Negative Pressure Wound Therapy and Other New Therapies for Diabetic Foot Ulceration

The Current State of Play

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KEYWORDS
- Negative pressure wound therapy
- Wound chemotherapy
- Diabetic foot ulcer
- Theragnostics

KEY POINTS
- An interdisciplinary team approach to limb salvage, combined with a vertical and horizontal strategy for wound healing, may reduce complexity and complications.
- Negative pressure wound therapy (NPWT) continues to be a critical tool in amputation prevention efforts throughout the world, and its indications clearly extend beyond diabetic foot ulcers.
- Fluid instillation with NPWT, otherwise known as “wound chemotherapy,” and ultraportable wound care system show tremendous promise.
- Beyond NPWT, the future of wound healing will rely heavily on theragnostics—tools and techniques that can help to quantify key parameters to rapidly direct therapy.

INTRODUCTION

Diabetes now affects more than 371 million people worldwide, with $471 billion spent in 2012 on diabetes-related health care.1 In 2012, 4.8 million people worldwide died of diabetes, of which half were younger than 60 years.¹ In the United States, 25.8 million people are now living with diabetes, representing 8.3% of the population, and 1.9 million new cases were reported in 2010.²

Up to 25% of people with diabetes will develop a foot ulcer at some point during their lifetime,³ with half developing infection and requiring hospitalization, and 1 in 5

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requiring amputation. Remarkably, care of the lower extremity occupies up to one-third of the total direct costs for diabetes. When compared with funded research and development as a total of overall federal diabetes research and development, this constitutes more than a 600-fold gap.

In 2006, more than 65,700 lower limb amputations were performed in people with diabetes in the United States alone, and people with a history of a diabetic foot ulcer have a 40% greater 10-year mortality rate than patients with diabetes without a foot ulcer. Of the people who undergo a major amputation, 20% to 50% will have their other limb amputated in 1 to 3 years, and greater than 50% will require an amputation in 5 years. After an amputation, the mortality ranges from 13% to 40% at 1 year, 35% to 65% at 3 years, and 39% to 80% at 5 years, which is clearly worse than for most malignancies.

When considering the overwhelming statistics, and the rising costs associated with diabetes, the need to develop a standardized protocol for management of the diabetic foot is critical. An interdisciplinary team approach, with members comprising primary care physicians, podiatric surgeons, vascular surgeons, orthopedic surgeons, plastic surgeons, infectious disease specialists, diabetologists, general surgeons, and pedorthist/prosthetists, has been shown to lower rates of amputation and complications in patients with diabetic foot ulcers.

Newer, more advanced wound care modalities have also emerged as a critical tool in limb salvage, along with a combined vertical and horizontal approach to wound healing. The vertical strategy for wound healing refers to covering important structures and filling defects with negative pressure wound therapy (NPWT), whereas the horizontal strategy uses skin grafting, bioengineered skin substitutes, and aggressive offloading.

**NPWT: MECHANISM OF ACTION**

NPWT involves the application of local subatmospheric pressure to a defect. This technique generally involves a wound interface, such as open-celled foam or gauze. This interface is connected to a pump of some type. The factors related to the effectiveness of NPWT are postulated to be multifold. It has been shown to decrease wound margins and promote granulation tissue formation and perfusion. It also serves to maintain a moist wound-healing environment. When a wound bed is moist, the lateral voltage gradient is maintained, and a greater potential exists for wound healing. Mechanical stimulation of a wound by NPWT contributes to improved wound healing through macrostrain and microstrain properties.

As NPWT is applied, the wound bed is subjected to a negative, deforming force that stretches individual cells and results in increased cell proliferation, fibroblast migration, and angiogenesis. In 2004, Saxena and colleagues reported that the V.A.C. Therapy system (Kinetic Concepts, Inc., San Antonio, TX, USA) was able to produce strains in vitro that were consistent with the levels needed for promoting cellular proliferation. The role of micromechanical forces in the induction of cell proliferation and division have been investigated with respect to the use of tissue expanders for reconstructive plastic surgery and distraction osteogenesis for bone lengthening.

The closed negative pressure system created by NPWT also facilitates the removal of exudate and infectious materials in a controlled manner. Wounds with excessive exudate have been shown to contain an increased number of matrix metalloproteinases (MMPs), which degrade the adhesion proteins necessary for wound repair. Furthermore, increased interstitial pressures can occlude the surrounding
microvasculature and lymphatics, which deprive tissue of vital nutrients and oxygen.\textsuperscript{16,19} Morykwas and colleagues\textsuperscript{20} reported a significant reduction in the number of organisms between days 4 \((10^8)\) and 5 \((10^5)\), in wounds undergoing treatment with NPWT. However, in a retrospective review of 25 patients, Weed and colleagues\textsuperscript{21} actually found an increase in the bacterial bioburden of 43\% of wounds treated with NPWT.

**CURRENTLY AVAILABLE NPWT DEVICES**

Several devices now exist that allow for the safe and effective delivery of NPWT. The most widely used system is the vacuum-assisted closure device, V.A.C. Therapy, which consists of a reticulated, open-cell foam, covered with a semipermeable adhesive drape, and connected to a negative pressure therapy unit via evacuation tubing. The types of foam used with NPWT have evolved over the years, and are now available in several varieties.\textsuperscript{13–15}

The traditional black-colored V.A.C. GranuFoam is made of a porous \((400–600 \mu m)\), relatively hydrophobic, polyurethane ether, whereas V.A.C. GranuFoam Silver has micro-bonded metallic silver impregnated into the foam. V.A.C. WhiteFoam exists as a white, premoistened, hydrophilic foam made from polyvinyl alcohol, and possesses a high tensile strength. This foam is particularly effective when used as a bolster for skin grafts and when granulation tissue formation is not the desired result, such as in deep space infections. The foam is engineered to apply a uniform pressure throughout the entire wound bed, with the negative pressure unit typically set between 75 to 125 mm Hg on a continuous or intermittent setting (Fig. 1).\textsuperscript{13–15}

**RATIONALE AND OUTCOMES**

In an early study on NPWT, Morykwas and colleagues\textsuperscript{20} reported a 4-fold increase in blood flow to the subcutaneous tissue and muscle of Chester pigs, when a V.A.C. Therapy system was applied at 125 mm Hg over 15-min intervals. Blood flow values decreased to below baseline at pressures greater than 400 mm Hg. The same authors also found that the increase in local blood flow subsided after a period of 5 to 7 minutes, but that an “off” interval of 2 minutes was sufficient for reestablishing the increase in blood flow.

More recently, in 2005, Timmers and colleagues\textsuperscript{22} applied V.A.C. Therapy to the healthy, intact forearm skin of 10 patients, and measured the response of cutaneous blood flow to negative pressure values between 25 and 500 mm Hg. The authors reported a significant increase in cutaneous blood flow at a negative pressure of 300 mm Hg, which is more than double the pressure that was used as the basis for previous studies. These investigators also found no decrease in the baseline blood flow at negative pressures approaching 500 mm Hg.

In 2005, Armstrong and Lavery\textsuperscript{23} published the results of one of the first multicenter randomized clinical trials on NPWT, comparing the proportion and rate of wound healing with NPWT versus standard moist wound therapy. The study, which took place over a period of 16 weeks and in 18 study sites, used data from wound healing in 162 patients with diabetes, with wounds secondary to partial foot amputation and evidence of adequate perfusion. The authors found that treatment with NPWT resulted in a higher number of healed wounds (56\% vs 39\%) and faster healing rates. Furthermore, the rate of granulation tissue formation was increased, and a potential trend toward a reduced risk of reamputation was noted.

In 2008, Blume and colleagues\textsuperscript{24} reported the results of a subsequent larger study focusing on NPWT. These investigators found that over a period of 16 weeks, a greater
proportion of diabetic foot ulcers achieved complete closure with NPWT compared with advanced moist wound therapy (43.2% vs 28.9%). In fact, patients receiving NPWT were noted to require fewer amputations.

**NOVEL USES: WOUND “CHEMOTHERAPY”**

Fluid instillation therapy, or “wound chemotherapy,” is another way in which NPWT can be used as an advanced modality in wound healing and limb salvage. The V.A.C. Ulta Negative Pressure Wound Therapy System, used in conjunction with V.A.C. VeraFlo Therapy, provides a mechanism for delivering and removing fluids across a wound site, while maintaining NPWT. The addition of fluids to a wound undergoing NPWT may be helpful when the wound is contaminated or infected.

Fluids such as Dakin solution (sodium hypochlorite), insulin, doxycycline, biguanide antiseptics, and several others have been reported and investigated in their use with NPWT. The instillation of Dakin solution prevents maceration and bacterial colonization within the wound, and the addition of insulin-like growth factor (IGF) has been shown to increase rates of wound healing. Furthermore, doxycycline, which is more commonly used for its antimicrobial properties, serves as a competitive inhibitor of MMPs, and tissue necrosis factor-alpha. It may also reduce inflammation in the wound through decreasing nitric oxide synthesis.
The V.A.C. VeraFlo and V.A.C. VeraFlo Cleanse dressings, which are made of polyurethane ester, are less hydrophobic than V.A.C. GranuFoam, and have a greater tensile strength. An important feature of the V.A.C. Ulta Therapy System is dynamic pressure control, which maintains a minimum negative pressure in between periods of fluid instillation. This aids in preventing leaks and accumulating excessive fluid at the wound site.

In a porcine study published in 2011, Lessing and colleagues were able to show a 43% increase in wound fill using V.A.C. VeraFlo Therapy compared with standard NPWT over a course of 7 days. In the study, the investigators used a saline instillation with a 5-minute soak time, followed by 2.5 hours of V.A.C. Therapy. An in vitro study sponsored by Kinetic Concepts, Inc. showed that V.A.C. VeraFlo Therapy combined with polyhexamethylene biguanide was able to reduce *Pseudomonas aeruginosa* bioburden in biofilm by 99.8% (Fig. 2).

**NOVEL FORM-FACTOR: ULTRA-PORTABLE NPWT**

Another advance in NPWT has been the Smart Negative Pressure (SNaP) Wound Care System (Spiracur, Inc., Sunnyvale, CA, USA). SNaP is a novel, non–electrically powered ultra-portable device that uses specialized springs to deliver NPWT. In contrast to other NPWT systems, the SNaP device does not use a battery for its operation and does not require charging. Designed for relatively smaller wounds, the SNaP Wound Care System is fully disposable and silent throughout its operation. SNaP is readily available for “off-the-shelf” use, which obviates the need for costly and time-consuming rental agreements that are commonplace with other NPWT devices.

Roughly the size and weight of a cell phone, the SNaP device may be worn discreetly around a patient’s leg and hidden beneath their clothing. The SNaP system consists of a cartridge, a hydrocolloid dressing layer with integrated nozzle and tubing, and a foam interface. The application process is simple and quick, and the cartridge, which doubles as the storage canister (60 mL capacity), can deliver negative pressures of 75, 100, and 125 mm Hg.

In a prospective, multicenter, randomized controlled comparative effectiveness study, Armstrong and colleagues treated 115 patients with noninfected, nonischemic, nonplanter lower extremity diabetic and venous wounds using either the SNaP Wound Care System or V.A.C. Therapy. Over a period of 16 weeks, and in 17 study centers, the authors reported that at 4, 8, 12, and 16 weeks, the SNaP-treated patients demonstrated noninferiority compared with the V.A.C.–treated patients with respect to percent decrease in wound area. In terms of promoting complete wound closure, the authors found that the SNaP Wound Care System was not significantly different than the V.A.C. System. The mean application time for the SNaP was significantly shorter than for the V.A.C., and patients treated with the SNaP Wound Care System reported improved activities of daily living and less interruption in sleep. They also noted an improvement in the noise level, with better levels of comfort in social situations, and overall wearability (Fig. 3).

**BEYOND DIABETIC FOOT ULCERATION WITH NPWT**

Certainly the indications for NPWT extend beyond the treatment of diabetic foot and venous leg ulcers. For example, NPWT can be used as an adjunctive treatment after the application of split-thickness skin grafts. NPWT can serve as a bolster dressing by preventing the accumulation of fluid beneath the graft site, which is a common cause of graft failure. In 2004, Moisidis and colleagues noted a qualitative improvement (50%) in the take of split-thickness skin grafts that underwent postoperative treatment with NPWT.
NPWT has also been shown to improve outcomes in the management of traumatic open fractures. In 2009, Stannard and colleagues\textsuperscript{35} published a prospective randomized study examining 58 patients with 62 open fractures who were treated with either standard wet-to-dry dressings or NPWT, and found that the group treated with NPWT was one-fifth as likely to develop an infection as the control group. The application of

Fig. 2. (A–C) A 55-year-old woman who presented with severe diabetic foot infection and septic shock. (D, E) After emergent debridement with application of NPWT for 10 days. (F, G) After 7 weeks of NPWT. (H, I) After application of split-thickness skin graft. Immediately after graft application, NPWT with white foam dressing was applied for 4 days. (J) Three months post operative.

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NPWT over closed-incision sites has also gained popularity recently. Through applying NPWT over a clean closed incision, the surrounding soft tissue is splinted and the wound bed is protected. Furthermore, the need for frequent dressing changes, especially on high-risk incision sites, is minimized, which has been shown in some cases to lower the incidence of dehiscence and infection.

The use of NPWT over closed-incision sites has been reported in cases of coronary artery bypass grafting, abdominal hysterectomy, revisional hip arthroplasty, transmetatarsal amputation, and high-risk fractures of the lower extremity. The negative pressure used over a closed incision is typically set between 75 and 125 mm Hg, and a nonadherent dressing is usually applied between the incision site and the foam layer.

The Prevena Incision Management System (Kinetic Concepts, Inc.) is a device specifically designed for applying NPWT over closed-incision sites. The system is compact, with a 45-mL canister, and includes a semipermeable incision dressing, impregnated with ionic silver. In 2012, Stannard and colleagues published the results of a prospective, randomized, multicenter clinical trial investigating the treatment of postoperative tibial plateau, pilon, and calcaneal fractures with closed-incision NPWT. The authors were able to demonstrate a decreased incidence of wound dehiscence and infection in 249 patients, with an even distribution of 263 tibial plateau, pilon, and calcaneal fractures. They found that the relative risk of developing an infection was 1.9 times higher in patients treated with standard postoperative dressings compared with those receiving closed-incision NPWT.

THERAGNOSTICS

Beyond NPWT, the future of wound care and limb salvage will rely heavily on the organization and integration of care, with an emphasis placed on identifying key points.
in healing and warning signs for recurrence. Technology that is portable, durable, automated, intelligent, ubiquitous, integrable, and affordable will have a significant impact on wound diagnostics and what is referred to as **theragnostics**. Improvements in wound measurement and inflammation and infection detection have the potential to greatly impact wound healing and limb preservation.

It is widely understood that the prognostic value of wound measurement correlates strongly with wound healing. However, the assessment of wound size is often overlooked because of the limited human and economic resources found in most clinical settings. Furthermore, accuracy in wound measurement can prove difficult because of the complex geometry of many wounds. Recently, advances in intelligent topographic recognition technology, as demonstrated by the handheld Aranz and Eykona devices, and improvements in metric reconstruction have addressed many of the current issues involving accurate and consistent wound measurement.

**PROTEASES**

Another way technology may pave the way for improved outcomes in wound care is in the assessment of inflammation, particularly the role of proteases in wound diagnostics. Proteases, which participate in the normal wound healing process through breaking down damaged extracellular matrix and connective tissue proteins, play a critical role in wound healing. If the level of protease activity is too high, the balance between tissue breakdown and repair can be disrupted. If this occurs, the inflammatory phase is prolonged and wound healing may be delayed.

MMPs represent a major group of proteases involved in custodial aspects of the dermal matrix in wound healing. A registry focused on markers of protease activity, in different types of wounds and at different stages of healing, could prove extremely useful in predicting wound healing. However, clinical signs do not always correlate with the presence of high protease activity. Thus, a point-of-care protease test could help guide clinicians select the most appropriate treatment for a difficult-to-treat wound. The bacterial colonization of wounds is yet another factor that contributes to delayed wound healing. Colonies of bacteria have been shown to be unique to the individual from whom they are taken, and genomic sequencing, which is rapid and affordable, could allow for individually tailored pharmacotherapy.

**THE FUTURE**

Advances in diagnostic equipment and computer-automated appliances will continue to change wound care. One example is a device capable of measuring peak plantar pressures during the stance phase of gait, which can be built into a shoe or sock and provide real-time feedback. This device could serve as an early warning system for high-risk patients. Another innovation could be pneumatic compression devices outfitted with accelerometry, which would allow dynamic changes in pressure, depending on the activity level of the patient.

The sharing of information between patients in Web-based communities is another way in which technology can transform health care. Many times patients find solace in knowing that they are not alone in their struggle, and that help is just a click away. Furthermore, the ability to track patients using a wound electronic medical record (WEMR) could increase patient safety and quality of care for years to come. A standardized database of clinically relevant variables, such as age, baseline laboratory values, wound area, narrative data, and culture and pathology reports, has the potential to identify wounds at risk for delayed healing. The WEMR has the potential to
change the current landscape of wound care through promoting research and enabling collaborative efforts between wound and limb salvage centers worldwide.42

SUMMARY

As of 2012, the number of people with diabetes is increasing in every country, and half of the people with diabetes do not know they are afflicted with the malady.1 Furthermore, it is believed that every 20 seconds a lower limb is lost around the world because of complications related to diabetes.6 In a short period, NPWT has transformed wound care across the globe, and other technologies are beginning to emerge that may provide clinicians with the tools necessary for identifying wounds at risk for delayed healing and recurrence. The future of diabetic limb salvage will rely heavily on these and other advances.

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