Blood Flow: First Circulation Time-Activity Curves

6

Introduction

Theoretically, the best method for evaluating pure regional blood flow with a radiopharmaceutical is to use a radiopharmaceutical that is not cleared, e.g., Tc-99m-RBCs, inject it intravenously, and acquire rapid serial images of the radiopharmaceutical as it passes through the structure(s) of interest during the first circulation. For practical reasons, radiopharmaceuticals that are partially cleared during the first circulation are used in most cases. In addition, it is difficult to measure regional blood flow accurately in absolute terms so the measurement of regional blood flow is generally performed on paired organs so the measurement(s) can be made in relative terms. This approach usually provides a normal side for comparison as an added benefit.

Table 6.1 shows four nuclear medicine studies which routinely include imaging of paired structures during the first circulation. Tc-99m-DTPA in the Brain Death Study is not cleared from the vascular space of the brain as long as the blood-brain barrier is intact. The radiopharmaceuticals in other three studies are partially cleared during the first circulation, but the resulting images can still be evaluated for blood flow. In addition to visual evaluation of the images, regions of interest (ROIs) can be placed over the paired structures of interest to generate time-activity curves. Currently, this is performed only in the two renal studies. In this chapter, the information content of these paired time-activity curves and the mathematics for extracting this information are analyzed.

The mathematics that apply to the first circulation of a radiopharmaceutical also apply to the first circulation of other imaging indicators such as CT density contrast material and MR magnetic susceptibility material (Table 6.1) [1–6]. However, because of the higher spatial resolution of CT, a time-indicator curve from the input artery can also be generated, which in turn can be used to deconvolve the time-indicator curve of the ROI, calculate the mean transit time through the region of interest, and directly calculate the blood flow of the region of interest using the

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Table 6.1 Radiologic studies that include imaging of paired structures during the first circulation

Procedure	Radiopharmaceutical/indicator	Extraction efficiency	Generate time-indicator curves
Renal Tubular Excretion Study	Tc-99m-MAG3	65 %	Yes
Renal Glomerular Filtration Study	Tc-99m-DTPA	Low	Yes
Bone Mineral Study	Tc-99m-MDP	Low	No
Brain Death Angiography Study	Tc-99m-DTPA	Very low	No
CT of the brain	I-127-iothalamate	Very low	Yes
MR of the brain	Gd-153-DTPA	Very low	Yes

central volume principle. Unfortunately, it is difficult to be sure that the input artery does in fact directly supply the entire blood flow into and through the ROI in question. The differences between evaluating blood flow with radiopharmaceuticals and CT density contrast are discussed in more detail at the end of this chapter (Convolution analysis is discussed in Chap. 7: Mean Transit Times: Convolution Analysis.).

Derivation of the Equation for Evaluation of Regional Blood Flow from First Circulation Time-Activity Curves

Regional blood flow can be noninvasively evaluated by injecting a relatively nondiffusible and noncleared radiopharmaceutical intravenously and recording its passage through paired peripheral structures such as the two cerebral hemispheres, two kidneys, or two lower extremities. The use of paired structures with the assumption that blood flow would normally be symmetrical simplifies the analysis by eliminating the need to correct for photon attenuation and by allowing blood flow to be evaluated in a relative fashion instead of in absolute terms.

The data is readily quantified by generating time-activity curves from paired regions of interest. It has been intuitively assumed that when the paired time-activity curves are symmetrical, the blood flow is likely to be normal and conversely; this assumption is usually, but not always, correct. It has also been assumed that relative blood flow can be calculated from the time-activity curves, but this has proved to be an oversimplification. Determination of the physiologic information content of first circulation paired time-activity curves is explored below [1, 2].

It should be noted that there are several nuclear medicine studies that are named perfusion studies but actually measure clearance: Lung Perfusion Study with Tc-99m-MAA, Brain Perfusion Study with Tc-99m-HMPAO/Tc-99m-ECD, Hepatic Artery Perfusion Study with Tc-99m-MAA, and Myocardial Perfusion Studies (multiple radiopharmaceuticals). In general, the results of these studies primarily reflect perfusion or blood flow, but not always. This discrepancy is discussed at greater length in Chap. 4: Evaluation of Clearance. It is also worth noting that strictly speaking the word perfusion implies the delivery of nutrients such as oxygen and glucose to tissues via the blood, whereas the studies in this chapter only evaluate blood flow with no implication relative to the delivery of nutrients.

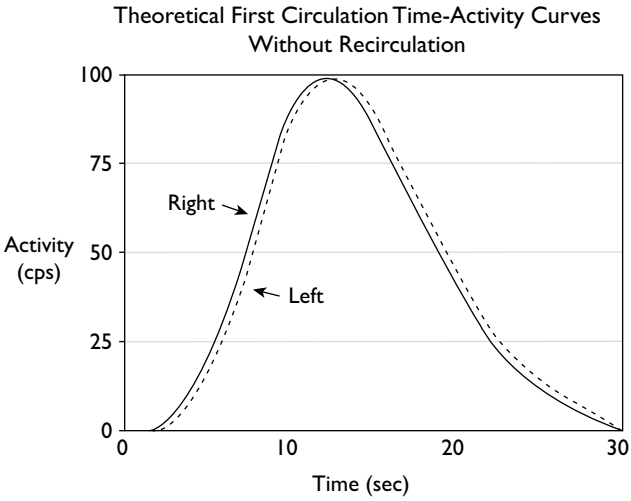

Fig. 6.1 Paired first circulation time-activity curves without clearance or recirculation. The bolus of tracer is elongated as it enters the ROIs because of laminar flow. The curve rises and falls to zero because of the absence of clearance and recirculation of the tracer (*cps* counts per second)

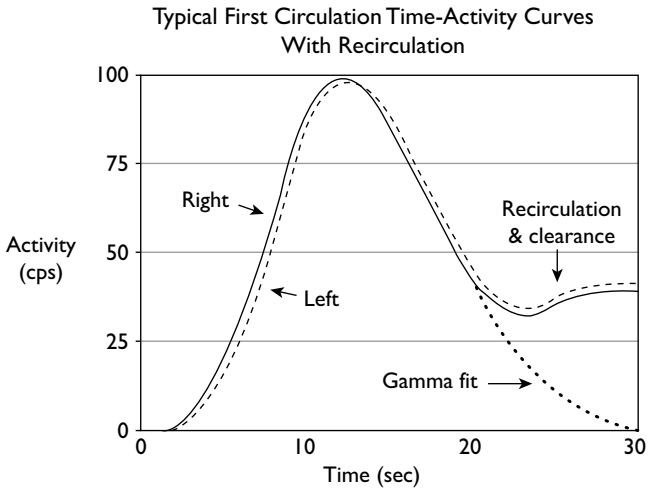

Fig. 6.2 Paired first circulation time-activity curves with clearance and recirculation. The time-activity curves never return to baseline because the leading edge of the first circulation reenters the ROIs before the tail end leaves and, in addition, some of the tracer may be cleared. However, a mathematical gamma fit has been performed to simulate a time-activity curve with no recirculation

Figure 6.1 shows the theoretical appearance of time-activity curves that would be generated from ROIs placed over paired structures following the intravenous injection of a nondiffusible and noncleared radiopharmaceutical during the first circulation without recirculation.

The time-activity curves that are actually obtained from the studies listed in Table 6.1 are different from those depicted in Fig. 6.1 because (1) some of the radiopharmaceuticals in question moves out of the vascular space, particularly Tc-99m-MAG3 in the kidneys, and (2) recirculating tracer reenters the ROIs before the end of the first circulation (Fig. 6.2). The end result is that the downslope of the time-activity curves never reaches zero.

However, it is theoretically possible to compensate for recirculation and clearance of the tracer by performing a "gamma fit" to the initial clinical time-activity curve (Fig. 6.2). See discussion below.

Mathematically, we start with the Stewart-Hamilton equation, which describes the relationship among the amount of an indicator that is injected intravenously, the cardiac output, and the integral of the concentration of an indicator, here a radiopharmaceutical, as a function of time at an arterial sampling site [7].

$$A = F_{CO} \times \int_0^T C(t)\,\mathrm{d}t \tag{6.1}$$

This equation states that if a given amount of radiopharmaceutical, A (μCi), is injected as a bolus into the proximal circulation and undergoes uniform mixing in a central chamber, then measurement of the concentration of radiopharmaceutical, $C(t)$ (μCi/mL), at some distal point during the first circulation. T and the concentration during recirculation are determined by extrapolation [4] will permit calculation of cardiac output, F_{CO} (mL/min).

It is important to note that the concentration and the mean transit time of indicator in the branches of the arterial system during the first circulation are related to volume and flow in such a way that the integral, $\int_0^T C(t)\,\mathrm{d}t$, is a constant regardless of the sampling site [1]. This fact is implicit in the Stewart-Hamilton equation since the terms, A and F_{CO}, are both constants for a given injection.

When an external detector is substituted for blood sampling, the Stewart-Hamilton equation becomes,

$$G \times A = F_{co} \times \int_0^T R(t)\,\mathrm{d}t / V_r \tag{6.2}$$

Here G is a conversion factor that converts the indicator, with units of disintegrations per second, to the reading of the external detector, $R(t)$, with units of counts per second, and V_r is the regional blood volume [5]. Since V_r is unknown and not easily determined, the integral with an external detector, $\int_0^T R(t)\,dt / V_r$, is significantly different from the integral with blood sampling, $\int_0^T C(t)\,\mathrm{d}t$. A modified form of Eq. 6.2 has been used to measure cardiac output with a radiotracer, external detection, and a single blood sample at equilibrium [8–10].

Equation 6.2 is now converted from an equation for cardiac output to an equation for regional blood flow by multiplying both sides by the fraction of the cardiac output which passes through the ROI.

$$G \times A \times F_r / F_{co} = F_r \times \int_0^T R(t)\,\mathrm{d}t / V_r \tag{6.3}$$

Here F_r is regional blood flow. Since the integral $\int_0^T R(t)\,dt / V_r$ is constant for all ROIs for a given injection, it can be seen that the fraction of the injected dose that passes through a ROI on the first circulation, $G \times A \times F_r / F_{co}$, varies directly with regional blood flow, F_r.

As the blood volume of the ROI, V_r, cannot be determined, it is desirable to eliminate this term using the relationship flow equals volume divided by the mean transit time (see Chap. 5: Mean Transit Time: Central Volume Principle).

$$G \times A \times F_r / F_{co} = 1/\bar{T}_r \times \int_0^T R(t)\,dt \tag{6.4}$$

Here "$\bar{T}_r$" is the mean transit time through the ROI. It is important to note that cancellation of the term V_r within the integral is equivalent to multiplying the constant, $\int_0^T R(t)\,dt / V_r$, times the blood volume of the ROI, V_r. Consequently, the resulting integral, $\int_0^T R(t)\,dt$, is linearly proportional to the blood volume of the ROI.

Equation 6.4, the equation for regional blood flow, contains three unknowns in addition to F_r and cannot be solved for a single ROI. For paired ROIs, regions one and two, the conversion factor, G; the injected dose, A; and the cardiac output, F_{co}, are the same for both ROIs and cancel giving,

$$\frac{F_{r1}}{F_{r2}} = \frac{1/\bar{T}_{r1} \times \int_0^{T_1} R_1(t)\,dt}{1/\bar{T}_{r2} \times \int_0^{T_2} R_2(t)\,dt} \tag{6.5}$$

Since the integral $\int_0^T R(t)\,dt$ reflects only regional blood volume, it can be seen from Eq. 6.5 that when the Stewart-Hamilton equation is modified for paired ROIs, it reduces to the form of relative flow equals relative volume divided by the relative mean transit time, or the central volume principle.

Figures 6.3 and 6.4 diagrammatically summarize the effects of branching and changes in regional volume, mean transit time, and flow on the physical shape of the bolus and the resulting time-activity curve for single pathways; cardiac output is constant.

Plug flow with the numbers representing tracer activity is depicted, but similar results would be expected for laminar flow. It can be seen that (1) the fraction of the injected dose which passes through a ROI varies with the fraction of cardiac output which passes through a ROI (Fig. 6.3); (2) when the volume of the sampling site is held constant (as with blood sampling and measurements per mL), changes in flow do not result in changes in the integral of the first circulation time-activity curve because of compensatory changes in the mean transit time (Fig. 6.3); and (3) when the volume of the sampling site is varied and the amount of indicator injected and

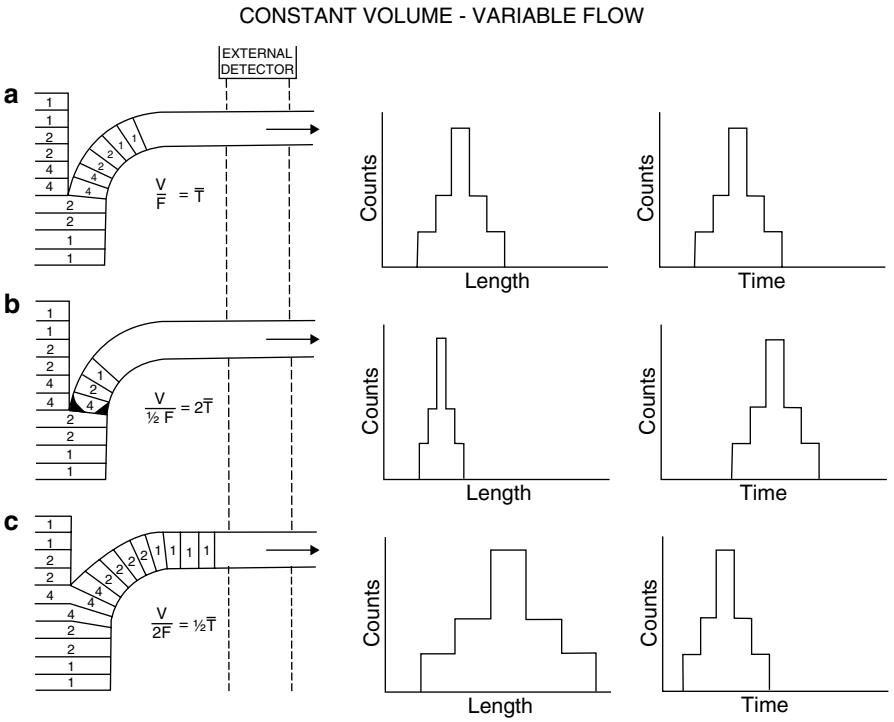

Fig. 6.3 The numbers in the vascular system on the left represent tracer activity (*1st column*). As flow is varied but volume is held constant in the side branch under study (**a**–**c**): (1) the amount of tracer passing through the side branch varies directly with flow (*2nd column*) and (2) when the volume of the sampling site is held constant (as with blood sampling and measurements per mL), changes in flow do not result in changes in the integral of the first circulation time-activity curve because of compensatory changes in the mean transit time (*3rd column*)

the cardiac output are held constant (e.g., multiple ROIs following one injection), the integral of the first circulation time-activity curve varies directly with the blood volume of the sampling site of ROI (Fig. 6.4). The equations beneath the side branches in Figs. 6.3 and 6.4 indicate that more than one combination of change in regional flow and volume can account for a change in mean transit time.

The equation for relative blood flow to paired ROIs, Eq. 6.5, can be solved if the mean transit times through the ROIs can be calculated. Unfortunately, the mean transit time through the ROIs cannot be determined from the time-activity curve from the ROI because the time-activity curve is a function of the physical shape of the bolus as it enters the ROI as well as the frequency distribution of transit times through the ROI [11]. This point is diagrammatically illustrated in Fig. 6.5.

Flow, volume, and the mean transit time are constant, but the shape of the time-activity curve varies with the physical shape of the bolus. The physical shape of the bolus depends mainly on the conditions of injection, laminar flow, and the distance from the injection site to the ROI.

The input of blood flow to the ROI is through one or more relatively small arteries making it difficult to determine the shape of the incoming radiotracer profile by

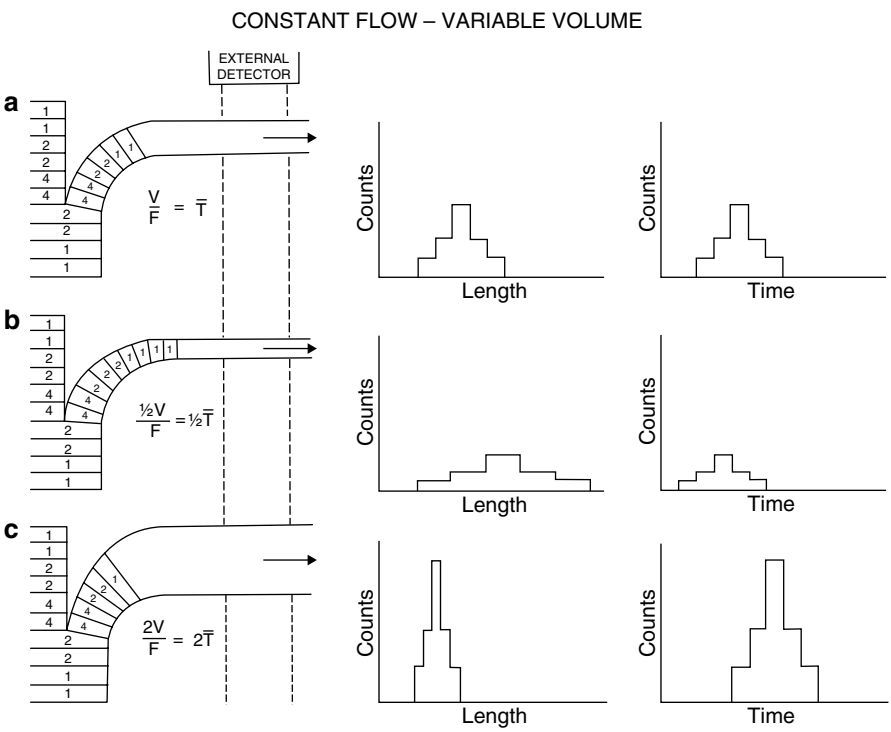

Fig. 6.4 As volume is varied but flow is held constant in the side branch under study (*1st column*), the integral of the first circulation time-activity curve varies directly with the blood volume of the sampling site of the ROI (*3rd column*)

imaging. If this difficult problem can be solved in the future, deconvolution analysis of the washout curve will yield the frequency distribution of transit times through the ROI and, thus, the mean transit time through the ROI. The mean transit time through the ROI could then be divided into the blood volume of the ROI to obtain the blood flow through the ROI specifically.

Although the relative mean transit time through paired ROIs cannot be measured, differences in the mean transit time from the point of bolus division in the aortic arch can be estimated by determining differences in the first moment time for each time-activity curve about the time of injection,

$$T_{\mathrm{m}} = \frac{\int_0^T t \times R(t)\,\mathrm{d}t}{\int_0^T R(t)\,\mathrm{d}t} \tag{6.6}$$

Here T_{m} is the first moment time about the time of injection, T is the end of the first circulation through the ROI, and t is instantaneous time. The first moment time represents the mean transit time from the point of injection to and through the ROI (more accurately, to some point within the ROI). Any difference between the first moment or

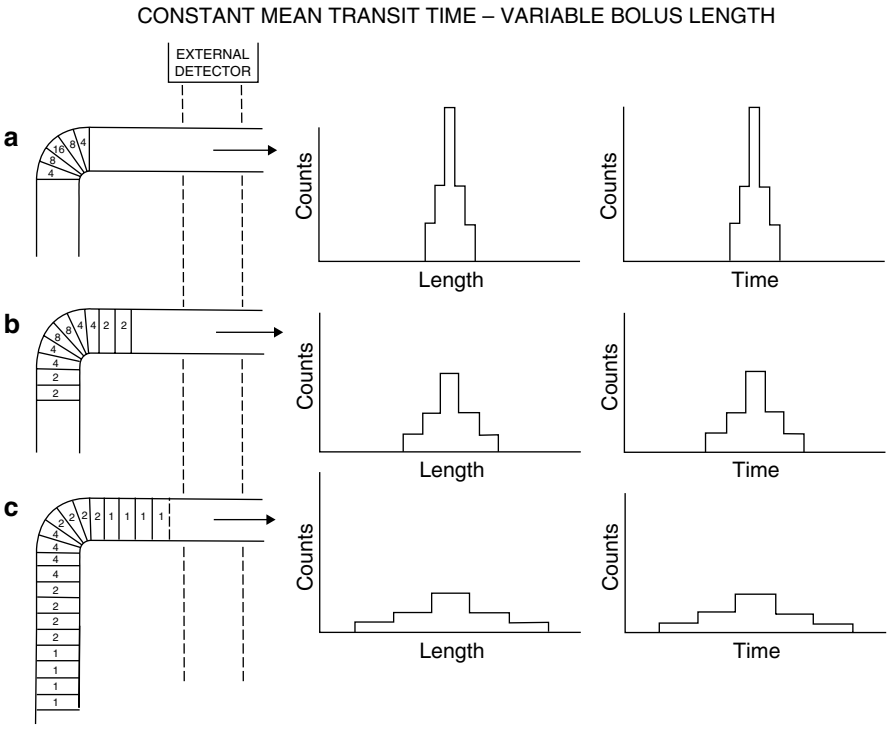

Fig. 6.5 Variable bolus shape. When the bolus shape is varied and all other parameters are kept constant (**a–c** in *1st column*), the time-activity curve varies directly with changes in bolus shape (*2nd column*). However, the area under the curve is constant (*3rd column*)

mean transit times from the point of injection to and through paired ROIs will reflect a difference in the mean transit times from the point of bolus division in the aortic arch to and through the paired ROIs because prior to that point there is only one bolus and one mean transit time. This concept is diagrammatically illustrated in Fig. 6.6.

Using the first circulation blood flow studies of the kidney as an example, regional renal blood flow can then be evaluated by measuring differences in the two physiologic parameters: (1) the mean transit time from the aorta to and through the ROIs and (2) regional blood volume. Regional blood volume is measured from the integral $\int_0^T R(t)\,dt$ as explained above. When a significant asymmetry exists in either of the two physiologic parameters, the abnormal time-activity curve of the pair is determined on the basis of other information in the nuclear medicine study or clinical data. Each time-activity curve of interest is then classified into one of the nine possible combinations of normal, increased, or decreased blood volume and normal, increased, or decreased mean transit time to and through the ROI (Fig. 6.7).

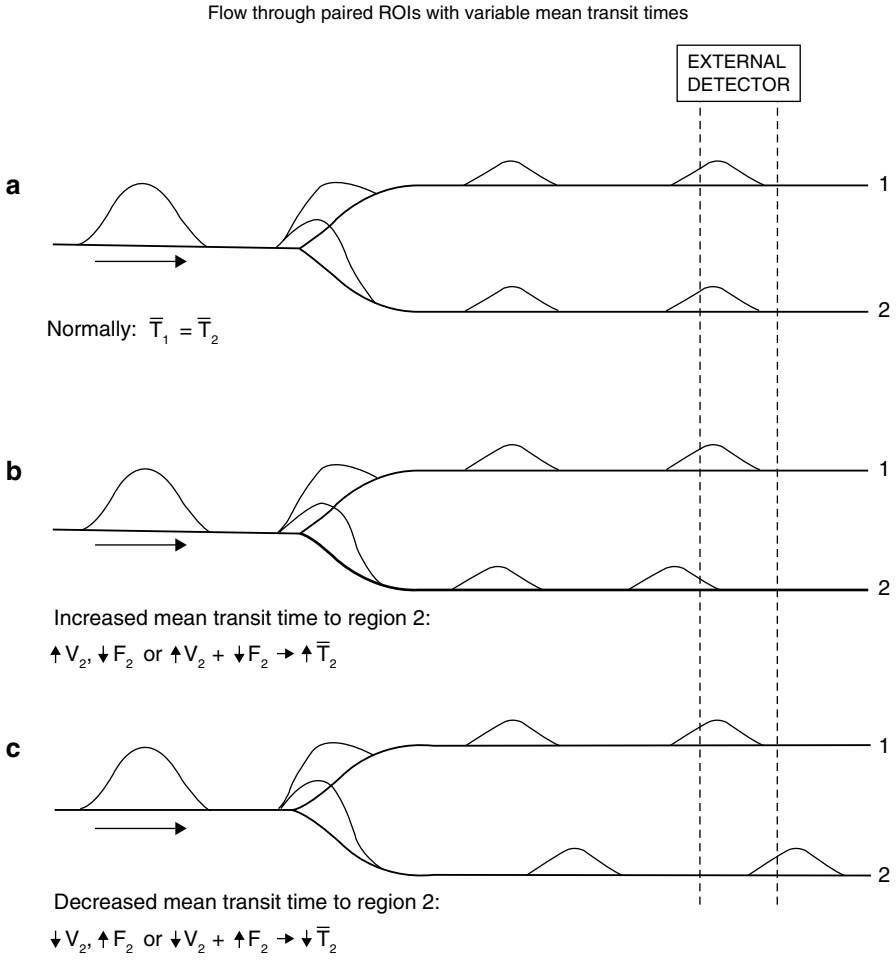

Fig. 6.6 If appropriate changes in flow and/or volume cause an increase in mean transit time in pathway two, the bolus will arrive later at the ROI (**a** v **b**). Conversely, with a decrease in mean transit time in pathway two, the bolus will arrive earlier at the ROI (**a** v **c**)

The findings are related to regional blood flow by the relationship flow equals volume divided by the mean transit time. However, the two physiologic parameters cannot be treated as a quotient because the meant transit time measurement is from the aorta to and through the ROI, not just through the ROI. Thus, the result is not always specific: a normal regional blood volume and an increased mean transit time to and through the ROI can be explained by either decreased flow through the ROI or an increased mean transit time from the aortic arch to the ROI (e.g., a long pathway secondary to collateral flow).

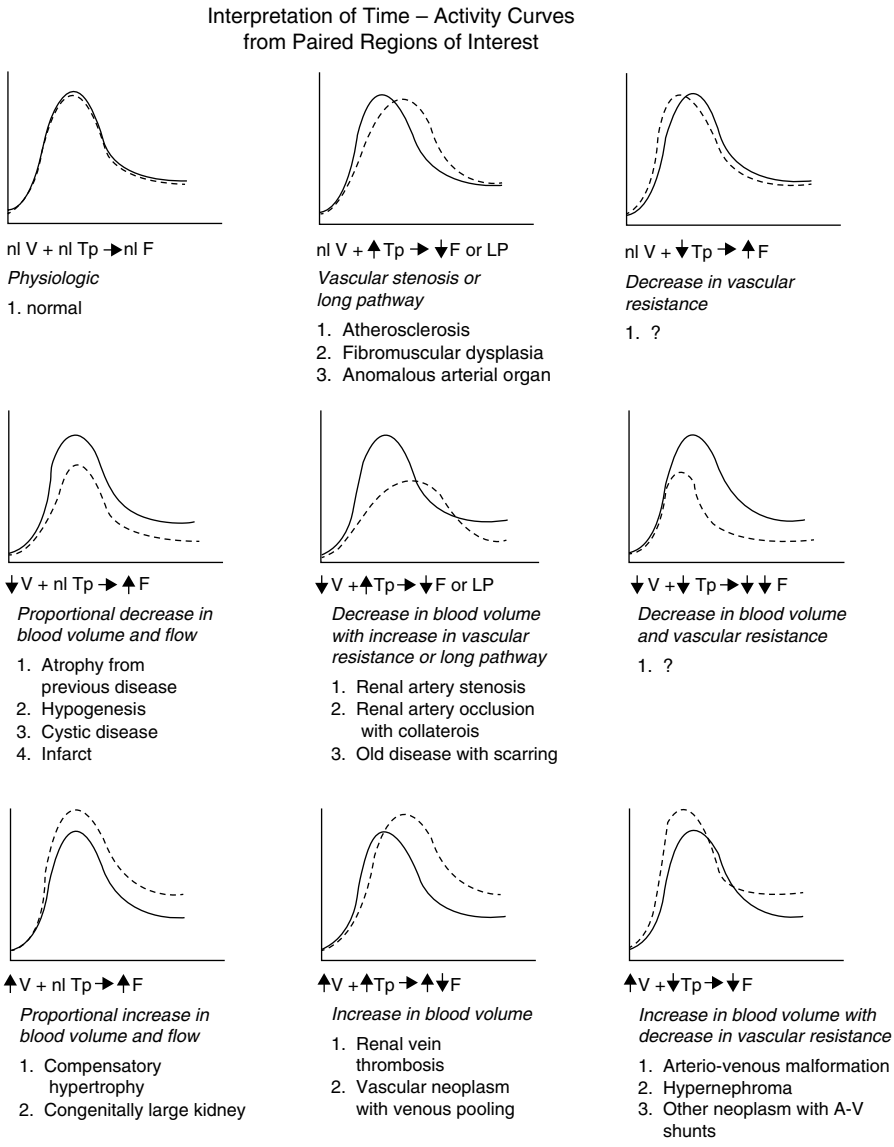

Fig. 6.7 Indices for regional blood volume and transit time to and through a ROI. Each parameter can be categorized as normal, increased, or decreased. This results in nine combinations of findings. Each of the nine different time-activity curve findings implies a pathophysiologic interpretation and a differential diagnosis (*F* flow; *V* volume; *Tp* peak time; *LP* long pathway; *broken line* is the abnormal curve)

Practical Considerations in Using the First Circulation Time-Activity Curves for Evaluation of Regional Blood Flow in Clinical Studies

When a radiopharmaceutical is introduced into the body intravenously in order to acquire images during the first circulation for evaluation of blood flow, an attempt is made to keep the radiotracer as compact as possible as it passes through the circulation. A relatively compact bolus of radiotracer will give a sharper rise and fall in the signal from the serial images that subsequently facilitates analysis. To this end, the injection is usually performed using the Oldendorf technique [12]. In this technique, a tourniquet or blood pressure cuff is placed on the arm and inflated to a pressure between venous and arterial pressure so that blood can enter the arm, but not leave resulting in engorgement of the distal veins.

The small volume of radiopharmaceutical is then injected into a vein, and the blood pressure cuff is quickly removed. The blood in the engorged peripheral venous system propels the radiopharmaceutical centrally to the heart from where it will be distributed systemically in proportion to the distribution of cardiac output. However, the radiopharmaceutical never arrives at the arterial site of interest in a compact form because of laminar flow (see Chap. 5: Mean Transit Time: Central Volume Principle). This phenomenon lengthens the bolus as a function of distance traveled. By the time the bolus reaches the capillary bed in the organ of interest, the bolus is quite long.

Laminar flow causes two problems. First, it lengthens the bolus so that it does not enter the distal ROI in a discrete fashion, and, second, before the elongated bolus has completely passed through the ROI during the first circulation, the leading edge of the recirculating bolus is already reentering the ROI. This phenomenon results in the time-activity curves shown in Fig. 6.2.

In order to calculate both the relative difference in the mean transit time from the aorta to and through the ROIs and the relative blood volume of the ROIs, it must be possible to integrate the time-activity curve during the entire first circulation of the radiopharmaceutical. To accomplish this in the face of recirculating radiopharmaceutical entering the ROIs before the entire first circulation bolus has left the ROIs, a process called a "gamma fit" is applied to the downslope of the time-activity curves (Fig. 6.2). The gamma fit function is a polynomial equation that is adjusted to match a time-activity curve from the arrival of tracer in the ROI to the point at which recirculation begins. The fitted curve is then extended to the baseline.

The evaluation process can be simplified by using indices of the two physiologic parameters in question: (1) the relative blood volume of the ROIs and (2) relative difference in the mean transit time from the aorta to and through the ROIs (Fig. 6.8). Three studies, one experimental and two clinical, have shown that the time of peak activity in the time-activity curve is a good index of the mean transit time from the aorta to and through the ROI, and that the activity level at equilibrium can be used as an index of the blood volume in the ROI [2, 13, 14]. These indices not only facilitate quantitative evaluation by not requiring the gamma fit process but allow visual evaluation as well.

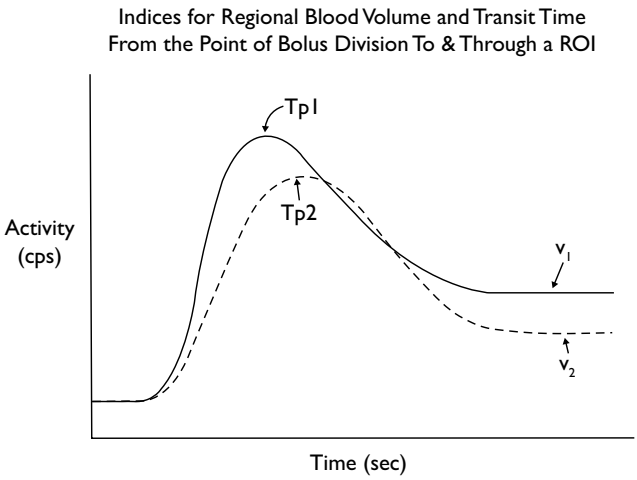

Fig. 6.8 On theoretical and experimental grounds, the amount of activity in a ROI at equilibrium varies with regional blood volume. And, on experimental grounds, the time of peak activity corresponds with the mean transit time from the point of bolus division to and through the ROI.

Clinical Experience with Analysis of the First Circulation Time-Activity Curves for Regional Blood Flow

The method of interpreting first circulation time-activity or time-indicator curves described above has been applied to cerebral blood flow in a variety of brain pathology [2, 14]. In one publication, 36 proven cases of brain pathology were collected from the literature with the requirement that each patient must have had a first circulation time-indicator study and that the curves were reproduced in the publication. In none of the cases were the curves interpreted using the physiologic method described above. In general, the first circulation time-indicator curves were merely characterized as abnormally asymmetrical [14].

Of the 36 cases, 11 were evaluated with radiotracer angiography and 25 were evaluated with dynamic CT. The proven etiologies were compared to the theoretical etiologies that had been published for the nine possible combinations of normal, increased, or decreased mean transit time to and through a ROI and regional blood volume [1]. Twenty six (72 %) of the cases fell into the predicted categories, three (8 %) fell into non-predicted categories, and seven (19 %) had etiologies that were not considered in the theoretical classification [14].

Modification of the Equation for Evaluation of Regional Blood Flow from First Circulation Time-Density Curves for Use with Computed Tomography

Software applications are available from the manufacturers of CT scanners that convert rapid serial images of the brain obtained during the first circulation of intravenous contrast material into parametric images that purport to show regional blood volume, mean transit time, and blood flow within each tomographic image [3–6]. The greater spatial resolution of CT images compared to gamma camera images allows placement of a region of interest over the anterior cerebral artery and generation of a time-density curve that can be treated as the input function to the region of interest of the portion of brain to be evaluated.

The mean transit time through the cerebral region of interest can be calculated by first deconvolving the cerebral time-density curve by the input time-density curve to obtain the frequency distribution of transit times or impulse residue function through the cerebral region of interest (see Chap. 7: Mean Transit Times: Convolution Analysis). Then the mean transit time through the cerebral region of interest can be calculated by dividing the integral of the impulse residue function by the value of the maximum height of the impulse residue function [3]. The contrast enhancement at equilibrium or the integral of the cerebral time-density curve can be used as a measurement of regional blood volume [2, 3]. At this point, the blood flow through the cerebral region of interest can be determined by dividing the regional cerebral blood volume by the mean transit time through the cerebral region of interest using the central volume principle [3].

This approach is critically dependent on the measured input curve being an accurate reflection of the true CT contrast density curve that enters the cerebral region of interest during the first circulation. However, some or all of the arterial input into the cerebral region of interest may come from arteries other than the anterior cerebral artery and have time-density curves that may differ from the time-density curve of the anterior cerebral artery. In addition, some arteries or veins may pass through the cerebral region of interest without connecting to capillary beds within the region of interest, in which case they would contribute to regional blood volume, but not to blood flow to the tissue within the region of interest.

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