Negative pressure wound therapy (NPWT) is used to treat a wide and growing range of problematic acute and chronic wounds. Continuous therapy delivered at \(-125\) mm Hg has been routinely recommended, despite consistent research findings suggesting potential advantages to the use of lower pressures and intermittent therapy. To enhance understanding and document the disparity between the body of NPWT science and current practice with respect to negative pressure levels and modes of therapy, a search of the English-language literature from June 1989 through May 2009 was conducted. Thirty-six publications found to contain directly relevant information (in vitro, in vivo, and clinical data) were examined. While lower negative pressures and intermittent therapy were associated in earlier studies with improved microvascular blood flow in porcine wound models and with reduced pain in patients, early system shortcomings discourage adoption of intermittent therapy. Subsequent preclinical studies confirmed the beneficial effects of intermittent therapy compared to continuous therapy on blood flow and granulation tissue formation and lower pressures (\(-75\) mm Hg or \(-100\) mm Hg) compared to higher pressure (\(-125\) mm Hg) on soft tissue blood flow. Considering the available preclinical evidence, reported patient pain, and common use of high-pressure continuous NPWT in clinical practice, high-quality randomized controlled clinical trials must be conducted to help clinicians optimize care.

**Key Words:** review, intermittent negative pressure wound therapy, low pressure, regional blood flow, granulation tissue

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with the system led to pain and disruption of tissue. In addition, various pumps and designs could not effectively accommodate intermittent therapy. Accurate control of pressures could not be established and maintained reliably over time.

Today, the most commonly cited beneficial mechanisms of NPWT are thought to be derived from 1) reduction of wound area secondary to negative pressure, 2) continuous removal of exudate and small tissue debris (following surgical debridement), 3) stimulation of granulation tissue formation, 4) reduction of interstitial edema and improvement of microvascular blood flow, and 5) physical/mechanical effects on cells. Expanding knowledge of these mechanisms of action has bolstered the case for exploring the potential of intermittent therapy and lower negative pressures.

The purpose of this review is to re-examine early NPWT evidence and highlight recent findings, with the goal of increasing understanding and exploring the disparity between the body of NPWT science and common practice with respect to negative pressure levels and modes of therapy.

Literature Review

A search of the English-language literature from June 1989 to May 2009 was conducted. Pub Med was searched using the terms negative pressure wound therapy, wound healing, regional blood flow, granulation tissue, laser Doppler velocimetry, vacuum-assisted closure, and topical negative pressure. Publications cited in Medscape related to NPWT also were examined. Original publications cited in the literature but not found in Pub Med were located using Google. In these instances, article titles or search terms such as intermittent NPWT, microvascular blood flow, rhythmic perfusion, microdeformation, and cellular stretch were used. Thirty-six publications found to contain directly relevant information (in vitro, in vivo, and clinical data) were examined and form the basis of the review.

The publications located in the search are reflective of the entire body of NPWT literature, which is dominated by clinical case reports, uncontrolled clinical trials, animal studies, and in vitro studies. It is important to note that no high-quality randomized controlled trials (RCTs) in NPWT are available that directly compare outcomes in specific types of patients and wounds, different levels of pressure and different pressure modes, or alternative NPWT systems, components, and protocols.

Early Evidence

Two early studies often are cited in discussions of the use of lower pressures and intermittent pressure, respectively. In 1989, Chariker et al. addressed the treatment of incisional and cutaneous fistulae using a closed suction drainage system, the first to include a dressing (moist gauze) that conformed to and filled the wound bed. The system also utilized a Jackson-Pratt Mini-Snyder hemovac drain and a transparent adhesive dressing to seal the wound site. The combination of the closed system and conforming dressing limited fibroplasia, improved contracture and re-epithelialization, and maintained a moist wound healing environment. Continuous pressure was applied at -60 mm Hg to -80 mm Hg. Seven patients with eight fistulae were treated with the system. Six fistulae were intestinal, one was renal, and one was a lymph fistula of the groin. All wounds closed by secondary intention in a mean time of 16 days (range of 8 to 23 days). The Chariker-Jeter system revolutionized the management of enterocutaneous fistulae complicating ventral abdominal wounds, which previously had been associated with mortality rates as high as 60%.

Morykwas et al.’s research at Wake Forest of NPWT in porcine models published in 1997 led to pressure recommendations of -125 mm Hg based on Doppler laser measurements of blood flow. This study is most frequently cited in the NPWT literature. Although negative pressures were measured in increments of 25 mm Hg (range 0 mm Hg to 400 mm Hg), only results at -125 mm Hg and -400 mm Hg were reported.

Often cited from these studies are four-fold increases in peak blood flow that occurred at -125 mm Hg immediately after pumps were turned on. However, in continuous mode, blood flow quickly returned to baseline and remained there. In sharp contrast, when intermittent negative pressure was applied (5 minutes on, 2 minutes off), large rises in blood flow were seen each time the pumps were turned back on, resulting in much greater total blood flow over each treatment period. In practice, the generalization of these contrasting and preliminary results linked to continuous pressure of -125 mm Hg led to considerable misunderstanding and oversimplification. More research was needed to clarify the most appropriate mode of therapy and optimal levels of negative pressure.

In evaluating the latest findings, it is important to reflect on other details of Morykwas et al.’s original work. In the same Wake Forest models, granulation tissue formation was measured; intermittent therapy resulted in 63.5% more granulation tissue than continuous therapy. In continuous mode, NPWT yielded increases in granulation tissue of 63.3% over saline-moistened gauze controls (no negative pressure). Intermittent therapy yielded granulation tissue formation results 103.4% greater than the controls.
The beneficial and superior effects of intermittent therapy (over continuous) on blood flow, granulation tissue formation, and other Wake Forest study factors led to the design of an intermittent setting for NPWT. However, during off cycles when pressures fell from -125 mm Hg to 0 mm Hg, re-expansion of the sponge dressing led to pain and tissue disruption. These drawbacks outweighed the potential benefits; as a consequence, the intermittent setting was rarely used. In addition, drops in pressure to 0 mm Hg and expansion of the foam dressing can result in loss of an airtight seal and the potential for fluid backflow into the wound.

Recent Research — Swedish Microvascular Blood Flow Studies

When microvascular blood flow is improved, higher levels of oxygen, nutrients, and infection-fighting cells become available to promote healing. The ability of the microcirculation to remove waste products, such as carbon dioxide, also increases. Several studies conducted by researchers at Lund University in Sweden have examined microvascular blood flow using laser Doppler in porcine models. The findings lend support for intermittent therapy and lower levels of negative pressure.

In 2004 and 2005, Wackenfors et al reported the results of microvascular blood flow research designed to examine in new detail the effects of different negative pressure levels of varying duration on various tissue types and at different distances from the wound edge. The first study, involving inguinal porcine wounds using pressures of -50 mm Hg to -200 mm Hg, noted increased blood flow closer to the wound in muscular versus subcutaneous tissue. A hypoperfused area where blood flow decreased during therapy was found immediately surrounding the wound edge and was especially prominent in subcutaneous tissue. The area of hypoperfusion increased with the use of higher negative pressures. When intermittent therapy was applied, blood flow in the zone of hypoperfusion increased and persisted well above baseline each time the pump was turned off, which the authors attributed to possible reactive hyperemia. Based on the results, the authors suggested pressures of -100 mm Hg for use in muscular tissue and -75 mm Hg in softer subcutaneous tissue to avoid potential ischemic events. The authors also noted that “intermittent therapy may further increase blood flow.”

A second Wackenfors study measured microvascular blood flow in a peristernal porcine wound model at pressures of -50 mm Hg to -200 mm Hg; results obtained were similar to those found in the inquinal wound study. Peak increases in blood flow occurred closer to the wound edge in muscular versus subcutaneous tissue. A zone of relative hypoperfusion was observed immediately surrounding the wound edge during therapy. The authors concluded that a pressure of -75 mm Hg or -100 mm Hg may effectively stimulate peristernal soft tissue blood flow without producing a large zone of relative hypoperfusion.

The Wackenfors studies suggest that negative pressures lower than commonly applied during NPWT can be used to tailor treatment to specific tissues, both optimizing perfusion and preventing ischemia.

Lindstedt et al used laser Doppler to measure blood flow in normal, ischemic, and reperfused myocardium (left anterior descending artery region) in several porcine NPWT models. Among pressure levels ranging from -50 mm Hg to -150 mm Hg (25 mm Hg increments), only -50 mm Hg resulted in statistically significant increases in myocardial microvascular blood flow during normothermia ($P = .028$ in normal myocardium and $P = .012$ in ischemic cardium, respectively, before and after NPWT). The same range of negative pressures was applied in a hypothermia model. Only a pressure of -50 mm Hg significantly ($P < 0.05$) increased blood flow, both in the myocardium and epicardium.

Another Lindstedt study in pig wounds compared blood flow following continuous pressure (-50 mm Hg) with intermittent pressure (-50 mm Hg, 5 minutes on, 2 minutes off). Both modalities resulted in increases in blood flow over baseline. Although the continuous and intermittent blood flow results were not shown to be statistically different from one another in the study, the authors noted that intermittent negative pressure had been associated with greater increases in granulation tissue during long-term use. During treatment of poststernotomy mediastinitis after coronary artery bypass graft (CABG), NPWT is in direct contact with the heart. Increases in granulation tissue formation in this setting may translate to endothelial proliferation, capillary budding, angiogenesis, and development of collateral vessels.

Potential Explanations for the Observed Benefits of Intermittent NPWT

Commonly cited benefits of NPWT include removing excess fluid, reducing edema, and lowering microbial counts in purulent wounds. A number of researchers have advanced theories as to why blood flow and granulation tissue formation are improved with intermittent compared to continuous NPWT. Based on laser Doppler studies in pig wound models, Wackenfors et al proposed that intermittent therapy increases overall blood flow and reperfuses a zone of hypoperfused tissue immediately surrounding the wound edge by means of reactive hyperemia during off times. Morykwas et al demonstrated initial rises in blood flow during continuous therapy return relatively rapidly to baseline in pig wound models. Philbeck et al theorized that capillary autoregulation may explain this desensitization of tissue with exposure to continuous pressure. In contrast, he notes that the rhythmic perfusion of tissue delivered by intermittent therapy is thought to overcome this desensitization and improve blood flow.

The utility of applying mechanical forces in wound healing has been demonstrated in both animals and humans and...
has been applied for many years in both orthopedic and reconstructive surgery. *In vitro* studies have shown that physical strain on cells is integral to wound healing and that for cells to properly divide and proliferate, an optimal level of cell strain is required, separated by periods of rest between cell cycles. Intermittent therapy may offer the periodic rest required by the cells. Suboptimal strain in wounds may result in suboptimal healing, while un-stretched cells may undergo apoptosis.

NPWT frequently has been recommended for jump-starting chronic wounds that have “stalled” — ie, failed to progress beyond the inflammatory phase to the next phase of wound healing. *In vitro* studies examining wound fluids and the differences in biologic processes between acute and chronic wounds suggest that NPWT improves wound bed conditions by removing barriers to healing and by maintaining a moist environment. In addition, while a single mechanical stretch such as in continuous NPWT is known to upregulate cells, intermittent therapy results in repetitive stimulation of secondary messengers. The repeated stretching of cells may explain the improved promotion of granulation tissue associated with intermittent therapy in the original Wake Forest studies in porcine models.

In his 2006 text based on an exhaustive review of more than 550 citations published in the peer-reviewed literature on vacuum therapy, Willy concludes that the common application of continuous pressure at -125 mm Hg, “appears to contradict theoretical expectations.” He states, “If vacuum therapy is used primarily to promote formation of granulation tissue, low intermittent suction should be applied.” Commenting on his own experience, he adds, “The author wishes to point out that he, too, has always used continuous negative pressure at 125 mm Hg. During the preparation of this book, however, he began to question the reasons behind using this mode and treatment setting.”

Willy recommends pressure levels of -50 mm Hg to -75 mm Hg for “tissues that are characterized by critical nutritive perfusion or are tender to pressure (eg, elderly patients with sacral pressure ulcers, impaired healing of large wounds involving subcutaneous fat, peripheral soft-tissue wounds with exposed small vessels such as the digital arteries of the foot, etc.).” He suggests higher pressure levels of -100 mm Hg or -125 mm Hg, “for adequately perfused wounds (eg, young patients with large soft-tissue defects and exposed muscle tissue).” Willy attributes significant benefits of NPWT to removal of interstitial fluid and reduction of edema. He theorizes that the “suction pressure” selected should create “non-homogeneous pressure conditions” to establish gradients that will allow streaming of interstitial fluid away from the wound, leading to improved perfusion. He recommends “pressure not be so high as to cause ischemia near the wound surface, and therefore, that pressure not be standardized to -125 mm Hg.”

**Pain and Negative Pressure Therapy**

Isago et al observed that reductions in continuous pressure reduced pain in patients. As a result, they designed a study using a rat model to determine the effects of lower pressures on wound volume reduction. The study showed that lower continuous pressures of -50 mm Hg and -75 mm Hg resulted in reductions in wound volume that did not differ significantly from those obtained using -125 mm Hg. The authors noted the need for further study of intermittent therapy with different dressings and various pressures.

Avoidance of sudden, jarring, and painful spikes between high and low pressures has been shown to mitigate patient pain. However, based on numerous clinical case reports, the dressing medium also must be taken into consideration to avoid pain during NPWT and dressing changes. For example, in-growth of granulation tissue into reticulated polyurethane foam that is in direct contact with the wound bed may result in pain and the loss of new tissue when the foam dressing must be changed, typically within 48 hours to minimize ingrowth. The need to medicate patients for NPWT and foam dressing changes (if a nonadherent layer is not used) may require the use of topical anesthetics, nonopioids, opioids, and adjuvants such as drugs to reduce fear and anxiety.

Opioid use is associated with serious risks, particularly among geriatric patients. Preventing pain and the need to use pain medications also may save time, resources, and other hidden costs.

In this review, no studies were found documenting the incidence and quantifying the extent of pain across specific wounds and patient populations associated with foam-based and other NPWT systems. Krasner has noted that the application and removal of one leading foam-based system is a source of procedural pain in “many” patients. At the same time, she describes a number of approaches that can be used to avoid or minimize pain. The issue deserves serious discussion and future study, considering that foam-based NPWT has been used in an estimated 3 million patients over the last 12 years.

**Dressing Comparisons**

The respective roles of NPWT dressings such as polyurethane foam and gauze on cellular stretch and other treatment outcomes remain largely unknown. Recently, Malmso et al compared moist gauze and polyurethane open cell foam under negative pressure in two studies using porcine wound models. In the first study of microvascular blood flow (in press), gauze and foam yielded similar blood flow responses at -75 mm Hg and -125 mm Hg. A second study compared the effects of gauze and open-cell foam on pressure transduction and wound contraction; both dressings were found to be equally effective.

No RCTs have compared moist gauze under negative pressure to foam, a prerequisite for fairly comparing available systems in terms of performance, pain management, quality of life...
for patients, ease of use, time-saving aspects, and total cost of treatment. The lack of evidence is unfortunate — foam- and gauze-based systems both have been commercially available for nearly 6 years. During the same time period, additional RCTs have been completed or are ongoing using traditional wet-to-dry gauze dressings as controls even though moist gauze under negative pressure is the relevant dressing for comparison.

**Discussion**

In the past 20 years of its increasingly rapid development, NPWT has been evolving with the goal of optimizing healing while minimizing pain and complications. Early studies and more detailed subsequent research have suggested potential advantages to the use of lower negative pressures and intermittent therapy as opposed to continuous therapy. Until the publication of recent detailed blood flow studies in animal models, the benefits of lower negative pressures (other than pain relief) were not completely apparent, and application of intermittent negative pressure was not a practical option with existing systems because of insufficient pressure control, pain, and sealing problems.

High-quality RCTs with standardized controls and protocols are needed to directly compare outcomes in specific types of patients and wounds, at different levels of pressure, and using different pressure modes, as well as to compare alternative NPWT systems, components, and protocols. No RCTs of this type have been conducted and published to date.

In the past, many trials have used similar design elements common to trials from the late 1990s — eg, continuous pressure at -125 mm Hg. Moving forward, the efficacy of these parameters compared to others needs to be examined because preclinical studies suggest better alternatives exist. Because continuous therapy at the relatively high pressure of -125 mm Hg has been recommended for more than 12 years, translating this information into immediate patient benefits represents a significant challenge to conventional thinking and practice.

The effect of using foam and gauze under negative pressure on the incidence of pain and actual costs of care must be quantified, and research is needed to examine wound bed tissue differences when using either foam or moist gauze or when applying a nonadherent layer and foam dressing.

When evaluating systems and protocols available today, and in the absence of study data, clinicians need to consider what combination of system components and attributes may optimize healing and how known NPWT mechanisms of action may affect outcomes of care. System customizability is a top priority. Clinicians also should remember that the mechanisms of NPWT and their potential effect on wounds are likely interrelated and complex and that all wounds are not alike.

**Conclusion**

A review of the literature relevant to the development of NPWT yielded many insights into the science of negative pressure for wound care, its original use, and the reasons needed for modifications to facilitate, rather than possibly compromise, healing. Additional research is necessary to test evolving concepts, particularly for a therapeutic approach that still is subject to numerous concerns. The proliferation of a number of new devices should inspire productive comparison that will provide information not only on economics of use, but also on what is ultimately best for the patient.

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