Asymptomatic peripheral artery disease (PAD) is an important marker for elevated risk of coronary and cerebrovascular disease. Symptomatic PAD adds to this burden by affecting quality of life and limiting function. This runs the spectrum of claudication impeding walking and mobility to critical limb ischemia with rest pain, gangrene, and risk of major amputation.

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Symptomatic PAD is a product of several abnormal factors. These include impaired blood flow to muscle and limb tissue because of stenosis or occlusion of the large conduit arteries, endothelial dysfunction affecting blood flow in all arteries, and abnormal muscle bioenergetics. Therapies for symptomatic PAD target these defects. For example, revascularization improves blood flow in large arteries, and risk factor modification, such as smoking cessation, walking programs, and hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, aims to improve endothelial function and muscle bioenergetics during exercise. Arteriogenesis and angiogenesis of the small arteries and capillaries may be mechanisms for some of the benefits from risk factor modification and are the foundation for cell-based therapies that offer the potential for improved perfusion in critical limb ischemia.

**Current Clinical and Research Approaches to Assessing PAD**

Currently, the clinical diagnosis of PAD relies on clinical symptoms, clinical signs, and physiological tests of blood flow at rest and exercise. These include segmental leg pressures, pulse volume recordings, and exercise ankle-brachial index. Imaging the anatomy of the arterial tree is only really required in the uncommon case when these components are discordant and diagnosis uncertain or for planning revascularization. Response to therapy is assessed by improvement in clinical symptoms and wound healing or prevention of major amputation, which are the primary goals as far as the patient is concerned. Physiological tests are used to help identify early recurrence of disease, for example, by identifying worsening ankle-brachial index or exercise tests. Although the value of simple arterial imaging with ultrasound is debated, CT and MR arterial imaging are usually not needed unless there is some diagnostic uncertainty or further revascularization is anticipated (eg, treating restenosis).

In the clinical research setting, several tools can assess the functional and anatomic aspects of PAD. Functional tests include standardized treadmill and corridor walking tests, conduit and microvascular endothelial function, and muscle metabolism. Quality-of-life instruments assess the impact of PAD and PAD therapies from the patient’s perspective. Anatomic tools most commonly used to assess mechanisms of functional deterioration, such as large artery stenosis or restenosis, include duplex ultrasound and angiography (eg, conventional or CT).

**Multimodality Imaging**

In this issue of *Circulation: Cardiovascular Imaging*, Stacy et al describe a new technique for assessing blood flow non-invasively. Their technique merges nuclear and CT imaging to quantify changes in blood flow in specific muscle regions. They studied a hindlimb ischemic model in the pig to show that changes in blood flow to specific muscle regions are quantifiable and show dramatic reductions in flow with occlusion of a proximal artery. The technique identifies some recovery in blood flow related to regional collateral recruitment and arteriogenesis of small arterioles over a 4-week period. Their postmortem studies show that increased blood flow on antemortem CT imaging relates to greater tissue capillary density.

The study provides a proof of concept for multimodality imaging using a well-described animal model of ischemia. The next challenge is determining how this technology could add to clinical and research practice. Although the current study demonstrated that this method can identify sudden dramatic changes in blood flow from a proximal arterial occlusion in a normal artery tree, the changes in flow in many patients with chronic PAD are likely more subtle. Because the current diagnosis and treatment paradigm in patients are appropriately focused on symptoms, signs, and physiology, it is unlikely that this method would supplant clinical assessment and well-validated physiological diagnostic tests, such as ankle-brachial index and walking indices. Like all imaging methods, this nuclear CT technique assesses arterial anatomy at rest and provides no information on dynamic factors that could determine response to medical therapy during exercise, such as endothelial function or muscle bioenergetics. Currently, imaging pre- and post-revascularization by percutaneous or bypass methods identifies a diseased arterial segment suitable for treatment. The clinical value of a multimodality imaging test measuring regional blood flow that is a product of large artery disease, small artery disease, and microvascular function requires specific evaluation in patients with PAD.
Prospects and Further Evaluation
Where would a combined nuclear CT assessment of blood vessel flow, predominantly related to arteriogenesis of small arteries, most likely gain traction? The obvious answer is in clinical trials to assess therapies promoting arteriogenesis, for example, cell-based therapies. Current clinical trials in patients with critical limb ischemia focus correctly on the effect of treatment on limb loss and wound healing. Given the failure of many cell-based therapies, a technique that helps quantify arteriogenesis in vivo could help identify therapies that require further study from those that should be abandoned.

The current study describes the technique of nuclear CT in a porcine model. The next stage should be to evaluate the technique in living humans to test its value for both clinical practice and research. This would include comparisons of this technique with current well-accepted symptomatic and physiological tests of walking function and blood flow. Other studies should assess the reproducibility of the technique across the spectrum of diseases more typical of the human condition. Arteriogenesis is highly valued in patients with critical limb ischemia without revascularization options. In these patients, it seems logical to assess the relationship of blood flow and anatomic changes using this multimodality technique to wound healing and prevention of amputation. If it can identify clinically meaningful arteriogenesis, the technique may identify novel cell-based therapies for larger clinical trials. For clinical practice, the incremental value of this technique compared with current tools will require data showing that this method can lead to changes in clinical management at an acceptable cost—a bar that is increasingly important in our era of greater demands on health resources.

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References

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