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Exchange of potassium and strontium in adult bone

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Abstract

The kinetics of exchange of strontium (^{85}Sr) and potassium (^{42}K) were studied in the midtibial cortical bone of 37 adult dogs. After injection of these two tracer cations and tracer-labeled albumin into the tibial nutrient artery, two types of observations were made: 1) collection of sequential venous samples to provide the outflow indicator-dilution curves and to calculate the extraction and retention at early times; and 2) detection of energy-selected gamma emissions via a detector over the tibia to give the time course of content of ^{42}K and ^{85}Sr in the tibia. Extractions of K^+ and Sr^{2+} were 50 and 60% during a single transcapillary passage. More Sr^{2+} than K^+ was retained in the first minutes. Their rates of washout over a 3-h period were similar. The interpretation is that the rate of uptake at extravascular sites is faster for Sr^{2+} than for K^+ , as is the rate of release, and that the extravascular volume of distribution for Sr^{2+} (adsorption sites in the interstitium or on bone) is much larger than that for K^+ (intracellular).

Keywords

bone-seeking isotopes; indicator-dilution curves; tracer kinetics; transcapillary passage; transport mechanism; residue function; fractional escape rate

TALMAGE AND MEYER (30) expanded the original concept of Howard (9) to include the postulate that the extracellular fluid space of bone is compartmentalized by a layer of osteocytic cells lining the surfaces of bone. The identity of the cells making up this hypothetical membrane is unknown. The idea is that this layer acts as a membrane that maintains a concentration gradient between the fluid space adjacent to the bone mineral and the interstitial fluid (ISF), which is in equilibrium with the blood. Neuman (24) and Neuman and Neuman (23) have estimated, in the chick calvarium in vitro, that the potassium concentration in bone extracellular fluid is inexplicably high.

Because any compartmentalization of potassium is likely to be regulated at barriers to exchange, this implies the high probability of compartmentalization of calcium. It seems important, therefore, to compare and contrast the rate of exchange of potassium with that of calcium or its near analogue, strontium (2,6,13). The multiple indicator-dilution technique allows the examination of both capillary permeability and cellular uptake rates and is suitable for studying potassium and strontium simultaneously in that paired comparisons can be made. The uptake by bone of numerous bone-seeking isotopes is impeded by the capillary membrane, which acts only as a passive barrier (5,10–12). Sucrose, which is inert and is not transported across cell membranes, serves well in such studies as a second reference substance for extracellular distribution, and albumin still serves as the primary reference, being limited to

the vascular space. With these aids, it was our goal to estimate the relative amounts of retention of K^+ and Sr^{2+} by the dog tibia and to examine the transport rates and retention in the light of the possible existence of a specialized bone membrane.

The purpose of this study, therefore, was to compare the transcapillary extractions of potassium and strontium and their retention at brief times (2–3 min) and over the first 3 h after injection and to try to interpret the observations in terms of membrane barriers and accessible volumes of distribution.

METHODS

Animal preparation

The animals studied were adult, male mongrel dogs weighing between 14 and 28 kg. All were given heparin (1,500 U) and anesthetized with intravenous pentobarbital sodium (30 mg/kg). The nutrient artery of the tibia was cannulated with a 0.58-mm ID cannula (Intramedic PE-50) for the injection tracers, as previously described (5). Stopping nutrient artery flow decreases clearance of ^{85}Sr from the tibial diaphysis by about one-third (3). The cognate bed of the nutrient artery was perfused in some animals by collateral flow at about two-thirds of the normal flow (3), and in others the artery was continuously perfused at chosen rates with blood from the dog taken before any tracers were injected (17). The ipsilateral femoral vein was cannulated with a T cannula (5.3-mm ID), and tributary veins just proximal to the site were ligated to prevent tracer from bypassing the cannula via collaterals. For the collection of sequential samples from the T cannula for outflow dilution curves, the vein was clamped proximal to the T; by collection of the total outflow for 3 min and then unclamping, approximately 99% of the tracer could be accounted for as the sum of tracer in the outflow plus that retained in the bone (10).

A small volume of solution (0.25–1.0 ml) containing three radionuclides was injected into the nutrient artery, an intravascular reference tracer, albumin, and a pair of permeable tracers, either ^{14}C -labeled sucrose and ^{42}K or ^{42}K and ^{85}Sr . The doses were 10 or 15 μCi for the ^{51}Cr - or ^{99m}Tc -labeled albumin, respectively, and 5–20 μCi for ^{14}C -labeled sucrose, ^{42}K , and ^{85}Sr . The injection was given over several seconds by slow manual injection to avoid raising the pressure unnaturally in the nutrient arterial system. Blood samples were collected every 5 s for 3 min from the femoral vein. In dogs with pump perfusion of the nutrient artery, the injection of isotopes was given as a short pulse over a few seconds.

Fractional tracer content of the tissue [$R(t)$] was monitored for 3 h by a 2-in. thallium-activated sodium iodide crystal placed over the subcutaneous surface of the tibial diaphysis. The recorded activity of the fractional tracer content at time t [$C^*(t)$] was divided by $C^*(0)$, the maximum value obtained after removal of the injection syringe and completion of the flush, so that

$$R(t) = C^*(t) / C^*(0) \quad (1)$$

[Injection was an impulse input in all washout studies of ^{42}K and ^{85}Sr and would have exactly the form of residue function as defined by Zierler (33).] For the measurement of flow, in some experiments only, 15 μCi of ^{25}I -labeled antipyrine (I-Ap) was injected quickly into the nutrient artery, and the area under the curve of $R(t)$ was used to estimate the blood flow per unit volume of bone (3,14). The I-Ap is washed out to a low level in 15–30 min. A detector placed over the opposite tibia indicated that recirculation was negligible.

At the end of 3 h the tibia was removed, cleansed of soft tissue, and weighed. The hematocrit (Hct) was either measured in the venous blood samples or, when the nutrient artery was

perfused with blood, in the blood used for perfusion. When the nutrient artery was perfused, it was assumed that there was no additional collateral flow. With nutrient artery perfusion, the plasma flow (F_s ; ml·100 g bone⁻¹·min⁻¹) equaled pump flow $\times (1 - \text{Hct})/(\text{wt of tibia})$. Flow values in these studies were similar to those used by Martin et al. (20) in an isolated tibial preparation and were well within the range for tibial diaphyseal cortical flow values observed by Morris and Kelly (21). When I-Ap washout was used, which provided $F_{I\text{-Ap}}$ (ml·100 g bone⁻¹·min⁻¹), this was translated to plasma flow because the hydrophilic tracers sucrose, K^+ , and Sr^{2+} do not enter erythrocytes as I-Ap does, and thus $F_s = F_{I\text{-Ap}} (1 - \text{Hct})$.

Isotopic activity of samples

For samples with ⁴²K, ¹⁴C-labeled sucrose, and ⁵¹Cr-labeled albumin, the samples were counted in two channels of a gamma well counter (Nuclear Chicago, model C-120-1); then, after 8 days or more were allowed to pass for the decay of the ⁴²K, the samples were counted again, as a check on accuracy, in a two-channel liquid scintillation system (Nuclear Chicago, Mark II) for the beta activity of ¹⁴C and ⁵¹Cr. For external detection, two channels were set up for the gamma peaks of the pairs of tracers. In three preliminary experiments, maximum values of instantaneous extraction (E_{max}) were calculated from the transport functions [$h(t)$'s] for potassium from both whole blood and plasma: the E_{max} estimates were 0.76 vs. 0.77, 0.44 vs. 0.38, and 0.54 vs. 0.58. These differences were not significant. Therefore, for venous samples of gamma emitters, either whole blood, accounting for the hematocrit, or plasma samples could be used; the results were as accurate with one method as with the other.

The dosages injected were calibrated by counting aliquots of the injectate, whose volume in the injection syringe was measured. The venous outflow dilution curves were normalized to $h(t)$, the fraction of dose reaching the femoral vein per unit time, by

$$h(t) = C(t) \cdot \frac{F_v}{q_0} \quad (2)$$

where $C(t)$ is the tracer concentration (in counts/min) in the outflowing blood, F_v is femoral vein flow, and q_0 is total counts from the injectate per minute. From the curves $h_R(t)$ for the reference tracer albumin and $h_D(t)$ for a permeating tracer, one can compute an apparent instantaneous extraction

$$E(t) = \frac{h_R(t) - h_D(t)}{h_R(t)} \quad (3)$$

as demonstrated by Crone (4). In the ideal situation, when this extraction represents a unidirectional flux out of the blood into an extravascular region, one can calculate a permeability-surface area product (PS_c) for the barrier that encloses the blood in the exchange region by the Crone-Renkin formula (4,27)

$$PS_c = -F_s \log_e (1 - E_{\text{max}})$$

or

$$\frac{PS_c}{F_s} = -\log_e (1 - E_{\text{max}}) \quad (4)$$

where F_s is plasma flow and $E_{\max}$ is an estimate chosen from $E(t)$ (the instantaneous apparent fractional extraction of a permeating species), usually the maximum smoothed value occurring during the upslope or peak of $h_R(t)$. We have reason to doubt that this formula is adequate for the estimation of PS_c in these studies; we suspect that return flux of tracer from the extravascular region to the bloodstream reduces the apparent extractions and leads to underestimation of PS_c by Eq. 4 (1,7). If permeation is a purely passive process in bone, as it appears from the data of Lemon et al. (17), the ratio of PS_c 's would be expected to be equal to the ratio of free-diffusion coefficients, given that the passages are uncharged and that there is no steric hindrance and no binding of solutes to endothelial surfaces. For reference, the diffusion coefficients are $D_{K^+} = 1.99 \times 10^{-5}$, $D_{Sr} = 1.33 \times 10^{-5}$, and $D_{suc} = 0.52 \times 10^{-5}$ cm²/s in water at 25°C (19,28). The permeant tracers, ⁸⁵Sr and ⁴²K, will be retained in bone longer than the reference tracer, labeled albumin. This retention at any specific time (T) after injection can be estimated from the venous outflow dilution curve

$$E_{\text{net}}(t) = \frac{\int_0^T [h_R(t) - h_D(t)] dt}{\int_0^T h_R(t) dt} \quad (5)$$

The fraction of the injected dose remaining in the tissues is also provided by the detection of gamma emissions over the tibia, giving $R(t)$, as in Eq. 1. When the reference tracer curve is complete, i.e., when all the albumin has washed out and $h_R(t) = 0$ at times greater than 2 or 3 min, then $E_{\text{net}} = R(t)$ for the permeating tracer.

Blood flow, F_{I-Ap} (ml·100 g bone⁻¹·min⁻¹), was estimated from the I-Ap residue function or washout curve, $R(t)$, with the use of a modification of the height-area method of Zierler (14, 33)

$$F_{I-Ap} = \frac{100\lambda}{\rho_b} \cdot \frac{1 - R(T)}{\int_0^T R(t) dt} \quad (6)$$

where $R(t) = C^*(t)/C^*(0)$, so that 1 represents the activity over the tibia initially when all the dose was introduced; λ is the tissue-blood partition coefficient for antipyrine (11); and ρ_b is the specific gravity of the bone (11). T was chosen to be 15 min when $R(T)$ was 10% or less.

The fractional escape rate (FER) is the ratio of the rate at which the tracer is leaving the tissue to the amount still residing within the tissue at each time, t

$$\text{FER} = \frac{\Delta R / \Delta t}{R(t)} \quad (7)$$

The FER may also be written as $d \log_e R(t) / dt$, which makes it obvious that the FER is equivalent to a rate constant at each time t , by measurement of the local logarithmic slope, such as taking the slope at each time on a semilogarithmic plot.

RESULTS

A typical outflow dilution curve is shown in Fig. 1 for albumin, sucrose, and potassium injected into a nonperfused nutrient artery. The return flux of sucrose is earlier than that for potassium, even though its estimated permeability-surface area product, PS_c is less; this indicates its smaller volume of distribution in the extravascular region. However, even at 3 min, the E_{net}

for sucrose is still about 15%, which indicates that there is a barrier to washout. For K^+ the retention is about 40% at $t = 3$ min, which is less than that for highly cellular organs but is still quite high in comparison with sucrose and therefore indicates a process of sequestration (cellular uptake or binding) in the extravascular region.

Tramcapillary extractions of K^+ and Sr^{2+}

MAXIMAL INSTANTANEOUS EXTRACTION—In 12 such experiments (Table 1), the mean $E_{\max}$ for ^{42}K was 0.58 ± 0.10 and for sucrose 0.32 ± 0.10 . The mean ratio of K^+ and sucrose permeability coefficients (P_K/P_{suc}) of 2, 28 was substantially less than the ratio of their free-diffusion coefficients, which is 3.8. We interpret this difference as being caused by substantial underestimation of PS_c for potassium; this occurred in spite of its greater retention, which reduces the return flux. This interpretation presumes that the return flux is not slowed because of the positive charge, an inference made from the study of Lemon et al. (17). They showed that there is no difference between the extraction of Sr^{2+} and that of F^- ; these have the same diffusion coefficients but opposite charges.

[In a similar set of experiments that made use of albumin, sucrose, and strontium, Davies et al. (5) observed that P_{Sr}/P_{suc} was 1.91 ± 0.35 (SD; $n = 11$), which was also less than the ratio of free-diffusion coefficients, 2.56. If potassium and strontium were compared on the basis of these results, the prediction of P_K/P_{Sr} would be $2.28/2.56$, or 0.89, again less than the ratio of free-diffusion coefficients, which is 1.50. However, this determination is quite indirect.]

Paired comparisons of K_+ and Sr^{2+} were made in seven experiments (Fig. 2 and Table 2). The critical points are that 1) the $h(t)$'s for Sr^{2+} were consistently lower than those for K^+ ; 2) the maximal values of the instantaneous extraction $E(t)$, $E_{\max}$ were greater for Sr^{2+} ; and 3) the retention at 3 min was greater for Sr^{2+} . The ratios of apparent permeabilities from Eq. 4, P_K/P_{Sr} , averaged 0.83, which is much less than the ratio of free-diffusion coefficients, D_K/D_{Sr} , of 1.5. This leads one to suspect that the estimates of the PS_c 's from Eq. 4 are erroneous, for the reduction in ratio is what one would expect when the conditions of Eq. 4 are not fulfilled (there should be no return flux) and the return flux of K^+ would be proportionally greater for K^+ than for Sr^{2+} , because retention of Sr^{2+} is greater.

To verify that these low ratios of P_K/P_{Sr} were not simply a result of inadequacy of perfusion in the tibia with unperfused nutrient arteries, we performed a series of unpaired experiments with continuous perfusion of the nutrient artery with blood. The results are listed in Table 3, and the observed $E_{\max}$'s for K^+ and Sr^{2+} are given in Fig. 3. As expected from the Crone-Renkin equation (Eq. 4, the continuous lines for PS_c 's at 0.5, 1.0, and 2.0 ml/100 g $^{-1}$ ·min $^{-1}$), the $E_{\max}$'s did diminish at higher flows. However, just as with the paired experiments, the ratios of P_K/P_{Sr} at any chosen flow, F_s , are seen to be lower than the ratio of D_K/D_{Sr} ; the PS_c 's averaged 0.83 ± 0.25 ($n = 9$) for K^+ and 0.99 ± 0.32 ($n = 7$) for Sr^{2+} , the unpaired ratio P_K/P_{Sr} , being 0.84. Thus all three series of experiments gave estimates of P_K/P_{Sr} in the range 0.83–0.89 on a total of 28 observations for K^+ and 25 for Sr^{2+} . Perfusing the nutrient artery at normal rates therefore made no difference in the relative extractions, and this reaffirms the impression that the extraction data should not be interpreted by means of the simplest capillary exchange model (Eq. 4), which does not account for return flux of tracer to the blood.

NET EXTRACTIONS AT $T = 3$ MIN. The forms of $E_{\text{net}}(t)$ for K^+ and Sr^{2+} are illustrated in Fig. 2 for a tibia perfused via its own collateral circulation. They are similar to those obtained with pump-perfused nutrient arteries. The retention of Sr^{2+} is consistently greater than that of K^+ . The data for a particular time, $T = 3$ min, for the net extraction $E_{\text{net}}(t)$ (Eq. 5) are provided for autoperfused midtibias in Table 2 (a paired comparison between K^+ and Sr^{2+}) and for pump-perfused nutrient arteries in Table 3 (unpaired comparison). The values for E_{net} ($T = 3$ min)

for K^+ were not different in the two sets, the overall mean for K^+ being 0.30 ± 0.10 ($n = 16$) and that for Sr^{2+} , 0.45 ± 0.09 ($n = 14$).

The longer retention of Sr^{2+} probably explains why the extractions for Sr^{2+} were as high as those for K^+ despite the lower diffusion coefficient. The mechanism is that retention in the tissue retards return flux of Sr^{2+} and causes the curve of $E(t)$ to be higher than it would be if there were more return flux. This improves the accuracy of estimating PS_c from $E(t)$ by Eq. 4, but it does not mean that the estimates of PS_c are wholly accurate for Sr^{2+} , for they could well be significantly underestimated, and probably are. However, the important feature is the dramatic difference between K^+ and Sr^{2+} in retention at 3 min, for both of these ions have significant volumes of distribution in bone (6).

Retention of Sr^{2+} and K^+ over 3-h periods, $R(t)$

The retention of K^+ and Sr^{2+} at longer times was examined by recording simultaneously for 3 h the intraorgan content, $R(t)$, for ^{42}K and ^{85}Sr in six dogs with collateral-perfused nutrient artery regions. $R(t)$ at zero time is the peak count recorded over the tibia and is 100%. Washout of K^+ was more rapid during the first minute after injection of the tracers, as expected from the curves of $E_{net}(t)$. After the first minutes, however, the rate of washout, the FER's (Table 4), became similar for K^+ and Sr^{2+} . The similarity in FER's during the period from the end of the 1st min to the 30th min, from the 30 to 60th min, and from the 60 to 150th min is shown in Table 4. The corollary of this similarity is that the greater retention of Sr^{2+} during the 1st min continues throughout the period of observation. The curves of Fig. 4 are approximately parallel, Sr^{2+} being higher, and only two of the curves show a tendency for $R_{Sr}(t)$ and $R_K(t)$ to approach each other. Because of the larger retention for Sr^{2+} , the parallelism shows directly that the absolute rate of loss for Sr^{2+} is greater than that for K^+ . The generality that is being demonstrated is that an FER is equal to a conductance for escape of tracer divided by its volume of distribution in the tissue; since the volume for Sr^{2+} is larger than that for K^+ , the conductance must be larger also.

The scales used in Fig. 4 need comment. The use of the logarithmic ordinate is common practice for tracer washout curves when the abscissa is a linear function of time. On such plots, these curves tend to be concave upward, indicating that the washout curves are not monoexponential. The geometric progression of times in the abscissas in Fig. 4 is also a log scale, which serves to shorten the length of the plots. A monoexponential curve, $\exp(-t/16)$, is shown in the upper left panel to illustrate how far from monoexponential the $R(t)$'s are. It is interesting that the plots give nearly straight lines; the straight lines drawn through the data have the general form

$$R(t) = R(t_0) \cdot (t/t_0)^{-m} \quad (8)$$

where t_0 is an arbitrary time on the straight line and $-m$ is the slope on the log-log plot. These slopes, from the data of Fig. 4, were similar for K^+ and Sr^{2+} , ranging from 0.08–0.25 (these extremes were both Sr^{2+}) and averaging 0.13 ± 0.05 ($n = 12$). Note that this is purely an empiric descriptive approach, which cannot be entirely interpreted as providing physiological insight.

The curves of Fig. 4 exhibit one feature that may be meaningful. Those for K^+ tend to be straight, whereas those for Sr^{2+} are bowed upward rather slightly but quite consistently. This difference may reflect some physiological feature of the system such as the nature of the process retaining Sr^{2+} in the tibia, e.g., diffusion into a surface region.

The residue curves were also recorded in the same dogs with pump-perfused nutrient arteries (Fig. 5). The E_{net} 's are given in Table 3. The retentions at 60 min averaged $11.5 \pm 2.2\%$ ($n = 3$) for K^+ and $21.9 \pm 11.4\%$ ($n = 7$) for Sr^{2+} . As in Fig. 4, all of these curves showed rapid

washout in the first minute and then slower, more prolonged washouts. At 120 min, the $R(t)$'s averaged $8.8 \pm 4.0\%$ ($n = 3$) for K^+ and $17.7 \pm 9.5\%$ ($n = 7$) for Sr^{2+} , still twice as much Sr^{2+} retained as K^+ .

DISCUSSION

There are differences in the behaviors of Sr^{2+} and K^+ . This finding is not very surprising, for the kinetics of Sr^{2+} exchange appear to be virtually identical to those of Ca^{2+} (16), and the divalent cation is the key one in bone crystal structure. K^+ is the normally abundant intracellular cation, which is high in concentration in the free ionic state in cells. For example, Hinke (8) showed that its concentration was 150–200 mM in barnacle muscle cells, and Lee and Fozzard (15) found it to be at a level of 134.9 mM in cardiac muscle cells. Neuman et al. (25) found that K^+ was not taken up in hydroxyapatite crystals; later, Triffitt et al. (32) demonstrated in rats that it was completely exchangeable. Contrarily, Sr^{2+} and Ca^{2+} certainly are not completely exchangeable, and the exchange rates of the crystals in bone probably take years, as was found for radium deposited in bones.

The comments bring out the conundrum posed by our data: Sr^{2+} is more rapidly extracted from the blood in a single passage than K^+ and most probably cannot enter its whole volume of distribution; K^+ has a higher diffusion coefficient but a lower initial extraction, but then the fraction that has entered the extravascular region in bone is retained about as well as the Sr^{2+} , despite the fact that its immediate volume of distribution is smaller. How can these apparent conflicts be resolved?

Perhaps a better quantitative approach to the problem might be obtained by using complex multiunit capillary-ISF-cell-bone matrix (and surface) models to account for the possible fluxes. The multiunit models of Rose et al. (29) and of Levin et al. (18), however, are probably not wholly suitable; they do account for cellular uptake and return flux but do not account for surface binding with diffusion into and out of a bone matrix. Even so, the main features of the processes for K^+ and Sr^{2+} appear to be at least qualitatively explicable in terms of a capillary-ISF-cell system.

The increased initial extraction of Sr^{2+} compared with K^+ is not explicable on the basis of a tightly limiting capillary barrier, for K^+ should have a higher permeability in any passive diffusional permeation process. Therefore, the explanation must be beyond the membrane: if both K^+ and Sr^{2+} had a high permeability so that return flux from the ISF to blood was rapid, the $E(t)$ for Sr^{2+} would become higher than that for K^+ if it is taken up more quickly than K^+ at some site in the ISF. Cellular uptake of K^+ is usually quite rapid; in the heart, the sarcolemmal exchange constant (PS_{cell}) is about $2 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$, which is many times higher than the flow in bones. But explaining the observations requires that the rate of unidirectional uptake of Sr^{2+} be higher than that of K^+ ; and if this is not likely to occur in the cells, then an alternative is adsorption of Sr^{2+} at superficial sites on bone matrix. This idea has the virtue that surface-binding processes are rapid, more so than membrane transport processes. Of course, these events need not all take place on bone surface; Sr^{2+} , Ca^{2+} , La^{3+} all bind to cell surfaces on the glycocalyx.

If that explains the more rapid extraction of Sr^{2+} than of K^+ , how can the similarity of the washout rates in Figs. 4 and 5 be explained? In general, escape from a cell has a rate constant equal to the permeability-surface area product (PS_{cell}) divided by the intracellular volume of distribution (V'_{cell}). The values of the FER (in Table 4) for $t = 30$ –60 min for K^+ are about $4 \times 10^{-3}/\text{min}$, whereas for the heart, where the perfusion is about 100-fold higher, the rate at $t = 30$ –60 min observed by Tancredi et al. (31) was only about $15 \times 10^{-3}/\text{min}$, about four times

higher in a highly cellular tissue. Thus the FER for K^+ is quite compatible with loss from an intracellular capacitance.

One might take this one step further. Because the FER is dominated by $PS_{\text{cell}}/V'_{\text{cell}}$ for K^+ , PS_{cell} can be estimated. Taking the cell space to be about 4% of bone volume (22) and with a K^+ concentration of 5 mM in plasma and 150 mM in the available cellular water (80% of the cell), the V'_{cell} for K^+ would be $0.8 \times 0.04 \times (150/5) = 0.96$ ml K^+ space/ml bone. Then $PS_{\text{cell}} = V'_{\text{cell}} \times \text{FER} = 0.96 \times 4 \times 10^{-3} = 3.84 \times 10^{-3}$ ml·ml bone⁻¹ min⁻¹. This again is compatible with K^+ permeabilities in myocardium when one considers the relatively small volume of cells in bone, 4%, as compared with the heart, 80% (26). It should be emphasized that these represent studies in a mature dog.

Making calculations regarding the basis of the efflux for Sr^{2+} is not as easy, but it is clear from the upward bowing of the Sr^{2+} in Fig. 4 that the process is different from that for K^+ . The shape is compatible with release from a surface. The slight increase in steepness with time of the R (t) in Fig. 4 is of the type seen with the transport in an organ dominated by flow but with a very large volume of distribution. This would apply to Sr^{2+} if the capillary permeability were high and the rate constant for exchange over a large surface area were also very high.

We conclude, therefore, that K^+ and Sr^{2+} are not greatly limited in their exchanges by the capillary barrier in these experiments but that their extravascular retention is by surface adsorption for Sr^{2+} and cell uptake for K^+ .

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FIG. 1.

Outflow dilution curves from femoral vein obtained after injection of ^{51}Cr -labeled albumin, ^{14}C -labeled sucrose, and ^{42}K into tibial nutrient artery at time zero. Fractional extraction for K^+ is higher than that for sucrose. Return of tracer from interstitial fluid to blood reduces the apparent instantaneous extraction $E(t)$ after 40th s so that later values are not useful for estimating permeability surface area product (PS) by the simple expression given in Eq. 3.

FIG. 2.

Dilution and fractional extraction curves for ^{42}K and ^{85}Sr . ^{42}K crosses downslope of reference curve before ^{85}Sr crosses reference curve; note that $E(t)$ goes to zero earlier for K^+ . This was true in all 7 expts. Similarly, the retention, $E_{\text{net}}(t)$, of Sr^{2+} is greater than that of K^+ .

FIG. 3. K^+ and Sr^{2+} extraction at different values of plasma flow during perfusion of tibial bone with blood. All points but one fall between curves for Eq. 3 and PS_c values of 0.5 and 2.0. Curves were given by Eq. 3.

FIG. 4.

Residue functions (washout curves) for tracer potassium and strontium from dog tibia after introduction into the nutrient artery. Data obtained at 0.5-min intervals for the first 5 min and at 2-min intervals thereafter. *Ordinate* is on a logarithmic scale; *abscissa* is plotted on a geometrically increasing time scale in order to expand form of data at early times and to shrink it at later times. On this plot, *straight line* indicates that escape rate is diminishing with time (as if multiexponential); that is, semilog plot would be concave upward. (For reference, a single exponential is diagrammed in *left upper panel*, $R(t) = e^{-t/16}$) Although potassium washes out faster in 1st min, note that curves thereafter have similar slopes for potassium and strontium. This would suggest that although transcapillary extraction of strontium is greater during the 1st passage, washout processes of tracers from tissue back into blood have similar time courses.

FIG. 5.

Residue functions—curves of tracer content, $R(t)$'s—are plotted against $F_s \times t$ (plasma flow $\times$ time). F_s is plasma flow produced by pumping blood of known hematocrit through tibial nutrient artery.

TABLE 1

$E_{\max}$ and PS/F values from indicator-dilution curves of ^{42}K and $[^{14}C]sucrose$

Dog	$E_{\max}$		PS_c/F_s		P_K/P_{suc}^*
	^{42}K	Sucrose	^{42}K	Sucrose	
C621	0.61	0.39	0.94	0.49	1.92
C667	0.62	0.38	0.97	0.48	2.02
C738	0.48	0.22	0.65	0.25	2.60
D49	0.74	0.53	1.35	0.76	1.78
D102	0.78	0.42	1.51	0.54	2.80
C975	0.53	0.34	0.76	0.42	1.81
D80	0.44	0.17	0.58	0.19	3.05
D191	0.61	0.36	0.84	0.45	2.09
D85	0.58	0.31	0.87	0.37	2.35
D371	0.52	0.29	0.73	0.34	2.15
D498	0.49	0.21	0.67	0.24	2.79
C735	0.49	0.28	0.67	0.33	2.03
Mean	0.58	0.32	0.89	0.40	2.28
SD	± 0.10	± 0.10	± 0.29	± 0.16	± 0.43
SE	0.03	0.03	0.08	0.04	0.12

$E_{\max}$, maximum value of instantaneous extraction; PS_c , permeability-surface area product of capillary barrier; F_s , plasma flow; P_K , permeability coefficient of potassium; P_{suc} , permeability coefficient of sucrose.

* $P_K/P_{suc} = -\log_e [1 - E_{\max}(K^+)] / -\log_e [1 - E_{\max}(suc)]$, because the surface area and flows cancel.

TABLE 2

$E_{\max}$, E_{net} and PS/F values from indicator-dilution curves of K^+ and Sr^{2+} by perfusion of nutrient artery region via collaterals

Dog	F_{I-Ap} , ml·100 g ⁻¹ ·min ⁻¹	Hct	F_s , ml·100 g ⁻¹ ·min ⁻¹	$E_{\max}$		PS/F		E_{net}	
				K	Sr	K	Sr	K	Sr
704	1.58	0.53	0.74	0.52	0.62	0.73	0.97	0.31	0.53
652	1.34	0.56	0.59	0.53	0.67	0.76	1.11	0.23	0.49
631	0.61	0.50	0.30	0.59	0.65	0.89	1.05	0.24	0.43
778	0.42	0.52	0.20	0.58	0.58	0.87	0.87	0.40	0.49
558	2.06	0.52	0.99	0.53	0.58	0.76	0.87	0.30	0.39
74	0.55	0.52	0.26	0.54	0.64	0.89	1.02	0.48	0.52
222	1.56	0.46	0.84	0.44	0.49	0.56	0.67	0.13	0.26
Mean	1.16	0.52	0.56	0.53	0.60	0.78	0.94	0.30	0.44
SD	±0.63	±0.03	±0.31	±0.05	±0.06	±0.12	±0.15	±0.11	±0.10

F_{I-Ap} , flow of antipyrine; F_s , plasma flow; $E_{\max}$, maximum value of instantaneous extraction; PS , permeability-surface area product; E_{net} , net value of extraction.

TABLE 3

Comparison of extraction for ^{42}K and ^{85}Sr by pump perfusion of tibial nutrient artery with blood

Dog	Run	^{42}K			$^{85}\text{Sr}^*$		
		F_s	$F_s \cdot \text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$	E_{net} (3 min)	F_s	$F_s \cdot \text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$	E_{net} (3 min)
799	1		1.27	0.62		0.65	0.68
	2		1.06	0.49		0.92	0.61
	3		1.56	0.38		1.46	0.35
G843	1		0.92	0.73		1.69	0.54
	2		0.82	0.66		1.03	0.52
	3		0.79	0.43		1.07	0.75
G983	1		1.25	0.47		1.03	0.66
	2		1.62	0.39		1.12	0.59
	3		1.52	0.36		± 0.35	± 0.14
Mean			1.20	0.50			± 0.09
SD			± 0.32	± 0.13			

Data are 3-min E_{net} values. F_s , plasma fluid; E_{max} , maximum value of instantaneous extraction; E_{net} , net value of extraction.

* Data from Lemon et al. (17).

TABLE 4

Fractional escape rates of K⁺ and Sr²⁺

Dog	F _{I-Ap} , ml·100 g ⁻¹ ·min ⁻¹	Hct	F _s , ml·100 g ⁻¹ ·min ⁻¹	Fractional Escape Rate, × 10 ⁻³ /min					
				t = 1-30 min		t = 30-60 min		t = 60-150 min	
				K ⁺	Sr ²⁺	K ⁺	Sr ²⁺	K ⁺	Sr ²⁺
E222	1.56	0.46	0.84	22	18	3.7	3.4	1.2	1.9
E165	0.74	0.55	0.33	18	17	2.5	4.6	1.3	2.2
D959	0.69	0.48	0.36	18	17	4.6	4.8	0.6	1.1
D996	1.87	0.45	1.03	19	23	3.2	4.8	2.8	2.6
E166	0.75	0.53	0.35	17	17	3.6	3.8	2.2	0.9
E78	1.03	0.39	0.62	24	28	4.1	6.8	3.6	3.6
Mean			0.59	19.7	20	3.6	4.9	2.0	2.1
SD (n = 6)			±0.30	±2.7	±4.6	±0.7	±1.2	±1.1	±1.0

F_{I-Ap}, flow of antipyrine; F_s, plasma flow.