Noninvasive Quantification of Regional Myocardial Perfusion With Rubidium-82 and Positron Emission Tomography
Exploration of a Mathematical Model

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Positron emission tomography (PET) centers without cyclotrons use generator-produced rubidium-82 ($^{82}$Rb) for assessment of myocardial perfusion. The aim of the present study was to determine whether myocardial blood flow could be assessed quantitatively with $^{82}$Rb and PET. Because the myocardial extraction fraction of $^{82}$Rb varies inversely and nonlinearly with flow and cannot be measured conveniently with PET, we used an experimentally derived mathematical function defining the relation between single-pass extraction fraction of $^{82}$Rb and flow to obviate the necessity of measuring the extraction fraction directly. Myocardial blood flow in absolute terms (ml/g/min) was estimated from dynamic PET scans after intravenous administration of $^{82}$Rb in intact dogs and compared with flows measured with radiolabeled microspheres. In 36 comparisons in 13 dogs studied at rest, or after coronary occlusion, reperfusion, or after coronary hyperemia induced with intravenous dipyridamole, over the flow range from 0.2 to 2.0 ml/g/min, estimates of perfusion with rubidium correlated well with flows measured concomitantly with microspheres, although there was a slight underestimation of flow with rubidium (flow by $^{82}$Rb=0.92×flow by microspheres−0.021, r=0.83). In general, estimates of flow in ischemic regions were less reliable than estimates for regions with normal flow. Thus, although the relation between myocardial extraction and retention of $^{82}$Rb and flow can vary under a variety of physiological and pathophysiological conditions, this study demonstrates the ability to obtain quantitative estimates of myocardial blood flow with $^{82}$Rb and PET under carefully defined conditions without measuring the extraction fraction directly. (Circulation 1990;82:1377–1386)

Noninvasive assessment of myocardial perfusion is of major importance for the detection of ischemic heart disease and for objective evaluation of the efficacy of treatments designed to augment blood flow. Nonetheless, absolute quantification of regional myocardial perfusion with scintigraphy using single-photon emitting radionuclides such as thallium-201 has been difficult to achieve because of the nonphysiological nature of the agents used and the physical limitations of conventional scintigraphic imaging.1

Positron emission tomography (PET) overcomes many of these limitations because of its capability to quantitatively measure the distribution of positron emitting radionuclides within organs of interest and is an attractive tool for the characterization of myocardial perfusion and metabolism when physiological meaningful tracers are used. When mathematically appropriate models are used to describe the biological behavior of the radiotracers, regional determinations of blood flow and metabolism can be made from analysis of the concentrations of the tracer in blood and cardiac tissue.

We and others have previously demonstrated that myocardial perfusion can be measured accurately with radiolabeled H$_2$O using a one-compartment mathematical model when the input function and tissue radioactivity were measured directly.2,3 More recently, we developed and implemented an approach that incorporates partial volume and spill-over corrections as parameters to be estimated within the operational equation in addition to flow and showed that myocardial perfusion can be determined
Cardiac centers without cyclotrons use generator-produced rubidium-82 chloride (\(82\text{Rb}\)) for estimates of myocardial perfusion. \(82\text{Rb}\) is a short-lived, positron emitter with a half-life of 75 seconds. Although \(82\text{Rb}\) has been used extensively for qualitative myocardial imaging,\(^6\)–\(^8\) quantitation of myocardial perfusion with \(82\text{Rb}\) is associated with a number of difficulties. Similar to other cationic flow markers such as thallium-201 and nitrogen-13 ammonia, \(82\text{Rb}\) is only partially extracted by the myocardium after a single capillary pass (i.e., extraction is flow limited).\(^1\) Thus, the extraction of rubidium into the myocyte is inversely and nonlinearly proportional to flow.\(^9\)–\(^11\) In addition to this inverse relation between flow and extraction fraction, Goldstein et al.\(^10\) demonstrated that the single-pass extraction fraction was also sensitive to changes in arterial pH, although other metabolic interventions such as \(\beta\)-blockade, administration of glucose and insulin, and inhibition of the Na-K ATPase pump did not significantly affect the relationship. These results were recently corroborated by Huang et al.\(^11\) Other investigations\(^9\)–\(^12\)–\(^14\) have demonstrated drugs that affect the Na-K ATPase such as ouabain or metabolic conditions such as prolonged ischemia and reperfusion do alter the extraction and retention of rubidium by the heart irrespective of plasma flow rates.

Accordingly, to quantify myocardial perfusion with \(82\text{Rb}\), the extraction fraction must be known accurately. Although \(82\text{Rb}\) extraction fraction has been measured in studies in open-chest animals using \(\beta\)-probes and a first-pass model,\(^10\)–\(^14\) extraction fraction is extremely difficult to measure noninvasively with current PET systems because of limited temporal resolution and the inconvenience of administering a bolus into the coronary artery for routine applications. When \(82\text{Rb}\) is administered intravenously, the input into the coronary artery is dispersed and tracer leaves the region of interest before achieving a maximum value, thereby violating one of the major assumptions of the first-pass model.\(^1\)

Because quantification of myocardial perfusion in absolute terms with PET is desirable and may be necessary for evaluating patients with multivessel disease in whom no “normal” area of the heart can be identified, in the present study we evaluated an approach for quantifying myocardial perfusion with \(82\text{Rb}\) that does not require direct measurement of the extraction fraction.

**Mathematical Basis of the Approach**

For partially extracted radiotracers, flow can be defined by the following equation:

\[
F = \frac{C_M(T)}{E \int_0^T C_a(t) \, dt}
\]

where \(C_M(T)\) is the uptake of the radiotracer in the myocardial tissue at time \(T\), (CPM/g), \(C_a(t)\) is the arterial blood concentration (CPM/ml), \(F\) is the flow (ml/g/min), and \(E\) is the extraction fraction of that tracer in the tissue. This model, which is based on Fick’s principle, assumes that tracer does not leave the cell during the data acquisition period.

Mullani et al.\(^15\) measured the first-pass extraction fraction of \(82\text{Rb}\) by the heart in open-chest dogs using external probes placed directly over the heart after an intravenous bolus injection of the tracer. They developed a mathematical model for estimating the \(82\text{Rb}\) extraction fraction based on a functional two-compartment model, and found that the relation between flow and extraction could be defined by the following equation:

\[
E = 0.55 \exp(-0.22 \times F)
\]  

If we assume that under carefully defined conditions, the relation between flow and extraction given by Equation 2 is valid, we can incorporate Equation 2 into Equation 1 to obtain

\[
F(0.55 \exp(-0.22F)) = \frac{C_M(T)}{\int_0^T C_a(t) \, dt}
\]

where now flow, \(F\), can be estimated if the tissue activity at time \(T\), \(C_M(T)\) and the arterial activity \(C_a(t)\) over period \(T\) can be measured with PET.

Although the arterial input function can be obtained accurately noninvasively by placing a region of interest in the region of the left atrial (or left ventricular) blood pool, tissue activity cannot be measured directly with PET because of partial volume and spillover effects. Partial volume, the underestimation of true tracer concentration, and count spillover, the contamination of activity in one region due to radioactivity from an adjacent one, are observed when imaging an object small with respect to the resolution of the tomograph. Thus, PET myocardial activity must be corrected by partial volume and spillover effects before Equation 3 can be used to estimate flow. These corrections can be accomplished by using the relation given by Equation 4.

\[
C_M(T) = \frac{C_{PET}(T) - F_{BM} C_a(T)}{F_{MM}}
\]

where \(C_M(T)\) is the true tissue activity at time \(T\), \(C_{PET}(T)\) is the observed PET tissue activity at time \(T\), \(C_a(T)\) is the blood pool activity at time \(T\), \(F_{MM}\) is the recovery coefficient of the tissue activity, and \(F_{BM}\) is the fraction of blood pool activity observed in the tissue. By replacing Equation 4 into Equation 3 we obtain

\[
F(0.55 \exp(-0.22F)) = \frac{C_{PET}(T) - F_{BM} C_a(T)}{F_{MM} \int_0^T C_a(t) \, dt}
\]
Thus, flow can be estimated directly from PET tissue and blood pool activity given that $F_{MM}$ and $F_{BM}$ are known. Although we have previously demonstrated that values for the partial volume and spill-over correction factors can be calculated from dynamic PET data using parameter estimation techniques,\(^4,5\) for the purposes of this study, we used fixed average values of 0.72 for $F_{MM}$ and 0.14 for $F_{BM}$. Averages were computed from a large number of values obtained in previous dog studies from our laboratory.\(^4\) Although $F_{MM}$ and $F_{BM}$ can and do change with conditions such as ischemia and reperfusion and can be estimated within the operational equation using some mathematical models,\(^4,5\) $F_{MM}$ and $F_{BM}$ cannot be estimated within the operational equation used in this study for rubidium because tissue tracer concentration is only measured at one (averaged) time point.

The relationship between uptake (the product of flow and extraction fraction) versus flow computed from Equation 2 is shown in Figure 1. The plot demonstrates the relation is almost linear for flows less than 1.5 ml/g/min but for flows greater than 2.5–3.0 ml/g/min, increases in flow lead to smaller and smaller changes in $^{82}$Rb uptake, and after a flow of approximately 4.0 ml/g/min, net uptake may actually decrease. Thus, at high levels of perfusion, a unique estimation of flow is not possible. Accordingly, this approach is insensitive for high flows.

The aim of the present study was to evaluate the ability to use the previously derived relation between extraction fraction and flow to obviate the need to estimate extraction fraction directly to estimate flow noninvasively using $^{82}$Rb and PET in dogs at rest, after myocardial ischemia and reperfusion, or in dogs with coronary stenosis, after mild hyperemia.

**Methods**

**Experimental Protocol**

Thirteen conditioned dogs were sedated with 1 mg/kg morphine subcutaneously after an overnight fast and anesthetized with 12.5 mg/kg of thiopental and 72 mg/kg of $\alpha$-chloralose administered intravenously. The dogs were intubated and ventilated with room air. One dog was studied without any intervention. In six intact dogs, regional ischemia was induced in the left anterior descending coronary artery by placement of a thrombogenic intracoronary copper coil as described previously.\(^16\) These dogs were studied 2 hours after angiographically documented occlusion. To evaluate the effects of transient occlusion, three other dogs were studied after a 15-minute occlusion of the left anterior descending coronary artery followed by reperfusion. In these dogs, transient occlusion was induced using a balloon catheter after full anticoagulation. In three additional intact dogs, coronary stenosis of 50–70% diameter narrowing was induced by placement of an intracoronary plastic stenosis in the left anterior descending coronary artery after anticoagulation with 500 IU/kg heparin i.v. as described previously.\(^17\) In dogs with coronary stenosis, and in two dogs with coronary occlusion, myocardial hyperemia was induced with intravenous dipyridamole infused at a dose of 0.14 mg/kg/min for 4 minutes. Flow estimates were made 4–5 minutes after completion of the infusion.

**Positron Emission Tomography**

Dogs were placed in a Plexiglas shell and positioned within PETT VI, a positron emission tomograph that permits the simultaneous acquisition of seven transverse tomographic slices with a slice-to-slice distance of 1.44 cm, a slice thickness of 1.39 cm,\(^18\) and a reconstructed resolution of 12.0 mm (full width at half maximum).\(^4\) A transmission scan, necessary for attenuation correction, was obtained using an external ring of germanium-68/gallium-68. To permit delineation of the blood pool, dogs inhaled 20–40 mCi of C$^{15}$O to label red blood cells in vivo. After a 30-second delay to allow residual C$^{15}$O to clear the lungs, emission data were acquired for 5 minutes. After completion of the C$^{15}$O data collection, 5 additional minutes were allowed for the decay of oxygen-15 ($t_{1/2}=2.04$ min). Then 30–40 mCi of

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Plot of relation between uptake of $^{82}$Rb (flow times extraction fraction) versus flow obtained when the extraction fraction is defined by Equation 2 (see text). It should be noted that for flow values greater than 2.5–3.0 ml/g/min increases in flow lead to smaller and smaller changes in $^{82}$Rb uptake indicating that the approach is insensitive at high flows.
generator-produced $^{82}$Rb (a gift from the Squibb Diagnostics Division of E.R. Squibb and Sons, Inc.) were administered intravenously. This was accomplished by eluting the generator into a 20-ml syringe, and after the desired radioactivity had been eluted, the tracer was administered by hand during 3–5 seconds in a total volume of 5–15 ml. Tomographic acquisition was initiated at the time of administration of the $^{82}$Rb and continued for 380 seconds. Data was collected in 5-second frames for the first 90 seconds after tracer administration, and in 30-second frames for the next 290 seconds. The arterial input function was obtained in seven studies in five dogs by monitoring the time-activity curve from a catheter exteriorized from the thoracic aorta by the femoral artery. The total volume of the catheter was less than 1.5 ml, and during data acquisition, the blood was allowed to flow freely from the catheter. Measured flow rates were never less than 20 ml/min so that the maximal delay from the tip of the catheter to the probe was less than 5 seconds. In addition, because of the high flow rates, dispersion was minimal. In these studies, arterial radioactivity was detected with a collimated gamma scintillation probe, and data were acquired on a minicomputer for subsequent analysis. The energy discriminator of the gamma probe was set to greater than 800 keV so that radioactivity from annihilation photons were not detected. In addition, the detector was shielded by more than 4 inches of lead so that background radioactivity in the catheter was zero even after administration of 40 mCi of radioactivity into the intact dog. For all the other dogs, the input curve was obtained noninvasively from a region of interest placed within the left atrial blood pool in reconstructed images.

The results of measurement of blood flow in absolute terms obtained with PET were compared with those obtained with radiolabeled 15-$\mu$m microspheres (3-M) administered concomitantly by a retrogradely placed left atrial catheter. While microspheres were administered, blood from a femoral artery was withdrawn at 10 ml/min with a constant withdrawal pump. After the dogs had been killed with an overdose of anesthesia and saturated KCl i.v., 10–20 transmural samples (approximately 1 g each) of myocardium from the anterior left ventricle and 8–12 samples from normal posterolateral myocardium were obtained. Blood flow samples in these were calculated with the standard microsphere reference technique. Regions were selected to correspond with large regions of interest readily identifiable from the reconstructed PET images. Although the use of radiolabeled microspheres to measure myocardial blood flow is considered the reference standard, underestimation of flow in tissue with low flows can occur.

**Analysis of Tomographic Data**

Tomographic data were reconstructed by filtered-back projection into 100 by 100 pixel images with pixel dimensions of 2.7 mm x 2.7 mm. To obtain myocardial time-activity curves in the tomographic reconstruction, three to four regions of interest (ROI) representing 1.0–5.0 cm$^2$ were interactively placed on one or two midventricular transverse tomographic reconstructions of the $^{82}$Rb images. These represented lateral, anterior, septal, and posterior regions. In addition a 0.75 cm$^3$ ROI was placed within the left atrial blood pool region to define the input function. Because $^{82}$Rb resides in both myocardium and blood in the early stages after the bolus injection, placement of myocardial regions of interest were performed with the aid of the $^{82}$Rb scan corrected for vascular radioactivity as previously described. Then, counts/pixel were calculated from each uncorrected $^{82}$Rb frame for each ROI defined.

**Calculation of Myocardial Perfusion from PET Data**

To calculate regional myocardial perfusion for each ROI, the area under the decay-corrected arterial curve from 0 to 225 seconds was calculated and the decay-corrected tissue activity from the time period between 130 and 320 seconds averaged and corrected for partial volume and spillover effects. The number obtained by dividing the corrected tissue activity by the total area under the input function as shown on the right hand side of Equation 5 was then used to calculate flow per unit volume in milliliters per gram per minute using a look-up table.

**Results**

**Myocardial Images**

After bolus intravenous administration of $^{82}$Rb, tracer is initially present in both blood and myocardium. During the subsequent 380-second imaging interval, tracer is extracted and retained in myocardium and clears from the blood, thereby enhancing the tissue to blood contrast. Figure 2 shows dynamic serial images of a midventricular slice from a dog scanned after administration of $^{82}$Rb 2 hours after myocardial ischemia was induced by placement of a thrombogenic copper coil in the left anterior descending coronary artery. Late images show the decrease in activity in the anterior region indicative of decreased perfusion to this region. The best delineation of the myocardium was obtained after correcting the reconstructed images for radioactivity remaining in the blood pool using a correction technique previously described. Figure 3 shows reconstructed $^{82}$Rb images of midventricular slices obtained from a normal dog (left) and from the dog imaged 2 hours after coronary occlusion and depicted in Figure 2.

**Regional Time-Activity Data**

Figure 4 shows the decay-corrected time-activity curves obtained from a dog with an induced occlusion of the left anterior descending coronary artery. The arterial blood curve shown by the solid line was obtained by direct sampling of the femoral artery.
Figure 2. Serial images of a midventricular slice from a dog scanned after injection of $^{82}\text{Rb}$ 2 hours after the initiation of thrombosis in the left anterior descending coronary artery. Radioactivity passes through the right and left ventricles and is extracted by myocardium. In these and all subsequent tomograms, lateral myocardium is left, anterior is uppermost and septum is to the right.
using external detectors, whereas the lateral and anterior tissue activity curves represented by the dotted and dashed lines were generated from regions of interest placed on a midventricular slice of the reconstructed dynamic PET images.

Tissue activity plateaus after 100 seconds and radioactivity in the anterior myocardium is much lower than that in lateral myocardium due to diminished flow in the ischemic region. The peak radioactivity observed in the tissue 25 seconds after tracer administration is due to the spill-over of activity from the blood pool into the tissue. By 100 seconds, much of the $^{82}\text{Rb}$ in the blood pool has cleared, but there is still a significant amount of activity remaining and consequently tissue radiotracer content must be corrected for spill-over. In all regions from dogs, tissue activity was found to be constant from 130 to 320 seconds (Figure 4). Thus, the tissue activity was averaged over this period to increase statistical accuracy.

Figure 5 shows the close match of the input function obtained noninvasively from dynamic scans from a region of interest placed in the left atrial blood pool with the arterial blood curve obtained by direct counting of blood from the femoral artery with an external detector. The arterial blood curve was scaled and shifted in time to correct for the time delay of appearance of tracer in the femoral artery compared with the left atrium and the difference in the scales of the two detection systems. This match indicates that there is no need to sample the femoral artery with external detectors because the left atrium curve obtained directly from the dynamic images appropriately defines the input function.

Correlation of Myocardial Blood Flow Estimated Using $^{82}\text{Rb}$ With Estimates Using Microspheres

Figure 6 shows the correlation between myocardial perfusion measured by PET and $^{82}\text{Rb}$ with the approach under evaluation and the flow calculated from labeled microspheres. Two flow values per intervention were generated, one representing flow in normal myocardium supplied by the left circumflex
Figure 4. Time-activity curves obtained from a dog with a left anterior descending coronary artery occlusion. Arterial blood curve (solid line) was obtained by direct sampling of the femoral artery using external detectors, whereas the lateral (dotted line) and anterior (dashed line) tissue regions were obtained from large regions of interest placed on a midventricular slice of the reconstructed dynamic $^{82}$Rb PET images. Arrows indicate the time period for which tissue activity was averaged to estimate regional myocardial perfusion.

The values calculated for the anterior region in the same slices were also averaged. Then, the percent of normal flow in the abnormal myocardium was calculated by dividing the averaged flow for the anterior region (abnormal region) by the averaged flow in the remaining regions (normal regions). The calculation of the percent of normal flow from the microsphere data was performed in a similar fashion. In 13 of 18 studies, the two ratios of flow agreed within 10%. Nonetheless, there are five instances in which the difference was greater than 10%. These are denoted by asterisks in Figure 7. In these cases, the percent decrease from normal flow in the anterior region is greater for the $^{82}$Rb data than for the microsphere data (i.e., flow was underestimated by $^{82}$Rb). Two of these discrepancies were from dogs reperfused after 15 minutes of left anterior descending coronary artery occlusion, two were observed in a dog with coronary occlusion studied 2 and again 24 hours after induction of thrombosis, and the last observation was obtained in a normal dog not undergoing intervention. Flow in these regions estimated with microspheres varied from 0.60 to 1.20 ml/g/min, whereas flow estimated with $^{82}$Rb varied from 0.26 to 0.50 ml/g/min.

Discussion

Measurement of myocardial perfusion in absolute terms (i.e., ml/g/min) is important for research applications in which quantitative measurement of flow and flow reserve is necessary and may be especially important in patients with multivessel coronary artery disease in which a “normal” region of myocardium, necessary for the qualitative approach, cannot be identified with certainty.

$^{82}$Rb has been used extensively as a tracer of flow and has been shown to be sensitive and specific for the diagnosis of coronary artery disease. Nonetheless, absolute quantification of regional myocardial perfusion with $^{82}$Rb and PET has been difficult to achieve because of the behavior of $^{82}$Rb in the heart.

Figure 5. Plot of input function obtained by sampling directly from the femoral artery with external detectors is shown by the solid line, whereas the input function obtained noninvasively from dynamic scans from a region of interest placed in the left atrium is shown by the solid circles. Close matching of the positron emission tomography (PET) curve to the curve obtained with external detectors obviates the need to obtain the input function by direct arterial sampling. Slight disparity after 70 seconds may be due to spillover or motion artifact in the curve obtained with PET. The more highly defined time-activity curve obtained by direct arterial sampling is due to the higher temporal resolution of the data acquisition using the external probe.
$^{82}$Rb is only partially extracted by the cells and its extraction decreases as flow increases so that the extraction fraction must be known or measured to estimate flow. In addition, under certain physiological and pathophysiological conditions such as may occur with prolonged ischemia or ischemia followed by reperfusion, the extraction and retention of rubidium by the myocardium may be affected independent of flow. Accordingly, quantification of myocardial blood flow in absolute terms with this tracer requires that the extraction fraction be known.

In the present study, we wanted to explore a simple, previously proposed method for quantifying myocardial perfusion with $^{82}$Rb that does not require direct measurement of the extraction fraction. To accomplish this, we assumed first that the uptake of $^{82}$Rb, the product of flow times extraction fraction, can be defined by Equation 1, which assumes that there is no egress of tracer from the cell during the data collection period, and secondly that the relation between flow and extraction can be defined by Equation 2. Because myocardial PET activity is contaminated by partial volume and spillover effects, we used Equation 4 to correct the tissue data for these effects. Because the matching of the arterial blood curves to the PET left atrial curves was close (Figure 5), the input function can be obtained directly with PET. In addition, this avoids the problems of time delays and dispersion of the input function induced by sampling blood from the femoral artery.

$^{82}$Rb data were collected for 380 seconds after tracer administration. In all studies, tissue activity was constant from approximately 130 seconds to 320 seconds. Thus, we chose to average data between this period to obtain the tissue activity, $C_M(T)$, where $T$ was chosen to be 210 seconds. Because the value of the integral of the input curve, \[ \int_0^T {C_a(t)dt}, \] will change depending on the value of $T$, the selection of $T$ is critical for the accuracy of estimates of perfusion. Although back-diffusion occurs after bolus administration of tracer in isolated hearts in which no recirculation is present, after intravenous administration in intact dogs, we did not observe any decrease in tissue activity from 130 to 320 seconds. Accordingly, we decided to define $T$ as the midpoint between these two points and average all tissue data during this period to increase the statistical accuracy of the data. It should be noted that the imaging interval used in the current experimental study is different than is typically used in qualitative $^{82}$Rb clinical imaging. For patient studies, rubidium is typically administered with an infusion system over a significantly longer period of time (typically 45–60 seconds or more), and the start of imaging is delayed for several minutes to allow for the clearance of tracer from the blood pool. The composite images obtained with such a clinical imaging protocol is therefore a composite of uptake and release of tracer from the myocardium and static scan protocols do not permit quantitative analyses.
The correlation obtained between flow estimated with $^{82}$Rb and that obtained with microspheres was close. Nonetheless, flow estimated by $^{82}$Rb slightly underestimated flow obtained with microspheres (flow with $^{82}$Rb = 0.92 × flow with microspheres − 0.021; r = 0.83). The underestimation of flow could be caused by deviation of the relation expressed in Equation 2, by $^{82}$Rb clearance from cells before 210 seconds, or by inaccurate partial volume and spillover corrections. Partial volume and spillover effects reflect not only the intrinsic resolution of the tomographic system used, but also of the dimensions of the object imaged. In the present study, we used fixed values of the tissue recovery coefficient, $F_{tissue}$, and for the spillover fraction, $F_{BM}$. These values vary from heart to heart and even from region to region, especially in ischemic or reperfused zones where thinning of the cardiac wall may be present. Thus, some of the scatter seen in our data might be due to the fact that the assumed $F_{tissue}$ value of 0.72 is too high especially for ischemic or reperfused regions. However, even with the approach recently developed and implemented in our laboratory whereby partial volume and spillover effects are estimated as parameters simultaneously with estimates of flow, accurate estimates of the tissue recovery coefficient in injured tissue are difficult to obtain.

The extraction fraction, E, is related to flow, F, and the permeability-surface area product, PS, by Equation 6. This equation, known as the Crone equation, is derived from a steady-state single capillary tissue model for unidirectional extraction into tissue of tracer carried by blood.21

$$E = 1 - \exp \left(-\frac{PS}{F}\right)$$  \hspace{1cm} (6)

This analytical equation leads to very high extraction fractions for low flow. When Mullani et al15 measured the extraction fraction of $^{82}$Rb using a first-pass model, they did not encounter very high extraction fractions at low flows. Thus, we believed that Equation 2, the empirical equation that Mullani et al fitted to their data, was more appropriate than the analytical relation (Equation 6) because the former represents the extraction of $^{82}$Rb in cardiac tissue more accurately.

The mathematical approach proposed here requires that the relation defined by Mullani et al (Equation 2) is correct and holds under all circumstances. If this relation is altered by disease, the technique will not be applicable. Goldstein et al10 and Huang et al11 have shown that most pharmacological and metabolic interventions do not alter the extraction of rubidium. On the other hand, a number of investigators9,12,14 have shown that after permanent coronary occlusion or ischemia followed by reperfusion, $^{82}$Rb uptake is reduced because of a relative decrease in $^{82}$Rb extraction, probably reflecting damage of the myocardial cells and breakdown in cell membrane function or due to decreased retention of $^{82}$Rb by the heart (increased back-diffusion). Accordingly, the approach using the empirically derived relation can only be used under carefully defined conditions and is inappropriate for estimation of flow after prolonged periods of ischemia or with reperfusion.

If $^{82}$Rb uptake is reduced due to cell damage associated with ischemia, our estimates of flow would be too low because our assumed extraction fraction would be too high (Equation 2). To determine if our intervention studies reflect a decrease in extraction fraction, we calculated for each intervention the percent of normal flow in the anterior region for the $^{82}$Rb data and compared the results with those obtained with microsphere data (Figure 7). In five of the 18 studies, the decrease in flow was much more pronounced when calculated by the $^{82}$Rb data. Because two of these studies were obtained in reperfused hearts and two of them were obtained in hearts subject to prolonged ischemia, the extraction fraction may not be accurately defined by the relation given in Equation 2. The true value for extraction fraction may be smaller because of cell damage and leakage of $^{82}$Rb out of the cell. This corroborates the data of Wilson et al9 and of Fukyama et al12. In injured regions, flow estimated by microspheres ranged from 0.59–1.2 ml/g/min. Flow estimated with $^{82}$Rb was lower, 0.26–0.50 ml/g/min. However, because one of the large discrepancies was observed in a normal dog (microsphere flow 0.62 ml/g/min. $^{82}$Rb flow 0.35 ml/g/min), one cannot discount the possibility that these differences are due, in part, to partial volume effects. These discrepancies highlight the necessity for an accurate estimate of regional extraction fraction as well as for the need to accurately correct for partial volume and spillover effects to quantify myocardial blood flow with $^{82}$Rb. Although it has been shown that extraction fraction can be calculated using probes with high temporal resolution and a narrowly defined field of view in animal experiments,10,14,15 to date, methods for calculation of first-pass extraction fraction of intravenously administered tracer using PET have not been developed.

**Clinical Implications**

The simple method presented in this manuscript has the potential for the quantification of regional myocardial perfusion with $^{82}$Rb and positron emission tomography under carefully defined conditions and could be adapted for use in a clinical environment for diagnostic purposes. However, because the relation between flow and extraction may not be constant with prolonged ischemia or with interventions such as reperfusion, the approach must be used cautiously when evaluating flow during these conditions. In addition, due to the relation between flow and extraction, the method is insensitive for flows above 2.5 ml/g/min, limiting its usefulness for calculation (either qualitatively or quantitatively) of flow reserve after exercise or pharmacological interven-
tions such as dipyridamole that result in coronary hyperemia. Further refinements in techniques to obtain regional estimation of extraction fraction and myocardial retention of tracer as well as estimates of recovery and spillover fraction from dynamic PET data will be necessary to extend the usefulness of the approach for quantifying myocardial blood flow.

Acknowledgments

We thank Howard L. James for technical assistance, the staff of the Washington University Medical School Cyclotron for production of C13O2, and Becky Leonard for preparation of the typescript.

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KEY WORDS • coronary blood flow • radioisotopes • tracers
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Circulation. 1990;82:1377-1386
doi: 10.1161/01.CIR.82.4.1377

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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