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CME

Arterial Spin Labeling MR Imaging Reproducibly Measures Peak-Exercise Calf Muscle Perfusion

A Study in Patients With Peripheral Arterial Disease and Healthy Volunteers

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CME Objective for This Article: 1. Explain the advantages of using an arterial spin labeling technique to measure calf muscle perfusion compared to first pass-perfusion with gadolinium based contrast agents. 2. Explain the basic technique of arterial spin labeling MR imaging. 3. Compare the options for obtaining post-hyperemic flow in PAD patients while in a MR Scanner.

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Arterial Spin Labeling MR Imaging Reproducibly Measures Peak-Exercise Calf Muscle Perfusion

A Study in Patients With Peripheral Arterial Disease and Healthy Volunteers

OBJECTIVES This study hypothesized that arterial spin labeling (ASL) magnetic resonance (MR) imaging at 3-T would be a reliable noncontrast technique for measuring peak exercise calf muscle blood flow in both healthy volunteers and patients with peripheral arterial disease (PAD) and will discriminate between these groups.

BACKGROUND Prior work demonstrated the utility of first-pass gadolinium-enhanced calf muscle perfusion MR imaging in patients with PAD. However, patients with PAD often have advanced renal disease and cannot receive gadolinium.

METHODS PAD patients had claudication and an ankle brachial index of 0.4 to 0.9. Age-matched normal subjects (NL) had no PAD risk factors and were symptom-free with exercise. All performed supine plantar flexion exercise in a 3-T MR imaging scanner using a pedal ergometer until exhaustion or limiting symptoms and were imaged at peak exercise with 15 averaged ASL images. Peak perfusion was measured from ASL blood flow images by placing a region of interest in the calf muscle region with the greatest signal intensity. Perfusion was compared between PAD patients and NL and repeat testing was performed in 12 subjects (5 NL, 7 PAD) for assessment of reproducibility.

RESULTS Peak exercise calf perfusion of 15 NL (age: 54 ± 9 years) was higher than in 15 PAD patients (age: 64 ± 5 years, ankle brachial index: 0.70 ± 0.14) (80 ± 23 ml/min – 100 g vs. 49 ± 16 ml/min/100 g, $p < 0.001$). Five NL performed exercise matched to PAD patients and again demonstrated higher perfusion (84 ± 25 ml/min – 100 g, $p < 0.002$). As a measure of reproducibility, intraclass correlation coefficient between repeated studies was 0.87 (95% confidence interval [CI]: 0.61 to 0.96). Interobserver reproducibility was 0.96 (95% CI: 0.84 to 0.99).

CONCLUSIONS ASL is a reproducible noncontrast technique for quantifying peak exercise blood flow in calf muscle. Independent of exercise time, ASL discriminates between NL and PAD patients. This technique may prove useful for clinical trials of therapies for improving muscle perfusion, especially in patients unable to receive gadolinium. (J Am Coll Cardiol Img 2012;5:1224–30) © 2012 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) affects more than 8 million adults in the United States (1). In addition to the increased cardiovascular mortality (2), patients with PAD have impaired exercise tolerance, reduced quality of life, and a decline in functional capacity over time (3). The ankle brachial index (ABI) is the traditional noninvasive measure of PAD; however, abnormal blood flow to the lower extremity measured by an ABI <0.90 does not correlate well with time to initial claudication and maximum claudication distance (4). ABI measures the ratio of the systolic blood pressure obtained at the ankle (highest of either dorsalis pedis or posterior tibial arteries) to the maximal brachial artery blood pressure. An ABI of 1.0 to 1.3 is considered normal; an ABI between 0.90 and 1.0 is borderline for PAD; and ABI <0.90 is diagnostic of lower extremity PAD.

We have shown that gadolinium-enhanced calf muscle perfusion measured by magnetic resonance (MR) imaging at peak exercise using a plantar flexion ergometer discriminates patients with PAD from normal subjects independent of exercise workload (5) and that it correlates with walking distance (6). We also used this technique in a clinical trial of lipid-lowering therapy in PAD (7) and showed that lowering low-density lipoprotein did not improve calf muscle perfusion in PAD. One important limitation to the use of gadolinium in MR imaging perfusion studies is the risk of nephrogenic systemic fibrosis in patients with chronic kidney disease and a glomerular filtration rate <30 ml/min/1.73 m^2 (8).

Arterial spin labeling (ASL) is an MR Imaging technique initially conceived in the 1990s (9) that is capable of quantifying perfusion in a spatially and temporally resolved fashion without the use of exogenous contrast (10). Water in arterial blood is given a different longitudinal magnetization from the surrounding tissue, which decays with T_1. Therefore, the magnetically labeled water in arterial blood acts as a tracer wherein inflowing blood is tagged and the rate at which it enters the imaging plane is measured. One acquires both tagged and control images to take advantage of the different states of magnetization seen with inflowing arterial blood compared with the surrounding static (9,10) tissue. The use of ASL to measure calf muscle perfusion in patients with PAD was first described by Wu et al. (11), who used a continuous ASL technique in the setting of thigh tourniquet occlusion to measure post-ischemic reactive hyperemia using the endpoints of peak hyperemic flow and time-to-peak perfusion.

In the present study, we aimed to determine if ASL MR imaging using a pulsed ASL technique would reliably and reproducibly quantify calf muscle perfusion measured at peak plantar flexion exercise. Furthermore, we studied whether ASL MR imaging could differentiate patients with PAD from normal subjects.

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

ASL = arterial spin labeling

CASL = continuous arterial spin labeling

CI = confidence interval

IQR = interquartile range

MR = magnetic resonance

PAD = peripheral arterial disease

PASL = pulsed arterial spin labeling

METHODS

Study design. We recruited normal subjects without known cardiovascular disease between the ages of 30 and 85 years. The normal volunteers had no history of tobacco use, hyperlipidemia, or diabetes and were free from any exercise-induced symptoms. Patients with PAD were recruited from the vascular lab and were between the ages of 30 and 85 years with symptoms of intermittent claudication and ABI between 0.4 and 0.9 measured during the screening period. Exclusion criteria included rest pain, critical limb ischemia, contraindication to MR imaging, or pregnancy. All subjects provided written informed consent prior to study enrollment. The study protocol was approved by the Human Investigation Committee at the University of Virginia.

Study protocol. MAGNETIC RESONANCE PROTOCOL. All subjects performed supine plantar flexion exercise using a pedal ergometer (5) until exhaustion or limiting symptoms. Images were obtained immediately following the end of exercise using a flexible calf coil in a Siemens 3-T Trio (Malvern, Pennsylvania). Patients with PAD had their most symptomatic leg studied. A metronome was used to guide the rate of exercise at 50 revolutions/min. At the end of exercise, 15 averaged ASL images were acquired using an ASL pulse sequence with single-shot echo-planar imaging readouts (field of view: 200 × 200 mm, matrix: 64 × 64, repetition time: 4,000 ms, echo time: 32 ms, slice thickness: 10 mm). Pulsed ASL was performed using the PICORE (Proximal Inversion With Control for Off-Resonance Effects) technique (12), which labels blood proximal to the imaged slice. Two potential sources of error in perfusion quantitation using pulsed ASL are the variable transit delay of spins from the labeling region to the imaging slice and the contamination of the perfusion signal by intravascular blood flowing through the slice. The Q2TIPS (QUIPSS [Quantitative Imaging of Perfusion Using a Single Subtraction] II with thin-slice TI_1 periodic saturation) technique minimizes these errors by applying a train of saturation pulses at the distal edge of the labeled region, thus producing a well-defined temporal bolus (13). The Q2TIPS technique was used in this study, with the train of saturation pulses starting at 700 ms (inversion time 1) and ending at 1,600 ms (saturation stop time), with the overall inversion time (inversion time 2) set to 1,800 ms (Fig. 1). The signal averaging was performed with motion correction. In order to verify reproducibility, repeat testing on different days was performed in a group of 12 subjects (5 normal, 7 PAD).

Data analysis. Perfusion was measured on post-processing relative blood flow axial images on a Leonardo workstation (Siemens Healthcare, Erlangen, Germany) by placing a region of interest in the calf muscle area with the greatest signal intensity. Care was taken in placement of the region of interest in the calf muscle to avoid the periphery of the muscle group where there can be contamination of blood flow with nearby vessels or artifact at the edge of the imaging plane. Data analysis was performed by 2 readers (A.M.W., R.J.) for measurement of interobserver variability. The relative blood flow images were quantitative perfusion maps expressed in ml/min − 100 g that were calculated during the online image reconstruction using a standard ASL model (14).

Statistical analysis. Primary outcome measures were peak calf muscle perfusion and plantar flexion exercise

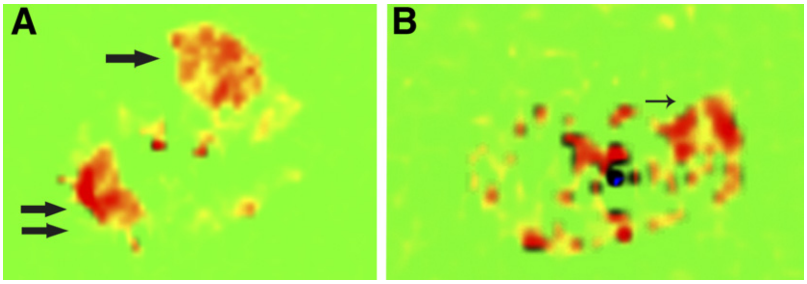

Figure 1. Post-Exercise ASL Calf Muscle Perfusion in a Normal Volunteer and PAD Subject

Shown is an axial image of the calf belonging to a normal volunteer **(A)** with increased muscle blood flow seen in **red** for both the anterior tibialis **(arrow)** and gastrocnemius muscles **(double arrow).** For the peripheral arterial disease (PAD) subject **(B)** the axial image shows increase calf muscle blood flow in the gastrocnemius **(thin arrow).** ASL = arterial spin labeling.

time. All patients' baseline characteristics were presented as mean ± SD for continuous variables and n (%) for categorical variables. Interobserver agreement was measured with intraclass correlation coefficient. Comparisons between normal subjects' and PAD patients' MR imaging and results were done with unpaired *t* test. The exercise time data was not normally distributed based on the Kolmogorov-Smirnov test for normality. Therefore, the exercise times between PAD patients and normal subjects were compared using a Wilcoxon rank sum test. Interquartile ranges (IQR) for the exercise times were reported. All statistical analyses were performed using PASW Statistics 18 (version 18.0.0, SPSS Inc., Chicago, Illinois).

RESULTS

Patients. The baseline patient characteristics for the study are presented in Table 1. There were 15 normal subjects (age: 54 ± 9 years), 5 of whom had ABI testing with normal mean of 1.08 ± 0.06, 15 PAD patients (age: 65 ± 5 years, $p < 0.001$ for age) with mild to moderate PAD (ABI: 0.70 ± 0.14) and an additional 5 normal subjects (age: 52 ± 6 years) who exercised to a pre-determined matched time of those with PAD (240 s).

Quantitative calf muscle perfusion. In the normal subjects, the anterior tibialis (9 of 15) and gastrocnemius (6 of 15) were the calf muscles with the highest calf muscle perfusion. In contrast, for all PAD subjects, the calf muscle with the highest perfusion was the anterior tibialis. Peak exercise calf perfusion (Table 2) was higher in the normal subjects (80 ± 23 ml/min – 100 g) than in the PAD patients (49 ± 16 ml/min – 100 g, $p < 0.001$). The normal subject exercised for a longer time (median: 660 s, IQR: 320 to 912 s) than the PAD subjects did (195 s, IQR: 135 to 285 s, $p < 0.005$). However, the 5 additional normal subjects who performed exercise matched to PAD (240 s) demonstrated higher perfusion (84 ± 25 ml/min – 100 g, $p < 0.002$) than did those with PAD. In the 12 studies of test-retest reliability, average group perfusion on the 2 different days was 69 ± 31 ml/min – 100 g and 66 ± 32 ml/min – 100 g and intraclass correlation coefficient 0.87 (95% confidence interval [CI]: 0.61 to 0.96). Interobserver agreement was excellent with an intraclass correla-

Table 1. Subject Characteristics

Characteristic	PAD (n = 15)	Normal Subjects (n = 15)	Normal Subjects, Matched Exercise (n = 5)
Age, yrs	64 ± 9	54 ± 9	52 ± 6
Ankle brachial index	0.70 ± 14	N/A	N/A
Male	6 (40)	7 (47)	2 (40)
Active tobacco use	8 (53)	0	0
Former tobacco use	3 (20)	0	0
Hypertension	12 (80)	0	0
Diabetes	7 (47)	0	0
Prior lower extremity stent	5 (33)	0	0
Prior lower extremity bypass surgery	3 (20)	0	0

Values are mean ± SD or n (%).
N/A = not applicable; PAD = peripheral arterial disease.

Table 2. MR Imaging Results

	PAD (n = 15)	NL (n = 15)	NL Matched Exercise Time (n = 5)
Exercise time, s	195 (135–285)	660 (320–912)*	240
Peak perfusion, ml/min – 100 g	48 ± 16	80 ± 23*	84 ± 25*

Values are median (IQR) or mean ± SD. *$p < 0.01$ versus PAD.
MR = magnetic resonance; IQR = interquartile range; NL = normal subjects; PAD = peripheral arterial disease.

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tion coefficient of 0.96 (95% CI: 0.84 to 0.99). The box plot (Fig. 2) demonstrates the difference in median perfusion between normal and PAD subjects.

The peak exercise perfusion data for the normal subjects alone at the 2 time points was 99.0 ± 19 and 94 ± 18 ml/min − 100 g with an intraclass correlation coefficient of 0.80 and for the PAD subjects was 47 ± 16 and 46 ± 23 ml/min − 100 g with an intraclass correlation coefficient of 0.78. The maximal exercise times for the study population as a whole was a median of 200 s (IQR: 152 to 332 s) and on repeat testing was 232 s (IQR: 172 to 357 s) with an intraclass correlation coefficient of 0.98.

DISCUSSION

This study examined a group of normal volunteers and patients with PAD using ASL MR imaging to quantitatively determine calf muscle perfusion at peak exercise without the use of exogenous contrast. We found that quantitative perfusion using ASL could be reliably obtained in both normal subjects and those with PAD. Interobserver agreement was excellent. We found a significant difference between peak calf muscle perfusion in normal and PAD subjects. In the normal subjects, whose exercise time was matched to that of the PAD subjects, calf muscle perfusion was similarly higher. These findings are similar to that found by gadolinium-enhanced measures (7). One advantage to ASL-based measures of calf muscle perfusion is the avoidance of administering intravenous gadolinium, particularly because a significant number of patients with PAD have chronic kidney disease. Those with severe chronic kidney disease are not candidates for gadolinium due to concerns for nephrogenic systemic fibrosis. In addition, ASL MR imaging offers the advantage of avoiding the need for intravenous access and directly quantifies perfusion rather than using signal intensity in the muscle after contrast infusion as a surrogate measure of blood flow.

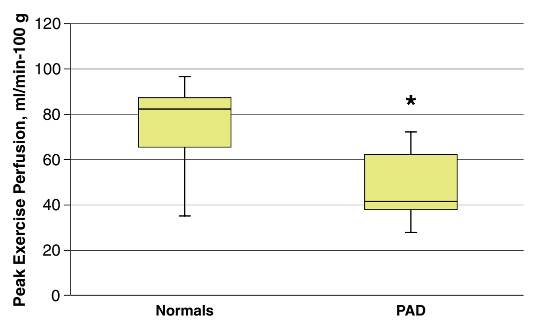

Figure 2. Box Plot of Median Peak Exercise Calf Muscle Perfusion in Normal and PAD Subjects

The **down whisker** represents the first quartile minus the minimum value and **up whisker** represents the maximum minus the third quartile. *$p < 0.001$ for PAD compared to Normals. PAD = peripheral arterial disease.

There are 4 types of ASL preparations that differ by the technique used to magnetically label the inflowing blood (15): 1) pulsed (PASL); 2) continuous (CASL); 3) pseudo-continuous; and 4) velocity-selective. We chose the PASL technique, which uses short radiofrequency pulses in the tagging plane to invert a thick region of spins (16) using the PICORE technique (12). Advantages of PASL imaging include a higher inversion efficiency and lower radiofrequency power deposition than other techniques (14). The Q2TIPS method improves the peripheral imaging by applying a train of radiofrequency saturation pulses during a prespecified period, which reduces systematic errors resulting from variable arterial transit delay and from contamination by intravascular signal (17).

To measure calf muscle blood flow with either ASL or contrast-enhanced techniques, a region of interest is placed in the calf muscle group that showed the greatest change in signal intensity after exercise. In 70% of our study subjects, the muscle group exercised by the pedal ergometer was the anterior tibialis, with the remainder using the gastrocnemius. In clinical trials, patients serve as their own control subjects and the same muscle group studied at baseline would need to be followed over time. An alternative approach to calf muscle exercise is measuring hyperemia after thigh occlusion. The latter technique could reduce the variability in muscle group stimulation that can be seen with plantar flexion exercise, which depends in part on exactly how the subject performs the exercise. However, exercise may be more physiologically relevant than occlusion/hyperemia, especially in the setting of PAD because exercise-induced symptoms (claudication) are the hallmark of the disease.

A recent study by Wu et al. (11) was the first report using CASL to measure calf muscle perfusion in patients with varying degrees of PAD. The CASL technique uses long, continuous radiofrequency pulses in a constant gradient field wherein the spins are continuously inverted as they travel through the inversion plane (14), resulting in a higher perfusion sensitivity than PASL. One important limitation to the current CASL technique is the need for continuous radiofrequency transmitting hardware that may limit its application to research scanners. Wu et al. (11) used a tourniquet system with a thigh cuff to create ischemia-hyperemia and measured peak hyperemic flow as well as time-to-peak. They found a graded dependence of the time-to-peak with the severity of PAD measured by ABI; however, the peak hyperemic flow was relatively preserved until the ABI was less than 0.7. There are 3 key differences between the present study and that of Wu et al. (11): 1) we used a PASL sequence not optimized for time-to-peak measurements; 2) instead of thigh occlusion, we studied patients at peak plantar flexion exercise while in the scanner; and 3) we report reproducibility and inter-reader reliability data. The thigh occlusion technique may be more physiologically relevant in PAD patients given their exercise limitation. However, the 2 techniques of stressing the calf in the MR imaging environment have not yet been compared head-to-head.

Ultrasound is another imaging modality used in patients with PAD to evaluate perfusion. A recent study used contrast ultrasound calf muscle perfusion imaging (18) with microbubbles to evaluate arterial perfusion reserve in normal subjects and patients with PAD using transient arterial occlusion. One of the challenges in using time-to-peak measurements is the bias introduced by changes in patient hemodynamic factors, such as volume status and cardiac output, which may change over time. A study by Lindner et al. (19), used contrast-enhanced ultrasound with intravenous injection of lipid-shelled octafluoropropane microbubbles to study microvascular blood flow in the gastrocnemius and soleus muscles at rest and after 2 min of plantar flexion exercise. They found that after correcting for diabetes, the only diagnostic tests that predicted severity of lower extremity PAD were contrast-enhanced exercise blood flow and perfusion reserve. At this point, we are unable to measure perfusion reserve with ASL MR imaging due to low resting blood flow in the calf muscle and insensitivity to the low flows due to low signal-to-noise ratios. The strengths of ultrasound for calf muscle perfusion include portability and lack of contraindications to patients with implanted ferrous metal. Future studies are needed to compare contrast-enhanced ultrasound and MR imaging methods for the evaluation of skeletal muscle perfusion in PAD.

Study limitations. To determine an area under the curve for test characteristics of ASL calf muscle perfusion, we would need to have invasive arterial monitoring with the use of microspheres to quantify perfusion in vivo. This study has been done in a small number of animals (20) that showed clear agreement between ASL calf muscle perfusion and microsphere measurements.

PAD patients were older than normal subjects were by 10 years on average. This age difference could influence the average calf muscle perfusion seen in the 2 groups, as age is known to affect calf perfusion measures (21). In a small study (21) of 6 young (26 $\pm$ 2 years old) versus 6 older (70 $\pm$ 2 years old) subjects, there as a significant difference in peak exercise calf muscle perfusion measured with ASL between the groups (60 $\pm$ 7 ml/min $-$ 100 g vs. 43 $\pm$ 10 ml/min $-$ 100 g, respectively). However, it is unlikely that a 10-year age difference could account for the extent of the difference between the normal and PAD subjects seen in our study.

Given time constraints, we studied only the most symptomatic leg for calf muscle perfusion. We are unable to measure work expenditure during the plantar flexion exercise using the current ergometer. Future studies will incorporate revisions to the ergometer where workload can be monitored.

Despite the promising contrast-enhanced ultrasound data using perfusion reserve (19), with the current ASL technique, we are unable to measure resting calf muscle perfusion; however, this is challenging even with MR imaging contrast-enhanced techniques due to low resting calf blood flow (22). At present, we do not have kinetic data for blood volume and mean transit time. Future ASL pulse sequences, including spiral data acquisition may facilitate obtaining this data.

CONCLUSIONS

ASL MR imaging using a pulsed ASL sequence is a reproducible, noncontrast technique for quantifying peak exercise blood flow in calf muscles. ASL MR imaging is able to discriminate between normal volunteers and patients with PAD independent of exercise time. This technique may be useful in clinical trials of therapies aimed at improving calf muscle perfusion in patients with PAD.

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Key Words: arterial spin labeling ■ magnetic resonance imaging ■ perfusion ■ peripheral arterial disease.

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