Transport of potassium-42 from blood to tissue in isolated mammalian skeletal muscles

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RENKIN, EUGENE M. *Transport of potassium-42 from blood to tissue in isolated mammalian skeletal muscles.* Am. J. Physiol. 197(6): 1205–1210. 1959.—A method is described for studying transcapillary diffusion of K^{42} in isolated perfused muscles of dogs. Blood flow and arteriovenous K^{42} differences are measured and blood-tissue clearance calculated by the Fick principle. A theoretical relation between blood flow and blood-tissue clearance is developed for a uniform circulation characterized by a constant permeability—surface area product (*PS*). The experimental observations conform reasonably closely to prediction. However, systematic variation in measured *PS* product with changes in blood flow and vascular resistance indicate that the capillary circulation is not uniform.

WITHIN THE PAST FEW YEARS, it has become generally appreciated that the transport or exchange of materials between blood in the capillaries and the surrounding tissues may be limited by the blood supply to the capillary bed as well as by the permeability of the capillary walls and tissues (1, 2). Experimental analysis of the relation between blood supply and blood-tissue transport has been restricted largely to those instances in which transport has been entirely blood flow limited, or very nearly so, in which case transport is simply equal to supply (3–5). The more general case, in which both blood flow and diffusibility determine the rate of capillary-tissue transport has been considered theoretically first by Kety (3) and later by others (2, 6), this author among them (7). However, experimental studies of transcapillary exchange in systems simple enough to permit crucial testing of a particular hypothesis are extremely rare. The present work was undertaken to develop a simple and straightforward method of measuring the rate of transport of a substance from blood to tissue in a single organ, and to use this method to test the theory relating blood flow and transcapillary diffusion previously advanced by the author (7).

Blood-tissue transport of radioactive K^{42} was measured by an adaptation of the well-known Fick principle in an isolated, surviving mammalian skeletal muscle, the vascular bed of which was perfused at carefully controlled and measured rates with blood containing a constant quantity of K^{42}. The use of K^{42} as a test solute satisfied two conditions necessary for the present study. *a*) Potassium is very rapidly transported across cell membranes in mammalian muscles (8, 9) and therefore cell membrane transport is eliminated as a possible rate-limiting factor. *b*) The amount of intracellular potassium in muscle is so great, compared with that present in plasma, that an almost infinite 'sink' is provided for the K^{42} which escapes from the capillaries, thereby minimizing back-diffusion. In both respects, the use of K^{42} for studying transcapillary exchange is exactly analogous to the use of carbon monoxide in the measurement of transalveolar diffusion in the lungs.

METHODS

General. Gracilis or gastrocnemius muscles of dogs anesthetized with pentobarbital were isolated from all nervous and vascular connections (10, 11) and perfused with heparinized blood obtained from the same dog. The perfusion apparatus was designed to supply blood of fixed composition at 37°C to the artery of the muscle under pulsating pressure (7). Mean arterial pressure could be set at any desired level. Venous blood drained from a single vein leaving the muscle at atmospheric pressure was collected in graduated tubes the filling of which was timed to measure mean blood flow. Blood flow was also monitored with a recording drop counter. To preserve the constant composition of arterial blood, no venous blood was returned to the perfusion reservoir.

After a steady blood flow had been established in each experiment, a trace amount of K^{42} was added to the blood in the reservoir of the perfusion apparatus and mixed well with it. Since uptake of K^{42} by dog erythrocytes is extremely slow (12, 13), all K^{42} activity was considered to remain in the plasma. On its way to the artery supplying the muscle, the blood flowed through a loop of thin polyethylene tubing around a G-M tube which measured arterial blood radioactivity. An identical counter measured the activity of venous blood before it was collected. Arterial and venous blood activity were re-

Received for publication July 27, 1959.

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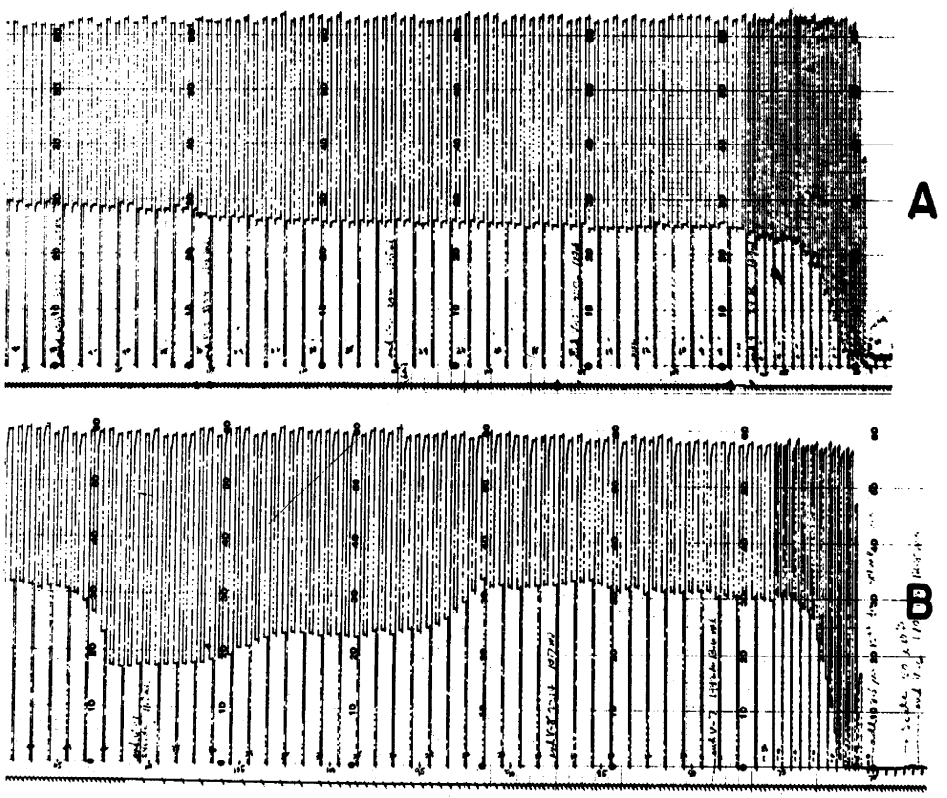

FIG. 1, *A* and *B*. Reproductions of 2 experimental records of K^{42} radioactivity in arterial and venous blood. *Abscissa:* elapsed time, reading *right to left*. *Ordinate:* radioactivity, the horizontal lines marked 0, 10, 20, etc. representing 0, 5, 10, etc. thousand counts per minute. The recorder pen moves alternately between arterial (*upper*) and venous (*lower*) levels of radioactivity. Every 2 cycles, it returns briefly to the zero mark. During the latter part of each record, the excursions to zero are 1 min. apart. At the beginning of each record, shorter counting intervals were used, and the zero excursions are 30 sec. apart. The line below the chart of radioactivity is the drop count record of blood flow, each diagonal mark representing 5 drops of blood. Each experimental record begins shortly before addition of K^{42} to the blood. In *record B* the count rate is insignificant at this time and represents background for the counters. In *A*, a higher rate is observed due to residual K^{42} in blood and muscle from a previous run. The addition of K^{42} in both cases is followed by the rapid rise of arterial radioactivity to a constant level. Venous radioactivity rises more slowly and reaches a lower plateau in 4–8 min. *A*, (*upper*) *exp. P-26*, gracilis 11.2 gm $[K^+]p$ 4.58 μEq/ml, hct. 0.51. Addition of K^{42} 139 min. after the beginning of the experiment (after K^{42} from a previous addition was almost completely washed out). Apparent K^{42} extraction is initially (8 min.) about 60% complete, diminishing to 53% after 40 min. Blood flow is initially 1.36 ml/min. and 1.38 ml/min. after 40 min., with no variation greater than 0.10 ml/min. during this time. Arterial pressure was 82 mm Hg. *B*, (*lower*) *exp. P-27*, gracilis 14.1 gm. Blood flow varied, K^{42} added 70 min. after the start of perfusion. See text and table 1. (The last period of the table is not included in the figure.) The venous radioactivity record lags behind the flow record due to the dead space of the cannulae and counting chambers.

corded continuously throughout each experiment (14). All measurements of radioactivity have been corrected for the spontaneous decay of K^{42} (12.44 hr. half-life).

Miscellaneous measurements. a) Arterial and venous plasma K^+ concentrations were determined by internal standard flame photometry. *b*) Total tissue K^+ was measured flame photometrically in several experiments after dilute nitric acid digestion of the entire dried, fat-free muscle. *c*) Total muscle weight was measured at the end of each experiment. The coarsely minced muscle was then dried to constant weight at 95°C to determine its water content, and the dry residue extracted with ether at room temperature to estimate total neutral fat. To determine whether any edema was produced during perfusion, the corresponding muscle from the opposite leg was taken as a control, and its water and fat content measured as above. The difference between their calculated fat-free wet weights on a percentage basis was taken as an estimate of edema formed. The best preparations showed no edema at the end of the experiment, but the majority had a water content about 5% greater than the controls. No variations were observed in the results which could be correlated with edema formation. The composition of these muscles with respect to water, dry solids, neutral fat and total potassium was closely similar to the control values published by Eichelberger, Akeson and Roma (15). All muscle weights given refer to fat-free wet weight corrected for any edema formation.

RESULTS

I. General Description of the Time-Course of Venous Blood Radioactivity During Constant Flow Perfusion

Figure 1*A* is a reproduction of a record of arterial and venous blood radioactivity in an experiment at constant blood flow. After addition of K^{42} to the reservoir as indicated arterial radioactivity remained constant (allowing for spontaneous decay). The venous curve shows two phases. *1*) A transient phase which appears to represent the washing out of nonradioactive blood present in the vascular bed and in the dead space of the connections at the moment the tracer was added, and its replacement with blood containing K^{42}. *2*) An almost level plateau which indicates nearly constant removal of K^{42} from the blood stream over the course of many minutes. A slight upward slope of the plateau is evident in this experiment, but the extraction of K^{42} from the blood was diminished by only 7% in 40 minutes.

TABLE 1. *Effect of Blood Flow on Potassium Transport — Exp. P-27, Gracilis 14.1 gm (K^+)p 5.27 μEq/ml, Hct. 0.47*

Art. Press.	Blood Flow	K^{42} Extraction Ratio	K^{42} Clearance	K^+ Influx
mm Hg	*ml/min × 100 gm*		*ml/min × 100 gm*	*μEq/min × 100 gm*
92	8.50	0.494	4.20	11.7
60	4.05	0.666	2.70	7.55
38	1.91	0.780	1.49	4.16
91	8.65	0.506	4.37	12.2
114	12.9	0.434	5.47	15.3

Discussion. Because the slope of the plateau is so slight, we may for present purposes consider the second phase as a close approximation to a steady state with respect to K^{42} transport. Under these circumstances, the removal of tracer from the blood may be expressed in terms of its fractional extraction (E).

$$E = \frac{A(a) - A(v)}{A(a)} \qquad (1)$$

where $A(a)$ and $A(v)$ represent arterial and venous levels of radioactivity at any time. The product of extraction and blood flow (Q) may be defined as the capillary clearance (C) of K^{42}:

$$C = QE = Q\,\frac{A(a) - A(v)}{A(a)} \qquad (2)$$

This term is analogous to the concept of renal clearance, and may be imagined as that quantity of blood from which the K^{42} is completely removed in a unit of time. In the experiment illustrated, the extraction was 60%, and thus capillary clearance is 60% of the prevailing blood flow or 0.82 ml/min.

If it is assumed that the physiological properties of K^{42} are identical to those of the ordinary isotopes of potassium, the total quantity of potassium transported from blood to tissue per unit time (K^+ influx) will be equal to the K^{42} clearance multiplied by the concentration of exchangeable potassium in the blood Since the erythrocyte K^+ is only slowly exchanged with that of the plasma, the following expression holds:

$$K^+ \text{ influx } (\mu\text{Eq/min.}) = C(\text{ml/min.}) \times (K^+) \text{ plasma } (\mu\text{Eq/ml}) \times (1\text{-hct.})$$

where C is the capillary clearance of K^{42} in terms of whole blood. If arterial and venous plasma potassium concentrations are equal, K^+ outflux equals K^+ influx. If they are unequal, the outflux may be calculated from the measured net flux and influx. In most experiments, net gain or loss of K^+ was very small compared to the unidirectional fluxes.

It is evident in figure 1*A* that the venous level of K^{42} does not remain truly constant, but rises slightly with time. This is attributed to the gradual accumulation of tracer in the tissues and its ultimate back-diffusion into the blood. If this effect were entirely ignored in the course of an hour long experiment, the final K^{42} clearances would be about 10% too low. This source of error may be corrected in either of two ways. *a*) The second phase plateau of the venous curve may be extrapolated to the moment of tracer addition, at which time back-diffusion must be zero. *b*) At the end of an experiment, the radioactive arterial blood may be replaced with non-radioactive blood, and the quantity of K^{42} which continued to come out in the venous blood (after the vascular washout period) measured. This represents back-diffusion at the end of the experiment, and intermediate values can be determined by interpolation.

If the level of K^{42} in the tissues $A(t)$ is known, *equation 2* may be modified to account for back-diffusion of tracer:

$$C' = Q\,\frac{A(a) - A(v)}{A(a) - A(t)} \qquad (2a)$$

This definition of capillary clearance corresponds to the term dialysance introduced by Wolf *et al.* (16) and used previously by the author (7). However, it seems simpler to apply the term clearance to all cases. All capillary clearance values listed in this paper have been corrected for back-diffusion of K^{42} wherever this has been appreciable. A more detailed discussion of back-diffusion and of the accumulation of K^{42} in perfused muscle and of its use in estimating the quantity of exchangeable potassium present is reserved for a subsequent paper (17).

II. Effects of Varying Blood Flow by Changing Arterial Perfusion Pressure (Constant Vascular Resistance)

At each new blood flow, a new plateau of venous K^{42} activity ensues. This is illustrated in figure 1*B*. Like the original plateau, each new one is not perfectly level, but slopes slightly upward. (This is not clearly evident in records as brief as in the figure, but has been amply verified in longer experiments.) When flow decreases, venous K^{42} falls, and therefore K^{42} extraction increases, tending to approach 100% at very low flows. As blood flow increases, venous K^{42} rises and extraction falls. The changes in extraction are completely reversible. On returning to nearly the original flow rate in the example shown, after two periods at lower levels of flow, very nearly the original extraction was established again. Love and Burch have recently demonstrated a similar phenomenon in the coronary circulation of intact dogs with respect to extraction of Rb^{86} (18).

Table 1 lists blood flow rates and K^{42} extraction ratios

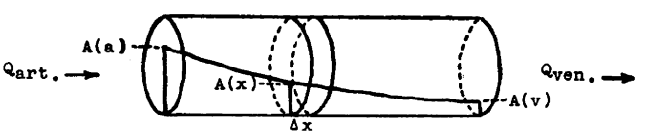

FIG. 2. Diagram of capillary model.

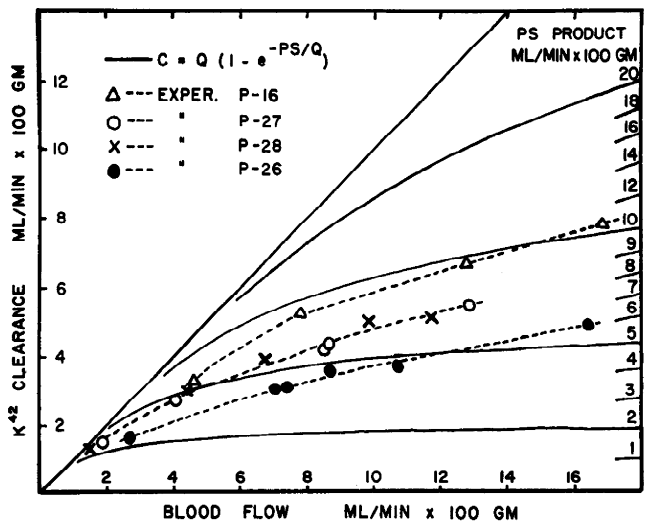

FIG. 3. Theoretical and experimental clearance-blood flow curves. The theoretical curves (*solid lines*) predict the following relations between capillary clearance and blood flow. At very high flows, clearance tends to approach a constant value equal to the *PS* product (limiting clearance). When blood flow is less than one-half the limiting clearance, clearance is nearly equal to blood flow, and transport is essentially blood flow-limited. When the blood flow equals the limiting clearance, the observed clearance will be only 63% of the limit. At twice this rate of flow, clearance will be 78% of the limit. The experimental curves are for transcapillary K^{42} clearance in mammalian skeletal muscles under 'control' conditions.

in the experiment described, which is typical of 16 in which more than two different rates of blood flow were studied. The values are listed as measured, at intervals of about 10 minutes. All have been corrected for back-diffusion of tracer. In the last two columns are listed the computed capillary K^{42} clearances and K^+ influxes. The relation between K^{42} extraction and blood flow is not reciprocal, so that clearance and influx increase regularly with increasing blood flow, though not in proportion to it. No exceptions to this qualitative rule were observed, as long as vascular resistance did not change appreciably. Quantitative changes in K^{42} clearance will be discussed below.

Discussion. Clearly there is no characteristic 'transcapillary exchange rate' of K^+ in blood perfused mammalian skeletal muscles. K^{42} transport from blood to tissue is a function of blood supply, but the relation between these two quantities remains to be determined. Superficially, extraction of K^{42} appears related to the time spent by a sample of blood in the vascular bed. At low blood flows, this time is long, and extraction approaches completion. At high flows, the time is shorter, and extraction is less. If we consider the removal of K^{42} (or any diffusible solute) from the blood stream as an interaction between *1*) diffusion out of the capillary network and *2*) perfusion through the capillary network, we can analyze the process mathematically (7, see also 16 for an analogous situation dealing with a form of 'artificial kidney'). Figure 2 is a simple model of the capillary bed in a muscle. Arterial blood enters at one end and leaves as venous blood at the other. A diffusible solute present in the entering blood escapes by diffusion all along the length of the capillary, and thus its concentration within the capillary network falls gradually as the blood approaches the venous end. This is the origin of the arteriovenous concentration (or radioactivity) difference observed.

In the figure, Δx represents a thin cross sectional slice of the capillary. K^{42} enters in the incoming blood. If its concentration here is $A(x)$, the total quantity entering the slice per unit time will be $QA(x)$, where Q is the blood flow. K^{42} leaves the slice by two routes: *a*) outflow in the blood leaving the slice and *b*) diffusion out of the slice via its wall. Outflow loss is equal to $QA(x + \Delta x)$ where the latter factor is the concentration of K^{42} in the blood reaching the end of the slice. Diffusion escape is described by Fick's law, and is equal to $PS\ \Delta x[A(x) - A(t)]$. P is the permeability coefficient of the diffusion barrier, S its surface area and $A(t)$ the concentration of the diffusible solute outside the capillary.[2]

When K^{42} is the diffusing solute, $A(t)$ may be taken as zero, for reasons given above, and the diffusion term becomes simply $PS\ \Delta xA(x)$. For any thin slice across the capillary bed, the equation of material balance is as follows:

$$\begin{array}{rcccl} \text{Inflow} & = & \text{Diffusion loss} & + & \text{Outflow} \\ Qa(x) & = & PS\,\Delta xA(x) & + & QA(x+\Delta x) \end{array} \qquad (4)$$

Taking the limit as Δx becomes smaller and smaller,

$$-Q\frac{dA(x)}{dx} = PSA(x) \qquad (5)$$

By integration over the entire length of the capillary (taken as unity):

$$A(v) = A(a)e^{-PS/Q} \qquad (6)$$

where $A(a)$ and $A(v)$ represent arterial and venous concentrations of K^{42}, respectively, and e is the base of natural logarithms. Thus venous K^{42} concentration is a function of arterial K^{42} concentration, the product of membrane permeability and surface area, and blood flow. According to the definitions of extraction and clearance given previously, we may write the following:

$$E = \frac{A(a) - A(v)}{A(a)} = 1 - e^{-PS/Q} \qquad (7)$$

and

$$C = Q(1 - e^{-PS/Q}) \qquad (8)$$

[2] It is important to note that in this usage, P is an 'over-all' permeability coefficient, describing the permeability of the entire diffusion pathway of the substance studied, in the present case, the capillary wall and the interstitial space between the capillary and the cell membrane. Permeabilities measured by the present method will consequently tend to be smaller than those for the capillary wall alone, as measured by Pappenheimer and his co-workers (6, 19).

TABLE 2. *Correlation of Blood-Tissue K^+ Transport With Spontaneous Vascular Tone*

Exp.	K^{42} Clearance,*	PS, Calculated,*	Vascular Resistance Art. Press.,
	ml/min. × *100 gm*	*ml/min.* × *100 gm*	*mm Hg 10 ml/ min.* × *100 gm*
P-43	3·3	4·0	144.
P-26	3.8	4.8	127.
P-40	4.0	5.1	95.
P-43†	4.0	5.1	115.
P-46	4.0	5.1	74.
P-15 (Ga)‡	4.3	5.6	74.
P-32	4.3	5.6	115.
P-41	4.6	6.2	158.
P-27	4.7	6.4	98.
P-34	5.0	7.0	88.
P-22	5.1	7.2	83.
P-48	5.1	7.2	86.
P-42	5·5	8.0	75.
P-44	5·7	8.5	86.
P-16 (Ga)‡	5·9	8.9	92.
P-42†	6.2	9·7	60.

* Clearances and *PS* products are measured at a flow rate of 10 ml/min × 100 gm tissue by interpolation on the experimental curves. † In *exp. 42* and *43*, spontaneous changes in vascular resistance occurred in the course of the measurements. ‡ All muscles are gracilcs unless indicated gastrocnemius (Ga).

In these equations the expression *PS*, the 'permeability-surface area product', replaced the symbol *P* alone as used by the author in previous work (7). The present usage brings the definition of *P* into line with that usually given for a biological membrane (6). The dimensions of *P* are moles diffusing per unit time per unit concentration difference and per unit surface area (here, moles/min. per mole/cm^3 concentration difference per cm^2 membrane surface). *S* represents the total capillary surface in 100 gm of muscle. The *PS* product has the dimensions of cm^3/min/100 gm tissue and corresponds to the maximum capillary clearance possible for a given substance in a capillary bed of given permeability and surface area. At finite blood flows past this membrane, a clearance smaller than this maximum will be realized, as specified by *equation 8*. In the present form of this equation, the terms *P* and *S* always occur as a product, and are not individually separable.[3]

In figure 3, a family of curves is drawn according to equation (8) showing theoretical clearance-flow relations for several arbitrary values of the produce *PS*. Against this background are plotted experimental K^{42} clearance measured in four representative experiments, including the one illustrated in figure 1*B* and in table 1. The experimental curves show a certain resemblance to the theoretical, but in all cases studied, the upward slope with increasing blood flow is steeper than predicted. The application of our simple schema to the capillary bed may still be substantially correct, if we imagine that the product *PS* is not constant, but increases with increasing blood flow or with increasing intravascular pressure.

The selection of experiments in figure 3 shows the extent of variation observed in the relation between K^{42} clearance and blood flow in these experiments. To some extent, the variability from preparation to preparation is associated with differences in the vascular tone of the muscles. The uppmost curve in the figure (*exp. P-16*) represents a rather widely vasodilated muscle, while the lowest (*exp. P-26*) represents one of the most vasoconstricted. In table 2, a list of 16 measurements on 14 perfused muscles is arranged in order of increasing K^{42} clearance at a blood flow of 10 ml/min. × 100 gm. This quantity may be taken as an indication of the level at which the clearance-flow curve falls on the diagram of figure 3. The corresponding *PS* product at this flow rate is also listed. A blood flow of 10 ml/min. × 100 gm is close to the upper limit of flows observed in resting skeletal muscles of dogs (10, 11), and vascular resistance at this flow is indicated by the arterial pressure necessary to maintain it. It will be observed that the experimental preparations in the middle of the table were perfused at arterial pressures close to those observed in intact resting dogs. In none of these experiments was anything done deliberately to alter the state of the vascular bed. Most high clearances were observed in muscles of low vascular resistance and most low clearances in muscles of high vascular resistance, but there were several exceptions to the general rule. Vascular tone cannot be the only factor which modifies the relation between blood flow and the capillary clearance of K^{42}.

GENERAL DISCUSSION

The present observations show clearly that in a muscle supplied by its vascular bed, a characteristic potassium exchange rate cannot be measured directly, and that the observed rate of transport from the blood stream to the tissue varies over a wide range depending on the blood flow. By measuring both blood flow and

TABLE 3. *Theoretical Effects of Nonuniform Capillary Circulation on Blood-Tissue Exchange. See Equation 8*

PS_I	PS_{II}	Q_{I+II}	Q_I	Q_{II}	C_I	C_{II}	C_{I+II}	PS_{I+II}
(1) Arteriovenous shunt								
10	0	5	2.5	2.5	2.4	0	2.4	3.4
10	0	10	5.	5.	4.3	0	4.3	5.6
10	0	20	10.	10.	6.3	0	6.3	7.6
(2) Fixed nonuniform ratio								
5	5	5	4·5	0·5	3.0	0.5	3·5	6.1
5	5	10	9.	1.	3.8	1.0	4.8	6.6
5	5	20	18.	2.	4.2	1.8	6.0	7.2
(3) Variable nonuniform ratio								
2	8	5	4·5	0.5	1.6	0.5	2.1	2.8
5	5	10	9·5	0.5	3·9	0.5	4.4	5.8
8	2	20	19·5	0·5	6.6	0.5	7.1	8.7

Subscripts I and II refer to *compartments I* and *II*, respectively. I + II refers to total tissue. PS = permeability-surface area product, Q = blood flow, C = capillary clearance. All values in ml/min.

[3] In the case of a substance which accumulates in the tissues in appreciable amounts, *eq. 8* may still be applied if the term dialysance is substituted for clearance (see 16, 7 and *eq. 2a*, above).

blood-tissue transport, it is possible to compute a transport coefficient, the *PS* product, which can be used to characterize the potentiality of a vascular bed for transport of K^+. This coefficient represents the maximal transcapillary clearance of potassium, attainable only theoretically at an infinite flow rate, but a knowledge of this quantity permits calculation of the clearance at any given flow rate (*eq. 8*), provided *PS* remains constant. The *PS* products for K^+ measured in the present experiments were subject to considerable variation from preparation to preparation and with changes of arterial pressure and blood flow in the same preparation. These variations are believed due partly to hemodynamic factors, but the mechanisms by which these act, and what other agents may be capable of modifying the *PS* product remain to be examined.

In view of the variability of the permeability-surface area product under different conditions, it seems necessary to consider the distribution of the total blood flow to the various parts of the capillary network. The schema described above applies strictly only to a uniformly perfused system of capillaries, that is, to one in which the volume flow in each vessel is proportional to the local *PS* product. In such a network, the total *PS* product will equal the sum of all local values. If circulation is not uniform, the over-all *PS* product will appear to be less than this sum. Nonuniform circulation may follow three basic patterns: *1*) arteriovenous shunting: a proportion of the blood passes through channels of very low (or zero) *PS*. *2*) A fixed part of the capillary bed representing a large fraction of total *PS* is perfused by only a small fraction of total blood flow. *3*) A part of the capillary bed is poorly perfused as in the preceding; but as total blood flow increases, more and more of this part becomes well perfused due to the opening of arterioles which were initially closed.

All of these patterns will result in an increase of capillary clearance with increasing blood flow which is more rapid than predicted for a uniformly circulated tissue. For illustrative purposes, we shall imagine the vascular bed to be divided into two regions, *I* and *II*, with *PS* products and blood flows distributed according to each of the three patterns above, and compute the regional and total clearances and the over-all *PS* products by means of *equation 8*. The results are given in table 3. The observed or effective *PS* products are less than the total *PS* in all instances of nonuniformity. They tend to approach the total *PS* product *a*) as total blood flow increases and *b*) as flow distribution becomes more nearly uniform. If nonuniformity of circulation exists in the isolated gracilis and gastrocnemius muscles, as the data appear to indicate, the observed *PS* products will refer principally to transcapillary exchange in the well-circulated, nonshunting tissue compartment (*compartment I* in the table).

The observations presented in this paper do not permit an objective choice to be made among the three patterns of nonuniform circulation considered above. However, on general grounds, arteriovenous shunting of a large fraction of total blood flow in skeletal muscle seems unlikely and the changes in effective *PS* attributable to a fixed nonuniform flow distribution are much smaller than those observed. Thus pattern (3), nonuniform distribution which varies with changes in blood flow or arterial pressure seems most likely. Furthermore, the observed correlation of *PS* with the state of vascular dilatation or constriction in different preparations can best be explained on the basis of opening and closing of parts of the capillary bed. This was essentially the conclusion reached in an earlier study of transcapillary diffusion kinetics in isolated hind legs of cats (7), although the heterogeneity of the hind leg tissues prevents direct comparison with the single muscles used in the present work.

In the paper to follow (17), it will be shown that tissue potassium in the perfused gracilis or gastrocnemius muscle must be represented as having at least two subdivisions with respect to ionic exchange with the blood. On the assumption that partition of total tissue K^+ is a consequence of nonuniform distribution of capillary blood flow, more information about the nature of the nonuniformity will be presented.

The author expresses his deepest appreciation to Dr. John Stephenson for advice on formulating the mathematical part of this paper, to Dr. Wendell N. Stainsby for help with the gastrocnemius muscle preparations and to Mr. Frank Perry and Mr. William Anderson for excellent technical assistance.

REFERENCES

1. WILDE, W. S. *Ann. Rev. Physiol.* 17: 17, 1955.
2. RENKIN, E. M. AND J. R. PAPPENHEIMER. *Ergebn. d. Physiol.* 49: 59, 1957.
3. KETY, S. S. *Pharmacol. Rev.* 3: 1, 1951.
4. JOHNSON, J. A., H. M. CAVERT AND N. LIFSON. *Am. J. Physiol.* 171: 687, 1953.
5. DOBSON, E. L. AND G. F. WARNER. *Am. J. Physiol.* 189: 269, 1957.
6. PAPPENHEIMER, J. R. *Physiol. Rev.* 33: 387, 1953.
7. RENKIN, E. M. *Am. J. Physiol.* 183: 125, 1955.
8. CREESE, R. *Proc. Roy. Soc., London. ser. B* 142: 497, 1954.
9. CALKINS, E., I. M. TAYLOR AND A. B. HASTINGS. *Am. J. Physiol.* 177: 211, 1954.
10. MARTIN, E. G., J. FIELD II AND V. E. HALL. *Am. J. Physiol.* 102: 476, 1932.
11. HIMWICH, H. E. AND W. B. CASTLE. *Am. J. Physiol.* 83: 92, 1927.
12. SHEPPARD, C. W., W. R. MARTIN AND G. BEYL. *J. Gen. Physiol.* 34: 411, 1951.
13. FRAZIER, H. S., A. SICULAR AND A. K. SOLOMON. *J. Gen. Physiol.* 37: 631, 1954.
14. HIGINBOTHAM, W. A. AND J. TILLINGER. Brookhaven Nat. Lab. Report 408(T-79), 1956.
15. EICHELBERGER, L., W. H. AKESON AND M. ROMA. *Am. J. Physiol.* 185: 287, 1956.
16. WOLF, A. V., D. G. REMP, J. E. KILEY AND G. D. CURRIE. *J. Clin. Invest.* 30: 1062, 1951.
17. RENKIN, E. M. *Am. J. Physiol.* 197: 1211, 1959.
18. LOVE, W. D. AND G. E. BURCH. *Circulation Res.* 7: 24, 1959.
19. PAPPENHEIMER, J. R., E. M. RENKIN AND L. M. BORRERO. *Am. J. Physiol.* 167: 13, 1951.