Perfusion Measured by MRI Using an Intravascular Tracer

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Highlight

- In MRI, a conventional gadolinium contrast agent (CA) is normally used as a tracer. Dynamic susceptibility contrast MRI (DSC-MRI) for brain perfusion imaging is the most common approach to which the theory of intravascular tracers is applied.
- DSC-MRI is based on dynamic T2*-weighted imaging, at high temporal resolution (1-2 seconds between time points), during the first passage of CA through the capillary network of the tissue of interest as well as in a tissue-feeding artery. Transient CA-induced signal changes are converted to CA concentration time curves, pixel by pixel, and maps of cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) are subsequently calculated.
- DSC-MRI suffers from a number of methodological complications, especially with regard to absolute quantification, including uncertainties in *in vivo* T2* relaxivities, arterial signal saturation and local geometric distortions at peak CA concentrations, arterial partial volume effects and arterial CA dispersion.
- Clinical applications of DSC-MRI comprise, for example, ischaemic stroke, dementia and trauma. Perfusion imaging is also applied to tumour characterization and grading as well as in the assessment of pharmacological efficiency and follow-up and outcome of treatment.

Physiological background

The microvasculature is characterized by exchange of fluid, oxygen, nutrients, hormones and anti-infective agents between blood and surrounding tissue, and also by removal of carbon dioxide and other waste products. The term perfusion refers to the flow of blood through the local capillary system of a tissue region. Perfusion or tissue blood flow F is traditionally quantified in terms of the volume of blood transported to a given mass of tissue per unit time, typically in units of ml/min/100 g. It is common to include other characteristics of tissue microcirculation and microvasculature in the perfusion imaging framework, for example, the mean transit time (MTT) (in seconds) and the tissue blood volume (BV) (in ml/100 g). Particularly in cerebral applications, it can be useful to gain access to estimates of blood volume and/or mean transit time, in addition to blood flow, because combined information may facilitate assessment of whether autoregulation mechanisms are engaged to maintain local blood flow in situations with altered perfusion pressure. Furthermore, the blood volume parameter may assist in identification of regions with angiogenesis/neovascularization.

Basic tracer considerations

The general relationship between blood flow, blood volume and blood mean transit time is given by the central volume theorem [1]:

$$F = BV/MTT \quad (1)$$

Perfusion quantification is based on tracer kinetics and monitoring of tracer concentrations over time. Different tracer molecules show different transit times when passing through the microvascular network of interest, and the function $h(t)$ describes the distribution (frequency function) of transit times (following an instantaneous input of tracer molecules at $t=0$). Another basic characteristic is the tissue residue function $R(t)$, defined as the fraction of tracer molecules still remaining in the tissue of interest at time t, after having entered the tissue at time t=0. An important and general relationship

between F and the relevant tracer concentrations, allowing for different tracer entrance times τ, is given by the convolution integral [2]:

$$C_t(t) = \rho\, F \int_0^t C_a(\tau) R(t-\tau) d\tau\,, \qquad (2)$$

where ρ is tissue density. C_t and C_a are the tracer concentrations (in M), as a function of time, in the tissue element and in the tissue-supplying artery (at the arterial inlet), respectively. The arterial CA concentration curve $C_a(t)$ is often denoted the arterial input function (AIF). Note that the indicator dilution theory, on which Eq. 2 is based, makes no specific assumptions about the internal tissue architecture or the tracer transport mechanisms within the tissue element.

Intravascular tracer theory: Dynamic susceptibility contrast MRI for brain perfusion imaging

In MRI, the most common application of the theory of intravascular tracers is DSC-MRI, used for measurement of cerebral perfusion parameters, primarily CBF, CBV and MTT. Numerous literature references of relevance to the summary below are provided in [3]. In DSC-MRI, a conventional paramagnetic gadolinium CA is used, assumed to act as an intravascular tracer in the presence of an intact blood-brain barrier (BBB). Note that gadolinium CAs reside in the plasma volume, and concentration estimates must thus be corrected in order to represent the whole blood. The CA is administered intravenously, during a relatively short injection time, often referred to as a bolus injection. During the subsequent passage through the circulatory system the CA bolus is further broadened, and, in practice, the arterial tracer arrives at the local capillary system during an extended time period, and the shape of the bolus upon arrival is described by the arterial input function (AIF).

In this context, the mean transit time (MTT) is the average time it takes for an intravascular tracer (representing blood or plasma) to pass through a microvascular or capillary system from the arterial to the venous side. MTT is defined as the expectation value of the transit time distribution $h(t)$, and it can also be expressed as the time integral of the tissue residue function, i.e.:

$$MTT = \int_0^\infty t h(t) dt = \int_0^\infty R(t) dt \qquad (3)$$

CBV is given by Eq. 4, including adaptation to the use of a plasma tracer (and different hematocrit levels in arteries and capillaries):

$$CBV = \frac{(1-Hct_{large}) \int_0^\infty C_t(t) dt}{\rho (1-Hct_{small}) \int_0^\infty AIF(t) dt}\,, \qquad (4)$$

where Hct_{large} and Hct_{small} are the hematocrit values in large and small vessels, respectively.

After appropriate corrections for the use of a plasma tracer, the measured tissue concentration curve $C_t(t)$ is given by the convolution of the impulse response function $\rho \cdot CBF \cdot R(t)$ and the AIF (*cf.* Eq. 2):

$$k_H C_t(t) = CBF[AIF(t) \otimes R(t)] = CBF \int_0^t AIF(\tau) R(t-\tau) d\tau, \qquad (5)$$

where "⊗" denotes convolution and k_H=[1- Hct_{large}]/[ρ(1- Hct_{small})]. Hence, the impulse response function $\rho \cdot CBF \cdot R(t)$ can be obtained by deconvolution of measured tissue and arterial concentration curves (*cf.* Fig. 1), and CBF is subsequently determined from the maximal value of this function, since R(0) = 1 by definition. Finally, MTT can be determined by the CBV-to-CBF ratio, according to the central volume theorem (Eq. 1).

DSC-MRI: Measurement and post-processing

After rapid intravenous injection of the CA bolus (at injection rates of the order of 5 ml/s), followed by a saline flush, the first passage of CA through the brain vasculature is monitored by T2*-weighted MRI. By independently acquiring $C_t(t)$ from the tissue of interest and the AIF from a suitable tissue-feeding artery, calculation of CBF, CBV and MTT maps becomes feasible (Fig. 1), as outlined above.

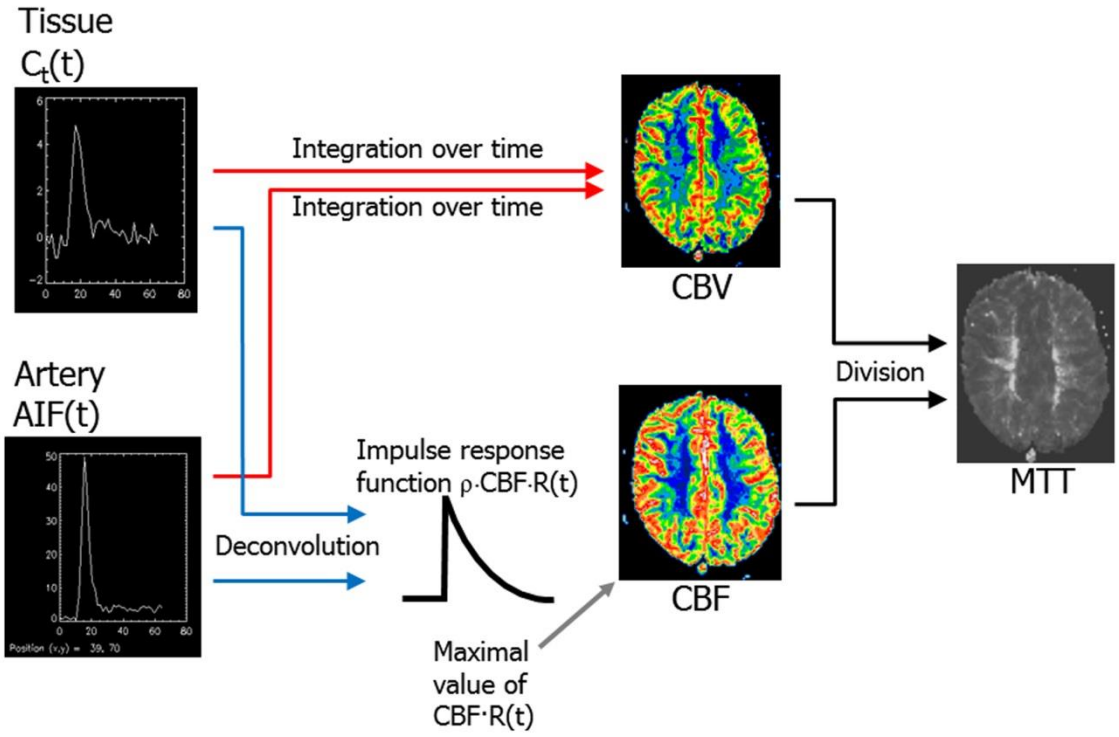

Figure 1. *Procedure for obtaining DSC-MRI maps of perfusion parameters (CBV, CBF and MTT) according to the bolus-tracking concept by use of an intravascular tracer.*

During its passage through the brain, the exogenous paramagnetic CA creates transient local magnetic field gradients which extend from the microvascular compartment into the surrounding tissue (although the CA itself is assumed not to leave the blood pool). These local CA-induced magnetic field inhomogeneities introduce a phase dispersion of the water proton spins, and a corresponding signal drop in T_2*-weighted images during the bolus passage. Gradient-echo (GRE) pulse sequences, not refocusing the spin dephasing caused by magnetic field inhomogeneities, are frequently used for this purpose. Spin-echo (SE) sequences also exhibit substantial signal loss in a DSC-MRI experiment due to spin diffusion in the CA-induced magnetic field gradients, in combination with T_2 shortening within the vascular compartment. For simplicity, all transverse spin dephasings caused by the CA are described in terms of T2* relaxation below, but analogous equations can obviously be formulated for the relationship between SE signal and the change in the transverse relaxation rate ΔR_2.

With regard to the readout technique in DSC-MRI, single-shot EPI (either GRE or SE) has been the dominating method of choice for monitoring of tissue and arterial signal-versus-time curves. The primary reason for its popularity is excellent temporal resolution (1-2 seconds between time points) in combination with whole-brain coverage. One alternative approach is to use 'principles of echo shifting with a train of observations' (PRESTO), which covers large regions with very short TRs.

The change in transverse relaxation rate ΔR_2* is often assumed to be proportional to CA concentration C (with a generally unknown proportionality constant, i.e., the T_2* relaxivity, denoted r_2*):

$$\Delta R_2^* = r_2^* C \qquad (6)$$

In heavily T_2*-weighted imaging, the signal development over time, *S(t)*, during the CA passage is given by:

$$S(t) = S_0 e^{-TE\,\Delta R_2^*(t)}, \qquad (7)$$

where S_0 is the baseline signal and *TE* is echo time. The concentration *C* of the contrast agent can thus be calculated according to Eq. 8:

$$C(t) = -\frac{1}{r_2^* \cdot TE} ln\left(\frac{S(t)}{S_0}\right) \qquad (8)$$

Since r_2* is generally not known in detail, concentration estimates are normally displayed in arbitrary units. Also, note that there is a risk of competing T_1 effects in the signal registration, not accounted for in Eq. 7.

DSC-MRI: Problems and pitfalls

The required deconvolution (*cf.* Eq. 5) is a delicate mathematical procedure, especially in the presence of noise. A number of model-dependent and model-free deconvolution algorithms have been proposed, as well as deconvolution using statistical approaches. Model-free matrix formulation of the convolution integral, solved by means of block-circulant singular value decomposition (SVD), has become a very common approach in DSC-MRI.

If the BBB is damaged, as commonly observed, for example, in tumor environments, the gadolinium chelate will enter the extravascular extracellular space. The assumptions of an intravascular tracer are then violated, and appropriate corrections are likely to be necessary, in particular for CBV assessment.

The conversion from signal to concentration, as described by Eqs 6-8 above, is complicated by the fact that the transverse relaxivity is likely to depend on the vessel size and the vascular topography, with substantially higher r_2* in tissue environments than in the arteries used for AIF registration. The resulting AIF area underestimation hampers accurate perfusion quantification in absolute terms. The T_2* relaxivity issue is further complicated by GRE observations of a quadratic ΔR_2*-versus-C relationship in oxygenated whole blood. This implies that the application of Eq. 8 to AIF data acquired from a whole-blood compartment might lead to incorrect AIF shape. One promising approach to accomplish a more linear CA response is to use phase-based AIFs.

Imperfect AIF registration can be caused by a number of additional methodological issues. Firstly, CA concentrations in large vessels are much higher than in tissue, and a TE that is reasonably well optimized for tissue regions is likely to cause signal saturation or signal clipping of the arterial signal at peak concentrations. Attempts have been made to employ a shorter TE for the slice targeting a brain-feeding artery, while at the same time using a longer TE for brain-tissue slices. Another commonly observed effect is arterial signal displacement during the bolus passage, at peak concentrations, due to the low bandwidth in single-shot EPI, and this can be reduced by employing higher-bandwidth pulse sequences such as segmented EPI. Furthermore, partial volume effects (PVEs) in the AIF registration are very complex in DSC-MRI. AIF rescaling using a venous output function, recently in combination with a prebolus CA injection [4], has been proposed to reduce parts of this problem. Finally, the measured AIF may not accurately represent the artery that actually supplies the tissue of interest. If arterial dispersion (bolus broadening) occurs between the site of registration and the location of the true arterial input, CBF and MTT estimates may be incorrect due to deconvolution with an erroneously shaped AIF. Effects of arterial dispersion can potentially be reduced by employing local AIFs or by accounting for dispersion effects in the deconvolution algorithm.

Although DSC-MRI-based perfusion estimates tend to show reasonable linear correlation with reference methods, as well as convincing relative CBV and CBF distributions, it is clear that DSC-

MRI estimates have generally been overestimated in absolute terms. A viable solution to this is to calibrate the DSC-MRI estimates, for example, by acquiring an additional, subject-specific and independent local or global CBV or CBF estimate, for example, a steady-state T_1-based estimate of the CBV, for rescaling the absolute level of the DSC-MRI estimates.

Applications and future perspectives

Clinical applications of DSC-MRI comprise, for example, ischaemic stroke, dementia, trauma and evaluation of interventional procedures in the brain. Perfusion imaging is also applied to tumour characterization and grading as well as in the assessment of pharmacological efficiency and follow-up and outcome of treatment. DSC-MRI might contribute to identification of the most malignant or aggressive parts of a tumor (potentially associated with neovascularization and leaky vasculature).

There are also a number of recent and ongoing methodological developments. For example, extension of the data analysis to extract additional information from the tissue residue curve or the corresponding transit-time distribution in connection with assessment of cerebral oxygen extraction and metabolism is intriguing [5]. Furthermore, quantitative susceptibility mapping (QSM) has been applied to CA concentration quantification in dynamic contrast-enhanced perfusion imaging [6]. Finally, it should be emphasized that the use of intravascular tracers for perfusion measurement is not limited to cerebral applications by DSC-MRI, provided that another type of CAs is employed; if a so-called blood pool agent is administered, the theoretical framework outlined above can successfully be applied to other organs in the body [e.g., 7].

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