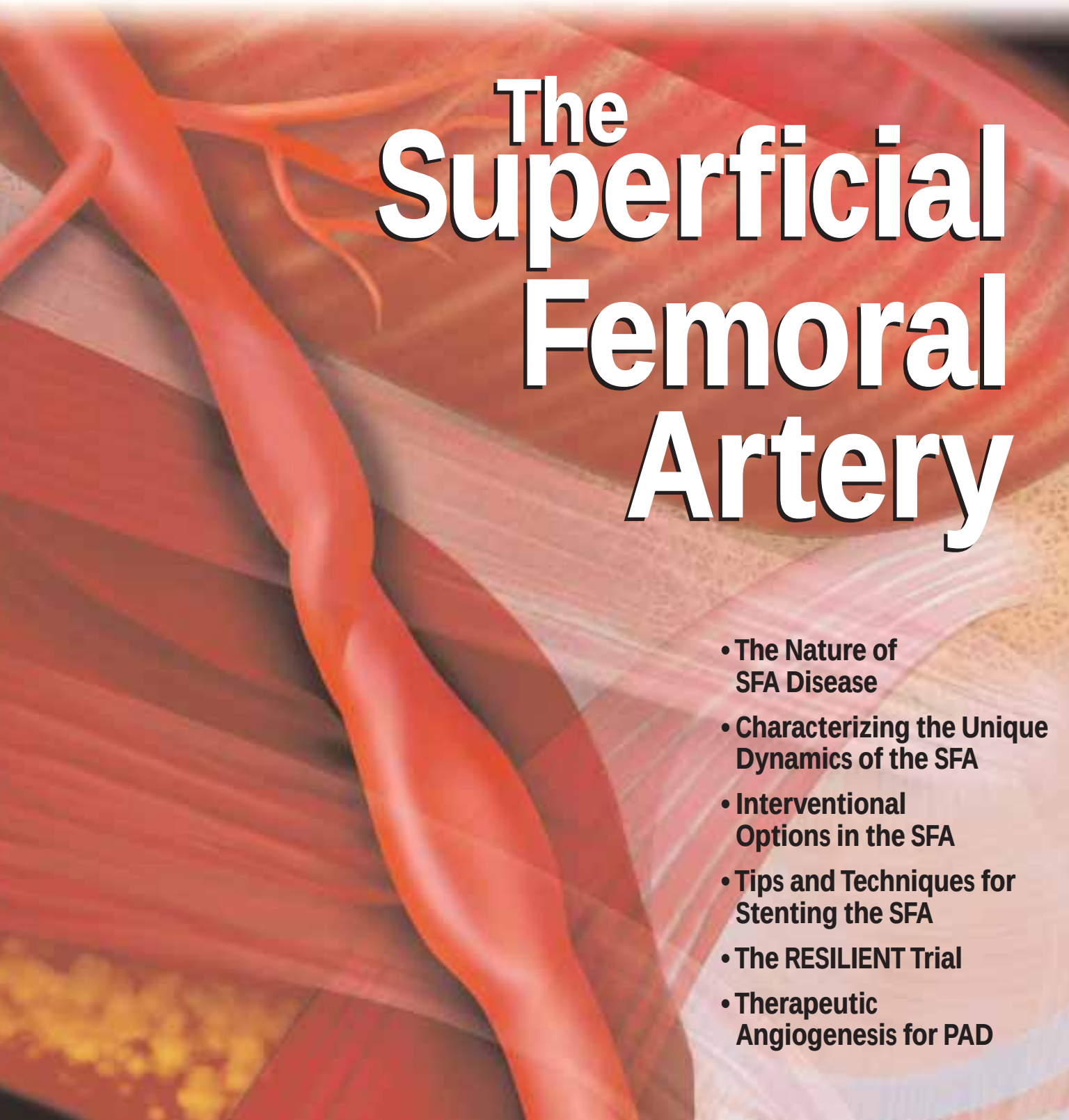
Produced under an unrestricted educational grant from Edwards Lifesciences LLC

Supplement to

Endovascular TODAY

October 2004



The Superficial Femoral Artery

- The Nature of SFA Disease
- Characterizing the Unique Dynamics of the SFA
- Interventional Options in the SFA
- Tips and Techniques for Stenting the SFA
- The RESILIENT Trial
- Therapeutic Angiogenesis for PAD

Contents

Authors

Brian H. Annex, MD, is an Associate Professor of Medicine and Director, Therapeutic Angiogenesis Research Program, Duke University Medical Center, Durham, North Carolina. Dr. Annex may be reached at annex001@mc.duke.edu.

Gary M. Ansel, MD, is Clinical Director for Peripheral Vascular Intervention, MidOhio Cardiology and Vascular Consultants, MidWest Research Foundation, Riverside Methodist Hospital, Columbus, Ohio. He may be reached at (614) 262-6772; gansel@mocvc.com.

Michael R. Jaff, DO, is Medical Director, Vascular Ultrasound Core Laboratory, Massachusetts General Hospital, Boston, Massachusetts. Dr. Jaff may be reached at (617) 726-5552; mjaff@partners.org.

Barry T. Katzen, MD, is the Founder and Medical Director of Baptist Cardiac & Vascular Institute, an affiliate of Baptist Health Systems of South Florida; and Clinical Professor of Radiology at the University of Miami School of Medicine in Miami, Florida. Dr. Katzen may be reached at (786) 596-5990; btkatzen@aol.com.

John R. Laird, MD, is Director of Vascular Medicine and Peripheral Vascular Interventions Washington Hospital Center, Washington, DC. Dr. Laird may be reached at (202) 877-5975; John.R.Laird@Medstar.net.

The Nature of SFA Disease

Understanding the link between PAD, symptoms, and diagnosis.

BY MICHAEL R. JAFF, DO

The irony of peripheral arterial disease (PAD) is that exercise, one of the traditional, first-line treatments for superficial femoral artery (SFA) disease (for all its proven benefits) is the very thing the real-life patient cannot or will not do because of leg pain and the debilitating nature of the disease.

This quandary is only going to become more common. With a rapidly aging population, the high prevalence of patients affected by SFA disease is alarming. In the PARTNERS study of 6,900 patients either over 70 years of age regardless of medical history, or over 50 years of age with a history of smoking and diabetes mellitus, 13% suffered from isolated peripheral artery disease (PAD), 16% had combined PAD and cardiovascular disease (CVD), and 24% had CVD alone, with 47% as the reference group of healthy normal patients without atherosclerosis.[1] These statistics suggest that preparing for the future and adapting to effective alternative therapies is the key challenge for today's physicians dedicated to the treatment of atherosclerotic vascular disease. This challenge should provide us with opportunities to increase our understanding and improve our therapeutic options.

The goals of therapy in all PAD cases are (1) to improve functional status and quality of life; (2) to preserve the limb; (3) to identify and treat systemic atherosclerosis; and (4) to prevent progression of atherosclerosis.

UNDERDIAGNOSIS OF PAD

A fundamental problem of PAD is that it is underdiagnosed. Most primary care specialists have not received formal training in the methods of diagnosis of PAD. The amount of training that family practitioners, internists, and even podiatrists get in vascular medicine and PAD is extremely low. The first obstacle is increasing the awareness of PAD among primary care physicians. Primary care physicians must understand that PAD is likely as common as other vascular diseases, such as coronary and carotid artery disease.

If these physicians understand the frequency of PAD (more than 10 million Americans suffer from PAD), and appreciate that many of these patients have been told that their symptoms are due to osteoarthritis or the normal aging process, their suspicion will be heightened.

Vascular specialists have to educate primary care physicians on how to identify the symptoms of PAD. One problem is that the classic description of intermittent claudication is not a scenario typically described by the patient. Most patients present with atypical symptoms: onset at variable walking distances, relieved often only by sitting or laying supine. If the physician is only listening for the classic description, he/she will misdiagnose the majority of patients with PAD. Of course, the physician must be able to distinguish claudication from any number of other ailments.

In order to identify functionally limiting cases of intermittent claudication, it is also necessary to perform a more comprehensive evaluation. One obstacle for primary care physicians is that they often have the misconception that all PAD patients have cold feet, absence of hair on the legs, or dystrophic toenails. There are patients with normal circulation who have these findings, and patients with advanced PAD who do not.

Finally, the finest screening test for cardiovascular disease is the ankle-brachial index (ABI). The ABI is a simple test that the physician can be taught in 15 minutes. The physician can then easily teach their medical assistants to perform the ABI. The CAPRIE study demonstrated that over a 3-year period, the risk of cardiovascular events increased by 10.2% for every 0.1 decrease in the ABI.[2]

An ABI will determine not only if the patient has PAD, but also if the patient has an elevated risk for heart attack, stroke, or death in the next 5 years. There is an inverse relationship between the relative risk of

cardiovascular events and deaths to the ABI. Doctors and patients alike must understand the association between cardiovascular events (eg, MI, CVA) and death and an abnormal ABI. PAD should be considered in any patient who is experiencing exertional leg pain, in any patient who is over 50 years old with a history of diabetes mellitus or tobacco abuse, and in all patients over 70 years old. The prevalence of PAD in the PARTNERS study was 29%.

There are five recommended action items for improving the early diagnosis of PAD: (1) increase awareness of PAD and its consequences; (2) improve identification of patients with symptomatic PAD; (3) initiate a screening protocol for patients at high risk for PAD; (4) improve treatment rates among patients who have been diagnosed with symptomatic PAD; and (5) increase the rates of early detection among the asymptomatic population.[3]

The National Institutes of Health has recently agreed to fund The PAD Coalition to raise awareness of the risks and symptoms of PAD in the general population with a broad multimedia advertising and marketing campaign. Vascular specialists must also take the initiative by speaking to community forums about the risks and treatments of PAD.

TREATMENT OF PAD

Even when PAD is appropriately diagnosed, current therapy is frequently not offered to these patients. Physicians have long suggested that treatment is limited to tobacco cessation and exercise. Novel pharmacotherapies (cilostazol) are available, and advances in endovascular revascularization strategies have provided new and effective therapeutic options for patients with PAD and SFA disease. Increased treatment will improve the patient's quality of life, save the limb, and allow for the detection and treatment of comorbidities.

Given the grave seriousness of PAD and the range of therapeutic options now available, there is no reason why treatment should not commence without delay. Today's therapeutic options allow for the ability to suit each patient's particular condition. The range of options begins with maximal medical therapy: cessation of smoking, a structured exercise program, and pharmacological treatment with antithrombotic/anticoagulant/thrombolytic agents, and novel agents such as cilostazol.

Patients with isolated SFA disease often have only mild to moderate symptoms of intermittent claudication, and rarely have critical limb ischemia. New endovascular therapies that offer potential advantages over surgery include PTA, bare and covered stents, atherectomy devices, thrombectomy devices, stent grafts, and radiation catheters/stents. With this range of available options, data supporting their safety, efficacy, and longevity all are critical to aid in developing strategies for effective treatment algorithms.

SFA DISEASE

The SFA is the most commonly diseased artery in the peripheral vasculature. More than 50% of all PAD cases involve the SFA. Why is this? (1) It is a long vessel, one of the longest in the body, and is surrounded by two major flexion points. (2) There are few collateral vessels promoting more diffuse disease. (3) Occlusions outweigh stenoses. (4) The adductor canal has nonlaminar flow dynamics, especially with walking. The forces exerted on the SFA include torsion, compression, extension, and flexion (Figure 1). These forces exert significant stress on the SFA and result in challenges for endovascular devices (stents).

Femoropopliteal surgical bypass is the standard, effective, invasive therapy for SFA atherosclerosis. If the distal anastomosis involves the above-the-knee popliteal artery, and autogenous vein grafts are used, patency rates are good. Still, surgical bypass grafts are not perfect. One study on the results of autogenous infrainguinal reconstruction, based on 5-year cumulative patency rates for 3,005 limbs, demonstrated a 2% operative mortality rate, a 5-year primary patency of 70%, and secondary patency of 81%. Complication rates are not insignificant, with hemorrhage <2%, graft thrombosis of 2% to 7%, and wound infection rates of 8% to 19%.[4]

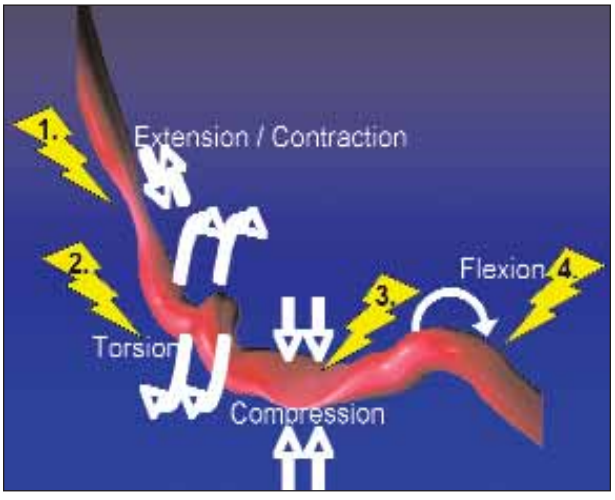


Figure 1. The forces exerted on the SFA include torsion, compression, extension and contraction, and flexion.

THERAPEUTIC OPTIONS IN THE SFA

The decision to intervene in the SFA is complex. If the patient has intermittent claudication—not critical limb ischemia—there is no urgency to revascularize. The choice is rarely PTA versus surgery; it is usually between interventional therapy and noninterventional medical management. Interventional therapy in the SFA remains controversial. The indications for intervention in SFA atherosclerosis are the same as in any patient with PAD: intermittent claudication that is interfering with lifestyle and critical limb ischemia.

CONCLUSION

The key question of treating SFA disease has been the choice between a stressful and potentially dangerous surgical approach or a less-invasive, but often less-effective, interventional approach to stent the diseased area. The potential advantages of endovascular therapy are highly attractive: significantly lower risk of wound infection; very low mortality rates; shorter length of hospital stay, which is a measurable economic benefit to the health care system; and faster return to families, activities, and work, which is of immeasurable benefit to the patient.

Ultimately, endovascular therapy for SFA disease must match surgical outcomes to be considered the preferred course of treatment. One study revealed that nearly half of all SFA angioplasties had a resultant clinical impact that was no better or in fact worse than prior to intervention.[5] If endovascular therapy is to be the preferred approach to SFA disease, these numbers need to significantly improve.

Promising improvements are on the horizon for bare-metal stents in the SFA. For example, initial data currently indicate that primary patency rates range from only 22% to 81% at 1-year for today's stents. Evolving technology with metal stents may result in significantly improved patency. The SIROCCO II randomized trial of bare nitinol stents to drug-eluting stents revealed 6-month patency rates >88%, which is as good as, or better than, surgical outcomes. These positive results may also be supported by other forthcoming studies such as the RESILIENT trial. Moreover, patency rates are sure to improve with other technologies and approaches, which include flexible self-expanding stents, lower-profile delivery systems, and improved patient selection.

Today's controversies in SFA treatment are based on as yet unanswered questions: Will therapy be better than the natural history of the disease? Will therapy complicate other options available to the patient in the future? Is the therapy durable?

As we progress with more studies of innovative devices, materials, and techniques, the answers to these questions will hopefully become more apparent. ■

Michael R. Jaff, DO, is Medical Director, Vascular Ultrasound Core Laboratory, Massachusetts General Hospital, Boston, Massachusetts. Dr. Jaff may be reached at (617) 726-5552; mjaff@partners.org.

1. Community based prevalence of PAD: PARTNERS. *JAMA.* 2001;286:1317-1324.
2. Dormany JA. CAPRIE study: ankle-brachial index predictor of ischemic events. *Cerebrovasc Dis.* 1999;9(Suppl 1):1-28.
3. Belch JJF, et al. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch Intern Med.* 2003;163:884-892.
4. Results of Autogenous Infrainguinal Reconstruction. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg.* 2000;31:1-2.
5. Gray BH, et al. Clinical impact on SFA angioplasty. *J Vasc Surg.* 1997;25:74-83.

Characterizing the Unique Dynamics of the SFA

The RESIStent Program.

BY KEVIN DRISKO

Currently only one stent, the Intracoil stent (ev3, Plymouth, MN), is approved by the FDA for use within the superficial femoral artery (SFA). Although the study data indicated that the device was safe in SFA lesions averaging 36 mm as compared to percutaneous transluminal angioplasty (PTA), the study was weak with regard to the inclusion of long lesions (17/146 lesions >90 mm), which typify the SFA disease process.[1] The lack of clinically proven alternatives for SFA disease, combined with several promising studies on the treatment of SFA disease with nitinol stents,[2,3] has led physicians to favor the use of biliary-indicated nitinol stents within the SFA. This practice is to be cautioned against, however, because the nitinol stents currently being used are only FDA cleared for a biliary indication, one that the FDA points out is obtained without long-term durability data: "Nonvascular stents are shown to be 'substantially equivalent' to legally marketed, similar devices indicated for the same use. Equivalence is demonstrated through submission of a premarket notification application [510(k)], which does not include clinical data or chronic bench tests such as pulsatile fatigue testing. Vascular stents, on the other hand, go through a more rigorous process to demonstrate that they are 'reasonably safe and effective' for their specific intended use."[4]

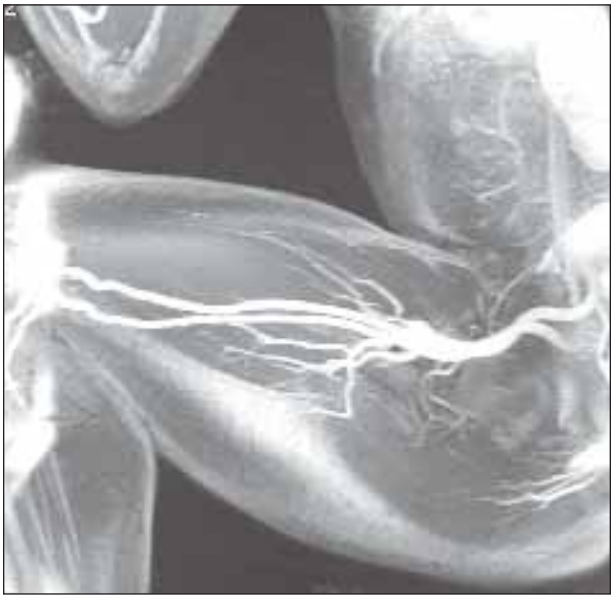


Figure 1. MRA of a normal subject's SFA while confined in the fetal position.

With the unveiling of the SIROCCO study results[3] and the increasing awareness of stent fractures,[5] stent manufacturers and implanting physicians desired to learn more about stent durability. SRI International, an independent, not-for-profit research and development organization in Menlo Park, California, and Stanford University have responded by establishing a consortium of stent manufacturers to develop the RESIStent (Reliability Enhancements and Service Improvements for Stents) Program [www.sri.com/psd/fracture/stents.html] aimed at assessing and improving stent durability. The group's efforts have attracted the attention and support of the interventional community, which desires the best outcomes for its patients, and the FDA, whose charter it is to ensure implantable devices are robustly evaluated prior to approval.

The program's goal is to provide tools for designing more durable and fracture-resistant stents. The focus is on the SFA, an artery subjected to large and repetitive multimode deformation and prone to atherosclerotic lesions.[5] To design robust, durable stents, the anatomical forces, environment, and cyclic displacements that the stents experience must be known. There are three parts

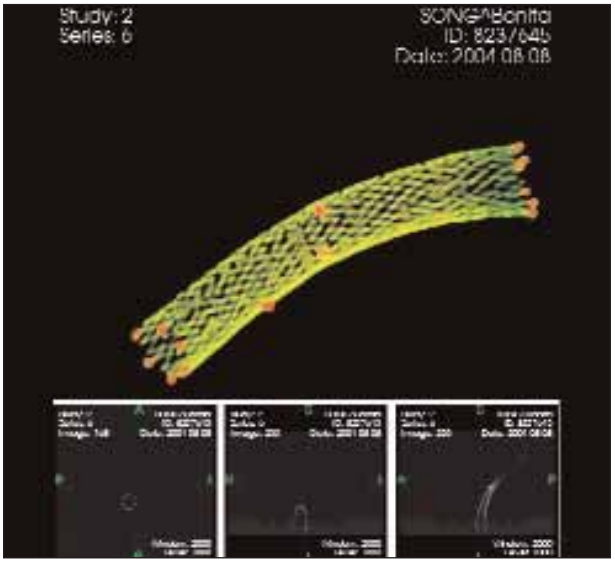


Figure 2. Detailed CT imaging of a self-expanding nitinol stent with copper markers for motion analysis.

to the RESIStent program: (1) measurements of *in vivo* displacements of the SFA via magnetic resonance angiography (MRA) imaging; (2) visualization of SFA stent deflection via computed tomography (CT) scanning; and (3) examination of explanted stents to assess the structural response of implants to the various vascular anatomies.

MRA IMAGING

Published literature documenting the dynamic motion of the SFA is minimal. Relatively few studies have been conducted to analyze the SFA, which, while fixed at the knee and infrainguinal ligament, is a dynamic and mobile artery.[6] The Stanford University Mechanical Engineering, Surgery & Pediatrics Department, under the direction of Charles Taylor, MD, is conducting the MRA evaluations proposed by the RESIStent team. Three-dimensional (3D) anatomical models are being constructed using contrast-enhanced MRA to characterize the anatomical changes experienced by the SFA during extreme physical motion. Subjects are being evaluated in two state-of-the-art magnets: a 0.5T GE interventional open-magnet to acquire 3D contrast-enhanced MRAs of the SFA during seated and squatting postures and a 1.5T GE conventional magnet for standard contrast-enhanced MRAs of the SFA. To date, data from three subjects have been evaluated, and the images collected (Figure 1) have allowed for the generation and reconstruction of 3D geometric models of the SFA. According to Dr. Taylor, the images to date have demonstrated variations in SFA anatomy both from subject to subject and from one leg position to another. The availability of data on the amount of bending, compression, and extension will be invaluable to the stent industry as it strives for more flexible and robust designs.

CT SCANNING OF STENTS

Concurrently with the general anatomical conditions being evaluated via MRA, Rebecca Fahrig, MD, an Associate Professor within the Stanford Radiology Department, is developing CT protocols to image implanted stents. Dr. Fahrig's primary goal was to develop a method of measuring stent geometry *in vivo* using a new rotational CT machine. "With this innovative equipment, we are striving to generate detailed images such that individual stent struts can be clearly visualized and implanted stents can be evaluated to determine the displacements and deformations they experience in response to limb motion," she commented. Dr. Fahrig's team is also taking the MRA data (Figure 2) to create an *in vitro* phantom that can be used to assess potential SFA stent designs without implanting them into subjects.

EXPLANTED STENTS

The third aim of the RESIStent Program is to examine stents that have been exposed to the body environment for signs of wear, corrosion, erosion, or other structural damage. SRI plans to examine explanted stents with both standard optical and high-magnification scanning electron microscopy to assess any surface or structural damage (Figure 3). This micro-damage assessment will be used in conjunction with the macro-scale deformation results

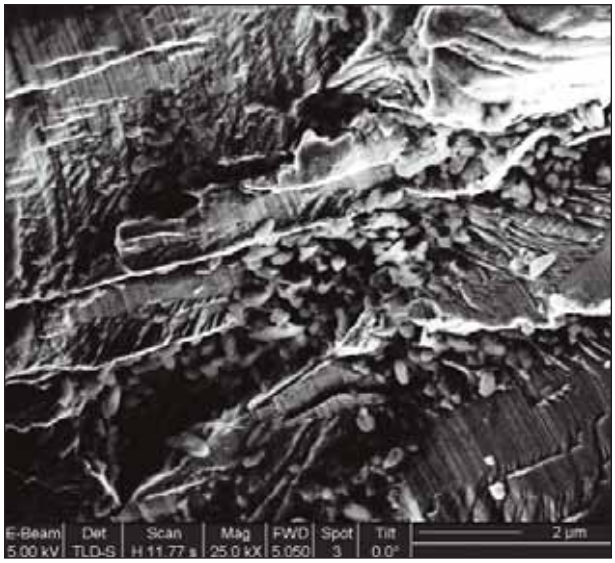


Figure 3. Fatigue striations on a failure surface of an explanted stainless steel coronary stent.

from the CT scans to determine how stents respond structurally. Mr. Scott Robertson of SRI is leading the explanted stent analysis and is seeking sources of explanted stents. "We hope to create a statistically-significant database and are relying on the medical community to provide us with explanted stents," said Mr. Robertson. "In return, we will make our observations and findings available to providers on their particular stents." The program is particularly interested in nitinol stents from the SFA, although SRI will gratefully accept and analyze any vascular stents. SRI is sensitive to the proprietary issues arising from this project and offers an independent, nonprofit perspective. Physicians who would like to participate are encouraged to contact Mr. Robertson at scott.robertson@sri.com for more information.

FUTURE ACTIONS

The program's efforts have attracted attention and support from both the interventional community and the FDA, as both groups desire to improve clinical outcomes for the treated population. It is hoped that the data generated in the RESIStent program will provide stent manufacturers with *in vivo* parameters as a basis for improved bench testing to support new device submissions, and ultimately allow for the design of stents that more closely match the rigorous requirements of the SFA. Additionally, several new industry sponsored SFA trials, namely Edwards Lifesciences' RESILIENT trial and Cook's ZILVER PTX (formerly DESTINY) study, are being initiated to assess the long-term benefits/limitations of SFA nitinol stents. ■

Contact information:

Kevin Drisko, is Senior Regulatory Manager at Edwards Lifesciences LLC, Irvine, California. He may be reached at (949) 250-2416; kevin_drisko@edwards.com.

Don Shockey, PhD, Director of SRI's Center for Fracture Physics, is coordinator of the RESIStent Program. Dr. Shockey can be reached at donald.shockey@sri.com.

Charles Taylor, MD, an Associate Professor of Mechanical Engineering, Surgery & Pediatrics at Stanford University, coordinates the MRA imaging protocols. Dr. Taylor can be reached at taylorca@stanford.edu.

Rebecca Fahrig, MD, Associate Professor in the Radiology Department at Stanford University, is developing the CT scanning protocols. Dr. Fahrig can be reached at fahrig@stanford.edu.

Mr. Scott Robertson, a Student Associate at SRI, is leading the effort to evaluate explanted stents. Mr. Robertson can be reached at scott.robertson@sri.com.

1. Food and Drug Administration. Intracoil Vascular Stent Summary of Safety and Effectiveness. P000033. April 2002.

2. Mewissen MW. Nitinol stents in the femoropopliteal arterial segment. *Endovasc Today*. 2003;2(4):29-34.

3. Duda SH, Pusich B, Richter G, et al. Sirolimus-eluting stents for the treatment of obstructive superficial femoral artery disease: six month results. *Circulation*. 2002;106:1505-1509.

4. Abel DA. Off-label medical device use. *Endovasc Today*. 2003;2(2):60-61.

5. Allie DE, Hebert CJ, Walker CM. Nitinol Stent Fractures in the SFA. *Endovasc Today*. 2004:7 22-34.

6. Wensing PJ. Arterial tortuosity in the femoropopliteal region during knee flexion: a magnetic resonance angiographic study. *J Anat*. 1995 186:133-139

Interventional Options in the SFA

An overview of the many options available to treat the diseased SFA.

BY JOHN R. LAIRD, MD

Based on the results of femoropopliteal percutaneous transluminal angioplasty (PTA), it is apparent that there is much room for improvement in treating disease of the superficial femoral artery (SFA). In the setting of diffuse disease or long occlusions, immediate success is seen in only 70% of cases, with a 3-year patency rate of only 20%. Even for ideal lesions, an immediate success rate of 95% is followed by 3-year patency rates of 75%. Overall, PTA has a 90% immediate success rate, with 3-year patency rates decreasing to 60%. These statistics suggest that we must continue to explore new options.

OPTIONS

IntraCoil (ev3, Plymouth, MN), with a coil-shaped design, is the only stent presently approved for treating the SFA. The IntraCoil results have been less than impressive, given the short lesions that were treated in this trial. In the IntraCoil study of 131 limbs with a mean lesion length of 3.3 cm, the acute angiographic success rate of 94.5% was overshadowed by a 9-month angiographic patency of 66.3%.[1]

Another current option, the Wallstent (Boston Scientific Corporation, Natick, MA), has produced 61% patency rates at 1 year. Again, longer lesions (>10 cm) proved difficult, with angiographic patency rates at 6 months of only 59%, whereas shorter lesions (<10 cm) treated with the Wallstent had a 6-month patency rate of 83%.[2]

A promising new option on the horizon is modern nitinol mesh stents. Although no nitinol stents are yet approved for use in the SFA, their benefits have been demonstrated. Their advantages include a 98% technical success rate and 92% patency at 6 months (76% at 12 months).[3]

Other advantages of nitinol stents are improved deliverability precision and minimal foreshortening. Newer generation nitinol stents offer 6-F sheath compatibility, longer lengths, and radiopaque markers for enhanced visibility on fluoroscopy. These stents provide the necessary versatility for use in the difficult-to-treat SFA (flexibility in multiple dimensions).

CLINICAL TRIALS

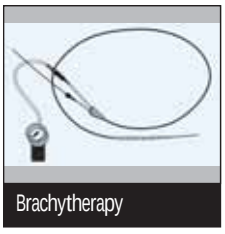
Five studies have demonstrated the significant improvements of the new generation of nitinol stents for the SFA: the German Multicenter Experience, the Mewissen trial, the BLASTER Trial, and the SIROCCO trials. The German Multicenter Experience was a retrospective review of 111 SFA stenting procedures at three sites. Smart stents (Cordis Corporation, a Johnson & Johnson Company, Miami, FL) were used in 76 procedures, and Wallstents were used in 35 procedures. The 6-month patency rate for Smart stents was 82% versus 37% for the Wallstent (personal communication).

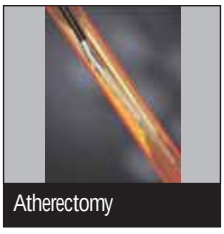
The Mewissen trial was an even more impressive demonstration of the Smart stent. A total of 246 stents were implanted in 137 limbs (122 patients) (mean lesion length, 12.6 cm). The technical success rate was 98%, with no occlusions at 30 days and patency rates of 92% at 6 months and 76% at 12 months.[3]

The BLASTER (Bilateral Lower Arterial STenting Employing Reopro) Trial at five US centers evaluated the feasibility of utilizing nitinol stents with and without intravenous abciximab for the treatment of femoral artery disease. The study looked at 50 cases with average lesion lengths of 15.1 cm. The preliminary results showed a 100% technical success rate with only 2% requiring target vessel revascularization (TVR) at 6 months, 11% at 9 months, and 17% at 12 months (or a 83% 1-year clinical patency rate).

The SIROCCO I and II Trials showed that bare-metal nitinol stents had a 100% technical success rate and a 6-month patency of greater than 88%.[4]

One of the concerns that has arisen from the SIROCCO trials is the potential for nitinol stent fracture when these stents are deployed in the femoropopliteal segment. Recent investigation has highlighted the various forces


Brachytherapy


Atherectomy


Cutting Balloon

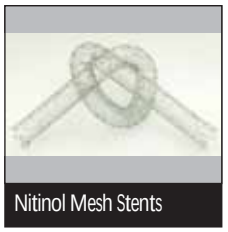

Cryoplasty


Excimer Laser

Device Type	How It Works	Best Use/Limitations
Percutaneous Transluminal Angioplasty (PTA)	Plaque fracture and localized dissection and stretching of the adjacent vessel wall	Focal lesions
Nitinol Coil Stents	Expands to a preset diameter coil; minimizes elastic recoil and seals dissecting flaps	Lesions at flexion points (behind knee)
Nitinol Mesh Stents	Nitinol mesh design provides balanced scaffolding to reduce recoil, prevent acute closure, and to facilitate long-term healing	Diffuse disease or longer occlusions
Covered Stents	PTFE graft material is inert with a very small pore size that limits tissue in-growth. Most are covered with an inert PTFE graft material over a nitinol skeleton that limits tissue ingrowth	Long occlusions; refractory restenosis
Laser	Pulsed excimer laser delivered intravascularly that uses the photoablative effect of laser light to ablate atherosclerotic and thrombotic material	Long SFA occlusions; tibial occlusive disease; and in-stent restenosis
Atherectomy	Uses a carbide cutting blade to shave plaque and debulk atherosclerotic lesions	In-stent restenosis; ostial stenosis; diffuse disease
Cutting Balloon	Longitudinally mounted atherotomes on surface of angioplasty balloon score lesion with incisions, allowing balloon to dilate the vessel	Bypass graft anastomotic stenosis; bifurcation stenosis
Cryoplasty	Angioplasty catheter that dilates and cools the plaque and vessel wall; cooling is achieved by inflating the balloon with nitrous oxide rather than saline	Long stenosis or occlusions; in-stent restenosis
Brachytherapy	Therapeutic radiation therapy (gamma emitters or beta emitters) delivered intravascularly to delay and limit the endothelialization process	Long stenosis or occlusions; in-stent restenosis
Mechanical Thrombectomy	These devices use rotational tips and/or suction to mechanically remove thrombus even when lytics are contraindicated	Acute or subacute occlusions


Nitinol Coil Stents


Covered Stents


Nitinol Mesh Stents


Mechanical Thrombectomy

	Notes	Clinical Success Rates in SFA	Availability
	Poor long-term patency rates for longer lesions; restenosis due to elastic recoil, constrictive remodeling, and neointimal hyperplasia	Patency rates range from 43% to 70% at 12 months, and about 25% to 50% at 5 years	FDA approved for both peripheral and coronary lesions
	Coiled stent design allows for bending, as well as shortening/elongation	No statistical improvement in revascularization rate at 9 months vs PTA (14.3% stent vs 16.1% balloon). However, significantly greater improvement in ABI (.19 vs .08) and lower early complication rate (1.5% vs 8.4%, P<.01) were seen	FDA approved femoral artery stent
	Versatile tool for long SFA disease; most nitinol mesh stents are ≤6-F sheath compatible, easy to use, and address acute elastic recoil unlike balloons and other debulking devices	Primary patency rates from 76% to 93% in long SFA lesions at 6-12 months, and 83% freedom from reintervention at 12 months[3-5]	Most are FDA approved for biliary use; new randomized SFA trials in progress
	Useful for stenting long lesions; spot stenting is to be discouraged. Caution should be utilized if important collateral vessels are to be covered because acute limb-threatening ischemia may occur if the stent graft should close	Preliminary results of PTFE-covered self-expanding stents in SFA in-stent restenosis suggest primary patency rates of 86% at 9 months may be possible in long lesions (average, 26.4 cm)	FDA approved for biliary or tracheal/bronchial use
	Useful for debulking SFA occlusions, facilitating subsequent balloon dilation and reducing the risk of thromboembolic events. In addition, excimer laser debulking prior to balloon angioplasty allows lower-pressure balloon inflations, which may reduce arterial wall stress and subsequent dissections, resulting in a reduced need for stent placement	PELA study compared laser-assisted PTA vs PTA alone to treat long SFA occlusions; 12-month laser-assisted patency rates were 49%; In the LACI trial 6-month limb salvage rates of 90% were observed	FDA approved for both peripheral and coronary lesions
	SilverHawk (FoxHollow Technologies, Redwood City, CA) provides more effective debulking than previous atherectomy devices; may eliminate the need for adjunctive balloon angioplasty. Time consuming in long lesions	TALON Registry of SFA, popliteal, and infrapopliteal; reported 6-month TVR rate of 11%	FDA approved for peripheral lesions
	May be useful for the treatment of recalcitrant stenoses; may be used as a stand-alone treatment or in conjunction with other treatment options	Cutting EDGE, a prospective, randomized, multicenter clinical trial that enrolled 340 patients with stenosed or thrombosed hemodialysis grafts; results pending	FDA approved for obstructed peripheral lesions
	Simple and easy to use; may be useful in longer lesions and areas in which stenting is not possible	Big Chill Registry demonstrated a 9-month TLR rate of 17.8%	FDA approved for peripheral lesions
	Primarily used to treat in-stent restenosis in coronary arteries; has been associated with late stent thrombosis; requires prolonged postprocedure use of potent antiplatelet therapy	Various SFA trials demonstrated patency between 60%-88% at 6 months; PARIS Trial showed no benefit for brachytherapy	FDA approved for treatment of in-stent restenosis of coronary lesions
	May reduce the need for thrombolytic therapy or minimize required dose	Pretreatment threatened limb ischemia 91%; posttreatment threatened limb ischemia 4% in the AngioJet Multicenter Registry	FDA approved for the peripheral, coronary, and/or AV dialysis grafts

that are applied to the stent when deployed in this location, including longitudinal compression and stretching, torsion, and extreme flexion. This highlights the importance of multidimensional flexibility for endoprostheses that are to be deployed in the SFA. One new stent that may be ideally suited for this application is the Edwards Lifesciences (Irvine, CA) LifeStent NT. This stent will be evaluated in the RESILIENT Trial, which is an important randomized, clinical trial comparing balloon angioplasty versus stenting in the SFA.

While stenting remains the preferred interventional therapy for many cases, there are many emerging technologies for the treatment of special cases that are revolutionizing the way we approach treatment of the SFA. Alternative strategies include debulking devices, cutting balloons, cryoplasty, lasers, covered stents, mechanical thrombectomy, total occlusion devices, brachytherapy, and drug-eluting stents (See Table on pages 10-11).

New atherectomy devices are able to excise large volumes of plaque from *de novo* and restenotic lesions. Their innovative features, such as in the SilverHawk System (FoxHollow Technologies, Redwood City, CA), include single-operator control with a monorail catheter that can treat multifocal and multivessel disease.

Another new option is cryoplasty for the prevention of restenosis. CryoVascular's (Los Gatos, CA) PolarCath Peripheral Balloon Catheter System is an angioplasty catheter that simultaneously dilates and cools the plaque and vessel wall in the treatment area. Cooling is achieved by inflating the balloon with nitrous oxide rather than saline. The cooling induces an acute phase change, which triggers apoptosis in smooth muscle cells, resulting in reduced neointimal formation, reduced collagen synthesis and reduced constrictive remodeling, with dissection rates of only 7%.

CONCLUSION

Disease of the SFA has long been one of the most debilitating conditions for patients and one of the most challenging puzzles for vascular specialists who treat them. The inherent nature of the disease and the SFA anatomy present numerous challenges to successful treatment and improved quality of life.

These emerging therapies are providing physicians and patients alike with many reasons for optimism. In the near future, endovascular options will include more advanced nitinol stents, more effective debulking devices, cryoplasty, total occlusion devices, and drug-eluting stents. These advances in technology will be accompanied by better adjunctive pharmacology. We are now at the advent of a new and exciting age of progress and improved healthy outcomes. ■

John R. Laird, MD, is Director of Vascular Medicine and Peripheral Vascular Interventions Washington Hospital Center, Washington, DC. Dr. Laird may be reached at (202) 877-5975; John.R.Laird@Medstar.net.

1. Food and Drug Administration. IntraCoil Vascular Stent Summary of Safety and Effectiveness. P000033. April 2002.
2. Martin EC, Katzen BT, Benenati JF, et al. Multicenter trial of the Wallstent in the iliac and femoral arteries. *J Vasc Interv Radiol.* 1995;6:843-849.
3. Mewissen MW. Nitinol stents in the femoropopliteal arterial segment. *Endovasc Today.* 2003;2(4):29-34.
4. SIROCCO II trial, presented at TCT 2004.
5. BLASTER trial, presented at TCT 2004.

Tips and Techniques for Stenting the SFA

Although stenting the SFA has been shown to be a successful, low-risk technique, the skill set of the operator will have a great impact on achieving a successful outcome.

BY GARY M. ANSEL, MD

The natural history of the patient with peripheral vascular disease (PVD) varies with the presenting symptoms. Symptoms in patients with claudication will worsen 45% of the time, but only approximately 5% of the nondiabetic population will face an amputation. However, 5-year mortality will be approximately 29% due to coexistent cardiovascular and cerebrovascular disease. Patients presenting with limb-threatening ischemia experience a mortality risk of approximately 31% at 2 years. The primary goal of any treatment of patients with PVD will be either limb salvage or relief of significant lifestyle-limiting symptoms. At the same time, evaluation and treatment of coexistent cardiovascular and cerebrovascular disease should be completed.

The superficial femoral artery (SFA) has certain unique characteristics that require special consideration when deciding on treatment options. First, occlusive disease in the SFA is the most common cause of limb claudication. Second, the adductor canal area is unique among arterial beds. This location is associated with more calcification, elastic recoil, and subsequently higher rates of disease recurrence after surgical or endovascular treatment. Third, patients with multilevel disease may be effectively treated with upstream stenosis relief. Fourth, what appears to be a focal stenosis on angiography may be underestimated (Figure 1). The true extent of disease that may lead to symptoms can be determined only through further noninvasive duplex examination or with adjunctive evaluation utilizing pressure gradients or intravascular ultrasound.

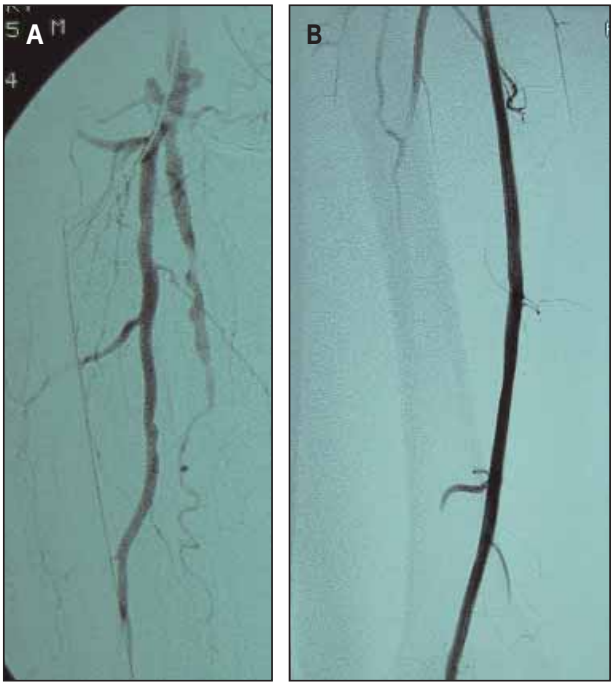


Figure 1. Typical long diffuse SFA disease before (A) and after stenting (B).

"The true extent of disease that may lead to symptoms can be determined only through further noninvasive duplex examination or with adjunctive evaluation utilizing pressure gradients or intravascular ultrasound."

INDICATIONS

Indications for peripheral intervention previously included limb-threatening ischemia (rest pain, nonhealing ulcers, and gangrene) or lifestyle-limiting claudication not able to be controlled by risk factor modification, exercise therapy, or medication. Historically, the best long-term results of endovascular therapy have been found in nonsmoking, nondiabetic patient with short lesions with larger vessels. However, as one might expect, many patients with PVD do not fit this description. Characteristics that increase the risk of invasive treatment include patients with renal insufficiency, cardiac comorbidities, vascular calcification, proximal iliac tortuosity, aneurysmal changes, and previous surgical

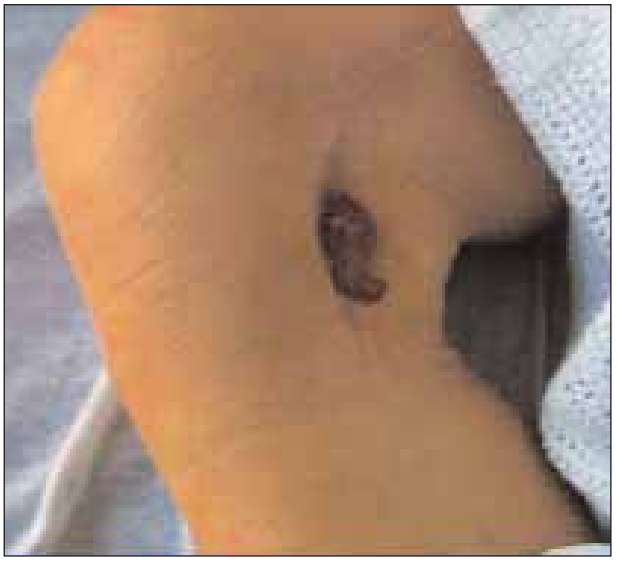


Figure 2. Wound infection is a surgical complication that occurs in an alarming 10% to 30% of cases.

iliofemoral bypass. These risks can be contrasted with the risk of complications associated with surgical therapy. These risks include wound infection (10-30%) (Figure 2), myocardial infarction (1.9-3.4%), early graft failure (0-24%), and operative mortality (1.3-6%).

PROCEDURAL TIPS

Before undertaking endovascular treatment of the SFA, the physician must carefully survey the individual patient characteristics. Vascular access, stenosis characteristics, concomitant iliac disease, contrast risk, technology to be utilized, and radiation exposure (patient and health care team) all must be considered. As previously stated, successful treatment of inflow vascular obstruction should be completed prior to treatment of the SFA disease. As with any interventional procedure, the treating physician should attempt to preserve surgical options whenever possible.

Contralateral vascular access is often the preferred technique for safest hemostasis. The vascular sheath should be of a braided nonkinking design. Optimal sheath placement can often be improved by utilizing fluoroscopy for landmark identification. However, although contralateral access may be safer for the patient, this technique may present higher doses of radiation and cervical spine risk to the health care team. Proper shielding and slave monitors should be of priority.

Other vascular access sites that may be utilized in special circumstances include antegrade femoral, popliteal, and brachial access (rarely). Antegrade access offers improved wire control but postprocedure hemostasis appears to be more problematic. It is also more difficult in an obese patient with an increased risk of both a low puncture site and retroperitoneal hemorrhage. Useful tips to consider during antegrade femoral access include: (1) consider using a micropuncture needle technique, which may reduce local hematoma; (2) use a sheath that is kink resistant; and (3) place a 4-F dilator in errant access before reattempting placement in the common femoral location.

The popliteal access is the "back door" to the SFA and useful for total occlusions that cannot be accessed from above. This artery lies deep in the popliteal fossa in close proximity to both nerve and venous structures. If femoral access is present, the popliteal artery is located with contrast administration. Localization of the popliteal artery is reliably obtained with ultrasound in the laboratory setting.

CROSSING TOTAL OCCLUSIONS

In our experience, total SFA occlusions can be easily crossed utilizing a straight hydrophilic .035-inch guidewire in 80% of cases. Of the remainder, 15% are easily crossed by advancing a looped guidewire with catheter support. The remaining 5% are crossed from the popliteal approach or by utilizing one of the recently available devices designed to cross total occlusions. Once the total occlusion is crossed, a catheter is advanced and intraluminal placement is confirmed with contrast administration. The hydrophilic wire is often exchanged

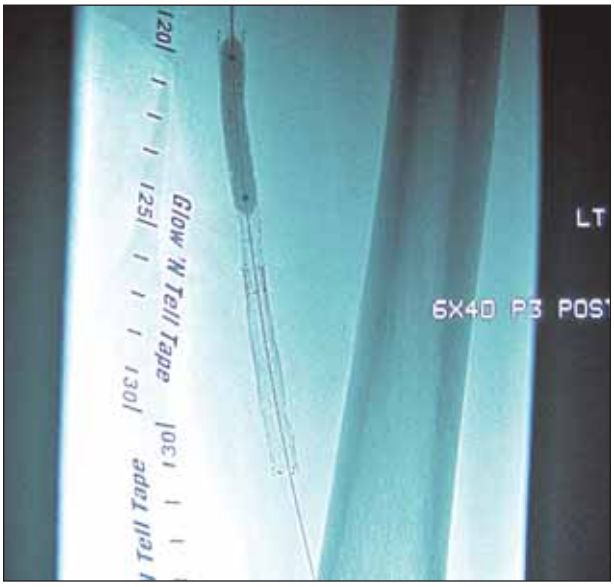


Figure 3. Postdilation of two nitinol stents in the SFA overlapped just slightly.

Figure 4. The LifeStent NT from Edwards Lifesciences.

for a .035-inch torque wire to prevent inadvertent wire perforation.

The experience and skills of the physician operator are just as important as the chosen techniques and technology. With the proper techniques, the operator can achieve successful vessel patency in more than 95% of patients.

STENT TECHNIQUES

Although only one nitinol stent has been approved by the FDA for the treatment of the SFA, research presented at the 2004 Transcatheter Cardiovascular Therapeutics (TCT 04) meeting from both Europe and the US appears to show acceptable efficacy and 2-year durability of some of the nitinol slotted tube stents. With proper technique, most modern stent systems can be placed within a few millimeters of the desired location and these stents are readily seen with modern day fluoroscopy. Most systems are 6-F sheath compatible. With increasing use of hydrophilic-coated outer sheaths, these systems can successfully traverse even severe iliac tortuosity. Predilation of the arterial stenosis is usually recommended. This allows for proper sizing of the stent as well as making sure that calcified lesions can be successfully predilated before stent placement. The stents are commonly sized at a 1.0-1.1 ratio, that is a 6-mm-diameter nitinol stent is placed in a 5.5- to 6-mm vessel. Proper sizing may be important to decrease metal fatigue. Significant oversizing of the stent may lead to constant strut pressure and theoretically fracture.

Self-expanding stents are constrained by an outer sheath. During retraction of the sheath, it is common for the constrained stent to advance. The outer sheath should be removed slowly to allow for adjustment before the stent opens and contacts the arterial wall. Pushing or pulling the stent delivery device may lead to stent deformation.

Theoretically, it appears to be beneficial to try and use as few stents as possible. However, most SFA lesions are long, and overlapping stents are frequently necessary. It is our practice to overlap minimally (approximately 5 mm) (Figure 3). The entire lesion should be covered by the stent, and it is our practice to not dilate the ends of the stent.

The variable lengths and characteristics of the different nitinol stents may play a role in deciding what type to place in different areas of the SFA. New stents, such as the LifeStent NT (Edwards Lifesciences LLC, Irvine, CA) have added significant flexibility to this technology (Figure 4), which hopefully will translate to even better results. Thrombolysis may be beneficial if there has been a recent change in symptoms or the lesion appears to be very soft.

After the procedure, the patient is commonly treated with long-term aspirin therapy. Many operators utilize clopidogrel for a few months, although the data are lacking. Duplex follow-up is an important adjunct. With this approach, assisted patency at 1 to 2 years can be very high, with associated improvement in functional status.

SUMMARY

Endovascular therapy of the SFA offers a low-risk technique for treating symptomatic PVD. The skill set and experience of the endovascular physician is a significant factor in determining success and safety. Public awareness and patient education are important. Patients must be better informed about the seriousness of their diagnosis from a cardiac standpoint, as well as the various treatment options. With regular surveillance and postprocedural follow-up, endovascular therapy in the SFA can lead to improved quality of life for this patient population. ■

Gary M. Ansel, MD, is Clinical Director for Peripheral Vascular Intervention, MidOhio Cardiology and Vascular Consultants, MidWest Research Foundation, Riverside Methodist Hospital, Columbus, Ohio. He may be reached at (614) 262-6772; gansel@mocvc.com.

The RESILIENT Trial

An overview of the trial to investigate the safety and efficacy of the Edwards LifeStent NT Self-Expanding Stent and Delivery System in the SFA and proximal popliteal artery.

BY BARRY T. KATZEN, MD

As balloon and delivery catheter technology evolved over the years, percutaneous transluminal angioplasty (PTA) became the mainstay of infrainguinal peripheral vascular interventional procedures. A survey of published literature (1986-2003) regarding the use of PTA in the superficial femoral artery (SFA), showed that chronic reintervention rates after PTA ranged from 12%[1] to 33%.[2] Acute failures associated with PTA procedures can exceed 25%,[3] with acute stent implantation being performed at a rate of 16%.[4]

Low long-term patency and high acute failure rates after angioplasty alone have led Edwards Lifesciences LLC (Irvine, CA) to initiate a prospective randomized trial to investigate the safety and efficacy of the LifeStent NT Self-Expanding Stent and Delivery System in the SFA and proximal popliteal artery.

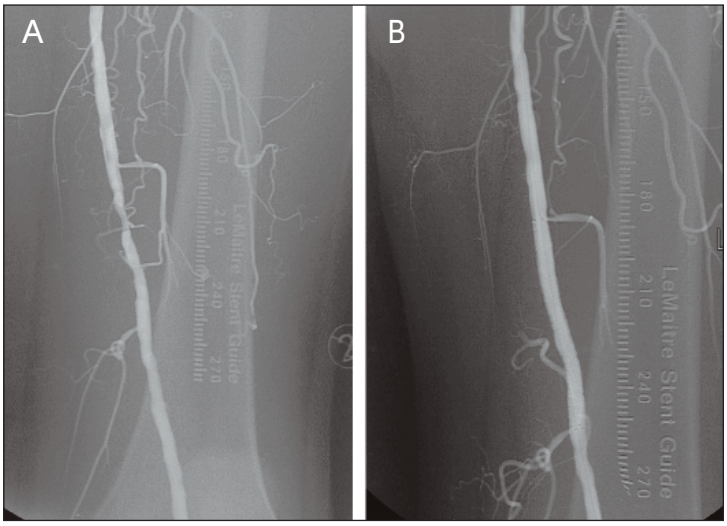


Figure 1. Left SFA angiogram showing high-grade stenosis pre-treatment (A). Completion angiogram following PTA and LifeStent NT placement (B). (Images courtesy of John R. Laird, MD).

THE RESILIENT TRIAL

RESILIENT is a prospective, multicenter trial of angioplasty alone versus angioplasty plus stenting in patients with peripheral vascular disease in the SFA and proximal popliteal artery. This is the first randomized trial of PTA versus stenting using new self-expanding, nitinol mesh stent technology, and should answer important questions about the value of SFA intervention with nitinol mesh stents versus PTA alone. The co-Principal Investigators of the RESILIENT trial include the author and John R. Laird, Jr, MD, co-Director of Vascular Care at the Washington Hospital Center in Washington, DC.

Patients enrolled in the RESILIENT trial have occlusions/stenosis ≤150 mm. The first RESILIENT patient was enrolled in July 2004 and enrollment will continue until a total of more than 200 patients are enrolled.

RESILIENT is a multicenter trial with up to 25 sites participating. Clinical follow-up occurs at 30 days, 6 months, 12 months, and annually for a maximum of 3 years.

Safety endpoints for the study include periprocedural death, stroke, myocardial infarction, emergent surgical revascularization, significant distal embolization in the target limb, and thrombosis in the target vessel. Efficacy endpoints for the study include vessel patency and target lesion/vessel revascularization (TLR/TVR).

While it is too early to discuss results, all investigators in the trial are excited about the potential of RESILIENT to answer important clinical questions regarding endovascular therapy of the SFA. ■

Barry T. Katzen, MD, is the Founder and Medical Director of Baptist Cardiac & Vascular Institute, an affiliate of Baptist Health Systems of South Florida; and Clinical Professor of Radiology at the University of Miami School of Medicine in Miami, Florida. Dr. Katzen may be reached at (786) 596-5990; btkatzen@aol.com.

1. Hewes RC, White RI Jr, Murray RR Jr, et al. Long-term results of superficial femoral artery angioplasty. *AJR.* 1986;146:1025-1029.
2. Jämsén TS, Manninen HI, et al. Long-term outcome of patients with claudication after balloon angioplasty of the femoropopliteal arteries. *Radiology.* 2002;225:345-352.
3. Soder HK, Manninen HI, Rasanen HT. Failure of prolonged dilation to improve long-term patency of femoropopliteal artery angioplasty: results of a prospective trial. *J Vasc Intervent Radiol.* 2002;13:361.
4. Schillinger M, Mlekusch W, Haumer M, et al. Angioplasty and elective stenting of de novo versus recurrent femoropopliteal lesions: 1-year follow-up. *J Endovasc Ther.* 2003;10:288-297.

Therapeutic Angiogenesis for PAD

An overview of the current status of, and future approaches to, treating PAD.

BY BRIAN H. ANNEX, MD

In treating peripheral artery disease (PAD), the goal of all therapies (pharmacological, physical exercise, surgical, and interventional) is to modify the underlying pathologic etiologies. These therapies do not increase blood flow to the ischemic limb. In selected patients, surgery and stenting can open obstructive atherosclerosis. There is now evidence that a new medical approach—therapeutic angiogenesis—may also address serious consequences of PAD.

ANGIOGENESIS

Angiogenesis is the growth and proliferation of new blood vessels from pre-existing vascular structures. In patients with PAD, blood flow to the limb(s) is reduced.

Therapeutic angiogenesis seeks to promote the growth of new normal blood vessels for the treatment of disorders of inadequate tissue perfusion. Vascular endothelial growth factor (VEGF) is one of many angiogenic growth factors. Despite the wide range of options, clinical trials completed to date have typically utilized a single cytokine growth factor such as VEGF. Even single factors have additional complexity, including VEGF, which exists in multiple isoforms.

EW-A-401

Edwards Lifesciences LLC (Irvine, CA) and Sangamo BioSciences (Redfield, CA) have collaborated during the past 4 years to develop EW-A-401, a therapeutic compound that encodes a zinc finger DNA-binding protein transcription factor (ZFP TF) designed to uniquely activate all isoforms of the VEGF-A gene to stimulate angiogenesis. ZFP is an engineered protein that permits it to interact with DNA binding sites. The fold is created by the binding of specific amino acids. Zinc finger proteins regulate the expression of multiple genes. The ZFP works upstream, causing expression of VEGF in naturally occurring proportions. One of the potential advantages of this process is that the ZFP regulates the endogenous VEGF and all the natural splice variants. In preclinical studies, EW-A-401 was shown to be effective in stimulating growth of functionally normal vessels and increasing blood flow in ischemic limbs.

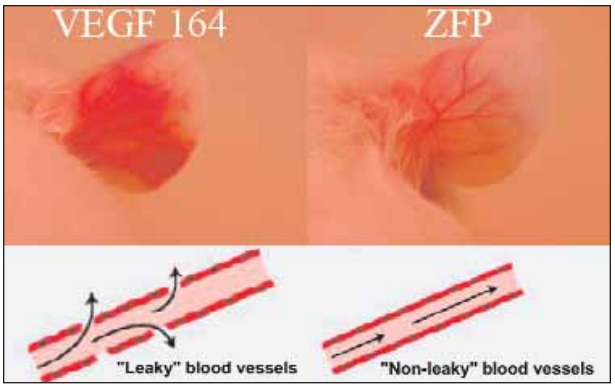


Figure 1. VEGF exists in multiple isoforms and the ZFP (right panel) leads to angiogenesis without producing leaky vessels that are produced when one isoform is used (left panel).

CLINICAL TRIALS

The first clinical trials of therapeutic angiogenesis in critical limb ischemia (CLI) were conducted by Jeffrey M. Isner, MD, and colleagues using IM Plasmid VEGF165 and IM Plasmid VEGF-2.

Subsequent trials in the US include the Genzyme Corporation (Cambridge, MA) study of intramuscular adeno-HIF-1α, which has completed phase I, and Aventis GenCell (Hayward, CA) trials with intramuscularly plasmid aFGF, now in phase II with completion expected this year (almost exclusively with Rutherford V), the Edwards Lifesciences (Irvine, CA) NIH-sponsored trial utilizing ZFP-VEGF in PAD that recently enrolled the first patient, and finally Ges MG (Osaka, Japan) is starting a 100-patient phase I/II Rutherford IV and V trial using intramuscular plasmid HGF.

A survey of the five placebo-controlled trials (VIVA, FIRST, AGENT, TRAFFIC, and RAVE) that have been instituted to study the actuality and efficacy of therapeutic angiogenesis indicate that there is promise for this approach, but more research is needed to understand the unique behavior and characteristics of various growth factors and the most effective dosage levels (Table 1).

TABLE 1. HUMAN CLINICAL TRIALS IN THERAPEUTIC ANGIOGENESIS

Trial	Sponsor	Factor-Form	Disease	Journal	Result
VIVA	Genentech, Inc.	VEGF165-pr	CAD	*Circulation* 2003	No difference vs placebo
FIRST	Chiron Corp.	bFGF-pr	CAD	*Circulation* 2002	No difference vs placebo
AGENT	Shering AG Collateral Therapeutics, Inc.	FGF4-Ad	CAD	*Circulation* 2002	No difference vs placebo
TRAFFIC	Chiron Corp.	bFGF-pr	PAD	*Lancet* 2002	Increase PWT bFGF at Day 90 (not 180)
RAVE	GenVec, Inc.	VEGF121-Ad	PAD	*Circulation* 2003	No difference vs placebo Dose dependent edema
	Genzyme Corp.	adeno-HIF-1α	PAD	N/A	TBD
	Aventis GenCell	aFGF	PAD	N/A	TBD
	AnGes MG	HGF	PAD	N/A	TBD
NIH-ZFP	Edwards Lifesciences	ZFP-VEGF	PAD	N/A	TBD

CAD, coronary artery disease; PAD, peripheral artery disease; TBD, to be determined.

VIVA

The VIVA Trial (Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis) is a double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of intracoronary and intravenous infusions of rhVEGF in 178 patients with stable exertional angina who were unsuitable for standard revascularization. Although the primary endpoint was negative, it is notable that the use of high doses of rhVEGF resulted in significant improvement in angina, angina frequency, and patient exercise treadmill tests.[4]

RAVE

The RAVE Trial (Regional Angiogenesis With Vascular Endothelial Growth Factor in Peripheral Arterial Disease) was a phase II randomized, double-blind, controlled study of safety and effectiveness of adenoviral delivery of vascular endothelial growth factor 121 in 105 patients with severe, disabling intermittent claudication from PAD. RAVE concluded that a single unilateral intramuscular administration of AdVEGF121 was not associated with improved treadmill exercise performance or quality of life over placebo, and could not support this VEGF therapy as a strategy for treatment of unilateral PAD.[5]

FIRST

The FGF Initiating RevaScularization Trial (FIRST) evaluated the efficacy and safety of recombinant human fibroblast growth factor FGF2 (rFGF2). FIRST was a multicenter, randomized, double-blind, placebo-controlled trial of a single-bolus intracoronary administration of rFGF2 at 0, 0.3, 3, or 30 µg/kg in 337 patients. Infusion of FGF2 was shown to improve symptoms at 90 days, but not 180, but there was no improvement in exercise tolerance or myocardial perfusion.[6]

AGENT

The Angiogenic Gene Therapy (AGENT) Trial evaluated the safety and anti-ischemic effects of five ascending doses of Ad5-FGF4 compared with a smaller number of placebo controls in 79 patients with chronic stable angina (exertional chest pain) pectoris angina and to select potentially safe and effective doses for subsequent study. The study was inaugurated to progress on the discovery that angiogenic response to myocardial ischemia can be augmented in animal models by gene transfer with the use of a replication defective adenovirus (Ad) containing a human fibroblast growth factor gene. Patients receiving Ad5FGF4 showed trends toward improved exercise times compared to the placebo group. There were no adverse effects. The investigators concluded that there was evidence of favorable anti-ischemic effects with Ad5-FGF4 compared with placebo and that angiogenic gene transfer with Ad5-FGF4 shows promise as a new, safe therapeutic approach to the treatment of angina pectoris.[7]

TRAFFIC

The Therapeutic Angiogenesis With Recombinant Fibroblast Growth-Factor 2 (TRAFFIC) study investigated whether infusion of intra-arterial rFGF-2 improved exercise capacity in 190 patients with moderate-to-severe intermittent claudication. In this study, peak walking times were improved for patients given a single dose and less for those administered with a double dose versus the placebo group. Adverse events were similar in all groups. Intra-arterial rFGF-2 resulted in a significant increase in peak walking time at 90 days; repeat infusion at 30 days was no better than one infusion. The investigators concluded that TRAFFIC showed evidence of clinical therapeutic angiogenesis by intra-arterial infusion of an angiogenic protein.[8]

FUTURE APPROACHES

There is evidence that therapeutic angiogenesis stimulated by VEGF-ZFP may have an effective role with a micro-level approach to re-establishing perfusion to the damaged tissue in PAD. A study by Sangamo Biosciences,[9] determined for the first time that local delivery of an engineered plasmid encoding a VEGF-ZFP induces angiogenesis.

To demonstrate the ability to promote therapeutic angiogenesis *in vivo*, we studied a preclinical model of hindlimb ischemia. This approach enhanced angiogenesis, increased proliferation, reduced apoptosis, and improved blood flow (both early and late).

Further encouraging evidence was presented in a separate contemporaneous Sangamo study[10] that demonstrated excellent results in the vasculature of mice ears (Figure 1). The investigators noted that this "clinically relevant setting" largely circumvented previously observed difficulties with hyperpermeability, producing creation of nonleaky blood vessels and an overall functional vasculature. It was further noted that expression of the new ZFPs *in vivo* led to induced expression of the protein VEGF-A, stimulation of angiogenesis, and acceleration of experimental wound healing. In addition, the neovasculature resulting from ZFP-induced expression of VEGF-A was not hyperpermeable as was that produced by expression of murine VEGF-A164 cDNA. It was concluded that the data establish, for the first time, that specifically designed transcription factors can regulate an endogenous gene *in vivo* and evoke a potentially therapeutic biophysiologic effect.

HUMAN TRIALS WITH ZFP-VEGF

A phase I/II IND clinical trial was initiated in 2004 with Robert Lederman, MD, as Principal Investigator at the National Institutes of Health. This trial is a placebo-controlled, double-blind study using dose escalation of 1.9, 60, 19, and 60 mg DNA administered intramuscularly through a single lower limb, with a primary safety period of 30 days. Efficacy will be explored through measurements of peak walking time, claudication onset time, ankle-brachial index, muscle biopsy, and local and regional blood flow. Additional studies with the ZFP-VEGF are currently being planned.

CONCLUSIONS

In PAD, a large number of patients have multilevel disease, and a sizeable fraction have total occlusion. Coronary stenting has shown that intimal hyperplasia is the major cause of restenosis, but in peripheral circulation below the inguinal ligament other factors may lead to reocclusion and restenosis.

It is necessary to distinguish between intermittent claudication and CLI; they are different diseases requiring different approaches. Ultimately, angiogenesis may be effective on outflow vessels and serve as adjunctive therapy to large vessel revascularization.

PAD is the preferable route for development of angiogenesis agents because the peripherals afford opportunity to perform studies of dosing and location of disease that is not as easily accomplished in coronary artery disease. There is no complex technology required, and there are numerous opportunities for imaging.

Although challenges remain, particularly in patient selection and trial design, many opportunities exist for both stand-alone and adjunctive therapies. Multiple new factors and approaches are on the horizon. With new trials, novel factors and approaches, new targets and cell therapy, therapeutic angiogenesis has the potential to revolutionize therapies and improve perfusion in patients with PAD. ■

Brian H. Annex, MD, is an Associate Professor of Medicine and Director, Therapeutic Angiogenesis Research Program, Duke University Medical Center, Durham, North Carolina. Dr. Annex may be reached at annex001@mc.duke.edu.

Contact information: The NIH-ZFP trial is currently enrolling patients. As an NIH-sponsored trial, all patient healthcare costs and associated travel expenses are paid by the NIH. For additional information on inclusion/exclusion criteria, or to refer patients for screening, please contact Robert J. Lederman, MD, Director, Cardiovascular Intervention, National Heart, Lung, and Blood Institute, Bethesda, Maryland; (301) 402-6769; lederman@nih.gov.

1. Henry T, Annex BH, et al for the VIVA Investigators. Vascular endothelial growth factor in ischemia for vascular angiogenesis. *Circulation.* 2003;107:1359-1365.
2. Rajagopalan S, Annex B, et al on behalf of the RAVE investigators. RAVE: Regional Angiogenesis With Vascular Endothelial Growth Factor in peripheral arterial disease. *Circulation.* 2003;108:1933-1938.
3. Simons M, Annex BH, et al. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2. *Circulation.* 2002;105:788-793.
4. Grines C, Watkins MW, et al. Angiogenic Gene Therapy (AGENT) Trial in patients with stable angina pectoris. *Circulation.* 2002;105:1291-1297.
5. Lederman RJ, Annex BH, et al for the TRAFFIC investigators. Therapeutic angiogenesis with recombinant fibroblast growth-factor 2 for intermittent claudication (the TRAFFIC study): a randomized trial. *Lancet.* 2002;359:2053.
6. Pasqualini R, Barbas III CF, Arap W. Vessel maneuvers: zinc fingers promote angiogenesis. *Nature Med.* 2002;8:1353-1354.
7. Dai Q, Huang J, Klitzman B, et al. An engineered zinc finger activating vascular endothelial growth factor (ZFP-VEGF) transcription factor plasmid DNA induces therapeutic angiogenesis in rabbits with hind-limb ischemia. *Circulation.* 2004; in press.
8. Rebar EJ, Huang Y, et al. Induction of angiogenesis in a mouse model using engineered transcription factors. *Nature.* 2002;8:1427-1432.

Endovascular TODAY