Total, non-nutritional, and nutritional blood volume in isolated dog hindlimb

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A method for the estimation of the distribution of effectively circulating total blood volume of a tissue (VT) into the nutritional (VC) and non nutritional (VB) segments of the vasculature is presented. VT is estimated from the indicator-dilution pattern of radioiodoalbumin, VB from the indicator-dilution pattern of radiorubidium, and VC is calculated as the difference between the two. In resting, denervated, donor-perfused dog hindlimb, VT = 1.49 ± 0.47 (SD) ml/100 g of tissue, VB = 1.10 ± 0.33 (SD) ml/100 g, and VC = 0.39 ± 1.17 (SD) ml/100 g, or VB consists of about 75% and VC 25% of VT. Justification for the use of Rb86 as a non-nutritional indicator is presented.

METHODS

Preliminary considerations: In order to estimate the total, non-nutritional, and nutritional blood volume in the dog hindlimb, a variation of the Stewart-Hamilton indicator-dilution (9) technique was employed. According to this technique, the effective circulating blood volume of a tissue may be estimated as the product of the mean transit time (MTT) of an indicator passing through the tissue and the tissue blood flow (FT). The vascular region concerned with volume estimation depends on the distribution of the injected indicator. This approach for estimating effective circulating tissue blood volume has been validated mathematically by Meier and Zierler (12). It is valid provided flow distribution through the region is constant during the determination and indicator washout from the region is complete. Moreover, the indicator must be uniformly mixed across the flow stream at the injection and sampling sites.

In the case of the hindlimb, the vascular regions lying between the femoral artery and vein consist of a number of subvolumes situated in series and parallel, and the estimate of total tissue blood volume represents the sum of these subvolumes. This relationship is illustrated in Fig. 1, where VA, VB, VC, and VT represent the arterial, bypass (shunt), capillary, and venous subvolumes.

Zierler (22) has indicated that the unit impulse response of such a vascular bed represents the sum of two unit impulse responses, one for each parallel component of flow. If α represents the fraction of total flow (FT) distributed to the capillary network, then (1-α)FT represents the shunt flow. The volume of the bypass segment and that portion of the large vessels associated with this fractional flow (VA(1-α)FT) is defined by (1-α)VT.
FIG. 1. Schematic representation of fractional distribution of blood flow between series and parallel subvolumes of muscle.

This volume defines the distributing system for a tracer which is completely extracted from the capillary circulation without return during a single circulation. The mean transit time of such a tracer would be synonymous to MTT_{A' BV'}. The difference between VT and V_{A' BV'} equals V_C + V_{A' BV'}. V_{A' BV'} is the fractional volume of the large vessels associated with capillary flow, \( \alpha F_T \).

An estimate of \( V_{A' BV'} \) may be obtained by means of the following considerations. If \( V_B \) is very low relative to \( V_{A' BV'} \), then MTT_{B} will also be very low relative to MTT_{A' BV'} and MTT_{A' BV'} will therefore be essentially equal to MTT_{A' BV'}. Furthermore, if one considers that \( V_{A' BV'} \) is related to \((1-\alpha)F_T\) as \( V_AV \) is to \( F_T \), then \( V_AV \) should equal \( F_T \times V_{A' BV'}/(1-\alpha)F_T \) which reduces to \( F_T \times MTT_{A' BV'}. \) In this case \( V_C \) would equal \( F_T (MTT_T - MTT_{A' BV'}). \)

How reasonable are the two assumptions used to formulate this approach? \( V_B \) certainly does have some finite value and therefore the assumed estimate of \( V_{A' BV'} \) will be an overestimate, as will \( V_AV \). Consequently, subtraction of \( V_AV \) from \( V_T \) will provide an underestimate of \( V_C \). The magnitude of underestimate will depend on the value of MTT_{B}. It is probable that \( V_B \) is very low and that MTT_{B} is therefore quite brief, so that the error introduced by assuming an insignificant MTT_{B} will be slight.

Moreover, if the major difference between the nutritional and non-nutritional circuits is the presence of the capillary network, then the arteriolar and venular transit times of both circuits would be comparable. In this case the estimation of \( V_C \) should provide a closer approximation of capillary volume than of nutritional volume.

With complete vascular mixing at injection and sampling sites, MTT_{A' BV'} should provide a representative estimate of MTT_{AV}. The arteries and veins can be regarded as two systems in series. The arterial system forms a single input-multiple output network, whereas the venous system forms a multiple input-single output network. Meier and Zierler (12) have indicated that injection at a single input with sampling from one of many outputs provides a volume estimate which includes a portion of each output channel situated a mean transit time from the injection site equal to that at the sampling site. Similarly, injection at one of many inputs with sampling at a single output provides a volume estimate which includes a portion of each input channel situated a mean transit time from the sampling site equal to that from the injection site. On this basis, MTT_{AV} should provide a reasonable estimate of MTT_{AV} and permit the calculation of \( V_AV \).

The rationale of the approach is illustrated in Fig. 2. The indicator used to obtain an estimate of circulating tissue blood volume was radioiodoalbumin (Fig. 2A). During the time of a single passage through the skeletal muscle, iodoalbumin is effectively restricted to the vasculature in accordance with blood flow distribution at the time of estimation. Thus, the venous indicator-dilu-
end-window Geiger-Müller detectors were opposed

direction of the venous effluent blood through a radioactivity-

carotid artery into an arterial reservoir from which it

A schematic illustration of the perfusion system is

A schematic diagram of experimental design.

ion pattern should reflect the capacity of the vascular
bed participating in blood flow distribution. The indica-
tor selected for the non-nutritional circuit was Rb$^{86}$
(Fig. 2B). Justification for this selection is presented
below.

Procedure. Mongrel dogs of both sexes ranging in weight
from 9.3 to 20 kg provided hindlimb preparations
ranging in weight from 800 to 1,650 g. The animals were
premedicated with intramuscular morphine sulfate (2
mg/kg), and anesthetized 30 min later with sodium
pentobarbital (15 mg/kg). The hindlimbs were ampu-
tated at approximately the midthigh region by doubly
ligating and cutting muscle bundles. The bone was
cleared, sawed, and plugged with bone wax. Then the
limb was maintained, connected by the femoral artery
and vein, and was perfused autologously without heparin
for about 1 hr in order to consolidate the clotting of the
stump. The limb was then transferred to the perfusion
system and perfused from a donor animal anesthetized
in the same manner as above. Immediately on transfer
of the limb to the donor system, heparin was admin-
istered in a dose of 10 mg/kg with 2 mg/kg boosters
administered every hour.

A schematic illustration of the perfusion system is
presented in Fig. 3. Donor blood was directed from the
carotid artery into an arterial reservoir from which it
was pumped at constant flow with a Sigmamotor pump
(PR-23-2.5 G-350) transducer. Scintillation and thin
end-window Geiger-Müller detectors were opposed
across the counting site. Radioiodinated-albumin pattern
were recorded by presenting the scintillation output to a pulse-height analyzer-log ratemeter-recorder
system. The pulse-height analyzer was adjusted to a
narrow window at the radioiodine peak in order to
provide a maximum ratio of detection of radioiodine to
radiorubidium. The rubidium outflow patterns were
recorded by means of a GM tube which was connected to
a log ratemeter-recorder system. Interposed between
the blood and the GM tube was a plastic absorber (thick-
ness 0.055 inches) which effectively absorbed all the
iodine beta emissions. Approximately 20–25 μc each of
albumin-I$^{131}$ and of Cl-Rb$^{86}$ were simultaneously in-
jected intra-arterially and venous outflow patterns
simultaneously recorded continuously and independ-
ently. At the dose range employed for each isotope, no
cross detection was recorded.

Intra-arterial injections were delivered in jet fashion,
thereby providing complete vascular mixing across the
flow stream at the injection site (1). Estimation of volume
contained within a model system employing a procedure
identical to that used in this study provided volumes
which deviated from the measured volume by ± 2.5 %
at 1 (SD). Total circulating volume was calculated as
$F_T \times MTT_T$, non-nutritional volume as $F_T \times MTT_R$, and
nutritional volume as $F_T(MTT_T-MTT_R)$.

RESULTS

Indicator-dilution patterns. Figure 4, curve A, illustrates
the venous outflow pattern of radioiodoalbumin after
rapid intra-arterial injection. Following the injection
there is a brief latent period after which the level of
radioactivity increases rapidly to a peak, then declines,
first rapidly and then more slowly. When plotted on
scillog coordinates, three exponential phases are ap-
parent. Freis (6) reported radioiodoalbumin patterns
from dog forelimbs which were biphasic with a transi-
tional phase frequently present. Phases (I and III) are
attributed to two populations of vascular circuits, one
possessing rapid and a second with relatively slow flow.

The transitional phase (II) is attributed to the appear-
ance of indicator from the slow circuit which contributes
to the outflow from the fast circuit to decrease the down-
slope. Phase III represents outflow from the slow circuit
with minimal contribution from the fast.

Downslopes II and III cannot be attributed to recir-
culation, since dilution of the venous effluent radioac-
tivity by the cardiac output reduces the recirculating
radioactivity to low levels. Furthermore, the interposi-
tion of the venous and arterial reservoirs and external
circuitry provide a dissociation in time of more than
1 min, whereas the third slope was well formed at ap-
proximately 1 min after indicator appearance before
recirculation has had an opportunity to be manifest.

Figure 4, curve B, shows a venous outflow pattern for
radiorubidium injected simultaneously with the radio-
iodoalbumin. Following the injection the rubidium out-
flow pattern displays early characteristics similar to those
of radioiodoalbumin until the peak level of radioactivity
is reached. At this point the level of radioactivity de-
clines first rapidly and then somewhat more slowly; however, the difference between the two slopes is slight compared to that of the radioiodoalbumin pattern. The first rapid phase of the rubidium downslope corresponds to the first phase of the radioiodoalbumin downslope but is usually more abrupt. The second rubidium slope seems to be related to the second radioiodoalbumin slope but is substantially greater. Since phase II is attributed to the superposition of indicator from the slow on the fast circuit outflow, the slight difference in the two rubidium slopes suggests only a slight contribution from a slow compartment. This interpretation is consistent with the effective absence from the rubidium outflow pattern of a slope comparable to the third radioiodoalbumin downslope. The differences between phases I and II of iodoalbumin and rubidium patterns can be essentially removed by tail-subtracting phase III of the iodoalbumin curve from the two earlier phases, in which case a pattern very similar to the radiorubidium pattern results.

**Tissue blood volumes.** The volumes of circulating blood contained within the total, non-nutritional, and nutritional circuits of the dog hindlimb are presented in Table 1. The total blood volume for all hindlimbs studied averaged 1.49 ml/100 g of tissue ± 0.47 (SD). The volume of blood contained within the non-nutritional circuit averaged 1.10 ml/100 g ± 0.33 (SD), and nutritional volume averaged 0.39 ml/100 g ± 0.17 (SD). Thus, approximately 75% of the total circulating hindlimb volume is contained within the non-nutritional circuit, whereas about 25% is situated in the nutritional circuit.

**DISCUSSION**

The procedure outlined above and the data derived therefrom are dependent on the assumption of essentially complete rubidium extraction from the nutritional circuit within a single circulation following intra-arterial administration. How well is rubidium extracted from the circulation? Sapirstein (15) reported that rubidium and potassium achieve a constant level in all organs of the rat, except the brain, within 9 sec. This rapid tissue equilibration implies substantial, if not complete, extraction of rubidium from the circulation within a few passages through the tissue. In view of the negligible brain extraction and the existence of some tissue shunting, it is likely that the extraction during the first circulation through the capillary network was essentially complete, with continuing tissue uptake occurring during the remainder of the 9 sec as a result of recirculation. Back diffusion, which would also alter the equilibration time by redistributing rubidium, does not appear to be appreciable until some time after 60 sec (14, 16). Rubidium, which is qualitatively similar to potassium, distributes to and is diluted by the same pool that contains potassium. The fluid volume of the hindlimb may be grossly divided into plasma, interstitial, and cellular compartments in the approximate proportion of 2, 25, and 60% of tissue weight, respectively (19). The normal concentration of potassium and presumably that which could be achieved by rubidium in these compartments is about 4 mEq/liter for plasma and interstitial and about 140 mEq/liter for cellular. Thus, the relative potassium and rubidium capacity of these tissue compartments is 0.1:1.25:184.0, or the extravascular compartment provides about 800 times dilution of extracted rubidium. This marked dilution should minimize back diffusion.

In order to become diluted, Rb must gain rapid access to the cellular compartment. Is the muscle tissue capable of accommodating complete Rb extraction? The permeability of the capillary wall is certainly sufficiently great to provide complete Rb extraction. Walker and Wilde (20) and Barlow et al. (3) report that about 225% of plasma K, or 12 mM, is exchanged across the capillary wall per minute, and Rb exhibits a permeating ability similar to K (11).

Effective Rb extraction from the capillary circulation also depends on the rate at which Rb penetrates the cell membrane. Sjodin (18) reports that at an extracellular Rb concentration of 5 mM, influx is 3.1 µmole/g per hr. However, the influx of Rb per unit of applied concentration increases as the extracellular Rb concentration decreases, so that an extracellular Rb concentration of 0.2 mM provides an Rb influx of 0.325 µmole/g per hr.

An estimate of the effective Rb concentration delivered to the cellular membrane by a 25-µC injection, at the specific activities used, diluted by blood flow and interstitial volume is of the order of 0.06 µM. Rb influx in micromoles per kilogram per minute at this concentration level, estimated by means of a rough extrapolation of Sjodin's data (18), is of the same order. Thus it appears that the influx of Rb into the cellular compart-
section of the hindlimb is probably capable of accommodating complete capillary extraction of Rb at the dose levels employed in this study.

Comparison of radioiodinated albumin and rubidium outflow patterns indicates that the radioiodoalbumin is recovered from a compartment which is not being effectively sampled by rubidium. Since radioiodoalbumin is effectively restricted to the vascular system during a single circulation, the rubidium recovered does not adequately reflect some slowly circulating vascular compartment. Moreover, with loading of the rubidium pool and with increased back diffusion into and the consequent recovery from the capillary circulation, a third slow phase somewhat comparable to the third radioiodoalbumin downslope becomes apparent in the rubidium outflow pattern. It is not likely that the variations in patterns represent differences in extraction of skin and muscle in the hindlimb, since skinned preparations exhibit similar characteristics. Renkin (14) also observed evidence of parallel channels in the skinned hindleg of the cat.

The relationships between the radioiodoalbumin and radiorubidium curves seen in this study differ significantly from those seen when comparable indicators are presented to a tissue with a small extravascular space such as lung. Yudilevich (21) found that loss of K or Na from the circulation results in a smaller area under the early portion of the dilution curve when compared to radioiodinated serum albumin (RISA). In addition, shortly after the peak concentrations are reached the curves intersect. Following the intersection, Na recovery exceeds RISA, reflecting the back diffusion of Na lost from circulation. When back diffusion is reduced, as occurs with K which penetrates into the cellular compartment, the downslope becomes comparable to or greater than RISA, depending on the effective volume of the extravascular space. Inasmuch as the lung has a small cellular compartment relative to muscle, the degree of extravascular dilution of K by lung will be appreciably less than by muscle and greater back diffusion will occur. This should provide a shallow downslope for lung and a very steep downslope for muscle.

The marked difference between the radioiodoalbumin and Rb downslopes in our study can be regarded as evidence of an insignificant back diffusion of Rb from the extravascular space because of the great extravascular dilution in muscle space as well as minimal recovery of Rb from the capillary circulation.

The evidence enumerated above is believed to provide adequate support for the assumption of substantial, if not complete, nutritional extraction of rubidium. It is therefore reasonable to consider that the bulk of the recovered Rb<sup>86</sup> reflects passage through non-nutritional circuits which effectively shunt blood past the capillary network.

A mean hindlimb volume of 1.49 ml/100 g of tissue appears to be low in light of data reported by others (2, 13, 16). Pappenheimer (13), by means of a hemoglobin infusion technique, estimated the total hindlimb vascular volume of the cat to be approximately 2.5 % of limb weight. However, the hemoglobin-infusion technique could provide an overestimation of the vascular capacity due to hemoglobin penetration into the extravascular compartment. Shadle et al. (16), using the indicator-dilution pattern of P<sup>32</sup>-labeled red cells, found the vascular volume of the dog hindlimb to be about 2.1 % of limb weight. The discrepancy between this report and our data may be due, in part, to hemolysis of injected labeled red cells which could result from the jet injection necessary to insure vascular mixing. This would permit P<sup>32</sup> to move extravascularly and subsequent back diffusion from the extravascular component could extend mean transit time and provide an overestimation of volume. On the other hand, this discrepancy may represent an underestimation in our study because of the presence of occluded and compressed tissue at the site of amputation, thereby providing tissue weight with diminished or no circulating blood volume.

The mean distribution of total vascular volume within the hindlimb indicates that approximately 75 % of the blood volume is contained within the non-nutritional circuits, whereas approximately 25 % is situated within the nutritional circuit. It should be noted that the nutritional volume estimate includes some portion of the distal arteriolar and venular elements which directly supply and drain the capillary network. The remaining vascular elements, which comprise the non-nutritional network, include large and small arteries and veins as well as any shuntlike channels such as arteriovenous anastomoses, preferential channels, and those capillary circuits in which the flow greatly exceeds diffusion capacity.

Green (8), using Mall's data, estimated small vessel capacity to be about 21 % of the total vascular capacity. Comparison of the nutritional volume estimate of 25 % with 21 % estimated by Green (8) for small vessel vol-

### Table 1. Total, non-nutritional, and nutritional circulating blood volumes of dog hindlimb

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Green (8), using Mall's data, estimated small vessel capacity to be about 21 % of the total vascular capacity. Comparison of the nutritional volume estimate of 25 % with 21 % estimated by Green (8) for small vessel vol-
ume is not as close an approximation as might appear. The estimate reported here was obtained from viable resting muscle under reasonably normal pressure gradients. Moreover, this preparation was capable of exhibiting vasomotor activity and, although denervated, was probably under some humoral vasomotor influence, so that some vascular segments of this preparation were probably not being perfused actively at the instant of analysis. Therefore, 25% should represent an underestimate of nutritional vascular capacity. Furthermore, Green’s calculations were based on Mall’s measurements made on postmortem intestine wherein the pressure gradients distending the vasculature were probably represented by the mean circulatory pressure (approximately 7 mm Hg) which is greater than central venous pressure and less than arterial, capillary, and venular pressures. Thus, in Mall’s preparations the vascular distending pressure in the arterial, capillary, and small venous segments of the vasculature would be below normal whereas that of the large venous segment would be greater than normal. Therefore, Green’s calculations of venous segments of the vasculature would be underestimated, whereas that of the large venous segment would be overestimated and arterial and small vessel volume based on Mall’s data would be greater than normal. Therefore, Green’s calculations of venous segments of the vasculature would be underestimated, whereas that of the large venous segment would be overestimated.

Recalculation of small vessel vascular capacity utilizing in vivo dimensions of Chambers and Zweifach (4) along with the numbers and lengths presented by Green provides an estimate of approximately 36% of total tissue blood volume. This estimate is more consistent with data obtained in our study. A comparison of our estimate with this calculated value would indicate that approximately 70% of the small vessel circuit was being perfused and sampled by our method. This high proportion of small vessel perfusion is not surprising even in the resting muscle, since the hindlimb was denervated and under no central vasocostrictor influence. Furthermore, the passage of blood through an external circuit before perfusing the tissue could result in the release of some vasodilators and thereby expand the distribution of blood flow.

In the introduction it was stated that a knowledge of Vc could provide an index of effective capillary surface area. If the average capillary has a diameter of 8 μ and a length of 100 μ, then the volume of the capillary will be about 5,000 μ. In this case, at a Vc of 0.4 ml/100 g of muscle, the number of capillaries participating in exchange would be about 8 X 103. At a surface area of 2,500 μ/capillary, effective capillary surface area for Rh extraction in the dog hindlimb is approximately 2,000 cm²/100 g. This is lower than the 7,000 cm²/100 g assumed by Pappenheimer (13).

At this time it is impossible to define which estimates of tissue blood volume are indeed the most accurate and reliable. However, the technique reported above provides a means whereby reasonably valid, repetitive, and physiologic estimates of dynamic blood volume distribution between nutritional and non-nutritional channels may be obtained.

REFERENCES