Peripheral arterial disease (PAD) remains the somewhat forgotten atherosclerotic vascular disease despite its high prevalence and association with significant cardiovascular morbidity and mortality. It is understudied relative to coronary artery and cerebrovascular disease and there are few guideline-based effective medical therapies. Exercise is one promising, yet underutilized therapy, and newer therapies, such as stem cell and gene therapies, are being gradually developed and tested. One of the limitations to the development of novel therapies is that there remains a paucity of validated and reproducible techniques to measure their effectiveness. The ankle brachial index (ABI) is an excellent screening technique to establish the presence of PAD, but it is insensitive to changes from therapies other than those that alter bulk arterial flow, such as percutaneous revascularization. Thus, the ABI is not particularly useful for studies of novel medical, stem cell, or gene therapies. Similarly, treadmill exercise performance and 6-minute walking times are dependent on patient effort, are not particularly reproducible, and thus imperfect for use in such studies. Even experts in the field cannot agree on which of these 2 exercise tests are most useful for studies in PAD.

To fill this void, several investigative groups have been recently developing novel magnetic resonance imaging (MRI) and magnetic resonance spectroscopic techniques aimed for use in clinical trials. Phosphorus magnetic resonance spectroscopy can be used to measure phosphocreatine recovery kinetics in the calf musculature at end exercise as a sensitive marker of ischemia and it correlates with treadmill walking time and as such may be used as a surrogate marker. However, magnetic resonance spectroscopy is not widely available which limits its potential use. First-pass contrast-enhanced MRI at peak exercise can be applied to quantify a semiquantitative calf muscle perfusion index normalized to the arterial input function and it correlates with 6-minute walk distance.

However, because of the complexities of modeling tissue blood flow, absolute quantification of blood flow is not yet possible with this technique, although it remains a long-term goal.

A noncontrast technique termed arterial spin labeling (ASL), a method developed in the early 1990s for measuring blood flow in the brain, does enable absolute flow quantification and avoids the use of gadolinium contrast. Wu et al applied continuous ASL to the measurement of time to peak perfusion during hyperemia and showed that it tracked with severity of PAD as measured by ABI. Our group applied pulsed ASL for the same purpose, but at peak exercise, demonstrating differences in peak perfusion between patients with PAD and matched controls. We recently showed that cuff occlusion hyperemia ASL measures were more reproducible than peak exercise measures in controls and patients with PAD, likely because of both differences in patient effort and in muscles used during plantar flexion exercise. Blood-oxygen-level–dependent MRI is yet another technique that measures tissue oxygenation and has been applied to PAD to show both lower peak change during postocclusion hyperemia and delayed recovery relative to controls.

These prior studies set the stage for the one in the current issue of Circulation: Cardiovascular Imaging. This group of investigators has been developing novel MRI methods in PAD for several years. In addition to ASL, they have studied blood-oxygen-level–dependent MRI and venous blood oxygenation, all using the cuff occlusion hyperemia paradigm. They subsequently put these MRI approaches together into a single MRI pulse sequence, combining measures of Perfusion, IntraVenous Oxygen saturation, and T2* (equivalent to blood-oxygen-level–dependent) or PIVOT that was piloted in healthy controls during cuff occlusion and hyperemia. PIVOT has a temporal resolution of 2 seconds and thus can measure the kinetics of perfusion, venous oxygenation, and T2*. In this study, the authors studied 96 patients with PAD with a broad range of ABI and 10 healthy controls with PIVOT. Peak values for perfusion were all lower and time to peak perfusion and T2* longer in PAD than controls. Increases in time to peak for all 3 measures correlated inversely to the ABI. However, peak perfusion values did not correspond to the ABI, which is not surprising because the ABI measures bulk arterial flow and does not take collateral flow into account. The authors demonstrate that the most reliable measures were time to peak perfusion and time to peak T2*.

PIVOT is an elegant technique and was carefully studied. The question remains, is it practical and useful for clinical trials? One of the strengths and, consequently, drawbacks of MRI is its technological versatility. Physicists and engineers...
can constantly develop exciting new pulse sequences that enable characterization of physiology in a myriad of ways. At times, innovation gets in the way of practicality. If the field is trying to develop techniques for use in clinical trials that can be implemented in a multicenter fashion and on scanners from different vendors, then simpler approaches using 1 reproducible technique may be more practical.

The other question that must be raised, are 3 measures truly better than 1? The venous blood oxygenation measure may not stand the test of time as it was only able to be measured in 77% of cases and was the least reproducible of the 3. In addition, one must ask whether time to peak perfusion is really measuring different physiology than time to peak T2*? Peak perfusion was measured in different muscle groups, whereas T2* was measured through the entire calf. Neither end point was correlated with walking performance in this study, so we do not know whether 1 is more physiologically meaningful than the other. In addition, the reproducibility of both measures, especially in patients with PAD, was modest and inferior to absolute peak ASL perfusion measures recently published.15 The authors suggest that the changes between time points in the same individual may be measuring clinically relevant changes, but 3 months is a relatively short-time frame for physiology of PAD to change significantly without an interval intervention. If one was designing a clinical trial and performing power analyses to minimize the n to study in each group, the most reproducible measure would be the most attractive. As the authors point out, the PIVOT measures may be best for measuring differences between groups, but perhaps not in a patient over time or with a particular intervention.

PAD is stepwise becoming a more robustly studied atherosclerotic vascular disease. The number of potential therapeutic interventions is steadily growing as is the number of potential surrogate end points for clinical trials for these interventions. The next step must be multicenter implementation of the techniques that are deemed most useful, practical, and reproducible. Only then will the field of testing these interventions fully mature. In the meantime, exciting novel approaches continue to develop, aimed at improved the understanding of the pathophysiology of PAD and serving as a window into atherosclerosis and its downstream effects.

Disclosures
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References
8. Hiatt WR, Rogers RK, Brass EP. The treadmill is a better functional test than the 6-minute walk test in therapeutic trials of patients with peripheral artery disease. Circulation. 2014;130:69–78. doi: 10.1161/ CIRCULATIONAHA.113.007003.
17. Englund EK, Langham MC, Ratcliffe SJ, Funning MJ, Wehrli FW, Mohler ER III, Floyd TF. Multiparametric assessment of vascular function in periph-


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Novel Magnetic Resonance Imaging End Points for Physiologic Studies in Peripheral Arterial Disease: Elegance Versus Practicality

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