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# What is perfusion, and how do we measure it?

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Highlights

- "Perfusion" is sometimes used in a loose way to describe different aspects of blood flow
- In a quantitative physiological sense, perfusion is the volume of arterial blood delivered to capillary beds within a gram of tissue per minute.
- Measuring the regional delivery of labeled microspheres that stick in the capillary bed is the gold standard for measuring perfusion
- Arterial spin labeling (ASL) approaches microsphere methods in a noninvasive way by magnetically tagging arterial blood
- Bolus-tracking experiments, following the local delivery and clearance of an intravascular agent such as Gd-DTPA, is less sensitive to perfusion itself but provides other clinically important measurements.

*Target audience:* Researchers and physicians involved in using imaging methods to measure organ blood flow.

## What is perfusion?

The term "perfusion" is sometimes used in a somewhat loose way, particularly in the MRI world, to describe different aspects of blood flow to a tissue. In a quantitative physiological sense, though, perfusion has a specific meaning: the volume of arterial blood delivered to capillary beds within one gram of tissue per minute (1). For example, in gray matter of the healthy human brain a typical value is 0.5 mL/g/min, often expressed as 50 mL/100g/min. This is the definition that is most useful because it directly describes the basic physiological function of blood flow: to deliver basic metabolic substrates such as glucose and oxygen to the tissue and to clear the products of metabolism, such as carbon dioxide and heat. For example, if $F$ is the perfusion (or "blood flow", the terms mean the same thing) defined in this way, and $C_A$ is the concentration of $O_2$ in the arterial blood, then the rate of delivery of oxygen to the capillary bed is $FC_A$, and if the fraction of delivered $O_2$ that is metabolized is $E$, then the oxygen metabolic rate ($J_{O2}$) is simply $J_{O2}=EFC_A$. In short, perfusion provides the rate constant for metabolism, at least in the sense that it determines the delivery rate of metabolites.

This becomes clearer if we simplify the units of perfusion and consider blood flow delivered to one mL of tissue rather than one gram of tissue (this definition is often more practical for imaging applications where flow is measured to an imaging voxel, and

the numerical values are similar for the brain where the density is about 1g/mL). The units of perfusion are then mL blood/mL tissue/min, or essentially units of inverse time ($min^{-1}$). Note that the oxygen metabolic rate also can be expressed in simpler units as concentration divided by time (mM/min). For our example, a typical value of $O_2$ concentration in the blood is $C_A$=8 mM, the extraction fraction $E$ is dimensionless with a typical value of 0.4, and as noted perfusion is typically about $F$=0.5 $min^{-1}$, so the $O_2$ metabolic rate is about 1.6 mM/min. Note that the typical concentration of $O_2$ as dissolved gas in tissue is only about 0.03 mM (2), because of the low solubility of $O_2$ in water, so for this metabolic rate the existing tissue $O_2$ would be completely exhausted in about 1 second if it was not continuously replenished by perfusion.

**Perfusion depends on delivery of blood rather than motion within the vessels**

Intuitively, it seems that an ideal way to measure blood flow would be to measure the velocity of blood within each of the capillaries of a capillary bed. The invasive technique of Laser Doppler Flowmetry (LDF) does this with microscopic imaging and measurements of the frequency shift of light reflected from moving red cells (3). In many animal experiments, this technique is used to monitor changes in blood flow. Somewhat surprisingly, however, LDF does not measure perfusion in the quantitative sense defined above. That is, measuring how blood is moving about *within* a vascular bed does not tell us how rapidly blood is being *delivered* to the vascular bed. For this reason LDF is sensitive to a change in blood flow (because the general motion of blood in the vessels tends to speed up when blood flow increases), but does not provide a quantitative measurement of perfusion.

**Microspheres are the gold standard for measuring perfusion.**

Based on the ideas above, the best way to measure perfusion is to measure the delivery of arterial blood. Microspheres do this in a direct way. Small particles that can be measured in tissue based on either their color or their radioactivity are injected into a major artery. These particles are designed to be small enough to be carried to the smallest vessels but too big to fit through those vessels. The injected microspheres then are distributed to each tissue element in proportion to the perfusion of that element, where they stick and can later be measured in sectioned tissues. Although considered the standard for measuring perfusion, this is clearly an invasive procedure and so is not appropriate for humans.

**Arterial spin labeling measures the delivery of labeled arterial blood.**

In its ideal form, the MRI method of arterial spin labeling (ASL) is essentially a noninvasive analog of the microsphere experiment, in the sense that arterial blood is labeled and the amount delivered to each voxel of tissue is measured before the label has had a chance to clear in venous blood. With ASL, arterial blood is labeled by inverting the magnetization outside the image plane, waiting for a delay period to allow the labeled blood to be delivered to the image plane, and acquiring an image (the tag image). A second image (the control image) is acquired without first inverting the arterial blood. If

this is done carefully, the subtraction (control – tag) then subtracts out the signal from the static spins and leaves only the signal of arterial blood delivered to the slice during the delay period (4, 5).

In practice several other issues need to be taken into account, including relaxation of the tagged magnetization, transit delays from the inversion band to the slice, and potential magnetization transfer effects of the pulse sequence design, and different variations of ASL reflect different approaches to solving these problems (6, 7). Note that the analogy of ASL with microspheres works only if the delay period is not long enough for the labeled blood to pass all the way through the capillary bed and exit the voxel in venous blood (8), and for longer delays this effect also has to be taken into account (9).

**Bolus-tracking methods measure several physiological parameters related to perfusion**

Another approach with many variations in practice is to inject an agent whose concentration in tissue can be measured and then follow the delivery and clearance of the agent from each tissue voxel with imaging. For example, a standard method for Positron Emission Tomography (PET) involves labeling water with $^{15}O$, a positron emitter. In MRI studies, a contrast agent such as Gd-DTPA alters the local $T_1$ of the tissue and so alters the MR signal strength, so the agent's passage through the tissue can be measured indirectly with dynamic imaging (10, 11). For bolus-tracking methods such as these, we can think of the basic method as measuring the delivery and clearance of the agent. As described above, the delivery component—the initial rise of the tissue concentration—is sensitive to perfusion. But what determines the clearance portion of the curve? Perfusion is one component, but not the only one.

The second tissue parameter that plays a key role in the clearance of the agent is the volume of distribution $\lambda$, defined as the fraction of the tissue volume that would be filled with the agent if the agent was allowed to come into equilibrium between blood and tissue. The examples above illustrate two extreme values of $\lambda$: for labeled water, which can diffuse into all of the tissue compartments, $\lambda$ is about equal to 1.0; however, in the healthy brain the contrast agent Gd-DTPA is expected to remain in the blood, and so $\lambda$ is only about 0.04, the typical blood volume fraction of tissue. The partition coefficient has a profound effect on the clearance of the agent. The time constant for clearance of the agent is about $\lambda/F$, so while for labeled water this time constant is about 2 minutes in the human brain, for Gd-DTPA it is only about 5 sec. Untangling these effects is even more complicated for an intravascular agent because the bolus itself, originating as a venous injection, is typically much broader than this characteristic clearance time and may be different in different locations. For this reason, it is necessary to make a local correction for the bolus width (deconvolution) to try to untangle perfusion from the kinetics of a bolus-tracking curve (12).

The important difference between a *diffusible* agent and an *intravascular* agent strongly affects whether the dynamic tissue concentration curve is more sensitive to perfusion or to blood volume. The basic behavior of the tissue concentration curve of a

delivered agent is that the initial delivery depends just on perfusion, but after the volume of distribution begins to fill the curve depends more on the clearance time, which depends on perfusion and the volume of distribution. If the full tissue curve (delivery and clearance) is measured, the area under that curve is simply proportional to $\lambda$, and is independent of the value of the perfusion. For this reason, the dynamics of an intravascular agent like Gd-DTPA give robust information on the local blood volume fraction ($\lambda$) but it is much more difficult to extract information on perfusion from such measurements. Untangling the effects of $F$ and $\lambda$ is even more complicated for an intravascular agent because the bolus itself, originating as a venous injection, is typically much broader than this characteristic clearance time and may be different in different locations. For this reason, it is necessary to make a *local* correction for the bolus width to try to untangle perfusion from the kinetics of an intravascular agent. In contrast, with ASL methods there is little time for the "label"—the inverted magnetization of water protons in arterial blood—to leave the tissue, so the clearance time does not come into play in determining the signal.

**Other aspects of blood flow are often important in clinical applications**

While it is difficult to measure perfusion itself with an intravascular tracer (even though such methods in clinical MRI are often described as "perfusion" imaging), the kinetics of an injected agent provide additional physiological parameters that are clinically useful. For example, in stroke the reduced perfusion leads to a delay in the *time-to-peak* (TTP) of the local tissue curve, which is readily measured with dynamic imaging of Gd-DTPA transit (13). Also, the longer clearance time due to reduced perfusion makes it easier to make a perfusion estimate from the kinetics of an intravascular agent. In this way bolus–tracking and ASL have complementary ranges in which they are robust. For normal healthy brain, ASL works well but it is difficult to derive a robust estimate of perfusion from the kinetics of an intravascular agent. In ischemia, though, bolus-tracking begins to work better as a way to measure perfusion, while ASL must contend with artifacts due to longer transit delays. In addition, bolus-tracking experiments can provide additional information on the integrity of the blood brain barrier: if the agent leaks out of the blood vessels a compartmental model can be used to derive a parameter called $K^{trans}$ (14). This parameter is essentially the rate constant for delivery of the agent to the extravascular space, and so is a product of perfusion $F$ and the extraction fraction $E$ of the agent, the fraction that diffuses into the tissue during a pass through the capillary bed.

These examples illustrate that a more complex signal, that cannot be reliably decomposed into a specific measure of perfusion, can nevertheless be very useful. Another example is the blood oxygenation level dependent (BOLD) signal used to map patterns of activation in the brain. In physiological terms this signal is complex, depending on the change of blood flow, blood volume and oxygen metabolism with neural activation. For this reason the BOLD response is not a good quantitative indication of the magnitude of the change in blood flow because of the unknown changes in the other physiological variables, but it is nevertheless a very useful tool for identifying areas in which neural activity changed in response to a stimulus.

## Conclusions

While a quantitative measurement of local perfusion is often a primary goal in perfusion imaging, the techniques involved are continually expanding to provide measurements of other physiological parameters related to blood flow. In addition to the other parameters available from measuring the kinetics of an injected contrast agent, new methods for ASL tagging are being developed to use velocity selective tagging to minimize transit delay effects (15) and selective vessel tagging to image perfusion territories (16).

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