Mean Transit Time: The Central Volume Principle

5

Introduction

The so-called central volume principle can be understood by referring to the diagram in Fig. 5.1. The central volume principle describes the relationship among flow, F; volume, V; and mean transit time, $\bar{T}$, as a simple equation [1, 2],

$$F\left(\mathrm{mL}/\mathrm{s}\right)=\frac{V\left(\mathrm{mL}\right)}{\bar{T}\left(\mathrm{s}\right)} \tag{5.1}$$

Here volume is the volume of the single compartment; flow is the constant flow of fluid into, through, and out of the single compartment; and mean transit time is the average transit time of all subpathways through the volume weighted by the volume of each subpathway. The equation can be rearranged to define the mean transit time,

$$\bar{T}\left(s\right)=\frac{V\left(\mathrm{mL}\right)}{F\left(\mathrm{mL}/\mathrm{s}\right)} \tag{5.2}$$

It is obvious from Eqs. 5.1 to 5.2 that if we know any two of the three factors or parameters in the central volume principle equation, we can calculate the third parameter. The easiest parameter to measure in clinical images is volume, usually blood volume. Once a radiopharmaceutical that is essentially confined to the vascular space reaches equilibrium, its relative distribution will reflect blood volume. The hardest parameter to determine is flow, usually blood flow, and therefore, volume and mean transit time are usually determined first and flow is calculated or estimated secondarily.

In addition to playing an important role in a number of nuclear medicine studies as discussed below and in the clinical part of the book, Part III, Quantitative Evaluation in Nuclear Medicine Studies, the central volume principle plays a significant role in the derivation of the equation for evaluation of first circulation

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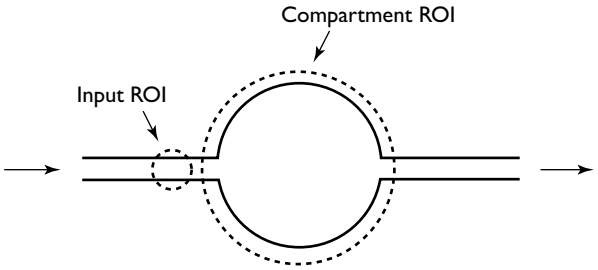

Fig. 5.1 Central volume principle. The drawing shows a simple single-compartment model. The *solid lines* depict a central compartment with a single input on the left and a single output on the right. The *broken circles* indicate regions of interest (*ROI*) for generating time-activity curves during the first pass of a bolus of activity through the model, i.e., no recirculation

time-activity curves, Chap. 6, Blood Flow: First Circulation Time-Activity Curves, and in the mathematical analysis of convolution and deconvolution, Chap. 7, Regional Transit Times: Convolution Analysis.

Conceptual Analysis of the Central Volume Principle

First, consider an instantaneous or impulse introduction of a bolus of radiopharmaceutical at the input to a compartment. Such an injection is sometimes referred to as a delta input or delta function and is depicted graphically in Fig. 5.2.

Now assume that there is plug flow through the compartment so that the transit times through all subpathways through the compartment are the same (Fig. 5.3a). There is no dispersion of the bolus as a function of time and distance traveled (times T, 2T, and 3T). However, in most flowing systems including biological systems, laminar flow predominates with the fastest flow in the center of the tube or vessel and the slowest flow at the margins. The cross-sectional velocity profile approximates a parabola and the bolus length elongates as a function of distance traveled (Fig. 5.3b).

Now consider the appearance of the time-activity curve from a ROI over a compartment generated from the passage of a plug bolus (Fig. 5.4). There appears to be one pathway with all of the activity entering the compartment at zero seconds and leaving it at 15 s. The mean or average transit time will be 15 s.

The mean or average transit time can be calculated by multiplying the amount of activity, 100 %, times the transit time of 15 s, and then dividing the result, 1,500 %-seconds, by the total amount of activity, 100 %, to give 15 s.

In Fig. 5.5 the amount of activity entering the compartment is unchanged and the activity again enters as an impulse bolus. However, now we have two pathways through the compartment. Each pathway contains one half of the total flow and, therefore, one half of the activity. In addition, the top pathway has one third less volume than before and, therefore, a shorter transit time by 5 s. Conversely, the bottom pathway has one third more volume and, therefore, a longer transit time by 5 s (Fig. 5.5). We can determine the mean transit time by calculating a weighted

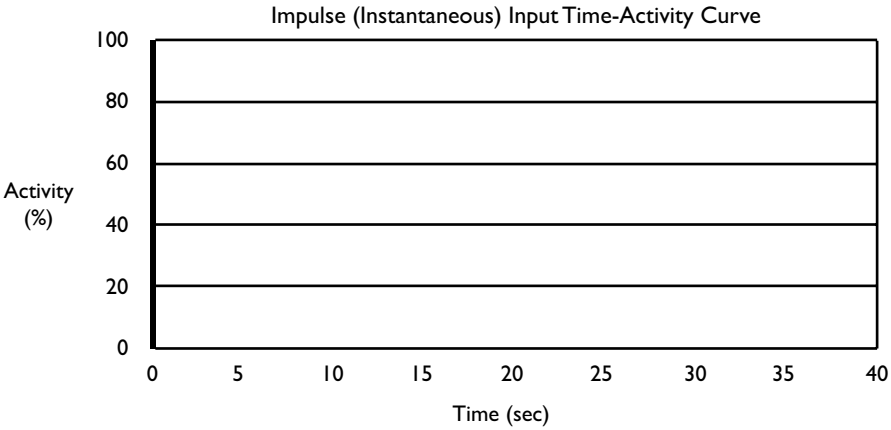

Fig. 5.2 Instantaneous or impulse injection. The curve is generated from the input ROI, not the compartment ROI (Fig. 5.1). The graph demonstrates an instantaneous or impulse input of activity into the compartment. This type of discrete input is also referred to as a delta function

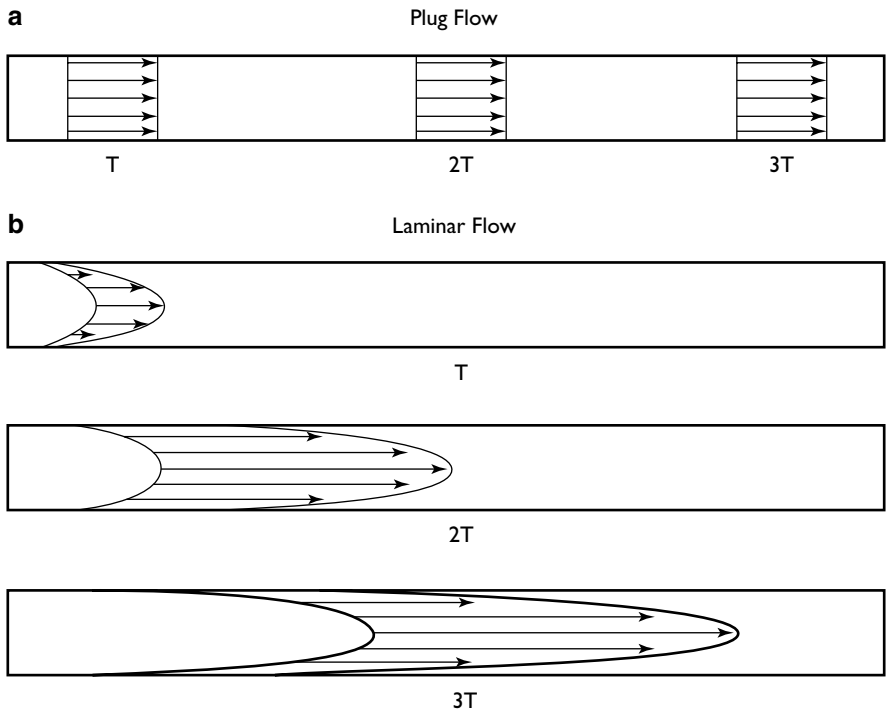

Fig. 5.3 Plug and laminar flow. Panel (**a**) demonstrates the behavior of plug flow at three sequential times (T, 2T, and 3T) after injection of tracer into a flowing system. The relatively discrete shape of the bolus of tracer does not change over time. Panel (**b**) demonstrates laminar flow, typical of biologic systems. Because flow is fastest in the center of a tubular system and falls to near zero at the margins, the bolus elongates as a function of distance traveled

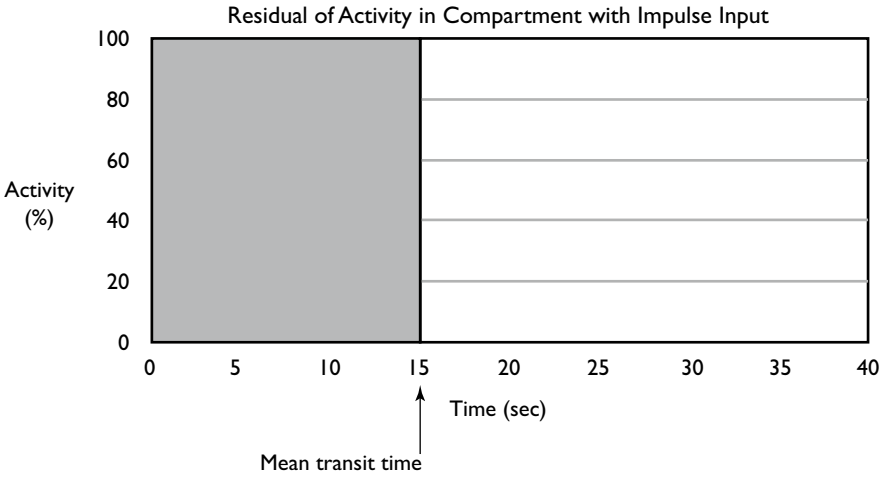

Fig. 5.4 Time-activity curve of plug flow through a compartment. The combination of an impulse introduction of tracer into a compartment and plug flow through the compartment results in a sudden onset of radioactivity in the time-activity curve at time zero, then constant activity, and finally a sudden drop in activity to zero at the time of the mean transit time, 15 s

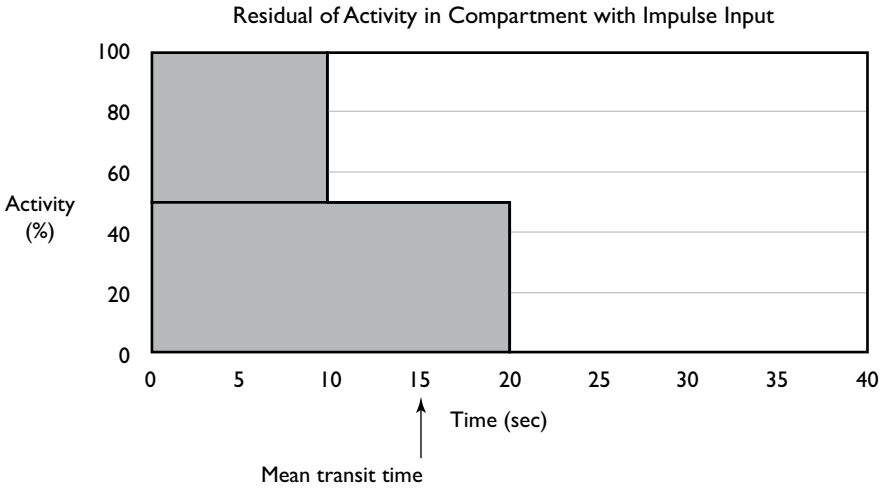

Fig. 5.5 Time-activity curve of plug flow through two pathways in a compartment. Each pathway contains one half of the total flow. The transit time in the *top* pathway is 5 s less than the mean transit time in Fig. 5.4 and the transit time in the *bottom* pathway is 5 s longer. Therefore, the average or mean transit time is unchanged at 15 s

average of the pathways through the compartment. In this case the calculation is 50 % times 10 s plus 50 % times 20 s divided by 100 % or again a mean transit time of 15 s. The overall mean transit time is unchanged as required by the fact that the total flow and volume are unchanged.

Mathematical Analysis of the Central Volume Principle

Now we will look at the general mathematical approach for calculating the mean transit time when there is an impulse input but no limit to the number of pathways, e.g., laminar flow (Fig. 5.6). The residual activity in the compartment is expressed as an equation in terms of activity as a function of time.

In general, in clinical studies, when a bolus of radiopharmaceutical enters and passes through a compartment, the time-activity curve from the compartment is the convolution of the shape of the input bolus and the fractional distribution of transit times through the compartment. However, in the special case when the entering bolus is an instantaneous impulse, the time-activity curve for the compartment will have the same shape as the frequency distribution of transit times (Figs. 5.6 and 5.7).

Then the mean transit time can be calculated by integrating the time-activity curve of the compartment, which has the same effect as weighting the prevalence of the different transit times, and dividing by the total activity, which is equivalent to the initial activity at time zero, A_0,

$$\bar{T}(\mathrm{s}) = \frac{\int_0^T A(t)\,\mathrm{d}t\,(\mu\mathrm{Ci\text{-}s})}{A_0\,(\mu\mathrm{Ci})} \tag{5.3}$$

or integrating the frequency distribution of transit times, which weights the prevalence or percentage of the different transit times, T_{Tran}, and dividing by the sum of the frequencies, or 100 % [1–4]. "T" is the end of the first circulation,

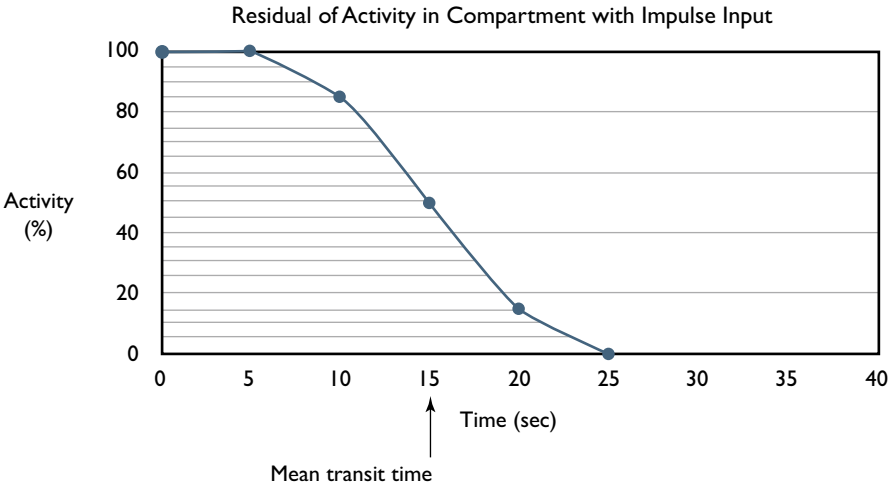

Fig. 5.6 Compartment time-activity curve with impulse input. Because the input is an impulse, all of the activity enters the compartment at zero time. At 5 s none of the activity has passed through the compartment, and at 10 s 20 % of the activity has passed through and out of the compartment. At 15 s an additional 40 % of activity has passed through the compartment and so forth

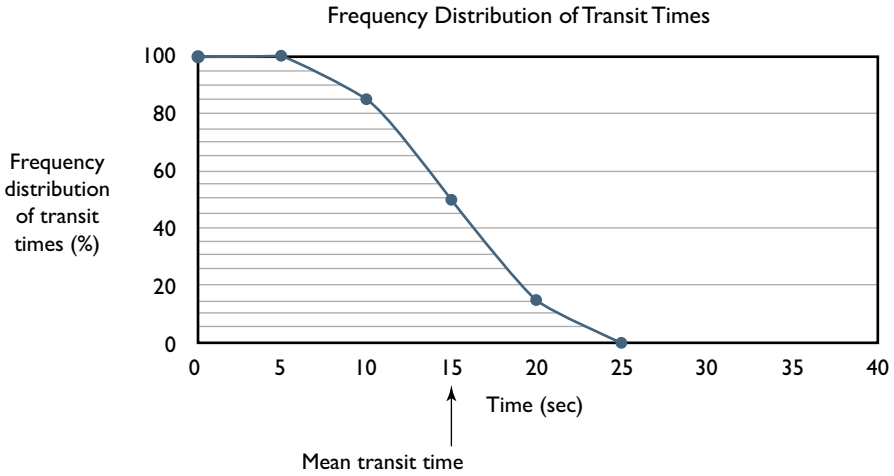

Fig. 5.7 Frequency distribution of transit times. This curve is identical to the one in Fig. 5.6 except for the units of the *Y*-axis. Here the units of the *Y*-axis is "frequency distribution of transit times" in percent rather than "activity" in μCi

$$\bar{T}(\mathrm{s}) = \frac{\int_0^T T_{\mathrm{Tran}}(t)\,\mathrm{d}t\,(\%\text{-}\mathrm{s})}{100(\%)} \tag{5.4}$$

Notice that the curves with units of either activity or percent of transit times effectively reflect the change in residual tracer within the compartment as a function time. Also, notice that the parameter and unit on the *Y*-axis, either percent or activity (μCi), appears in both the numerator and denominator and cancels.

Clinical Applications of the Central Volume Principle

A number of nuclear medicine studies involve the central volume principle, either in studies that are based on flowing fluid, such as blood or cerebrospinal fluid, or that are based on peristalsis (Tables 5.1 and 5.2). However, no nuclear medicine study utilizes the central volume principle in its pure form. The problem is that no nuclear medicine study has a simple compartment and an impulse injection at the entrance to the compartment. Table 5.3 lists the variants of the central volume principle that are found in nuclear medicine studies.

The Ventricular Shunt Study with Tc-99m-DTPA measures the washout half time of the shunt reservoir, which assumes that the tracer is uniformly distributed in the reservoir immediately following injection. The small volume of the reservoir and the turbulence caused by the injection make this assumption reasonable. Thus, the movement of the activity out of the compartment is a washout from the compartment and not a transit time through the compartment.

Table 5.1 Studies that involve the central volume principle, continuous flow, and measurement of a transit time

Study	Radiopharmaceutical	Transit time parameter	Upper limit of normal
Cisternography	In-111-DTPA	Subarachnoid space: lumbar to superior sagittal sinus	24 h
Ventricular Shunt Study	Tc-99m-DTPA	Shunt reservoir: half time of washout from reservoir	Varies with manufacturer
Cardiac Gated Blood Pool Study	Tc-99m-red blood cells	Pulmonary vascular space: right ventricle to left ventricle	6 s
Hepatobiliary Study	Tc-99m-trimethylbromo-IDA	Biliary tract: hepatocytes to extrahepatic bile ducts	10 min
Renal Glomerular Filtration Study	Tc-99m-DTPA	Tubular lumens: glomeruli to calyces	5 min
Renal Tubular Secretion Study	Tc-99m-MAG3	Tubular lumens: tubular cells to calyces	5 min

Table 5.2 Studies that involve the central volume principle and measurement of a transit time but with intermittent movement

Study	Radiopharmaceutical	Transit time parameter	Upper limit of normal
Esophageal Motility Study	Tc-99m-sulfur colloid in water	Esophagus: 90 % emptying	15 s
Gastric Emptying Study	Tc-99m-sulfur colloid labeled oatmeal	Gastric: half time of emptying	60 min

Table 5.3 Variants of the central volume principle in nuclear medicine studies

Form of central volume principle	Study example	Transit time parameter	Measurement compared to $\overline{T}$
Standard	None	Mean transit time	=
Compartment washout	Ventricular Shunt Study	Washout half time	1/2
Leading edge, impulse injection	Cisternography	Leading edge transit time	<
Leading edge, no impulse injection	Hepatobiliary Study	Leading edge transit time	<
Percent emptying, peristalsis	Gastric Emptying Study	Half time of emptying	< or >

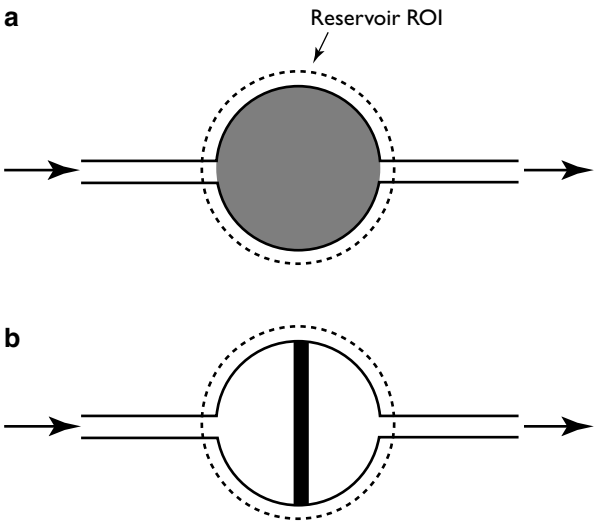

Fig. 5.8 Washout half time vs. mean transit time. In the case of the mean transit time through a compartment, the tracer is injected as an impulse at the input. In the case of the washout transit time, the tracer is initially evenly distributed throughout the compartment (**a**). If the tracer is conceptually concentrated in the mid plane of the compartment, the left to right average distribution is unchanged and it can be understood that the washout transit time will be half of the mean transit time (**b**)

Panel a of Fig. 5.8 shows the tracer (in gray) evenly distributed throughout the reservoir. Panel b shows the tracer after it has been conceptually moved in equal amounts from the left and right sides of the reservoir to the center plane. Thus, when the tracer is evenly distributed throughout the compartment initially, the effective volume that the tracer has to pass through is half the volume of the compartment. Since the washout half time equals one half of the mean transit time of the reservoir, the mean transit time could be easily calculated but rarely is because the adjustment can be made in the normal range.

Although the central volume principle requirement that the input to a compartment be instantaneous is rarely met, it is met in the Cisternography Study. Here the tracer, In-111-DTPA, is injected into the cerebrospinal fluid of the lumbar thecal sac. It then flows upward into the intracranial subarachnoid space and around the cerebral hemispheres and finally is absorbed by the arachnoid villa of the superior sagittal sinus. The problem with applying the standard central volume principle is that the cerebrospinal fluid compartment has a complicated shape and is never entirely within the field of view at a given time. Instead, the leading edge transit time is measured visually, no ROIs are used.

The evaluation of the leading edge transit time through the pulmonary vasculature in the Cardiac Gated Blood Pool Study with Tc-99m-RBCs is unique in that it is determined visually from the leading edge at the beginning and end of the compartment, i.e., from the leading edge appearance of the first circulation of tracer in

the right ventricle to the leading edge appearance of tracer in the left ventricle. The most common cause of an increased pulmonary leading edge transit time is left ventricular failure, which causes a decrease in cardiac output, i.e., flow, and pulmonary congestion, i.e., an increase in pulmonary vascular volume. Both changes cause an increase in the pulmonary vascular transit time.

In three studies, the Hepatobiliary Study, Renal Tubular Secretion Study, and Renal Glomerular Filtration Study, the leading edge transit time through parenchyma is measured visually (Table 5.1). In each study it is impractical to determine when the leading edge enters the parenchymal excretory pathway so the time of injection is used. This modification works because the transit time from site of injection to organ parenchyma is short, approximately 15 s, compared to the time it takes for the tracer to pass through the parenchyma and reach the proximal excretory collecting system of the respective organs, 10 min for the hepatobiliary system and 5 min for renal parenchyma. In the case of the two renal studies, the parenchymal transit time is also measured with ROIs and time-activity curves. The half time from the peak should occur by 10 min after the peak.

In the case of the Esophageal Transit Study and the Gastric Emptying Study, the initial input is relatively quick and at the proximal end of the compartment in question, similar to an impulse input. But the esophagus and stomach do not have fixed volumes and the movement is secondary to peristalsis, not constant flow. In addition, it is more convenient to measure a standardized normal percent of emptying at a standard time after tracer administration rather than to try to measure a mean transit time.

The central volume principle is at work to a varying degree in a number of other nuclear medicine studies, but in those studies evaluation of a transit time is not considered to be clinically useful.

The clinical uses of the central volume principle will be discussed in greater detail in Part III, Quantitative Evaluation in Nuclear Medicine Studies.

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