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Perfusion magnetic resonance neuroimaging

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ABSTRACT

The clinical appliance of perfusion is being continuously developed, and it is closely related to technology development. The role of perfusion neuroimaging in the management of acute stroke has been to prove reduced regional blood flow and to give the contribution in the identification of ischemic areas, respectively, the regions of hypoperfusion that can be treated by thrombolytic and/or endovascular recanalization therapy. There are two main approaches to the measurement of cerebral perfusion by magnetic resonance (MR). The aim of this article is to compare different measuring approaches of MR perfusion neuroimaging.

Key words: Magnetic resonance imaging; perfusion-weighted imaging; dynamic sensitive contrast enhanced; arterial spin labeling; perfusion

INTRODUCTION

Perfusion of the tissue is the basic physiological parameter that is closely related to the function of the tissue. Perfusion is closely related to the delivery of oxygen and other nutrients to the tissue. Term "perfusion" is also used for accentuating the contact with the tissue, or in other words, with the capillary blood flow.Perfusion disorders are the leading causes of medical morbidity and mortality. For these reasons much effort has been invested into its measuring, it is important to make a difference between the perfusion and blood flow that is conducted along the main arteries and veins (1).

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The role of perfusion neuroimaging in the management of acute stroke has been to prove reduced regional blood flow and to give the contribution in the identification of ischemic areas, respectively, the regions of hypoperfusion that can be treated by thrombolytic and/or endovascular recanalization therapy (2). During last years, there was a description of a few non-invasive methods of measuring perfusion by magnetic resonance imaging (MRI). The biggest effort was invested in MR perfusion imaging of brain (3).

There are two main approaches to the measurement of cerebral perfusion by MR. The first approach is the application of egsogene, intravascular, and non-diffusible contrast agents. Usually contrast agents being used are on the basis of gadolinium that highlights either effects of sensibility of signal echo to gadolinium-based contrast agents, as first-pass dynamic susceptibility contrast enhanced (DSC) perfusion or effects of relaxation of signal echo in

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application of gadolinium-based contrast agents, as dynamic contrast-enhanced (DCE) MR perfusion. Other approach is the application of endogenous contrast agent using magnetic water spins of arterial blood, as diffusion tracer of flow in arterial spin labeling (ASL)

Dynamic susceptibility contrast enhanced (DSC) MR perfusion, also known as bolus tracking or perfusion-weighted imaging so far, has been the main MR perfusion imaging method used in diagnostics of acute stroke (4). It is based on induced loss of signal sensitivity to T2* weighted sequences, which is the result of gadolinium-based contrast agent passing through capillary circulation.

DCE MR perfusion, also known as permeable MRI, is based on the acquisition of a series of T1 weighted images before, during and after the administration of extracellular low-molecular contrast medium (5).

However, the application of gadolinium contrast agent is dose limited because it was proven that it causes nephrogenic systemic fibrosis and it creates deposits in neural tissue, even in patients with regular kidney function (6,7).

ASL is the perfusion method for quantitative measuring of cerebral blood flow (CBF) that uses arterial fluid as endogenous tracer, and thus it does not require the application of gadolinium contrast agents. Because of it being non-invasive, it is safe to repeat measuring, and it can be used for following the course of the disease or the effects of therapy (8). The main idea in ASL is to obtain a labeled and control images, where static tissue signals are identical, but magnetization of inflowing blood is different. Water molecules in arterial blood are labeled by RF impulse that saturates water protons. Subtraction between labeled and control images eliminates the static signals and the remaining signals are linear measures to the perfusion, which is corresponding to the CBF (9).

In clinical application, two basic types of ASL techniques are used: Continuous ASL (CASL) and pulse ASL (PASL) (10,11). CASL uses long and RF pulses (1–2 s) together with a constant gradient field that induces free-flowing led adiabatic inversion on the shorter spin plane, usually under imaging field (12). Because of certain limitations pseudo CASL has been introduced as an alternative method and it represents a derivative of PASL and CASL.

PASL uses short (5–20 ms) radio-frequency pulses to convert thick spin slices into labeled slices close to the region of imaging (13). Perfusion imaging is a quantization method that is quantified as flow (mL/min) compared to tissue mass (usually on 100 g of brain tissue). Perfusion balanced imaging is mostly used in strokes to differentiate the normal perfusion tissue from benign oligemia and infarct nucleus. Likewise, it can be used for determining the reserve of blood flow in the patients with chronic cerebrovascular abnormalities. Perfusion imaging can be easily combined with other MR techniques as MR angiography for the assessment of blood vessel passability and diffusion-weighted imaging and for the assessment of ischemic damage of brain parenchyma (14).

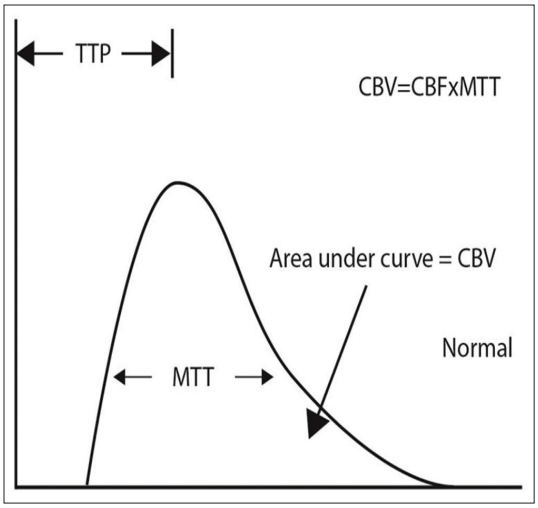
Perfusion measuring is based on the analysis of hemodynamic curve time-to-signal generated when tracer passes through brain circulation. This curve can be processed by various softwares for extracting parameters that reflect either CBF and cerebral blood volume (CBV) or mean transit time (MTT) that is related to the formula CBV=CBF X MTT, known by the name central volume principle (Graph 1). In the normal brain, the autoregulation maintains CBF on 50–60 mL/100 g/min (15).

MRI PERFUSION METHODS

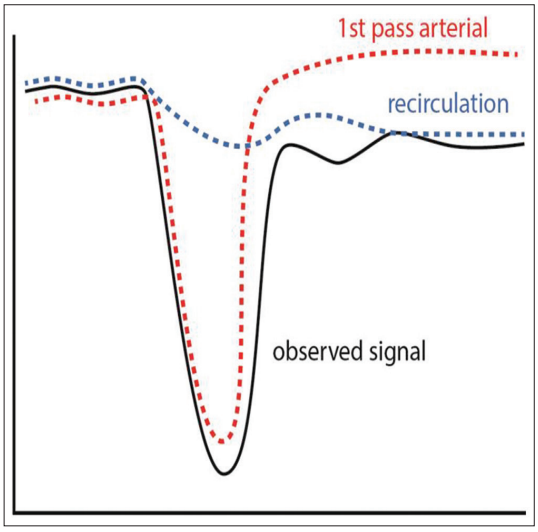
As it was said earlier there are basic approaches to MR perfusion: Perfusion with the application of egsogene contrast medium as perfusion tracer and perfusion that uses water that enters the blood composition as endogene tracer.

Dynamic susceptibility contrast (DSC)-MRI

This technique is based on T2 or T2* weighted imaging sequences, in two-dimensional (2D) or three-dimensional (3D) dynamic acquisition. Mostly the gradient echo (GE), technique has been used (GE) due to its better contrast-noise ratio (CNR) (16). Standard dose of gadolinium chelate (0.1 mmol/kg) is being applied intravenously. Microscopic gradients cause spin dephasing and they spread along these gradients, which is the result of signal loss in T2 and T2* weighted images (17). When GE acquisition is used the static field inhomogeneity appears in great blood vessels, which



GRAPH 1. Tracer concentration curve.



GRAPH 2. Hemodynamics of contrast means in dynamic susceptibility contrast-enhanced.

is the result of signal loss due to the presence of microscopic disorder of magnetic field in blood vessels. Besides, dephasing in small blood vessels causes signal loss due to diffusion (18). The advantage of GE acquisition is the increase of CNR. However, great disadvantage is the contamination of great blood vessels (19). Absolute quantification of DSC perfusion data requires the knowledge on contrast material concentration in blood vessels. This value, called arterial input function (AIF), is acquired by measuring the concentration curve on artery that supplies the region of interest. Unlike relative data on perfusion, the quantification curve of tissue concentration is technically performed by AIF, CBF and functional tissue remain that represents contrast quantity that remains in tissues in the unit of time (20). Final acquired values are greatly dependent on AIF measuring, namely, there are certain difficulties with this measuring. AIF is related to heart function, vascular tone, selection of artery, and selection of arm into which contrast agent is applied and most importantly to partial volume effect that is related to small diameter and volume measuring of intracranial blood vessels (21,22). Model used for perfusion quantification is based on physical principles of tracer kinetics for non-diffusional tracers and it relies on assumption that contrast material is deterred intravascular at untouched blood-brain barrier (23). Considering the fact that imaging is based on T2/T2* sequences, contrast agent bolus causes the reducing of MR signal intensity while passing through microvascular structures. Time curve acquired by measuring can be divided into three phases: Base line, first bolus passage, and recirculation period (Graph 2).

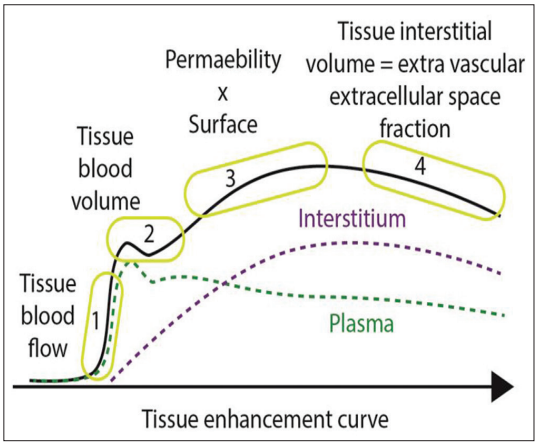
If blood-brain barrier is dysfunctional or it "leeks," DSC data can be compromised. This relates to the relative shortening of T1 water in the presence of parenchyma contrast extravasation that reduces or excludes reducing of T2* effect of signal intensity (25-26). DSC MRI remains clinic standard among the perfusion techniques, but because of the mistakes that appear and that are related to data processing due to various reasons, including the difference in relaxivity between tissue and blood basin (27) and problems related to the disintegration of blood-brain barrier, as mentioned above, other kinds of perfusion techniques have been developed, first of all, DCE MRI.

DCE MRI

DCE MRI is other egsogene contrast based method. After the application of paramagnetic contrast agent, hemodynamic signal dependent on T1 relaxation time is increased due to the T1 reducing time effect (28). DCE MRI uses fast and repeated T1-weighted images to measure changes of signal induced by paramagnetic tracer in tissues to

display time function. T1 time is not dependent on extravasation. Extracellular contrast diffuses from the blood, the speed of its diffusion is determined by the blood perfusion and permeability of capillaries and their surface. Reducing the T1 relaxation rate caused by the contrast agents is the mechanism of tissue strengthening. DCE MRI perfusion uses measurement data to display the permeability of blood-brain barrier and its relationship toward extracellular extravascular space. The same transmission that "confuses" DSC perfusion, is measured by DCE using a dynamic T1-weighted sequence. Duration of acquisition is often over few minutes for DCE (unlike DSC, where it is about 60 s). This time enables measuring the passing of contrast agent through extracellular extravascular space. There are few methods for the data interpretation. The simplest method is the examining the curves of signal intensity through the time period of imaging in the region of interest. Rate or incline of wash-in and wash-out curves for more regions of interest can be visually estimated (Graph 3). Semiquantitative methods can be also used, where measurement maps can be created to show the incline of wash-in and wash-out curves, time of the maximal connection, as well as the time of coming. This measuring is similar for more advanced DCE parameters; however, they also reflect multiple physiological processes, including permeability, volume of extracellular extravascular space, and blood flow (29-31). The difficulty in this measurement technique is the fact that the effects of T1 dependent changes are less than T2* effects measured by the DSC technique (32).

One of the main limitations in this technique, at the same time, the reason why it has not got wider use in clinical practice, is the difficulty of kinetic molding of DCE tracer. Earlier researches with DCE-MRI have used one-part model that did not allow CBV quantification (33,34). Further on, this model loses the validity in the passing through blood-brain barrier. Later studies have evaluated CBV and CBF quantification of DCE MRI using two-part model (35,36), which has not given good results, and it has classified DCE MRI on the secondary position compared to DSC.



GRAPH 3. Hemodynamic curve in dynamic contrast-enhanced.

ASL

Brain perfusion can also be measured using the technique of ASL that uses magnetically labeled water of arterial blood using radiofrequency pulses, as endogene diffusion tracer for CBF measurements (37). It provides the curve of absolute perfusion tissue value. ASL is completely non-invasive technique, without using contrast agents or ionizing radiation and it is possible to repeat it unlimited number of times in all pathological conditions. ASL is based on the technique of ASL where after the delay time that serves for labeled blood spins to get to the brain tissue, the labeled images scanning is performed. These labeled images contain signals both from the labeled water protons and static tissue water (38). Depending on the spin labeling technique, control images are also collected, where the labeling of arterial spins was not conducted, and the difference between the control and labeled images provides us with the perfusion measurement data of labeled blood from the arteries that have come to the tissue. The time during which the tracer can be used is regulated by the longitudinal time of blood relaxation, that is, in the interval from 1300 to 1750 ms, depending on the strength of magnetic field (39) (Figures 1 and 2).

There are three main approaches to spin labeling: PASL, CASL, and pseudo CASL (PCASL). In the literature, fourth approach is also mentioned – velocity selective ASL; however, this method is considered to be still developing and it requires additional validation for routine clinical usage.

PASL uses short RF pulses to rotate thick spin slice proximally from the region of planning.

CASL uses long and continuous RF pulses to perform inversion of the slim slice of spins immediately before

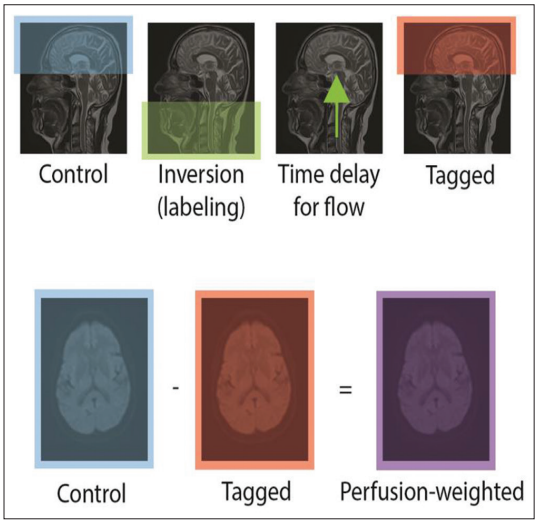


FIGURE 1. The manner of collecting data in the arterial spin labeling technique.

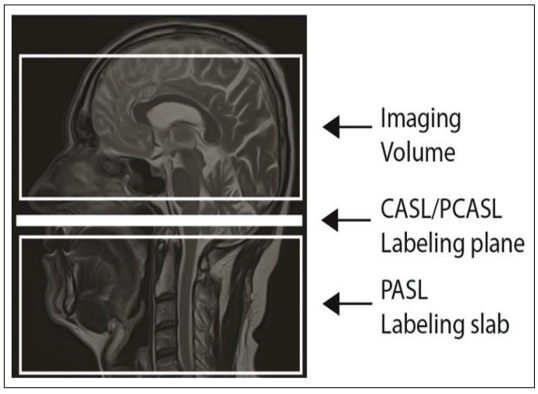


FIGURE 2. The place of spin labeling depending on the arterial spin labeling technique.

the region of planning. As the name itself indicates in CASL, it happens continuously while the spins pass through the region of labeling. Although this technique leads to higher perfusion sensitivity than PASL, continuous RF pulse stores a great quantity of energy into the patient that potentially can surpass Specific Absorption Rate (SAR). Further on, hardware that generates continuous pulse is not always available on many commercial scanners, and CASL mainly requires specific coils, that would span certain SAR and magnetization transfer (MT) limits (40).

As an answer to limitations PCASL has been developed, it has imitated labeling mechanisms of CASL, without inherent deficiencies. This is achieved by fast repeating of gradients and RF impulses to achieve almost continuous labeling with high efficiency but without hardware requirements and MT effects that appear in CASL (41).

Considering that the contrast for the ASL technique is related to blood labeling, ASL is not based on T2/T2*/T1 based sequences. Sequences with short time to echo (TE) are mostly used to strengthen signal-noise ratio (SNR), and with a long time to repetition to allow the labeled blood to come to the imaging field. For the scanning dynamic acquisition is used, based on Look-Locker method, with 2D or 3D excitation (42). Usually, single-shot GE-echo-planar imaging sequences are used. Two factors usually contribute to macrovascular signal: Vascular crushing gradient and later delay time. Under the term, "crushing gradient" gradient insertion after excitation pulse is implied, or sensitized T2 motion module, that can reduce vascular artifacts. The elimination of these signals is based on the spin speed in the direction of gradient (most often in the direction legs-head). When the vascular crushing gradient is used due to additional gradients, or T2 preparatory module usage effective TE will be prolonged thus installing T2 (or T2*) contrast into ASL image and reducing SNR. This should be considered during the calculating of CBF (43). With short delay time the labeled blood remains in the great blood vessels during the imaging time. Bipolar gradients with really low b value are used for signal crushing from the great blood vessels. Due to this if crushing gradient is not used, or if short delay time is used after the labeling, ASL signal is contributed by great blood vessels. This is applied to both GE and spin echo sequences. For the contrast this contribution can be reduced using crushing gradient and long delay time. In this case, small blood vessels mostly contribute to ASL signal.

CLINICAL APPLIANCE OF PERFUSION METHODS

Clinical appliance of perfusion is being continuously developed and it is closely related to the technology development. In general, perfusion methods are used for the diagnostics of cerebrovascular disorders, as well as brain tumors (44). It is also introduced into the management of dementia

diagnostics and into the diagnostics of acute stroke. DSC MRI remains standard for all the pathology that requires brain perfusion (45). DSC can be used not only for the estimation of microvascular disorders but also for the estimation of four basic lesion parameters including CBV, CBF, MTT, and TTP, which derivate from multidynamic T2* weighted sequences (46).

DCE MRI is also used in brain pathology, especially in tumors. However, due to the inability of CBF estimation, this method is more often used in the estimation of diseases of breast, prostate, and pelvis. It is popular for the estimation of the activity of medicamentous therapy in the brain. It is the standard perfusion method for perfusion imaging of non-brain pathology (47,48). DCE MRI is useful for the accurate mapping of blood volume in tumor lesions. It can be used for the determination of tumor gradus, determining the effect of radiotherapy effects, monitoring the therapy response in chemotherapy.DCE MRI has got the potential to provide biological information in the angiogenesis of tumor and vascular function of tumor of the head and neck (49). A combination of DCS and DCE MRI imaging can help in understanding and management of complex and different pathology of brain tumors (50).

ASL, as non-invasive perfusion technique, is especially interesting. It is commercially available in MRI systems of all the major manufacturers and it more and more enters into the clinical practice. Its non-invasive and quantitative nature makes the technique especially attractive for the vulnerable populations of patients, such as older people, children, oncological patients with a difficult vein approach and patients with renal insufficiency. Currently, there are enough proofs that support its clinical appliance in dementia, neuro-oncology, and cerebrovascular disease, with clear advantages in the sense of improvement and earlier diagnosis (51-53).

CONCLUSION

DSC MRI is used for the measurement of transit flow, covering whole brain and quick scanning time. DCE MRI is used for measuring blood volume, measuring the permeability of blood-brain membrane and for the reducing the artifacts. ASL is good for measuring the blood flow, and due to the technique that does not use the application of contrast means can be used in children and pregnant women. Bolus methods with the application of contrast means provide better sensitivity with better space resolution, and ASL method provides the possibility of measuring the CBF signal without the application of contrast means.

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