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EDITORIAL

Arterial spin labeling: its time is now

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It has been more than two decades since arterial spin labeling (ASL) perfusion MRI was introduced [1, 2], yet its impact on research and clinical studies is just starting to be broadly appreciated. ASL has gone from an infancy where it was practiced in small animals by just a few experts, to a childhood of initial experience in humans and in more laboratories, and finally through an awkward adolescence where emerging capabilities were masked by imperfect coordination of methods, analysis, and distribution. As evidenced by the richness and variety of studies in this special edition of MAGMA, ASL has become a mature technology where widespread development and testing, exploration of clinical and research applications, and movement toward consensus on approaches are occurring today.

While ASL methods are now advanced enough to provide routine, quantitative sequences for brain ASL and competent methods for some organs outside the brain, remaining limitations and the ongoing spirit of innovation in the community continue to drive new developments in ASL methods. Perhaps, nowhere is this more evident than in the wide assortment of labeling methods (and associated acronyms) that continue to be introduced and improved. In this issue alone, we see a paper on an innovative approach to mixing continuous and pulsed ASL [3], an exploration of the challenges of pseudo-continuous labeling in humans at 7 Tesla [4] and an investigation into unintended effects of pulses to shape the labeling bolus [5]. The exciting and exploding area of vessel-selective labeling to map perfusion territories is represented here by the New Concept article on random vessel encoding [6].

A key issue restricting the reliability of ASL studies is the effect of motion and other instabilities on noise and artifacts in ASL. The successful approach of background suppression [7, 8] is emphasized in the article of Maleki et al. [9], where suppression is optimized and used to image blood flow to the eye. Since background suppression does reduce ASL signal by a significant factor, the community remains uncertain whether or how much background suppression to use. For example, neither the reproducibility study of renal blood flow [10] nor the study of pulmonary perfusion in cystic fibrosis [11] employs substantial background suppression. Integrally related to the choice of background suppression is the choice of acquisition sequence. Traditionally, single-shot imaging with echo-planar imaging was used to minimize motion sensitivity, but the improving speed of other approaches and the reduced motion sensitivity provided by background suppression have encouraged the use of RARE, balanced SSFP [12], and even 3D spiral [8, 13] or GRASE [14] sequences for acquisition. A key question in the choice and design of sequences is how many different images are required for quantification. Multiple images are required when T1 and especially transit time measurements are needed.

The use of ASL in broad clinical populations has stimulated interest in better understanding arterial transit times from the labeling region to the imaged tissue. Techniques to minimize transit time errors in measurements of perfusion have been described [15, 16] and employed successfully in numerous clinical studies. Still, the measurement of transit time can help to improve quantification of flow and may also provide a separate measure of vascular health or disease. Measurement of transit time typically requires the acquisition of multiple images with different labeling

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parameters [17, 18]. Improved sensitivity with array coils and higher field strength and improved fast imaging techniques have made acquiring these images more practical. An example comparing measurements of transit time with several different labeling strategies is included in this issue [19]. This study supports the feasibility of measuring transit time and helps to fuel the growing interest in obtaining transit measurements as part of an ASL study.

As highlighted by several articles in this issue, ASL can play a role in a broad range of applications from pure physiologic research to clinical diagnosis. Because ASL provides a stable, quantitative measure of blood flow and tissue function, it lends itself readily to the study of pharmacological effects. As demonstrated in the study of Zelaya et al. [20] using fentanyl, the use of ASL to study drug action and effect is gaining increasing attention. In the brain, where drugs or other treatments can have regionally specific effects, the easy ability to study functional changes induced by the drug without a task may help to make ASL a staple in the evaluation and monitoring of new therapies. Pharmacologic or physiologic modulation of flow to other tissues is also a growing area of interest.

The temporal stability of ASL is in contrast to that of the blood oxygenation level–dependent functional MRI technique with which it is often associated. The relationship between the two physiologic effects of flow and oxygenation as well as the MRI technologies themselves has been a frequent area of study [21]. Certainly, the stability of ASL [22] makes it the technique of choice for looking at changes in resting function on the timescale of most pharmacologic and treatment studies. However, the boundary between the two has been blurred somewhat by the intense interest in BOLD "resting" fluctuations [23]. The stability and quantitative nature of ASL continues to make it a compelling tool to study both spontaneous and induced fluctuations in the cerebral activity.

Perhaps, a key landmark in the advancement of ASL was the introduction of commercial brain ASL sequences on clinical scanners over the past few years. These sequences, along with a growing body of research studies evaluating disease effects on ASL, have made clinical applications of ASL a reality. Sensitivity to flow and angiogenesis in tumors, neurodegenerative diseases, epilepsy, and of course cerebrovascular disease and stroke all suggest an important clinical role. A key function of the research community will be to communicate with and respond to clinicians as the technology is integrated into the complex decision-making process for diagnosis of individual diseases.

The brain is certainly not the only tissue where ASL has a research and clinical role. As highlighted in several articles of this issue, ASL can be used outside of the brain in kidneys [10], lung [11], retina [9], and other tissues. For these applications, the techniques honed in brain studies are often not well matched to the motion and susceptibility environments of the target tissue or their flow and transit times, so continued technical development is required to realize the potential of these applications.

ASL is naturally suited to the measurement of perfusion, but a number of other potentially interesting parameters may be imaged or measured using ASL techniques. Work on these extensions of ASL will likely be a focus of research over the next decade.

ASL can provide information on the vascular supply to tissue. As we have seen in the article by Wong and Guo [6], it can provide information on which vessel is the source of the blood flow. But beyond that, ASL can be used as a technique for angiography [24]. Though ASL angiography faces stiff competition from contrast and TOF approaches, precision of labeling, both in timing and location, permit precise dynamic inflow and vessel-selective angiography [25]. On the finer scale, ASL can also be used to quantify the blood volume of the arterioles and capillaries prior to the diffusion of the tracer out of the microvasculature [26, 27].

Since some of the ASL signal can come from the microvasculature, studies of the characteristics of that signal can provide additional information. ASL can be used to assess vascular permeability to water and characterize the blood–brain barrier [28]. Measurement of the T2 or T2* of the microvasculature signal may permit an assessment of the oxygenation of microvascular blood [29], though some model of permeability would be required to determine where in the arteriole/capillary/venule network the signal originates.

The breadth of development directions remaining should not indicate that ASL is too immature to consider for broad use. In fact, the accelerating use of ASL raises questions of standardization and consensus on best practices. As a potential quantitative biomarker for large-scale studies and clinical trials, ASL would provide more powerful results if the values and images could readily be compared across studies, sites, and groups. As described in the included news article [30], one initiative toward standardization for dementia studies has been started by the European Union with the goals of developing standard imaging and quantification methods. How to achieve standard approaches to quantification and potentially acquisition while leaving room for innovation in approach from researchers and scanner vendors will be a challenging question to address in the coming years.

I hope the articles in this issue convey some of the excitement and opportunity I see for ASL development, research applications, and clinical translation. With such talented, diverse, and interdisciplinary groups active in the field, I eagerly look forward to what the next decade of research will achieve.

Conflict of interest DCA is an inventor on patents related to continuous and pseudo-continuous labeling methods for ASL and receives royalties and research support from GE Healthcare.

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