Mean Transit Time: Proof and Esophageal Example

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The transit of radioactive tracers in human systems provides information of physiologic and diagnostic importance. A simple, nontechnical proof is offered for the formula for computation of mean transit time as area/height of a time-activity curve. It is specifically applicable to esophageal transit, and may also serve to illuminate other uses in nuclear medicine. The alternative centroid formula for mean transit time differs in meaning but is compatible with the area/height formula. Considerations regarding mean transit time suggest ways to determine the attenuation of radioactivity that affects a compartment under study.

The transit of radioactive tracers in human systems provides information of physiologic and diagnostic importance. An area/height formula for mean transit time (MTT) has been previously demonstrated (*1–3*). Thus:

$$MTT = A/h, \qquad \text{(Eq. 1)}$$

where, in a radioactive tracer study, A is the area and h is the height of a time-activity curve representing transit through a compartment. More specifically, A represents the total counts accumulated, and h represents the counting rate of the total amount of tracer administered, with A and h being identically affected by tissue attenuation and efficiency of the counting instrument.

Among many applications in nuclear medicine is the computation of esophageal MTT (*4*). Drawing on this example, the author proposes a simple formulation of the proof, less technical than the standard one (*1–2*), that area/height equals mean transit time.

PROOF

Consider a compartment (e.g., the esophagus) that is defined in its entirety as a region of interest (ROI), extending between the inlet and the outlet of radioactive particles dispersed in a nonradioactive carrier medium. As the tracer material passes through the esophagus, a scintillation camera registers the radioactivity in the region and, with the aid of computer processing, a time-activity curve is generated. We assume: 1) that the particles have a constant counting rate per unit mass, 2) that the region is subject to equal attenuation throughout (which may sometimes be achieved using a correction technique), 3) that there is a period of time when all the particles are simultaneously within the region, 4) that all the particles that enter also leave the region, and 5) that none of them return, as we wish to register only the transit of an initial pass. So long as those conditions are met, there are no restrictions as to the shape of the curve to which the formula is applied, and the flow rate of fluid need not be constant.

We characterize the material under study as consisting of n radioactive particles with masses $m_1, m_2, \ldots m_n$, with the counting rate per unit mass (as registered in the detector) designated k. The various particle masses may be the same or different. Their total mass is given by:

$$M = m_1 + m_2 + \ldots + m_n. \qquad \text{(Eq. 2)}$$

Each particle has its own individual transit time through the region, $t_1, t_2, \ldots t_n$, and we seek their mean as an average over the mass of particles.

The maximum counting rate, or height, h, of the curve, occurs during the period of time when all the particles are within the ROI, and therefore clearly represents the counting rate of the entire portion. But this quantity is also calculable as the total mass of particles times the counting rate per unit mass (k). Hence:

$$h = kM. \qquad \text{(Eq. 3)}$$

Each particle makes a contribution to the area, A, of the curve (i.e., the total counts accumulated). For the *i*th particle, this contribution consists of the product of three factors: m_i, its mass; k, the counting rate per unit mass; and t_i, its individual transit time—the length of time that it spends in the compartment. Summing the individual contributions, we have:

$$A = m_1kt_1 + m_2kt_2 + \ldots + m_nkt_n. \qquad \text{(Eq. 4)}$$

Analogously to any average, one computes MTT by summing the individual mass-times-transit-time products, and dividing by the total mass:

$$MTT = (m_1t_1 + m_2t_2 + \ldots + m_nt_n)/M. \qquad \text{(Eq. 5)}$$

We multiply numerator and denominator on the right side of Eq. 5 by k:

$$MTT = (m_1kt_1 + m_2kt_2 + \ldots + m_nkt_n)/kM.$$

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Substituting from Eqs. 3 and 4, we have the area/height formula:

$$MTT = A/h. \quad \text{(Eq. 1)}$$

DISCUSSION

In nuclear medicine, applications of Eq. 1 for MTT, or its reciprocal representing flow/volume, have included cerebral vascular flow (*5–9*), pulmonary ventilation (*10–13*), gastric emptying (*14,15*), and transit of tracers through the esophagus (*4,16*) and kidneys (*17–22*). Analysis has been of whole systems and of regions as small as pixels, the latter forming the basis of parametric images. In some instances, when the formula was not rigorously applicable, A/h has still had potential for empirical diagnostic use. Often, to make the plots of raw data amenable to analysis by Eq. 1, one or more of the following steps have been performed: correction for decay or variable attenuation, background subtraction, smoothing, curve stripping, deconvolution, curve fitting as to an exponential function or gamma variate, and extrapolation beyond the time of actual measurements.

The time-activity curves to which Eq. 1 may be applied take various forms, as illustrated in figure 1.

Figure 1A is a hypothetical form in which the particles are a cohort, entering and leaving the compartment in perfect simultaneity. The resulting plot is rectangular. As all the particles have the same transit time, equal to the width of the rectangle, the mean must also equal the width. Since height times width equals area, this is a case in which it is obvious that MTT = A/h. It may be noted that if height but not width is varied, there is a proportionate increase in area, and consequently MTT remains unchanged.

Figure 1B represents the case of instantaneous introduction of the tracer material (spike input) followed by its gradual departure from the compartment. In this instance, h is the initial and maximal counting rate. This case is exemplified by studies of pulmonary ventilation in which the transit of radioactive gas out of the lungs is evaluated from a curve that begins when an equilibrium state of tracer in the lungs has already been achieved (i.e., mean washout time determined, disregarding washin). This figure also illustrates the problem that exists when some of the tracer still remains in the region at the end of the period of observation. It may be solved by extrapolation, for example, fitting an exponential function and integrating the area to infinite time.

An elucidation of the area/height formula by Lassen and Perl (*3*) is best understood with reference to the form of the spike input. In their presentation, the area under the curve is filled by a set of stacked horizontal bars, each bar representing the transit of one component, and MTT is obtained as the mean of their lengths.

Figure 1C is a more general form, which approximates the curves of esophageal transit to which Eq. 1 has been applied in the author's laboratory (*4*). Specifically, we have obtained the MTT of the rapid component of a swallowed bolus of ^{99m}Tc sulfur colloid in water traversing the entire esophagus. The curve rises steeply but not as a spike. There follows a plateau and a more shallow decline. This example can be related to the previously listed assumptions as follows:

1. The assumption of constant counting rate per unit mass is approximately true for the colloidal particles that are used. If one abandons that assumption, the proof can still be easily reframed to produce MTT as an average over units of radioactivity instead of mass. The calculated MTT applies to the nonradioactive carrier medium (water) if one makes the reasonable assumption that particle mass (or radioactivity) is uniformly distributed therein.

2. With the customary anterior positioning of the scintillation camera, our results have been consistent with nearly equal attenuation along the length of the esophagus except for decreased attenuation proximally, for which we have employed

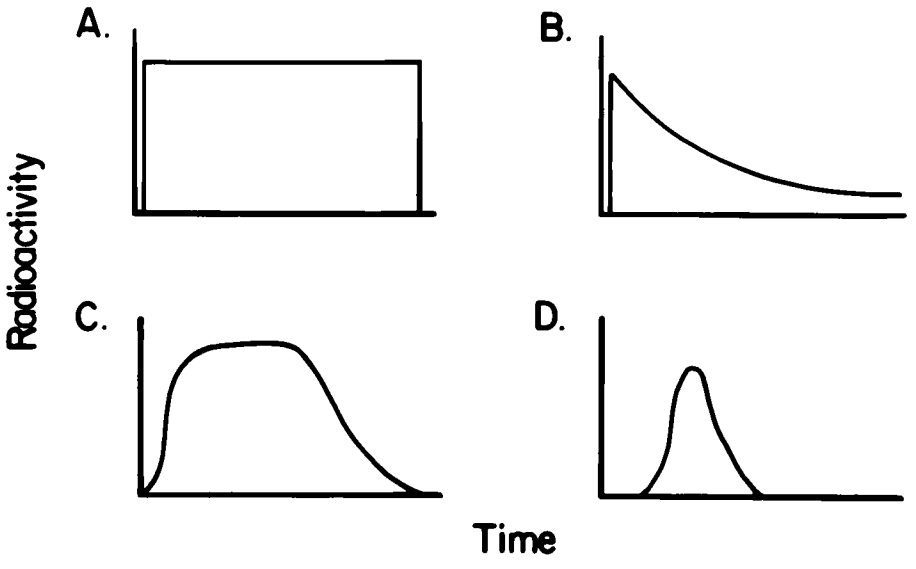

FIG. 1. Various forms for time activity curves. (A) Hypothetical rectangular form; (B) Representation of instantaneous introduction of tracer material; (C) Approximation of esophageal transit curves; and (D) Curve form in which the curve does not supply h.

an empirical correction of the curve. [The posterior projection may provide more constant attenuation (*23*).]

3. A period of time when all the particles are simultaneously within the esophagus is inferred from the existence of an interval when the curve manifests a nearly constant plateau of activity (mean counting rate = h) and significant activity is no longer detected in the pharynx and not yet detected in the stomach.

4. The condition of all the activity leaving the ROI is satisfied, not by the unprocessed esophageal curve, however, but by one of the two curves resulting from its decomposition. They represent rapid and residual components, and it is the rapid component curve that descends to zero like that of figure 1C, and provides the basis for application of Eq. 1.

5. None of the particles that have passed into the stomach return to the esophagus except in instances of gastroesophageal reflux, which are relatively rare under the conditions of the test procedure. Such reflux can be detected from images, and also generally results in a distinctive late rise in esophageal activity.

Figure 1D illustrates a curve form that may be obtained if there is no time when the particles are all in the compartment. The curve therefore does not supply h. This may apply, for example, to the curve for tracer transit through an individual segment of the esophagus that is so small that some particles will have exited before the last particle enters (e.g., the middle third). In this case, one might obtain h from the time-activity curve of the whole esophagus. In general, in cases like that of figure 1D, MTT can be computed from the curve using Eq. 1 if and only if h is known from other data and the other assumptions are also met. In the example of an esophageal segment, errors due to variable attenuation along the organ might be magnified, and one must again isolate the rapid component curve from that of the residual component and also eliminate any contribution of particles returning to the segment by intraesophageal retrograde motion. The latter is a common occurrence, which complicates the computation of MTT for a segment but not for the whole esophagus.

Equation 1 may be compared with an alternate formula (*3,24*) for computing mean transit time from time-activity curves:

$$MTT' = \sum[Q(t)t]/\sum Q(t), \qquad \text{(Eq. 6)}$$

where Q(t) is the number of counts accumulated in each of numerous sequential time segments of equal length resolved over the whole course of the curve, and t is the time of occurrence of each segment. The numerator is a summation of counts times time of occurrence for every segment, and the denominator a summation just of counts. In a seeming anomaly, the denominator is the area under the curve, like the numerator of Eq. 1. But mean transit time has a different meaning in Eq. 6 (*25*) (hence MTT' here rather than MTT). MTT equals the mean transit time *through* the selected ROI from which the curve has been obtained. MTT', on the other hand, is the elapsed time from a specified zero-time point (e.g., when the tracer was administered) to the mean time of residence of particles in the selected region. The mean transit time *through* a channel equals the difference between MTT' values for suitable ROIs at its outlet and inlet. An example of the application of MTT' is that of Fouad et al. (*26*) to the computation of pulmonary mean transit time, in which the outlet and inlet curves were derived from left and right ventricular ROIs, respectively.

Equation 6 may be called the centroid formula, for MTT' corresponds with the center of gravity of a time-activity curve relative to its time axis (i.e., the t value where a stiff cut-out of the curve balances on a knife blade). Equations 1 and 6 are in no sense incompatible (*3*) and sometimes might each be applicable to the same problem.

There are occasions when it is useful to measure the attenuation of radioactivity that affects a compartment being studied by nuclear medicine techniques. Approaches to this problem emanate from considerations in the study of MTT that have been discussed.

When the height of a time-activity curve represents the detected counting rate, h, of the whole portion of tracer, and when we have also measured the counting rate, H, of the unattenuated material, h/H provides a measure of the attenuation. In other cases, A and H are known, but not h, as in some instances of curves like that of figure 1D. Then Eq. 1 does not suffice to calculate MTT. In such cases, one might compute MTT as the difference in MTT' values obtained from time-activity curves of suitable small outlet and inlet regions using Eq. 6, substitute the result in Eq. 1, solve for h, and then determine h/H.

In conclusion, a formulation of the proof that area/height equals MTT has been presented. It is one that is simple, specifically applicable to esophageal transit as studied in the author's laboratory (*4*), and also illuminating of other uses in nuclear medicine.

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