Diffusion and Perfusion Magnetic Resonance Imaging

Applications to Functional MRI

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Chapter 11

Part II

Methods Using Blood Pool Tracers

Leon Axel

The use of a tracer substance to study blood flow depends on a variety of assumptions about the tracer substance, its means of administration and measurement, and its interaction with the extravascular space. It may also require some assumptions about the nature of the vascular bed. However, within the limits of these assumptions, tracers can provide useful quantitative information about blood volume and blood flow. We can consider the behavior of tracer substances as spanning a continuum from purely intravascular tracers (e.g., small particles or large molecules), through the more complicated behavior of common MRI and CT contrast agents, which can show significant extravascular exchange even on their initial transit through tissue (except for the central nervous system with an intact blood-brain barrier), to freely diffusible tracers and extracted or deposited tracers. The latter two categories are considered elsewhere. In this chapter we shall review the principles in the use of blood pool tracers, that is, tracers that stay within the intravascular spaces, to study perfusion. We will also consider some of the consequences of non-ideal behavior of the tracer (extravascular exchange).

BASIC PRINCIPLES

The fundamental principle underlying tracer methods is that of "conservation of matter." That is, if a quantity, M, of the tracer is injected into the blood flowing into an organ and the concentration in the draining blood, $c_d(t)$, is monitored over time (Fig. 1), if the tracer is not extracted in the tissue it must all eventually leave via the draining blood. Thus, if the flow into which the tracer is injected is F, then the total amount of tracer leaving the organ must be equal to M:

$$\int F c_d(t)dt = M \qquad [1]$$

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If F is unchanging, we can calculate the flow from the rearranged equation

$$F = M/\int c_d(t)dt \qquad [2]$$

(If the flow is pulsatile, this will give the mean value of F). This is referred to as the *Stewart-Hamilton equation* (1–3).

A number of assumptions and approximations are necessary to apply this to the measurement of flow:

1. The flow must be stable and unaffected by the tracer, i.e., the tracer must not affect the circulation and must have negligible volume itself. (This is what we mean by a "tracer").
2. The tracer must be thoroughly mixed with the blood so that the sampling will be representative.
3. The concentration of the tracer can be accurately measured.
4. The recirculation of the tracer (coming around for a second or further pass through the blood circulation) must be negligible or capable of being corrected for.

Equation [1] has been used for the calculation of cardiac output by the monitoring of arterial concentration of a tracer substance following the intravenous injection of a known quantity of the tracer. Classically, the tracer used for cardiac output determinations was indocyanine green dye. Now it is more likely to be "heat," with the use of thermodilution, but the principles are the same. Hamilton's principal contribution to the development of indicator (tracer) dilution methods was the use of methods to try to correct for recirculation; Hamilton used an exponential (a straight line on a semi-log plot) to extrapolate the curve of tracer washout beyond the appearance of recirculation.

Although Eq. [1] does not explicitly require that the tracer be administered as a bolus, this injection is usually kept as brief as possible, e.g., for effective correction for recirculation. The sampling site need not generally be right at the outflow from the organ, but may be at a more distal site. As long as the area under the

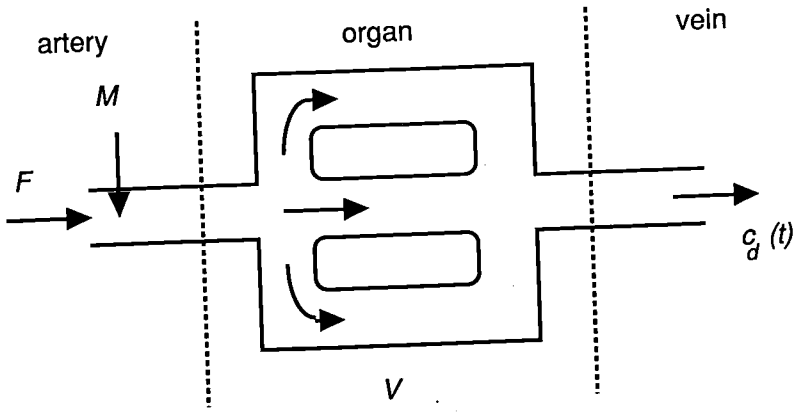

FIG. 1. Schematic diagram of tracer study with injection of amount of tracer *M* into arterial supply, with flow *F* through organ with distribution volume *V*. Tracer concentration in draining vein is $c_d(t)$.

curve of concentration as a function of time remains the same, any delay introduced by sampling at a more distal site will not affect the result. Similarly, the integral of the concentration of tracer in an artery after intravenous injection will reflect the cardiac output, *not* the flow through the artery being sampled. Also, note that Eq. [1] will hold (in principle) for any kind of tracer (intravascular or diffusible), as long as it is not extracted or retained in its passage through the organ and it exits rapidly enough that recirculation effects can be corrected for. In practice, however, the need to correct for recirculation will significantly limit the acceptable amount of extravascular exchange of tracer.

The Stewart-Hamilton equation permits us to calculate the flow through an organ from the area under the concentration-time curve of the draining blood and knowledge of the amount of tracer injected into the inflow to the organ. The "first moment" of the concentration-time curve in the draining blood can also be used, to give us additional information (Fig. 2). We

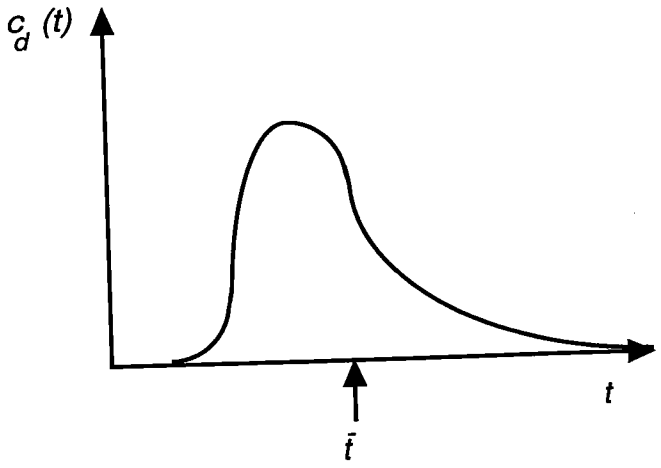

FIG. 2. Schematic time course of tracer concentrations in draining veins after bolus injection upstream from organ at time $t = 0$. Area under curve is equal to *M/F*. First moment ("centroid") of curve, the MTT, is equal to *V/F*.

define the first moment, $\bar{t}$, of the tracer concentration curve, $c(t)$ as:

$$\bar{t} = \frac{\int_0^\infty tc(t)dt}{\int_0^\infty c(t)dt} \qquad [2]$$

It can be shown that if we inject the tracer as an ideal bolus into the inflow to the organ at time $t = 0$, the first moment of the resulting concentration-time curve in the draining veins, $\bar{t}_d$, is equal to the ratio of the volume, *V*, occupied by the tracer during its passage through the organ (the vascular volume for an intravascular tracer) to the flow, *F* (3–5):

$$\bar{t}_d = \frac{\int_0^\infty tc_d(t)dt}{\int_0^\infty c_d(t)dt} = \frac{V}{F} \qquad [3]$$

This time is called the "mean transit time" (MTT). The smaller the volume or the greater the flow rate, the shorter the MTT will be. It is typically on the order of a few seconds or less for blood pool tracers. If the injected tracer exchanges with the extravascular space, the effective volume of the organ to be traversed by the tracer will be greater and the MTT will be prolonged. If the sampling site is moved further downstream, the additional volume for the tracer to traverse will be reflected in a prolonged MTT. In any case, if we have independent knowledge of *V*, we can calculate *F* from the MTT. Alternatively, if we know *F* independently, we can calculate *V* from the MTT.

In practice, the tracer cannot generally be administered as an instantaneous bolus injection into the input to the organ. Rather, it is delivered over a finite period, which will result in a corresponding prolongation of the observed transit time of the tracer. Specifically, if the tracer transit function is "linear" (unaffected by time delays or tracer concentration), the observed transit, $c_{obs}(t)$ will be given by the "convolution" of the transit function resulting from an ideal unit instan-

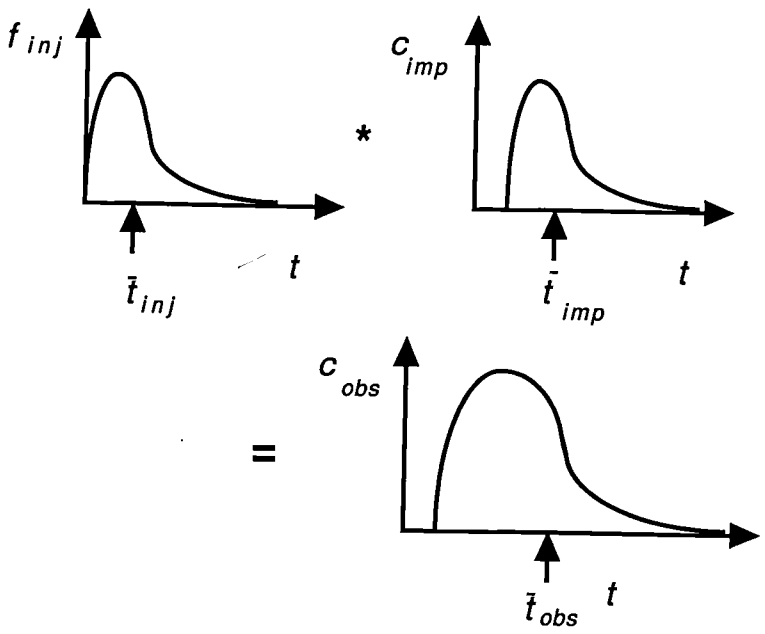

FIG. 3. Effect of prolonged input of tracer, $f_{inj}(t)$, is convolution with hypothetical tracer concentration for "impulse" (bolus) injection, $c_{imp}(t)$, to yield final observed tracer concentration curve $c_{obs}(t)$. The sum of the corresponding first moments of the curves, $\bar{t}_{inj}$ and $\bar{t}_{imp}$, is equal to the first moment of the observed tracer curve $\bar{t}_{obs}$.

taneous bolus injection (the "impulse response"), $c_{imp}(t)$, and the actual injection function, $f_{inj}(t)$ (Fig. 3):

$$c_{obs}(t) = \int_0^t f_{inj}(t')c_{imp}(t - t')dt' = f_{inj}(t)*c_{imp}(t) \quad [4]$$

It can be shown (5) that the first moment of the observed tracer transit $\bar{t}_{obs}$, will be given by the sum of the first moments of the injection function, $\bar{t}_{inj}$, and the ideal impulse response, $\bar{t}_{imp}$ (the desired MTT):

$$\bar{t}_{obs} = \bar{t}_{inj} + \bar{t}_{imp} \quad [5]$$

Thus, even with a prolonged injection function, if we can find the mean time (first moment) of the injection, we can use Eq. [5] and subtract it from the observed tracer transit time to calculate the "ideal" MTT.

TISSUE PERFUSION DETERMINATION WITH BLOOD POOL TRACERS

In imaging studies of the transit of a tracer through an organ, we often cannot directly image the particular arteries and veins supplying and draining a tissue region of interest. Even if they can be identified, the effects of volume averaging in the imaging process may prevent direct measurement of the tracer concentrations within the vessels from the images. Thus, we wish to try to estimate a measure of the perfusion from the images of the transit of the tracer through the parenchyma of the tissue itself. In addition, this has the potential to give us information about regional heterogeneity of perfusion that we could not get from the tracer concentration in the mixed draining blood alone. However, this can also complicate the analysis process and may lead to the need for further assumptions to be fulfilled in order to carry out the analysis (6).

The impulse response in a draining vein to a bolus injection into the arterial input can be considered as reflecting the distribution of transit times through the organ, $h(t)$. Similarly, we can characterize any component part of an organ by its corresponding transit time distribution. In either case the MTT (global or regional) will be given by the first moment of $h(t)$. If, instead of the concentration in the outflow from the organ, we look at the (normalized) concentration remaining in the organ, the "residue function," $R(t)$, we find:

$$R(t) = 1 - \int_0^t h(t)dt = \frac{c_t(t)}{c_t(0)} \quad [6]$$

where $c_t(t)$ is the tissue concentration of tracer after an ideal bolus injection into the tissue at time $t = 0$ (Fig. 4). It can be shown (4–6) that the area under the residue function is equal to the MTT:

$$\int_0^\infty R(t)dt = \text{MTT} = \frac{V}{F} \quad [7]$$

The actual observed tissue tracer concentration is proportional to the flow to the tissue, and the initial tissue concentration immediately after an ideal bolus into the arterial input would provide a map of the regional perfusion:

$$c_t(0) \propto F \quad [8]$$

Thus the area under the observed tissue concentration-time curve (correcting for recirculation) will be propor-

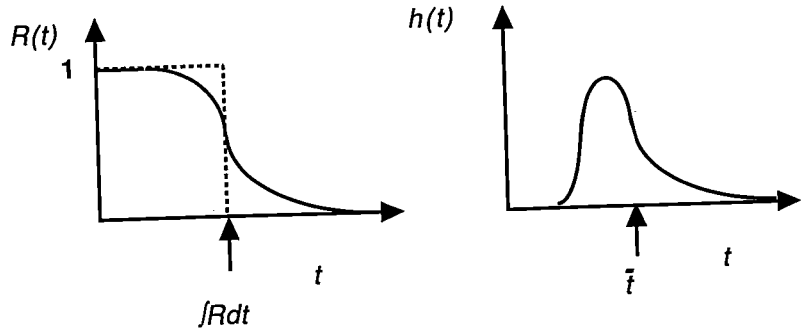

FIG. 4. The area under the curve describing the residual concentration of tracer in the tissue after a bolus injection, $R(t)$ (Eq. [6]), is equal to the first moment of the curve of the corresponding concentration of tracer exiting the tissue, $h(t)$.

tional to the effective tracer distribution volume (the vascular volume of the tissue for a blood pool tracer) and *not* the flow, as the flow will cancel out:

$$\int_0^\infty c_t(t)dt \propto V \qquad [9]$$

If we independently know the MTT, the area under the residue function can be used to find V and thus we can calculate F.

We have seen that the zeroth moment (area) of R is related to the first moment of $h(t)$. If we try to use the tissue concentration of tracer as an approximation of the concentration in the draining veins, we will generally *not* find the correct value for the MTT by calculating the first moment of the tissue tracer concentration function (7–9), as this is related to the *second* moment of h. For the particular case of a simple exponential washout of the tracer, as we expect with a freely diffusible tracer, the first moments of the residue function and the exit function will, in fact, be equal, and both will yield the MTT. On the other hand, for the example of ideal "plug flow," with the bolus of tracer all exiting the tissue at the same time, after a delay due to transit through the tissue vessels, the first moment of the residue function will be a factor of two smaller than the correct value for the MTT, and the flow will be overestimated by a factor of two. If we do not know the specific shape of $h(t)$, we cannot predict the relationship between its first and second moments, and thus cannot know *a priori* the relationship between the first moment of $R(t)$ and the MTT.

USE OF VESSEL IMAGES TO CORRECT AND CALIBRATE TISSUE TRACER CURVES

Although there may be systematic differences between the first moment of the residue function and the desired MTT, if different regions have similar scaling factors, the relative values of the first moment of the residue function may still provide useful information on the relative values of the regional MTTs. The observed tracer transit through the tissue must still be corrected for the prolonged input function actually delivered through the arterial supply. To do this, we note that we may often be able to recognize distinct images of branches of the major arterial vessels supplying the tissue of interest in the same image planes as the tissue itself. If the imaging technique provides sufficient resolution, we may be able to identify picture elements (pixels) whose change in intensity from baseline is principally determined by the arterial concentration of tracer. We can then calculate the corrected first moment of $R(t)$ from Eq. [5], using the first moment of the pixels representing the artery to estimate $\bar{t}_{inj}$. Note that if there are collateral vessels between the arteries imaged and the tissue of interest, they can contribute an additional delay that may need to be taken into account when calculating the corrected tissue transit time.

We can use the integral of the tissue tracer concentration (for an intravascular tracer, correcting for recirculation) to find an estimate of the blood volume of the tissue, in order to calculate F from our estimate of MTT. This will require some means of calibration of the tracer concentration values from image intensity changes if we wish to calculate anything other than the relative values in different regions. (Note that relative values may be all that are needed for some applications, e.g., if some areas are known to be normal and can be used for comparison). If a sufficiently large blood vessel is included in the image such that some pixels representing "pure blood" can be confidently identified, then the relative areas under the tracer concentration-time curves (correcting for recirculation) of the blood and the tissue regions can be used to calculate the fractional blood volumes of the tissue (7,10). Alternatively, if a delayed image is obtained when the blood tracer concentration has settled into a quasi-equilibrium, and a simultaneous blood sample is obtained for direct measurement of tracer concentration, the calibration of the blood vessel image intensity can be found (including volume averaging effects).

An alternative approach to using the estimate of the input function provided by arterial images to correct the observed tissue tracer concentration is to use "deconvolution" to, in effect, undo the convolution pro-

cess defined in Eq. [4] and calculate the tissue response to an ideal bolus of tracer. The initial values of the corrected tissue tracer curves would give the relative perfusion values and the area under the (normalized) $R(t)$ curves would give the MTTs from Eq. [7]. If the absolute concentration of tracer in the input can be calibrated, as above, the initial values of the corrected tissue curves will yield the absolute perfusion. In practice, deconvolution is very sensitive to noise and is likely to give erroneous results if applied naively. However, using a restricted deconvolution that takes advantage of our *a priori* models of $R(t)$, such as that it will be monotonically decreasing, can enable more robust correction for the effects of extended input functions (11,12).

One approach that has often been taken to simplify the analysis of perfusion from imaging studies of tracer kinetics is to simply look at the peak tissue concentration during the initial transit after a bolus injection. However, this will directly reflect perfusion only if the entry of tracer is completed prior to any loss of tracer in the veins (13). This condition will not be met in general, especially with more rapid flow rates. If images of draining veins are included in the field, an estimate of (pooled) exiting tracer can be used to try to correct for this, but this will only be an approximation, at best.

The correction for recirculation will also require some *a priori* assumptions about the shape of the tracer concentration-time curve. A useful form to take for such curves, which empirically is often found to fit them well, is a "gamma variate" (14), given by the product of a power of time (to give an initial rising portion) and a negative exponential (to give a falling tail). This can be used to fit such a curve to the observed portion of the tracer concentration as a function of time up to the appearance of recirculation. The remainder of the fit curve is then assumed to represent the concentration that would have been observed in the absence of recirculation. This will require finding the "best" values for four variables (K, t_0, r, and b) in an expression of the form:

$$c(t) = K(t - t_0)^r e^{-(t-t_0)/b} \qquad (t > t_0)$$

and

$$c(t) = 0 \qquad (t < t_0) \qquad [10]$$

These fit parameters can then be used to calculate values of the functional parameters related to the tracer's tissue transit (15), e.g.,

$$\bar{t} = t_0 + b(r + 1) \qquad [11]$$

and

$$\int c(t)dt = Kb^{r+1}\Gamma(r + 1) \qquad [12]$$

where Γ is the gamma function.

This fitting can be carried out on a pixel-by-pixel basis over the image (perhaps after some smoothing) and the resulting values of the functional parameters used to create functional images displaying the regional variation of the parameters (15).