Regional Transit Times: Convolution Analysis

7

Introduction

There are five nuclear medicine studies in which a series of time-dependent images depict the movement of the radiopharmaceutical through a structure (Table 7.1). If a region of interest (ROI) is placed over the structure of interest, the shape of the resulting time-activity curve is determined by a combination, or convolution, of the shape of the incoming bolus of radiopharmaceutical and the spectrum of transit times through the structure of interest. The structure of interest may be either the vascular bed of an organ or an excretory pathway through the parenchyma of an organ.

The first four studies in Table 7.1 include rapid serial images during the first circulation of a radiopharmaceutical through a vascular bed for the purpose of evaluating blood flow through paired regions of interest. Two of these studies include the routine generation of time-activity curves, the Renal Tubular Secretion Study with Tc-99m-MAG3 and the Renal Glomerular Excretion Study with Tc-99m-DTPA, and two studies do not, the Brain Death Study with Tc-99m-DTPA and the three-phase Bone Mineral Study with Tc-99m-MDP of the lower extremities. However, the same principles that are used to evaluate paired time-activity curves can be used to visually evaluate the paired structures in the rapid serial images acquired during the first circulation.

There are three studies in Table 7.1 that include rapid serial images during the movement of a radiopharmaceutical through an excretory system that excretes molecular waste from the blood. Two of these studies are of paired organs: the Renal Tubular Secretion Study with Tc-99m-MAG3 in which serial images depict the tracer moving from the tubular cells through the tubular lumens to the calyces and the Renal Glomerular Filtration Study with Tc-99m-DTPA in which serial images depict the tracer moving from the glomeruli through the tubular lumens to the calyces. One study is of an unpaired organ: the Hepatobiliary Study with Tc-99m-trimethylbromo-IDA in which serial images depict the tracer moving from the hepatocytes through the liver parenchyma into the extrahepatic biliary tract.

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Table 7.1 Nuclear medicine studies that include serial images of tracer moving through the vascular or excretory pathway of an organ

Procedure	Radiopharmaceutical	Parameter	Paired structures	Time-activity curves
Renal tubular secretion study	Tc-99m-MAG3	Blood flow	Yes	Yes
		Parenchymal transit	Yes	Yes
Renal glomerular filtration study	Tc-99m-DTPA	Blood flow	Yes	Yes
		Parenchymal transit	Yes	Yes
Bone mineral study (three phase)	Tc-99m-MDP	Blood flow	Yes	No
Brain death angiography study	Tc-99m-DTPA	Blood flow	Yes	No
Hepatobiliary study	Tc-99m-trimethyl-bromo-IDA	Parenchymal transit	No	No

Time-activity curves are generated in the two renal studies, but not in the hepatobiliary study.

In all of these studies and for evaluation of both blood flow and excretion through parenchyma, the radiopharmaceutical bolus will be elongated as it approaches the organ of interest, even though it starts out as a discrete plug bolus at the site of intravenous injection (Fig. 7.1). The elongation of the bolus is caused by the physical process of laminar flow, which causes the length of the bolus to increase in proportion to the distance traveled through the vascular system.

Figure 7.2 demonstrates how variation in bolus shape affects the time-activity curve shape with all other factors held constant. However, in keeping with the Stewart-Hamilton equation, the area under the time-activity curve remains constant.

One difference between the application of convolution analysis to the study of vascular systems and excretory systems is that, while vascular systems involve just one set of transit times added sequentially to the incoming elongated bolus, excretory systems have an additional process, clearance via an extraction mechanism, that moves the radiopharmaceutical from the blood into the excretory pathways. This extra biologic process adds another variable, which may have a significant impact.

Convolution and its inverse, deconvolution, are mathematical concepts that will be explained in some detail below [1, 2]. Although the actual calculations are not performed in nuclear medicine studies, a conceptual knowledge of convolution and deconvolution is helpful in interpreting blood flow and excretory images [3]. Examples of the use of these concepts are given in the various chapters of Part III, Quantitative Evaluation in Nuclear Medicine Studies.

Conceptual Analysis of Convolution

Consider the simple diagram in Fig. 7.3. There is a central compartment with one way for fluid to flow in on the left and one way for fluid to flow out on the right. In addition, regions of interest (ROIs) are drawn at the location of fluid input and around the compartment as a whole.

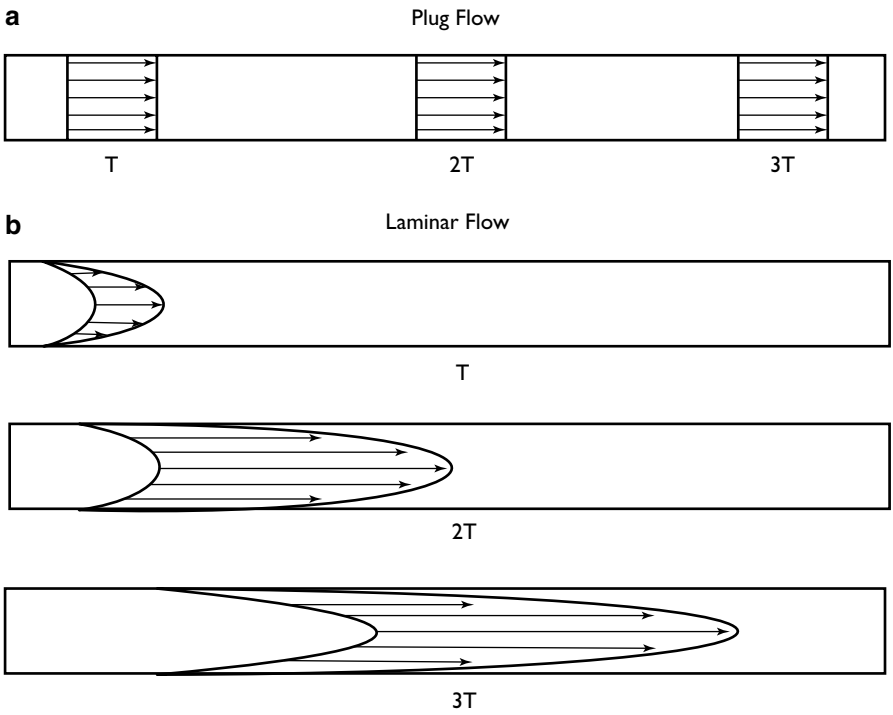

Fig. 7.1 Plug and laminar flow. Panel **a** demonstrates the behavior of plug flow at three sequential times (T, 2T, and 3T) after injection of tracer into a flowing system. The relatively discrete shape of the bolus of tracer does not change over time. Panel **b** demonstrates laminar flow, typical 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 distance traveled (T, 2T, and 3T)

In the case of evaluating blood flow through the vascular system of an organ, the input structure on the left represents the arterial inflow into the organ, the compartment represents the vascular system within the organ, and the output structure on the right represents the venous flow out of the organ. In the case of an excretory system like the renal tubular secretion system or hepatobiliary system, the input structure represents the arterial supply to the parenchyma, the compartment represents the parenchyma, and the output structure represents the excretory structures that carry fluid from the parenchyma, i.e., calyces and more distal excretory structures in the case of the kidneys and extrahepatic biliary tract in the case of the liver and hepatobiliary system.

For both vascular and excretory systems, there are thousands of individual pathways through an organ. Not all of the vascular or excretory pathways will have the same transit time. The transit time may vary because the pathways have different: amounts of flow, lengths, or luminal diameters. In disease the variation in transit times through these pathways often increases greatly.

Figure 7.4 shows the distribution of transit times through the compartment in Fig. 7.3.

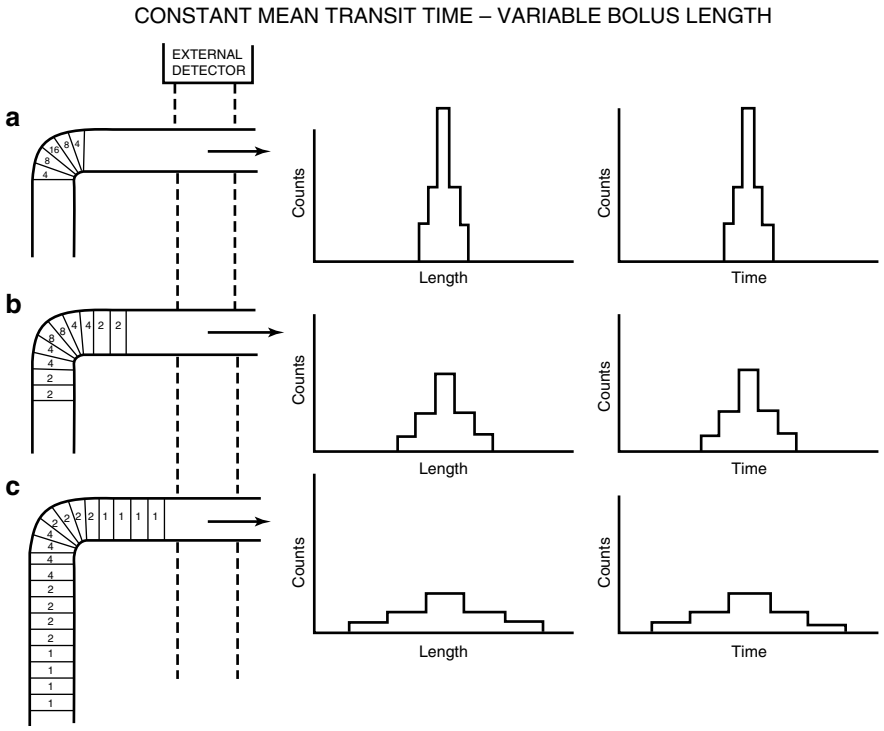

Fig. 7.2 Variable bolus shape. When the bolus shape is varied (**a**–**c**) and all other parameters are kept constant, the time-activity curve varies directly with changes in bolus shape (*1st* and *2nd columns*). However, the area under the curve is constant (*3rd column*)

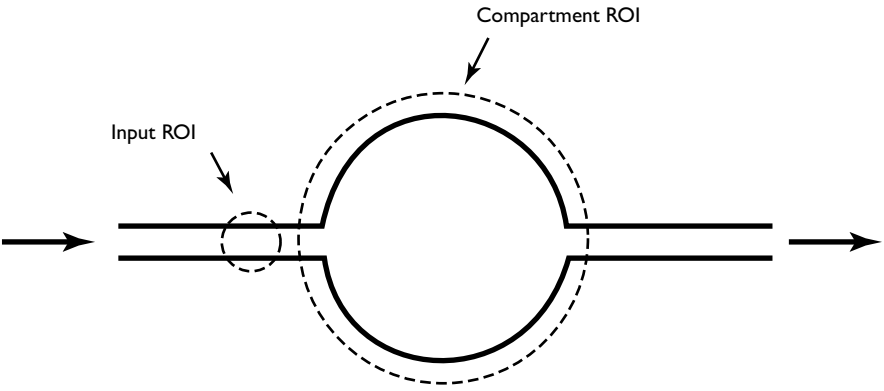

Fig. 7.3 Simple single compartmental model. The *solid lines* depict a single central compartment with a single input on the left and a single output on the right. The *broken circles* indicate regions of interest (ROIs) for generating time-activity curves during the passage of a bolus of tracer

Figure 7.5 depicts an instantaneous or impulse injection of tracer into the compartment. The time-activity curve is recorded from the ROI over the input site, not the compartment itself.

A true instantaneous injection is never encountered in the clinical setting. However, it is useful to initially look at a simple impulse injection before considering the more complex situation of an input bolus that is spread out over distance and time.

Figure 7.6 shows the percent of activity left in the compartment as a function of time assuming that the activity was introduced into the compartment as an impulse

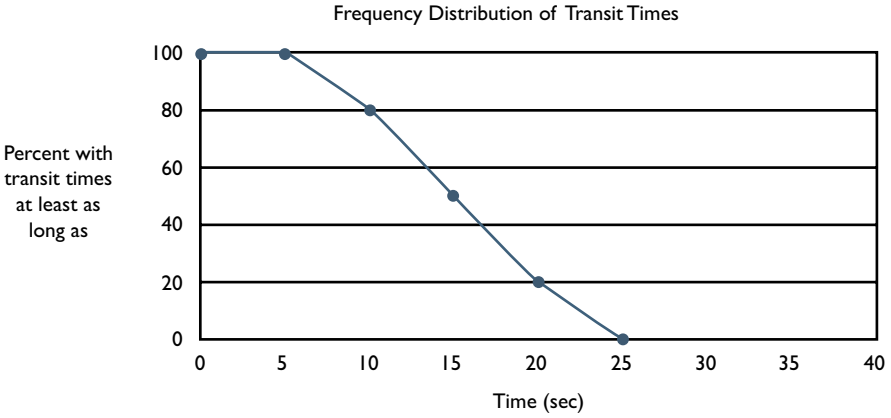

Fig. 7.4 Frequency distribution of transit times through a compartment. The graph shows that the shortest transit time through the ROI is 5 s and the longest is 25 s

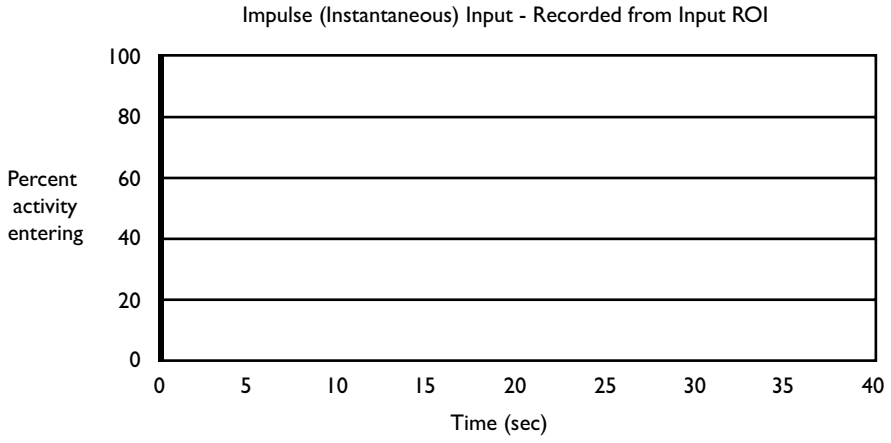

Fig. 7.5 Impulse introduction of tracer. The graph shows an impulse introduction of tracer into the compartment. The time-activity curve is from the ROI at the input to the compartment, not from the compartment itself

or instantaneous injection. Again, 100 % of the radiopharmaceutical enters the compartment initially at one point in time. Then at 5 s none of the radiopharmaceutical will have exited the compartment, at 10 s 20 % of the original amount will have exited, at 15 s 50 % will have exited, at 20 s 80 % will have exited, and by 25 s all of the tracer will have exited. The curve is unchanged from the curve of the distribution of transit times in Fig. 7.4 except for the units on the Y-axis because all of the radiopharmaceutical enters the compartment simultaneously and the transit times are determined by measuring the transit time of individual pathways and displaying them with the same starting time. This is the simplest form of the convolution. No deconvolution is needed.

Table 7.2 presents the same simple impulse input example, but in table form. First, notice that the red numbers in the first row and first column are times in seconds. Second, notice that the green numbers in the second row are the percent of tracer exiting the compartment at the indicated time. Thus, no tracer exits at 0 or 5 s, 20 % of the original amount exits at 10 s, 30 % of the original amount exits at 15 s, another 30 % of the original amount exits at 20 s, and the final 20 % exits at 25 s. Third, notice that the blue numbers in the second column indicate the amount of the incoming bolus that enters the compartment as a function of time. In this case the total amount of radiopharmaceutical is 100 and all of the radiopharmaceutical enters at time zero. The numbers within the outlined black rectangle indicate the amount of radiopharmaceutical remaining in the compartment as a function of time. At zero and 5 s 100 % remains in the compartment, at 10 s 80 % remains, at 15 s 50 % remains, etc. There is no activity in the other cells within the box because the entire input bolus enters the compartment at time zero. The bottom row of the entire table shows the sum of activity that remains in the compartment as a function

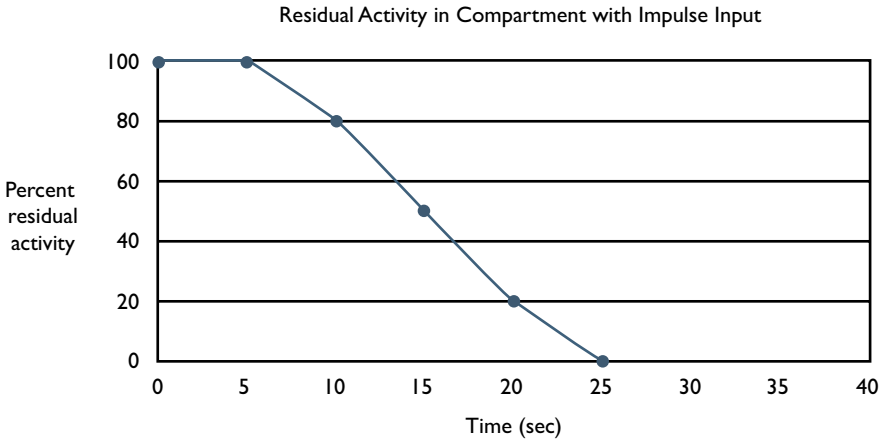

Fig. 7.6 Residual activity in a compartment vs. time. The graph shows residual activity in a compartment as a function of time following an impulse input. With an impulse injection, the curve will be identical to the frequency distribution of transit times (Fig. 7.4)

of time. The amounts are the same as the first row within the black rectangle because, again, no activity enters after time zero.

Now we consider the effect on the graphs and table if the input bolus is a typical non-impulse bolus. Fig. 7.7 shows the shape and activity as a function of time of an incoming bolus that has length because of laminar flow. We will discuss the curve

		Input										
	Sec		0	5	10	15	20	25	30	35	40	45	Sum
Percent exiting			0	0	20	30	30	20	0	0	0	0	
	0	100	100	100	80	50	20	0					350
	5	0											0
	10	0											0
	15	0											0
	20	0											0
Activity in ROI			100	100	80	50	20	0	0	0	0	0	350

Sum = Sum of counts from each cohort as it passes through ROI.

Table 7.2 Convolved activity in compartment with impulse input. Sum = Sum of counts from each cohort as it passes through ROI

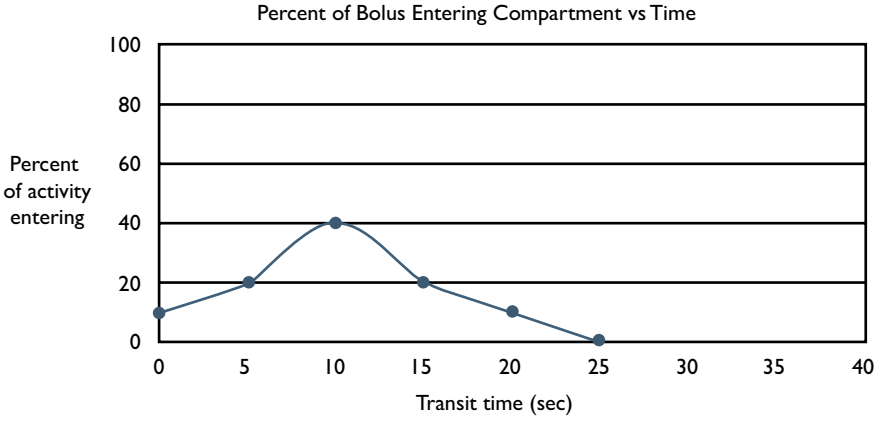

Fig. 7.7 Percent of bolus entering compartment vs. time. The graph shows the percent of a typical non-impulse bolus entering a compartment over time. The elongated bolus enters the compartment over 25 s. This curve is generated from the input ROI in Fig. 7.3

in discrete terms, but in actuality it would be continuous. Ten percent of the incoming bolus enters the compartment at 0 s, 20 % enters at 5 s, 40 % enters at time 10 s, etc. This means that at each of the time points that we are considering, 5 s intervals, a new cohort of activity will begin to pass through the compartment with the distribution of transit times shown in Fig. 7.4 and the residue versus time curve shown in Fig. 7.6. The time-activity curve in Fig. 7.7 is generated from the input ROI in Fig. 7.3.

Table 7.3 presents the information for compartment activity when the input is distributed over time as is typical in clinical studies. Compared to Table 7.2 the second column (blue numbers) now shows tracer entering the compartment over five successive points in time. In addition, within the black rectangle (corresponding to the compartment), the amount of residual activity for each entering cohort is shown as a function of time with the appropriate weighting for the amount entering and the appropriate time shift to reflect the time of entry into the compartment. The total amount of activity in the compartment at any one point in time is shown in the bottom row opposite the heading "Activity in ROI."

In general, for a given amount of radiopharmaceutical, the time-activity curve from the compartment ROI will be much broader and flatter with a non-impulse input compared to an impulse input (Fig. 7.8).

		Input										
Sec		0	5	10	15	20	25	30	35	40	45	Sum
Percent exiting		0	0	20	30	30	20	0	0	0	0	
0	10	10	10	8	5	2	0					35
5	20		20	20	16	10	4	0				70
10	40			40	40	32	20	8	0			140
15	20				20	20	16	10	4	0		70
20	10					10	10	8	5	2	0	35
Activity in ROI		10	30	68	81	74	50	26	9	2	0	350

Sum = Sum of counts from each cohort as it passes through ROI.
Activity is in arbitrary units.

Table 7.3 Convolved activity in compartment with non-impulse input. Sum = Sum of counts from each cohort as it passes through ROI. Activity is in arbitrary units

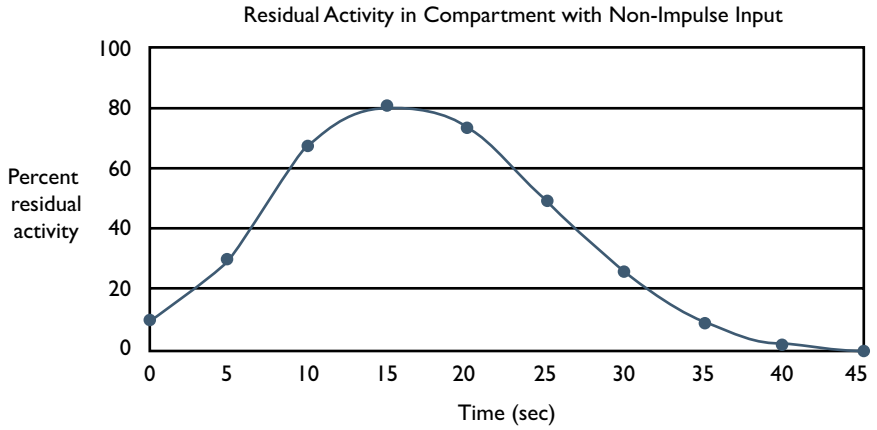

Fig. 7.8 Residual activity in a compartment with a non-impulse input. The residual activity curve with a non-impulse input is the convolution of the elongated input curve and the distribution of transit times through the compartment

Mathematical Analysis of Convolution

The same concepts of convolution presented above in terms of graphs and tables will now be presented mathematically. However, it is important to note that the following equations do not need to be solved, or even directly used, in order to apply the concepts of convolution to image interpretation.

The mathematical version of convolution is the time-activity curve (expressed as a function) for the non-impulse input curve, $f(i)$, convolved with the transit time distribution curve (expressed as a function) for the compartment, $f(g)$, to yield the observed time-activity curve (expressed as a function) of the passage of the radiopharmaceutical through the compartment, $f(a)$,

$$f(a) = f(g) \otimes f(i) \tag{7.1}$$

where '$\otimes$' is the convolution operator, which performs the same three operations demonstrated above in graphical and table form. The three operations are: (1) weighting the parenchymal response by the amount of radiopharmaceutical entering the parenchyma at a given time (multiplication), (2) shifting the resulting curve in time to correspond to the changing entry time (subtraction), and (3) summing the resulting time-activity curves to produce the final observed parenchymal time-activity curve or function (addition).

Equation 7.1 can be expanded in calculus form as the convolution integral,

$$A(t) = \int_0^T I(u)\ G(t-u)\, du \tag{7.2}$$

where on the left hand side $A(t)$ is the observed compartmental time-activity curve or function and on the right hand side: (1) the two functions within the integral, input and response, are multiplied together to give the appropriate cohort weighting, (2) the variable u produces the cohort time shift (T is the end of the first circulation), and (3) the integral summates the cohorts.

If it were possible to measure the input time-activity curve, $I(u)$, as the radiopharmaceutical bolus entered a vascular bed or excretory region, then the input curve could be used to deconvolve (the inverse of convolution) the time-activity curve generated from the structure under study, $A(t)$, which in turn would yield the transit time function for the vascular or excretory region of interest (Fig. 7.4). The transit time function can be used to calculate the mean transit time through the region of interest. The mean transit time is of great interest because, in conjunction with the regional blood volume of a structure, it can be used to calculate the flow through the structure using the central volume principle (see Chap. 5, Mean Transit Time: Central Volume Principle). Unfortunately, nuclear medicine studies, at least currently, do not have the spatial resolution to generate accurate input time-activity curves.

Clinical Applications of Convolution and Transit Times

We will use the Renal Tubular Secretion Study with Tc-99m-MAG3 as an example of how to evaluate the transit time of a radiopharmaceutical through an excretory organ in a clinical study. There are actually two transit times that are evaluated in the Renal Tubular Excretion Study: (1) blood flow to and through the kidneys and (2) passage of the tracer through the parenchyma. Here we will only discuss evaluation of the parenchymal transit time, which is quantitated both visually and with time-activity curves. Then, in Part III, Quantitative Evaluation of Nuclear Medicine Studies, we will examine the specific approach to the evaluation of transit times in all of the nuclear medicine studies that involve transit times, integrate the transit time findings with other physiologic parameters, and survey examples of diseases that cause abnormal transit times.

Figure. 7.9 shows a complete set of images from a normal Renal Tubular Secretion Study in the top half of the composite, and documentation of the placement of ROIs and resulting time-activity curves in the bottom half. We will focus on the components that relate to evaluating the transit time through the excretory pathways of the renal parenchyma. The pertinent images and time-activity curves are the so-called delayed images from 1 min to the end of the study at 30 min (Fig. 7.10) and the time-activity curves generated from the cortical ROIs (Fig. 7.11), respectfully.

The cortical ROIs are used instead of the whole-kidney ROIs so that the time-activity curves reflect just the renal parenchyma without contamination from activity in the collecting system, i.e., calyces, infundibula, and renal pelvis.

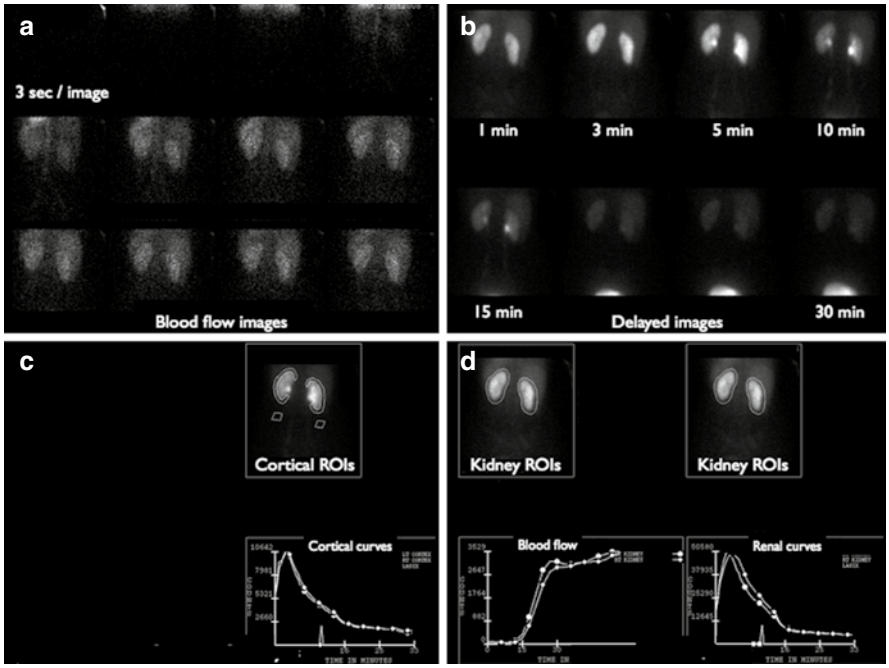

Fig. 7.9 Normal renal tubular secretion study with Tc-99m-MAG3. The *upper left* panel shows the blood flow images. The *upper right* images are the delayed images. The *lower two* panels show the placement of ROIs and the resultant time-activity curves

As explained above the evaluation of parenchymal transit cannot be done in the ideal way of using deconvolution to generate a curve of residue transit times because of the difficulty of measuring the input time-activity curve to the renal parenchymal. However, parenchymal transit times can be evaluated in a fairly robust fashion using visual evaluation of the images and analysis of the cortical time-activity curves.

The visual evaluation of the images relative to transit times begins by checking the first circulation blood flow images (Fig. 7.9a) to determine if there was any problem with the incoming time-activity curve, most commonly because of an extravasated injection. This is done by looking to see how many 3 s images show the aorta; it should be no more than four images or 12 s.

Then the delayed images (Fig. 7.10) are visually compared to a mental image of normal. The leading edge transit time through the renal parenchyma, i.e., the time that activity is first seen in the collecting system, should occur between 3 and 5 min, i.e., the upper collecting systems should appear in the 3 or 5 min image. A delay, beyond 5 min, indicates a prolonged parenchymal transit time and usually acute renal disease, e.g., acute tubular necrosis. The prolonged parenchymal transit time may be caused by parenchymal edema and narrowing of the tubular lumens. Chronic

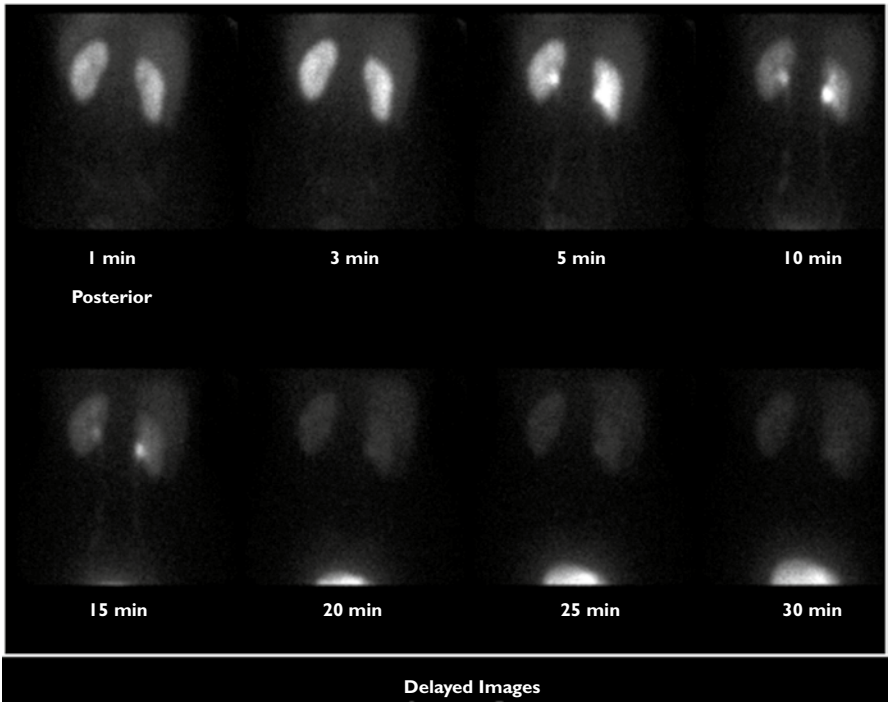

Fig. 7.10 Delayed images from Fig. 7.9. These images are used to determine the leading edge transit time trough the parenchyma. Normally, activity should be seen in the calyces by 5 min

renal disease without an acute component usually does not significantly prolong the parenchymal transit time, e.g., chronic glomerulonephritis.

The cortical time-activity curves provide a more quantitative measure of the leading edge transit time through the parenchyma (Fig. 7.11). The upper limits of normal is 4 min consistent with the criterion that activity should be seen in the collecting system no later than in the 5 min image.

Since the concentration of activity in the blood peaks soon after injection of the radiopharmaceutical and then continuously falls, the activity in the renal tubular lumen will also peak with the initial excreted activity and then gradually fall. Thus, after a time sufficient for the leading edge of activity in the tubular lumen to reach the calyces (leading edge transit time), there will be more activity leaving the parenchyma than entering it (Fig. 7.12).

In addition to the leading edge transit time, there is a second measurement that is useful in evaluating parenchymal transit time, the time following peak activity at which the cortical (parenchymal) time-activity curve reaches a value that is half of the peak value, that is, the half peak time. Normally, the half peak value

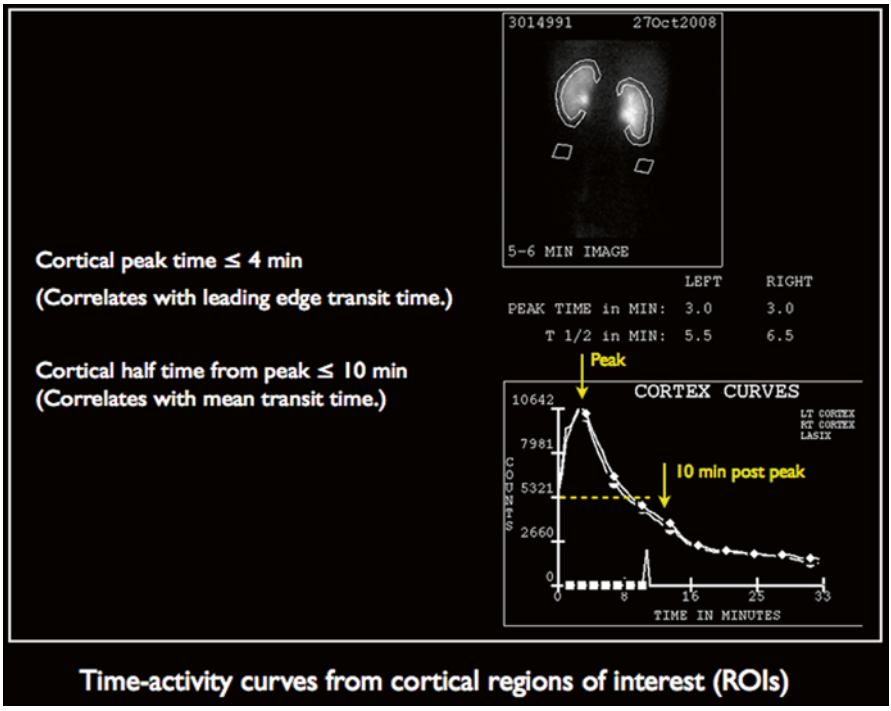

Fig. 7.11 Normal cortical time-activity curves. The peak time of the cortical time-activity curve corresponds to the leading edge transit time. In addition, the peak activity should drop at least in half by 10 min after the peak time

occurs by 10 min from the peak time (Fig. 7.11). This measurement is relatively sensitive to the mean parenchymal transit time. Any prolongation of the half peak time beyond 10 min is another indication of a prolonged parenchymal transit time and of an acute renal parenchymal process such as acute tubular necrosis.

It is not infrequent to have a normal leading transit time, i.e., excretion of activity into the collecting structures by 5 min, but a prolonged half peak time, i.e., half peak time of more than 10 min after the peak. This combination usually results from regional variation of disease and transit times in the kidney. If at least twenty percent of a kidney is normal, the parenchyma will excrete enough radiopharmaceutical with a normal transit time to give a normal leading edge transit time. However, because eighty percent of the kidney has a prolonged transit time, the overall half peak transit time will be prolonged. An example of a disease that typically causes this combination in transit time parameters is acute pyelonephritis. Visual evaluation of the images will show normal tracer washout in some of the renal parenchyma and delayed tracer transit in the rest of the parenchyma.

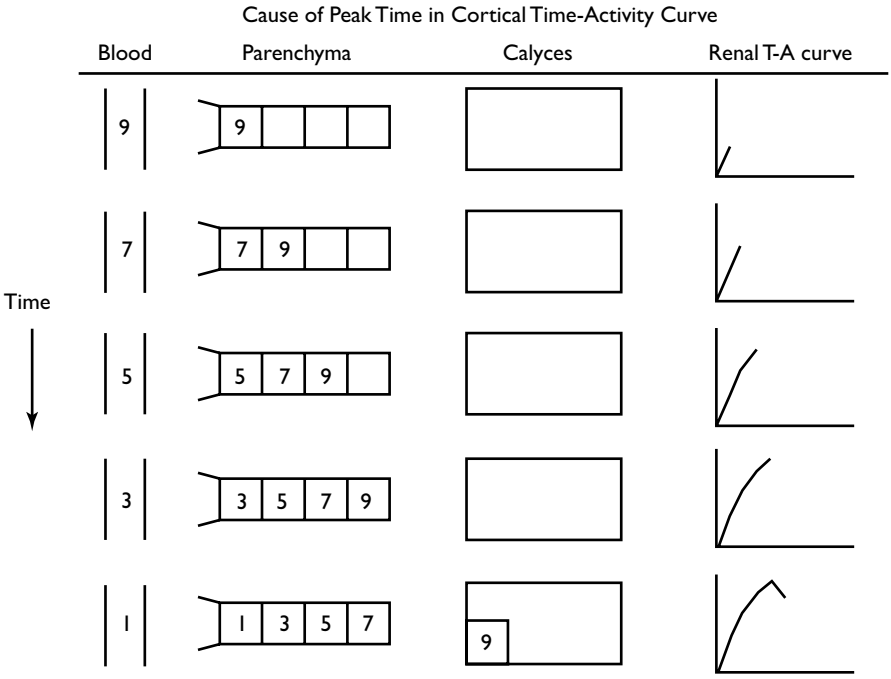

Fig. 7.12 Cause of peak time in cortical time-activity curve. This diagram shows the concentration of tracer in the blood falling after the initial introduction of tracer. This phenomenon causes the concentration of tracer entering the tubular lumen to fall over time as well. Thus, when activity first leaves the tubular lumen and enters the calyces, more activity will leave the parenchyma than enters and the cortical time-activity curve will peak

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