

Quantification of Perfusion Using Bolus Tracking Magnetic Resonance Imaging in Stroke

Assumptions, Limitations, and Potential Implications for Clinical Use

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Background—MR techniques have been very powerful in providing indicators of tissue perfusion, particularly in studies of cerebral ischemia. There is considerable interest in performing absolute perfusion measurements, with the aim of improving the characterization of tissue “at risk” of stroke. However, some important caveats relating to absolute measurements need to be taken into account. The purpose of this article is to discuss some of the issues involved and the potential implications for absolute cerebral blood flow measurements in clinical use.

Summary of Comment—In bolus tracking MRI, deconvolution of the concentration-time course can in theory provide accurate quantification. However, there are several important assumptions in the tracer kinetic model used, some of which may be invalid in cerebral ischemia. These can introduce significant errors in perfusion quantification.

Conclusions—Although we believe that bolus tracking MRI is a powerful technique for the evaluation of perfusion in cerebral ischemia, interpretation of perfusion maps requires caution; this is particularly true when absolute quantification is attempted. Work is currently under way in a number of centers to address these problems, and with appropriate modeling they may be overcome in the future. In the interim, we believe that it is necessary for users of bolus tracking perfusion data to be aware of the current technical limitations if they are to avoid misinterpretation or overinterpretation of their findings. (*Stroke*. 2002;33:1146-1151.)

Key Words: cerebral blood flow ■ cerebral ischemia ■ contrast media ■ magnetic resonance imaging
■ perfusion ■ stroke

The term *perfusion* normally refers to the delivery of blood at the level of the capillaries, where exchange of oxygen and nutrients between blood and tissue takes place. When quantified, perfusion is measured in units of milliliters per 100 g per minute. MR techniques have been very powerful in providing indicators of tissue perfusion in the brain in the former, nonquantitative sense; indeed, they have been shown to contribute important new information not accessible by any other MR technique to date. One of the major applications has been in the assessment and management of patients with acute stroke, with numerous recent reports demonstrating the key role of perfusion MRI, mostly in combination with diffusion MRI since the latter is believed to provide an early marker of cytotoxic edema (see Reference 1 for a recent review).

Many of the recent perfusion MRI studies have been concerned with predicting the eventual infarct volume in patients who have suffered an ischemic insult, with a major aim of selecting the most appropriate patients for possible therapeutic intervention. A large number of these studies have shown a regional mismatch between diffusion abnormality

and perfusion deficit (eg, References 2–4), while others have shown the presence of perfusion abnormalities even in the absence of any abnormality on structural or diffusion MRI.^{5–7} Although these areas of mismatch are generally believed to be “at risk” of infarction,¹ their fate is evidently quite variable.^{8–11} A number of studies have shown a significant correlation between perfusion MRI parameters and lesion outcome measures, but their sensitivity and specificity are in general poor.^{9–11a} Therefore, there is increasing interest in improving the characterization of the mismatch area between the diffusion and perfusion abnormalities, with the aim of differentiating tissue that will eventually be infarcted from tissue that will remain viable. To this end, many attempts have been made to perform absolute measurement of perfusion parameters and to find a combination of “threshold” values that will help to predict tissue viability and therefore the likely infarct growth. However, some important caveats relating to absolute measurements need to be taken into account.¹² The purpose of this article is to discuss some of these issues and the potential implications for absolute cerebral blood flow (CBF) measurements in clinical use.

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At present, dynamic susceptibility contrast (DSC) MRI, usually referred to as *bolus tracking*, is the MRI technique most commonly used for the clinical evaluation of perfusion in cerebral ischemia (see Reference 13 for a recent review). This technique involves the rapid intravenous injection of an MR contrast agent and the serial measurement of the signal loss during the passage of the bolus through the tissue.¹⁴ The concentration of the contrast agent (measured from the change in T2 or T2*) in a region of interest (ROI) can be expressed as follows^{13,15}:

(1)

$$C(t) = k \cdot CBF \cdot [C_a(t) \otimes R(t)] = k \cdot CBF \cdot \int_0^t C_a(\tau) R(t-\tau) d\tau$$

where $R(t)$ is the residue function, ie, the fraction of contrast agent concentration at time t for the case of an ideal instantaneous bolus injected at $t=0$, $C_a(t)$ is the arterial input function (AIF), ie, the concentration of contrast entering the ROI at time t , \otimes indicates the convolution operation, and k is a proportionality constant that depends on a number of parameters, including the hematocrit levels (since the contrast agent is only in the plasma volume) and the brain tissue density. The convolution operation in Equation 1 accounts for the fact that for a nonideal bolus, part of the spread in the concentration-time curve is due to the finite length of the actual bolus.¹³ It is generally believed that deconvolution of Equation 1 (for a more detailed description of deconvolution, see Reference 15) provides an accurate measurement of CBF, and measurements of absolute CBF (in units of milliliters per 100 g per minute) have recently been reported in healthy volunteers and patients.^{11,16–22}

Some of the new generation of MR scanners now provide the necessary software and hardware to calculate perfusion maps by means of deconvolution. With the widespread availability of this postprocessing technique, there is likely to be an increase in the use of CBF maps for the clinical evaluation of stroke. However, there is a potential danger of the maps generated with the use of DSC MRI being misleading in some circumstances, with important clinical implications. Although deconvolution of the concentration-time course could in theory provide accurate quantification, there are several assumptions in the tracer kinetic model used in the quantification of perfusion, and many of these assumptions may be invalid in cerebral ischemia. This opinion article discusses some of the most important assumptions in the quantification of DSC MRI data and the potential implications for the quantitative measurement of CBF in stroke. There are 3 main assumptions: arterial input function, tissue characteristics, and cross calibration.

Assumption 1: Arterial Input Function

One of the main assumptions is related to the AIF. The calculation of CBF from Equation 1 requires knowledge of the AIF, which in practice is estimated from a major artery (eg, the middle cerebral artery or the internal carotid artery), with the assumption that this represents the exact input to the tissue. Any delays and dispersion of the bolus that are introduced during its passage from the site of AIF estimation

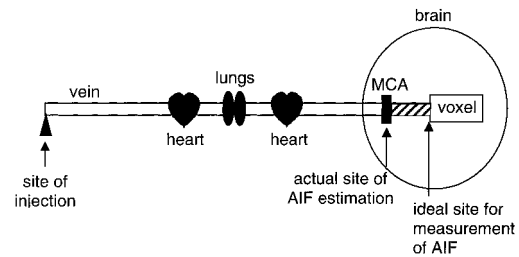


Figure 1. Schematic diagram of the path taken by a bolus of contrast agent. By estimating the AIF in a major artery (middle cerebral artery [MCA] in this figure), the delay and dispersion (spread) of the bolus are accounted for from the site of injection (vein) through the heart and lungs up to the site of measurement. However, the extra delay and dispersion introduced during the path from the major artery to the tissue of interest (represented by the diagonal hatched path) are not taken into account. The model used in the quantification of perfusion interprets this delay and dispersion as occurring within the tissue of interest, therefore introducing errors.

to the tissue of interest (Figure 1) will therefore introduce an error in the quantification of CBF, and this error could well vary from one region to another because of differences in the amount of delay and dispersion for different regions.²³ Recent numerical simulations²³ that use singular value decomposition (SVD)¹⁵ have assessed the errors introduced in the quantification of perfusion by various degrees of delay and/or dispersion. It was shown that delays of 1 to 2 seconds (similar to the typical time resolution used in DSC MRI studies) can introduce an approximately 40% underestimation of CBF and an approximately 60% overestimation of mean transit time (MTT). These delays are not uncommon in patients with cerebrovascular disease, and the associated errors are further increased if there is also dispersion of the bolus.²³ Although the simulations were done with the use of SVD, these conclusions are not limited to this deconvolution approach. While some other approaches could be less sensitive to bolus delay,^{21,24} all methods will be affected by the presence of dispersion because the kinetic model that is used cannot differentiate between this dispersion and the true intravoxel dispersion on which the theory is based²³ (Figure 1). Therefore, the presence of bolus delay and dispersion can lead to very misleading information in stroke, where there may commonly be vessel occlusion, stenosis, or collateral circulation.

These statements are illustrated by the 2 cases shown in Figure 2. In both cases, perfusion imaging provides important information about tissue pathophysiology. However, in the second of these cases, there is considerable scope for misinterpretation of the nature of the abnormality. The data in Figure 2A are from a 5-year-old boy with sickle cell disease and bilateral moyamoya syndrome, who had an acute right hemiparesis 5 weeks before the MRI examination. The T2/diffusion images showed a chronic left occipital infarct. However, the perfusion abnormality extends beyond that area, with reduced CBF and prolonged MTT in a noninfarcted region in the right hemisphere. The CBF ratio (right side to left side) was 0.50. The gamma-variate fitting to the regional concentration-time course indicated that the bolus arrived at both regions at approximately the same time (0.01 seconds

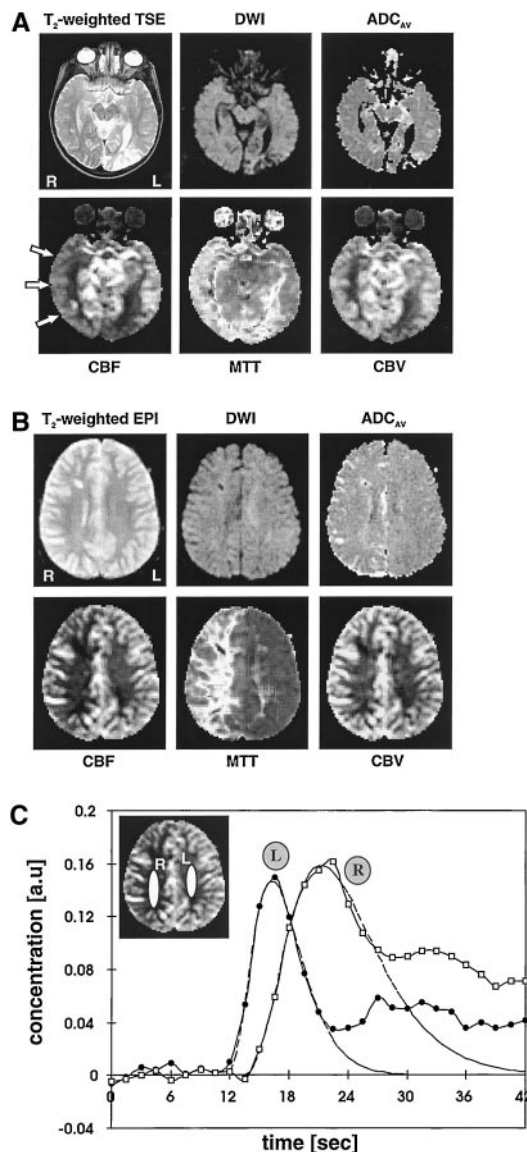


Figure 2. Data from 2 children illustrate a potential problem of using deconvolution analysis in the presence of cerebrovascular disease. **A**, Five-year-old boy with bilateral moyamoya syndrome. Although the T2/diffusion images showed a chronic left occipital infarct (top row), there was also an extensive CBF abnormality in the right hemisphere (bottom row; arrows), with increased MTT in equivalent regions. TSE indicates turbo spin echo; ADC_{AV} , average apparent diffusion coefficient; R, right; and L, left. **B**, Six-year-old boy with right internal carotid artery stenosis; in this case the deconvolution analysis gives misleading information. Although there was only a small mature infarct in the right frontal white matter (top row), there was a very extensive perfusion abnormality throughout the right hemisphere (bottom row). EPI indicates echoplanar imaging. **C**, Concentration-time course for 2 regions (see inset). There was an approximately 1.75-second delay in the arrival of the bolus to the right region. This delay introduced an underestimation in the calculated CBF, making the CBF maps unreliable. See text for more information. Panel A is part of a figure previously published in *Ann Neuro*⁶ and is reprinted with permission (copyright 2001, John Wiley & Sons Inc).

apart). Therefore, the 0.50 ratio is likely to reflect (in the absence of significant dispersion) a true 50% reduction in the right CBF compared with the left side. Figure 2B and 2C show the DSC MRI data from a second patient, a 6-year-old

boy with right internal carotid artery stenosis. Although there was only a small mature infarct in the right frontal white matter (with no other abnormality on diffusion or structural MRI), there was a very extensive perfusion abnormality throughout the right hemisphere (Figure 2B). The CBF ratio (right side to left side) estimated from the deconvolution analysis was approximately 0.55, which is similar to the value obtained for the first patient. However, in contrast to the first patient, a regional analysis of the concentration-time course for the 2 regions showed that the bolus arrival was delayed by approximately 1.75 seconds on the right side compared with the left side (Figure 2C). This delay would introduce an underestimation in the calculated CBF of approximately 40% and a MTT overestimation of approximately 60% in the right region.²³ Therefore, the perfusion maps in Figure 2B are misleading in the sense that the bolus delay can almost completely account for the apparently low CBF value observed in the map; the actual CBF is probably close to normal. As discussed previously,²³ although the effect of delay can, in principle, be accounted for by shifting back the peak, the effect of dispersion (which to a varying degree is likely to be associated with any delay) cannot easily be corrected. Such correction would require modeling of the vascular bed and generalization of the kinetic model to include dispersion effects.^{23,25}

There are a number of additional difficulties. In particular, absolute CBF quantification requires an absolute measurement of the AIF, and this leads to further problems. For example, there is a potential problem associated with partial volume effects as a result of the relatively low spatial resolution of the images commonly used in DSC MRI. Some corrections have recently been suggested,^{22,26,27} and, in general, they involve scaling of the estimated AIF. However, the effect in some cases might be more complicated because the partial volume could involve perfused tissue, which would also influence the shape of the AIF. The effect of partial volume can be further complicated by the angular dependency of the signal phase since this angular dependency is different for the extravascular and the intravascular contributions,²⁸ and the total signal in the pixel (weighted average of the intravascular and extravascular signal) will be dependent on the orientation of the vessel with respect to the direction of the applied magnetic field. In any case, an uncorrected partial volume will introduce an underestimation of the AIF, with a corresponding overestimation of CBF (see Equation 1).

A question arises regarding the "ideal" place for AIF measurement. To minimize the error from partial volume effects, the AIF should be measured in a large artery. However, there is an additional conflicting requirement that the AIF should be measured as close as possible to the tissue of interest to minimize bolus delay and dispersion. This may not be possible in practice in some cases with high-grade stenosis or occlusion, where the AIF from the contralateral side or from an ipsilateral artery upstream to the abnormality is commonly used. However, it should be noted that vascular abnormalities downstream from the place of AIF estimation are not the only potential source of errors when an ipsilateral AIF is used. In a study of patients with carotid artery stenosis, Lythgoe et al²⁰ compared the perfusion maps generated by

using AIFs from either the contralateral or the ipsilateral middle cerebral artery. Their results suggested that there is still some increased bolus dispersion (compared with the contralateral AIF) when an ipsilateral AIF is used even if the ipsilateral AIF is measured distal to the stenosis. However, there is no consensus regarding the effect of measuring the AIF in different places. While some studies have shown similar bolus shape,²⁹ later studies have reported differences depending on the site of sampling.^{20,30} There is, therefore, no unique answer to the ideal place for AIF measurement, and the vessel selection will depend on the particular vascular abnormality of the patient, as well as on a compromise between any remaining degree of bolus delay/dispersion and the partial volume effect. Furthermore, although in practice a single AIF is used for each whole slice, ideally a different AIF for the normal and the abnormal areas would be used.

The determination of the AIF is also dependent on the sequence type used (gradient echo or spin echo). While gradient echo is sensitive to total vascular space, spin echo is more specific to the microvasculature.²⁸ As a consequence of the latter, it has been suggested that spin-echo sequences cannot provide an absolute measurement of the AIF.³¹ In contrast, because of susceptibility-related signal changes during the acquisition window, artifactual signal shifts to neighboring voxels have been described,³² which are expected to be larger in gradient-echo sequences. Therefore, the reliability and diagnostic value of perfusion-related maps generated from gradient-echo or spin-echo sequences are still subject to debate.

Assumption 2: Tissue Characteristics

The tissue characteristics (which may be different in the presence of pathology) can influence the proportionality constants involved in the quantification of CBF in 2 ways. First, the concentration of contrast agent (in both the tissue and the AIF) is assumed to be linearly proportional to the change in relaxation time T2 and T2*.^{14,28} This proportionality constant has been shown to be tissue dependent³³ and therefore is likely to vary also with pathology. Second, deconvolution of Equation 1 provides information about the product of k -CBF. Therefore, absolute measurements of CBF require knowledge of the constant k and hence of the brain tissue density and the hematocrit levels (in both capillaries and large vessels). To obtain absolute CBF, values for the density of tissue, large-vessel hematocrit values, and a uniform value for the capillary hematocrit are usually assumed.^{11,16–18,21,24} Although the density of tissue may not be expected to vary substantially during the acute stages of ischemia (before the development of vasogenic edema), that is not necessarily true for the hematocrit levels in the tissue. For example, increased capillary hematocrit levels have been reported during acute ischemia,³⁴ and decreased levels have been reported during chronic carotid artery stenosis.³⁵ The resultant percent CBF error is approximately one third of the percent change in capillary hematocrit value (normal value approximately 0.25), eg, a 30% increase (or decrease) in hematocrit introduces approximately 10% underestimation (or overestimation) of CBF. It is interesting to note that many of these issues are relevant to relative as well as absolute

measurements of CBF. For example, a local change in hematocrit levels would also affect measurements of relative CBF.

Assumption 3: Cross Calibration

Instead of assuming values for the proportionality constants, an alternative approach for measuring absolute CBF involves cross calibration with another perfusion technique.¹⁹ Thus, an empirical scaling to absolute units can be obtained. However, similar to the problems of fixing the values for the proportionality constants, this scaling constant (usually obtained from normal volunteers) should be used with caution because it is likely to vary with pathology. An extra correction factor was proposed recently based on improving the correlation in a group of 5 patients with carotid artery occlusion, but the accuracy at low flows is still limited.²²

Other Limitations and Implications

Quantification of cerebral blood volume (CBV) is generally believed to provide a robust measure with the use of DSC MRI, and it is therefore interesting to discuss the implications of these sources of errors on measurement of CBV. Since CBV is proportional to the area under the peak,¹³ its measurement can be insensitive to bolus delay and dispersion.²³ For example, the effects of delay and dispersion do not influence the quantification of relative CBV in the data shown in Figure 2C. The ratio of the peak area in the right to the area in the left ROI is 2.1. This corresponds to a 110% increase in the CBV in the right relative to the value in the left, suggesting a compensatory vasodilatation in the ipsilateral ROI. However, CBV does not depend only on the area under the peak but is given by the following expression¹³:

$$(2) \quad CBV = \frac{1}{k} \frac{\int C(t) dt}{\int C_a(t) dt}$$

Therefore, any changes in the proportionality constants mentioned above (eg, hematocrit levels) or errors in the quantification of the area under the AIF (eg, partial volume effects) will introduce errors in the quantification of absolute CBV. These unaccounted errors may be the reason for the lack of agreement regarding the prognostic value of an increase in absolute CBV in acute stroke.¹⁰ Furthermore, although initial studies indicated that CBV was the best predictor of tissue outcome, recent studies have suggested that CBV alone does not have very high sensitivity and specificity.^{9–11} Therefore, although relative CBV can be immune to some of the errors described, accurate measurements of CBF (and MTT) in addition appear to be necessary for a better characterization of tissue outcome.^{9,11}

An alternative approach for analysis of DSC MRI is by direct calculation of summary parameters (eg, time to peak, maximum peak concentration, and full width at half maximum). However, summary parameters are also affected by many of the aforementioned problems. For example, the presence of delay and dispersion will introduce a prolonga-

tion of time to peak and full width at half maximum and a decrease of maximum peak concentration, even if the CBF does not change. Furthermore, the use of summary parameters has some additional disadvantages. As observed in the early 1990s, none of the summary parameters provide a direct measure of perfusion.³⁶ Moreover, summary parameters do not take account of differences in AIF between patients. Perthen et al,³⁷ using numerical simulations, have shown that none of the summary parameters represent a robust measure of perfusion since they showed very large variability within the representative AIF range studied. The dependency on the AIF could be reduced, but not eliminated, by the use of relative summary parameters (eg, relative to a normal region).

Finally, it should be noted that many of these limitations also affect other perfusion techniques. For the case of MR arterial spin labeling (ASL) techniques (see Reference 13 for a recent review), long transit times between the labeling site and the voxel (eg, because of the presence of collaterals) cause fundamental difficulties. As a result of the loss of labeling during these long transit times (due to T1 decay), the ASL techniques have the potential problem of not being able to differentiate between no flow (no signal in the ASL image because CBF=0) and very long transit times (no signal in the ASL image because of full relaxation of the labeled blood, regardless of the CBF value). Although DSC MRI cannot measure CBF accurately in these situations, it can still differentiate between these cases. Some modifications have been suggested to minimize the effects of long transit times in ASL,^{38,39} but the required choice of sequence parameters may become impractical. Other non-MR techniques also have assumptions and limitations when quantification of CBF in cerebral ischemia is attempted. For example, measurement of perfusion with the use of dynamic CT also requires an intravascular tracer and is based on a kinetic model similar to that of DSC MRI. Therefore, it can also be affected by delay, dispersion, hematocrit levels, and partial volume effects.⁴⁰⁻⁴² Alternative methods (such as single-photon emission CT and positron emission tomography), although based on different principles, are not free of their own assumptions and limitations. However, a discussion of these limitations is beyond the scope of this opinion article.

Summary

In summary, we believe that DSC MRI is a very powerful technique that provides unique information for the evaluation of cerebral ischemia. We and other centers use it routinely to help in the assessment and management of patients with cerebrovascular disease. However, with the increasing availability of DSC MRI as a "black-box" technique on modern scanners, we believe that it is appropriate to urge caution in interpretation of perfusion maps at the present stage of development. This is particularly true when absolute quantification is attempted,¹² but it is important to note that this is the case in some circumstances (see above) for relative measurements as well. Work is currently under way in a number of centers to address the problems underlying the quantification of CBF, and with appropriate modeling these problems may be overcome. In the interim, we believe that, in making use of the invaluable information provided by bolus

tracking perfusion data, users should be aware of the current technical limitations if they are to avoid misinterpretation or overinterpretation of their findings.

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