INVESTIGATIVE NUCLEAR MEDICINE

First-Pass Measurements of Regional Blood Flow with External Detectors

Nizar A. Mullani and K. Lance Gould

University of Texas Medical School at Houston, Houston, Texas

A powerful, simple model has been developed for measuring regional blood flow using first-pass tracer kinetics with external detectors such as fast positron emission tomographs (PET). Its derivation is based on the hypothesis that during the first transit of a bolus of activity through an organ there exists a period during which the tracer has not left the region of interest, so that the venous concentration of the tracer is zero. Provided that this condition is met, measurement of blood flow can be obtained in any organ with any radiotracer since there are no requirements in the derivation of the model for diffusion or extraction characteristics of the tracer. The general model has been demonstrated for a special case in the heart using intravenous bolus injections of rubidium-82 with regional positron detectors (beta probes) and validated by comparison with independently determined flow by labeled microspheres over a wide range of flow values from zero to five times normal resting coronary blood flow.

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Positron emission tomography (PET) (*1*) has become an important tool for measuring regional blood flow in man. For use with PET there are several techniques and mathematical models (*2–5*), most of which require that the radiotracer be highly extracted in the organ and/or washed out of the organ at a rate determined by the flow to that organ. By observing the rate of washout of the radiotracer from a region of interest, an estimate of flow to that region can be made, provided that the clearance of the tracer is determined only by the flow to that region, and that recirculation and metabolism of the tracer do not affect its clearance rate.

There are also a number of radiotracers that are partially extracted but do not wash out during the data acquisition time, such as N-13 ammonia (*6*) or rubidium-86 in the heart (*7*). For these tracers there is a widely used flow model (*8*) that incorporates the extraction fraction of the tracer uptake in the equation expressed in the following way:

$$\text{Flow} = \frac{\text{(uptake of tracer)}}{\text{(extraction fraction)} \times (\int \text{arterial concentration})}$$

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

However, flow estimates obtained with this model are usually underestimated at high flow values because extraction fraction is a complex function of flow that decreases at high flow rates. The application of this flow equation is discussed in greater detail in the validation section of this paper.

Saperstein (*9*) hypothesized that during the initial pass of the tracer through an organ there exists a time, before the tracer reaches the venous drainage, when all the tracer is within the region of interest and that it can be considered to be totally extracted. To the best of our knowledge this concept has not been fully exploited or validated as a means of measuring blood flow in a small region with external detectors. We have therefore developed a mathematical model based on this hypothesis for the measurement of blood flow in any organ with any tracer provided one major condition is met. This condition requires that the time for making the blood-flow measurement be short enough such that none of the radiotracer has left the ROI during the period of data acquisition.

We present the model as a general one having potentially broad applications, and validate it for the specific case of measuring myocardial perfusion in the heart using Rb-82 and regional external detectors. It demonstrates that blood flow can be measured accurately in the

myocardium with Rb-82 for a wide range of flow values up to five times normal resting rate. We shall derive the first-pass flow model for the general case and then show how this model can be applied as a special case for use with Rb-82 in the heart, with consequent potential application for positron imaging in vivo.

First-pass flow model. The physical model that describes the detection of the transit of a bolus of radiotracer through a region, V, under a detector can be described by its input and output functions as shown in Fig. 1, where V_c is the volume of distribution of the tracer and $C_c(t)$ is its instantaneous concentration at any time t. The detector's response function, P(t), can be described by the following difference equation:

$$\epsilon_1 P(t) = \epsilon_2 \int_0^t FC_a(x)dx - \epsilon_3 \int_{\bar{t}}^t FC_v(x)dx, \qquad (1)$$

where $C_a(t)$ is the arterial concentration, $C_v(t)$ is the venous concentration, F is the flow rate to that region, $\bar{t}$ is the minimum time delay of the radiotracer through that volume, x is a variable of integration, and ϵ_1, ϵ_2, and ϵ_3 are constants defining the detection efficiencies for P(t), $C_a(t)$, and $C_v(t)$ respectively. This equation restates the basic law of conservation of mass, that the amount of radioactivity detected under the probe is equal to the amount that has been delivered to that volume minus the amount that has left. The theory underlying Eq. (1) is sometimes referred to as the Fick principle.

The venous output concentration is expressed as $C_v(t)$, and if t is smaller than $\bar{t}$, the venous concentration is zero, and the total amount delivered to the region of detection up to that time is under the field of view of the detector. Therefore for t less than $\bar{t}$:

$$\epsilon_3 \int_0^{\bar{t}} C_v(x)dx = 0 \text{ for } t < \bar{t} \qquad (2)$$

And as long as this condition holds, Eq. (1) simplifies to

$$\epsilon_1 P(t) = \epsilon_2 \int_0^t FC_a(x)dx \qquad (3)$$

and

$$F = \frac{\epsilon_1 P(t)}{\epsilon_2 \int_0^t C_a(x)dx} \qquad (4)$$

This equation is identical to the one used for measuring blood flow with microspheres, since in both cases the extraction fraction of the radiotracer is unity and all the first-pass tracer delivered to the region up to time t is located in the volume of interest. Thus, no tracer outflow occurs from that volume and the condition that $C_v(t) = 0$ is satisfied. Our derivation of the first-pass flow equation shows that, regardless of the extractability of the radiotracer, a time $t < \bar{t}$ exists during which the tracer outflow is zero and the tracer can be treated as if completely extracted up to that time.

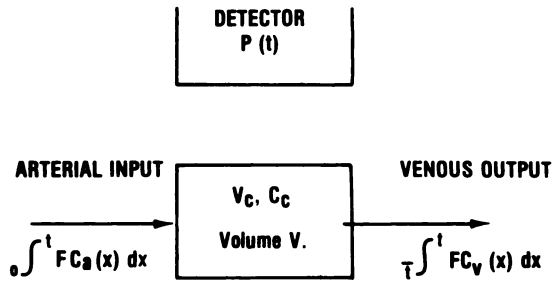

FIG. 1. Physical model for detection of a bolus of radiotracer by external detection, where V is volume of detection, $C_a(t)$ is arterial concentration of tracer, $C_v(t)$ is venous concentration, F is regional flow, and t is minimum transit time of tracer through volume V.

Flow can be determined from Eq. (4) at any time $t < \bar{t}$ by dividing the probe counts by the integrated arterial concentration up to time t. However, the error in flow measurement due to the statistical quality of the data can be minimized when both the numerator and the denominator in Eq. (4) are determined at their maximum values. In the following section we shall derive a special case of the model for measuring flow at the peak-counts time (t_m) when the total first-pass arterial concentration has been delivered to the ROI.

Peak-counts flow model. The general first-pass flow model of Eq. (4) can be extended to a special case that simplifies the computation of flow and minimizes the errors in the measurements. In any special case where $t_m < \bar{t}$, the detector's count rate will reach a maximum when arterial input to the ROI ceases; both this input and the venous drainage are then zero and the entire injected bolus is in view of the detector, whose count rate is momentarily steady, at maximum. Flow can then be computed by dividing the peak counts by the first-pass arterial concentration integrated up to time t_m. Justification for this special case is shown below:

Differentiation of Eq. (1) yields

$$\epsilon_1 \frac{dP(t)}{dt} = \epsilon_2 FC_a(t) - \epsilon_3 FC_v(t) \qquad (5)$$

and at peak activity time, t_m,

$$\epsilon_1 \frac{dP(t_m)}{dt} = 0 = \epsilon_2 FC_a(t_m) - \epsilon_3 FC_v(t_m) \qquad (6)$$

This equation states that at the peak-counts time, t_m, the rate of arterial input is equal to the rate of venous output from that region. If the time t_m is smaller than $\bar{t}$ then by our assumption $C_v(t_m) = 0$ and therefore,

$$\epsilon_2 FC_a(t_m) = \epsilon_3 FC_v(t_m) = 0$$

Therefore, at t_m the external detector records no change in activity and the total first-pass input of activity to that region is under the field of view of the detector.

The general first-pass flow equation can therefore be modified to the following peak-count flow equation:

$$F = \frac{P(t_m)}{\int_0^{t_m} C_a(t)dt} \quad (7)$$

Validity of the peak-counts flow model depends on the relationship between the peak-counts time, t_m, and the transit time delay, $\bar{t}$. Transit times of tracers through an organ have been studied in detail by several researchers (*10–13*). They have demonstrated that there is a distribution of transit times for a bolus of tracer through a region that is determined by the several lengths of the capillaries in that tissue. These transit times are longer if the tracer crosses the capillary wall and is distributed in either the interstitial space or the cellular space. Thus there is no fixed transit time for a bolus but rather a distribution in which there can be some very short transit times and some much longer. These transit-time distributions may be different for each radiotracer and for each organ being studied.

For the general first-pass flow model of Eq. (4) we would be safe in requiring that the time at which flow is computed be shorter than the smallest transit time of the tracer through the region of interest. This requirement would certainly satisfy the theoretical condition for the flow model to be valid. However, accurately determining the transit-time distribution of a tracer for a small region is not practical, since it requires arterial and venous sampling of the blood activity. Thus, some approximations may be required to simplify the relationship between t_m and $\bar{t}$, or indirect methods may be needed to verify that at time t_m the venous output concentration can be approximated to zero.

One of the indirect methods for justifying the use of peak-counts time, t_m, for flow measurements uses the relationship that at time t_m, $FC_a(t_m) = FC_v(t_m)$. If $C_a(t_m)$ is zero then $C_v(t_m) = 0$ and the requirement for the peak-counts flow model is satisfied. Figure 2 shows typical time-activity curves for the arterial input function (measured over the aorta) and the myocardial uptake of Rb-82. At peak-counts time t_m, the arterial input function can be approximated with a value of zero and therefore

$$FC_a(t_m) = FC_v(t_m) \cong 0$$

Thus, for this special case of rubidium in the heart, we have shown that very little of the first-pass bolus of rubidium has left our region of interest and that the approximation $C_v(t_m) \approx 0$ is valid.

The error that results from this approximation is quite small, as demonstrated by the results of our flow validation, but it would be expected to increase at higher flow values as the transit time becomes shorter.

Validation of the peak-counts flow model. We have chosen to validate the general first-pass flow model by measuring blood flow in the heart with Rb-82. The use of rubidium in the heart as a flow tracer has been studied by several investigators (*14–16*). Recently Budinger et al. (*17*) and Selwyn et al. (*18*) have measured the uptake of Rb-82 in the heart by external detectors as a function of flow and found that the amount taken up is not linearly related to flow. This nonlinear relationship is caused by the partial extraction of rubidium in the heart, which decreases as flow is increased. Several attempts have been made to compensate for this nonlinearity by correcting the flow value by incorporating the extraction fraction in the following flow equation

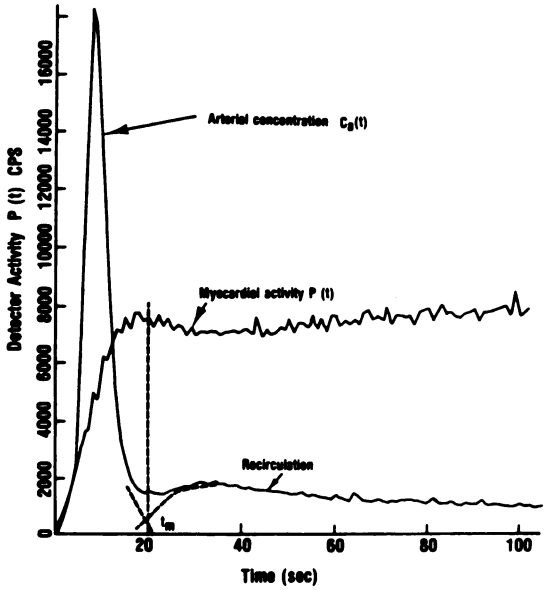

FIG. 2. Temporal relationship between arterial concentration as measured over aorta and myocardial counts. It shows that total first-pass activity has been delivered to myocardium at peak-counts time t_m. This relationship between peak counts and arterial input function has been used to verify that, at t_m, venous concentration can be approximated to zero since $C_v(t) = C_a(t_m) \cong 0$.

$$FE = \frac{C(T)}{\int_0^T C_a(t)dt}$$

where E is the extraction fraction of rubidium in the myocardium, C(T) is the myocardial counts at time T, and $C_a(t)$ is the arterial blood concentration. Unfortunately, the method used in estimating extraction for these earlier studies was incorrect and the resulting flow values underestimate high flows rates. Recently we demonstrated a different way of determining extraction fraction by modeling tissue uptake of tracer and measuring its first-pass extraction fraction. This approach results in a linear flow measurement when compared with flow measurements using labeled microspheres for a wide range of flow values. Validation of this method for the use of Rb-82 in dog hearts measured with beta probes

(*19*) has been presented by Mullani et al. (unpublished data). However, it is a complex calculation that is difficult to implement for perfusion imaging using PET.

We have used the data from the above study to verify the current peak-counts flow model, which is mathematically different from the above equation since it does not require the estimation of extraction fraction. Since the details of the experiment are presented elsewhere, only a brief description of the experimental protocol will be offered here to demonstrate that the newer, simpler model fits the experimental data.

Ten open-chested dogs were studied with beta probes placed against the myocardium. Beta probes are radiation detectors that have a high detection efficiency for positrons and low detection efficiency for the annihilation radiation. In these detectors a small plastic scintillator (1 cm diam by 0.3 cm deep) is coupled to a photomultiplier tube (PMT). The signal from the PMT is amplified and energy discriminated by conventional NIM Bin instrumentation; the resulting logic pulse is sent to a computer for on-line monitoring of the activity curves. Two such beta probes are used to monitor the myocardial counts and the arterial concentration. The detection efficiencies ϵ_1 and ϵ_2 are obtained before each experiment by calibrating the two detectors against a known standard.

For each flow study, a 10-cc bolus injection of Rb-82 (in saline solution) was made in the femoral vein. Myocardial activity was measured with the beta probes, and arterial blood was withdrawn at a fixed rate by a Harvard pump to monitor arterial activity. Simultaneous measurements of flow were obtained with labeled microspheres during each flow study. Myocardial flow was varied from 0.1 to 4.7 ml/min-g by a combination of dipyridamole and phenylepherine to increase flow and coronary occlusion to decrease it. After each experiment the animal was killed, samples of myocardial tissue under the beta probes were excised, and blood flow was determined by the microsphere method.

Blood flow was computed from Eq. (7) by dividing the peak myocardial counts by the first-pass arterial concentration for each study (corrected for detector efficiencies). Results from these 10 experiments are shown in Fig. 3, which shows myocardial blood flow by Rb-82 and microspheres plotted against each other. A linear correlation was found between these two independent measurements of flow with a linear correlation coefficient of $r = 0.965$ and a slope of 0.92. The correlation is highly significant ($p < 0.001$), proving that the general first-pass flow model is valid. The slight deviation of the line from unity of slope could be a result of several problems such as systematic error in the experimental protocol for the two measurements, or a lower value of peak counts at high flow due to escape of the rubidium in the venous drainage. Further studies will investigate the source of this minor error. However, the present results show that the peak-counts flow model is a simple and accurate way of estimating blood flow with diffusible tracers.

DISCUSSION

We have derived a general first-pass flow model and verified a special case of this model for measuring blood flow by the peak-counts method. The model is accurate yet simple, and should successfully measure blood flow in any organ with any radiotracer, since there are no requirements in its derivation for diffusion or extraction of the tracer. The only major condition that needs to be satisfied is that the time at which the measurements are made for flow computation should be shorter than the transit time of the bolus through the region of interest. For application to other organs, this condition can be experimentally tested or adjusted by varying the bolus size, the rate of injection, and the time at which the

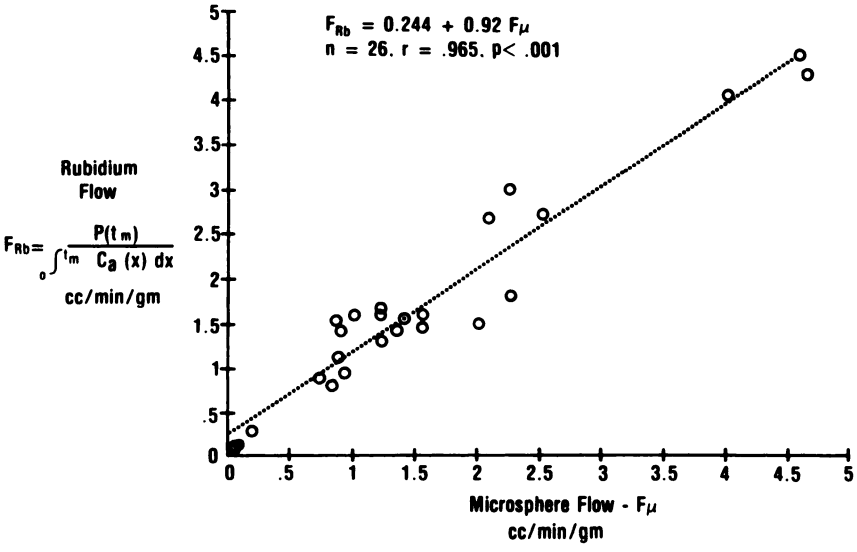

FIG. 3. Validation of general first-pass flow model for myocardium using rubidium-82 and beta probes. Myocardial blood flow as determined by peak-counts model is plotted against blood flow determined independently by labeled microspheres. Excellent linear correlation is found for these two methods for a wide range of flow values.

measurements are made. For the case where the tracer remains in the vascular bed without diffusing into the extravascular space, such as rubidium in the brain (*20*), the transit time will be quite short and a time t smaller than t_m may have to be used with the general flow equation to determine blood flow.

It is important to emphasize that this model is independent of whether the tracer is metabolically trapped or extracted, and therefore is applicable for measuring blood flow over a wide range of flows and metabolic conditions.

Our model is especially suitable for use with regional detectors such as those in PET. However, due to the dynamic nature of the model, this application will need fast positron cameras having high detection efficiency and fast count-rate capabilities, such as the newer generation of time-of-flight positron cameras. Since the accuracy of this model is determined by the statistical quality of the peak counts and the integrated arterial concentration, large bolus injections of short-lived tracers such as Rb-82 and O-15 will be required. Further studies are needed to define the limitations to the broad application of this model for PET imaging of other organs under various conditions.

The use of the generator-produced Rb-82 ($T_{1/2}$ = 74 sec) becomes extremely attractive for measuring blood flow in the heart and potentially in the brain and other organs. The availability of Rb-82 generators and the potential for the development of specially designed inexpensive PET cameras will make this technique accessible for clinical application in man without the necessity of on-site cyclotrons. Gould et al. (*21*) have shown that early, mild coronary artery stenoses can be detected with PET by measuring the perfusion defect in the myocardium under conditions of pharmacogenic coronary dilation. This perfusion imaging at high coronary blood flow is an important diagnostic tool. If coronary blood flow can be accurately measured at high flow rates, the use of Rb-82 and PET for detection of early coronary artery disease could become a widely useful clinical tool.

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