Published in final edited form as:
Neuroimage. 2012 August 15; 62(2): 672–675. doi:10.1016/j.neuroimage.2012.01.015.

Perfusion MR Imaging: Evolution from Initial Development to Functional Studies

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Abstract

A critical indicator of tissue viability and function is blood delivery to the capillary bed (referred to as perfusion or tissue/capillary blood flow), so the measurement of this process has been pursued by many MR scientists. Perfusion MRI is currently an effective tool to non-invasively quantify cerebral blood flow (CBF) and to easily obtain its relative change due to neural activity or other stimulus. This article describes the author's experiences in perfusion MRI over the past quarter-century, including initial development of the field, development of a flow-sensitive alternating inversion recovery (FAIR) MRI technique, development of a functional oxygen consumption MRI measurement approach, validation of the FAIR technique, characterization of perfusion changes induced by neural activity, and determination of arterial blood volume.

Keywords

fMRI; perfusion; CBF; oxygen consumption; FAIR

Initial development of perfusion MR measurement techniques

Delivery of blood to a capillary bed (referred to as perfusion, or tissue/capillary blood flow) is a critical indicator of tissue viability and function. A major goal of many MR scientists has therefore been to measure this tissue perfusion. Perfusion can be determined from MR measurements with blood flow tracers which either freely diffuse to extravascular tissue or are impermeable, and with knowledge of the arterial input function of these tracers. During a graduate career at Washington University in St. Louis (1984-1988), my PhD project under the supervision of Joseph Ackerman was to determine tissue perfusion with deuterium NMR spectroscopy following a bolus injection of deuterated water into mouse tumor as a freely-diffusible blood flow tracer (Ackerman et al. 1987; Kim and Ackerman 1988b; Kim and Ackerman 1988a). This approach assumed that tracers distribute the region of organ instantaneously and homogeneously after a bolus injection, subsequently wash out from the labeled region by ongoing blood flow. Then, time-dependent NMR data of deuterated water in the labeled region was fitted by a Kety's first-order washout decay model (Kety 1949) and its rate constant was converted into quantitative blood flow rate (Kim and Ackerman 1988a). At the same time, two other MR approaches were developed to attempt perfusion measurement; Massachusetts General Hospital (MGH) used the contrast agent Gd-DTPA

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(Johnston et al. 1987) and Dennis Le Bihan used an IntraVoxel Intra-Motion (IVIM) diffusion approach (Le Bihan 1988). The Society for Magnetic Resonance in Medicine (now the International Society for Magnetic Resonance in Medicine) then organized two workshops: “Magnetic Resonance Imaging of Blood Flow” (March 13-14, 1989, Philadelphia, PA), and “Future Directions in MRI of Diffusion and Microcirculation” (June 7-8, 1990, Bethesda, MD) to discuss the tremendous efforts to advance proposed techniques, to understand underlying mechanisms, and to apply these methods to different organs. I attended the first workshop, before switching to the field of structural NMR in 1989. Materials from both workshops were reported as special issues of Magnetic Resonance in Medicine in May 1990 and June 1991, respectively. John Detre and Jack Leigh at the University of Pennsylvania had successfully measured brain perfusion by deuterium NMR following a bolus injection of deuterated water into the carotid arteries (Detre et al. 1990). Later, with Alan Koretsky and Donald Williams at Carnegie Mellon University, they developed a novel and non-invasive arterial spin labeling (ASL) method using magnetically labeled arterial blood as an endogenous tracer in rats (Detre et al. 1992) (see Alan Koretsky's article of ASL developments in this issue). These initial developments in the late 1980s and early 1990s form the basis of current perfusion MR measurement techniques.

Advent of BOLD fMRI and the need for quantitative fMRI tools

I returned to the *in vivo* NMR field when I joined the Center for Magnetic Resonance Research (CMRR) at the University of Minnesota in late 1991. There, I was assigned by Kamil Ugurbil to work with Ravi Menon, Seiji Ogawa and David Tank on 4-Tesla human fMRI projects (Ogawa et al. 1992) (see Kamil Ugurbil's article in this issue). Soon after the initial success of BOLD fMRI, we realized that there were large vessel contributions to the signals, which became an intense research focal point (Lai et al. 1993; Menon et al. 1993; Kim et al. 1994) (see Ravi Menon's article in this issue). Consequently, alternative fMRI methods sensitive to a single physiological parameter, like cerebral blood flow (CBF), were pursued. In 1993, the Society of Magnetic Resonance in Medicine organized the workshop “Functional MRI of the Brain” (June 17-19, 1993, Arlington, VA). In this workshop, various perfusion imaging approaches were presented, including exogenous tracer approaches by Jim Ewing at Henry Ford Hospital and Alan McLaughlin at NIH, contrast agent methods by Bruce Rosen at MGH, IVIM by Jeff Neil at Washington University and Dennis Le Bihan at NIH, and ASL by Alan Koretsky at Carnegie Mellon University. A major push to find new approaches for perfusion measurement was underway in the MR research community.

Development of perfusion-based fMRI

Within the CMRR at the University of Minnesota, there were discussions about approaches to measure blood flow, including an inflow-sensitive slice-selective inversion recovery technique. In the original human fMRI studies at the CMRR (Ogawa et al. 1992), we had attempted slice-selective inversion recovery fMRI (in addition to BOLD) in early 1992, but we did not produce any meaningful results. The MGH group did successfully obtain fMRI data with slice-selective inversion recovery (Kwong et al. 1992), by which time the focus of interest at the CMRR had turned to BOLD fMRI. In 1994, Kamil Ugurbil and Peter Erhard (then a postdoc at the CMRR) collaborated with Robert Edelman at Beth Israel Hospital on 4-T human brain investigations with the endogenous inflow tagging technique of Echo Planar Imaging and Signal Targeting with Alternating Radio frequency (EPISTAR), which inverts spins on the inferior side of the imaging slice. Since EPISTAR CBF measurements are qualitative and not quantitative (Edelman et al. 1994), I did not become interested in this specific approach until hearing Robert Edelman's lab's presentations at the Society for Neuroscience (SFN) 24th Annual meeting at Miami Beach in Nov. 13-18, 1994 (Warach et al. 1994), which demonstrated improved fMRI activation localization devoid of large vessel

contributions. Due to heavy rain during the SFN meeting and unfamiliarity with the other attendees, I spent free time with my hotel room-mate Ravi Menon (currently a Professor at the University of Western Ontario and at Robarts Institute) discussing our future research directions, as we were both then new assistant professors. I decided to pursue perfusion imaging and temporal dynamic fMRI studies. During this meeting I came up with an idea for inflow-sensitive slice-selective and non-slice-selective inversion recovery (IR) for the separation of inflow signals from stationary spins, where theoretically the difference of the two IR images is directly related to perfusion.

After returning from the SFN meeting, I implemented this pulse sequence on a human 4-T system and evaluated the inversion profiles of adiabatic full-passage radiofrequency (RF) pulses. My first experiments (Nov. 28-30) attempting to quantify baseline CBF by obtaining inversion time-dependent ASL did not produce meaningful results. After initial disappointment, I applied this approach to a series of human fMRI studies with internal volunteers (Dec. 26-28), to convince myself that this technique measured relative CBF changes. I coined this perfusion technique “Flow-sensitive Alternating Inversion Recovery” (FAIR), and rushed to submit this finding to Magnetic Resonance in Medicine (submission date: Feb. 6, 1995). This initial work on FAIR was presented at the Society for Magnetic Resonance (SMR) 3rd Scientific Meeting (August 19-24, 1995; Nice, France) and published in the September issue of Magnetic Resonance in Medicine (Kim 1995a). After my presentation and publication, a few MR scientists expressed that they had the same or similar ideas, which had been unknown to me previously. An identical approach had been proposed in the angiographic field (Nishimura et al. 1987), as well as in a P41 grant proposal by Kamil Ugurbil. Also, CBF measurements based on the same concept, but with multiple inversion times had been independently and concurrently performed by Kenneth Kwong and his colleagues in human brain (Kwong et al. 1995), and by Axel Hasse and his colleagues in rat brain (Schwarzbauer et al. 1996).

Initial fMRI studies with these perfusion imaging techniques had definitely created enthusiasm for single physiological parameter studies, avoiding the BOLD fMRI limitations. A variety of pulsed ASL techniques were developed for refining and overcoming shortfalls of the EPISTAR and FAIR techniques (Wong et al. 1998). And at about the similar time, Alan Koretsky's laboratory was working on accurate quantification and sensitivity enhancement with continuous ASL techniques in the rat brain (Zhang et al. 1993; Silva et al. 1995).

Initial effort to determine oxygen consumption rate changes

Once I was convinced that the FAIR technique indeed measured perfusion changes, I began the following experiments; 1) inversion time-dependent perfusion contrast (Dec. 28, 1994), 2) BOLD *vs.* CBF fMRI (Jan. 5, 1995), and 3) FAIR fMRI with bipolar flow-crushing gradients (Jan. 5, 1995). In addition to these studies, I also collaborated with Peter Erhard to compare EPISTAR with FAIR, and with Nikolaos Tsekos (then a CMRR graduate student and currently an associate professor at the University of Houston) on myocardial perfusion studies with FAIR; both works were presented as abstracts for the SMR 3rd Scientific Meeting in 1995 (Erhard et al. 1995; Tsekos et al. 1995). My major focus in the early FAIR studies was to compare CBF and BOLD data to attempt an estimate of oxygen consumption changes. Functional MRI was performed on nine human subjects during finger movements at 4 T for comparison between CBF fMRI and BOLD fMRI with echo times of 20 and 30 ms. These results were submitted as an abstract for the SMR 3rd Scientific Meeting (deadline: April 11, 1995), which was subsequently rejected. But this same data was presented as a proposed means to estimate oxygen consumption changes at the 2nd International Conference on Functional Mapping of the Human Brain, and at the 1996 SMR

meeting (Kim and Ugurbil 1996a; Kim and Ugurbil 1996b). This work led to the successful determination of cerebral oxygen consumption rate changes (Kim et al. 1997; Kim and Ugurbil 1997; Kim et al. 1999), an important brain imaging research parameter.

Validation of CBF quantification by FAIR perfusion MRI

Although my initial publication of the FAIR technique measured relative CBF changes during stimulation, I was also interested in quantifying CBF values. When I evaluated FAIR images of human brains acquired at different inversion times (TI), I found that angiographic-like images were obtained at short TI values, while perfusion-weighted images were obtained with TI > 1.2 s. Then during the 1995 SFN meeting in San Diego (Nov 11-16), I had important encounters which led to independent, parallel collaborative projects — FAIR studies at 9.4 T in rat brain, and a comparison of relative CBF changes measured by FAIR (at 4 T) vs. PET in human brain.

During my poster presentation of the FAIR technique (Kim 1995b), I met Steve Jones from the Cleveland Clinic (currently from Allegheny General Hospital in Pittsburgh), who suggested that I work with Costantino Iadecola at the University of Minnesota (currently a professor at Cornell University). This led to a productive and important collaboration with Costantino Iadecola. The first collaborative project was validation of CBF quantification with the FAIR technique in rat brain (Tsekos et al. 1998). Our initial effort (with Nikolaos Tsekos as my lab's postdoc) gave unexpected contrast due to the inflow of fresh blood to the non-slice selective IR slab (from outside the head coil) during long TI intervals. So we built a rat body coil for 9.4 T, and found that CBF measurements in rat brain with the FAIR technique and long TI under normo- and hypercapnia agreed extremely well with those measured by iodoantipyrine autoradiography in the same animal model. The paper reporting these results (Tsekos et al. 1998) was the first 9.4-T paper from the CMRR. Costantino Iadecola was a consultant on every vascular physiology project in my lab during my University of Minnesota tenure, and was a tremendous resource for my lab's physiological imaging research.

At the SFN meeting I also met David Rottenberg (a PET researcher at the Veterans Hospital in Minneapolis) and we discussed various projects. He was working on a NIH Program Grant Application for Human Brain Mapping, for which the MGH group was going to propose a project on the temporal resolution of fMRI. After learning of my group efforts to determine the limit of fMRI temporal resolution (Kim and Richter 1996), he invited me to give an informal presentation to his PET research group. David later asked me to participate in his Human Brain Program grant application. I delivered my proposal (Project #1: Temporal Resolution of fMRI) right before the submission deadline, and luckily, this grant was funded on 9/30/96 as P20 MH57180. Since local PET researchers were my collaborators, I asked Steve Strother (then a PET researcher at the Veterans Hospital in Minneapolis; currently a professor at the University of Toronto and the Rothman Institute) whether there were PET measurements of tracer appearance time to different brain areas. Steve gave me one paper showing blood transit time differences among different brain regions of 1 to 2 seconds (Iida et al. 1988). With this knowledge I abandoned serious pursuit of CBF quantification in humans due to the large variation in blood transit time and short arterial blood T_1 values. Instead, I focused on comparing relative CBF changes measured by FAIR vs. PET in same human subjects, collaborating with both Steve Strother and David Rottenberg (Kim et al. 1996; Zaini et al. 1999), and became convinced that relative CBF changes could be accurately measured by FAIR, despite concerns of large vessel contributions to signal, transit time changes, etc.

Through the “International Neuroimaging Consortium” directed by David Rottenberg in early 1996, I met Olaf Paulson from Denmark and Iwao Kanno from Japan, both top-notch physiologists who would be my future collaborators, helping to shape my research.

Characteristics of functional perfusion imaging: spatial and temporal responses

Afonso Silva (currently an NIH investigator) had developed a two-coil continuous ASL technique (one coil for carotid arterial spin labeling, the other for brain imaging) for rat studies in Alan Koretsky's laboratory (Silva et al. 1995) before joining my laboratory as a postdoctoral fellow in August 1997 with the intent to extend his perfusion studies to humans. Since the 4-T human system was down at the time, all human experiments in my lab were performed at the research centers of other collaborators (temporal studies with Ravi Menon and oxygen consumption studies with Olaf Paulson). Afonso therefore implemented his two-coil continuous ASL technique on our 9.4-T animal system, teaming up with graduate student Sang-Pil Lee (currently an assistant professor at the University of Kansas) to determine the spatiotemporal relationship between CBF and BOLD responses in the primary somatosensory cortex of anesthetized rats during forepaw stimulation (Silva et al. 1999) (see Afonso Silva's article in this issue). Afonso went on to develop a fast pseudo-continuous ASL technique, obtaining 100-ms temporal resolution (Silva and Kim 1999), and measured CBF and BOLD responses at the middle and the surface of the somatosensory cortex (Silva et al. 2000), finding that CBF response onset time in the middle of the cortex precedes that of the cortical surface, and both regions have similar times to peak response. These were the first cortical depth-dependent fMRI studies (Duong et al. 2000; Silva et al. 2000).

One of the most important challenges at the time was improving the spatial specificity of fMRI. Based on intrinsic optical imaging studies (Malonek and Grinvald 1996), it was assumed that activation induces increases in blood delivery to a much larger area than just the neuronally active site. Appropriate stimulation models are essential in order to examine the spatial specificity of fMRI signals, so we adopted the cat orientation column model from neuroscientist Dae-Shik Kim (currently a professor at the Korea Advanced Institute of Science and Technology) when he joined my lab. Timothy Duong, a postdoctoral fellow (currently a professor of the University of Texas at San Antonio) and Dae-Shik worked together to examine the fMRI properties of cat visual cortex, performing FAIR fMRI studies with orientation-selective stimuli, and finding a spatially-specific CBF response to cortical columns of size ~1 mm (Duong et al. 2001).

Separation of perfusion signals into CBF and arterial CBV

During the course of perfusion studies with TI-dependent FAIR (Kim and Ugurbil 1996c; Kim and Tsekos 1997) and bipolar gradient-applied ASL (Ye et al. 1997), it became evident that arterial vessel contributions to ASL signals were significant. An important issue in my lab was to understand the discrepancy between CBF values determined by one-coil continuous ASL with magnetization transfer (MT) effect vs. two-coil ASL without MT effect. In 2002, I asked a new graduate student, Tae Kim (currently an assistant professor at the University of Pittsburgh) to perform ASL experiments on a two-coil system with varied MT levels by applying additional MT-inducing pulses. Quantification of perfusion should be independent of measurement method, but our finding that the CBF value determined from ASL with MT is higher vs. without MT indicated a differing contribution of arterial blood. This allowed us to separate the arterial blood and extravascular/capillary contributions to signals, and subsequently to develop techniques for arterial CBV measurement with ASL (Kim and Kim 2005; Kim and Kim 2006). These approaches were then implemented to

measure dynamic arterial CBV and CBF changes induced by neural stimulation (Kim et al. 2007).

Closing remarks

Since ASL techniques do not require exogenous agents, this non-invasive perfusion MRI methodology can be used repeatedly in the same subjects for quantitative baseline measurements, and as an effective tool for determining relative changes induced by external stimuli in fMRI studies. However, it is still necessary to increase the sensitivity of the technique and to find alternative MRI methods to accurately determine low perfusion rates. Because ASL sensitivity is closely related to T_1 of arterial blood, the increases in blood T_1 at higher magnetic fields are advantageous for signal sensitivity.

Acknowledgments

Over past quarter-century, I was fortunate to have Joe Ackerman, Kamil Ugurbil and Seiji Ogawa as outstanding mentors who encouraged and supported my research efforts, and to collaborate with many excellent colleagues, enabling the contributions from myself and my lab members to the field of perfusion MRI. I thank all of my colleagues at the CMRR (University of Minnesota) and at the University of Pittsburgh, and also thank the grant funding agencies including NIH, National Alliance for Research on Schizophrenia and Depression, Whitaker Foundation, and McKnight Foundation for their financial support.

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