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Quantitative Cerebral Blood Flow Measurements Using MRI

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Abstract

Magnetic resonance imaging utilized as a quantitative and noninvasive method to image cerebral blood flow. The two most common techniques used to detect cerebral blood flow are dynamic susceptibility contrast (DSC) perfusion MRI and arterial spin labeling perfusion MRI. Herein we describe the use of these two techniques to measure cerebral blood flow in rodents, including methods, analysis, and important considerations when utilizing these techniques.

Keywords

Cerebral blood flow; Dynamic susceptibility contrast; Arterial spin labeling; Magnetic resonance imaging

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1 Introduction

Magnetic resonance imaging (MRI) can be used to noninvasively image cerebral blood flow (CBF) to study normal physiology and pathophysiology with high temporal and spatial resolution. CBF MRI has been used to investigate vascular remodeling in brain disorders, including stroke and cancer [1].

There are two common techniques to measure CBF based on MRI: (1) dynamic susceptibility contrast (DSC) perfusion MRI [2, 3], which involves administration of an exogenous intravascular contrast agent, or (2) arterial spin-labeling (ASL) perfusion MRI which noninvasively and magnetically labels the endogenous water in blood [4]. DSC works by imaging the dynamic passage of the bolus of contrast agent. The area under the signal ($\Delta R2^*$) versus time curve approximates cerebral blood volume. The mean transit time of the bolus can also be derived from the signal versus time curves and CBF is determined using cerebral blood volume divided by mean transit time. DSC is efficient but some subjects with renal disease develop side effects (such as nephrogenic systemic fibrosis) and DSC is incompatible with dynamic functional MRI due to the long half-life of the contrast agent allowing only one measurement per bolus injection.

Arterial spin labeling (ASL) noninvasively utilizes arterial blood water as an endogenous tracer by magnetically labeling, either by inverting or saturating, the hydrogen spins of the incoming blood (i.e., in the neck area). When the magnetically labeled blood water flows into the region of interest (i.e., the brain), the mixing of blood and brain water changes the water T1 of the brain. By measuring the labeling efficiency (equivalent of an arterial input function), different mathematical models can be used to calculate CBF. ASL is totally noninvasive, and the magnetically labeled water has a short half-life (approximately blood spin-lattice relaxation time constant T_1) making it possible to perform multiple repeated measurements, which can be used to augment spatial resolution and/or signal-to-noise ratio. Both CBF techniques have been used in humans. This chapter describes the MRI procedures to image CBF using the DSC and ASL techniques in rodents.

2 Materials

2.1 Animals and Agents

1. Rats (200–250 g).
2. Anesthetics (isoflurane, urethane, or pentobarbital, etc.; *see* Note 1).
3. Common surgical tools and supplies.
4. Catheters and PE-50 tubing for contrast agent injection outside the scanner.
5. Contrast agent for DSC method (but not ASL): Magnevist (gadolinium diethyltriaminepentaacetic acid Gd-DTPA) or ProHance (gadolinium 10-(2-hydroxy-propyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid).

[1]Different anesthetic agents have different effects on cerebral blood flow values. Comparisons of CBF across different studies need to be made with caution.

2.2 MRI

1. Bruker 7 Tesla scanner (Billerica, MA).
2. 40-G/cm BGA12 gradient insert (ID = 12 cm, 120-μs rise time).
3. Animal holder equipped with ear and tooth bars.
4. Radiofrequency (RF) transmitter/receiver coil for brain imaging.
5. RF transmitter coil for arterial spin labeling at the neck position for ASL (but not DSC option) (*see* Note 2).
6. Switch box to actively detune RF coils for ASL (but not DSC option) (*see* Note 3).

2.3 Peripheral MRI-Compatible Monitoring Equipment and Animal Support

1. Oximetry (heart rate, arterial oxygen saturation)—(MouseOx, Starr Life Sciences).
2. Noninvasive respiration monitoring via force transducer—(MR-compatible small animal monitoring & gating system, SA Instruments).
3. Circulating warm water bath.
4. Temperature feedback regulator (Digisense, Cole Palmer) and temperature sensor.
5. Warm water pad.
6. Anesthetic delivery system, such as vaporizer, if needed.
7. Standard infusion pump for DSC option.

3 Methods

3.1 Animal Preparation

1. Place a rat in an anesthesia box with 4–5 % isoflurane continuously fed to the box until the animal is sufficiently anesthetized. Check the paw reflexes by pinching the paws and looking for reflex withdrawal to ensure adequate anesthesia.
2. Maintain the anesthesia level using 1.5 % isoflurane mixed with house air delivered by nose cone placed over the animal's nose. Different anesthetics can be used if preferred, but be aware that this will affect CBF (*see* Note 1).
3. Place the rat into the head holder with ear bars and tooth bar to immobilize the skull and minimize animal motion throughout the scanning procedures.
4. The rat is then moved to the scanner holder which should have a temperature-controlled water pad to maintain the rat's body temperature at 37 ± 0.5 °C. A rectal temperature probe should be inserted using lubrication to prevent damage to the internal organs (*see* Note 4).

[2]For ASL we described the use of a continuous ASL sequence with separate labeling and imaging coils. Many variations of ASL exist and different scanners may have different sequences available or may have hardware limitations preventing some methods. All methods give reasonably similar results with some advantages and disadvantages. For more information, *see* [17, 18].
[3]For ASL, the imaging coil needs to be detuned while the labeling coil is transmitting to avoid artifacts and inaccurate CBF values.

5. Place the force transducer to monitor respiration underneath the rat. Connect the MouseOx sensor to one of the hind paws and secure with tape. The MouseOx system will enable the user to monitor the rat's physiology throughout the imaging procedures.

3.2 MRI (See Fig. 1)

1. For ASL MRI, the animal should be positioned so that the labeling coil is at the neck, to allow labeling of blood flowing through the carotid arteries (*see* Note 5).
2. Position the RF coil as close to the center of the region of interest as possible. Secure the RF coil with tape (*see* Note 6).
3. Tune and match the RF coil by adjusting the 1H resonance frequency (300 MHz at 7 T) and impedance.
4. Use a position scan to position the area of interest on the *x*, *y*, and *z* directions to ensure the area of interest is centered in the scanner. Increase the field of view (FOV) if needed.
5. Run auto-shim or manual shim as needed to improve the image quality (*see* Note 7).
6. Calibrate the RF pulses for given pulse shapes and durations. This can be set up to occur automatically.
7. Perform a pilot scan using a 2D gradient-echo FLASH or RARE sequence (10–30 s). Based on the pilot scan, plan five to eight 1.5 mm coronal slices to cover the region of interest in the brain.
8. T2-weighted images are acquired using the RARE pulse sequence (echo time per echo = 6.5 ms) with two different effective echo times (52 and 104 ms), echo train length = 16, and 16 signal averages. Typical parameters are data matrix = 64 × 64, FOV = 2.56 cm × 2.56 cm, eight 1.5-mm coronal slices, spectral width = 50 kHz, TR = 2–3 s, 90° flip angle with pulse shape Gaussian or Sinc3, and pulse duration 1–2 ms.
9. For ASL, single-shot, gradient-echo, echo-planar-imaging (EPI) acquisition is used. Paired images are acquired alternately—one with arterial spin labeling (labeled image) and the other without (control). Typical MR parameters are data matrix = 64 × 64, FOV = 2.56 cm × 2.56 cm, eight 1.5-mm coronal slices, TE = 12 ms, and

[4]Stable maintenance of animal physiology under anesthesia is important since CBF is affected by physiological parameters, such as blood gases and temperature. Maintain the animal's body temperature within 37 °C ± 0.5 °C, as body temperature decreases under anesthesia. A circulating temperature-controlled heat pad is ideal for this. Additionally, the rodents physiology should be monitored continuously using a MouseOx system while under anesthesia.

[5]Variability in the common carotid and vertebral arteries across animals can lead to quantification errors with ASL. Proper calibration of RF power and efficient labeling must be ensured to avoid quantification errors. This can be done by acquiring multiple short CBF scans with arrayed RF labeling power to find the optimal power to provide the maximum CBF. However, too high of labeling power can begin to directly saturate the brain and will be seen as very bright areas in the CBF maps in the posterior brain.

[6]For surface coils, avoid pressing the coil too hard on the animal's head as it would increase "loading," which decreases SNR.

[7]High-order localized shimming on the brain can improve image quality and reduce distortion in EPI images. However, for ASL, we have found that this can cause poor shim quality outside of the brain leading to poor labeling efficiency at the neck, so first-order global shimming may be preferable.

TR = 2 s (90° flip angle). Continuous arterial spin labeling (cASL) is employed with separate imaging and labeling coils, using a 1.78-s square radio frequency pulse for the labeling coil in the presence of a 1.0 G/cm gradient along the flow direction such that the condition of adiabatic inversion is satisfied. The sign of the frequency offset of the label pulse is switched for non-labeled images. The number of averages is typically 40 or more, depending on the required SNR (*see* Note 5). Please see the following references for more details [5–11].

10. For DSC, single-shot, gradient-echo, echo-planar-imaging (EPI) acquisition with matrix=64×64, FOV=2.56 cm×2.56 cm, three to five 1.5-mm slices, TE = 20 ms, TR = 0.333 s, and 22° flip angle. Preload the i.v. line with 0.15–0.2 ml of gadolinium contrast agent (typically 3 ft of PE-50 tubing will hold such a volume). Start the DSC acquisition consisting of a scanning period of 1 min. Twenty seconds into the acquisition, deliver the contrast agent in a single bolus flush of saline. Continue the DSC acquisition for another 40 s (*see* Note 8).

3.3 Animal Recovery

1. At the conclusion of imaging, remove the rat from the scanner. Discontinue the anesthesia once you have removed the rat from the holder for the scanner. Place the rat on a heating pad on the low setting until it is fully awake and ambulatory.
2. Once the rat is awake and ambulatory, it can then be returned to its home cage for recovery.
3. The animal should be monitored throughout the day for signs of distress.

3.4 Image Analysis

1. Image analysis can be done using custom written codes or various freely available MRI analysis tools. Image calculation can be done using custom written codes or software available online such as ASLtbx (University of Pennsylvania) or DSCoMAN (Duke) [9, 13]. If needed, image co-registration can be performed using software such as Statistical Parametric Mapping (SPM, University College London). Image display can be done with software such as SPM or STIMULATE (University of Minnesota). Several other free software programs are also available to process and display MRI images (*see* Note 9).
2. For ASL acquisitions, CBF images (S_{CBF}) with intensity in units of ml/g/min are calculated [10, 11, 14] pixel by pixel using

$$S_{CBF} = \frac{\lambda / T_1 \cdot (S_c - S_L)}{(S_L + (2\alpha - 1)\, S_c)},$$

T1 dépend du champs magnétique

Trouver la valeur du T1 du cervau normal à 3T ou 1,5T

[8] Injection of the contrast agent must be done as a bolus (as fast as possible but without damaging the vessels) through the tail vein or femoral vein.

[9] Note that there are multiple equation models to calculate CBF via ASL and DSC approaches. We presented here common models for CBF calculation. The accuracy of CBF measurements by MRI is still an active area of research.

where S_C and S_L are signal intensities of the control and labeled images, respectively. λ, the brain-blood partition coefficient of water, is ~0.9 ml/g for averaged gray and white matter [15]. T_1 is the longitudinal relaxation time of the brain, which is about 1.6–1.8 s at 7 T [16]. α is the labeling efficiency which has been measured to be 0.75–0.9 in animal models [5, 7] (*see* Notes 2 and [9]).

3. For DSC-CBF calculation, the change in the transverse relaxation rate ($\Delta R2^*$) is calculated using

$$\Delta R2*(t)=\frac{-\ln\ (S(t)/S_0)}{TE},$$

Requete sur les champs DICOM Dpd machine++

where $S(t)$ is the signal intensity at time t, S_0 is the pre-contrast baseline signal intensity, and TE is the pulse sequence echo time. Hemodynamic parameters can be generated by deconvolving the change in tissue concentration over the first pass of contrast agent with an arterial input function using singular value decomposition [2, 3]. The area under the curve of $\Delta R2^*$ versus time gives the cerebral blood volume (CBV). The mean transit time (MTT) can be determined from the shape of the curve, and CBF is calculated as CBV/MTT (*see* Note 10).

S0 avant arrivée du Gado

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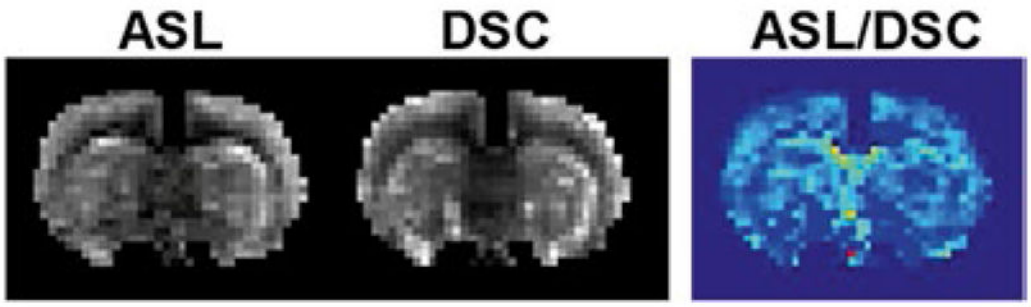

Fig 1.

Examples of CBF maps (in ml/g/min) from both ASL and DSC methods in the same rat. The ratio of CBF from ASL/DSC is also shown. Some brain structures should be able to be distinguished in the CBF maps, such as the corpus callosum with low blood flow. Figure adapted from Tanaka et al. [12]