How to image CBF in the mouse brain

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Introduction: how can we measure CBF in the rodent brain?

Assessment of tissue perfusion in the brain has been the focus of many clinical and research studies, and a variety of MRI techniques for measuring capillary blood flow have been proposed for human and animal studies.

Dynamic susceptibility contrast (DSC) in the rodent brain?

Although DSC is sensitive enough to provide reliable relative measurements of blood flow and blood volume even in low-flow conditions in humans, absolute quantification is still difficult. In small rodents, depending on the anesthetic used and the brain region, capillary blood flow can be 2–10 times higher than in humans. A dynamic first-pass measurement of the contrast agent through the organ therefore would require extremely short bolus injections and imaging times. Also, repetition of a dynamic susceptibility contrast MRI measurement is only possible after complete washout of the contrast agent, precluding serial measurements in most cases.

Arterial Spin Labeling

Arterial spin labeling (ASL) MRI techniques have been widely developed and used in clinical research studies, but were originally developed in animals. In ASL, high capillary blood flow is advantageous because the signal is directly proportional to capillary flow. Owing to the increase in T1 with field strength, the high B0 fields commonly used in small-animal MRI are also beneficial, although T2 effects partly counterbalance this advantage for certain readout techniques. Moreover, ASL permits comparatively easy and reliable quantitative measurements of cerebral blood flow (CBF) which can be repeated during the experiment. Its repeatability along with its ability to provide quantitative measurements also eases follow-up studies and enables functional brain studies. ASL MRI is therefore the method of choice for mapping capillary blood flow in small rodents.

Available ASL Methods

Pseudo-continuous, continuous and dynamic ASL

With these techniques, magnetic labeling is achieved distal from the slice(s) of observation. Continuous techniques require dedicated labeling coils and drivers whereas pseudo-continuous techniques mimic a continuous label with a standard transmit coil and minimize magnetization transfer effects by a special pulse scheme. All of these techniques were shown in theory and experimentally to provide significantly better sensitivity than their pulsed ASL counterparts, however a quantitative assessment of blood flow appears more difficult in absolute terms. Dynamic ASL techniques use a particular time-dependent function for continuous labeling to add important information to the CBF measurement, such as arterial transit times and tissue T1.

Pulsed ASL – FAIR

In animal studies, Flow-sensitive Alternating Inversion Recovery (FAIR) is the most widespread labeling scheme for pulsed ASL. The readout of the magnetization difference produced by inflowing blood into the capillary system is less efficient than in continuous ASL due to long recovery periods, but the labeling zone is placed symmetrically and close to the observation slice leading to better robustness with respect to arterial transit times and to an easier modeling. FAIR, however, has some limitations when multi-slice experiments are to be performed. Look-Locker inversion-recovery techniques were first proposed for rodent cardiac applications, but also had their entry into brain studies. They were shown to provide slightly better sensitivity than classical FAIR techniques and to open new ways to the exploration of the magnetization dynamics after labeling including assessment of the shape of the “magnetic bolus”. Look-Locker techniques also provide an inherent and simultaneous measurement of T1.
Current challenges in mouse brain ASL

Anesthesia and animal position
Anesthetics have a known impact on either cardiac function, brain function or microvascular hemodynamics, and the combination of all these effects will lead to modifications of CBF measured. In particular, isoflurane, the most commonly used anesthetic, has a known vasodilatory effect. Besides interpretation of absolute baseline CBF measurements, this can also impact the results obtained on animal models, since it will also modify the response of the vascular system to challenges as found in pathology. Preconditioning in stroke by isoflurane is an example, in which the anesthetic directly interferes with vascular function in a beneficial way. Gaseous anethetics in general tend to increase CBF, whereas barbiturates or a ketamine/xylazine combination will diminish CBF. Vertical MR systems generally have higher field strenghts and are therefore advantageous for ASL assessment of CBF. The animal position, however, modifies baseline CBF, and horizontal systems should be preferred. In pulsed ASL, due to very rapid circulation of blood in rodents, it is necessary to provide large labeling zones including a significant portion of the body. Larger volume excitation coils in horizontal systems are therefore an advantage.

Transit times, influence of larger vessels and venous outflow
Not only CBF, but also blood flow in larger arteries and veins is high in small rodents. Recent approaches take into account that the exchange time between capillary blood and tissue is not negligibly small, and that a significant portion of labeled blood will not contribute to the ASL signal. Arterial bulk flow can produce overestimation of the measured CBF. Compared with human studies, however, arterial transit times (for blood traveling from the labeling zone to the imaging slice) are very small and can, in general, be neglected.

What can we learn from CBF mapping in mouse brain?
ASL has provided useful, sometimes essential information in mouse model studies of various human pathologies. Findings, limitations and challenges will be discussed on the following models.

- tumors
- stroke (MCAo model)
- infectious disease
- Alzheimer's disease

ASL has also contributed to a better understanding of brain activation fMRI. Especially the combination of BOLD and blood volume information along with CBF measurements permit to obtain valued information on vascular function.

Conclusions
The use of ASL as a quantitative CBF measurement and mapping tool is unique because it permits both longitudinal studies and the assessment of diffuse modifications of absolute CBF, which are not related to a specific region. CBF measurements are generally done along with other MRI modalities and strengthen the observations made.

References
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