Quantitative Assessment of Perfusion by Magnetic Resonance

Quantitative Magnetic Resonance Imaging of Human Brain Perfusion at 1.5 T Using Steady-state Inversion of Arterial Water

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Perfusion Imaging

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MR Perfusion Studies with T_1-Weighted Echo Planar Imaging

Article by Kenneth K. Kwong,‡ David A. Chesler, Robert M. Weiskoff, Kathleen M. Donahue, Timothy L. Davis, Leif Ostergaard, Terrence A. Campbell, and Bruce R. Rosen; Magn Reson Med 1995;34:878–887

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Editor's Note

In these three articles, a group of closely related methods is used to produce quantitative resting-state maps (images) of cerebral perfusion by using magnetic resonance imaging (MRI) without exogenous tracers or any other invasive means. Each of the methods relies on the ability of MRI to magnetically label tissue that flows into an imaging slice and to compare the signals in that slice with and without the label applied. Although the techniques are still technically challenging in their present form, rapid advances in the field are likely to result in practical measures of brain perfusion in the clinic.

Introduction

Magnetic resonance imaging has for years been regarded as the pinnacle of *in vivo* structural brain imaging, boasting both high intrinsic contrast and superb spatial resolution, combined with essentially complete noninvasiveness. Yet, for all of its virtues, it has offered little help in such common diseases as Alzheimer's, other dementing disorders, or neuropsychiatric abnormalities. In fact, with all of its power, structural MRI cannot distinguish the brain of a comatose subject from that of one who is awake. Traditionally, these types of functional imaging questions have been the domain of the radionuclide technologies, such as positron emission tomography (PET) and single photon emission computed tomography, in which many subtle abnormalities of function can be seen, albeit at lower spatial resolution and with the use of small amounts of radiation.

Magnetic resonance imaging, however, is a modality with considerable unused potential. Only a few years ago, Rosen et al. developed a method, based on tracer kinetic

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principles, for the assessment of relative cerebral blood volume (rCBV), and this method is now widely adapted by clinics [1]. Using ultra rapid echo-planar imaging (EPI) [2], they observed the signal change that occurs as a bolus of injected contrast agent passes through the cerebrovasculature. The signal change itself may be converted to contrast agent concentration by straightforward models. Based on the central volume principle, integrating the contrast agent concentration over time can produce maps of CBV for each pixel in the image. Such pictures have demonstrated dramatic power is the assessment of a wide variety of circulatory abnormalities, such as stroke and functional breakdown of the blood-brain barrier.

Summary: Quantitative Magnetic Resonance Imaging of Human Brain Perfusion at 1.5 T Using Steady-state Inversion of Arterial Water

Objective

To determine whether the use of a noninvasive magnetic resonance (MR) technique for quantitative imaging of brain perfusion at 1.5 T may be successfully used for quantitative measurement of perfusion in human brain as opposed to the risks and expense of methods that use exogenous tracers

Materials and Methods

All experiments were conducted on a 1.5 T imaging system. Human studies were performed with a protocol approved by the Institutional Review Board of the University of Pennsylvania, including informed consent from all volunteers.

Volunteers were asked to lie still with eyes closed, foam padding was used to limit head motion, and ear plugs were used to reduce the noise of the gradient coils. Lights in the magnet room were turned off, the static magnetic-field shim was manually optimized, and the proton water signal was centered on resonance. A two-dimensional, refocussed, gradient-echo pulse sequence was used to acquire inversion and control images. An off-resonance radio-frequency pulse was inserted in the interpulse interval, and an axial 5-nm-thick slice was imaged. Methods to minimize the sensitivity of the image to susceptibility effects as well as to attenuate residual transverse magnetization created by the inversion pulse were undertaken.

The effect of respiratory status was studied in a set of three normal volunteers as well.

Data analysis was performed with appropriate statistical approaches resulting in values used to estimate the effective degree of inversion. Region-of-interest analyses of perfusion maps were performed as well. All analysis was based on the theory that continuous inversion of the arterial water supplying the brain results in a small decrease in the steady-state image intensity.

Results

- The T1 of uncoagulated whole blood was determined to be 1.4 s based on a multiple-point, inversion-recovery measurement.
- Computed spin simulations and measurements in experimental flow phantoms were performed to determine the dependence of the inversion efficiency on the adiabaticity factor, the result of which corresponds to 98% efficient inversion.
- The 98% efficient inversion, combined with the duty cycle and the estimated transit time yields an effective degree of inversion.
- To visualize the effect of the irradiation on blood flow in the internal carotid artery, cardiac-gated images were acquired with the same parameters as in the above calculations, but with the inversion gradient in the frequency-encoding direction.
- Inversion was observed during every phase of the cardiac cycle.
- Images were acquired to determine the degree of saturation caused by the inversion pulse as a function of the frequency offset for the choice of pulse parameters used in the perfusion experiments, such that the labeling pulse results in significant saturation of spins in the image plane. An adequate control image must balance this effect, which may be accomplished by changing the sign of the offset frequency of the labeling pulse. There is also relatively little variation of the off-resonance effects across the slice thickness.
- Inversion of arterial water was observed to result in a decrease in signal intensity in all parts of the brain.
- Perfusion differed significantly in each of the three respiratory states studied (hyperventilation, rest, and breath holding) such that cerebral perfusion increased during hypoventilation and decreased during hyperventilation.

Conclusions

These results demonstrate that quantitative images of brain perfusion can be obtained from human brain at 1.5 T with a commercial imaging system. The advantages of this technique are that it is noninvasive, it does not require exogenous tracers, arterial blood sampling, or ionizing radiation, and it allows for measurement of absolute values for cerebral perfusion. Because the effects on image intensity obtained by arterial inversion are extremely small at 1.5 T, however, potential sources of error must be carefully minimized.

In addition, because this is a steady-state technique, acquisition of inversion and control images cannot be interleaved. This necessitates very good temporal stability in the imaging equipment as well as careful restriction of patient motion. There are additional steps which may be

taken to obtain a higher effective degree of inversion and increase the perfusion effect, as well as eliminate the signal loss caused by cross relaxation.

The authors feel that successful measurement of brain perfusion using this approach will enhance the diagnostic capabilities of MRI for neurologic disease. Because the risks of this technique are essentially those of routine MRI, one may perform repeated studies of the same individual and more easily perform perfusion studies in children. Finally, the increased spatial resolution of MRI, the automatic registration of perfusion images with highly detailed anatomical images, and the ability to conduct an integrated multinuclear examination represent important advantages of MR perfusion imaging over existing methods for studies in human brain.

Summary: Perfusion Imaging

Objective

To determine whether the noninvasive use of H nuclear magnetic resonance imaging to generate perfusion maps in the rat brain is effective, thus being readily applicable to human studies

Materials and Methods

Male Sprague-Dawley rats were anesthetized, orally intubated, and maintained. A femoral arterial line was used to monitor blood pressure and sample blood gases. Temperature was monitored with a rectal probe and maintained with a circulating water pad. Brain blood flow was altered either by sacrificing the animal by halothane overdose or by altering plasma pCO_2 levels by adjusting the respiratory volume or by adding 2.5% CO_2 to the ventilated gas mixture.

H images were obtained with a Bruker 4.7-T, 40-cm-bore Biospec II imaging spectrometer operating at a proton frequency of 200 MHz. The rats were isolated from physical vibrations caused by the imaging gradients, with heads placed in an 8-cm-diameter H imaging coil. A 64- x 64-matrix spin-echo imaging sequence was used with the following settings: echo (TE) time, 34 ms; repetition (TR) time, 2 s; slice thickness, 2 mm; and field of view, 50 mm, resulting in a pixel size of $0.8 \times 0.8 \times 2$ mm. TR time was varied; saturation was performed by using a series of slice-selective pulses and applied proximally either to the brain in the neck region or to a control region outside the brain. Control or proximal saturation images were alternated, the saturation pulse and gradient were applied every 30 ms, and spoiler gradients were applied as well to eliminate signal from moving spins. These gradient pulses were adjusted to minimally attenuate diffusing spins while eliminating more rapid spins.

Images were processed with a two-point smoothing function and interpolated to a matrix. Two sets of control and proximal images were summed for calculation of perfusion maps, using the Bloch equation describing the Z magnetization in brain, but modified to include the flow effects.

The theory by which perfusion images were obtained was tested through a number of different methods to prove that possible effects besides perfusion were not present in the study.

Results

- The determination of flow used is independent of imaging parameters. Thus, a quantitative perfusion map can be generated from images obtained with proximal and distal saturation and with a T map.
- A difference image between control and proximal saturation shows the amount of saturated spins accumulated owing to blood flow. The intensity in the region of the brain is clearly seen and is significantly greater than the intensity in the surrounding muscle.
- Only 0.6% of total brain water is arterial, suggesting that even if the spoiler gradients had no effect, the contribution of labeled arterial spins is small.
- At most, spins relax 25% before exchanging with tissue water. Most of the saturated water in the blood will exchange in a significantly shorter time, indicating that neglecting relaxation before exchange probably results in only a small underestimation of flow.
- Perfusion measurements obtained from images resulting from the study were compared with values from previously reported research; results indicate that the assumptions of complete saturation of blood water and negligible relaxation of the spine until after exchange with tissue water, which are used to quantitate perfusion, are valid.
- Individual pixel flow values are increased in the periphery of the brain, consistent with increased cortical flow. Some regions of very high flow seen bilaterally at the base of the brain may relate to the arterial supply. Some intensity is also seen outside the brain and is likely to be an artifact arising from the chemically shifted lipid signal.
- The size of the perturbation of the tissue water caused by proximal saturation of blood is small. It would be even smaller at the field strengths currently in use for human imaging because T1 is shorter at lower fields. One way to increase the effect would be to selectively invert the incoming spins rather than to saturate them.

Conclusions

The authors have shown that proximal saturation of blood flowing into the brain leads to a detectable effect on brain H image intensity. This intensity can be used to determine intravoxel values of blood flow. Perfusion images can thus be made totally noninvasively, without

exogenous tracers. Determination of brain perfusion by this technique gives results which are in agreement with accepted techniques. The authors feel that this technique should be useful for studying the physiology of rat brain and should be readily applicable to human studies, allowing flow maps to be obtained with H imaging resolution.

Summary: MR Perfusion Studies with T_1-Weighted Echo Planar Imaging

Objective

To develop a new technique for measuring steady-state perfusion by using selective and nonselective inversion pulses

Materials and Methods

Researchers used selective and nonselective echo planar inversion recovery spin echo sequences for all studies. The selective inversion pulse was an adiabatic inversion pulse. The nonselective inversion pulse was the same diabatic pulse with the slice-selective gradient moved 10 ms after the inversion pulse such that there is no slice-selective gradient under the 180° inversion pulse. All studies were performed on a GE 1.5-T Signa imager, retrofitted for echo planar inversion.

Researchers performed *in vivo* single-slice studies in either the axial plane or the coronal plane on eight healthy human volunteers, and eight tumor patients. Images were collected in one of two ways: in four healthy subjects and all eight patients, researchers collected image pairs of a single slice at a fixed inversion time (TI), interleaving selective inversion and nonselective inversion, undertaking simple image subtraction. In the other four healthy subjects, researchers acquired images at several TI values to enable T_1 measurements.

Researchers obtained flow-weighted images by subtracting a flow-insensitive image from a flow-sensitive image. They used the resulting images as an index of steady-state flow values.

Results

- In four normal subjects, perfusion-weighted, subtracted images showed good gray-white contrast. High signal differences at deep gray matter—caudate, putamen, and thalamus—were observed.
- In three tumor patients with high tumor cerebral blood volume, perfusion-weighted subtracted images showed large tumor signal differences compared with surrounding tissue.
- In five tumor patients, the perfusion-weighted, subtracted images consistently showed regions of low signal difference at tumor sites with low cerebral blood volume.
- A typical ΔR_1 map showed much less gray-white flow contrast than a typical ΔT_1 map.

Conclusions

By subtracting T_1-weighted images, the authors obtained good flow contrast images for cortical gray matter, deep gray matter, and tumors having high and low flow. Although the authors acknowledge a slight signal difference caused by using two different inversion sequences, they conclude that experimental gray matter flow values were larger than—and could be separated from—such systematic errors.

The authors improved their understanding of gray-white flow contrast by paying attention to two problems: the partial volume of cerebrospinal fluid with tissues and different T_1 values of blood from tissue. They demonstrated that ΔT_1 maps could be used qualitatively to counteract the effect of the partial volume of cerebrospinal fluid. They also demonstrated that taking the longer blood T_1 into account improves the gray-white flow contrast.

Commentary

Based partly on these results, Belliveau and his co-workers showed that maps of cerebral blood volume changed reliably in the presence of sensory stimulation [3]; only 1 year later, members of the same group [4] and others [5] produced the first reports of what is now known widely as functional MRI (fMRI) or blood oxygenation level-dependent (BOLD) MRI. In this method, changes in blood oxygen content are examined by using rapid MRI during conditions of various brain activity levels (e.g., contrasting the signal during periods of sensory stimulation and rest). The growth in this field has been explosive, based partly on its sensitivity and very heavily on its relative ease.

Exciting as both of these MRI-based functional assays are, however, the results in a few disease entities have been disappointing. Neither, for example, is able to distinguish a comatose from an awake brain. The rCBV method fails because it produces only *relative* regional maps of blood volume, and the BOLD technique comes short because it is sensitive only to *differences* in conditions and produces no useful resting-state measures. It is thus with considerable excitement that MRI specialists are watching the developments described in these articles. Briefly, these investigators and others are attempting to develop quantitative resting-state measures of blood flow and/or perfusion that share the noninvasive nature of BOLD MRI. Once realized, such methods will almost certainly have tremendous impact, promising to give maps of regional brain differences that can be compared accurately across individuals and norms to provide objective measures of resting brain activity levels.

The methods are relatively simple. They rely on the fact that through a variety of methods the MR signal can be used to "tag" or label selectively either stationary or moving tissue. The paper by Detre et al. describes a straightforward "saturation" tag. Here the authors applied a 90° (saturating) radio frequency pulse to the tissue in the neck and collected the signal from a slice of tissue in the brain. Saturation results in complete loss of NMR signal—thus the signal from *incoming* blood was removed. When they compared the brain images with and without the proximal saturation, they showed a reduction in signal that could be used to make a reasonable estimate of blood flow. Many factors, however, make this original method difficult in humans. After a saturating pulse, the signal returns to normal at the magnetic relaxation rate, T1. Because of the transit time between the saturating and imaging slices, the T1 relaxation reduces the effect. Since this depends on the blood velocity, it is difficult to estimate and adds considerable error to the method. Further, the transit time to different tissues may be variable. Since these early experiments were performed on rats, the transit distance (and thus transit time) was minimized.

A slightly different approach was tried in humans in the paper by Roberts et al. Rather than using a saturating (90°) pulse, they used a 180° (inverting) pulse. Largely because this results in a doubling of the degree of signal change, this approach proved sensitive enough to demonstrate altered brain perfusion in three different physiologic states: rest, hyperventilation, and breath holding. Technical challenges abound with this method, though, and the group clearly noted that the method required, for example, extraordinary stability of the MR instrument to visualize the very small perfusion-related signal changes. The directly dependent MR measure is a change in apparent T1 relaxation rate of the tissue, for example. To convert this to units of blood perfusion, it is necessary to know the T1 of the tissue first. Constructing accurate T1 maps *in vitro* is not a trivial task and requires significant imaging time in itself.

Kwong and his group incorporated ultrafast EPI and a clever but simple scheme of alternating two different forms of radio frequency-inverting pulses [4]. A nonselective inversion pulse can be applied to the entire tissue volume by transmitting the RF pulse in a homogeneous magnetic field. A selective inversion pulse can be applied to a single slice of tissue by transmitting the identical pulse in the presence of a magnetic field gradient. The difference in the two images reflects the effects only of tissue (blood) flowing into the slice. The use of EPI minimizes some of the more challenging sources of error including subject motion between studies and medium-term equipment instability. The human images showed the predicted results of good gray-white contrast (as the perfusion to gray matter is higher) and of increased perfusion to tumors of high cerebral blood volume and decreased perfusion in low blood volume tumors.

From these initial reports, a broad family of new technologies has begun to emerge. While the problems of quantitation are not trivial to solve, they are not intractable either, and considerable attention is now being paid to the rapid and accurate determination of brain T1 maps and to extension of these saturation-based methods to multislice techniques. Based on their noninvasiveness, their modest hardware requirements, and the general popularity of magnetic imaging, this reviewer fully expects that the quantitative perfusion measurements by MRI will supplant not only the BOLD method in fMRI, but may be a powerful and practical replacement for many resting-state PET exams.

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