Application: Functional ASL, Pharma Perfusion MRI & Reactivity Measurements

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1. Introduction
An important feature of brain perfusion is that it can adjust itself based on tissue demand and others conditions. This property is to some extent more clinically relevant compared to baseline perfusion only, because deficits in many brain disorders are often most pronounced when the brain is asked to perform a demanding task. Therefore, perfusion techniques are sometimes used in a dynamic manner in which brain perfusion is measured under two or more different physiologic conditions, from which the capacity of blood supply regulation is evaluated. In this lecture, applications related to dynamic measurement of perfusion are discussed.

2. Evaluation of neural activity with perfusion measurement
The most widely used fMRI technique is called BOLD fMRI (1-4), which is based changes in oxygenation levels of the venous blood. However, one of the main limitations of this technique is that the signal intensity itself is of arbitrary units and, in particular, the baseline signal does not reflect any physiologic information. The perfusion measure, on the other hand, is directly related to physiologic property in terms of blood supply and thus is much easier to interpret compared to BOLD. Furthermore, perfusion based fMRI can be used to simultaneously evaluate baseline neural activity (by baseline CBF) and evoked neural activity (by CBF during the activated state) (5).

Experimental setup of perfusion based fMRI is similar to a BOLD fMRI, except that the pulse sequence typically used ASL rather than T2*- weighted BOLD sequence. Because ASL often requires the acquisitions of two images (control and label) in order to obtain a CBF image, the temporal capability of the ASL sequence is lower (less than half) compared to that of BOLD. Consequently, it is difficult to perform event-related fMRI with ASL. Instead, ASL is most suited for fMRI paradigm that has a long period (e.g. block design fMRI). As a matter of fact, studies have shown that ASL fMRI provides the most advantages when the two states (used for generating fMRI contrast) are acquired minutes or hours apart from each other (6).

This feature is primarily due to the noise characteristics of the ASL time series. It is well known that the noise in BOLD time series is characterized by a 1/f decay (7). That is, the noise level is high at lower frequency and it decays rapidly at higher frequency. For ASL time series, however, the noise spectrum is relatively flat across all frequency values (7). This is primarily because of the subtraction operation used in ASL. The subtraction between control and labeled images effectively applies a high pass filter on the time course and consequently the lower frequency noise is dramatically reduced. Therefore, the sensitivity in detecting activation in long-period paradigm is enhanced.

3. Perfusion measurement under pharmacological challenge
Given the above mentioned advantages of perfusion measurement compared to BOLD, this technique is uniquely suited to the studies of hemodynamic changes under pharmacological challenge. First, pharmacological challenge is usually associated with a
slow response. It sometimes takes minutes to hours for a drug to take its effect. During this period, slow frequency signal drift in BOLD time course is likely to be very pronounced due to hardware instability, physiologic fluctuation, and other factors. Therefore, it could become very difficult to distinguish a true drug response from a spurious signal fluctuation. ASL signal is less susceptible to fluctuations related to hardware instability. A second reason is that pharmacological challenge often has both a neural effect and a vascular effect. That is, administration of the drug may alter neural activity on the one hand, but may alter vascular tone on the other hand. Under these circumstances, a quantitative measure would be highly desirable which may allow one to disentangle the neural and vascular effects.

It should also be noted that, for pharmacological challenges on animal models, a commonly used method is a CBV-based technique using injection of a R2*-enhancing exogenous contrast agent (8,9). This agent is known to be intravascular, thus its signal enhancing effect is proportional to the amount of blood in the voxel, known as CBV. When CBV changes upon challenge, the MR signal intensity (which is usually T2* or T2 weighted) will show a corresponding change. The main advantage of this method is that it has a higher sensitivity (across all frequency ranges) compared to BOLD. A limitation of this method is that the procedure involves the injection of exogenous agent and the response may be dependent on the dosage of the contrast agent.

4. Perfusion measurement in the assessment of vascular reactivity.

Under many clinical circumstances (e.g. stroke, vascular dementia), one is primarily interested in the vascular health of the brain. The ability of the blood vessels to dilate (or constrict) reflects a critical dynamic property of the vasculature. One can perform perfusion measurements under baseline and vascular challenging conditions to obtain an assessment of this parameter, often terms vascular reactivity. A number of vascular challenges can be applied. One of the most common challenges is the infusion of acetazolamide (sold under the trademark Diamox) (10). Acetazolamide is a carbonic anhydrase inhibitor, which prevents the body from eliminating CO2 generated by tissue metabolism. As a result, the CO2 concentration in the blood becomes higher after the infusion. Since CO2 is a potent vasodilator, in healthy vessels it is expected to increase CBV, CBF and blood oxygenation. Therefore, one can use any of these parameters to evaluate physiologic changes in the blood vessels. Among various techniques, the BOLD is expected to be most sensitive, but CBF and CBV can provide more physiologically relevant metrics.

Another approach to conduct the physiologic challenge is to use inhalation of CO2 gas mixture (11). One can add 3-6% of CO2 to the breathing air and compare the MR signal under this condition to that under regular room-air breathing. Inhalation of 3-6% of CO2 is well tolerated and provides a simply approach to modulate the CO2 level in the blood. An advantage of the CO2 inhalation method is that the input function to the vessel can be quantified, which is the end-tidal CO2 level. Therefore, since one knows both the inputs and outputs of the system, one can better characterize the response function of the system. This is not feasible for acetazolamide infusion. An advantage of the acetazolamide approach is that it requires minimal subject cooperation.

5. Conclusions
Aside from the ability to evaluate baseline perfusion, the perfusion techniques can also be used to assess dynamic changes in vasculature, which includes a large spectrum of application studies in understanding normal physiology and pathophysiology.

6. References


