

Regional Blood-Flow Measurement in Rabbit Soft-Tissue Tumor with Positron Imaging Using the C¹⁵O₂ Steady-State and Labeled Microspheres

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The C¹⁵O₂ steady-state method, with tomographic measurement of H₂¹⁵O, has been used to measure blood flow in normal muscle tissue and a soft-tissue tumor (V2) in rabbits. The method has been validated in a rabbit tumor model by comparison of the data with that observed using microspheres labeled with Sc-46 and Ga-68. The blood-flow values found with the C¹⁵O₂ steady-state method, after correction for tissue blood volume, agree well with values gained with labeled microspheres. The effect of blood volume on apparent blood flow in tumor was about 50%. The tissue/blood partition coefficients were 0.94 ± 0.05 for healthy tissue and 1.16 ± 0.15 for tumor tissue. After correction for partition coefficient and blood-volume effects, the blood-flow value for normal tissue was 4.1 ± 1.3 ml/min-100 cc, and for the tumor tissue 10.7 ± 2.3 ml/min-100 cc.

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Blood flow can be determined in vivo by a number of methods. The use of a diffusible indicator that is removed from tissue in proportion to blood flow is based on the Kety-Schmidt principle (1-3), also referred to as the washout technique. Measurements are carried out with external detectors and single-photon emitters (4). This method has been extended to emission tomography with both positron (PET) and gamma emitters (5), but these techniques tend to give poor spatial resolution (6,7). Ter-Pogossian and co-workers in 1969 (8) made cerebral blood-flow (CBF) measurements using a single bolus of blood labeled with H₂¹⁵O, ¹⁵O₂, or C¹⁵O₂, and later Raichle and co-workers (9) used a single bolus of O-15-labeled water injected intra-arterially. Huang et al. modified this method to a single-breath inhalation of C¹⁵O₂ (10). Reasonably accurate measurements may prove possible with improved instrumentation (11,12).

The steady-state technique was described by Russ et al. in 1974 (13,14). For this method either the constant

administration of O-15-labeled water (15) or, more commonly, the continuous inhalation of C¹⁵O₂ gas (16) is used. Oxygen-15 in the C¹⁵O₂ is rapidly converted in the lung by carbonic anhydrase (17) to H₂¹⁵O. This conversion and the short half-life of O-15 allow steady state to be reached within a few minutes. The values for blood flow can be obtained from the steady-state concentration of labeled water in tissues according to the model described by Subramanyan et al. (18). This principle has been used in many clinical investigations with PET. Although the techniques would be valid for any tissue, much of the work has been applied to the brain (19-21).

The ideal technique for measuring blood flow requires an agent that is extracted from the blood instantaneously and whose activity remains constant in the tissue. The measurement of tissue concentration will then reflect blood flow (22,23). The classic example is the use of labeled microspheres, which have an extraction efficiency approaching 100%. These must be given intra-arterially, so their use in human studies is limited. Chemical agents that approach this behavior include N-isopropyl-[¹²³I]amphetamine or ¹³NH₃ (24-26), and pH-shift agents (27,28).

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The objective of this study was to confirm in a rabbit tumor model the validity of the $C^{15}O_2$ steady-state technique for measuring blood flow. The findings were compared with those obtained using Ga-68-labeled human serum albumin microspheres, which were in turn calibrated with Sc-46 microspheres. The $C^{15}O_2$ steady-state method was used to observe changes in blood flow in tumor and surrounding tissue. We also studied the effect of water content and tissue blood volume on the flow measurement in tumor tissue, since these factors have an important role in blood-flow quantification.

The estimation of tissue blood volume was done with ^{11}CO , and a simulation method was developed to study the relation of tissue blood volume and the tissue blood partition coefficient of water.

MATERIALS AND METHOD

Preparing a mixture of Ga-68 and Sc-46 microspheres.

The Ga-68 microspheres were prepared according to the method developed by Hnatowich (29). Gallium-68 EDTA was eluted from a Ge-68 \rightarrow Ga-68 generator (on alumina support) with 0.05 M EDTA. Ten milliliters of Ga-68 EDTA were added to 30 ml of concentrated hydrochloric acid (HCl) and mixed. The $^{68}GaCl_3$ formed was separated on a small column (diam 4 mm, length 20 mm, on an ion-exchange resin support*), which was rinsed with 6 N HCl both before and after the addition of radioactivity. The eluate containing $^{68}GaCl_3$ was adjusted to pH 3.0 with 0.05 M Na_2HPO_4 and 1 N NaOH. Human serum albumin microspheres (10–35 μm diam) were labeled in an ultrasonic water bath for 15 min at 50–60°C, and their specific activity was determined (30). The Ga-68-microsphere suspension was mixed with a known activity of Sc-46 microspheres (15 \pm 3 μm diam) and vortexed.

The behavior of the Ga-68 microspheres was assessed in two different ways in vivo. The distributions of Ga-68 microspheres and Sc-46 microspheres after their injection into the left ventricle was compared in samples of rabbit tissue. In addition, 0.5 mCi (0.5 million particles) of Ga-68 microspheres were injected into the jugular vein of a dog, and arterial and venous blood samples were collected for 1 hr. A positron image of the chest was made at 5 min after injection. About 90% of the injected Ga-68 microspheres was trapped in the lungs during the first 5 min. Two percent of the injected activity was found in both arterial whole blood and plasma 1 hr after injection. This activity was probably released from the Ga-68 microspheres.

Animal procedures. Samples of V-2 tumor were implanted into the left thigh of New Zealand white rabbits. In about 2 wk the tumor had grown to an average diameter of 6–8 cm, with that of the necrotic area 2–3 cm, and experimental measurements were carried out. For

positron studies animals were anesthetized with i.m. ketamine hydrochloride and acepromazine, and the anesthesia was continued throughout the whole study. First, the catheter was placed into the abdominal aorta via the femoral artery. Positron tomographic imaging was performed using the $C^{15}O_2$ steady-state technique. After inhalation of $C^{15}O_2$ gas for 6–9 min, steady-state activity in the tissue was achieved. During imaging, arterial blood samples were collected from the femoral catheter. Adopting the method developed by Bartrum et al. (31), another catheter was positioned under fluoroscopy through the common carotid artery into the left ventricle. The aorta was visualized by the flushing of contrast medium. A mixture of microspheres labeled with Ga-68 and Sc-46 was injected into the left ventricle through this catheter, and a second imaging was normally started 40 min after starting the first.

Several landmarks on the animal, and fixed lines produced by two perpendicular lasers, were used to relocate the animal in exactly the same position, in both x and y directions, as in the $C^{15}O_2$ study. After completion of the positron imaging, the rabbits were killed. Tissue samples were selected for gamma counting of Ga-68 and Sc-46 on the basis of 2D- and 3D-positron images. The tumor was cut into slices corresponding to the positron images, the mid level being the most important slice. For gamma counting these slices were usually divided into 8–10 smaller pieces corresponding to the number of pixels found in positron images, the pixel size being 1 \times 1 \times 1.4 cm. The samples of growing tumor surface and necrotic center were also verified histologically. The blood-flow studies were performed in two normal and five tumor-bearing rabbits.

Positron imaging. Conventional two-dimensional imaging was performed with the positron camera (32) using a motion protocol developed to improve spatial resolution by moving the detector arrays $1/5$ of the intercrystal distance five times in directions alternately parallel with and perpendicular to the crystal array. The final image consisted of 25 shifted and overlaid images.

Transverse-section imaging was performed by rotating the camera heads around the animal from 0° to 180° by increments of 12°. At each angle the detector arrays were translated over six steps, each $1/6$ of the intercrystal distance, giving 90 frames of collected data.

Calibration measurements to get counts/pixel/ $\mu Ci/cc$ were performed for each study using the same measurement protocol and, to minimize the effect of scattering, with the same activity range as in the real study. Also "fins" above detector arrays were used to decrease scattering. Fins are parallel lead strips in a frame. The depth of the frame is 2.5 cm and the strips are separated by 2.8 cm from each other. The calibration source was a Ga-68 bottle (diam 15 cm) corresponding to the thickness of the rabbit. Measurements were repeated

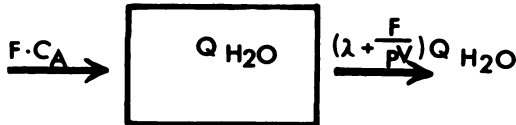
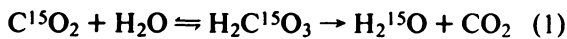


FIG. 1. Schematic for measurement with $C^{15}O_2$ steady-state technique, F -regional blood flow, (C_A) = arterial $H_2^{15}O$ concentration, λ = physical decay constant, p = tissue/blood partition coefficient, and $Q(H_2O)$ = steady-state activity.

after one gallium-68 half-life, and at least five measurements were included for each calibration curve.

Data were stored and transverse sections reconstructed using a computer system with 32K bytes of core memory. The software system used was PL/S, a higher-language system developed at our institution (33). The image format used a 64×64 matrix expanded to 256×256 with a 128-level gray scale. From one set of data, tomograms were normally computed for ten planes spaced at 1.4 cm or 2.8 cm with the plane thickness depending on the size of the tumor.

Blood-flow measurements with the $C^{15}O_2$ steady-state technique. When $C^{15}O_2$ is inhaled, water in the blood is labeled with O-15 by the in vivo reaction (17)



The labeled water is a diffusible tracer. The change in activity (mCi/min) in the tissue volume assayed by the detector is the difference between the mCi/min entering the tissue volume and the mCi/min leaving it (Fig. 1). According to the Fick principle (34)

$$\frac{dQ(H_2O)}{dt} = FC(H_2O) - \left(\lambda + \frac{F}{pV} \right) Q(H_2O) \quad (2)$$

where F is regional blood flow (ml/min), $C(H_2O)$ is the arterial $H_2^{15}O$ concentration (mCi/ml), λ is the physical decay constant of O-15 (0.338/min), V is the tissue volume (ml) and p is the partition coefficient of water between tissue and blood. After the prolonged inhalation of $C^{15}O_2$, the steady-state activity $Q(H_2O)$ is given by the solution of Eq. (2) with $dQ(H_2O)/dt = 0$, and regional blood flow can be calculated by the equation

$$\frac{F}{V} = \frac{\lambda Q(H_2O)}{C(H_2O) - \frac{Q(H_2O)}{pV}} \quad (3)$$

According to Eq. (3), blood flow is dependent on the tissue/blood partition coefficient and the tissue volume.

In the mathematical model it is assumed that the tissue volume is occupied by perfused tissue only, but in reality a certain volume of blood is included. In two rabbits the tissue blood volume was measured using the inhalation of ^{11}CO . The ^{11}CO content on the count/pixel level in the images and the blood samples taken at the beginning and end of 3D-imaging were calibrated to

correspond to $\mu Ci/cc$ values. Because inhaled CO will bind to hemoglobin (35), the percentage of blood volume in a regional tissue can be determined directly from the relation of 3D-images and blood samples. The values obtained reflect blood both in major vessels and in tissue capillaries.

We determined the value for the tissue/blood partition coefficient of water by experimentally measuring blood flow with microspheres, and the tissue and blood activity concentrations by the $C^{15}O_2$ steady-state method. The partition coefficient can be calculated from Eq. (3). Tissue activities were corrected for the percentage of regional blood volume as measured with ^{11}CO .

In addition we simulated the dependence relationship between the tissue blood volume and the partition coefficient under steady-state conditions (Fig. 2). The total tissue volume includes a proportion of blood volume that could be expressed by the following equation

$$Q(H_2O) = xC(H_2O) + (1 - x)Q_r(H_2O), \quad (4)$$

where $Q(H_2O)$ is the measured steady-state activity in tissue ($\mu Ci/cc$), x is the percentage of blood volume in tissue, $C(H_2O)$ is the measured activity concentration in blood, and $Q_r(H_2O)$ is a real tissue activity. By giving to x different values, we can calculate corresponding real-tissue activities $Q_r(H_2O)$. The partition coefficient corresponding to each x value can be calculated from the following:

$$p = \frac{F[Q_r(H_2O) - xC(H_2O)]}{x[Q_r(H_2O) - FC(H_2O)] + F[C(H_2O) - Q_r(H_2O)]}, \quad (5)$$

using blood-flow values determined by microspheres and

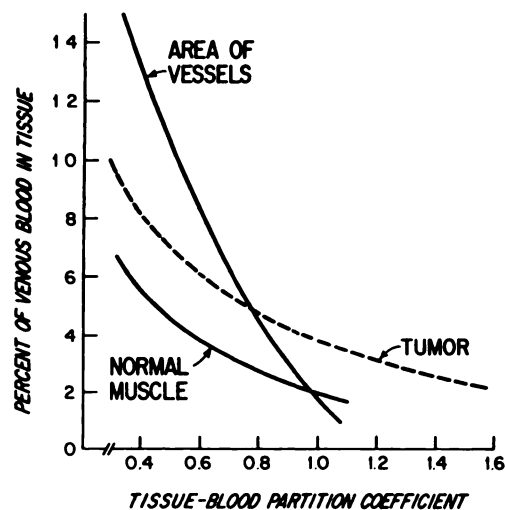


FIG. 2. Simulated relationship of tissue blood volume and tissue/blood partition coefficient. Area of vessels contains point where larger arteries enter tumor. Tumor curve represents average surface area of tumor. Normal muscle curve contains values from healthy hind legs.

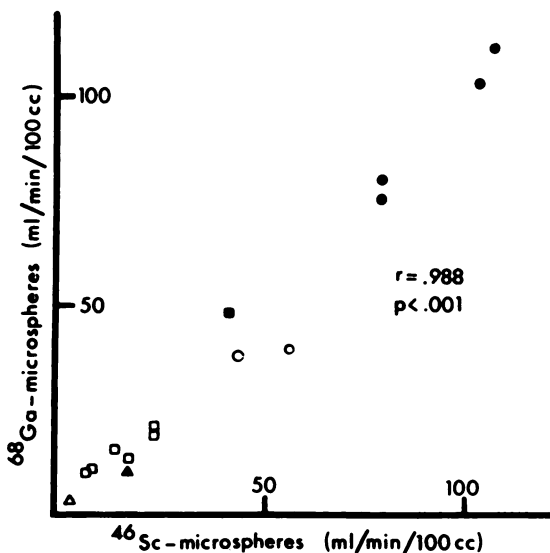


FIG. 3. Comparison of Ga-68 and Sc-46 microspheres in tissue samples, (●) = kidney, (▲) = liver, (■) = lung, (○) = heart, (▲) = muscle, (□) = brain.

blood activity values measured at steady state. Simulation curves for tissue/blood volume plotted against tissue/blood partition coefficient were calculated for each animal for three different regions of interest: (a) the region of the highest activity containing a small area of the main arteries entering the tumor tissue, (b) the tumor surface, and (c) the contralateral healthy muscle tissue. These curves can be used in the determination of partition coefficients when the blood volume is determined independently (as, for example, with ¹¹CO), or conversely to estimate blood volume when the tissue/blood partition coefficient is known.

In order to study its contribution to changes in the tissue/blood partition coefficient, the total water contents of tumor, muscle, and blood were obtained by drying thin tissue layers in a heatbox for 2-3 days at 90-95°C, until the dry weight remained unchanged for 12 hr.

Blood-flow measurement with microspheres labeled with Ga-68 and Sc-46. The microsphere technique used for measuring regional blood flow involves the use of labeled microspheres of such dimensions as to prohibit their passage through the capillary bed. The human serum albumin microspheres labeled with Ga-68 varied in diameter between 10 μm and 35 μm (mean 20 μm) according to the manufacturer's specifications. Because the labeling procedure with Ga-68 had to be done separately for each study, we also used commercially available Sc-46-labeled plastic microspheres (diam of 15 ± 3 μm)⁺ to calibrate the labeling and behavior of Ga-68 microspheres. A mixture of both labeled microspheres was injected directly into the left ventricle of the rabbits.

We used the method developed by Bartrum et al. (31) for measurement of regional blood flow based on the use of arterial blood samples as a reference. If microspheres are injected into the left ventricle, are thoroughly mixed with blood, and do not recirculate, the arterial blood will have a constant ratio, R, of microspheres, Q (mCi), to unit flow, F (ml/min):

$$R = Q_i/F_i, \tag{6}$$

where i refers to the organ of interest.

For determination of the constant R, we obtained a reference blood sample taken by a Harvard withdrawal pump, connected to a catheter in the abdominal aorta. The collection of blood was started just before the moment of injection of microspheres into the left ventricle and continued for 1 min following injection. The activity of the collected blood was measured and the flow rate of the Harvard pump determined separately using the same catheter. The withdrawal rate used was 3.0 ± 0.1 ml/min. The typical number of counts obtained for the calibration of R value using Ga-68 microspheres was 20,000 counts/ml-min and for Sc-46 microspheres 3000 counts/ml-min. The difference in counts was due to the initial injected dose.

TABLE 1. BLOOD FLOW (ml/min-100 cc) IN NORMAL AND TUMOR TISSUE OF RABBITS

Tissue	Number of studies	In vitro			In vivo		
		Ga-68 microspheres	Sc-46 microspheres	Ga-68 microspheres	BV* = nc [‡] p [†] = 1	BV = c [§] p = 1	BV = c p = c
Leg muscle	7	3.4 ± 0.7	3.4 ± 0.8	4.1 ± 1.3	5.9 ± 1.5	4.1 ± 1.3	4.1 ± 1.3
Tumor							
surface area	5	11.7 ± 2.6	12.3 ± 1.8	11.3 ± 1.8	17.7 ± 4.7	11.3 ± 1.3	11.2 ± 1.3
necrotic area	2	2.9	3.0	4.9	5.4	5.1	5.0
average tumor	5	10.8 ± 2.4	10.5 ± 2.1	10.4 ± 2.5	14.2 ± 2.9	11.4 ± 2.1	10.7 ± 2.3

* BV = Blood volume of tissue.

† p = Tissue/blood partition coefficient of water, corrected value for leg muscle 0.94, for tumor tissue 1.16.

‡ nc = Uncorrected.

§ c = Corrected.

TABLE 2. RELATIONSHIP OF TISSUE BLOOD VOLUME AND TISSUE BLOOD PARTITION COEFFICIENT IN NORMAL AND TUMOR TISSUE OF RABBIT

Case	Tissue	Regional blood flow ml/min-100 cc (1)*		Tissue blood volume (volume %) (2)†	Tissue/blood partition coefficient of water (3)‡
1	Leg muscle	3.4	(3.0-3.8)	2.9	0.90
	Tumor surface	12.6	(10.7-13.8)	15.0	1.05
2	Leg muscle	3.7	(3.3-4.3)	8.9	0.94
	Tumor surface	12.4	(10.9-15.3)	23.9	1.16
3	Leg muscle	5.4	(4.6-6.7)	2.0	0.94
	Tumor surface	11.5	(7.5-14.5)	3.6	1.16
4	Leg muscle	3.3	(2.8-4.3)	3.3	0.97
	Tumor surface	11.8	(10.3-13.9)	7.8	1.27
5	Leg muscle	2.6	(2.3-2.9)	2.8	0.94
	Tumor surface	11.1	(10.2-12.4)	8.7	1.16

* (1) Bloodflow values are the mean of three microsphere measurements. Range in parentheses.

† (2) Tissue blood volume was determined from curves in Fig. 2 using a tissue/blood partition coefficient of 0.94 for normal tissue and 1.16 for tumor.

‡ (3) Tissue blood partition coefficients were calculated with Eq. (3).

RESULTS

The values for regional blood flow using Ga-68 and Sc-46 microspheres in different tissues of rabbits show a good linear correlation ($r = 0.988$, $p < 0.001$) (Fig. 3), suggesting that both sets of microspheres are distributed identically and Ga-68 microspheres can be used for measuring blood flow. Table 1 contains the regional blood-flow values in tumor and healthy muscle tissue, determined in vitro and in vivo by the different techniques. Blood-flow values for healthy muscle tissue were calculated as the mean of measurements from healthy contralateral hind legs. For γ -counting, the tumor was divided into parts, so that the highest-activity surface and inner necrotic parts were counted separately. PET tomogram areas corresponding to the counted tissue samples were chosen and regional blood-flow values were calculated from the three-dimensional static tomograms after calibration of counts/pixel to $\mu\text{Ci}/\text{cc}$. There is no statistically significant difference between the regional blood-flow values determined by Ga-68 and Sc-46 microspheres in vitro. The accuracy of in vitro microsphere measurements is dependent mainly on the accuracy of the R value [see Eq. (6)]. The percentage variation of regional blood flow with both microspheres was 21% in healthy tissue and varied from 15% to 22% in tumor tissue. In the tumor's necrotic area the variation was 41-80% reflecting mainly the difficulty of accurately separating the necrotic area.

The accuracy of PET using the microsphere technique is a function of the accuracy of the sensitivity and resolution of positron imaging. Scattering is also an important source of error. The difference in blood-flow values

obtained for healthy tissue when determined by Ga-68 microspheres and compared with in vitro counting was 20.5%. This difference is due mainly to scattering. The calculation of blood flow using the C^{15}O_2 steady-state technique is based on Eq. (3). The accuracy is dependent on that of PET and the mathematical model.

In Table 1, Column 6 shows blood-flow values without blood-volume correction. The value of 1.0 was used for the tissue/blood partition coefficient of water. The following column contains blood-flow values corrected for the tissue blood volume. The percent of tissue blood volume in healthy muscle tissue measured by ^{11}CO was determined to be 3.1 ± 0.3 , and for the tumor tissue it varied between 8% and 15%. Therefore, in correcting blood flow values, 3.1% was used for the healthy tissue and for the tumor tissue values obtained with simulation measurements (Fig. 4, Table 2). The last column presents blood-flow values corrected for blood volume and partition-coefficient values. The latter were calculated on the basis of blood flow measured experimentally with

TABLE 3. MEASURED WATER CONTENTS IN RABBIT TISSUES

Tissue	Water content (%)
Leg muscle	82.4 ± 2.7
Blood	82.9 ± 1.5
Tumor	
surface area	85.0 ± 3.9
necrotic area	85.5

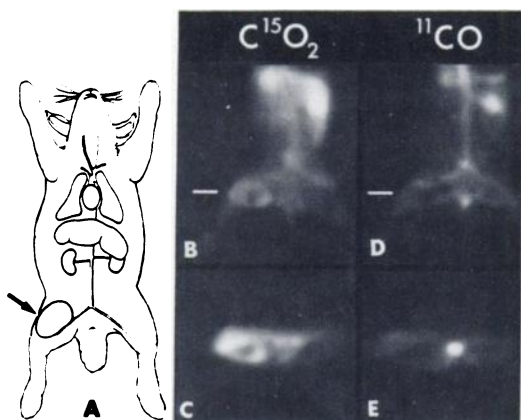


FIG. 4. Blood flow measured with $C^{15}O_2$ steady-state technique. (A) sketch of rabbit, arrow indicating tumor; (B) 2D-image and (C) 3D cut at middle level of tumor. Images D and E represent blood volume measured with ^{11}CO in same areas.

microspheres, and blood and tissue activities obtained with the $C^{15}O_2$ steady state, corrected for blood volume using ^{11}CO inhalation. The mean values of 0.94 ± 0.05 and 1.16 ± 0.15 were used for partition coefficients in normal and tumor tissues, respectively.

Table 2 shows the relation of tissue/blood volume and tissue/blood partition coefficient in the rabbit tumor model with the $C^{15}O_2$ steady-state method. Tissue blood volume in tumor was about three times that in normal tissue. Table 3 presents the measured water content of normal leg muscle, tumor, and blood. On the basis of our measurements, the total water content of normal tissue is lower than that of blood, whereas that of tumor tissue is higher. The area with the highest measured percentage of water is inside the tumor.

In Figure 4, B and C show 2D- and 3D-images of blood flow measured with the $C^{15}O_2$ steady state, and D and E the 2D- and 3D-images of blood volume measured with ^{11}CO . The increase of blood volume in the tumor area is evident. Figure 3 also indicates the sensitivity for tumor detection on the basis of increased blood flow, and indicate the imaging properties of the equipment used.

Figure 5 contains an anatomical line drawing of a rabbit. B is a conventional 2D-image of the distribution of water using the $C^{15}O_2$ steady-state technique; C is a quantitated tomogram at the middle level of the tumor; D and E are corresponding images obtained with Ga-68 microspheres. The necrotic area inside the tumor can be seen clearly with both techniques. However, the quantitative values of blood flow in the necrotic area found with positron imaging (5.0/min-100 cc) are clearly higher than those determined by in vitro measurements (2.9 ml/min-100 cc).

DISCUSSION

The $C^{15}O_2$ steady-state technique is a convenient and widely used method for measuring regional blood flow.

However, the quantitation is sensitive to three factors: the tissue's blood volume, the tissue/blood partition coefficient, and the magnitude of flow itself. The steady-state activity level achieved with the $C^{15}O_2$ steady-state technique has a nonlinear relation to blood flow (18). The nonlinearity is not so pronounced at low blood flow (<30 ml/100 cc-min), and in our experience the regional blood flow in soft-tissue tumors of muscle falls within this limit. Tissue blood volume can also be measured by other techniques, including $CO-11$ inhalation, but the partition coefficient is difficult to determine directly.

When the values for regional blood flow from the $C^{15}O_2$ steady state-technique are compared with those obtained from labeled microspheres, it can be seen that the mathematical model for the $C^{15}O_2$ measurements provides good estimates for healthy tissue but higher values than the microsphere measurements in tumor tissue. This is caused partly by the increased blood volume in tumor tissue and partly by the changed partition coefficient. We have attempted to resolve the value of the partition coefficient indirectly, basing our calculation on the relationship between tissue blood volume and tissue/blood partition coefficient using for blood flow the original values determined with microspheres. The values obtained for healthy tissue are near unity, the mean being 0.94 whereas the values for tumor tissue range between 1.05 and 1.27, the mean being 1.16. The change of the partition coefficient in tumor tissue is due mainly to the increased water transport across the cell membrane. The measured water content in necrotic tumor tissue is higher than that in other parts of tumor and in normal tissue. In estimating the tissue blood volume with Eq. (4), we have used for the average blood activity the values measured for arterial blood, and this may have caused a small overestimation of the final blood volume, even though the measurements were made

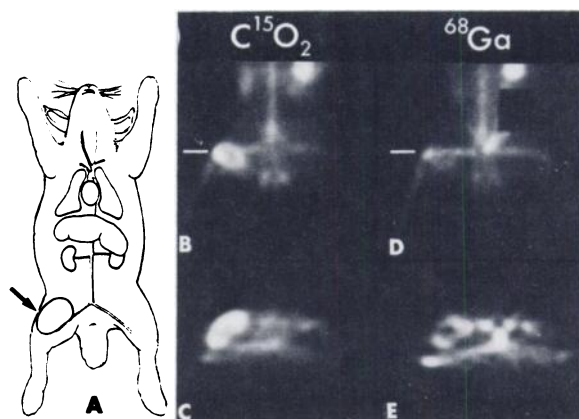


FIG. 5. Distribution of water in tumor: (A) sketch of rabbit, arrow indicating tumor; (B) and (C) 2D image of distribution of water using $C^{15}O_2$ steady-state technique and quantitative tomogram at middle level of tumor; (D) and (E) corresponding images obtained with Ga-68 microspheres.

at the steady state. The values for tissue blood volume obtained by means of simulation studies agree well with the values from CO-11 measurements. For the healthy tissue the range of all five measurements is 2.0–8.9%. There is one exceptionally high blood-volume value, and the range without that study is 2.0–3.4%. The tissue blood volume found with CO-11 measurements is 3.1. For tumor tissue the blood-volume values vary between 3.6% and 23.9%, with the highest value occurring in the same rabbit as that with the highest blood volume for the normal tissue. Based on our measurements, the blood volume on the surface of the tumor is 3.2 times that in normal tissue. This is the main reason for the difference in blood-flow measurements with microspheres and with the $C^{15}O_2$ technique.

If the $C^{15}O_2$ steady-state technique is used for blood-flow measurement of soft-tissue tumor, the values without correction for tissue blood volume are about 50% too high. The change in the partition coefficient has a smaller effect on the final results in tumor tissue, since the increased blood volume in the tumor area is caused mainly by the increased vascularity in the tumor.

In the healthy tissue we have not found any significant difference between the distribution of Ga-68 and of Sc-46 microspheres. In vitro, we have been able to measure the activities of both nuclides from the same sample. If we compare the blood-flow values of healthy tissue measured with Ga-68 under in vitro and in vivo conditions, the in vivo measurements from positron imaging tend to be slightly higher. That difference can be caused by technical problems. With low activity levels, scattering will be one source of error, and it is extremely difficult to select exactly the same portion of tissue in the positron image as that measured in vitro. An additional concern is that the count level of the measuring point in the necrotic tumor area is dependent on the nearby high activity of the surface area of tumor, because the size of the necrotic area is near the limit of resolution of imaging (32).

On the basis of our measurements, blood flow in tumor tissue is about three times that in normal tissue. Its quantitation might be useful both in determining the extent of soft-tissue tumor and in assessing the efficacy of therapy.

FOOTNOTES

* BIO-RAD Laboratories.

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REFERENCES

1. KETY SS, SCHMIDT CF: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. *Am J Physiol* 143:53–66, 1945
2. KETY SS, SCHMIDT CF: The nitrous oxide method for the quantitative determination of cerebral blood flow in man. Theory, procedure and normal values. *J Clin Invest* 27: 476–483, 1948
3. KETY SS: Theory of blood-tissue exchange and its application to measurement of blood flow. *Meth Med Res* 8:223–227, 1960
4. LASSEN NA, LINDBJERG F, MUNCK O: Measurement of blood flow through skeletal muscle by intramuscular injection of xenon-133. *Lancet* 1:686–689, 1964
5. LASSEN NA, HENRIKSEN L, PAULSON O: Regional cerebral blood flow in stroke by ^{133}Xe inhalation and emission tomography. *Stroke* 12:284–288, 1981
6. KUHLE DE, EDWARDS RQ, RICCI AR, et al: The Mark IV system for radionuclide computed tomography of the brain. *Radiology* 121:405–413, 1976
7. BROWNELL GL, CORREIA JA, ZAMENHOF RG: Positron instrumentation. In *Recent Advances in Nuclear Medicine*. Vol 5, Lawrence JH, Budinger TF, eds. New York, Grune & Stratton, 1978, pp 1–49
8. TER-POGOSSIAN MM, EICHLING PO, DAVIS DO, et al: The determination of regional cerebral blood flow by means of water labeled with radioactive oxygen 15. *Radiology* 93: 31–40, 1969
9. RAICHLE ME, MARKHAM J, LARSON K, et al: Measurement of local cerebral blood flow and metabolism in man with positron emission tomography. *Federation Proceedings* 40: 2331–2334, 1981
10. HUANG SC, PHELPS ME, CARSON RE, et al: O-15 water clearance method for measurement of local cerebral blood flow (LCBF) with positron computed tomography (PCT). *J Nucl Med* 22:P16, 1981 (abst)
11. ERIKSSON L, BOHM C, KESSELBERG M, et al: A four ring positron camera system for emission tomography of the brain. *IEEE Transactions on Nuclear Science*. Vol NS-29. No 1. pp 539–543, 1982
12. BURNHAM C, BRADSHAW J, KAUFMAN D, et al: A positron tomograph employing a one dimension BGO scintillation camera. *IEEE Transactions on Nuclear Science*. Vol NS-30. No 1. pp 661–664, 1983
13. RUSS GA, BIGLER RE, McDONALD JM, et al: Oxygen-15 scanning and gamma camera imaging in the steady-state. *J Nucl Med* 15:529–530, 1974
14. RUSS GA, BIGLER RE, TILBURY RS, et al: Whole body scanning and organ imaging with oxygen-15 at the steady-state. *World Federation of Nuclear Medicine and Biology*. First World Congress of Nuclear Medicine, Tokyo, Japan, 1974, pp 904–906
15. JONES SC, ROBINSON GD, ALAVI A, et al: Tandem van de Graaf accelerator production of positron labeled radiopharmaceuticals for clinical use. In *Nuclear Medicine and Biology Proc of the Third World Congress of Nuclear Medicine and Biology*. Reynaud C, ed. Paris, 1982, pp. 2120–2124
16. JONES T, CHESLER DA, TER-POGOSSIAN MM: The continuous inhalation of oxygen-15 for assessing regional oxygen extraction in the brain of man. *Br J Radiol* 49:339–343, 1976
17. WEST JB, DOLLERY CT: Distribution of blood flow and ventilation-perfusion ratio in the lung, measured with radioactive CO_2 . *J Appl Physiol* 15:405–410, 1960
18. SUBRAMANYAM R, ALPERT NM, HOOP B, et al: A model

- for regional cerebral oxygen distribution during continuous inhalation of $^{15}\text{O}_2$, C^{15}O , and C^{15}O_2 . *J Nucl Med* 19:48-53, 1978
19. ALPERT NM, ACKERMAN RH, CORREIA JA, et al: Measurement of cerebral blood flow and oxygen metabolism in transverse section—preliminary results. *Acta Neurol Scand* 60 (Suppl 72):196-197, 1979
 20. FRACKOWIAK RSJ, LENZI GL, JONES T, et al: Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: Theory, procedure and normal values. *J Comput Assist Tomogr* 4:727-736, 1980
 21. JONES T, RHODES CG, HEATHER JD, et al: The ability to measure quantitatively in three dimensions regional tissue metabolism and blood flow using oxygen-15 and a positron emission tomograph. IAEA Symposium on Medical Radionuclide Imaging. SM-247/23, Vol II, IEAE, Vienna, pp 323-332, 1981
 22. YIPINTSOI T, DOBBS WA, SCANLON PD, et al: Regional distribution of diffusible tracers and carbonized microspheres in the left ventricle of isolated dog hearts. *Circ Res* 33:573-587, 1973
 23. HEYMANN MA, PAYNE BD, HOFFMANN JIE, et al: Blood flow measurement with radionuclide-labeled particles. *Prog Cardiovasc Dis* 20:55-79, 1977
 24. WINCHELL HS, HORST WD, BRAUN L, et al: N-isopropyl- ^{123}I -p-iodoamphetamine: Single-pass brain uptake and washout; binding to brain synaptosomes; and localization in dog and monkey brain. *J Nucl Med* 21:947-952, 1980
 25. HILL TC, HOLMAN BL, LOVETT R, et al: Initial experience with SPECT (single-photon computerized tomography) of the brain using N-isopropyl I-123 p-iodoamphetamine: Concise communication. *J Nucl Med* 23:191-195, 1982
 26. PHELPS ME, HOFFMAN EJ, COLEMAN RE, et al: Tomographic images of blood pool and perfusion in brain and heart. *J Nucl Med* 17:603-612, 1976
 27. KUNG H, TRAMPOSCH K, WICKS R, et al: Synthesis and biodistribution of I-123 HIPDM: A new brain perfusion imaging agent. *J Nucl Med* 23:P22, 1982 (abst)
 28. KUNG HF, TRAMPOSCH KM, BLAU M: A new brain perfusion imaging agent: [I-123] HIPDM: N,N,N'-trimethyl-N-(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propanediamine. *J Nucl Med* 24:66-72, 1983
 29. HNATOWICH DF: Labeling of tin-soaked albumin microspheres with ^{68}Ga . *J Nucl Med* 17:57-60, 1976
 30. HNATOWICH DF: A method for the preparation and quality control ^{68}Ga radiopharmaceuticals. *J Nucl Med* 16:764-768, 1975
 31. BARTRUM RF, BERKOWITZ, DM, HOLLENBERG NK: A simple radioactive microsphere method for measuring regional flow and cardiac output. *Invest Radiol* 9:126-132, 1974
 32. BROWNELL GL, BURNHAM CA: A multicrystal positron camera. In *Instrumentation in Nuclear Medicine*. Vol. 2, Hine GJ, Sorenson JA, eds. New York, Academic Press, 1971, pp 136-159
 33. BROWNELL GL, BURNHAM CA, CHESLER DA: Transverse section imaging of radionuclide distribution in heart, lung and brain. In *Reconstruction Tomography in Diagnostic Radiology and Nuclear Medicine*. Ter-Pogossian MM, Phelps ME, Brownell GL, eds. Baltimore, University Park Press, 1977, pp 293-307
 34. FICK A: Uber die messung des blut quantums in den Herzventrikeln. *Verhandl. d. phys. med. Ges. zu Wurzburg* 2, XVI 1870 (Quoted in its entirety by Hoff HE and Scott HJ Physiology) *N Eng J Med* 239:122-123, 1948
 35. GLASS H, BRANT A, CLARK JC, et al: Measurement of blood volume using red cells labeled with radioactive carbon monoxide. *J Nucl Med* 9:571-575, 1968