Despite continued advancements in revascularization using both open surgical and endovascular techniques, peripheral arterial disease (PAD) as a cause for chronic ulceration remains a highly morbid diagnosis. The natural history of PAD rivals many forms of cancer, with a 5-year mortality rate of 50%. Patient outcomes can be predicted based on their ankle-brachial index (ABI) at presentation. Those with critical limb ischemia (CLI) with symptoms including rest pain, ulceration, or gangrene have the lowest ABI—usually <0.4—and carry an annual mortality rate of 20%. The risk of limb loss, persistent disability, and poor quality of life are more the rule than the exception for these CLI patients.

Ulcer healing rates have been incompletely studied, but Marston et al showed a 52% healing rate at 12 months in ulceration patients treated medically without revascularization. Open revascularization probably improves upon the healing rate at 12 months (75%), but 19% of patients may lose ambulation status, and 5% will lose independent living status.

The location of the devitalized tissue also affects amputation risk, healing potential, and quality of life. Dosluoglu et al confirmed we anecdotally know that necrotic heel ulcerations do poorly, and that even with revascularization, the short- and long-term amputation risk is significant. The patients who are at greatest risk are medically debilitated from a nutritional standpoint, nonambulatory, and/or with end-stage renal disease.

As vascular physicians, it is imperative to recognize the diagnosis of PAD and specifically CLI as the cause of chronic ulceration. Often, poor circulation is complicated by peripheral neuropathy, poor skin nutrition, and hygiene. A multidisciplinary approach is required to maximize wound healing. At our wound care institution, we use a three-pronged approach of:

1. Noninvasive assessment of the arterial circulation
2. Revascularization when clinically able based on anatomy and surgical risk
3. Aggressive local wound care both before and after revascularization

These measures, in addition to controlling patients’...
medical comorbidities and maximizing their nutrition-al status, give the greatest chance for wound healing, limb salvage, maintenance of independence, and over-all survival.5

NONINVASIVE METHODS OF ASSESSING CIRCULATION

Multiple noninvasive modalities exist to predict successful wound healing in the face of PAD by assessing the quality of tissue oxygenation surrounding the wound. These serve as a guide for wound therapy and assist the physician in determining which patients may or may not require revascularization. Important patient factors that also affect the decision to revascularize include ambulation status, mental status, presence of chronic kidney disease, and the extent and location of necrosis. Bedridden, patients with dementia are best served with primary amputation and do not require noninvasive testing. Noninvasive arterial testing should be performed in all other cases aiding in the objective evaluation of the need for revascularization.

Arterial testing modalities can be subdivided into two groups (Table 1):

(1) Assessment of macrocirculation
   • ABI and segmental systolic pressures

(2) Assessment of microcirculation
   • Toe-brachial index (TBI), skin perfusion pressures, transcutaneous oxygen levels, or transcutaneous carbon dioxide levels

According to the 2007 Trans-Atlantic Inter-Society Consensus (TASC II) document, it is generally accepted that multilevel disease of the macrocirculation is the major determinant for the development of CLI; however, disruption in the microcirculation leads to failure of wound healing despite correction of their macrocirculatory disease.1 For this reason, the noninvasive assessments of microcirculation have emerged as useful tools predicting healing potential. At our wound center, we obtain toe pressures upon initial evaluation to assess microcirculation of the ischemic ulcer patient. Also, further investigation of the microcirculation is helpful after revascularization or to further evaluate any nonhealing wound.

TBI and Evaluation of Photoplethysmography Waveform

The ABI is obtained by comparing the highest ankle pressure at the anterior tibial, peroneal, or posterior tibial artery with the highest brachial artery Doppler pressure. This ratio when normal is 1, and it is markedly diminished in CLI patients (usually <0.4).

Calciﬁed tibial arteries can lead to false elevation of the ABI, limiting the utility of this measurement, particularly in diabetics and hemodialysis-dependent patients. The TBI is obtained by comparing the great toe pressure (obtained with photoplethysmography [PPG]) to the highest brachial pressure obtained with Doppler ultrasound. Digital arteries are rarely calciﬁed, and thus the TBI provides a reliable marker of perfusion and healing. A normal TBI is considered 0.7 or higher. CLI is deﬁned by TASC II criteria as a toe pressure <30 mm Hg or <50 mm Hg in a patient with active gangrene or ulceration.1 In patients with extensive tissue loss or amputation of the great toe, the second toe can be used for TBI. The toe pressure measurement has been shown to be superior to either the absolute ankle pressure or transcutaneous oxygen level for identifying CLI and predicting the course of disease.6 Skin perfusion pressure has been shown to be equivalent to toe pressure measurement in predicting the healing rate of ischemic ulcerations.7

The shape and amplitude of the toe PPG waveform also predicts wound healing and is complimentary to the standard TBI measurement. Pulse wave amplitude <4 mm has been associated with the presence of rest pain and ulcerations with a stronger odds ratio than an absolute toe pressure of <30 mm Hg alone.8 Also, in patients with CLI, reduced toe pulse wave amplitude of <4 mm has been associated with an increased risk of amputation as well as all-cause mortality.9 Further pulse wave analysis, such as pulse delay, amplitude reduction, and waveform asymmetry, accurately identiﬁes signiﬁcant PAD. Pulse wave analysis was found to be concurrent with ABI ﬁndings 90% of the time and 100% sensitive for detecting high-grade stenoses. Of the parameters studied, pulse wave delay showed the greatest accuracy.10,11

| TABLE 1. NONINVASIVE ARTERIAL TESTING VALUES SUGGESTING INABILITY TO HEAL |
|-----------------------------|-----------------------------|
| **Macrocirculation**        | **Microcirculation**        |
| • ABI <0.4                  | • Toe systolic pressure <30 mm Hg |
| • Ankle systolic pressure <50 mm Hg | • Pulse wave amplitude <4 mm |
|                            | • Skin perfusion pressure (SPP) <40 mm Hg |
|                            | • Transcutaneous oxygen <10 mm Hg |
|                            | • Transcutaneous carbon dioxide >100 mm Hg |
|                            | • Capillary density <20 mm² |
Skin Perfusion Pressure

The measurement of SPP was first introduced in 1967. Since that time, three modalities of determining SPP have evolved, all of which measure the exact pressure above which skin blood flow ceases when compressed externally. Radioisotope clearance relies on isotope washout with cuff deflation, whereas PPG monitoring detects resumption of pulsatile flow, and laser Doppler detects red blood cell flow as cuff pressure decreases. A SPP of >40 mm Hg is considered adequate for wound healing.12

A recent study compared SPP to ankle pressure, toe pressure, and transcutaneous oxygen pressure. Using a laser Doppler and 5.8-cm cuff to obtain SPP on the dorsum of the foot showed an independent ability to predict wound healing, without the limitations of tibial artery calcification or previous great toe amputation. The study also showed a strong positive predictive value when combining an SPP >40 mm Hg with a TBI of >30 mm Hg.13

Transcutaneous Measures of Oxygen and Carbon Dioxide Pressures

Transcutaneous oxygen pressure (TcO2) measurements are also a well-documented method of assessing tissue perfusion with a cutoff value of <10 mm Hg, suggesting CLI. TcO2 measurements can be affected by leg edema as well as positioning of the limb during testing.6 These variables have challenged the reproducibility and reliability of measuring TcO2. Despite these difficulties, Ubbnick et al noted that TcO2 coupled with capillary density and laser Doppler perfusion measurement were an accurate prediction for the level of amputation to heal.14 In this study, a TcO2 of <10 mm Hg correlated to 1-year limb survival rates of 15%, whereas there was 88% limb survival with TcO2 of >30 mm Hg. The TASC II document also supports TcO2 as a means to assess microcirculation in patients with CLI.1

Transcutaneous carbon dioxide (TcCO2) tension has also been recently reported to be a predictor of wound healing. This study revealed a clinically significant difference between TcCO2 levels in patients with CLI as defined by other standard noninvasive measures including ankle and toe pressures, SPP, and TcO2. A cutoff value of TcCO2 >100 mm Hg was used to define CLI.15

LOCAL WOUND CARE IN THE FACE OF CLI
The DIME Method for Systematic Wound Care

In addition to identifying and addressing vascular insufficiency as the driving force of ischemic ulcerations, we have found using a systematic approach to local wound care minimizes wound-healing time. A helpful wound care pneumonic for management of any chronic wound is DIME: debridement, infection, moisture control, and edge.

Debridement of ischemic wounds should be avoided before revascularization. It is more favorable to maintain a dry wound bed and to minimize the bacterial load by daily washes with either povidone-iodine or chlorhexidine. After revascularization, debridement of slough and eschar is vitally important to stimulate wound healing by removing a bacterial haven for growth. Regular debridement reduces the necrotic burden and bacterial load and slows the production of inflammatory cytokines and matrix metalloproteinases.16 Although debridement can be performed by surgical, enzymatic, autolytic, and mechanical means, we most commonly use serial surgical debridement (Figure 1).17 This is particularly important after revascularization.

Infection is a well-known hindrance to wound healing. It should be evaluated when there is a delay in wound healing despite revascularization. Any patient who develops acute changes in pain or exudate should be seen promptly and undergo appropriate testing for active infection. Infection before revascularization is uncommon given that the arterial flow is inadequate to support bacteria growth, just as it is inadequate to maintain tissue health. Following revascularization, the re-establishment of tissue oxygenation to devitalized tissue predisposes to infection. Wound care products that promote antimicrobial activity by ionic silver, iodine, or medical-grade honey provide a reasonable topical agent.

Maintaining a moist wound bed is imperative to proliferation of granulation tissue. Technological advances in wound care products offer the patient more than the traditional wet-to-dry dressing. Calcium alginites and, to a lesser extent, collagens help to wick away wound exudate while maintaining an ideal level of moisture. There is also a large variety of foam dressings and wound fillers that have large absorptive capacities. On the other hand, desiccated wounds benefit from the moisture provided by hydrogel dressings (Table 2).

The final concept in the DIME acronym is that of the wound edge and alludes to use of advanced wound care products. They should be considered only after the aforementioned wound care objectives are maximized. Skin substitutes are the most common of the advanced wound products used in our office. Multiple choices exist including dermal acellular con-
structs, dermal cellular constructs (approved at this time for diabetic foot wound use only), and composite cellular constructs that are composed of both an epidermal and dermal layer of bioengineered human skin equivalent. Although expensive, human skin equivalents have proven overall cost effectiveness in reducing time to healing and avoidance of amputation.18,19

Another commonly utilized advanced wound product is topical platelet-derived growth factor; however, efficacy and cost-effectiveness data are mixed.20

**TABLE 2. PROPERTIES OF WOUND CARE PRODUCTS FOR TREATING ISCHEMIC ULCERATIONS**

<table>
<thead>
<tr>
<th>Product Class</th>
<th>Enhances Debridement</th>
<th>Stimulates Granulation</th>
<th>Absorbancy (+++++)</th>
<th>Available With Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginates</td>
<td>+</td>
<td>+</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Collagens</td>
<td>+</td>
<td>+</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>Foams</td>
<td>+</td>
<td>+</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>Hydrogels</td>
<td>+</td>
<td>+</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>Wound fillers</td>
<td>+</td>
<td>+</td>
<td>+++++</td>
<td>+</td>
</tr>
</tbody>
</table>

**Improving Microcirculation When Revascularization Options Are Exhausted**

There remains a sizable portion of the CLI population that either has no revascularization option or those who despite revascularization have suboptimal
improvement in the microcirculation and thus continued delayed wound healing. The 142-patient database compiled by Marston et al at the University of North Carolina followed ischemic ulcer patients through conservative therapy much like that outlined by the DIME pneumonic. They found that, although slow, there was wound healing in 52% of patients at the 1-year interval. The amputation rate was 23% overall, but not all patients in the database met the noninvasive lab criteria for CLI.

Several emerging therapies offer the potential to further improve wound healing rates in patients with persistent microcirculatory deficits. Use of intermittent pneumatic compression shows promise in improving wound healing and measurable improvements in microcirculation. A recent retrospective study of CLI patients revealed an increase in wound healing from 17% in the control group versus 58% when intermittent pneumatic compression was added to maximal medical management and local wound care. Spinal cord stimulation has been proposed as a treatment for CLI to both control pain and for wound healing; however, the data have been mixed. Klomp et al reviewed five randomized controlled trials on SCS and were unable to determine clinically significant success in the SCS groups over best medical treatment. Hyperbaric oxygen therapy, although seemingly ideal for CLI due to the ability to raise TcO2, has yet to show clinically significant benefit in patient populations other than diabetic foot ulcers, whereas hyperbaric oxygen therapy is recommended as adjunctive therapy for Wagner stage III and IV ulcerations.

**SUMMARY**

Clearly, healing a wound in the face of CLI stretches far beyond the angiography suite or operating room. A multidisciplinary approach involving noninvasive assessment of wound healing followed by prompt revascularization when possible and aggressive wound care are all necessary for successful patient outcomes. At our institution, we expedite care by using a systematic approach to each patient and by combining a broad physician specialty base to include vascular surgeons, vascular internists, and general surgeons in caring for our patients. Just as the world of revascularization is quickly advancing, so is that of local wound care. Better understanding of microcirculation is needed in order to further supplement revascularization and ultimately yield better success in healing wounds in the face of CLI.

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