Steady-State And First-Pass Contrast Agent Methods To Evaluate Cerebral Blood Volume (CBV), Vascular Morphology And Permeability.

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A wealth of functional information can be derived from MRI exams when using MR contrast agents. Depending on the choice of contrast agent type, dose, and rate of administration along with the choice of imaging sequence a study can be primarily sensitive to the T1 or T2 effects of a contrast agent, and can provide measures of cerebral blood volume (CBV) and flow (CBF), vascular morphology and permeability under steady state or dynamic conditions.

In this course we will describe relaxivity, or T1-based approaches to 1. measure CBV under steady-state conditions and 2. vascular permeability using dynamic contrast-enhanced (DCE) methods. Next, susceptibility (T2, T2*) methods will be discussed, including 3. measurement of CBV using dynamic susceptibility contrast methods (DSC) and 4. measurement of CBV and vascular morphology under steady-state conditions using long-lived intravascular susceptibility agents.

For each topic issues regarding MRI quantification of physiologic parameters will also be discussed. The issues regarding each of these techniques primarily result from the fact that MRI contrast agents are unique among diagnostic agents in that the MRI signal is rarely a direct measure of contrast agent concentration. Rather it depends on the effect that the contrast agent has on the tissue water magnetization (i.e., T1, T2, T2*). Therefore, to correctly interpret contrast agent studies, an understanding of the effect of water movement on the MR signal is critical.

1. Steady-State T1 (Relaxivity) Studies for the Measurement of CBV

Relaxivity is the term given to describe the constant of proportionality describing the relaxation efficiency of the contrast agent. The most commonly used relaxivity agents are gadolinium (Gd)-chelated contrast agents. Though Gd agents increase the 1/T2 of water protons roughly the same amount that it increases 1/T1, the effect is greater on T1 rates since in tissue 1/T2 >> 1/T1 before contrast. Therefore these agents are often referred to as T1 agents. Typically T1-weighted imaging protocols are used with typical doses (eg 0.1mmole Gd / kg) of Gd agents. For the steady-state studies, described next, Gd is typically bound to a large molecular weight moiety such as albumin [1] or polylysine [2].

There is a long history of using long-lived intravascular T1 agents for measuring tissue blood volume in animals (eg [3-5]). One of the earliest of these studies was performed in normal rat brain where CBV changes reflected changes in brain pCO2 [4]. The studies were performed in animals because long-lived T1 agents did not exist for

human use, until recently [6]. The approach used to measure the tissue blood volume alternated between looking at pre and post-contrast signal differences (ΔS) and pre and post-contrast T1 relaxation rate differences ($\Delta R1$). Implicit in the choice of calculation model is an assumption regarding the rate of water exchange between the intravascular and extravascular tissue compartments. Specifically, the ΔS model is most appropriate if the water exchange rate is slow relative to the difference between the compartmental exchange rates [7]. Alternatively calculation of CBV from $\Delta R1$ is most appropriate if the exchange rate is fast. In brain, with an intact blood brain barrier the vascular-extravascular exchange rate is relatively slow [8]. However, with pathologies, such as brain tumors, where the blood brain barrier is often disrupted, this may not be the case. Studies have demonstrated that the accuracy of the CBV measurement will depend on the choice of measurement and analysis model, as well as the choice of imaging paramaeters [7]. However, the sequence parameters can be chosen to minimize the influence of water exchange (eg short TR sequences) [7, 9].

Overall, steady-state T1 methods, using long-lived intravascular contrast agents have the advantage of high spatial resolution due to the ability to measure over a longer period of time. However, due to lack of FDA-approved long-lived intravascular T1 contrast agents for CBV measurements in patients, these type of studies are presently limited to animals. Finally, the maximum obtainable contrast to noise is limited to the size of the space being measured. For example, in normal brain with a blood volume of approximately 2%, contrast differences, when using an intravascular contrast agent, will not be much greater than 2%.

2. DCE (T1) Studies for the Measurement of Brain Vascular Permeability

There exist two principle approaches to the dynamic imaging of contrast agent through the brain. The first is dynamic contrast enhanced (DCE) approach, which is usually assumed to indicate T1-weighted approaches. The second is dynamic susceptibility approach (DSC) which is typically used to indicate a T2 or T2* weighted approach. Here we describe the basic principles of DCE-MRI as used in the brain.

Dynamic contrast-enhanced MRI (DCE-MRI) is the acquisition of a time-series of MR images before, during and after the administration of a T1 contrast agent. Unlike conventional contrast agent enhanced MRI, which simply provides a snapshot of enhancement at one time point, DCE-MRI provides a fuller description of the wash-in and wash-out contrast kinetics within tissue. Often the analysis of such data has taken the form of simple descriptors such as time to peak (ie enhancement slope) or peak enhancement. In an effort to provide more quantitative data directly related to underlying tissue parameters a variety of pharmacokinetic models have been applied to fit the data. Recently, a consensus was reached regarding a standard DCE pharmacokinetic model, the underlying assumptions, definitions and labeling of the fitted parameters [10]. Though this consensus model makes certain assumptions, such as a negligible vascular space, which does not always apply [11], it serves as a good reference point for all subsequent DCE studies.

The general approach to the collection of DCE data is to use a fast gradient-echo T1 weighted sequence. Typically a three-dimensional spoiled gradient-echo image with short TR (TR < 7msec), minimum TE (TE < 1.5msec) and low flip angle (≈ 30°) is used [12]. The images are acquired every few seconds to minutes. Improved quantitation of estimated gadolinium concentration requires the acquisition of a pre-contrast T1 map. For these pharmacokinetic models, a measure of the arterial input function (AIF) is also required. To obtain the AIF the measurement protocol must have sufficient temporal resolution [13], especially when the contrast agent is administered as a bolus. Often the AIF cannot be measured directly and a common AIF is used. However, determination of individualized AIFs, has been shown to improve study reproducibility [14].

The resulting DCE signal intensity measurements of the tissue reflect a composite of tissue perfusion, vessel permeability, and the volume of the extravascular-extracellular space (EES). While the vast majority of studies using the DCE approach have been outside the CNS (eg [12, 15-17]), a few studies have used DCE-MRI for evaluation of brain tumors [11, 14, 18]. In the brain DCE is only useful in pathologies, such as brain tumors, where the blood brain barrier is disrupted and the Gd contrast agent extravasates. Thus, only under these conditions can the DCE approach provide measures of vascular/BBB permeability.

3. DSC (T2, T2*) Studies for the Measurement of CBV

In 1990, Rosen et al [19] demonstrated that if a bolus of a Gd (gadolinium)-chelated contrast agent was administered, and images acquired during this administration, a transient decrease in signal intensity occurs. This transient signal decrease could be converted into a concentration-time curve, from which cerebral blood volume (CBV) could be computed for each image pixel, thus providing a CBV image map. Since the arterial contrast agent concentration is typically not measured, these maps show relative CBV values and are therefore usually termed rCBV maps.

This approach is based on the principle of susceptibility contrast. Specifically, if a high concentration of a Gd contrast agent is confined to the vasculature, as is the case under bolus conditions and with an intact BBB, a difference in susceptibility or "magnetizability" between the vessel and tissue occurs. The resulting susceptibility gradient induces a transient decrease in the signal intensity, which is proportional to the fraction of blood volume within the image pixel. This susceptibility effect, which results in a signal decrease, is obviously different from the increased brightness observed on standard MRI images where T1 or relaxivity effects dominate. By using this dynamic susceptibility contrast (DSC) MRI method, the differences between gray and white matter can be distinguished since gray matter has about twice the blood volume as white matter. This is the method that was used to create the first MRI image of functional activation in the brain [20]. Several groups are also using this approach to evaluate rCBV in brain tumors [21-32]. Preliminary findings suggest that MRI-derived rCBV may better differentiate histologic tumor types than conventional MRI and provide information to predict glial tumor grade [22, 23, 30, 33-36].

A typical rCBV image protocol lasts only about 1-3 minutes, with images collected approximately every 1 second throughout this time period. For the first 30-60 seconds baseline images are acquired. Next, a bolus of contrast agent is administered while the collection of images continues both during and after contrast-agent administration. To create the rCBV maps the signal versus time data is converted into T2 relaxation rate ($\Delta R2$) versus time data, which is proportional to tissue contrast agent concentration. This data is then integrated (added up over time) to give rCBV for each image pixel. This describes the most basic implementation of a DSC rCBV protocol and the data analysis. Though seemingly simple there are several issues regarding implementation and analysis that must be considered in order to appropriately use these methods. Several of these issues are briefly discussed here.

To acquire DSC image data, fast imaging techniques are required. In most cases, echo planar imaging (EPI) methods are used. Though some have used fast gradient echo methods such as FLASH [25, 26, 28] the time resolution is not as good compared to EPI methods, and therefore the quality of. the FLASH data is less than that of EPI. Most, if not all, newer clinical MRI systems have the high-speed (EPI) capabilities.

There also exists a choice in the type of EPI sequence to use. Investigators use either gradient-echo (GE)-EPI techniques or spin-echo (SE)-EPI techniques, or an image sequence that acquires both GE and SE data [30, 35]. The difference between GE and SE methods is their sensitivity to vessel diameter. While GE techniques are equally sensitive to all vessel diameters, SE methods have a maximal sensitivity to microvessels [27]. Thus, when collecting both GE and SE data, maps of total and microvascular blood volume can be determined.

The image sequences used are T2 or T2* weighted so that they are sensitive to the susceptibility effect described above. To maximize this sensitivity attention must be paid to the choice of imaging parameters. Detailed analyses of the signal to noise ratio of rCBV maps, and its dependence on the choice of experimental parameters and processing strategies, has been undertaken [27, 29]. Briefly, to maximize the signal to noise ratio of the rCBV maps it was recommended that the input bolus duration be as short as possible, that a sufficient number of baseline images are collected, and that the imaging parameters (TE, TR) be optimized for the dose of contrast agent. In addition straightforward integration of the signal time course, rather than a gamma-variate fit of the time course seems most reliable.

Additional issues arise when using DSC methods to determine rCBV in brain tumors. In particular, determination of brain tumor rCBV from the contrast-enhanced MRI signal can be complicated by a leaky blood-brain barrier, as is often the case with tumors. Under these conditions, contrast agent leaks out of the vasculature into the brain or tumor tissue. This leakage effect may lead to an underestimation of rCBV for two reasons. First the gradient of susceptibility may be reduced leading to a reduced T2* effect. Second, a decrease in the tissue T1 will compete with (or diminish) the decrease in signal due to decreased T2. Several strategies have been proposed to

diminish the T1 leakage effect. Some have used T1 insensitive sequences, such as low flip angle or dual echo approaches [22, 37, 38] or presaturation of the EES with the administration of a pre-injection dose of contrast material [30, 35, 39]. Others have also applied post-processing correction algorithms [30, 35, 37, 40]. Though the leakage effect acts to confound the rCBV measurement it can also be used to provide information about the aggressiveness of tumors or the effects of therapy (eg [41]).

4. Steady-State (T2, T2*) Studies for the Meausurement of CBV and Vascular Morphology

Contrast agents that have much larger magnetic moments and magnetic susceptibilities than the tissues in the body are called susceptibility contrast agents. When compartmentalized a susceptibility gradient is set up between the compartment containing the contrast agent and the compartment without the agent. Thus diffusion of water molecules through these gradients alters the phase of the associated proton transverse magnetization thereby promoting dephasing and a decrease in T2 or T2*. Consequently these susceptibility agents are also often referred to as T2, T2* agents. (This describes the same fundamental principle underlying the DSC studies described above.) Either superparamagnetic or highly concentrated paramagnetic contrast agents can be used as susceptibility contrast agents. DSC studies described above are based on using a high (ie bolus) dose of Gd-chelated contrast agent. Here we describe use of the longer-lived superparamagnetic contrast agents such as MION [42] or AMI-227. The plasma half-life of the agents in rats can be several hours.

The iron oxide agents have been used by many groups to image CBV changes in brain with activation (eg [43-45]) and to monitor changes in brain and tumor blood volume [46, 47]. In addition by collecting both T2*-weighted and T2-weighted images, using GE and SE sequences, an index of mean vessel diameter can be measured [48, 49]. These measurements have been shown to be useful in characterizing brain tumor growth and response to therapy [46].

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