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MRI in Lower Extremity Peripheral Arterial Disease: Recent Advancements

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Abstract

Evaluation of peripheral arterial disease by cardiovascular magnetic resonance imaging continues to develop. Of the clinical diagnostics tests currently available, magnetic resonance angiography is well established as one of the preferred techniques for determining areas of arterial occlusive disease affecting the lower extremities. Despite this, there have been new developments in non-gadolinium based contrast-enhanced studies as well as testing done at higher field strength scanners. In the research arena, magnetic resonance spectroscopy, calf muscle perfusion imaging and atherosclerotic plaque evaluation all have made significant advancements over the last year. These techniques are gaining traction as surrogate endpoints in clinical trials of novel therapeutics aimed at alleviating symptoms in patients with peripheral arterial disease.

Keywords

Peripheral arterial disease; Cardiovascular magnetic resonance; Magnetic resonance angiography; Magnetic resonance spectroscopy

Introduction

Cardiovascular magnetic resonance (CMR) imaging of peripheral arterial disease (PAD) affecting the lower extremities began as a high resolution road-map of the arterial tree, useful for diagnosis of disease and planning revascularization procedures. Over the past 20 years, clinical research in use of CMR in patients with PAD has grown tremendously and includes magnetic resonance angiography (MRA), perfusion imaging, spectroscopy, atherosclerotic plaque characterization, and molecular imaging. In addition to advances in clinically applicable CMR, the field has developed further with the use of imaging surrogate endpoints in clinical trials of PAD¹. We will aim to review the important work done in PAD using CMR over the last year, with a focus on what areas need further study.

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Magnetic Resonance Angiography

Magnetic resonance angiography provides high resolution images to evaluate the arterial system from the aorta through the distal run-off vessels. MRA can be performed using contrast-enhanced (CE-MRA) or non-contrast (NC-MRA) enhanced approaches. CE-MRA uses gadolinium (Gd) based contrast agents, resulting in an increased arterial spin resulting from a shortened T1 relaxation after administration. Advancements in NC-MRA are particularly exciting given concern over nephrogenic systemic fibrosis in patients with advanced renal disease ².

CE-MRA traditionally uses the bolus-chase method to acquire first-pass images from the aortic bifurcation to the feet following Gd-based contrast agent administration ³. CE-MRA using Gd-based contrast agents has been performed at 1.5T with excellent diagnostic ability for PAD affecting the lower extremities ⁴. A recent study compared the diagnostic accuracy of 3T versus 1.5T CE-MRA for PAD ⁵. For an identical contrast dose, there is a significantly greater contrast-to-noise ratio for a MRA done at 3T compared to 1.5T, with equivalent test characteristics.

An area with limited capability for CE-MRA has been visualizing in-stent lesions. However, recent work with high-resolution, steady state, CE-MRA using gadofosveset trisodium resulted in excellent sensitivity and specificity (>95%) for superficial femoral artery in-stent stenosis ⁶ (Figure 1). Another area of development is the reduction of venous contamination seen with MRA done at 3T for diabetic patients. Li et al ⁷, found that the simple addition of calf compression during MRA significantly reduced venous overlap in the leg and foot, resulting in better diagnostic accuracy.

A variety of NC-MRA techniques have come to the fore ⁸ including 2-D time of flight ⁹, electrocardiogram gated, fast spin echo (including 3-D using sampling perfection with application of optimized contrasts using different flip angle evolution, SPACE) ¹⁰, balanced steady state free precession with arterial spin labeling and quiescent-interval single shot (QISS) MRA ¹¹. Currently available NC-MRA of the lower extremities are performed with ECG gating or pulse gating (with an oximeter) in order to synchronize data acquisition with the cardiac cycle. A recent pilot study ¹² used a self-gating method with a phase contrast navigator module in order to match the image acquisition with the cardiac cycle. There was some loss of image quality, but this technique would allow for NC-MRA in patients with ECG gating issues.

The QISS method for NC-MRA was recently evaluated in a two center trial compared with CE-MRA for patients with known or suspected PAD and found to have nearly equivalent diagnostic performance ¹³. MRA with QISS results in a rapid study (average of 6.4 minutes), giving providers a viable clinical alternative to CE-MRA in patients with a contraindication to Gd-based contrast agents. A small study of QISS NC-MRA demonstrated overestimation of stenosis degree in 6.3% of segments, but had a sensitivity of 98.6% and specificity of 96% for detection of stenosis > 50% ¹⁴. In the calf station at 3T, CE-MRA out performed NC-MRA (3-D, TSE sequence) given that 122/288 segments were not assessable due to image quality, mostly limited by patient motion artifact¹⁵.

An exciting advance in NC-MRA is whole body imaging using different imaging techniques for the thoracoabdominal aorta and the aortoiliac to popliteal regions. NC-MRA performed at 3T is another new development in the field. 3T NC-MRA would provide increased SNR and longer T1 relaxation times resulting in improved contrast between the blood and surrounding tissues ⁸. However, NC-MRA at 3T faces challenges due to nonuniform B1 transmit field and problems with SAR due to the RF-intensive sequences used.

Characterization of the degree of macrovascular obstruction on MRA is traditionally done with a description of each lesion and the degree of stenosis, and can be cumbersome for a referring provider to have an overall perspective of the disease severity. A run-off resistance (ROR) score¹⁶ divides the arterial tree into four segments (abdominal, pelvic, thigh and calf) with weighting by individual vessel factors and multiplied by the degree of occlusion. The ROR was compared with ankle brachial indices in PAD¹⁷ patients with a significant negative correlation found, $r=-0.513$, $p<0.001$.

Perfusion Imaging

Clinically, information about blood flow to the lower extremities is inferred by the ankle-brachial index (ABI). The ABI provides a rough estimate of the relative blood flow in the ankle compared to the brachial artery. As an alternative, CMR offers high resolution perfusion images with functional information and the ability to obtain post-exercise or reactive hyperemia data following a thigh-cuff occlusion technique. Calf muscle perfusion imaging in patients with PAD using CMR is done with either contrast enhanced first pass perfusion or non Gd-based techniques such as arterial spin labeling (ASL) and blood-oxygen-level-dependent (BOLD).

Initial work in contrast enhanced first-pass perfusion imaging in the calf muscle was done immediately following a symptom limited exercise while in the MR scanner¹⁸. Investigators have added rest imaging to the protocol¹⁹, imaging PAD patients both at rest and post-exercise while in a 3-T scanner so as to assess perfusion reserve. However, exercise perfusion measures were more reliable than perfusion reserve as the denominator in calculation of the latter is rest blood flow which is quite low and variable in PAD.

A recent small study²⁰ in 10 patients with PAD and 10 healthy volunteers examined the reproducibility of contrast-enhanced MRA at 1.5 T using 2D cine MR phase contrast angiography for flow measurements in the popliteal artery as well as perfusion imaging with dynamic contrast-enhanced perfusion imaging and the non-contrast technique of dynamic BOLD imaging in the calf muscle. Phase contrast imaging (PCI) for macrovascular flow was highly reproducible in both populations, however the perfusion imaging did not perform as well. In a related study²¹, PCI of the popliteal artery was measured at rest and post-peak hyperemic conditions after thigh cuff occlusion in order to generate a measure of flow reserve, with a small interreader coefficient of variation. The resting flow in PAD patients was significantly lower compared to healthy volunteers (4.9 ± 1.6 versus 11.1 ± 3.2 mL/s, $p<0.01$) with a similar difference noted at maximum hyperemic flow, generating a difference in absolute flow reserve of 2.4 ± 1.6 versus 5.3 ± 1.3 mL/s, $p<0.01$. Interestingly, the absolute flow reserve (the difference between peak hyperemic flow and resting conditions) could reliably differentiate between those with PAD and controls; however the relative flow reserve (the ratio between the two measures) did not discriminate.

Non Gd-based techniques for calf muscle perfusion, namely ASL and BOLD, are exciting techniques to quantify the skeletal muscle blood flow in PAD. ASL²² uses control and tagged images where arterial blood is “tagged” by radiofrequency pulses. Perfusion is determined by the signal difference between the two images. ASL in the calf muscle can be performed with either a continuous (CASL) or pulsed (PASL) approach, both of which can generate time-to-peak and peak hyperemic flow measurements. Wu et al²³, measured calf muscle perfusion in healthy volunteers and those with PAD following thigh cuff occlusion. A complementary study using pulsed ASL was recently performed immediately following peak exercise using a pedal ergometer in the MR scanner (Figure 2)²⁴, which found a significantly lower quantitative peak calf muscle perfusion in those with PAD compared to age-matched healthy volunteers.

BOLD imaging of the calf muscle depends on changes in hemoglobin oxygen saturation in the microvasculature. This technique can distinguish between healthy age matched volunteers and those with PAD using post-reactive hyperemia which results in lower T2* maximal values and longer time-to-peak for the PAD group ²⁵. A recent review of BOLD by Partovi et al ²⁶ explains the technical and analysis considerations required to conduct research studies involving BOLD in PAD patients.

Energetics and Metabolism

Magnetic resonance spectroscopy (MRS) using 31-phosphorus has been validated in patients with PAD as capable of discriminating the presence of significant arterial occlusive disease compared to healthy volunteers ²⁷. This technique can measure the recovery kinetics calf muscle phosphocreatine, a reservoir of high energy phosphates generated by mitochondria, immediately following maximal calf muscle exercise. Calf muscle phosphocreatine recovery kinetics with MRS is useful in clinical studies of patients with PAD, both following revascularization ²⁸ and medical therapy ²⁹. In patients with PAD following lower extremity percutaneous revascularization, there was a significant improvement in phosphocreatine kinetics compared to baseline, however it did not reach the same level as healthy volunteers ²⁸. In a small study of patients with hypercholesterolemia begun on statin therapy ³⁰, there was a prolongation of phosphocreatine recovery time after 4 weeks, despite normal serum creatinine kinase levels and the absence of myopathic symptoms. MRS may improve our understanding of the pathophysiology underlying statin induced myopathy. In a study of healthy subjects, changes in 31-P MRS were measured with leg ischemia resulting from tourniquet application and found that ischemic preconditioning positively influenced the phosphocreatine production during reperfusion ³¹.

MRS with 31-P for patients with PAD provides insights into the mechanisms of disease. This is an exciting field for research, however this technique has not yet translated into clinical practice. With high field scanners (3-T and above), enhanced automated data processing ³² and more widespread distribution of spectroscopic capability, there exists the potential for developing MRS into a clinically valuable tool for patients with PAD.

Atherosclerotic Plaque Evaluation

CMR evaluation of atherosclerotic plaque in the lower extremities includes 1) morphology analysis (volume, thickness, area), 2) compositional measurements (quantifying the burden of lipid core, fibrous cap, hemorrhage, calcium) and 3) activity markers (neovascularization and inflammation) ³³. In order to study atherosclerotic plaque in smaller vessels, requirements include ³³ high signal-to-noise ratio, high resolution and clear delineation between the blood, vessel wall and surrounding tissues. Black-blood imaging allows for excellent delineation of the vessel wall and can be performed using in-flow suppression (IS), double inversion recovery (DIR) and motion-sensitized driven equilibrium (MSDE) ³³.

The burden of atherosclerotic plaque affecting the lower extremities can be elegantly evaluated with CMR. Validation work done in the superficial femoral artery ³⁴ served as a springboard for clinical trials using quantification of atherosclerotic plaque ³⁵ including the recent ³⁶ WALCS III study. This trial evaluated 454 individuals with ABI < 1.0 using cross-sectional MR imaging of a 12 consecutive 2.5mm segments of the SFA and also included walking tests. Interestingly, after adjusting for confounders such as age or comorbidities as well as accounting for the ABI and leg symptoms, the presence of a greater SFA plaque burden and smaller lumen size were independently associated with worse functional performance. Although a resting ABI is an inexpensive and easily obtainable measure of the presence of PAD, exercise performance was independently predicted by the burden of atherosclerotic plaque measured by CMR. In another recent study, asymptomatic diabetic

patients were found to have a greater burden of atherosclerotic plaque in the SFA on CMR imaging compared to age-adjusted controls³⁷. A natural history study of atherosclerotic plaque in the SFA over two years³⁸ found an increase in vessel wall area by 5.23% with an unchanged lumen area, thus demonstrating evidence of positive remodeling (Figure 3). It is critical to have data from well designed natural history studies to serve as a benchmark when designing clinical trials.

Until recently, CMR of atherosclerotic plaque in the lower extremity was primarily done by studying a small segment of the proximal SFA in the most symptomatic leg, just distal to the bifurcation of the femoral artery. Since patients may have diffuse disease throughout the SFA, it would be ideal to obtain a larger field of view. Brown et al³⁹ used an eight channel surface coil to image 25cm of bilateral femoral arteries at 3T. In 5 volunteers with PAD, the investigators obtained multicontrast bilateral images with 1mm in plane resolution using time-of-flight, T1-weighted, T2-weighted and proton density-weighted images acquired all within 45 minutes. Better blood suppression will be required however since the current spatial saturation did not always provide for adequate delineation of the vessel wall. Another option for more rapid assessment of femoral artery plaque using CMR uses an automated segmentation and a 3-D black blood sequence⁴⁰ (3-D motion-sensitized driven equilibrium prepared rapid gradient echo sequence, called 3-D MERGE) to image up to 50 cm of the femoral artery wall. Although performed in only 6 participants, results were encouraging with similar vessel wall measurements for the manual and semi-automated segmentation, with only 1–2% of the usual time necessary for segmentation.

It is well established that non-obstructive atherosclerotic plaque can be at high risk of rupturing the thin cap fibroatheroma and resulting in an acute thrombotic event. Evaluating plaque composition and studying changes in atheroma with medical therapy is an important area of investigation. In addition to the high resolution angiographic images and functional data obtained by measuring perfusion or metabolism, CMR provides a window into atherosclerotic plaque composition³³ using multi-spectral MR imaging (T1, T2 and proton-density weighting). Initial work done in the carotid arteries^{41;42} and aorta⁴³ revealed that MRI could measure plaque volume and reliably differentiate four atherosclerotic plaque components: fibrous cap, lipid-rich core, intraplaque hemorrhage and calcification. Similar evaluation in the femoral arteries has been slower to develop, with one study to date evaluating the relationship between plaque eccentricity and composition in the SFA⁴⁴ which found that areas with eccentric plaque also had a larger atherosclerotic burden, with greater lipid and calcium content. Gadolinium-based contrast agents can allow for better visualization of the fibrous cap and as well as demonstrate plaque vascularity and inflammation.

Molecular Imaging

Molecular imaging with CMR provides can provide unique information about the underlying cellular processes which influence PAD, particularly with respect to the vulnerable plaque and investigating novel atherosclerotic therapies. Two of the more notable molecular contrast agents are iron oxide and lipoproteins which have been tested in murine models of atherosclerosis. Microparticles of iron oxide causes signal dropout with MR due to its paramagnetic state and have been conjugated to endothelial adhesion molecules which hone to the arterial wall⁴⁵. Lipoproteins such as recombinant high-density lipoprotein (HDL) can be used as a contrast agent for molecular imaging of atherosclerotic plaques^{46;47}. To date, these techniques are limited to pre-clinical models, but are exciting areas for future translational studies.

Molecular imaging with 18 fluorine-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) and either computed tomography or MR is limited currently to the research arena given the lack of clinical studies showing a prospective benefit. 18F-FDG-PET/CT can quantify inflammation within atherosclerotic plaques, however much of the work has been done in carotid arteries. A recent small, prospective, multicenter study⁴⁸ surprisingly found no correlation between uptake on 18fluorine-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) in patients with PAD undergoing femoral artery atherectomy and CD68 level (as a measure of macrophage content). There were several notable limitations to this small study which likely influenced the negative results. Future studies will likely include FDG-PET imaging done in concert with MRI.

Conclusion

Future developments in clinical trials of therapeutics aimed at symptomatic PAD will likely utilize CMR imaging surrogate endpoints to determine changes in atherosclerotic plaque burden, improvements in calf muscle energetics, alterations in perfusion and insight into the molecular processes underlying PAD. CMR based techniques are attractive for clinical trials of PAD as they are non-invasive, require relatively small study populations due to sensitivity and reproducibility and are not cumbersome to execute¹. New clinical trials in PAD using CMR surrogate endpoints will need to show a correlation between the imaging findings and patient outcomes.

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Figure 1.

Patient with prior SFA stent and recurrent claudication. Panel A (first pass CE-MRA) shows proximal peri-stent stenosis of $> 50\%$ with in-stent occlusion. Panel B (steady-state CE-MRA) shows $> 50\%$ stenosis proximal and within the stent which correlates with the digital subtraction angiogram (Panel C). Panel D shows fluoroscopy of the SFA stent. *With kind permission from Springer Science and Business Media: European Radiology, [6].*

Figure 2.

Arterial spin labeling images after peak calf muscle exercise in a healthy, age matched volunteer (left) and a participant with PAD (right). The area of maximal signal intensity (arrows) is seen in red, corresponding to the muscle with the greatest measurable perfusion. The participant with PAD had a noticeably lower signal intensity in the anterior tibialis muscle group compared to the healthy volunteer.

Figure 3.

Magnetic resonance imaging of the carotid artery (top panel) and superficial femoral artery (bottom panel) with T1-weighted double inversion recovery. Eccentric atherosclerotic plaque remodeling shown over the 2 years of follow-up. (*By permission of Oxford University Press [38].*)