# Arthur C. Lee, MD

The interventional cardiologist shares his insights on below-the-knee interventions and the future of renal denervation and drug-coated balloon technologies.

**What are some unique access techniques you have recently employed when treating patients who have critical limb ischemia (CLI)?**

With all the CLI interventionists I have been able to meet across the country and world, I am quite sure nothing I am doing is "unique," but for myself, the cornerstone of access remains the utilization of ultrasound guidance. This has helped to increase options for access, thus improving procedural success rates. Ultrasound-assisted access also improves patient and operator safety by reducing radiation, contrast, and complications.

Tibiopedal access remains an important tool in CLI intervention, and I have used this more and more over the past 5 years. Previously, I would perform transcollateral angioplasty more commonly. Tibiopedal access gives you more support and more options in terms of treatment, however, and transcollateral percutaneous transluminal angioplasty has become rare except for transpedal arch approaches.

Ultrasound makes it possible to access almost any location that can be imaged, including occluded arteries both above and below the knee. This has included occluded native superficial femoral arteries (SFAs) and occluded SFA stents. This has also included occluded tibial vessels, which can be particularly challenging. One method that can be employed to help with this is to place a wire in the occluded tibial vessel via a pedal loop or collateral. The occluded tibial vessel is much easier to visualize by ultrasound with the bright wire echo "marking" the target vessel. I have had an unusual situation in which antegrade tibial access made sense to open a severe pedal stenosis when the proximal tibial vessel could not be opened, but there was a well-developed collateral to the distal tibial vessel. Peroneal artery access can be challenging due to difficulty getting a high-resolution image on ultrasound. I have yet to try this but have been considering using echo contrast to help with visualization in difficult peroneal access situations.

**When do you consider a retrograde-first approach to treating lower limb CTOs?**

I consider retrograde access first in cases when there are flush occlusions, such as the SFA or any tibial vessels. The indication for the procedure is very important, as most of my early tibial access was performed in CLI patients. However, as my experience and comfort level has grown, I have less hesitation for treating severe claudicants with a retrograde approach, as well. I include this during an informed consent discussion of risks and benefits.

I also consider a retrograde-first approach when there is any tibial occlusion. Factors that go into my decision are patient factors, such as how long they can lie still on their backs (age, dementia, chronic back pain, contractures, etc) and anatomical factors such as distal vessel size and characteristics, as well as how difficult antegrade access would be to achieve (due to body habitus, previous iliac intervention or surgery that makes contralateral access difficult, or hostile groin).

**How is orbital atherectomy being used in the pedal vessels to treat CLI patients?**

Orbital atherectomy can help to treat calcified vessels in the foot just as it does in the SFA and tibial vessels. There is a misconception that the pedal vessels are spared from calcification, but this is not true. I commonly see severe calcification in the CLI patient population, and this has led to very high inflation pressures with failure to expand the lesion, dissection, or eventual balloon rupture. Balloon delivery can be difficult with severe calcification, and orbital atherectomy can assist as an adjunct. I recommend an advanced experience in using the device before attempting pedal artery atherectomy and using it very judiciously below the ankle, as the risk of complication can be higher due to vessel size, tortuosity, and limited distal runoff.

**In which CLI cases do you believe embolic protection is absolutely necessary?**

I do not use distal protection very often for my below-knee CLI interventions. In this territory, I most

*(Continued on page 96)*

*(Continued from page 98)*

commonly employ orbital atherectomy and angioplasty or angioplasty alone. In the case of multilevel intervention for CLI where an SFA lesion needs to be treated in addition to tibial work, I will usually use either some sort of atherectomy or stenting. If SFA atherectomy is performed as part of a CLI case, I have a low threshold for distal protection if I use directional atherectomy. Of course, this depends on lesion characteristics, such as the length of the lesion, calcification, and whether it is a total occlusion. Although the rate of clinically relevant distal embolization has been low in my hands (and confirmed in the DEFINITIVE LE trial [Covidien, Mansfield, MA], where filter usage was 22%), the CLI patients are typically the patients with poor runoff who can least afford any amount of embolic debris.

Although embolic protection for orbital atherectomy can be used, I have not used it. I think with careful technique and case selection, the risk of slow flow is extremely small. With that said, I don't think the use of distal protection can ever be faulted, and it should be up to each individual operator and his or her experience and comfort level.

## How might the results of SYMPLICITY HTN-3 affect the renal denervation (RDN) market going forward?

The results of SYMPLICITY HTN-3 (Medtronic, Inc., Santa Rosa, CA) were a shock to many in the medical community. The trial, which was recently presented at ACC and published online in the *New England Journal of Medicine*, was well-designed and well-executed, and the investigators along with the team of researchers should be commended. There have been numerous studies showing a significant clinical effect of RDN, not only on blood pressure, but even on left ventricular hypertrophy and atrial fibrillation.

This highlights what we see so often in medicine, when multiple small studies show an effect, only to be disproved in a randomized controlled trial. However, the body of data before HTN-3 should not be disregarded based on one trial. I think the pendulum of zeal for RDN was perhaps ahead of itself. These results call for some pause and reevaluation of the technology, but at the same time, I hope the pendulum does not swing too far in the opposite direction. By no means do I believe this is, or should be, the end of RDN. I hope to see more research into the physiology of the renal sympathetic system and how we might be able to measure the contribution of this pathway in an individual patient, thereby being better able to identify responders. A method like this would also be useful to confirm that denervation has actually taken place after utilizing one of the RDN devices to better determine the most effective way to utilize the current and future device platforms.

If I were practicing in Europe, where the technology is commercially available, I would probably exercise some equipoise. However, I think many real-world patients may still benefit from the procedure, as the everyday patient population we treat is very different from the patients enrolled in this and other planned trials. In fact, the patients enrolled in the trial are almost an "artificial" group of patients created by the study protocol to try to isolate the effect of the procedure. Compliant patients willing to take five medications at maximal doses over the long term are hard to come by in daily practice. This may also be why the SYMPLICITY global registry, which just reported 6-month follow-up of 1,000 patients in a more real-world setting, showed an efficacious 20 mm Hg decrease in systolic blood pressures in denervated patients. I am pleased to hear that most of the companies with renal denervation programs have announced that they will continue their research programs in this field.

## Why do you think some companies remain enthusiastic about RDN, but others are pulling out?

In this economic and health care environment, every company has to carefully decide where they strategically devote resources. As you know, the cost of trials and the cost of bringing a product to market are astronomical, and return on investment has to be a major part of the equation. The results of SYMPLICITY HTN-3 may have made the road to developing a cost-effective and reimbursable therapy for hypertension that much longer, causing some companies to pause or drop out of the space and bringing flashbacks of carotid stenting and its state of perpetual CMS limbo.

## Do you think the results of IN.PACT DEEP are class effect? Do you expect all drug-coated balloons to react the same in the tibial arteries?

I believe there is, to some extent, a class effect to the drug-coated balloons (DCBs), especially when you look at the data we have from the SFA trials across multiple platforms as long as there has been an excipient married to the paclitaxel. With that said, though, I believe there will be significant differences between the platforms being studied in terms of dosage, excipients, and

By no means do I believe this is, or should be, the end of RDN.

coating processes. These differences play a major role in the drug uniformity, percentage of drug loss in transit, percentage of drug transferred to the arterial wall, and amount of potential microembolization. I am very excited and pleased with the encouraging 12-month results just announced in the IN.PACT SFA trial and hope the benefits are sustained long term. We should see 1-year data from the LEVANT 2 trial in the next few months, as well.

The femoropopliteal territory is clearly different from the tibial vessels. The higher prevalence of calcium in the tibial vessels may play a role in the uptake of paclitaxel. Perhaps vessel prep or debulking will be needed. CLI patients also tend to lack the collateralization that is more likely to be present in claudicants, and thus any amount of distal embolization can be more significant. It would not be a big surprise if the tibial territory amplified any potential differences in the different platform characteristics currently being tested. The below-the-knee (BTK) In.Pact Amphirion balloon (Medtronic, Inc.) used in the IN.PACT DEEP trial differs not only from its competitors in terms of excipient and drug dosage, but also from the company's own SFA DCB, in that the drug was applied with the balloon in a wrapped state. This is not to say that it was an inferior process of drug application—just an example of a difference among DCB platforms.

**What are your thoughts on the current trial designs for BTK DEB? What data are you looking forward to seeing?**

Ultimately, I believe trial design will end up being key to the success or failure of the BTK DCBs. To clarify, the IN.PACT DEEP trial did not meet its efficacy endpoint but did meet its safety endpoint. There were concerning trends in the safety endpoint, but these did not meet statistical significance. We have seen efficacy of BTK usage of the In.Pact Deep DCB in multiple registries out of Europe and even one from Japan and one randomized trial out of Europe. The DEBATE BTK trial was randomized and has 2-year follow-up. None of the worrisome trends seen in IN.PACT DEEP were observed in these other trials.

CLI patients are very complex and have multiple reasons for poor wound healing, such as pressure and biomechanics of the foot, neuropathy, superimposed infection, nutritional status, concurrent venous disease, and compliance, all in addition to arterial insufficiency. Enrollment in the BTK trials has been slow because of all these factors that have led to significant exclusion criteria to try to minimize the influence of these variables. With that said, the IN.PACT DEEP trial had wider inclusion criteria than the currently enrolling LEVANT BTK trial (Bard Peripheral Vascular, Inc., Tempe, AZ). For example, IN.PACT DEEP included Rutherford category 6 patients and hemodialysis patients and had no restriction of wound location on the foot, including calcaneal and plantar locations, which can be particularly challenging wound locations.

With the complexity of these patients and the multiple factors that play a role in poor wound healing and limb loss, the challenge of these trials is to try to isolate the cases in which the hemodynamic factors related to arterial insufficiency are playing the greatest role. This will give the best chance of showing the efficacy of DCBs in improving primary patency rates, reducing target lesion revascularization, and hopefully improving limb salvage rates and other hard endpoints without the contamination of so many other variables (some of which may be suboptimally addressed and thus, affect the outcome of the study).

I believe the timing of the interim analysis and Medtronic's decision to prematurely stop the IN.PACT DEEP trial was helpful for the other ongoing trials, as it gave them pause to reevaluate their own trial designs and make better decisions on future planned revisions. I am also happy to hear that Medtronic is not abandoning the CLI-BTK space but will continue to revamp their DCB program. I see loose similarities among BTK DCB trials, patent foramen ovale closure trials, and even the RDN trials, in which there are multiple variables, multiple potential etiologies, comorbidities, and multidisciplinary participants, and the effect of the therapy has the potential to be diluted by the complex interplay of all these factors. ■

*Arthur C. Lee, MD, is the Director of Peripheral Vascular Intervention at the Cardiac and Vascular Institute in Gainesville, Florida, and practices at the North Florida Regional Medical Center. He has disclosed that he has served as consultant/proctor for CSI, on an advisory board for Bard, as a proctor for Covidien, and that he is an investor in Sapheon and Avinger. Dr. Lee may be reached at leeivc@gmail.com.*