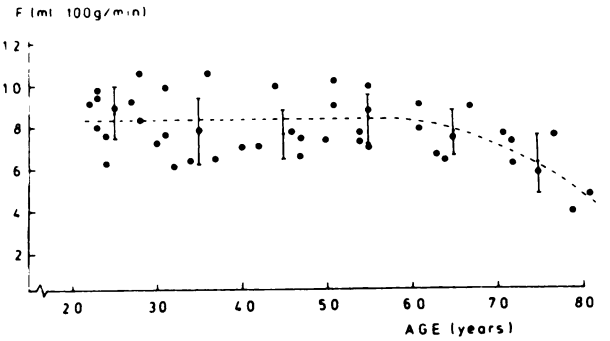

FIG. 2. Mean perfusion of proximal femur in healthy persons (dashed line), with individual measurements shown as solid circles. Vertical bars represent ±1 s.d. of the mean in the 10-yr interval.

The nonhematopoietic bone perfusion (Fig. 4) behaved like the mean bone perfusion. The blood flow between the ages of 20 and 55 was 7.1 ± 1.2 (s.d.) ml/100g/min. The 95% confidence limits for the flow were 4.7 and 9.5 ml/100g/min.

The total skeletal blood flow, calculated using the value of 8.3 ml/100g/min for the mean skeletal perfusion, was 870 ml/min, which corresponds to 14.7% of the estimated cardiac output (5900 ml/min).

The mean bone perfusion, calculated either per unit surface area or per kilogram of body weight, also decreased with age. However, the variations between the perfusion values of different persons were over 1.5 times those in Figs. 2–4.

The correction for recirculation of xenon increased the mean bone perfusion by 5.1%. The effect of recirculation on the result for nonhematopoietic tissues of bone was always less than 4%. Without the recirculation correction, the perfusion of red marrow was underestimated by 9–22%.

Table 2 shows the results from the washout-curve analysis. In two patients over age 55, both showing a rapid component in the washout curve, the fractional weights were 9.5 and 10.7% and the fractional flows 18.0

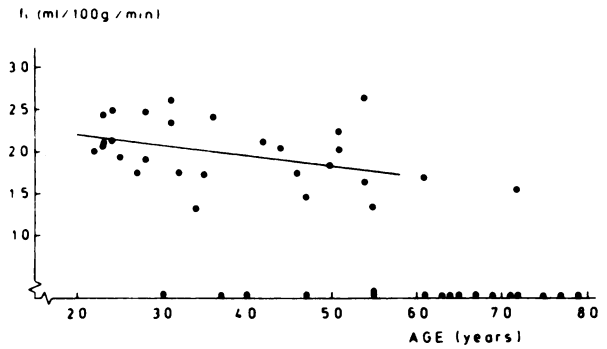

FIG. 3. Perfusion of red marrow as a function of age. The line describing perfusion between ages of 20 and 55 has been drawn through points not equal to zero. Patients who had no rapidly falling segment in the washout curve are shown as solid circles on a horizontal axis.

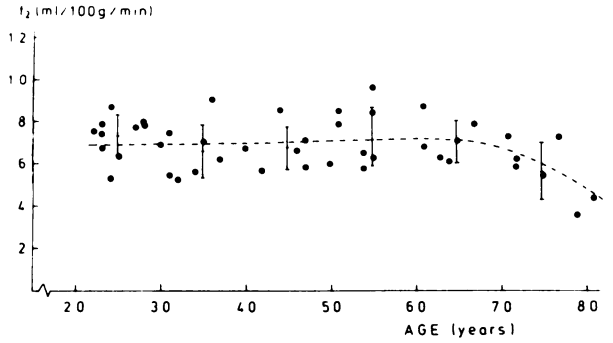

FIG. 4. Perfusion of nonhematopoietic tissues of bone as a function of age (dashed line). Bars represent ±1 s.d. in the 10-yr interval.

and 19.5%, respectively. These patients were not included in Table 2.

Table 3 summarizes the results from the morphometric measurements of the microscopic sections. The data show that the volumetric fraction of red marrow, V_{VH}, varies somewhat in the patients investigated.

DISCUSSION

One of the basic assumptions of the Xe-133 bone washout method is that the tracer can be thought of as distributed in bone between the hematopoietic and the nonhematopoietic compartments. The hematopoietic compartment contains a number of blood cells in various stages of maturation. It is not possible to estimate the solubility of Xe-133 in the various stages of cell development. Therefore, we have estimated its solubility in the combined white- and red-cell masses (*13*), which are the main constituents of active bone marrow. The nonhematopoietic compartment consists of several tissues—bone mineral, organic matrix, connective tissue, intraosseous fat, and water—but we treat them as a single compartment. This can be justified if the situation is looked at from the point of view of xenon. Although the partition coefficient of fibrous tissue has not been measured, its influence on the partition coefficient of nonhematopoietic tissues of bone cannot be great, since the amount of fibrous tissue in healthy human bone is small. The influence of intraosseous water is also considered slight (*13*). Accordingly, the most significant tissues for the behavior of xenon in bone are intraosseous fat, bone mineral, and organic matrix. The partition coefficient of intraosseous fat is nearly ten times that of the component consisting of bone mineral and organic matrix (*13*). Therefore, intraosseous fat dominates the partition coefficient of the nonhematopoietic tissues of bone and the slowly falling segment of the washout curve. The change in the amount of intraosseous fat with age in healthy persons has been taken into consideration in λ_2, which increases as a function of age (*13*).

The nonhematopoietic compartment determines the whole washout curve in cases where the bone contains no red marrow. This is consistent with the finding of this study that after the age of 55, the rapidly falling segment of the bone washout curve was absent in 11 out of 13 patients. The presence of this segment in the other two subjects may be due to physiological variation. The findings are also in accordance with the earlier result of Custer and Ahlfeldt (*8*), who showed that red marrow vanishes from the proximal part of femur in older subjects.

The second basic assumption in the method is that the compartments are coupled in parallel with respect to blood flow. The nourishment of the proximal femur is provided by the metaphyseal and epiphyseal arteries and the nutrient artery of the femur. Wootton (*21*) has shown, using microspheres, that about 40% of the blood flow entering the femur goes to the capillary bed of the diaphyseal bone marrow before reaching the cortex. This indicates that blood flow behaves as if it were coupled in series with the bone marrow and femur cortex. However, the proximal femur following fusion of the growth cartilage is nourished principally by the metaphyseal arteries. In the rabbit femur, the nutrient artery is responsible for about 33% of the blood supply of the upper metaphyseal-epiphyseal region (*22*). Part of this blood may be coupled in series with the diaphyseal marrow's capillary bed before reaching the proximal femur, but most of the blood entering the upper femur is coupled in parallel between the compartments.

There are only a few reported measurements of blood flow in the trochanteric region of human femur. Simon et al. (*23*), using iodoantipyrine (I-131) and pertechnetate (Tc-99m), obtained a value of 6.2 ± 2.9 ml/100g/min for blood flow in the trochanteric region in patients who were strongly suspected of having aseptic necrosis of the femoral head. Our value is consistent with this value but higher than that of 4.1 ml/100g/min for

TABLE 2. DATA FROM ANALYSIS OF WASHOUT CURVES

Age	Fractional weight		Fractional flow		Washout rate constant	
	$w_1(m)$	$w_2(m)$	$w_1(F)$	$w_2(F)$	k_1 (min^{-1})	k_2 (min^{-1})
20–50	0.10 ± 0.04*	0.90 ± 0.03	0.23 ± 0.07	0.77 ± 0.07	0.18 ± 0.05	0.014 ± 0.003
>55	0	1.0	0	1.0	0	0.009 ± 0.004

* mean ± 1 s.d.

TABLE 3. MORPHOMETRIC DATA FOR HISTOLOGICAL SECTIONS FROM CANCELLOUS BONE OF PROXIMAL FEMUR

Patients	Sex	Age	Volumetric fraction (%)			Fractional mass (%)		
			V_{VH}	V_{VF}	V_{VB}	m_{VH}	m_{VF}	m_{VB}
1	F	28	34.7	41.4	23.7	28.5	30.0	41.5
2	M	32	17.9	59.6	22.5	15.1	44.4	40.5
3	F	36	19.5	60.1	20.4	16.8	45.7	37.5
4	F	37	33.0	29.0	38.0	23.6	18.3	58.1
5	F	37	13.2	67.2	19.6	11.5	51.9	36.6
6	F	38	21.9	65.5	12.6	20.5	54.3	25.2
7	F	49	28.6	46.0	25.4	23.1	32.9	44.0
mean			24.1	52.7	23.2	19.9	39.6	40.5
±1 s.d.			8.1	14.2	7.7	5.8	13.0	9.8

a mixed bone as measured by Wootton et al. with F-18 (*2*). The perfusion is significantly lower than the value of 11.7 ± 0.3 ml/100g/min reported by Charkes et al. (*1*) for a mixed bone using a five-compartment model with fluoride (F-18) kinetics. The estimated fraction of cardiac output flowing to the skeleton was 16.8%, while our value was 14.7%.

The perfusion of red marrow has not been measured in man. The values obtained are low compared with the values of 15–110 ml/100g/min measured in animals (*24–30*). Only in very active phases of blastic cell crisis in chronic granulocytic leukemia have we found values of the order of 40 ml/100g/min for bone-marrow blood flow. Most of the values in animal experiments represent blood flow in bone marrow, which may contain, in addition to red marrow, fatty marrow with a perfusion rate of 6.3 ml/100g/min (*30*). The perfusion rate is dependent upon the amount of fatty marrow, which depends on the age of the animal. Since the animals investigated have been rather young, the perfusion rate may be overestimated. In young rabbits the observed high perfusion rates have been ascribed to the higher hematopoietic activity of bone marrow (*24*). The same may also hold for man, since a decrease in red marrow perfusion with age was noted. At the ages of 20 and 50 the total bone-marrow blood flow is about 300 and 250 ml/min, respectively, if it is assumed that the mass of red marrow is 1400 ml (*14*). A similar value has also been estimated by Jones (*32*). It corresponds to about 5% of the estimated cardiac output, and is slightly smaller than the 7.6% reported for rabbits (*25*).

Figure 3 shows that there are no perfusion values between 0 and 12 ml/100g/min. Actually, a measurement point which is shown as zero may lie somewhere inside these limits. When the counting statistics of the rapidly falling segment are poor, the fast component cannot be resolved reliably. In practice we have found that, using the present injected dose of tracer, we can resolve the washout curve into its components relatively easily when the fractional flow $w_1(F)$ of the red marrow, $A_1/(A_1 + A_2)$, is greater than 0.1.

Age-induced changes in skeletal blood perfusion have not been measured in man. In animals, a diminution of blood flow has been observed in peripheral bones such as the femur (*4–6*). Several assumptions can be made concerning the decrease of bone perfusion. Red marrow concentrates in the axial skeleton with advancing age. As noted in this study, only two patients over 55 had a rapidly falling segment of the washout curve, indicating the existence of hematopoiesis. Since the perfusion rate in red marrow was higher than in the nonhematopoietic tissues of bone, the disappearance of the red marrow would lead to a decrease in blood flow. The decrease in the cardiac output with age (Table 1) may also have an effect on skeletal blood flow. The decrease in the capillary network with age would lead to a diminution of blood flow, as noted in animals (*4*). The decrease in physical activity and changes in hormonal function are also possible reasons for the decrease of blood flow. At the age of 80 the skeletal blood flow seems to be half the value at middle age.

The study showed that the subject's sex need not be taken into consideration in bone-circulation measurements, and the same holds for body weight and surface area. The blood flow expressed in relation to body weight or surface area decreased linearly as a function of age, but since the variations of the blood flow values were about 1.5 times those of Figs. 2–4, their use was rejected.

In the preliminary report of the Xe-133 washout method (*9*), we used the fractional flows instead of the fractional weights in Eq. (1) as the coefficients of the compartmental perfusions. This may be valid for local Xe-133 injection studies (*10*) but can lead to overestimation of flow in the intravenous Xe-133 injection method if the distribution of xenon between the compartments and blood is not instantaneous. We also overestimated the partition coefficient of red marrow: subsequent experiments have shown that it was high by a factor of ~1.5 (*13*). After appropriate corrections the

bone perfusion is found to be approximately 30% lower than the values presented in our preliminary work (*9*).

The correction for arterial recirculation of Xe-133 on the mean bone perfusion was relatively small, and is of the same order of magnitude as the errors made in the estimates of half-time from the washout curves (*9*). Therefore, when only bone perfusion is studied, the correction for arterial recirculation is not necessary. This makes the measurement easier, since one need not record the expired-air curve. It is quite possible that, instead of the expired-air curve, a curve measured with a well-collimated detector over the heart could be used to estimate the recirculation correction (J. T. Kuikka, personal communication). When we are studying blood flow in red marrow, a correction has to be performed since, without it, the red-marrow flow can be underestimated by 9–22%.

The bone perfusion rate in the trochanteric area of the femur may not be the same as the average in the skeleton. The proximal femur contains trabecular bone, whose perfusion is greater than in diaphyseal cortex by a factor of almost 1.5 (*30*). The perfusion of the whole femur can be representative of the skeleton (*33*), but the perfusion of the proximal femur is greater than that in a mixed bone. The above-mentioned fraction of the blood flow entering the skeleton may then be overestimated. We have recent measurements indicating that the blood flow in the proximal femur correlates well with that of the anterior superior iliac spine. Therefore, it seems that blood-flow changes in the trochanteric region may be representative of those occurring in the skeleton.

Because of the small number of histological bone specimens, it was not possible to determine the amount of red marrow at different ages. The values of the morphometric measurements for the amount of red marrow are somewhat higher than the fractional weights obtained from the washout curves. This may be due to the age difference of the patients between the morphometric and washout-curve measurements. Nevertheless, they are in relatively good agreement with the values of the Xe-133 method. These findings support the validity of the partition coefficients measured earlier and the basic assumptions used in the Xe-133 bone blood-flow method.

FOOTNOTE

* Wild M 501.

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