Measuring Myocardial Perfusion Using Arterial Spin Labeled MRI: Promise and Challenges

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MRI arterial spin labeling (ASL) is a non-contrast technique that can quantify tissue blood flow. It is most commonly applied to the brain (1) and kidney (2); however, it also has potential application to other organs including the heart (3). Used for the heart, ASL might eventually play a role in cardiac pharmacological stress testing, where it could be used to detect inducible ischemia due to coronary artery disease (CAD). An important advantage of ASL is that it does not utilize an exogenous contrast agent, so it can be applied repeatedly and it can be used in patients where contrast agents are contraindicated. However, the major challenge associated with ASL is in overcoming its inherently low sensitivity to blood flow. At typical magnetic field strengths of 1.5 – 3 Tesla and with myocardial blood flow in the range of 0.5 – 4 ml/g/min, ASL generates signal changes of only approximately 1 – 8% in flow-sensitized acquisitions compared to control acquisitions. Drs. Zun and Nayak, in conjunction with Dr. Wong, previously developed a pulse sequence for human cardiac ASL at 3T that uses flow alternating inversion recovery (FAIR) for flow sensitization and steady-state free precession (SSFP) for data sampling with high signal-to-noise ratio (4). The present study by Zun, Nayak, and colleagues evaluates this sequence in the setting of clinical stress testing to detect CAD.

The major contribution of the present study by Zun and Nayak is the demonstration that ASL can detect reduced perfusion reserve in ischemic segments of patients with angiographically-proven CAD compared to patients shown not to have CAD. In segments supplied by angiographically-proven coronary stenoses, the average perfusion reserve measured by ASL was 1.44, which was significantly lower than an average value of 3.18 in patients without CAD. This is a promising result that is in good agreement with a number of previous quantitative studies using different methods. Important next steps in the evaluation of cardiac ASL would be to determine an optimal perfusion reserve threshold and to determine the sensitivity and specificity of ASL for detection of CAD.

Because myocardial blood flow is relatively low at rest and low blood flow produces small ASL signal changes, when applied at rest, the noise in flow measurements is relatively large compared to the flow values themselves. This limitation is clearly acknowledged by the authors. However, this effect leads to significant uncertainty in the measured resting flow values and subsequently to variability in measurements of perfusion reserve. When applied to a group of patients, average perfusion and perfusion reserve values agree well with prior

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data. However, when applied to individual patients, the level of uncertainty may be too large to achieve good sensitivity and specificity.

Perfusion is quantified in ASL by subtracting a control image from a tag image, resulting in an image that depicts blood that has entered the slice during the time between tagging and imaging. Because ASL is a subtractive technique, it is particularly susceptible to subject motion between the tag and control image. As has been pointed out by Zun and Nayak, physiological noise (primarily motion artifact) is most likely the most important factor contributing to noisy estimates of tissue blood flow. In their earlier work, they estimated that physiological noise was 3.4 times higher than thermal noise in normal volunteers at rest (4). In the current work, they estimated that the physiological noise for the stress ASL scans was roughly 2.1 times larger than that at rest.

A significant source of physiological noise is respiratory motion between the acquisition of the tag and control images. Because the difference signal resulting from the inflow of blood is so small relative to the background image intensity, even small amounts of motion can corrupt the difference image. In the current study, respiratory motion was reduced by breath-holding, and a single tag-control pair was acquired during a single breath-hold. Then, the resulting difference signals from six such tag-control pairs were averaged. While breath-holding is generally effective at motion artifact reduction, in the challenging environment of cardiac ASL, further respiratory artifact reduction will be necessary, as noted by Kun and Nayak. Further artifact reduction will likely be possible using image post-processing methods.

An alternative to a breath-held acquisition is a free-breathing acquisition with navigator gating and motion correction. Free-breathing acquisitions have been studied for a variety of cardiac MRI applications, such as coronary MR angiography. Wang and colleagues recently published a free-breathing, navigator-gated myocardial ASL method with nonrigid motion correction (5). In their evaluation of this method in normal volunteers, they observed a reduction of subtraction errors when using motion correction. In a test-retest study, they observed an increase in reliability when using motion correction, with the intraclass correlation coefficient increasing from 0.61 to 0.89. These encouraging results suggest that similar motion correction methods could be applied to the breath-held acquisition of Kun and Nayak and also achieve a reduction of physiological noise. Further study will be needed to determine whether a multiple-breath-hold acquisition or a free-breathing acquisition will be preferable for use in patients.

One factor that increases the level of physiological noise in myocardial ASL is the proximity of the left ventricle (LV) blood pool to the myocardium (4). With FAIR tagging, the difference signal in the LV blood pool is typically 30–40 times brighter than the adjacent myocardium. This large difference signal can result in spurious signal in the myocardium. Kun and co-workers have proposed technical solutions to this problem, including the use of diffusion sensitizing gradients and more sophisticated tagging schemes that selectively exclude the left atrium and the left ventricle. These methods may prove to be effective.

To date, the principal method of reducing the effect of this LV signal is to increase the spatial resolution of the imaging readout. The acquired spatial resolution is finer than that supported by the underlying signal-to-noise ratio (SNR) of the ASL signal, which means that pixel averaging over large regions of interest (ROIs) is required for accurate quantitation. Some of the results reported in this study are based on ROIs the size of a myocardial segment in a six-segment model, thus providing no spatial resolution within a segment. Thus, the potential advantages of the higher spatial resolution of MRI relative to

nuclear methods may not be realized. Future studies will be needed to evaluate whether subendocardial defects can be detected using myocardial ASL

The pulse sequence that was developed by Zun and Nayak acquires images at a single inversion time (TI), which is sufficient for estimating myocardial blood flow. There is some concern that blood transit delay variations, which could occur in the setting of CAD, could reduce the accuracy of perfusion quantitation with a single-TI acquisition. Multi-TI data has the potential to quantify blood transit delay in addition to blood flow, thereby eliminating the potential for error, and transit delay may also be diagnostic in the setting of coronary artery stenosis detection. The study by Wang and his colleagues employed a multi-TI sequence and used it with a kinetic model to estimate both tissue perfusion and transit delay. Future studies may be warranted to investigate the advantages and disadvantages of single-TI vs. multi-TI methods for cardiac stress testing. Also in the realm of pulse sequence improvements is the question of spatial coverage and multislice or three-dimensional acquisitions. The Kun and Nayak method acquires a single mid short-axis slice. Future cardiac ASL sequences should seek to improve upon the limited coverage that has been achieved to date. There are a variety of rapid MR imaging methods, such as parallel imaging, that could expand the coverage to three dimensions with similar image quality.

The results from this study demonstrate that there is potential for myocardial ASL to evolve into a clinically useful technique. It is a challenging technical problem and significant technical challenges remain. However, such challenges are not unusual in the field of MRI research. For example, when magnetic resonance angiography (MRA) was initially developed, it often relied on signal subtraction and the results were not robust. However, after significant research efforts by research groups worldwide, it eventually evolved into a reliable clinical tool. Myocardial ASL is still in its infancy. Improvements in SNR are possible through such methods as improved radiofrequency coils and more efficient tagging schemes. With further research, we can expect significant improvements in reliability and utility. It is not possible to say at this time what its role will be relative to SPECT, PET and first-pass MRI, but it may evolve into a useful clinical tool for certain patient populations. It may also be useful as a surrogate endpoint in studies of new therapies, given that it can be repeated without risk to the subject.

In summary, the recent paper by Zun and Nayak demonstrates the potential of ASL as a diagnostic test in the setting of clinical cardiac stress testing. While the initial results show promise, significant challenges related to the variability of the measurements, spatial resolution and spatial coverage remain.

Acknowledgments

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