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Myocardial Perfusion with Rubidium-82. I. Measurement of Extraction Fraction and Flow with External Detectors

Nizar A. Mullani, Richard A. Goldstein, K. Lance Gould, Salma K. Marani, David J. Fisher, Harold A. O'Brien, Jr., and Michael D. Loberg

University of Texas Medical School, and Graduate School of Biomedical Sciences, Houston, Texas, Los Alamos National Laboratory, Los Alamos, New Mexico, and E. R. Squibb and Sons

Accurate measurement of the regional extraction of a diffusible radiopharmaceutical is essential for the quantifying of regional blood flow, and may also provide an important physiologic or diagnostic indicator of the cellular viability of an organ in man through external detection by positron emission tomography. However, extraction fraction of a diffusible tracer usually decreases as flow increases, and thus noninvasive methods for measuring flow are nonlinear unless the extraction fraction can be measured independently. This report describes the theoretical basis and documents the applicability of this theory for determining, with external detectors, the first-pass regional extraction fraction of rubidium-82 by the heart, following a single intravenous bolus injection of the tracer. Measurement of extraction fraction was found to be independent of flow, thereby making it possible to determine accurately with a single intravenous bolus injection of rubidium-82, the regional blood flow in the myocardium at up to five times normal resting flow.

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Measurement of the regional extraction fraction (*1*) of a diffusible radioactive tracer in tissue is essential for the determination of the regional blood flow and the rate constants characterizing tracer uptake in that tissue. However, to date the only accurate method of measuring extraction fraction with a single injection of a tracer has required arterial and venous sampling in order to obtain the concentrations of the radiotracer in blood entering and leaving the organ. This approach is highly invasive, since it requires insertion of catheters into the arteries and veins of the organ of interest, and is therefore not applicable for routine diagnostic or investigative use. Furthermore, it does not permit measurement of regional differences in extraction but instead provides only an average extraction fraction for the whole organ, various parts of which may have widely divergent extractions.

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For reprints contact: Nizar A. Mullani, Div. of Cardiology, University of Texas Medical School, 6431 Fannin, Houston, TX 77025.

Accurate measurements of global extractions in animals have been obtained by the multiple indicator dilution technique developed by Chinard et al. (*2*). In this method two or more tracers are injected simultaneously and the venous outflow concentration of each is monitored. If one of the tracers is used as a reference, with known extraction characteristics, then the extraction of the second tracer can be evaluated. This technique has been extended to residue detection with external detectors, and is used extensively for measuring extraction fraction of such tracers as oxygen, glucose, and ammonia with positron emission tomography (PET) (*3*).

Partially extracted radiotracers have been used for measuring regional blood flow in man by assuming that flow and extraction are coupled as in the following equation (*4*)

$$FE = \frac{U_T(T)}{\int_0^T C_a(t)\,dt}, \qquad (1)$$

where $U_T(T)$ is the uptake of the radiotracer in an organ after a time T, $C_a(t)$ is the arterial blood concentration, F is the flow rate, and E is the extraction fraction of that tracer in the tissue. This equation assumes that there is no washout of the activity from the organ during the observation time, T. Extraction fraction is not constant for all flow values, and is in fact a complex function of the permeability and surface area of the diffusion membranes across which the tracer is extracted (*5*).

Raichle et al. (*6*) have used external detectors to obtain estimates of extraction fraction in the monkey brain: they applied the "B/A" method after single bolus intracarotid injections of a tracer, then compared the results with those obtained by the Fick principle. With the former approach, a small bolus containing tracer is injected in an artery close to the region of interest, and the peak counts registered by the external detector represent the total amount delivered to that region, whereas the amount of activity detected after the bolus has left the region represents the total amount extracted. However, the B/A method overestimates extraction fraction when used with intravenous bolus injections because A does not represent the total amount injected, due to recirculating tracer. Blood-flow measurements are therefore underestimated. Thus, it is reasonable to suggest that the B/A method is not applicable for measuring the extraction with a single i.v. bolus injection of a tracer.

In order to find a suitable method for estimating the extraction fraction of a tracer from a single i.v. bolus injection, we have developed a mathematical model to derive a first-pass extraction fraction ($E_{N/M}$) for measuring blood flow in the myocardium with rubidium-82 (*7*). Although it has been validated for the special case of Rb-82 uptake in the myocardium, the mathematical model presented here may be applicable to measuring extraction fraction of other radiotracers in different organs by external detectors.

THEORY AND METHODS

Extraction of rubidium in the myocardium. This has been studied extensively in the past 20 yr (*8–11*). To characterize the kinetics of rubidium transport from the blood to the cell, Sheehan and Renkin (*9*) proposed a three-compartment physiological model comprising (a) the vascular space, (b) interstitial space, and (c) cellular space. The transport of rubidium from one compartment to another can be described by the rate constants k_{12}, k_{21}, k_{23}, k_{32} (Fig. 1), where k_{12}, k_{21} represent the forward and backward transfer rates of tracer from the vascular to the interstitial space, and k_{23}, k_{32} those between the interstitial and the cellular space. Using paired-tracer techniques, Ziegler and Goresky (*10*) have shown that the major resistance to the transfer of rubidium from blood to cell occurs at the capillary and the cell membranes, and that the rate constants for the net transport of rubidium across these two boundaries are approximately equal under normal physiologic conditions. However, at elevated flows after coronary vasodilation, the rate constant characterizing the net transport of rubidium from vascular space to interstitial space is increased, whereas that for the uptake of rubidium by the cell from the interstitial space remains unchanged. Moreover, the constant k_{32} for the release of rubidium from the cell is very small and can be neglected if the observation time is shorter than 3 min (*10*).

The rate constant representing the net transfer of rubidium across the capillary membrane is related to the PS product (permeability × surface area), and the net extraction fraction, E, can be expressed as a function of P, S, and F as follows:

$$PS = -F \ln(1 - E),$$

where F is the flow in that region (*15*). Tancredi et al. (*12*) have measured the PS products for potassium, for the capillary membrane (PS_{cap}), and for the cell membrane (PS_{cell}) in isolated dog hearts, using a paired-tracer technique. However, to simplify measurements of extraction, Sheehan (*9*) has shown that a lumped PS product (PS_{1c}) can be used to represent the net transfer of a tracer from blood to cell, where

$$\frac{1}{PS_{1c}} = \frac{1}{PS_{cap}} + \frac{1}{PS_{cell}}.$$

This lumped PS product is related to the net extraction of rubidium by the cells from the blood by the following relationship:

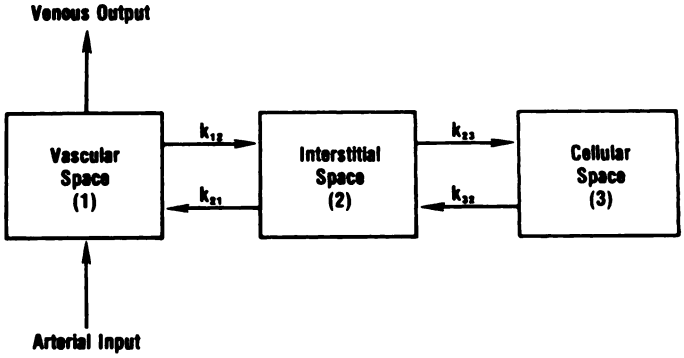

FIG. 1. Three-compartment anatomical model as proposed by Sheehan (*9*) for transport of rubidium from blood into cell. Compartments are (1) vascular space, (2) interstitial space, and (3) cellular space. Rate constants k_{12} and k_{21} describe forward and backward diffusion of rubidium across capillary wall, and k_{23} and k_{32} represent uptake and release of rubidium by cell from interstitial space. The rate constant for release of rubidium from cell, k_{32}, is quite small for normal myocardial cells and can be approximated by zero for studies that are shorter than 3 min.

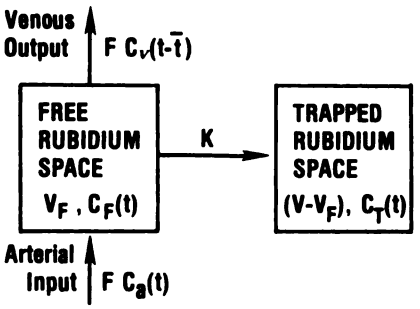

FIG. 2. Functional two-compartment model used by us to describe rate of uptake of rubidium from blood to cell. The three-compartment model of Fig. 1 has been reduced by using single lumped PS_{1c} product to represent net extraction of rubidium from blood into cell, with single net rate constant, k, for this transfer. F is flow to the region, $C_a(t)$ arterial concentration of rubidium, $C_v(t - \bar{t})$ venous concentration of rubidium, V_F volume of free rubidium space with concentration $C_F(t)$, and $(V - V_F)$ is volume of trapped rubidium space with concentration $C_T(t)$.

$$PS_{1c} = -F \ln(1 - E_{Rb}),$$

where E_{Rb} is the lumped extraction fraction.

The use of a lumped PS product suggests that the extraction of rubidium in the myocardium can be represented by a single extraction fraction, E_{rb}, and that the three-compartment physiologic model (Fig. 1) can be simplified to a functional two-compartment model (Fig. 2), where the two compartments are the cellular (trapped rubidium) space and the extracellular (free rubidium) space. A single rate constant, k, can then be used to represent the rate constant for the net transfer of rubidium from the free to the trapped rubidium space, since the egress of the rubidium from the cell is negligible if the duration of the study is shorter than 3 min (*10*). From here on we shall call these two compartments by their functional names, trapped rubidium space and free rubidium space. Based on this functional two-compartment model we shall develop a mathematical model for estimating the lumped extraction fraction, E_{Rb}, with external detectors, independent of measuring coronary flow.

First-pass extraction model. A radioactive tracer injected into the blood appears as a bolus of concentration, $C_a(t)$, at the anatomic region of interest under the detector. This tracer enters a sample volume, V, under the detector consisting of two functional compartments. The first is a free-tracer space, V_F, having a concentration of tracer, $C_F(t)$, that is determined by the arterial input, the venous washout, and the transfer of the tracer to the trapped space. The second compartment is a trapped-volume space, $(V - V_F)$, with tracer concentration $C_T(t)$, from which the radiotracer does not significantly wash out during data acquisition.

As the radiotracer accumulates in the trapped space, then at any time t, the count rate detected by an external probe or detector, P(t), measures the sum of the activities in the two compartments, thus:

$$P(t) = V_F C_F(t) + (V - V_F)C_T(t). \quad (2)$$

P(t) can also be expressed as the integral difference between the input and output to the volume V, i.e.,

$$P(t) = \int_0^t FC_a(x)dx - \int_0^t FC_V(x - \bar{t})dx, \quad (3)$$

where F is the blood flow through the probe's sample volume V, $C_v(t - \bar{t})$ is the venous concentration of radioactivity leaving the region, $\bar{t}$ is the minimum transit-time delay of the bolus for flow through the volume V, and x is a variable of integration. The transit-time delay is determined by several factors such as the bolus rise time, size of the volume being monitored, and the flow rate to that volume. Moreover, this transit-time delay is not single-valued but has a distribution of delay times determined by the variable lengths of the capillaries and the volume of distribution of the tracer (*13*).

The total amount of radioactivity, Q(t), that has been delivered to the probe's sample volume, V, at time t, is the sum of the radioactivity detected by the detector, P(t), plus the accumulated amount that has left the region of interest, expressed as:

$$Q(t) = P(t) + \int_0^t FC_v(x - \bar{t})dx. \quad (4)$$

Extraction fraction, as defined by Crone (*1*), is the ratio of the amount of radiotracer trapped to the total amount delivered. Then extraction fraction of the tracer at time, t, can be expressed as:

$$E(t) = \frac{(V - V_F)C_T(t)}{P(t) + \int_0^t FC_v(x - \bar{t})dx}. \quad (5)$$

This extraction fraction can also be expressed in terms of the arterial concentration by substituting Eq. (3) in the denominator of Eq. (5). Then,

$$E(t) = \frac{(V - V_F)C_T(t)}{F\int_0^t C_a(x)dx},$$

and once again E(t) is also a function of flow. Thus there are two unknowns, E(t) and F, that are difficult to measure separately with a single tracer unless some special conditions are imposed on the time at which these measurements are made.

If the time at which the extraction fraction is measured, t, is less than the transit-time delay, $\bar{t}$, then the radioactivity has not reached the venous space and all the activity delivered to that region is within the field of view of the detector. Thus $C_v(t - \bar{t})$ is equal to zero and extraction fraction in Eq. (5) can be expressed as

$$E(t) = \frac{(V - V_F)C_T(t)}{P(t)} \quad t < \bar{t}. \tag{6}$$

This general equation for measuring extraction fraction with external detectors can be used for most diffusible tracers as long as the condition that $t < \bar{t}$ is realized.

It is now necessary to determine under what practical conditions of extraction measurements the venous egress is zero or can be approximated by zero.

Differentiation of Eq. (3) yields:

$$\frac{dP(t)}{dt} = FC_a(t) - FC_v(t - \bar{t}), \tag{7}$$

and at peak-counts time, t_m, the first derivative

$$\frac{dP(t_m)}{dt} = 0.$$

From Eq. (7), the detector shows no change in count rate at time t_m, so the total in-flow and out-flow from that volume must be equal. Since the arterial input must equal the venous outflow, then if the arterial concentration is zero, the venous output must also be zero. That is,

$$FC_v(t_m - \bar{t}) = FC_a(t_m) = 0 \tag{8}$$

We have shown experimentally, for the case of intravenous bolus injections of Rb-82 to the myocardium (*14*), that $C_a(t_m)$ is close to zero for small rapid bolus injections of Rb-82 and that $C_v(t_m - \bar{t})$ can therefore be taken as zero. If $C_v(t_m - \bar{t}) \cong 0$ then at the peak-counts time, t_m, all the activity that has been delivered to the sample volume, V, is in the field of detection and $P(t_m)$ represents the total amount of tracer delivered to that volume in the first pass. Thus, for the special case of Rb-82 in the canine myocardium, it has been shown that the condition $C_v(t_m - \bar{t}) = 0$ is met for all practical purposes.

First-pass extraction fraction is then defined as the amount of tracer trapped in the region during the passage of the bolus when all the first-pass bolus has been delivered and none (or very little) has left that region. Therefore the first-pass extraction fraction can be expressed as:

$$E(t_m) = \frac{(V - V_F)C_T(t_m)}{P(t_m)} = \frac{N}{M}, \tag{9}$$

where N is the amount of radiotracer extracted into the trapped-space volume at time t_m, and M is the maximum count rate registered by the external detector. This extraction fraction, $E_{N/M}$, is the first-pass unidirectional extraction of a tracer in the region of interest before any recirculation or egress of the tracer occurs from that region.

The B/A extraction fraction can be mathematically expressed as follows:

$$E_{B/A} = \frac{(V - V_F)C_T(T)}{P(t_m)} = \frac{B}{A}. \tag{10}$$

While the B/A method may not be applicable for measuring the extraction fraction with i.v. bolus injections, it is one of the methods used for measuring extraction fraction with a single injection of a tracer. We shall therefore measure extraction fraction by the B/A method (as well as our method) to demonstrate that the B/A method is not applicable for i.v. injections of Rb-82. For this tracer and the myocardium, we have found that when the $E_{N/M}$ extraction is used in Eq. (1), the resulting flow values correlate linearly with flows determined by the microsphere method. We shall therefore assume that the first-pass extraction fraction, $E_{N/M}$, as formulated in this text, is appropriate, and will present a method for measuring it with external detectors.

Application of the extraction model to rubidium-82 in the heart. In order to estimate the amount of Rb-82 extracted into the trapped space, it is necessary to model the first-pass kinetics of the radioactivity in the detector's sample volume. This model was developed using an approximation for the concentration $C_F(t)$ in the free space, based on the shape of P(t) obtained with an intravenously injected bolus of Ga-68 EDTA in the myocardium. Since the EDTA molecule does not enter into the myocardial cell but merely crosses the capillary wall into the interstitial space (*15*), a major portion of the bolus passes through the region of interest.

Based on these data, the concentration of tracer in the free space was found to be adequately described by the following equation:

$$C_F(t) = bte^{-at}, \tag{11}$$

where b and a are constants that determine the scaling factor and the decay rate of the concentration curve.

This function is therefore used to approximate the shape of the free concentration activity curve for a Rb-82 bolus injection in the heart. The rate of change of the concentration of the radiotracer in the trapped space, $C_T(t)$, is proportional to the concentration of tracer in the free space as expressed by:

$$\frac{dC_T(t)}{dt} = kC_F(t), \tag{12}$$

where k is the rate constant for the net transport of the radiotracer from the free tracer space to the trapped space and is assumed to be constant for the duration of the data collection. With integration of Eq. (12) and substitution for $C_T(t)$ in Eq. (2), P(t) can be expressed as:

$$P(t) = V_F C_F(t) + (V - V_F)k \int_0^t C_F(x)dx \tag{13}$$

Substitution of Eq. (11) for $C_F(t)$ into Eq. (13) yields:

$$P(t) = V_F bte^{-at} + (V - V_F)k \int_o^t bxe^{-ax}dx \quad (14)$$

This can be simplified to

$$P(t) = b_1 te^{-at} + b_2 \int_o^t te^{-ax}dx \quad (15)$$

where $b_1 = V_F b$ and $b_2 = (V - V_F)kb$

Equation (15) expresses activity in the sample volume of a detector as the sum of an input function or free-space activity (the first term) and the accumulated, trapped radiotracer (the second term).

Experimental protocol and data analysis. Ten mongrel dogs were studied with beta probes (*16*) to acquire the data for the validation of this model. Under anesthesia, a left thoractomy exposed the heart, and catheters were inserted into the left atrium, femoral vein, and the ascending aorta. Myocardial blood flow was varied from 0.1 to 4.7 ml/min/g by a combination of constricting the LAD artery and injections of dipyridamole and phenylephrine. Two beta probes were placed against the myocardium to record the radioactivity during the injection of a bolus of Rb-82. These beta probes are thin plastic scintillators (a disk 10 mm in diam by 3 mm thick disk of Ne 104 scintillators coupled to a photomultiplier tube), which have a high detection efficiency for the positrons from Rb-82 and low efficiency for the annihilation radiation. Since the positrons have a limited range in tissue (*17,18*) only a small volume of the myocardium (10 mm in diameter by approximately 3 mm deep) can affect the beta probes. One of the beta probes was faced with lead sheet 1 mm thick, which blocks the positrons but allows the annihilation radiation to be detected so that it can be used to monitor the background radiation levels during a study. The pulses from the beta probes were amplified and energy selected at approximately 350 keV. The accepted events were then counted in a dual scaler and transferred to a computer at intervals of 1 sec. Before each experiment, the beta probes were calibrated, with and without lead, using a uniform source of Rb-82, to compute the correction factors for the detection efficiency of each detector.

The Rb-82 chloride tracer was obtained from a Sr-82 → Rb-82 generator (*19*) by eluting it with 0.9% NaCl solution. A 10-cc bolus of this tracer was injected into the femoral vein as fast as possible, followed immediately by a 10-cc bolus of saline solution to flush the catheter. Approximately 0.5 to 2.0 mCi of Rb-82 was used with each injection, depending on the age of the generator. During each study, arterial blood was withdrawn at a constant rate from the ascending aorta, using a Harvard pump, for a total of 150 sec. At the end of this period, the withdrawn blood was transferred to a beaker and, starting at 180 sec after the injection of the tracer, the two beta probes were used to measure the arterial concentration of the blood in the beaker.

Myocardial blood flow was also measured simultaneously by the labeled microsphere technique (*20*). Each measurement was done with microspheres 15 μm in diameter, labeled with one of the following radionuclides: Co-57, Sn-113, Sr-85, Nb-95, and Sc-46. The micro-

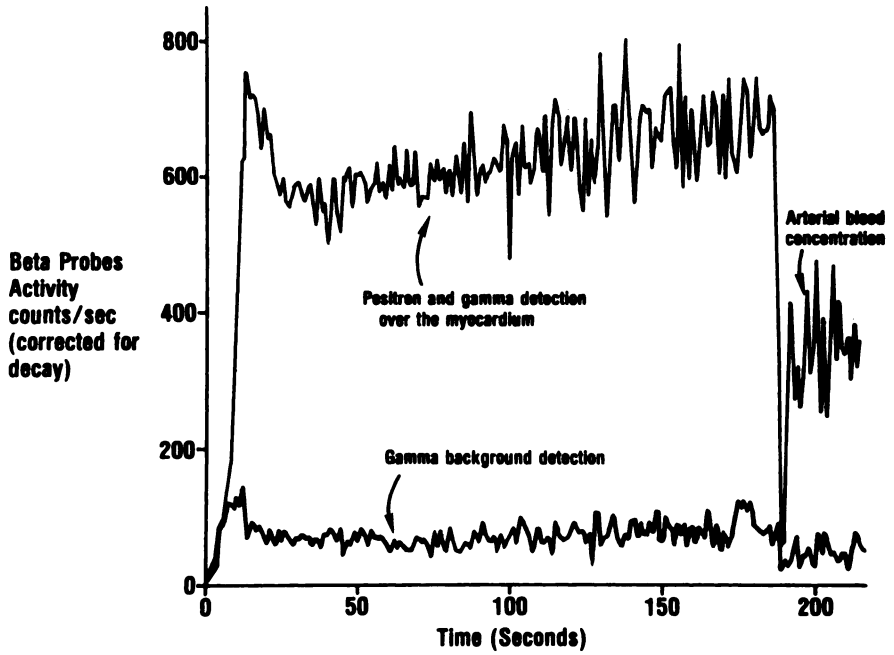

FIG. 3. Example of data collected by two beta probes over myocardium during intravenous bolus injection of Rb-82 chloride. Data are corrected for Rb-82 decay. Top curve represents total activity monitored by one beta probe, and bottom curve background photon radiation detected by beta probe faced with lead. At end of 150-sec data collection period, both probes are placed over beaker containing collected arterial blood, to measure average arterial concentration of Rb-82. Injection of tracer is at zero time.

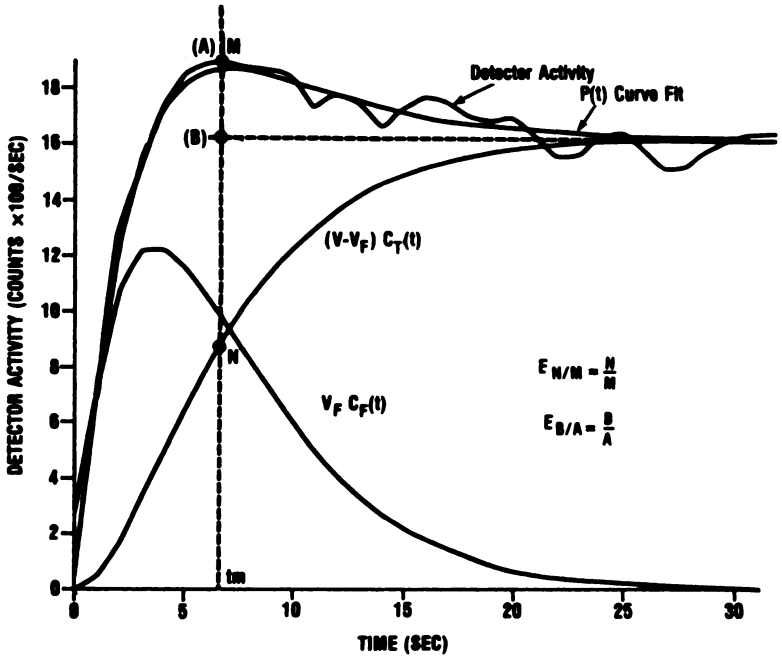

FIG. 4. Example of curve fitted to observed data from beta probe positioned over myocardium, P(t), using Eq. (15). Probe data are decomposed into free-rubidium activity $V_FC_F(t)$, and trapped rubidium activity $(V - V_F)C_T(t)$, as discussed in text. Also shown are two techniques that have been used to estimate first-pass extraction fraction, $E_{N/M}$, and B/A extraction fraction, $E_{B/A}$.

spheres were injected into the left atrium during each rubidium study and the arterial concentration of the microspheres was obtained from the same blood withdrawn for the rubidium study. Samples of the myocardium under the beta probe, ~3 mm thick, were obtained and blood flow was computed for that volume for each of the labeled microsphere injections. Based on the measured ratio of counts per microsphere, we calculated that at least 1600 microspheres were present in each sample, thus providing a statistical accuracy of ±5% (*21*).

Data from each rubidium study were first corrected for the physical decay of Rb-82, and the photon background was subtracted (with appropriate corrections for the detection efficiencies of each detector) from the beta probe activity. Figure 3 shows typical precordial curves (corrected for decay) obtained by each beta probe for a Rb-82 injection.

The background-subtracted data were then smoothed using a three-point smoothing algorithm, and Eq. (15) was fitted to the initial 30–40 sec of the data using a Gauss-Newton least-squares algorithm. The curve-fitting algorithm was reproducible given the appropriate range of starting values for a, b_1, and b_2. For the case where the blood flow was low due to imposed ischemia, the data had to be smoothed with a five-point smoothing algorithm to average out the random noise.

Each detector's activity curve was decomposed into the free rubidium activity, $V_FC_F(t)$, and the trapped rubidium activity, $(V - V_F)C_T(t)$, as demonstrated in Fig. 4, which also shows an example of the curve-fit, P(t), to the detector's activity data. Extraction fraction, $E_{N/M}$, was computed by dividing the instantaneous trapped rubidium activity, N, at the peak-count time, t_m, by the peak counts, M, registered by the detector. The $E_{B/A}$ extraction fraction was obtained by back extrapolation of the probe data from their plateau value at the end of the 25-sec period to obtain B, then dividing it by the peak counts, A, at time t_m.

Flow by the rubidium method was computed from Eq. (1) for each of the studies using the extraction fraction $E_{N/M}$ obtained from the curve-fitting algorithm. The arterial blood sample was withdrawn for 150 sec so as to minimize errors due to the recirculating tracer. Myocardial uptake of Rb-82 at that time was used to compute the flow, assuming that loss of rubidium from the cell is minimal at that time. It is assumed that the free rubidium concentration at that time is negligible relative to the trapped rubidium activity, and therefore the beta-probe activity represents the myocardial concentration of rubidium. Also, since the same beta probes were used to count the myocardial uptake and the arterial blood concentration of Rb-82, the detection efficiencies for these two readings are the same and therefore cancel out when flow is computed. Thus regional blood flow is obtained by dividing the myocardial uptake counts at 150 sec by the product of the extraction fraction and the integrated arterial concentration up to that time.

RESULTS

The uptake of Rb-82 cation in the myocardium has been shown by Budinger et al. (*22*) and Selwyn et al. (*11*) to be related nonlinearly to blood flow, due to the decrease in extraction fraction of rubidium at high flow rates. We have measured the extraction fractions $E_{(N/M)}$ and $E_{(B/A)}$ for rubidium in the myocardium as a function

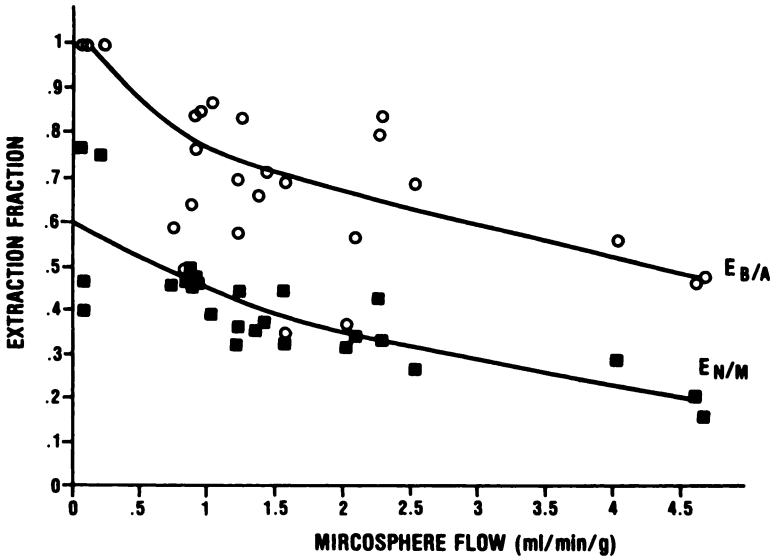

FIG. 5. Extraction fraction of Rb-82 in myocardium as function of flow rates, determined by microsphere method. B/A method overestimates extraction, whereas the N/M method produces smaller extraction values. Myocardial blood flow as measured by Rb-82 using N/M extraction fraction correlates linearly with blood flow determined by labeled microspheres at up to five times normal flow rates (cf. Fig. 6).

of flow, and these are plotted in Fig. 5. As predicted, the extraction fractions decrease with higher flow rates. However, the $E_{B/A}$ extraction fraction is overestimated. Average extraction fractions at normal resting flow rates (0.75–1.5 ml/min/g) were found to be 0.68 ± 0.148 for the B/A method and 0.415 ± 0.059 for the N/M method. Extraction fractions measured at very low (ischemic) values of flow have a larger random error due to the reduced amount of rubidium reaching the region of interest.

Myocardial blood flow, determined using the B/A extraction fraction, results in a nonlinear relationship compared with microsphere-determined flow (Fig. 6). However, flow determined by the N/M extraction fraction results in a linear relationship against microsphere-determined flow up to five times the average resting control flow. The regression equation was found to be $F_{rb} = 0.216\ (\pm 0.081) + (0.867 \pm 0.41)F\mu$, where F_{rb} is the flow measurement by Rb-82 using the first-pass extraction fraction, and $F\mu$ is the flow measured with microspheres. The regression coefficient for n = 26 was found to be r = 0.974 ($p < 0.001$). If the intercept is forced to zero, the slope of the regression line is then changed to 0.95 thus indicating that the low flow estimates have a larger random error. The slope of the regression line shows an underestimation of flow by the rubidium method, which may indicate that at high flow rates the $E_{N/M}$ extraction fraction is slightly overestimated. This error would occur if M, representing the total amount delivered, is underestimated due to either the partial egress of the bolus at the peak-count time t_m, or to a lower value of M produced by the smoothing algorithm. This needs further research.

DISCUSSION

The mathematical formulation for estimating extraction fraction by external detectors, and its application to a diffusible tracer such as Rb-82, show for the first time that flow and extraction can be accurately uncoupled in Eq. (1) with a single i.v. bolus injection. These results demonstrate that the first-pass extraction

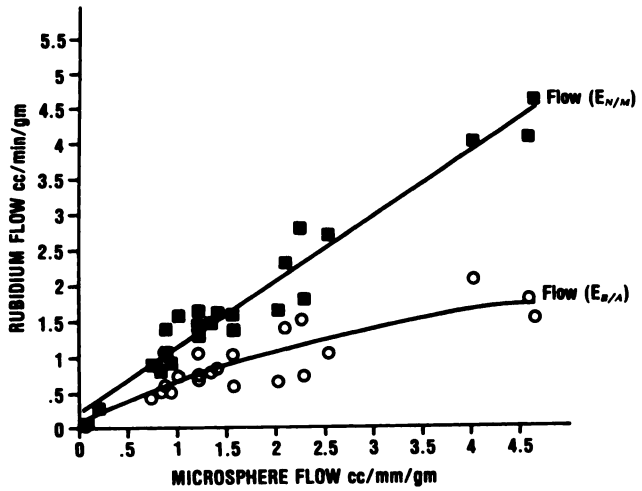

FIG. 6. Comparison of flow values obtained with first-pass, $E_{N/M}$, extraction fraction and $F_{B/A}$ extraction fraction, plotted against flow as measured with labeled microspheres. Rubidium-measured flow (F_{rb}) using first-pass extraction fraction is linearly related to microsphere-measured flow: $F_{rb} = 0.216\ (\pm 0.081) + (0.867 + 0.041)F\mu$; regression coefficients are n = 26, r = 0.974, and $p < 0.001$. Slope of regression line changes to 0.95 if intercept is force-fitted to zero.

fraction, $E_{N/M}$, should be used when estimating the regional flow by Eq. (1) with i.v. bolus injections of Rb-82. This technique may be applicable with several other diffusible tracers such as palmitate and oxygen, where an accurate estimate of the first-pass extraction fraction and the rate constant k are important physiological indicators of metabolic activity.

The concept of a functional model that decomposes the observed detector response into a free tracer concentration and a trapped concentration may not be valid for all diffusible tracers. However, for Rb-82 in the myocardium it is a simple, accurate way of modeling the fate of that tracer as it passes through the region. Proof of its validity has been shown by the excellent curve fit that is obtained with the observed activity, and the resulting linear relationship obtained between flow measurement made with microspheres and Rb-82.

Uncoupling extraction fraction from flow can also be achieved by measuring flow either independently with another tracer, or by the peak-count flow model of Mullani and Gould (*14*) with the same tracer. Once flow is determined, the extraction fraction can be calculated quite easily. Since the lumped extraction fraction is related to the lumped PS product for transport of a tracer from blood to cell, there exists the possibilty of assessing myocardial viability by measuring extraction fraction and computing this PS value under different physiological conditions.

The use of generator-produced Rb-82, together with PET recording, will make regional assessment of extraction fraction and flow more accessible to other researchers. Perfusion imaging of the myocardium at high flows may provide a very sensitive test for the detection of early coronary artery disease in man, as demonstrated by Gould (*23*). Measurement of extraction of rubidium in the brain to assess the viability of the blood-brain barrier has already been proposed by Yen et al. (*24*), and with a quantitative method of estimating the regional PS product it may become important in tumor or stroke therapy. There are also strong indications that rubidium will be useful for measuring blood flow and extraction in the kidneys and the liver. The application of Rb-82 to other organs such as the lungs and the spleen needs to be explored with this method for determining blood flow and extraction fractions.

We must express some caution in applying this dynamic model to PET imaging. There are several issues, such as sensitivity of the PET cameras, bolus sizes required for man, and cardiac gating, that need to be studied in detail before quantitative regional perfusion imaging can be achieved with PET and Rb-82. Some simplifications and approximations may need to be made to the model for application to PET imaging. As an example, in order to reduce the complications of computing the least-squares fit for each region of the myocardium, we can show that the amount of rubidium extracted by the myocardium during the first pass of the tracer can be expressed in terms of the known arterial concentration as follows:

$$\frac{(V - V_F)C_T(t_m)}{\int_0^{t_m} C_a(t)dt} = \frac{(V - V_F)C_T(T)}{\int_0^{T} C_a(t)dt} \quad \text{for } T \gg t_m.$$

Since the model shows that the concentration of free rubidium is quite small relative to the trapped rubidium concentration after a long time, T, then from Eq. (2) we can make the approximation that $V_F C_F(T) \cong 0$ and

$$P(T) \cong (V - V_F)C_T(T)$$

Thus, an estimate of the amount of rubidium extracted by the myocardium at the peak-count time, t_m, can be obtained from the above relationship without curve fitting,

$$(V - V_F)C_T(t_m) = \frac{P(T)\int_0^{t_m} C_a(t)dt}{\int_0^{T} C_a(t)dt}.$$

If the peak counts $P(t_m)$ are accurately known, the first-pass extraction fraction $E_{N/M}$ can easily be computed using Eq. (9) without the need for a complicated curve-fitting algorithm. Whether the peak counts can be measured accurately with the existing PET cameras is an issue that needs further study.

Since the peak-count flow model (*14*) and this model require an accurate estimate of the peak counts recorded during the first pass of a tracer through the region, the accuracy of the flow measurement will be determined by how well the peak counts are measured. From our observations of the beta-probe data, the peak-count time, t_m, ranges from 3 to 25 sec, depending on the flow rate to that region. Thus a very short time is available to measure the peak count, which may be further complicated by the need to gate the data collection with the cardiac cycle and/or wobble the detectors in PET for finer sampling. A modification of the single-bolus injection technique used here may be required to extend the total data-collection time that would be needed to measure peak counts accurately. One such scheme may use several bolus injections (sequential, pulsed injections) separated by approximately 30 sec, which with an appropriate model could average the peak counts collected for each injection. The advantage of this approach is that at any one time only a small bolus of tracer is injected and therefore the error due to random coincidences can be kept low. The effects of gating and wobbling are averaged for a longer time, thereby reducing the sampling errors. This technique is now being studied by the authors for application with the TOFPET I (*25*) positron camera together with methods of improving the statistical accuracy of the peak count by integrating the

data during the rise time of the myocardial activity curve.

Finally the validity of this model and its application to measurement of myocardial blood flow and extraction remain to be established—especially under a wide range of conditions such as ischemia, acidosis, alkalosis, etc.—before its application as a diagnostic research tool can be trusted.

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