injection. These data are readily available from studies that evaluate the extraction of tracers by different organs. For coronary circulation, the shortest transit for rubidium, as well as for other incompletely extracted tracers, is less than 8 sec (*2,3*). Rubidium is seen in the earliest venous sample in which the strictly intravascular tracer appears, indicating that part of the rubidium is intravascular during the first pass. Thus, the shortest transit time for rubidium is the same as that of any intravascular tracer.

The first-pass model using the peak-counts method as proposed by the authors requires that the total first-pass input of activity to that region (of interest) be under the view of the detector prior to any washout. This requirement is related to the shortest transit time. In both myocardial and cerebral studies using external detector and different tracers injected as extremely short arterial boluses, the washout of the tracers from the region of interest is seen at less than 8 sec postinjection, indicating that the input bolus must have a duration of less than 8 sec for the peak-counts method to be valid (*4,5,6*). Yet Mullani and Gould show that the input bolus has a much longer duration (Fig. 2, p 579). Measured from the time when the arterial concentration reached 2000 counts (1/9 of maximum) to when the activity declined to 2000 counts, the bolus duration is 12–13 sec. Therefore, venous outflow must have occurred before cessation of arterial input and their sampling time of t_m. This leads to a systematic underestimation of blood flow by the peak-counts method with corresponding decrease of the slope from the ideal slope of unity.

This requirement for the short duration of input bolus places a limitation on the applicability of the first-pass model. Since in most cases an arterial injection is required to achieve this short bolus, the intravenous applicability of this method is quite limited.

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Reply

The first-pass model for regional blood flow (*1*) is based on the assumption that during the first several seconds of the transit of a bolus of tracer through a region, there exists a minimum transit-time delay, t_d, during which the tracer is entering the region but has not begun to leave it. During that time therefore, the venous egress from the region is zero and can be ignored to yield the following equation for measuring regional blood flow:

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

where, P(T) is the detected count rate from the region of interest, $C_a(t)$ is the arterial concentration, F is the flow, and T is less than t_d.

[Note: In the original paper, $\bar{t}$ was used to indicate the minimum transit-time delay (TTD). In this manuscript, $\bar{t}$ is replaced by t_d to remove the possibility of mistaking the minimum transit-time delay for the mean-transit time defined by V/F (*4*).]

As long as the detection time, T, is smaller than the minimum transit-time delay, t_d, regional blood flow can be measured in any region regardless of whether the tracer is extracted or not. In theory, this model is valid except when the transit time becomes extremely small.

The first-pass model of regional blood flow was modified to a peak-counts model by using the properties of the mass balance equation, since at the peak-count time, t_m, the rate of change of the detected count rate is equal to zero. At the peak, therefore, the rate of input of the tracer from the arterial side equals the rate of its exit through the venous side. The peak-counts model has several advantages, as described by Mullani and Gould in their manuscript. However, as Yen (*2*) points out in his letter to the editor, the peak-counts model may be of limited application in those situations in which the venous egress may not be negligible at the time of peak counts.

The errors in blood-flow measurements by the peak-counts model will depend on the bolus size, bolus duration, the minimum transit time of the bolus through the region of interest, and the extraction of the tracer. This subject needs to be studied experimentally in greater detail before exact determination can be made on the limitations of the peak-counts model. However, in the absence of any published data on the regional characteristics of transit times, we wish to present some of our preliminary data (unpublished) in order to suggest that the errors may not be large and to clarify the problem to the readers. These preliminary data will also indicate where future experimental data are needed.

The effect of bolus size on the measurement of extraction fraction and blood flow was evaluated using the first-pass extraction fraction method of Mullani et al. (*3*). Various volumes of rubidium-82 chloride were injected in the femoral vein of a dog and the myocardial count rate was measured with a beta probe over the heart. Bolus injections ranging from 1 to 20 cc were made in less than one second for each injection followed by a 10-cc saline flush. There was very little difference in the measurement of blood

TABLE 1. EFFECT OF BOLUS SIZE ON ESTIMATION OF FIRST-PASS EXTRACTION FRACTION OF RUBIDIUM-82 AND BLOOD FLOW IN MYOCARDIUM

Bolus size (cc)	Extraction fraction	Regional blood flow (ml/min-g)
1	0.32	2.5*
2	0.383	2.08
5	0.363	1.96
10	0.384	1.99
20	0.384	2.01

* The 1 cc bolus injection was statistically poor due to small amount of radiotracer injected.

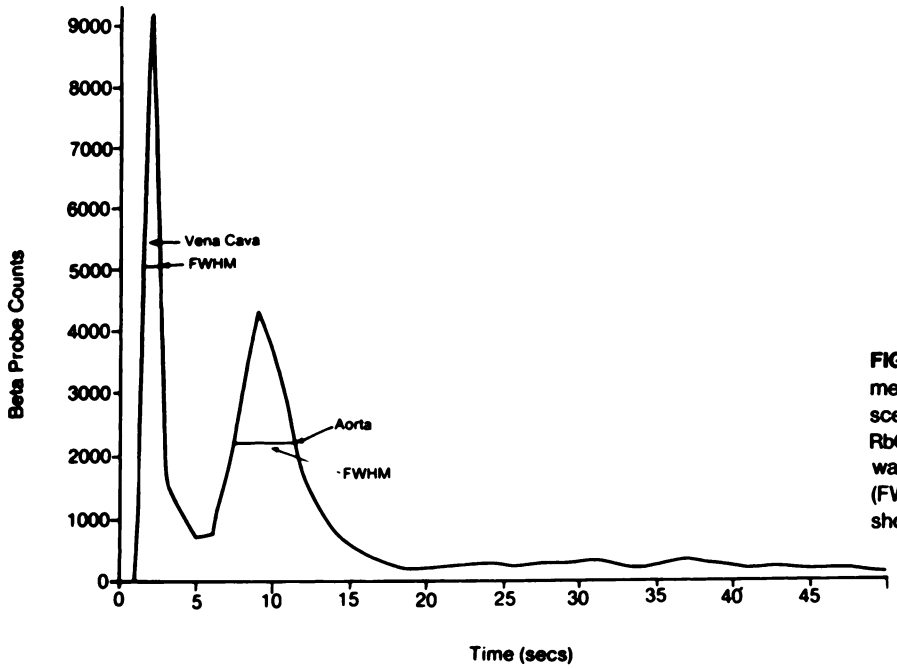

FIG. 1. Example of bolus duration as measured over inferior vena cava and descending aorta for 10 cc bolus injection of RbCl in femoral vein. Injection time of bolus was approximately 1 sec. Measured widths (FWHM) of these concentration curves are shown in Table 2.

flow for the different bolus volumes used in the experiments. Table 1 lists the different bolus sizes, the extraction fractions, and blood-flow. The 1-cc bolus injection resulted in a significant amount of noise in the data due to the small amount of injected radioactivity. Comparison of peak-counts measured with different bolus sizes is not appropriate in this experiment because the concentration of the radiotracer was not kept constant for each of these injections, due to the short decay time of the radiotracer and variation of the tracer concentration with elution volume from the generator. Table 1 shows that, at constant flow, changing the bolus size did not change the measurement of flow or extraction fraction by the first-pass model. The principle of measuring the first-pass extraction fraction and flow, based on the assumption of negligible venous egress before peak-counts time, appears to hold true for different bolus sizes.

The effect of duration of bolus injelction of the radiotracer was studied by injecting a 10 cc bolus of tracer at various rates in the femoral vein of a dog. Intravenous injections undergo a broadening of the bolus duration at arterial sample sites due to the transit-time spread (TTS) of the tracer through the lungs and the heart. In order to assess the effect of this spread through the cardiopulmonary (CP) circulation on the bolus shape and duration in the arterial distribution, tracer activity was recorded by beta probes placed over the inferior vena cava and the descending aorta proximal to the kidneys. Examples of the data collected in a dog are shown in Fig. 1.

The effect of the cardiopulmonary circulation on the bolus duration can be expressed mathematically as a convolution (*4*,*5*) of two functions, namely, the vena-cava concentration function and the distribution function for the cardiopulmonary transit time, as follows:

$$C_A = C_b * h_{CP}$$

where, C_A is the function describing the aortic concentration of the tracer, C_b is the venous concentration function of the tracer during the injection, h_{CP} is the distribution function of the transit time for RbCl in the cardiopulmonary circulation of a dog, and * represents a convolution operator.

For ease of computation, Gaussian functions were fitted to the radioconcentrations monitored over the vena cava and the aorta, as an approximation to the cardiopulmonary transit-time distribution functions. While this is not strictly correct, it does provide us with an easy method of deconvolving the lung transit-time in distribution function and assigning the standard full width at half maximum (FWHM) method to indicate the transit-time spread. Table 2 lists the various injection times, the corresponding FWHM of the Gaussian function for the vena cava, and that of the aorta. The deconvolved transit-time distribution function for the cardiopulmonary system ranges from 4 to 7 sec for an approximate average transit-time spread of 5 sec, FWHM, for the bolus through the lungs. This transit-time distribution function will dominate and largely determine the duration of the bolus for injections of up to 3 sec duration for the dog and the Rb chloride tracer. As an example, a 3-sec-bolus injection will result in an arterial concentration bolus with a width of 6 sec FWHM, compared with 5 sec

TABLE 2. DECONVOLVED TRANSIT TIMES OF i.v. BOLUS OF Rb-82 THROUGH CARDIOPULMONARY CIRCULATION OF DOG*

Exp.	i.v. bolus duration	Aortic activity duration	Cardio-pulmonary transit time
1	1	4.2	4.07
2	1.5	5	4.8
3	2.3	5	4.43
4	2.5	5	4.33
5	3.33	6.66	5.8
6	1.88	5.6	5.3
7	1.5	6.9	6.7

* Transit times are computed for different durations of bolus injection. All measurements are expressed as full width at half maximum (FWHM) for Gaussian curve. All units are in seconds.

TABLE 3. COMPUTER-SIMULATED VALUES OF OBSERVED PEAK AND BLOOD FLOW FOR SIMULATED BETA PROBE OVER HEART WITH 1 m,l/min/g OF FLOW.*

Extraction	t_d	t_m	$\int^{t_m} C_a(t)dt$	$\int_{t_d}^{t_m} C_v(t)dt$	OBS peak	Flow
E = 0	3.000	3.713	124.061	12.190	111.871	0.902
	4.000	4.498	144.979	6.429	138.550	0.956
	5.000	5.341	162.198	3.192	159.005	0.980
	6.000	6.230	175.470	1.505	173.965	0.991
	7.000	7.152	185.168	0.679	184.489	0.996
	8.000	8.099	191.963	0.296	191.668	0.998
	9.000	9.064	196.571	0.125	196.446	0.999
	10.000	10.041	199.617	0.051	199.566	1.000
	11.000	11.026	201.593	0.021	201.572	1.000
E = 0.2	3.000	3.948	130.838	15.857	114.981	0.879
	4.000	4.643	148.297	8.130	140.166	0.945
	5.000	5.434	163.799	3.995	159.804	0.976
	6.000	6.290	176.217	1.877	174.340	0.989
	7.000	7.191	185.505	0.846	184.659	0.995
	8.000	8.125	192.110	0.368	191.742	0.998
	9.000	9.080	196.633	0.156	196.477	0.999
	10.000	10.051	199.643	0.064	199.579	1.000
	11.000	11.033	201.604	0.026	201.578	1.000
E = 0.4	3.000	4.412	142.926	22.490	120.436	0.843
	4.000	4.906	153.930	11.030	142.901	0.928
	5.000	5.596	166.466	5.330	161.136	0.968
	6.000	6.393	177.455	2.490	174.965	0.986
	7.000	7.257	186.062	1.122	184.940	0.994
	8.000	8.167	192.353	0.489	161.864	0.997
	9.000	9.108	196.736	0.207	196.52	0.999
	10.000	10.069	199.685	0.085	199.600	1.000
	11.000	11.043	201.621	0.034	201.586	1.000
E = 0.6	3.000	5.771	169.164	36.902	132.26	0.782
	4.000	5.533	165.436	16.947	148.490	0.898
	5.000	5.951	171.775	7.976	163.799	0.954
	6.000	6.609	179.898	3.695	176.203	0.979
	7.000	7.393	187.160	1.663	185.498	0.991
	8.000	8.253	192.833	0.726	192.107	0.996
	9.000	9.162	196.939	0.308	196.632	0.998
	10.000	10.103	199.770	0.127	199.642	0.999
	11.000	11.065	201.655	0.052	201.603	1.000

* Extraction fraction and t_d are varied over physiological range.

for a pulsed bolus intravenous injection of less than 1 sec in duration. Other tracers may have different transit-time distributions and the resulting bolus durations, depending on their interaction with the lung tissue.

The relations between the bolus duration, minimum transit-time delay, and the peak count rate are complex. Experimental measurement of these variables has not been carried out, since there is no readily apparent way of measuring the regional distribution functions in vivo. However, measurements of transit-time delays for the whole heart have been made by sampling the tracer concentration in the coronary sinus after an aortic injection. These indicator-dilution techniques have shown that the delay in transit time through the myocardium of the whole heart ranges from 3 to 15 sec (*6,7*), depending on coronary blood flow and the volume of distribution of the tracer. Whether these results can be applied to regional measurements is an open question. We can obtain some insight into the limitations of our model by applying some computer simulation techniques using available data.

It is intuitively obvious that if the bolus duration is very short, such that the total bolus duration is shorter than the minimum transit time, t_d, arterial tracer input will cease before venous egress begins, and the whole bolus will lie within the region of interest. Thus, short bolus durations satisfy a special case of the peak-counts model, which states that the arterial concentration is equal to the venous concentration at the peak-counts time, both being zero. This condition was the stated assumption made in our original paper

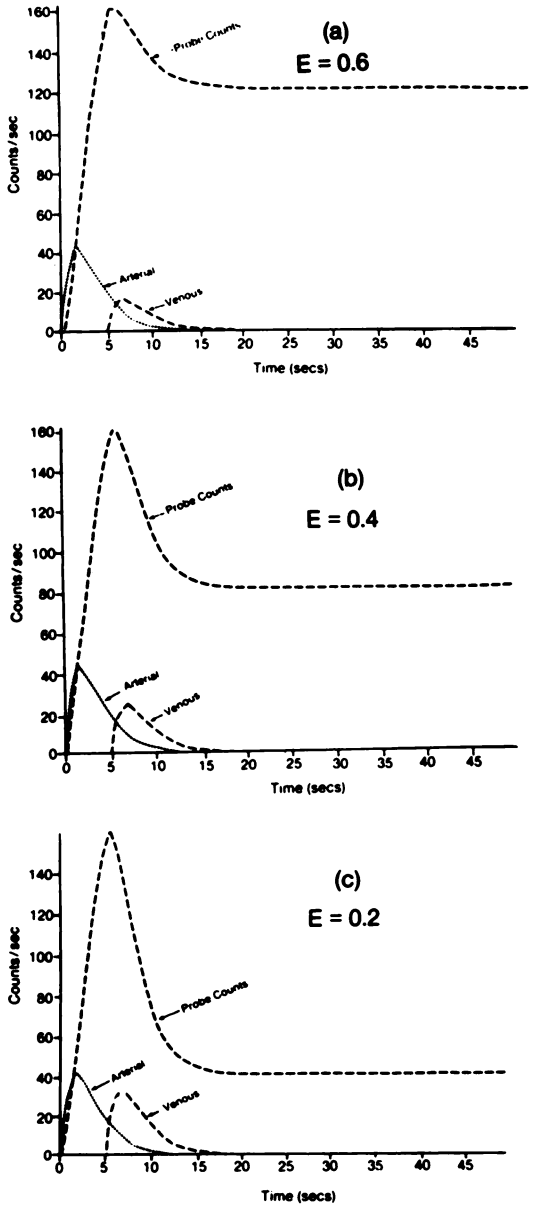

FIG. 2. Computer-simulated beta probe counts for myocardium [Eq. (2)] using arterial concentration curve measured over aorta of dog at normal resting flow. Gamma variate function of form ate^{-bt} was fitted to arterial concentration curve. Delay time, t_d, is fixed at 5 sec. (a) E = 0.6, (b) E = 0.4 and (c) E = 0.2.

describing the peak-counts flow model. However, as we are aware and as was pointed out by the reviewers, this assumption may not be generally true for all situations.

In order to evaluate the errors in the peak-counts model for cases where the bolus duration is longer than the delay time through the tissue, we carried out a computer simulation using the following data and conditions. Arterial activity was recorded over the aorta of a dog for a typical intravenous injection of 10 cc and was fitted to a gamma-variate function of the form ate^{-bt}. A worst case assumption was made that the venous concentration of the tracer leaving the myocardium can be represented by the same mathematical functional form as the arterial input function, except that it is delayed by a time t_d and that the integrated activity under the venous curve is (1-E) times the total input, where E is the extraction fraction. In reality the venous activity curve will be broader than the arterial curve due to the transit-time distribution of the myocardium. Consequently, the errors due to early venous egress would be less than those estimated by making this worst-case assumption for the computer simulation.

Equation (2), below, was used in the computer simulation to describe the relation between the recorded myocardial activity and the input and output functions to and from the sample volume of myocardium. Minimum transit-time delay, t_d, and the extraction, E, were varied over the full range of possible values that could exist in vivo. A fixed flow rate of 1 ml/min-g was assumed in the computer simulations as the standard true flow in order to assess the error in blood-flow measurements with peak-counts model for the cases where the bolus duration was greater than t_d.

$$P(T) = F\int_0^T C_a(t)dt + (1 - E)F\int_{td}^T C_a(t)dt \qquad (2)$$

Table 3 lists the values of peak count rate, the time integral of arterial concentration delivered, the time integral of venous concentration that has egressed, and the flow measured by the ratio of the peak-count rate divided by the time integral of the arterial concentration delivered to myocardium up to t_m. Some representative curves for the detected counts, using different extraction fractions for a fixed delay time of 5 sec are shown in Fig. 2 (a, b and c) for extraction fractions of 0.6, 0,4, and 0.2.

In the computer simulation the times to peak-counts were found to be related to the extraction fraction, E, such that a higher extraction fraction results in longer time to peak counts. Since the error in the peak-counts model is caused by venous egress of the tracer occurring during the time t_d to the time t_m, an extension of the time t_m will cause a larger error. However, in that case the total amount that can escape from the region will be smaller with highly extracted traces. These two conditions thus have opposing effects on the measurement errors.

The ratio, F'/F, of the measured flow with venous egress to true flow can be expressed as follows:

$$\frac{F'}{F} = 1 - \frac{(1 - E)\int_{td}^{tm} C_a(t)dt}{\int_0^{tm} C_a(t)dt} \qquad (3)$$

Equation (3) shows that the errors in the flow measurement using the peak-counts model will depend on E, t_d, and t_m. Computer-

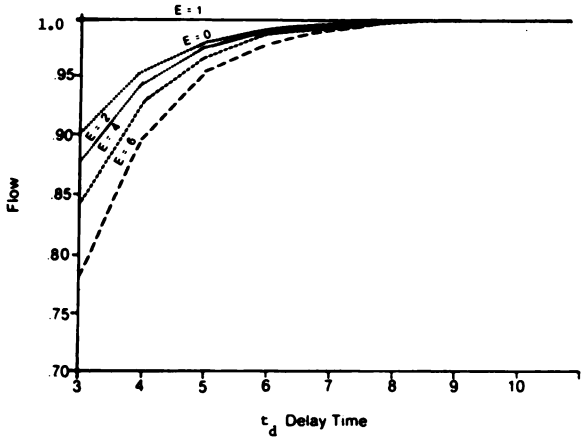

FIG. 3. Simulated measurements of flow using peak-counts model for various different delay times and extraction fractions. Mathematical formulation for this simulation is shown in Eq. (2), and tabulated data for the different variables are in Table 3. As extraction fraction increases beyond 0.6, error due to venous egress of tracer also decreases, since more tracer remains trapped in tissue.

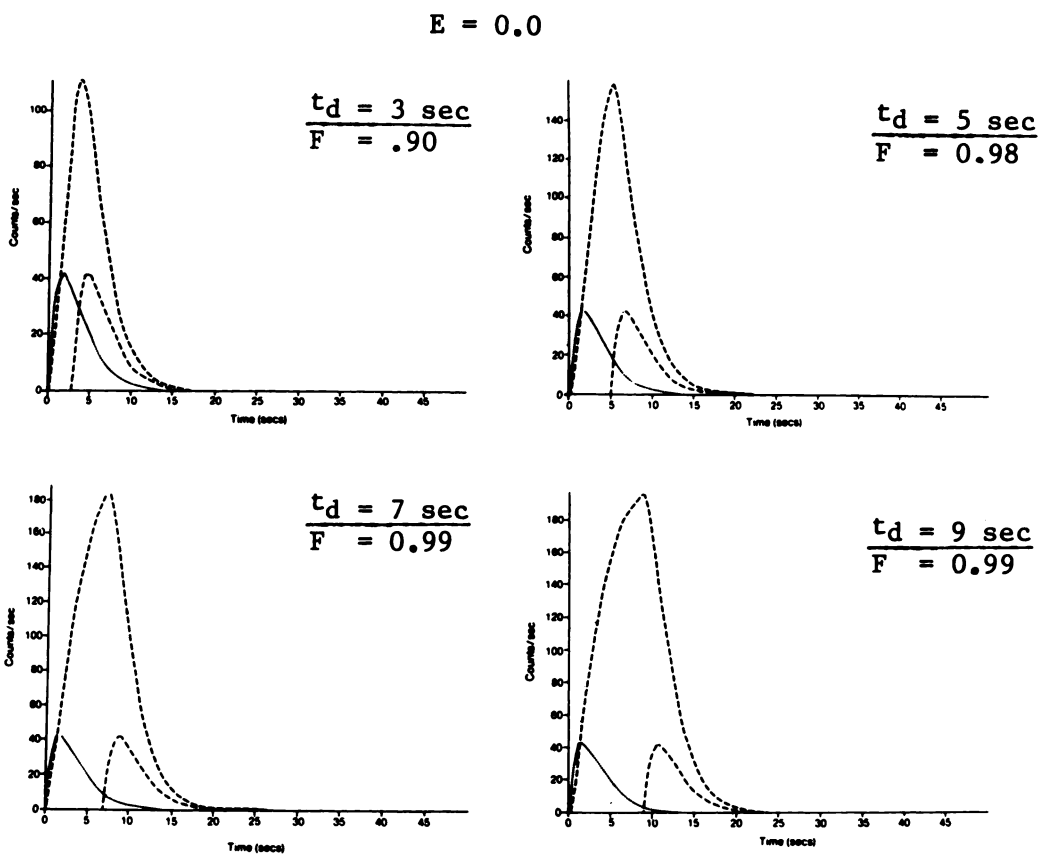

FIG. 4. Computer simulation of detected activity for cases where E = 0 (*no* extraction), e.g., for Rb-82 in brain, or for contrast agents used for x-ray absorption enhancement. Four different delay times are shown. Measured flows using peak-counts model are 0.9, 0.98, 0.99, and 0.99 for delay times of 3, 5, 7, and 9 sec, respectively.

simulated measurements of flow as a function of the delay times and extraction fractions are shown in Fig. 3 for a normal resting flow of 1 cc/min-g. These simulations demonstrate the interrelationship between extraction, transit times, and flow measurements.

The present simulations show that the errors in flow measurement range down to at most 23% lower than true flow as measured by tracers with total extraction, where there is no venous egress. This analysis may explain the slight systematic underestimation of myocardial blood flow measured with the first-pass model using Rb-82 as compared with microsphere measured flow in our study (*1*). However, we firmly believe that direct experimental measurements of the venous egress of the tracer are necessary in order to document these estimated errors. Thus, there are limitations on this model, as on any model, such that systematic error in the measurement of blood flow occurs under certain circumstances. Whether this error is sufficiently small to be acceptable or not will depend on the application and the particular requirements for accuracy. It is our opinion that a 10–20% *systematic* error in the measurement of flow should not limit the application of this model in most clinical studies—particularly, since there is *no* other method to measure regional perfusion noninvasively with partially extracted tracers.

An additional advantage of the first pass blood-flow model is the option of measuring blood flow with a tracer that is poorly extracted, or even not extracted at all. Ours is the first mathematical model for measuring regional blood flow noninvasively with a vascular tracer. In Fig. 4 we show some typical examples of computer-simulated detected activity for the case where there *no* extraction of the tracer. The errors in blood-flow measurement, for the different delay times are shown in Fig. 3, and Table 3 indicates that, for a nonextracted tracer, a maximum error of 10% is made for a transit-time delay of 3 sec in the peak-counts model. Thus, it should be possible in theory, to measure regional blood flow in the brain with Rb-82 where it is not extracted (*8*), or to measure regional blood flow with a fast dynamic TCT or NMR scanner using nonextracted contrast or paramagnetic agents.

There is no doubt that the first-pass regional blood-flow model is extremely powerful in a number of applications. Since the limitations of this model stem from the transit time of the bolus and the bolus duration, a more practical limitation to the application of this model is the requirement for the fast dynamic imaging needed to record a statistically sufficient number of counts for an accurate measure of the peak count rate.

Our initial experimental data and theoretical analysis of the first-pass blood-flow model suggest that it has the potential for widespread application. However, assessing the extent of its capabilities or limitations will require further experimental studies. We therefore believe that it may be premature to make a judgment on the applicability of this model at the present time.

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