Regional Blood Flow by Fractional Distribution of Indicators

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ABSTRACT

SAPIRSTEIN, LEO. A. Regional blood flow by fractional distribution of indicators. Am. J. Physiol. 193(1): 161-168, 1958.—K\(^{42}\) Cl, Rb\(^{86}\)Cl and iodoantipyrine (\(I^{131}\)) were given in single intravenous injections to rats. The isotope content of the organs and the arterial blood concentrations were studied as a function of time. K\(^{42}\)Cl and Rb\(^{86}\)Cl reached a stable level in all organs other than the brain in 6-9 seconds and maintained this level until 64 seconds. The arterial concentration curves for the isotopes showed that the injected dose was almost completely transferred into the arterial system at about 6-8 seconds. The isotopes showed subsequent recirculation amounting to about 40% of the original dose between the first recirculation and 64 seconds. The organs which displayed stability during the period of recirculation must have had extraction ratios from zero time less than 1.00 but equal to that of the whole body. The fractional uptake of indicator by such organs must therefore have been equal to their blood flow fraction of the cardiac output. The brain reached its maximum content of Rb\(^{86}\) and K\(^{42}\) in 5-6 seconds; both isotopes then disappeared rapidly. The brain was thus shown to have a lower extraction ratio toward these isotopes than the body as a whole; its flow fraction could not therefore be measured by their use. Most organs failed to show stability of their iodoantipyrine content between 9 and 64 seconds; this indicator is not suitable for the measurement of the flow fraction of such organs.

By combining values for the cardiac output and the fractional uptake of K\(^{42}\) in dog organs, regional blood flow values were obtained. For those other organs where flow values by other methods are available, the agreement was good. The following blood flow values were obtained in the major organs of the dog: Heart (coronary flow), 1.0 ml/gm/min.; kidney, 3.0 ml/gm/min.; liver, 1.2 ml/gm/min. (0.4 ml/gm/min. hepatic artery, 0.8 ml/gm/min. portal vein); skin, 0.07 ml/gm/min.

It was shown elsewhere (1) that between 5 and 60 seconds after the intravenous administration of K\(^{42}\)Cl to rats, the manner in which K\(^{42}\) was distributed among the organs did not change demonstrably with time. It was argued from this that the fractional distribution of K\(^{42}\) corresponded to the fractional distribution of the cardiac output.

The blood flow values obtained for other organs than the brain were in fair agreement with accepted values based in most cases on findings in other species. The brain values were exceedingly low. It was suggested that though the low cerebral values might be genuine, they might have resulted from a fall in K\(^{42}\) content of the brain preceding the first observation. The present study was undertaken to investigate this possibility. In the course of the study, the techniques employed were modified and the theoretical basis of the method was revised and expanded. The application of the method to the dog has made possible comparison of the results obtained with blood flow values obtained by other methods in the same species.

METHODS

The rats used in these studies were young female albinos (225–275 gm) of uniform stock.
The animals were fasted for 18 hours before use, but were allowed free access to water.

Nine healthy mongrel females were used in the dog experiments. These animals were selected for uniformity in weight (6-8 kg). Obviously immature, obviously old, pregnant and lactating animals were rejected. No other precautions were taken to insure uniformity in the experimental group. The animals were fasted for 18 hours before use, but allowed free access to water.

The three indicator substances employed were K\(^{42}\)Cl, Rb\(^{86}\)Cl and 4-iodoantipyrine (I\(^{131}\)). Isotopic potassium and rubidium were obtained from the Oak Ridge National Laboratories. Iodoantipyride was obtained from Abbott Laboratories. The K\(^{42}\)Cl shipments were dried and taken up in a volume of 0.85% NaCl sufficient to bring their K\(^{39}\) concentration to 4-5 mEq/l. In rats the injected dose given in a volume of 0.4-0.5 ml contained 5-10 \(\mu\)c of K\(^{42}\). In the dog experiments, the solution was similarly prepared, but 25-50 \(\mu\)c was given in a volume of 2.0-2.5 ml. Rb\(^{86}\)Cl shipments were dried and taken up in 0.85% NaCl. Five-microcurie doses in 0.5 ml were used. Iodoantipyride was made up in the same manner as Rb\(^{86}\)Cl but without preliminary drying. The injected solution contained 5 \(\mu\)c/0.5 ml.

In the rat organ experiments, the animals were anesthetized with 40 mg/kg of pentobarbital sodium by the intraperitoneal route. A femoral vein was exposed, and the isotope injected using a 0.5-ml tuberculin syringe. The injection time was less than 0.5 seconds. The animals were killed by cutting through the thorax just below the axillae with a mallet driven axe. The timing was accurate to \(\pm\)1 second.

Other rats of the same stock were used for the construction of arterial curves of indicator dilution. The technique was the usual one used in indicator dilution determinations of cardiac output, modified for application to the rat as follows: the indicator was injected in the femoral vein in a volume of 0.1-0.2 ml containing 0.5-1.0 \(\mu\)c of the indicator. Carotid arterial blood samples were collected through a PE 20 polyethylene catheter, 15 cm in length, which delivered into a sample collector which permitted 90 collections to be made per minute (2). The bleeding rate was 25-30 \(\mu\)l/collection. The points used in the construction of the portion of the curve employed in the calculation of the cardiac output were obtained within 8 seconds after the injection of indicator.

In the calculation of the cardiac output, the observed concentrations of indicator in the arterial blood were summated up to the time of the first recirculation (identified as the first recognizable deviation from rectilinearity on the semilog plot of concentration). To this value was added the sum of the converging geometric series of values extrapolated from the rectilinear descending limb. The sum of real and extrapolated concentration values was used as the denominator in the usual equation for the calculation of the cardiac output.

The amount of indicator transferred from the venous to the arterial circulation at any time was calculated by multiplying the cardiac output so obtained by the summated arterial concentration constructed from real points up to the time under consideration.

It must be stressed that the summated arterial concentration curve used for the calculation of indicator transfer is not identical with the summated arterial concentration used in the calculation of cardiac output. Up to the time of recirculation the former value is smaller, for the extrapolated sum is not included in it; after recirculation, it becomes larger for the real values of arterial concentration are in excess of those extrapolated from the descending limb of the semilogrithmic plot.

In the dog experiments, indicator dilution curves were made upon the same animals employed in the organ work. After anesthesia with 30 mg/kg of pentobarbital by the intravenous route the K\(^{42}\)Cl was injected into a femoral vein. A Cournand needle in the opposite femoral artery served for the sampling of arterial blood at 30 collections/min. The animals were killed at 20-120 seconds by the rapid intravenous injection of 20 ml saturated KCl.

The determination of arterial concentrations of all isotopes was made upon whole blood samples pipetted into planchetts and counted with an end window Geiger-Muller tube. Five-tenths-milliliter samples of dog blood and 0.02
ml samples of rat blood measured in a hemoglobin pipette were taken for counting. The arterial concentrations were plotted on semilog paper as a function of time. The initial portion of the curve was used for the determination of the cardiac output in the usual manner. Standards were made from the injected solutions. In the case of the short lived K$_{42}$, standard counts were made every 15 minutes, and the blood counts referred to the arithmetic mean of the two closest standards.

The indicator content of dog organs was determined upon an aliquot of a digest of the entire organ. Such digests were made by covering the organs with 6 N HCl in Mason jars and cooking in a pressure cooker for 3-4 hours at 20 pounds pressure.

The counting of rat organs was simplified by the availability of a very large (1 l. capacity) well counter with 4 pi geometry (obtainable from The Nucleonic Corp. of America, Brooklyn, N. Y.). The whole organ was placed in a Dixie cup and its gamma radiation counted after insertion into the well. Despite the low yield of gamma disintegrations in K$_{42}$ breakdown and the low efficiency of gamma counting, the counting rate was satisfactorily high since the whole organ, rather than an aliquot, was measured.

RESULTS

Organ Content of Indicator as a Function of Time: Rat. Table 1 shows the results of an experiment in which three groups of rats, consisting of 28 animals each, received K$_{42}$, Rb$^{86}$ or iodoantipyrine (II$^{113}$), and were killed in groups of four at 3, 6, 9, 12, 16, 32 and 64 seconds. The results are similar to those of three other experiments of the same type.

In general, the organs show continued accumulation of K$_{42}$ and Rb$^{86}$ through the first 9 seconds, and then stabilize their content until 64 seconds. The brain behaves exceptionally, showing its maximum content of isotope before 9 seconds, and declining precipitously, so that between 9 and 64 seconds it contains less than 0.2% of the injected dose, compared with the maximum value of 0.6-0.8% at 6 seconds. This behavior is more clearly illustrated in figure 1 which shows the cerebral K$_{42}$ content as a function of time at 1-second intervals in another experiment.

The behavior of the organs toward 4-iodoantipyrine is radically different. Only the brain, skin and carcass show a stable content of this indicator. The heart, kidneys and gut all lose the label continuously during the first minute, while the liver accumulates it progressively.

Although no effort was made to collect the blood spilled when the animals were killed, the recovery of the isotopes in animals killed between 9 and 64 seconds averaged 102% of the amount administered. From this it would appear that negligibly small quantities of the indicators remain in the blood after 9 seconds. (This statement should not be interpreted to indicate that the recirculation of indicators is insignificant.)

Organ Content of K$_{42}$ as a Function of Time: Dog. Table 2 shows the K$_{42}$ content of the organs in three groups of dogs killed at 20-39, 40-59 and 60-120 seconds after the administration of K$_{42}$Cl. There is no evidence of system-

### Table 1. ConTenT OF K$_{42}$, Rb$^{86}$ AND I$_{113}$ IN ORGANS OF RATS AT VARYING TIMES AFTER SINGLE INTRAVENOUS INJECTION OF K$_{42}$ OR Rb$^{86}$, Cl OR IODOANTIPYRINE (I$^{113}$) BY VEIN

<table>
<thead>
<tr>
<th>Time, sec.</th>
<th>Brain</th>
<th>Heart</th>
<th>Kidneys</th>
<th>Liver</th>
<th>Gut and Spleen</th>
<th>Skin</th>
<th>Carcass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K</td>
<td>Rb</td>
<td>I</td>
<td>K</td>
<td>Rb</td>
<td>I</td>
<td>K</td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td>0.7</td>
<td>0.56</td>
<td>2.1</td>
<td>7.8</td>
<td>10.5</td>
<td>4.2</td>
</tr>
<tr>
<td>6</td>
<td>0.6</td>
<td>0.81</td>
<td>0.58</td>
<td>2.7</td>
<td>14.2</td>
<td>14.0</td>
<td>9.3</td>
</tr>
<tr>
<td>9</td>
<td>0.3</td>
<td>0.11</td>
<td>0.63</td>
<td>3.2</td>
<td>2.7</td>
<td>2.4</td>
<td>14.0</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
<td>0.11</td>
<td>0.85</td>
<td>3.1</td>
<td>2.7</td>
<td>2.0</td>
<td>15.3</td>
</tr>
<tr>
<td>16</td>
<td>0.2</td>
<td>0.12</td>
<td>0.90</td>
<td>3.4</td>
<td>2.4</td>
<td>1.8</td>
<td>17.8</td>
</tr>
<tr>
<td>32</td>
<td>0.2</td>
<td>0.11</td>
<td>0.73</td>
<td>3.0</td>
<td>2.7</td>
<td>1.0</td>
<td>16.1</td>
</tr>
<tr>
<td>64</td>
<td>0.1</td>
<td>0.11</td>
<td>0.64</td>
<td>3.0</td>
<td>2.6</td>
<td>0.8</td>
<td>16.1</td>
</tr>
</tbody>
</table>

Each value represents the average of 4 rats. All values as percentage of injected dose.

* Values from another series of 30 rats in which the heart chambers were carefully rinsed with 3 washes of toluene to remove isotope in the contained blood.
FIG. 1. K\(^{42}\) content of rat brains as a function of time after K\(^{42}\) Cl i.v. in 23 rats killed at 1-sec. intervals after injection. Killing by mallet-driven axe. Each value up to 9 sec. represents the average in 2-4 animals.

Dilution Curves. Rat. Typical dilution curves for K\(^{42}\) in the rat with 90 sample collections/min. are shown in figure 2 (rats 4 and 7). Ordinarily, 2 seconds is required for the appearance of K\(^{42}\) in the artery after its injection in the femoral vein. The curve then rises for a further 1-2 seconds. The descending limb is usually fixed by five points (3 sec.), and the first clear evidence of recirculation usually occurs at 6-8 seconds. Eight such curves were made; all were similar both qualitatively and quantitatively. Four other curves were made at 35 collections/min. to display the late behavior of the curve. Two such curves are shown in figure 2 (rats 2 and 3).

Four dilution curves made with Rb\(^{86}\) at 90 collections/min. showed no significant difference from those made with K\(^{42}\).

Eight curves made with iodoantipyrine (I\(^{131}\)) showed delayed appearance of label in the artery, a lower peak value, and a shallower decline. These distortions in the curve were attributed to the existence of a pulmonary reservoir for iodoantipyrine. This interpretation was confirmed by the finding that as much as 7% of the injected iodoantipyrine could be found in the lungs at 5 seconds. The comparable value for K\(^{42}\) was 2.5%. Although the excess pulmonary iodoantipyrine was quickly washed out of the lungs, its effect was sufficient to diminish the slope of the down limb of the arterial dilution curve. Recirculation could not therefore be identified with certainty and dilution curves obtained with iodoantipyrine could not be used for the cardiac output calculations.

The cardiac output of the rats calculated from the K\(^{42}\) and Rb\(^{86}\) dilution curves averaged 205 ml/kg/min. This figure for the cardiac output of the rat is in good agreement with that obtained by Bullard (3) (210 ml/kg/min.) employing indicator dilution methods, and in fair agreement with that obtained by Blood et al. (4) by the direct Fick method (46 ml/min. in 180-200-gm rats).

At the time of the first recirculation 93-97% of the injected K\(^{42}\) or Rb\(^{86}\), calculated from the product of the cardiac output and the sum of arterial concentrations up to recirculation, had appeared in the arterial blood. This calculation was not made for iodoantipyrine.

Dog. Like others (5) we have found that up to the first recirculation the dilution curves made by Evans blue and K\(^{42}\) are almost indistinguishable from each other, indicating that there are no appreciable pulmonary losses of K\(^{42}\). (The curves are not quite indistinguishable. Just as is the case with iodoantipyrine, the peak is depressed and the down slope decreased. The effect, however, is very small. The average peak depression is about 6%; recirculation can always be identified; and the cardiac output determination by Evans blue and either K\(^{42}\) or Rb\(^{86}\) is the same.) The appearance time in the femoral artery after femoral venous injections is 6-8 seconds; the curve attains its maximum within 4 seconds of appearance and the down slope with K\(^{42}\) is fixed by real points for 6-8 seconds. Conn (6) has reported similar results with K\(^{42}\) in the dog. In his reported curve, the peak is seen at 3 seconds after the first appearance of indicator in the arterial blood, and the rectilinear semilogarithmic decline is interrupted by recirculation 8 seconds later.

The cardiac output of the nine dogs studied averaged 170 ml/kg/min. This average, based on the K\(^{42}\) dilution curves, is in good agreement with our normal values based on hematocrit dilution after single injections of autogenous plasma (7).

DISCUSSION

The present method for measuring the distribution of the cardiac output is based on the fact that the uptake of an indicator by an
organ can be described as the product of its blood flow, the integrated arterial concentration of the indicator, and the organ's extraction ratio for the indicator. The uptake of indicator by the whole body can be described as the product of the cardiac output, the integrated arterial concentration of the indicator and the whole body's extraction ratio for the indicator.

As used here and subsequently, the extraction ratio is defined as the ratio between the integrated arteriovenous concentration difference and the integrated arterial concentration from the moment of injection of indicator to the moment under consideration.

Since the arterial blood concentrations which supply an organ and the remainder of the body are essentially equal to each other, it follows that organ uptake is related to body uptake as is organ blood flow to cardiac output, whenever it is the case that the organ and the whole body have the same extraction ratio.

If there existed indicators which did not recirculate at all the extraction ratio of every organ would be identically 1.00 and each organ's uptake would describe its blood flow fraction. At the present time, no such indicators are known. For indicators which do recirculate, with each recirculation, those organs which have high extraction ratios will accumulate indicator, while those which have low extraction ratios will give it up. Only one condition exists in which the indicator content of an organ can remain stable in relation to the whole body uptake from the moment of its delivery to the organ onward; this is the condition in which the extraction ratios of the organ and of the whole body are identical.

The results with iodoantipyrine, shown in table 1, illustrate the behavior of a substance whose extraction ratio differs from organ to organ. The heart, kidneys and gut lose indicator throughout the 1st minute. By this fact, these organs are shown to have lower extraction ratios for the label than the body as a whole. The liver, which gains indicator continually, must have a higher extraction ratio than the whole body; the brain, skin and carcass, with stable isotope contents, must have the same extraction ratio as the whole body. Clearly, the uptake of iodoantipyrine by the changing organs cannot be employed in any simple manner to describe their flow fractions.

### Table 2. Percentage of Administered K⁴² Found in the Organs of 9 Dogs at Various Times After Intravenous Injection of K⁴⁸Cl

<table>
<thead>
<tr>
<th>Organ</th>
<th>Killing Time, sec.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-49</td>
</tr>
<tr>
<td>Heart</td>
<td>4.9</td>
</tr>
<tr>
<td>Kidneys</td>
<td>10.6</td>
</tr>
<tr>
<td>Skin</td>
<td>5.1</td>
</tr>
<tr>
<td>Gut</td>
<td>13.2</td>
</tr>
<tr>
<td>Stomach</td>
<td>2.4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.2</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.1</td>
</tr>
<tr>
<td>Liver</td>
<td>10.1</td>
</tr>
<tr>
<td>Tongue</td>
<td>0.7</td>
</tr>
<tr>
<td>Lungs</td>
<td>4.8</td>
</tr>
<tr>
<td>Carcass</td>
<td>45.2</td>
</tr>
</tbody>
</table>

Each value represents 3 determinations.

The behavior of K⁴² and Rb⁶⁸ is quite different. For every organ other than the brain, the indicator content has become constant by 9 seconds. At this time, the amount of isotope transferred into the arterial system can be calculated by multiplying the minute output by the integrated arterial concentrations. For both isotopes, the value ranges from 102-104% of the dose injected. From 9 to 64 seconds, there are no systematic changes in the indicator content of any organ. Evidently, every organ other than the brain has the same extraction ratio during the first 64 seconds as the whole body.

The unique behavior of the brain toward the alkali metal isotopes is shown in the changes which occur between 6 and 9 seconds (table 1) and in the second by second changes illustrated in figure 1. The K⁴² or Rb⁶⁸ carried to the brain when they are at peak concentration in the arterial blood is swept through immediately. The extraction ratio of the brain for these indicators is thus demonstrated to be much lower than that of the body as a whole. Just as the uptake of iodoantipyrine cannot be used to estimate the flow fractions of the organs which change their content of this indicator with time, the cerebral uptake of the alkali metal isotopes cannot be employed for the cerebral flow fraction measurement.

The fact that organs other than the brain show constancy of content of K⁴² and Rb⁶⁸ with time was originally interpreted (1) to indicate that no recirculation of either indica-
Fig. 2. Typical arterial indicator dilution curves for K$^{42}$ (rats). Injections in femoral vein; samples from carotid artery. Rats 4 and 7, 90 samples collected/min. Rats 2 and 3, 35 samples/min. Ordinates blood K$^{42}$ concentration in cpm/.02 ml.

Examination of figure 2 shows that this interpretation is untenable. The linear extrapolation of the descending limb of the concentration curve describes the arterial concentration in the absence of recirculation. Displacement of the real curve above this extrapolated line must be due to recirculating isotope. The amount of isotope recirculating can be estimated by multiplying the cardiac output by the area enclosed between the real and extrapolated curves.

In the four animals in which K$^{42}$ dilution curves were available to 1 minute, this calculation showed that 40% of the injected dose (35-46%) had undergone arterial recirculation. Why then was there no movement of isotope from those organs with low extraction ratios to those with high extraction ratios?

The answer, though simple, is surprising. That redistributions did not occur must have resulted from equality of the extraction ratios of every organ which showed this behavior. This implies that the integrated concentrations of label in the venous blood from every such organ must have differed from each other by a quantity insignificantly small in relation to the integrated arteriovenous concentration difference.

Direct evidence in support of this proposition is available from the studies of Sheppard et al. (8). In the dog, 60 seconds after the injection of K$^{42}$ the integrated venous concentrations of the renal, femoral and hepatic veins differed from each other by less than 10% of the value of the integrated arteriovenous concentration difference at the same time (data from figs. 3 and 4, Sheppard et al., loc. cit.). The jugular venous integral, as might be expected, had a radically different value from the other venous integrals.

A tentative explanation of this behavior is as follows: under the experimental circumstances (basal condition, short time intervals, K$^{39}$ concentration in the injected solution at plasma concentration), the uptake of K$^{42}$ by any organ is a pure exchange reaction, in which the organ behaves as an inert reservoir of immediately exchangeable K$^{39}$ through which there flows a stream of K$^{39}$ labeled with K$^{42}$. In such a system, there can be no specific affinity of any organ for K$^{42}$ other than that which is described in terms of the size and perfusion rate of the reservoirs. If the blood flow through the organs, and the size of their reservoirs of immediately exchangeable K$^{39}$ are approximately proportional to each other, similarity of the extraction ratios of K$^{42}$ from organ to organ would be the expected result. One may speculate that the quantity of exchanging K$^{39}$ in the interstitial fluids and cells served by each capillary vessel is roughly constant, and that the blood flow through any organ is directly related to the number of open capillaries. It would follow that blood flow and the quantity of exchanging K$^{39}$ in each organ are directly related to each other.

Though similarity of extraction ratios for K$^{42}$ and Rb$^{86}$ from organ to organ, makes it feasible to determine the flow fractions of a number of organs simultaneously, it is not a necessary condition for the determination of the measurement of blood flow to any one region by this method. The sole requirement
for the flow measurement to any area is that it has the same extraction ratio for the indicator employed as the body as a whole. This can be demonstrated by showing that the area in question has an indicator content which is time independent over the interval proposed. The nature of the indicator is immaterial.

For example, the skins and carcasses of rats all show constancy of uptake of K42, Rb86, and iodoantipyrine between 9 and 64 seconds. Correspondingly, the fractional uptake of each indicator should describe the fraction of the cardiac output which these areas receive. In fact, the results (table 1) are substantially the same for all three indicators despite their chemical differences. The constancy of the cerebral uptake of iodoantipyrine will be shown elsewhere to make possible the measurement of cerebral blood flow (8a).

In its present form, the method can only be applied to groups of homogeneous animals. This follows from the condition that organ uptake must be demonstrated to be independent of time once the injected label has been transferred from the venous to the arterial circulation and the fact that each time determination is terminal.

Two possible sources of error in the application of the method should be stressed. Both are concerned with the possibility that anatomical or physiological shunts may exist for the indicator employed. Blood flowing through a shunt with a perfusion rate which is very large in proportion to its volume may escape detection in the organ in which it is located, even when the most meticulous care is devoted to early timing, for the label may have passed through the organ in the time interval between two examinations. Conversely, the burden of isotope carried by the shunted blood, will, on its return to the arterial system, be redistributed to exchanging areas, giving values for their fractional uptake of indicator in excess of their fraction of the cardiac output.

In the case of K42 and Rb86 in the rat anesthetized with pentobarbital, the amount of such shunting which occurs appears to be very small. Since constancy of isotope content has been established in the organs by 9 seconds (table 1), and since the first recirculation has occurred in the arterial concentration curve at 6.0–8 seconds, it may be presumed that shunted isotope is, at most, that amount which recirculates between 6.0 and 9 seconds. Isotope recirculating later is presumably derived from exchanging pools; the possibility of earlier recirculations concealed under the exponential limb of the isotope dilution curve cannot be entirely excluded but appears highly unlikely. The dilution curves prepared at 90 collections/min. with K42 and Rb86 suggest that 2.1% (1.5–4.0%) of either isotope recirculates in the time under consideration. The values for recirculation are calculated by comparing the area between the real and extrapolated values above the arterial dilution curve up to 9 seconds to the area under the ‘cardiac output’ dilution curve.

The amount of the alkali metal isotopes which recirculates is surprisingly small, in view of the fact that the brain appears to act as a shunt for them, and is usually considered to be perfused by 14% of the cardiac output. This value, however, is based on man where the brain:body mass ratio is over 2%. In the case of the adult rat, where the brain:body mass ratio is much smaller (9), the cerebral fraction of the cardiac output would be expected to be less. In another article (8a), it will be shown that the cerebral blood flow fraction of the rat is only 1–2% of the cardiac output. This is almost as large as the total recirculation detected at 9 seconds; one may surmise that extracerebral shunting of K42 and

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cardiac output, %</th>
<th>ml/min/kg dog</th>
<th>ml/min/gm organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>11.1</td>
<td>19</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart</td>
<td>5.2</td>
<td>9</td>
<td>1.0</td>
</tr>
<tr>
<td>Liver (total)</td>
<td>30.0</td>
<td>51</td>
<td>1.2</td>
</tr>
<tr>
<td>Liver* (artificial)</td>
<td>10.0</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>Liver* (portal)</td>
<td>20.0</td>
<td>34</td>
<td>0.8</td>
</tr>
<tr>
<td>Pancreas†</td>
<td>1.6</td>
<td>2.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Spleen†</td>
<td>1.3</td>
<td>2.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Gut†</td>
<td>14.5</td>
<td>24.8</td>
<td>0.7</td>
</tr>
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<td>Stomach†</td>
<td>2.5</td>
<td>4.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Skin</td>
<td>4.9</td>
<td>8.4</td>
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</tr>
<tr>
<td>Carcass</td>
<td>44.3</td>
<td>75.8</td>
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</tr>
<tr>
<td>Whole dog</td>
<td>100</td>
<td>160</td>
<td>17</td>
</tr>
</tbody>
</table>

* Values added to make total liver value.
† Values added to make portal value.
Rb\textsuperscript{86} is essentially nil. It will, however, be recognized that the existence of any shunt will produce a positive error in every other flow determination; but since this error is about 2% the circumstances studied it seems improbable that it can be detected.

Further evidence that extracerebral shunting of K\textsuperscript{42} is of minor consequence is available from the studies of Sheppard et al. already referred to (8). Early appearance of K\textsuperscript{42} at high concentrations, in the venous drainage of the organs, such as would be expected if shunting occurred, was observed only in the area of jugular drainage. The renal, femoral and hepatic veins displayed no evidence of shunting. Similar results, showing the absence of shunts for K\textsuperscript{42} in the human kidney, have been reported by Black and his co-workers (10).

The application of the present method to the dog makes possible comparisons of the results with those found by other techniques in the same species. Blood flow values for the dogs used in this study are given in table 3. Since there was no observable change with killing time, the averages for all animals are presented together. The values in the first column are the percentage of the cardiac output perfusing each organ; the second column gives the blood flow in ml/min/kg body weight; the third column expresses the values as ml/min/gm organ.

Considering biological variability and methodological uncertainties, the agreements are surprisingly good. For example, the renal blood flow by the present method is 19 ml/kg/min. The corresponding value, given by Houck (11), corrected for Hct, is 21 ml/kg/min. The splanchnic blood flow by the present method is 30% of the cardiac output or 51 ml/kg/min. The value agrees well with that found in dogs by Pratt, Burdick and Holmes (12) who used the BSP method and sampled blood through a London cannula (49 ml/kg/min.); and it is in fair agreement with that reported by Sapirstein and Reininger (13), using Rose Bengal, and sampling blood from a surgically produced common hepatic vein (57 ml/kg/min.). The division of flow between the hepatic artery and the portal system (2:1) is in close agreement with some previous values (14, 15); however, different ratios have been reported (16).

The coronary flow value (4.5% of the cardiac output; 1.0 ml/gm/heart/min) agrees reasonably well with the values summarized by Gregg (17). The difference in the techniques and animals, and the great variability encountered in using the accepted techniques, caution against the overinterpretation of this similarity.

Since blood flow values for the other organs given in table 3 have not been determined by other methods in the dog, they are presented for interest rather than for purposes of comparison.

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