DEPLETION OF ^{18}F FROM BLOOD FLOWING THROUGH BONE

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The positron-emitting isotope ^{18}F has been shown to be useful in outlining both normal bones and bone lesions by external scanning (*1,2*). It has been suggested (*3*) that the initial uptake of ^{18}F by bone depends solely on its rate of delivery to bone, i.e., on the blood supply, and that the efficiency of extraction of the isotope by bone is very high, perhaps as much as 100% at each blood passage. The blood supply is obviously an important factor since the bone can take up only as much isotope as is delivered to it. It is, however, questionable whether the blood supply is the sole factor which determines the retention of ^{18}F by bone even during the few hours after injection when this short-lived isotope can be measured.

A large body of evidence in the literature indicates that the initial process by which a pulse label of bone-seeking isotope is taken up is one of exchange between the radioactive element in the blood and the same or a similar stable element on metabolically active surfaces in bone. In the case of radioactive calcium or strontium the exchange is probably with pre-existing stable calcium on crystal surfaces or in ionization shells, while ^{18}F exchanges with stable fluoride or other anions in the same locations. Immediately after the initial process of surface exchange, the isotope begins to be incorporated into new crystals of bone salt and to diffuse into deeper layers of bone, but these processes are so slow that they are unimportant quantitatively during the first few hours. If the initial uptake of a label is indeed due predominantly to exchange, then, as soon as the specific activity in the blood has fallen below that on the bone surface, the concentration on the bone will begin to fall owing to reverse exchange. These relationships, as they influence calcium kinetics in man, are summarized in a review by Heaney (*4*). Rowland (*5*) has shown by radioautography that in rabbit bone ^{45}Ca on the surfaces of vascular channels reaches a maximum between 11 min and 1 hr post i.v. injection and declines significantly by 4 hr.

In a recent study (*6*) we have found that the kinetics of ^{18}F and ^{47}Ca in rabbit bone are very similar qualitatively, although there are quantitative differences. The work was not done primarily for the study of bone blood flow, but it was done under conditions in which the blood flow was essentially constant. From the data obtained we were able to calculate the change with time in the rate of depletion of the isotopes from the blood flowing through bone. The results of these calculations will be presented here.

MATERIALS AND METHODS

Adult male albino rabbits were used. The ^{18}F was carrier-free and was in solution in physiological saline. The ^{47}Ca was in the form of calcium chloride and had a specific activity of 140 mCi/gm ^{40}Ca. The isotope solutions were brought to a pH of about 5 and were injected intravenously into an ear vein. The dose of ^{18}F was about 200 μCi; that of ^{47}Ca was about 40 μCi.

Blood samples were obtained from a different vein from that used for injection every 5–10 min shortly after injection and every 15–20 min at later times. The animals were killed by an overdose of pentobarbitol at intervals of 5 min–3 hr after injection. A total of 35 rabbits was used. After sacrifice one tibia was dissected out and cut in pieces transversely. The results reported here were obtained from specimens from the mid-shaft. They consisted of cortical bone from which the marrow had been removed.

Specimens of blood or bone were placed in small plastic vials, weighed and counted in a well scintillation counter with a multichannel analyzer. The spectra were integrated over the 0.51-MeV peak of ^{18}F and the 1.31-MeV peak of ^{47}Ca and were analyzed to calculate the activity of each isotope. Results were expressed as percent of injected dose per gram of blood or per gram of bone.

Under these experimental conditions the blood flow through bone is essentially constant. From the

Received Dec. 4, 1968; revision accepted Aug. 12, 1969.

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experimental data the depletion of isotope from blood flowing through bone was calculated as follows:
Let

D = depletion factor = the fraction of the isotope in blood which is retained in bone at each passage of blood through bone. This depletion factor depends not only on the rate of transfer of isotope from blood to bone but also on the rate of release of isotope from bone to blood.

U(t) = uptake = concentration of isotope in bone at time t as percent of injected dose per gram of wet bone.

F(t) = concentration of isotope in blood as percent of dose per gram of blood at time t.

B_f = blood flow as grams of blood per gram of bone per minute.

The increase in concentration in bone between any two times, t_1 and t_2, is given by

$$U(t_2) - U(t_1) = DB_f \int_{t_1}^{t_2} F(t)\,dt$$

and

$$DB_f = \frac{U(t_2) - U(t_1)}{\int_{t_1}^{t_2} F(t)\,dt}.$$

RESULTS AND DISCUSSION

The product of blood flow (B_f) and depletion factor (D) was calculated for ^{18}F and ^{47}Ca for different times after injection of the isotopes from the averages of the values for the concentrations in blood and cortical bone. The results are shown in Table 1 and are also shown graphically on a logarithmic scale in Fig. 1.

It is clear that the product of blood flow times depletion factor falls progressively throughout the experimental period. Since the blood flow is constant, it follows that the depletion factor decreases. This is true both for ^{18}F and ^{47}Ca although there are quantitative differences which are thought to be due partly to differences in the rates of the exchange reactions. The maximum depletion factor is to be expected at time t = 0 when there is no isotope in the exchangeable pool to return to the blood.

The product DB_f of the tracer at t = 0 is equal to the fraction of the traced (stable) element taken up by bone at each blood passage times the blood flow. Here we exclude the amount of stable element released into the circulation. This product is equal to the ratio of the rate of transfer of the traced element from blood to bone to the concentration of the same element in blood. In other work (*6*) to be reported elsewhere, we obtained data by serial external scanning of rabbit tibias corrected for soft tissue activity. These data were then submitted to compartmental analysis. In this analysis we assumed a compartmental model consisting of two compartments and a two-way reaction between blood and bone. The average value for the ratio of the rate of transfer of stable element from blood to bone to its concentration in blood was, for fluoride, 2.0×10^{-5} mg/gm bone/min, and for calcium, 0.0053. The concentration of stable calcium was determined experimentally. The concentration of stable fluoride in the plasma of the rabbits was not known but was assumed to be 0.25 ppm. This is the value which has

TABLE 1. CHANGE OF PRODUCT OF DEPLETION FACTOR (D) AND BLOOD FLOW (B_f) WITH TIME AFTER INJECTION

Time after inj. (min)		D × B_f	
t_1	t_2	^{18}F	^{47}Ca
0	5	0.081	0.066
0	10	0.080	0.053
10	20	0.072	0.050
20	40	0.057	0.035
40	60	0.047	0.021
60	80	0.033	0.015
80	100	0.015	0.008

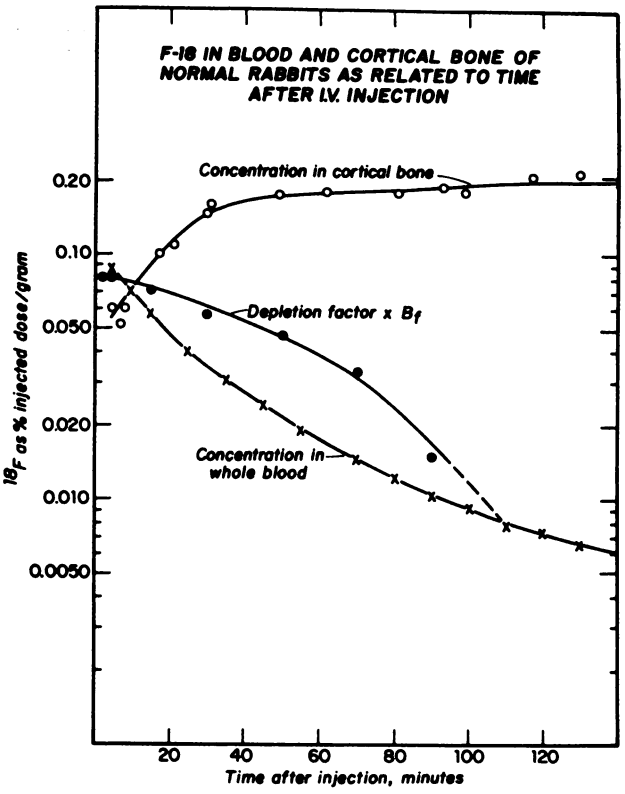

FIG. 1. ^{18}F in blood and cortical bone of normal rabbits as related to time after i.v. injection.

been reported for the rat (*7*), and it is within the range which has been found for man (*8*). From the rates of transfer and the concentration of stable fluoride and calcium we calculated the product DB_f at $t = 0$. The product is 0.08 for stable fluoride, which is identical with the value for ^{18}F shown in the table for the first 5 min. In the case of stable calcium the value obtained using the total concentration of calcium in plasma was 0.036 compared to 0.066 for ^{47}Ca. This discrepancy can be explained by the fact that only the ionic calcium in plasma is available for exchange with bone, whereas about half of the calcium in plasma is protein bound. If, instead of using the total calcium concentration, we use the value for ionized calcium obtained from the McLean nomogram (*9*), we obtain a DB_f value of 0.071. This is in reasonable agreement with 0.066, which is shown in the table for ^{47}Ca in the first 5 min.

The most reasonable explanation of the fall of the depletion factor with time is that the relative amount of isotope released from bone by exchange compared with that which is taken up increases as the specific activity of the exchangeable pool increases and as the specific activity of the blood decreases. The difference in the amount of isotope taken up by bone minus that which is released will determine the depletion factor. The depletion factor should become negative when the specific activity of the blood falls below that in the exchangeable pool. It was found (*6*) that the concentration of ^{18}F in bone reached a maximum 2–3 hr after injection and then began to fall slowly. The data in the table are limited to 2 hr, and thus no negative values are demonstrated.

It should be noted that the analysis given here is based on the assumption that the amount of isotope which is incorporated permanently in new crystals during a 2-hr period is negligibly small compared to that in the exchangeable pool. For much longer times the amount of isotope permanently incorporated will become significant, and the depletion factor will be overestimated.

The variation of DB_f with time in the first 10 min after injection is very small, and it may be reasonable to assume that the depletion factor is close to unity. Accordingly, at this time DB_f represents the minimum blood flow. At later times, however, the decrease in the depletion factor is so rapid that any calculation of minimum blood flow from tracer uptake in bone will result in an underestimation of blood flow.

The results presented here are in harmony with the processes postulated for calcium and strontium in the references cited, and are here shown to apply to both calcium and fluorine. The rate of blood flow imposes an upper limit on the total amount of isotope which can be deposited in bone in a given time. Within this limit the amount of isotope which actually is in bone in a given short time after injection is determined by the size of the exchangeable pool. This in turn depends on the size of the metabolically active surfaces in the bone, which is the parameter which is usually of clinical interest.

SUMMARY

Data have been obtained on the variation in the activity of ^{18}F and ^{47}Ca in the blood and cortical bone of rabbits with time after intravenous injection of the isotopes.

It is shown that the depletion of isotope from blood on each passage through bone decreases with time.

ACKNOWLEDGMENT

This work was supported in part by AEC Contract AT (30-1)-910 and by NCI Grant 08748.

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