Section 1 **Techniques**

Chapter 1

Imaging of flow: basic principles

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Key points

- Indicator dilution techniques for measuring blood flow have existed for more than 100 years.
- Indicators may be either intravascular, or freely diffusible.
- Early techniques establishing the mathematical framework for flow (the Fick principle, Kety–Schmidt method, and central volume principle) were mainly based on arterial and venous blood sampling.
- Tissue perfusion measured by MR techniques may be either based on bolus contrast agent injection, or non-invasive, endogenous "magnetic" labeling of inflowing blood.
- MR perfusion is one of a variety of techniques now available for tomographic imaging of flow; competing techniques such as SPECT, PET, and CT are also able to produce perfusion images.

Introduction

The flow of blood to an organ is a fundamental physiological factor affecting tissue health, growth, and repair. Blood flow and volume are perturbed in many disease conditions, most notably in vascular disease and in tumors. The ability to determine non-invasively blood flow and blood volume using imaging methods therefore has important diagnostic and therapeutic implications. Since the early days of radiological imaging, scientists and physicians have been searching for methods that can accurately and non-invasively depict the major blood vessels of the body, and measure blood flow in tissue. For instance, X-ray projection imaging of blood vessels (angiography) was first demonstrated in 1927 by Moniz [1], using iodinated contrast agents injected intravascularly, while early measurements of tissue blood flow were based on the inhalation of freely diffusible tracers (e.g., nitrous oxide [N_2O] [2], or radioactive xenon or krypton [3]). Subsequently, stable (i.e., non-radioactive) xenon was used in conjunction with X-ray computed tomography (CT) to image cerebral blood flow (CBF) [4], while other methods such as single-photon emission CT (SPECT) [5, 6] and positron emission tomography (PET) [7, 8] imaging using a variety of radiotracers also became available. More recently, dynamic CT perfusion imaging using bolus injection of iodinated contrast agents has been growing in popularity [9], particularly as fast multi-slice CT scanners have become widely available.

With the emergence of magnetic resonance imaging (MRI) as a clinical imaging modality in the 1980s and 1990s, MRI methods were developed for both angiography and perfusion. Perfusion imaging methods based on exogenous contrast media [10, 11] as well as completely non-invasive methods based on "magnetic labeling" of inflowing blood [12, 13] were developed. Compared to radioactivity- or X-ray-based perfusion methods, MR perfusion offers the advantage of the absence of radiation (particularly important for patients sensitive to radiation, such as children) as well as a synergistic combination with other MRI techniques that offer exquisite soft tissue contrast and spatial resolution. Today, MR perfusion imaging is increasingly being used in clinical practice. However, accurate quantitative perfusion imaging using MRI also involves many technical challenges.

This chapter describes methods for measuring blood flow, looks back at the history of such

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measurements, and presents the central concepts for flow measurements with their corresponding mathematical expressions. Indicator dilution techniques are the main focus, and will be discussed mainly in the context of perfusion in the brain, but with the understanding that such techniques can often be applied to other organ systems. While this chapter will briefly consider measures of bulk flow in large vessels, it will principally focus on measures of perfusion, i.e., measures of flow that estimate the delivery of blood to the microvessels of an organ.

The Fick principle

Modern measurements of vascular physiology began with Adolf E. Fick's description of a method based on the conservation of mass [14]. The heart-lung system has a single flow input, the vena cava, and a single output, the aorta. The difference in oxygen concentration in arterial and venous blood, $c_a - c_v$, is the change of oxygen concentration in the blood as a result of oxygen consumption by the body's metabolism. If we assume that the rates of cardiac flow (F_c – the cardiac output or "minute volume") and oxygen consumption are constant, then $F_c(c_a - c_v)$ is the amount of oxygen per unit time consumed by the body. Mass balance requires that the quantity per unit time of oxygen exiting the heart-lung system via the aorta equals the amount that came in *via* venous blood, plus the amount of oxygen added during blood passage through the lungs:

$$F_c c_a = F_c c_v + VO_2 \tag{1.1}$$

where VO_2 is the rate of oxygen extraction from the lungs. Thus, cardiac output can be calculated as:

$$F_c = \frac{VO_2}{c_a - c_v} \tag{1.2}$$

The Fick principle, relying as it does on mass balance in flow, provides a robust and remarkably simple basis for an important physiological measurement, cardiac output. However, it is invasive in that it requires arterial and venous blood sampling, and the measurement of VO_2 requires that a closed-circuit breathing apparatus be constructed, with provision for in-line carbon dioxide capture, and a means of replacing the oxygen consumed by the patient. While the Fick principle's clinical significance as a means of measuring cardiac output has declined, its underlying principle – mass balance in flow – remains the theoretical basis for nearly every method of flow measurement.

The central volume principle

The central volume principle was first stated by Stewart [15] as a corollary of the Fick principle, and reiterated by Hamilton *et al.* [16]. Using a linear systems approach, Meier and Zierler [17] generated a closely reasoned presentation of this principle. That paper and subsequent elaborations [18, 19] remain the most elegant and easily understood presentations of indicator dilution theory.

Figure 1.1, similar to that in Meier and Zierler's article [17], represents all the paths that a particle of indicator might take in a vascular system (with volume V) from point A to B. It is assumed that the system is stationary or time-invariant, i.e., that flow rates and paths do not change with time, and that the system has a single input and output. The separate pathways show additive behavior in this linear system, and the system can be decomposed into a sum of smaller and smaller components with single inputs and outputs, until only single capillaries remain. In linear systems terminology, the microvasculature is a "passive reciprocal linear two-port network" [20]. It is reciprocal because the same behavior of the system would be observed if the input and output (points A and B in Figure 1.1) were reversed. It is also assumed that all possible pathways are in-line with the supplying and draining vessels. The indicator injected at point A can be freely diffusible, entirely intravascular, or confined to the vasculature plus specific tissue compartments. The only restriction is that the indicator not be trapped in the system, which is equivalent to the absence of pools in the system (which would equal unaccounted losses of mass flow). Note, however, that the nature of the indicator does affect the inference drawn about the volume of the system.

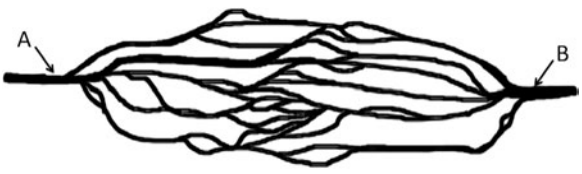

Figure 1.1 A schematic illustration of the paths of the particles of a flow indicator in a vascular system with a single input (A) and output (B). For a freely diffusible indicator, these paths do not necessarily correspond to the paths taken by blood.

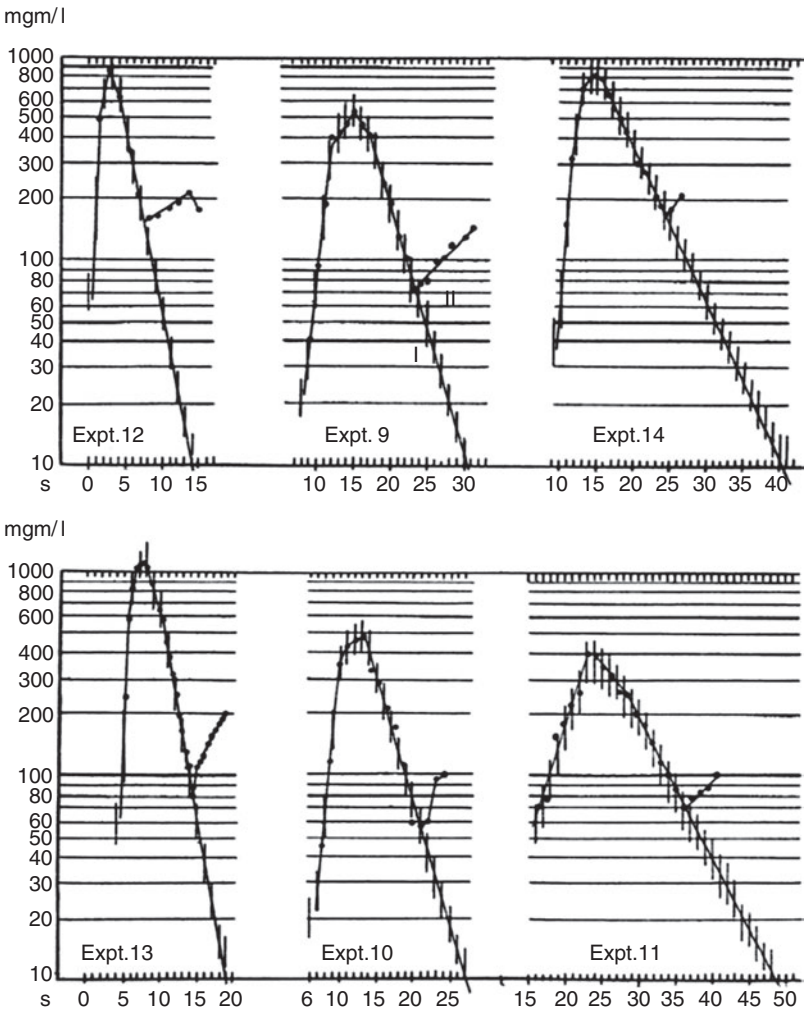

Figure 1.2 Concentration of phenolphthalein dye sampled at various points in the arterial tree of a dog after a bolus venous injection (left ventricle, expts 9, 10, 11, 13; right ventricle, expt. 12; and femoral artery, expt. 14). The log-linearity of a portion of each of the clearance curves is evident. There was very good agreement between estimates of cardiac blood flow made by this method and estimates made by the Fick procedure [21].

If a quantity Q of indicator is injected at point A as an ideal bolus (i.e., a Dirac "delta function") at time $t = 0$, there will be a time lag before the first appearance of the indicator at the exit of the flow system (point B), followed by a rapid rise to a peak concentration, and a more gradual clearance. Figure 1.2, taken from experiments conducted in dogs by Moore *et al.* [21], shows examples of such data, with the concentration of an easily detectable dye (phenolphthalein) sampled at various points in an arterial tree. Note the semi-logarithmic scale of the ordinate in those plots, and the log-linearity of the terminal portion of each clearance curve, indicating that the tracer concentration is decreasing exponentially with time, a sign of a "well-mixed" flow system. The logarithmic slope of the clearance in a well-mixed system should be proportional to the system's flow divided by its volume. The early use of dyes such as phenolphthalein in flow experiments generated the label of "dye dilution," or "indicator dilution" for experiments that utilized a substance that could be assumed not to be metabolized or otherwise trapped in the system.

To derive the central volume principle, consider $Q(t)$, the quantity of tracer that has left the system at point B at time t. The instantaneous quantity of the tracer ($dQ(t)/dt$) leaving the system at point B during the time interval dt equals the (assumed constant) flow F times the instantaneous concentration $c_B(t)$ at point B times dt: $dQ(t) = F \times c_B(t) \times dt$. Thus, if Q is the total amount of tracer injected,

$$\int_0^\infty \frac{d}{dt} Q(t)dt = Q \tag{1.3}$$

and thus

$$Q = F\int_0^\infty c_B(t)dt \tag{1.4}$$

If tracer quantities and concentrations can be measured directly, this leads to the calculation of the flow according to

$$F = \frac{Q}{\int_0^\infty c_B(t)dt} \tag{1.5}$$

The *transport function*, or the frequency function of transit times, $h(t)$, is defined as follows

$$h(t) = \frac{Fc_B(t)}{Q} \tag{1.6}$$

This quantity has units of inverse time (e.g., 1/min or 1/s). These units result because the product $h(t)dt$ – a unitless quantity – represents an infinitesimal (or instantaneous) probability that a particle of indicator injected at point A at time $t = 0$ will appear at point B at time t. The product $h(t)dt$ therefore is the probability density function (i.e., normalized distribution) of transit times. The ratio on the right-hand side of Eq. (1.6) expresses the amount of tracer passing through point B at the instant t as a fraction of the total injected amount Q.

Therefore $\int_0^\infty h(t)dt = 1$.

To continue with the analogy to probability theory, the cumulative density function (or cumulative distribution function, $H(t)$) and the residue function $R(t)$ are defined:

$$H(t) = \int_0^t h(\tau)d\tau \tag{1.7}$$

$$R(t) = 1 - H(t) \tag{1.8}$$

$H(t)$ is the proportion of indicator particles that have traversed the system from A to B from time 0 to time t, and $R(t)$ is the proportion that remain in the system. Clearly, since all the fluid that enters the system must eventually leave, $H(t) \to 1.0$ as $t \to \infty$.

Note that the major difference between classical indicator dilution experiments and modern imaging-based perfusion techniques is the sampling location (see below, External monitoring of indicator concentration). After a bolus input in classical indicator dilution experiments, with sampling performed at point B, the common output vessel of the system, the recorded concentration over the time course of the experiment is a scaled version of the transport function $h(t)$. In imaging experiments, the concentration of indicator in the tissue under observation (voxel) measured over time is a scaled version of the tissue residue function $R(t)$.

The flow rate at which the subset of fluid with transit time t leaves the system is $Fh(t)dt$, where F is the flow in unit volume per unit time. The volume of fluid contained in all microvascular pathways with common transit time τ therefore is $\tau Fh(\tau)d\tau$. To calculate the total volume occupied by tracer (i.e., the distribution volume) between points A and B, we can sum all these separate microvascular pathways, by integrating over all possible values of τ, assuming constant flow (F):

$$V = F\int_0^\infty \tau h(\tau)d\tau \tag{1.9}$$

Remembering that $\int_0^\infty h(t)dt = 1$, it follows from the second mean value theorem for integration that the mean transit time for all indicator (and therefore fluid) particles in the system is expressed as the $h(t)$-weighted average of transit times:

$$\bar{t} = \int_0^\infty th(t)dt \tag{1.10}$$

The combination of Eqs. (1.9) and (1.10), then, yields the *central volume theorem*:

$$V = F\bar{t} \tag{1.11}$$

where $\bar{t}$ is the mean transit time between point A and point B for an indicator particle, and V is the volume of the system accessible to the indicator between point A and point B.

Note that the residue function $R(t)$ has a special relation to the mean transit time since $R(t) = 1 - H(t)$. We can integrate by parts to demonstrate that:

$$\int_0^\infty R(t)dt = \int_0^\infty [1 - H(t)]dt = \{[1 - H(t)]t\}_0^\infty + \int_0^\infty th(t)dt = \int_0^\infty th(t)dt = \bar{t} \tag{1.12}$$

The relationship $\bar{t} = \int_0^\infty R(t)dt$ is intuitively clear in that a longer mean transit time results in a larger residual at each point of time.

The central volume theorem, freely diffusible indicators, and intravascular agents

It is useful to distinguish two model systems in which the indicator is either an entirely intravascular agent (never leaving the vasculature), or a freely diffusible indicator, where it is assumed that indicator concentration in tissue is in equilibrium with that in the venous drainage. While the underlying central volume theory remains the same, quite different systematic errors may occur due to the differences in clearance times of the two systems, and different experimental requirements.

In current MR practice, the labeled water of the arterial spin labeling (ASL) experiment [12, 13, 22–26] is usually considered to be a freely diffusible indicator. However, this is an approximation, since the single-pass extraction fraction of water in gray matter [27] is about 0.8. For the central volume theorem, one immediate question arises as to what volume should be considered – the whole tissue, the blood and tissue separately, or some weighted average of the blood and tissue. The tissue homogeneity model (THM) [28, 29] approach, based on the early work of Johnson and Wilson [30], can address this problem, estimating not only flow, but also vascular volume and extraction fraction. However, the signal-to-noise ratio (SNR) of ASL usually limits the practical application of THM. For CBF in small animals, careful comparison between ASL and autoradiography measurements indicates that ASL slightly overestimates CBF [31]. In humans, where the transit time from the labeling slab to the imaging plane can be comparable to the blood T_1 relaxation time (or even longer than T_1 in the presence of cerebrovascular disease), the major systematic error may be to tend to underestimate flow.

The question of extraction also applies to MR perfusion studies that use intravascular injection of contrast agents, since the central volume theory assumes that no leakage of indicator occurs, but in various organ systems (and in pathology) extravasation of contrast into tissue frequently occurs. Again, with sufficiently high-quality data (e.g., high SNR), flow, extraction fraction, vascular volume, and possibly interstitial volume can be estimated [32–34], but the technical requirements for the MR sequence are formidable, as are the post-processing procedures. Even if no leakage occurs, problems in the application of the central volume theorem to imaging data can persist. Note that the volume of the system is defined by the two sampling points (Figure 1.1). If A is placed in the middle cerebral artery (MCA), and B is placed at a collecting venule, then the volume of the system is the entire path volume taken by indicator particles that eventually exit at the collecting venule. If indicator particles are freely diffusible, then the volume V is the entire tissue volume plus vascular volume, while if indicator particles are confined to the vasculature, the volume of the system is restricted to the vascular volume. Note also that classical tracer dilution experiments measure vascular tracer concentration in the input and output vessels by direct blood sampling, while MRI experiments usually estimate arterial and tissue tracer concentrations from MR signal changes. In addition, the apparent vascular and tissue concentrations estimated from MR are affected by partial volume considerations because of the finite spatial resolution of MRI. Even when not contaminated by a major vessel, the "tissue" concentration determined by MR will be a combination of tissue and capillary concentrations. For an intravascular tracer, the microvascular concentration can be estimated by knowledge of the blood volume (fractional volume of vessels in the tissue), which is important for consideration of transport gradients between microvessels and interstitium in models of leaky vessels.

The effect of input functions: convolution

So far, only the case of the response of the vascular system to an impulse (i.e., the Dirac delta function) has been considered. In practice, contrast agents are administered over a period of time, and are further mixed by their passage through the heart-lung system, thus resulting in an input function to the organ system under study that has significant duration and also non-uniform amplitude with time. However, in linear systems, if the response to a delta function is known, the response to any other physically realizable input function can be constructed *via* convolution.

The input concentration of the indicator in the blood, $c_A(t)$, is known as the arterial input function (AIF), and generally will be a smoothly varying function of time, with a finite integral. At each time t, the venous output $c_B(t)$ will no longer just reflect pathways of transit time t, as in the case of an ideal impulse input function. Instead, $c_B(t)$ represents a weighted sum of pathways with different transit times. A typical arterial

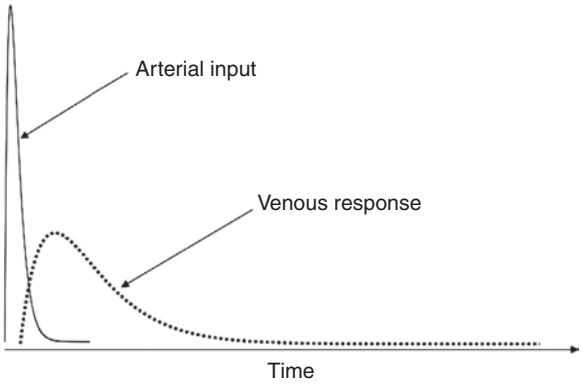

Figure 1.3 The arterial input and the venous response are related by the tissue residue function; due to dispersion in the tissue, the venous response has lower amplitude and delayed clearance compared to the arterial input.

input is illustrated in Figure 1.3, as well as a corresponding venous response. If the first small time interval (dt) of the input is represented as a delta function (with an appropriate weighting), then the response of the system to this input is well understood – it is the transport function, $h(t)$. Likewise, the next small interval of the AIF can be represented as a delta function with appropriate weighting, and so on until the entire AIF up to a time t is covered. Then the portion of the venous response from $\tau = 0$ to $\tau = t$, $c_A(0)$ to $c_A(t)$, can be expressed as the sum of responses to the weighted inputs, or in the limit as the AIF intervals are brought to zero, as an integral. Mathematically, this is expressed as a convolution:

$$c_B(t) = \int_0^t c_A(\tau)h(t-\tau)d\tau = (c_A \otimes h)(t) \qquad (1.13)$$

where the symbol $\otimes$ denotes convolution, as defined in the integral expression. Equation (1.13) describes the response of most flow systems to an arbitrary, physically realizable, input. Since it is so general, it is the basic equation of nearly every measure of flow.

Applications of the central volume principle

The heart-lung and brain vascular systems are two critically important systems. For an entirely intravascular indicator, assuming a total heart volume of about 350 ml, a lung vascular volume of about 2.2 ml/kg body weight, a cardiac output of 5 l/min (83.3 ml/s), and a 70 kg body weight [35], one arrives at a heart-lung vascular volume of about 500 ml and a mean transit time (MTT = $\bar{t}$) of about 6 s.

In the brain, the mean vascular volume and flow are about 3.5 ml/100 g, and 50 ml/100 g/min [36], respectively. This yields a mean transit time (and dominant time constant) of about $(3.5 \times 60)/50$ s, or 4.2 s for an entirely intravascular indicator such as gadopentetate dimeglumine (Gd-DTPA) in normal cerebral microvasculature. If the indicator used is freely diffusible (e.g., one of the noble gases or water, here assumed to be freely diffusible), the working volume becomes about 1 ml/g (here assuming idealized values of a density of 1.0 for tissue and a blood–brain partition coefficient, λ, of 1.0), and the mean transit time becomes about 7 min. As noted above, λ is actually slightly less than 1.0 for water (commonly estimated at 0.9 ml/g as a whole brain average [37]), which should be applied as a small correction factor in ASL experiments.

These order-of-magnitude calculation for two systems in series should serve both as an illustration of the use of the central volume principle, and a caution as to the difficulties of using a purely intravascular indicator for estimating CBF. As we have shown, the time constant of the heart-lung system at rest is about 6 s, which is the dominant time constant. Although this shortens under exercise, it also lengthens with age and pathology. In a clinical setting, then, 6 s is probably a lower limit for the time constant of the heart-lung system. A bolus venous injection will then have a major concentration–time output behavior that is shaped by the heart-lung vascular system. This output is then directed to the input of the brain vascular system, with its 4.2 s time constant. The difficulty then becomes apparent when CBF is to be estimated from the relationship $\bar{t} = \frac{V}{F}$, i.e., from an estimate of the time constant of the brain vascular system. The problem is that if the input to a downstream system has slower time constants than the characteristic times of the downstream system, the major response of the downstream system is simply to follow, with a small time lag, the shape of the input. This makes the inference of the time constants of the downstream system difficult and inherently unstable.

The Kety–Schmidt technique

We return to the Fick principle, but now applied to flow in the brain, and specifically using a freely diffusible gaseous indicator. In the initial studies by Kety and Schmidt, the indicator was N_2O which was measured via in vitro analysis in arterial and venous

samples [2, 38, 39], while in later studies the use of the inert radiogases ^{85}Kr and ^{133}Xe, detected by external scintillation detectors, became more common. N_2O studies continued for many years, and were even still in use for comparison in early MRI-based CBF studies which used fluorinated hydrocarbons as the MRI indicator [40].

In the Kety–Schmidt N_2O clearance technique, the indicator N_2O is administered in non-anesthetic concentrations *via* inhalation for a period of time that is long compared to the longest expected time constant of clearance. Conversely, an uptake experiment can be performed, in which the concentration of N_2O starts at zero and approaches saturation. In either case, the Fick principle can be applied to the system as depicted in Figure 1.1, so that the differential change in the quantity of indicator in the system during any differential period of time is equal to the amount of indicator carried in minus the amount carried out:

$$dQ_{tis}(t) = (Q_{in} - Q_{out})dt \tag{1.14}$$

where $Q_{tis}(t)$ is the quantity of indicator in the tissue, Q_{in} and Q_{out} are the quantities of indicator carried in and out of the tissue, respectively, and t is time. If both sides of the equation are divided by the mass of the tissue compartment, M, and it is noted that $Q_{in} = FC_p(t)$, and $Q_{out} = FC_v(t)$, where F is the total flow to the tissue compartment, $c_p(t)$ is concentration of indicator in the arterial plasma as a function of time, and $c_v(t)$ is the venous concentration, then

$$dc(t) = f(c_p(t) - c_v(t))dt \tag{1.15}$$

where $c(t)$ is the concentration of the indicator in the tissue compartment, and f is the *specific* flow, *i.e.*, the flow per unit mass of the tissue compartment. If a freely diffusible indicator is in use, then the tissue concentration is in equilibrium with the effluent venous concentration, with a proportion described by the blood–brain partition coefficient, λ.

If direct measurements of both arterial and venous concentrations are available, as in the Kety–Schmidt technique, the analysis stops at this point. With the substitution $c(t) = \lambda\ c_v(t)$, Eq. (1.15) can be directly integrated to yield an expression for flow. For a clearance experiment where indicator concentration approaches a constant value with increasing time, specific flow, with units of ml/100 g/min, is determined as:

$$f = \frac{100\,\lambda\,c_{sat}}{\int_0^\infty [c_p(t) - c_v(t)]dt} \tag{1.16}$$

where c_{sat} is the equilibrium concentration of freely diffusible indicator in cerebral venous blood. Examples of the type of data typically produced by a Kety–Schmidt experiment are shown in Figure 1.4.

The Kety–Schmidt technique has the unique advantage that it is an essentially model-independent estimate of total CBF. Among its results that should be taken as "benchmarks" are that average CBF (remembering that this is a specific measure of perfusion, i.e., perfusion per

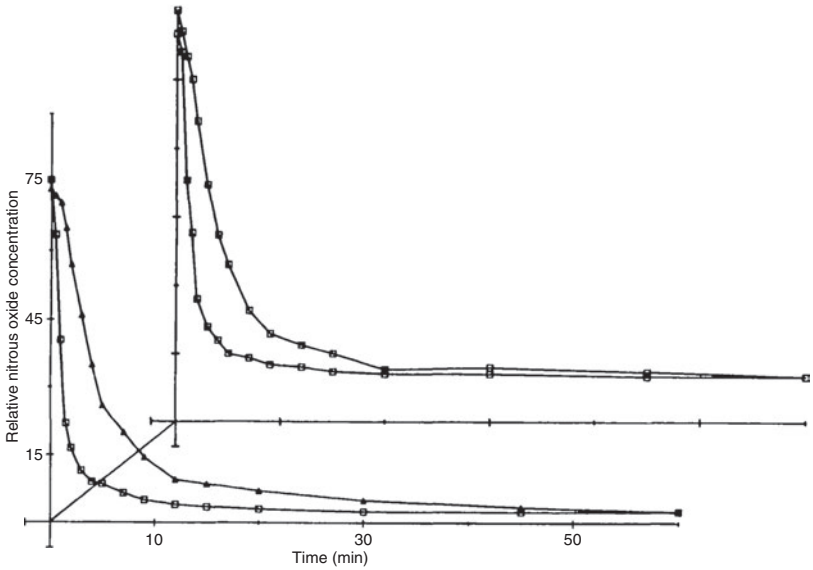

Figure 1.4 Typical data (N_2O concentration vs. time) from a washout Kety–Schmidt experiment in a cat under control conditions (foreground) and after administration of freon-22 (background). First, a steady-state concentration is achieved in which the arterial and venous N_2O concentrations are the same, at which point, the N_2O is switched out of the breathing circuit. In both studies, the lower curve is arterial concentration and the upper curve is venous concentration of N_2O. CBF is proportional to the saturation concentration of indicator divided by integrated arteriovenous difference. In this instance, application of freon-22 increased CBF, as evidenced by the smaller arteriovenous difference during the washout period.

unit mass of tissue) in the general population decreases from the age of 20 onward by about 3% per decade [41], and that average CBF in a healthy young population is about 60 ml/100 g/min [42]. Interestingly, if the aging population is selected such that conditions which in younger subjects would be judged pathological (e.g., white matter hyperintensities on MRI, or atrophy) are absent in the aged population, CBF is not significantly different from that of a young and healthy population.

The central volume and the Kety–Schmidt principles [Eq. (1.16)] are related. Clearly, the quantity $[c_p(t) - c_v(t)]$ must be related to the residue function, $R(t)$, since the instantaneous arteriovenous difference is a measure of the instantaneous difference between indicator delivered and indicator leaving the system. Thus, an integral of the arteriovenous difference over time must yield a quantity related to the mean transit time of the indicator.

As a simple example, suppose that $c_p(t)$ is a step function (Heaviside function) ($c_p(t) = c_0$ for $t < 0$, $c_p(t) = 0$ for $t \geq 0$), and that the tissue compartment has a uniform specific flow of $f = \frac{F}{V} = k$ (units ml/100 g/min). The specific flow f equals CBF. Per the central volume theorem: $k = f =$ CBF = CBV/MTT, where CBV is cerebral blood volume. In a well-mixed situation, the log linear tail of a concentration–time curve in a Kety–Schmidt experiment has a negative slope of F/V: $c(t) = \exp(-kt)$. Then the integral in the denominator of Eq. (1.16), $\int_0^\infty [c_p(t) - c_v(t)]dt$, becomes $-\lambda c_{sat} \int_0^\infty e^{-kt} dt$, or $\frac{\lambda c_{sat}}{k}$, as due to the step function input, the venous concentration equals the equilibrium (saturation) concentration c_{sat} at $t = 0$. For $t \geq 0$, the operand of the integral reduces to $c_v(t)$, as $c_p(t) = 0$. Thus, the venous output can be modeled with a single exponential decay $c_v(t) = \exp(-kt)$. Considering the scaling factor of 100, one sees that this calculation produces an identity in Eq. (1.16), thus demonstrating the quantity $\int_0^\infty [c_p(t) - c_v(t)]dt$ to be equal to the mean transit time $\bar{t}$, scaled by $\frac{\lambda c_{sat}}{CBV}$.

External monitoring of indicator concentration

Up to this point, all discussion of tissue flow estimation has been based on measurements of input and output concentrations of an indicator. Since in practice this would usually require invasive arterial and venous sampling for each organ system, it is seldom used. Rather, imaging-based CBF techniques will usually measure indicator concentrations in tissue. Various "indicator-detection pairs" that have been used are: inert xenon gas with CT detection of xenon's X-ray absorption [4, 43–47] (Figure 1.5), iodinated contrast agent with X-ray absorption [48–54] (Figure 1.6), gamma-emitting radiotracers with detection by SPECT [6, 55], positron-emitting radiotracers with detection by PET [8, 36, 56–58] (Figure 1.7), paramagnetic contrast agents with MRI detection that utilizes either T_2^* [59–64] (Figure 1.8) or T_1 [32–34] contrast as a measure of tissue concentration, and spin-labeled endogenous blood with MRI detection [12, 13, 65–67].

If we begin with the ideal situation of a Dirac delta function input of a quantity q_0 of indicator into the system at time t = 0, then at any time after the introduction of the indicator, an external detector will sense the amount of indicator *remaining* in the system, $Q_T(t)$:

$$Q_T(t) = q_0[1 - H(t)] = q_0 R(t) \tag{1.17}$$

The quantity of tracer in the tissue $Q_T(t)$ at each point in time t is $Q_T(t) = Vc_t(t)$, where V is the tissue volume under observation and $c_t(t)$ is the tissue concentration. Consequently, the integral of the detected tissue concentration over time curve multiplied by the tissue volume will be the mean transit time scaled by the introduced tracer amount q_0:

$$\int_0^\infty Vc_t(t)dt = V\int_0^\infty c_t(t)dt = \int_0^\infty Q_T(t)dt$$
$$= \int_0^\infty q_0[1 - H(t)]dt = q_0\bar{t} \tag{1.18}$$

While the total quantity of tracer entering the system is $q_0 = F\int_0^\infty c_a(t)dt$ under all circumstances, Eqs. (1.17) and (1.18) are no longer accurate representations of the tissue tracer quantity over time if the AIF is not instantaneous. Here, the key to the mathematical examination of the processes governing the relationship between the AIF and the tissue concentration lies in the decomposition of the problem into the components of tracer quantities entering and leaving the tissue at each point in time.

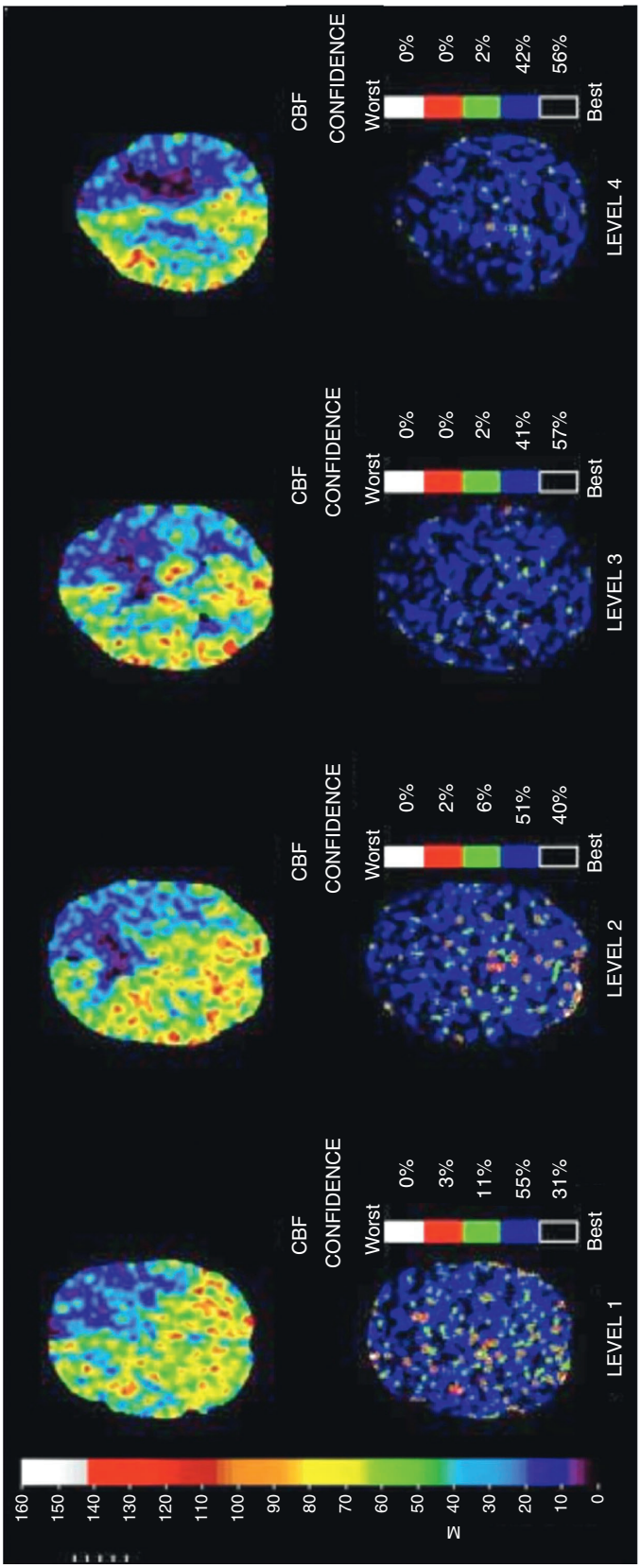

Figure 1.5 Xe-CT CBF maps from four slices (levels) in a patient with a right MCA occlusion and corresponding flow deficit. Note that the right side of the image corresponds to the patient's right-hand side. CBF was measured using the freely diffusible indicator, inert xenon, and CT Hounsfield units to estimate the indicator concentration–time curve in each pixel. Accompanying maps of goodness-of-fit for each slice are provided. Figure courtesy of Dr. Howard Yonas, University of New Mexico, Albuquerque, NM, USA.

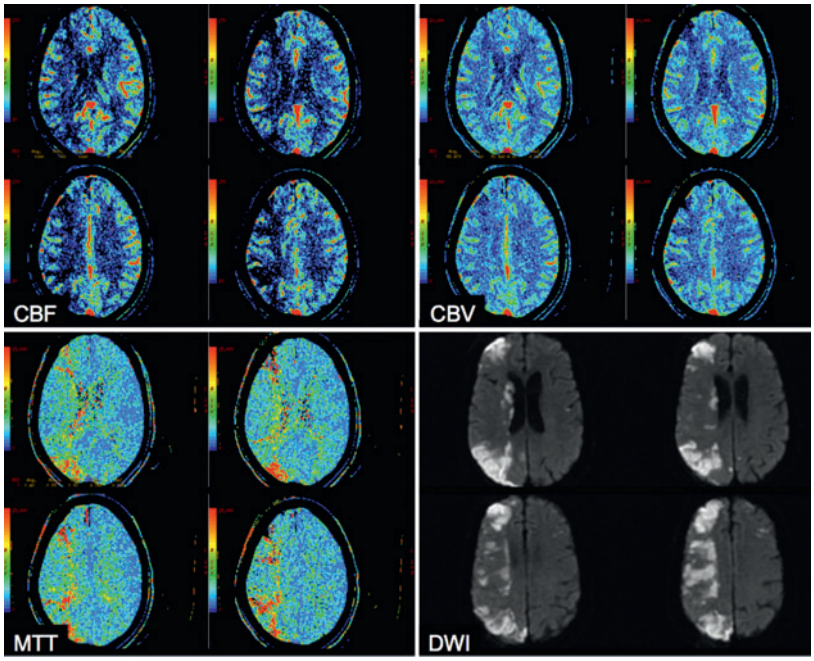

Figure 1.6 CT perfusion images from four slices calculated using bolus injection of non-ionic iodine-based contrast agent (iopamidol) in a 60-year-old male with an embolic right MCA stroke. CBF, CBV, and MTT maps showing reduced blood flow and blood volume and increased mean transit time respectively in the ischemic right hemisphere, corresponding areas of restricted water diffusion suggesting acute ischemic infarction seen on diffusion-weighted MRI scan (DWI). Figure courtesy of Dr. Rajan Jain, Henry Ford Hospital, Detroit, MI, USA.

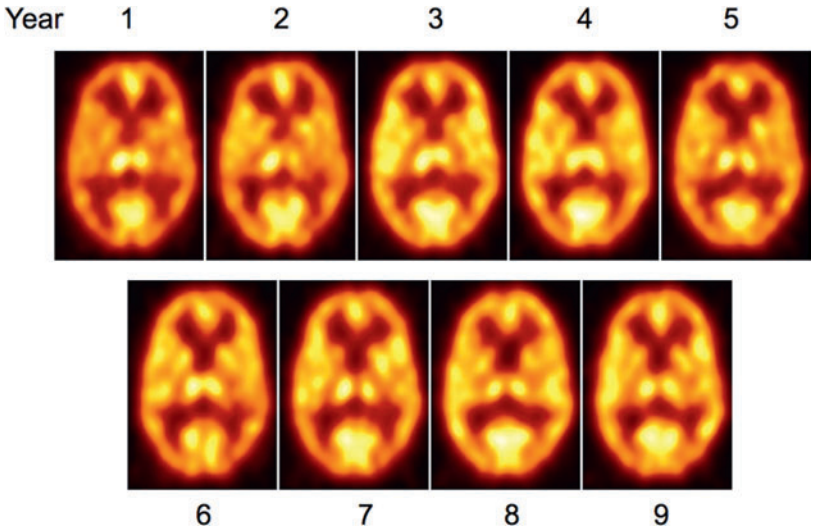

Figure 1.7 $H_2{}^{15}O$-PET CBF images in a normal elderly subject scanned every year over a 9-year period. Pixel resolution is 6.5 mm with data collection of 1 minute following intravenous injection of ^{15}O-labeled water. Excellent reproducibility and relatively stable flow from year to year is observed. Figure courtesy of Dr. Susan Resnick, National Institute on Aging, Baltimore, MD, USA.

The quantity $Q_I(t)$ of indicator entering the tissue at time t is

$$Q_I(t) = FC_a(t)dt \tag{1.19}$$

where $C_a(t)$ is the arterial concentration of the tracer. The quantity of tracer $Q_o(t)$ leaving the tissue at time t is, following from Eq. (1.18) and the definition of:

$$Q_o(t) = Fc_V(t)dt = F\,.\int_0^\infty c_a(t-\tau)h(\tau)d\tau dt$$
$$= F\,.\int_0^\infty c_a(\tau)h(t-\tau)d\tau dt \tag{1.20}$$

where $c_v(t)$ is the venous concentration of the tracer. The quantity remaining $Q_T(t)$ in the tissue at time t is