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Clinical Review

The mechanisms of action of vacuum assisted closure: More to learn

Dennis P. Orgill, MD, PhD,[a] Ernest K. Manders, MD,[b] Bauer E. Sumpio, MD,[c] Raphael C. Lee, MD, PhD,[d] Christopher E. Attinger, MD,[e] Geoffrey C. Gurtner, MD,[f] *and* **H. Paul Ehrlich, PhD,[g]** *Boston, MA, Pittsburg, PA, New Haven, CT, Chicago, IL, Washington, DC, Stanford, CA, and Hershey, PA*

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THERE HAS BEEN RAPID ADOPTION OF VACUUM-ASSISTED CLOSURE (VAC) TECHNOLOGY to treat many acute and chronic wounds despite a rudimentary understanding of the biologic mechanisms of action and few well-controlled, prospective, randomized clinical trials of its use.

An expert panel carried out a selected review of published literature regarding the mechanisms of action of the VAC device in the context of published clinical studies.

The current literature suggests primary mechanisms of action of the VAC device may include the following: (1) drawing the wound edges together; (2) stabilization of the wound environment; (3) decrease in wound edema and removal of wound exudate; and (4) microdeformations of the wound surface. Secondary effects include increased angiogenesis, granulation tissue formation, and, in some cases, a decrease in bacterial bioburden.

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INTRODUCTION

The clinical evidence for the efficacy of the VAC device is mostly in retrospective case series. A few randomized control studies have shown efficacy in diabetic foot infections, pressure ulcerations, and skin grafts. Additional research into the mechanism of action will provide a better understanding of how to best use current devices and help make improvements in future device design.

With our aging population and increases in obesity and diabetes, problem wounds are becoming an increasing burden to our healthcare system. In addition, clinicians are faced with an array of problem wounds from military and domestic trauma as well as from complex surgical procedures. Better, cost-effective methods of closing difficult wounds efficiently will reduce the pain and amputation rates associated with wounds. Despite the theoretical promise of topically applied growth factors, there is currently only a limited clinical role with only 1 commercial product available for clinical use in the United States.[1] Other methods, such as bioengineered skin substitutes, have been successful in certain defined areas of wound healing, but most advanced wound care products in use today are based on the principle of moist wound healing defined by Winter and Scales in the 1960s.[2,3]

WOUND HEALING PHYSIOLOGY

Acute wounds progress through a complex series of biochemical and cellular events described as the phases of wound healing: hemostasis, inflammation, proliferation, and remodeling. Successful wound healing is contingent on the orchestration of a myriad of biochemical signal pathways from a wide range of cell types during the

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Table. Health technology assessment summary

Health technology assessment	*Conclusions*	*Comments*
Ontario Health Technology Advisory Committee, 2004[14]	VAC therapy may be useful for healing various types of wounds but effectiveness could not be empirically quantified	- Small sample size and patient populations - Poor study design - Outcome measures could not be compared
AHRQ/BlueCross/BlueShield, 2004[15]	Body of evidence insufficient to support conclusions about effectiveness	- Small number of studies - Inadequate randomization in most studies - Study groups not comparable
Cochrane Review, UK, 2003[16]	Weak evidence of effectiveness	
Centre for Clinical Excellence, Australia, 2003[17]	VAC may have advantages over other forms of wound dressings studied but too few reports to say	- 3 articles met inclusion criteria - No Level I or II were identified
NHS Quality Improvement Scotland, 2003[18]	Limited evidence for effectiveness and adverse events	- Saline gauze is not standard treatment of wounds in Scotland - Need for more RCTs
Cochrane Review, UK, 2001[19]	Weak evidence that TNP is superior to gauze dressings	- Small sample sizes - Methodological limitations

VAC, Vacuum-assisted closure; *AHRQ*, Agency for Healthcare Research and Quality; *RCT*, randomized clinical trial; *TNP*, topical negative pressure.

4 phases. Chronic wounds, in contrast, do not make an orderly progression through the phases and are unable to complete the sequence. The lack of wound progression can be due to a number of factors, including increased protease production, infection, nutritional state, vascular disease, and radiation. Common to chronic wounds is a decreased proliferative response in the healing cascade. There are a variety of pharmacologic, cellular, biochemical, and mechanical methods that alter the normal wound healing sequence.[4-6] Correcting defects in the normal healing phases or devising methods to accelerate wound healing would be of great benefit. For an active proliferative process to occur in wound healing, the fundamental drivers of mitogenesis should be considered, which include growth factors, extracellular matrices, and mechanical forces.

VAC DEVICE

Argenta and Morykwas[7] and Morykwas et al[8] first described the beneficial use of the vacuum assisted closure (VAC) device for wound healing in 1997 (Kinetic Concepts, Inc., San Antonio, TX). The device consists of a vacuum pump, a canister with a connecting tube, an open-pore foam, and a semiocclusive dressing. Although suction devices have commonly been used to drain surgical sites and investigators such as Fleischmann et al[9] have described a vacuum-sealing technique, the VAC device has gained increased popularity among users over the past decade. A number of other devices have or will be marketed based on the concept of wound suction, which is sometimes referred to as *negative pressure wound therapy*. Although these devices share some of the same design characteristics of the VAC device, we restricted our review to the VAC device and the most common interface material, the open-pore polyurethane ether foam, because of a lack of peer-reviewed articles about other devices. The polyvinyl alcohol foam is a white, nonadherent foam that is used by some clinicians over viscera and to reduce pain with dressing changes; there are no Level I or II studies using this type of foam.

Since the original reports,[7,8] more than 500 peer-reviewed papers in the medical literature have been published describing the effect of VAC in a number of wound types. Most of the reports have been case series and retrospective reviews, with a few prospective, randomized studies published in the areas of diabetic foot infection,[10,11] pressure sores,[12] and skin grafts.[13] Several systematic reviews of VAC technology have also been published (Table).[14-19] Although a number of independent reports suggest compelling evidence, the small number of prospective, randomized studies makes it difficult for public health policymakers to assess clinical efficacy.[20] The following is a selected review of the current literature and description of current knowledge regarding the mechanism of action of the VAC device.

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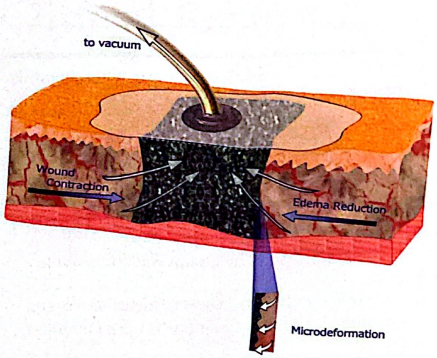

Fig 1. Proposed mechanisms of action of the VAC device. The device covers the wound and keeps the wound surface moist and insulated. For deformable wounds, the device can be used to pull the edges together (macrodeformation). It removes extracellular fluid and wound exudate and causes microdeformation at the foam-wound interface. Secondary effects include changes in blood flow, wound biochemistry, systemic inflammatory response, and bacterial load.

MECHANISM OF ACTION OF VAC DEVICE

Primary effects. There are 4 primary mechanisms of action of the VAC device described in the literature: (1) contraction of the wound (macrodeformation); (2) stabilization of the wound environment; (3) removal of extracellular fluid; and (4) microdeformation at the foam-wound interface (Fig 1).

Contraction of wound (macrodeformation): Skin and soft tissues have a natural tension in their normal state. When an incision is made through the skin, it naturally pulls apart. For example, in patients with midline abdominal wounds that are left open, there is shrinkage of the abdominal wall that is referred to as *loss of domain.* Maintaining approximation of tissues during wound healing allows for earlier closure by delayed primary or secondary intention. Studies of traumatic abdominal injuries have shown that use of a modified VAC device can allow for subsequent wound closure and may circumvent the need for skin grafts over viscera.[21] The open-pore polyurethane foam that is used with the VAC device efficiently transmits pressure and evacuates exudates. When exposed to suction at 125 mm Hg, the foam volume decreases by about 80%.[22] The shrinkage is in 3 dimensions, and the amount of shrinkage of the wound will mostly be determined by the deformability of the surrounding tissues.

The effect of the macroscopic deformation of tissues as a result of VAC placement will depend on the type of tissue treated. For example, placement of the VAC device into an incisional wound in an obese abdomen with a large amount of deformable skin and soft tissue will result in near approximation of the wound edges. In contrast, use of the device on scalp wounds causes minimal contraction of the wound edges, with the foam shrinkage occurring mostly perpendicular to the wound surface.

For deformable wounds, cutting the foam in a strategic fashion will facilitate wound closure by allowing the wound edges to come together more quickly. Depending on the structural characteristics of the foam, the foam exerts mechanical forces on the tissue exposed to the VAC device.[23] For example, in a circumferential extremity wound, there is a theoretical possibility for circumferential shrinkage of the foam to cause a compressive force on the underlying tissues (Fig 2). Kairinos et al[24] recently confirmed this hypothesis in humans treated with VAC therapy for 48 hours. In this same study, they showed that tissue pressures were increased when measured about 1 cm from the wound with the VAC in place. These pressures increased as suction levels were increased; over time, there was some normalization of these pressures.[24] Quantitative modeling of this phenomenon will be important to predict changes in wound volume as a function of the anatomic location of the wound and the patient age and body habitus.

Stabilization of wound environment: The VAC device uses a semiocclusive polyurethane drape that has limited permeability to gases and water vapor and impermeability to proteins and microorganisms. The dressing is typically changed every 2–3 days, which eliminates the discomfort of the daily dressing changes typically associated with traditional gauze-based dressings. Gauze dressings can allow evaporation of fluids and concentration of proteins at the wound surface and eventually produce a scab that delays healing. In contrast, moist wound-healing modalities, such as alginates, promote angiogenesis and the breakdown of necrotic tissues while decreasing pain.[2,3] The VAC device appears to evacuate fluid with its accompanying electrolytes and proteins, thereby keeping the osmotic and oncotic gradients at the wound surface theoretically stable. Objective studies, however, are needed for confirmation. Clinicians using the VAC device have noted that part of the wound will desiccate if a small hole develops in the overlying drape.[25]

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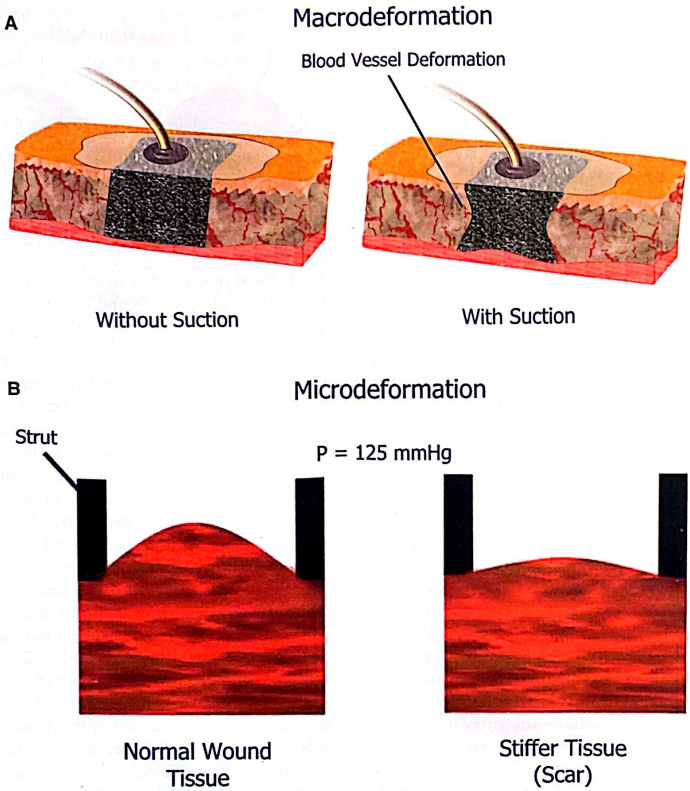

Fig 2. Wound deformation. (*A*) Macrodeformation: The foam contracts when vacuum is applied and can cause tension on wound edges to bring the wound edges together, which might potentially cause a compressive force on circumferential wounds. (*B*) Microdeformation: The VAC device causes rapid formation of granulation tissue that mirrors the foam surface. Stiffer tissue will deform less with the same foam pore size and suction.

The physical properties of the polyurethane ether foam very likely contribute to the efficacy of the VAC device by allowing efficient pressure distribution and removal of exudates. The currently available polyurethane ether foam (black foam) has a mean pore size of 423 μ, a mean pore volume (when uncompressed) of 97%, a bulk modulus of elasticity of 3.06 kPa (23 mm Hg) when 50% compressed, and a Poisson's ratio of 0.0 (K. Kieswetter, KCI, San Antonio, TX, personal communication, December 2007). Based on clinical experience, one suction device is adequate for most large wounds. However, more than 1 suction pump may be necessary in patients with very large wounds involving a large extremity or trunk area. More clinical information about the flow and pressure distribution characteristics of the foam in large and highly exudative wounds would help clinicians determine the optimal number of suction ports to apply.

The thermal conductivity of the VAC device will be an aggregate of the conductivity of the overlying semiocclusive drape and the polyurethane foam (Fig 3). Because the compressed foam is likely to be saturated with liquid during application, the thermal conductivity will be on the order of water or 0.014 (calorie per second [cal/s] meter degrees Celsius [m C°]) and will be roughly comparable to tissue at a similar thickness. Additional heat transfer is minimized because of the reduction of

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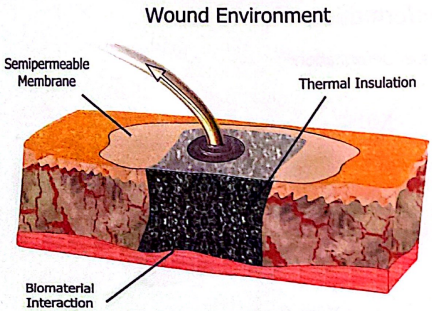

Fig 3. Wound environment. The VAC device keeps the wound moist and warm compared with dry dressings that allow the wound to dry out and form a scab. The VAC device also acts as an insulating layer.

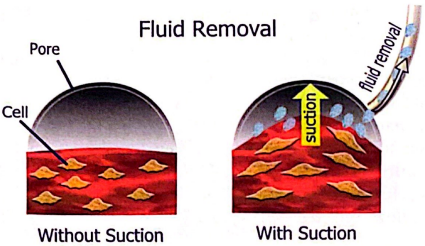

Fig 4. Fluid removal. The foam distributes the vacuum evenly throughout the wound and allows for transport of extracellular fluid to the wound surface.

evaporation of water from the wound surface. A randomized study by Kloth et al[26] showed that normothermic wound therapy speeds wound healing in chronic, full-thickness pressure sores. More work with actual temperature measurements and water content of the wound and foam would be helpful in better understanding this mechanism of action.

The uniform apposition of a skin graft or artificial dermal matrix to the underlying wound is critical for optimal take. Randomized studies of skin graft take comparing VAC devices to conventional bolster dressings have shown better, more reliable take in the skin grafts and dermal matrices when they are bolstered with a VAC device.[27] Jeschke et al[27] compared 11 patients treated with a combination of artificial dermis (Integra; Integra LifeSciences, Plainsboro, NJ), fibrin glue, and VAC therapy with 6 patients that received Integra covered with a compression dressing. The researchers found a significant increase in the Integra take and a decreased time to apply the autograft in the study group.[27] Moisidis et al[13] designed a prospective, randomized study in which skin-grafted wounds were divided into 2 areas—1 treated with VAC and the other treated with a standard bolster dressing. They were able to show improved graft take in the areas treated with the VAC device. Two weeks after grafting, the VAC-treated areas appeared to be of better quality than the bolster group.

Decrease in edema and removal of wound exudate. An obvious consequence of VAC therapy is the ability to evacuate wound exudates. Clinicians are well aware that edema impedes healing and recommend elevation and compression of extremities to decrease edema and facilitate healing. Swelling from edema may actually cause compression of cells within the extracellular matrix, thereby decreasing their intrinsic tension, resulting in a decreased proliferative response (Fig 4). Application of a distributed suction allows direct evacuation of fluid from the extracellular space and appears to decrease edema (Fig 4). In compartment syndrome of the extremities, there is massive swelling that necessitates release of fascial compartments to maintain perfusion and prevent cell death. By removing extracellular fluid, the VAC device may hasten resolution of compartment syndrome after fascial release and allow for earlier closure of the fasciotomy wounds. In addition, there may be an increase in blood flow when the edema fluid concentrated around small blood vessels is evacuated, but more research is needed.

Yang et al[28] retrospectively compared lower extremity fasciotomies and demonstrated that the wounds could be closed in an average of 6.7 days with the VAC device versus 16.1 days without the device. Weiland[29] used VAC devices in combination with hyperbaric oxygen therapy in 3 complex lower extremity crush injuries and suggested that both modalities may be synergistic in decreasing edema. DeFranzo et al[30] showed decreases in the extremity circumference and ≤500 ml/24 h removal of fluid from lower extremity wounds with exposed bone. The fluid flow past cells in the wound may also exert important shear stresses that could modulate cell function.

At a basic level, tissue is composed of both fluid and solid phases. Within the extracellular matrix, the fluid phase is the interstitial electrolyte solution, whereas the solid phase is the collagenous extracellular matrix. Mechanically deforming this biphasic material results in 2 phenomena, (1) a strain field is established in the solid matrix upon which the cells are anchored, and (2) a flow of

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fluid is created within the interstices of the matrix.[31] Thus, cells are subjected to mechanical stretch mediated by their attachments to the matrix and shear stress due to fluid flow. It is well established that fluid shear stresses can regulate cellular proliferation and biosynthetic responses in cell cultures.[32] In addition, the movement of ions in solution past matrix glycoproteins establishes electric fields (ie, streaming potentials) that can also stimulate cellular responses.[33,34] In VAC therapy, tissue deformation occurs by moving interstitial fluid and deformation of the solid phase, which is a process similar to what happens when one squeezes a wet sponge. Mechanical loading directly drives the flow of interstitial fluid and mechanical deformation of structural macromolecules such as collagen.

Murphey et al[35] measured interstitial pressure adjacent to the VAC device in an animal model and found a gradient of pressures out to nearly 1 mm from the wound surface when suction was applied. Theoretically, cells embedded in the tissue are also deformed or, at the least, subjected to forces that tend to deform the cell membrane. Furthermore, deformation of tissue leads to changes in ionic concentrations of the interstitial fluid as well as generation of interstitial electrical currents.[31] To date, studies on shear stress have primarily concentrated on endothelial, bone, and intestinal epithelial cells, and the results may not be directly translatable to wounds.[36-39] In addition, there are notable toxic materials within the wound, including bacteria, inflammatory cytokines, and matrix metalloproteinases (MMPs). A preliminary study from Stechmiller et al[40] showed a significant decrease in TNF-alpha from VAC wound fluid extracted from pressure sores during the course of 1 week.

Argenta and Morykwas[7] and Morykwas et al[8] recognized the importance of fluid removal as a significant benefit of the VAC device. Fluid removal is critical in burns to modulate the 3 zones of injury originally described by Jackson.[41] Jackson described a zone of stasis that is a potentially reversible area of the burn, which can be made worse by hypoperfusion and edema. In experimental partial-thickness porcine burns, Morykwas et al[42] saw significant decreases in burn depth when the wounds were treated with the VAC device. According to Jackson's description, the zone of stasis exists for only the first 24 hours after injury; this zone then becomes incorporated into either the zone of hyperemia (tissue should recover) or coagulation (irreversible tissue loss).[41] The effect of the VAC device was to decrease the accumulation of edema fluid, thereby limiting the depth of cellular death. The observed decrease in burn depth has clinical importance because superficial 2nd-degree burns have the capacity to heal, whereas deep 2nd-degree burns are best treated with the more invasive method of excision and grafting.[42] In 7 patients with bilateral burns, Kamolz et al[43] studied perfusion and the amount of fluid removed. In this small study, their impression was that the VAC device increased perfusion to the hand, and they removed a clinically relevant volume of extracellular fluid (≤500 ml).

Intraabdominal hypertension can lead to intraabdominal compartment syndrome. Release of the abdomen can be a lifesaving event but leaves the patient with a very large, open wound with potential complications of infection, hernia, and fistula. The VAC device provides a method to keep the wound moist, draw the wound together to minimize loss of domain, and evacuate excess abdominal fluid. The bowel is covered with a plastic drape to avoid direct contact of the polyurethane foam with the bowel. Many centers perform VAC changes on open abdomens every 2–3 days in the operating room with successive closure of the abdominal wound. Using this approach, skin grafting directly over bowel can be avoided in many cases.[21]

Microdeformation at the foam-wound interface. Wolff[44] recognized the fundamental role of mechanical force in regulating tissue growth, repair, and remodeling more than a century ago. Tissue adaptation to changing physical stresses is a basic requirement for growth and survival of living systems.[32] Application of mechanical loading of tissues results in deformation. The magnitude of the biomechanical responses described above is dependent on the stiffness of the tissue to which the VAC is applied and the dynamics of the mechanical loading. If there is a rapid pressure change, then the flow of interstitial fluid will be more rapid. If the pressure change is applied slowly, then interstitial flows will be more gradual and matrix stress applied to cells will be much less. Thus, it is likely that the biologic response to VAC loading will depend on the frequency of vacuum application. There is limited published work done on phasic VAC therapy. Morykwas et al[8] applied 125-mm Hg suction to porcine wounds using a 5 minute on/2 minute off cycle and noted increased blood flow in the area and an increase in hyperproliferative tissue. Wackenfors et al[45] applied 125 mm Hg of pressure with the VAC device on porcine wounds intermittently with increasing periods of time between the "on" vacuum and "off" vacuum. They observed

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that peak blood flow in the tissues decreased during the "on" periods and increased 40–50% above baseline when the vacuum was turned off.[45] The optimal waveform for the VAC device has yet to be determined for specific wound types.

For biphasic materials, mechanical deformation imposed on the surface defuses through the matrix at a rate that depends on tissue hydraulic permeability, matrix stiffness, and deformation kinetics.[34] Thus, both shear and deformation forces acting on cells are dependent on the rate at which the fluid flows through the matrix. The precise mechanisms by which the frequency of imposed stress influences cellular response are not well described.

Microdeformations induce cellular proliferation and angiogenesis in vivo.[22] Skin expands as a result of stretch in growth, morbid obesity, aging, and pregnancy. We commonly take advantage of this effect in tissue expansion that shows a well-defined proliferative and angiogenic response.[46] Ilizarov's pioneering work on bone lengthening[47,48] showed that introducing gradual traction on bone leads to osteogenesis and that skin, muscle, and nerve could lengthen in tandem. A controlled distraction rate of 0.25–0.7 mm per day in experimental animal models showed increased cellular proliferation. In soft tissue, Pietramaggiori et al[49] showed both a vascular and proliferative response when rat ears were placed under tension.

Often, in clinical practice, a number of wounds that have minimal exudate into the VAC canister have a dramatic proliferative response to VAC therapy. Huang et al[50] and Huang and Ingber[51] illustrated that nonmalignant cells require tension to divide and proliferate. Mechanical stresses cause physiologic changes in cell function through a mechanism referred to as *mechanotransduction.*[52] According to the basic cell model proposed by Huang et al[50] and Huang and Ingber,[51] much of the mechanotransduction cell signaling occurs through the cytoskeleton. Integrins are also known to be important in mechanotransduction and can transmit surface signals to intracellular signaling mechanisms to alter gene transcription. To date, most mechanotransduction experiments have been conducted on vascular cells, osteocytes, and enterocytes.[37]

The currently known responses of vascular cells to mechanical stimuli include inhibition of apoptosis, upregulation of cell signaling molecules (such as extracellular signal-regulated kinase pathway, Jun N-terminal kinase, stress-activated protein kinase, and p38), changes in gene expression, and increases in proliferation.[53,54] McNulty et al[53] showed greater cell death and less cell migration and proliferation of fibroblasts with gauze under suction than with VAC or static controls. Nishimura et al[54] observed differences in human dermal fibroblast response under different frequencies of stretch. Jacobs et al[55] showed increased collagen organization and maturation and increased expression of vascular endothelial growth factor and fibroblast growth factor-2 in a rat wound model using VAC compared to control.

Saxena et al[23] reported a mathematical model of a wound treated with the VAC device. The open-pore polyurethane sponge was modeled as a rigid device with a uniform pore structure in a 2-dimensional model. Linear elastic properties for the underlying tissue were assumed. The model showed that the wound would be compressed where it was in contact with the foam and, under tension, in the void between the foam struts. The result was an undulating surface where the wound contacted the foam. Increasing the vacuum or the pore size resulted in increased wound deformation. Increasing the stiffness of the wound, a common phenomenon during the healing process, decreased the deformation of the wound. When the model was compared to histologic cross sections of wounds treated with the VAC device, there was a remarkable similarity in the deformation pattern. The authors hypothesized that lengthening the wound surface on a microscale (microdeformation) resulted in stretching the cells within the wound.[23] The model predicted that the VAC device induced average tissue strains in the range of 5–20%, depending on the stiffness of the wound and foam characteristics. These strains are consistent with the range shown to promote cellular proliferation in vitro.

The optimal physicochemical properties of the interface materials have not yet been elucidated, but a properly designed interface material may be critical to device performance. The current polyurethane foam appears to have been discovered empirically. A previous study by Scherer et al[22] shows that the foam by itself causes a vascular response of the wound. Application of suction to the foam induces microdeformations of the wound bed and induces both cellular proliferation and robust angiogenesis. The concept of microdeformation will be an important future area of investigation.

Secondary effects. *Speeds wound healing.* Joseph et al[12] randomized patients with pressure sore(s) to use of a VAC device or normal saline dressings; they found a decrease in wound volume of patients treated with the VAC device at 6 weeks (78% vs

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30%). Eginton et al[56] designed a cross-over, randomized trial in diabetic foot wounds and showed a decrease in wound volume of 59% vs 9%. Larger studies in different wounds types are needed to better understand this effect.

Increases in blood flow around wounds: Because of one or more of the primary mechanisms described above, there is an eventual increase in blood flow in the wound due to the VAC treatment. When a clinician changes a VAC device a few days after application, increased granulation tissue with numerous small blood vessels is observed on histologic sections.[23] To study potential increased perfusion to the tissues, most investigators have used the noninvasive laser Doppler device. Although useful, laser Doppler does not determine blood flow directly, and so results from studies using the device need to be interpreted with caution. Laser Doppler measures red cell velocity and converts it to blood flow by a derived formula. A decrease in vessel diameter can cause increases in fluid velocity even though the overall flow is decreased. Timmers et al[57] showed that laser Doppler readings increased when a VAC device was placed on normal human skin. Morykwas et al[8] showed similar results on open porcine wounds using an implantable Doppler probe. Wackenfors et al[45] measured blood flow around a porcine groin wound treated with VAC and found an area of hypoperfusion within about 1.5 cm from the wound edge.

Ichioka et al[58] designed an experimental model that quantitatively visualized the wound bed microcirculation under subatmospheric application. They determined that a gauge pressure of –125 mm Hg significantly increased blood flow in the wound bed immediately after pressure application and for 1 minute after pressure release. In contrast, application of –500 mm Hg caused a decrease in blood flow, reaching statistical significance after 5 minutes. Recently, Kairinos et al[59] measured tissue perfusion in healthy human subjects with a radiotracer technique and showed a decrease in perfusion that correlated to increased values of suction. Further studies using thermal diffusion technology, corrosion casting, fluorescent particles, or radioactive tracer methods may be more useful in providing a more thorough understanding of the angiogenic response to the VAC device and the appropriate type and application of negative pressure to which the wound is exposed.

Changes in bacterial burden: Morykwas et al[8] first described a decrease in bacterial load using the VAC device in experimental pigs. The mechanism behind the observation is not clear, and there may be several factors that influence the total bacterial burden of the wound, such as direct removal of bacteria and alterations in blood flow. Clinical results from other centers have yielded mixed results. Moues et al[60] studied 54 patients in a prospective, randomized trial in which one half of the patients were assigned to VAC therapy and the other half was assigned to dressing changes with normal (0.9%) NaCl. The researchers found that patients with wounds culturing nonfermentative, gram-negative bacilli had decreased bacterial loads over time, whereas patients with wounds culturing *Staphylococcus aureus* had increased bacterial levels over time.[60]

Alterations of the polyurethane foam may be an important mechanism to better treat bacterial colonization. One method involves coating the polyurethane foam with silver. Gerry et al[61] reported on 2 patients with complex venous stasis ulcers that were unresponsive to conventional VAC therapy but that responded well to the use of a silver-impregnated foam with the VAC device. Instillation of solutions into the foam and wound via the vacuum pump, a technique popularized by Moch et al,[62] may provide another method to help keep bacterial levels low in wounds. The issues of biofilms and defensins will be important future areas of research.

Changes in wound biochemistry and systemic response: The expression of genes by cells in the wound and the regulation of gene expression are likely to be important factors in explaining the mechanisms of action of VAC therapy. Greene et al[63] studied the MMP profiles in 3 debilitated patients undergoing VAC therapy. In 1 area of each wound, the foam was not placed in contact with the wound bed. Wound biopsy samples comparing areas of foam contact with non-foam contact showed dramatic differences in angiogenic response and decreases in the MMP-9/NGAL (neutrophil gelatinase-associated lipocalin) and MMP-2. Shi et al[64] performed a consecutive, 1 week study of chronic wounds and showed a decrease in MMP-1 and MMP-13 that was determined by real time-polymerase chain reaction of wound biopsy samples. The researchers[64] hypothesized that the decreased MMP activity decreased the breakdown of the wound connective tissue matrix, thereby blocking the inhibitory effects of MMPs on wound healing. The biologic response in the wound likely has some systemic effect. Norbury and Kieswetter[65] showed a decrease in circulating monocytes and interluekin-6 36 hours after injury in porcine wounds treated with the VAC device.

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Improves wound bed preparation: Surgeons recognize that a nicely granulating wound is likely to be favorable for skin grafting. Lack of granulation tissue is commonly seen in radiation or vascular wounds. Morykwas et al[8] showed a greater than 60% increase in granulation tissue formation with application of VAC to porcine wounds in comparison to wounds treated with moist gauze. Further porcine studies showed that a 125-mm Hg vacuum resulted in faster formation of granulation tissue than either 25 mm Hg or 500 mm Hg.[66] Armstrong and Lavery, in conjunction with the Diabetic Foot Study Consortium,[10] performed a prospective, randomized controlled study of 162 diabetic foot amputation sites; their study's primary endpoint demonstrated a greater rate of closure of the VAC group compared to the control group using standard wound care at 112 days (56% vs 39%).

Blume et al[67] studied diabetic foot wounds in 2 groups of patients; they noted that granulation tissue covered the wound more quickly in the group of patients treated with the VAC device, resulting in faster wound closure, than the group of patients receiving standard treatment. Vuerstaek et al[68] carried out a prospective, randomized trial of lower extremity ulcerations, mostly venous in nature, and compared the effect of VAC therapy with standard compression therapy. When the wounds had filled with granulation tissue, the researchers applied 4-mm punch full-thickness skin grafts to the wounds. Wounds healed faster in the VAC group (29 vs 45 days), and the time to wound bed preparation was also shorter (7 vs 17 days).

DISCUSSION

The VAC device most commonly is used with an open-pore polyurethane ether foam that appears to be an important component and contributes to several of the device's mechanisms of action by providing an efficient removal of exudate, evenly distributing pressure within the wound, and inducing angiogenesis. The compressibility of the foam allows for the VAC device to exert tension on many types of wounds, drawing the edges together. In skin grafts, the foam provides a uniform distribution of the vacuum, which results in a more reliable take of skin grafts. Effective fluid removal is important for swollen or edematous wounds, such as burns or the wounds used to relieve a compartment syndrome. Furthermore, microdeformations of the wound surface seem to induce a mechanotransduction mechanism that alters genomic expression to promote increased vascular growth and alter wound biochemistry. Additional research in biomaterial properties of the foam, surface coatings, optimal pore structure, and mechanical properties will be important to identify the optimal interface material.

Clinical research with wound healing devices is challenging due to the heterogeneity of the wounds treated by clinicians, the variability of response, the lack of agreement on the best endpoint metrics, and the difficulty of blinding the treatment arms. Most studies of the VAC device are case reports or retrospective clinical studies, often without optimal controls. Carefully designed clinical trials based on our recent understanding of wound healing should add to our understanding of the mechanisms of action. The advances in molecular biology, including gene chips, proteomics, zymography, and advanced methods to study cell biology, provide powerful tools for both basic scientists and clinicians to elucidate mechanisms of action.

The mechanotransduction and alterations in extracellular fluid may be 2 of the unique mechanisms of action of the VAC device. The time course of the biologic response to microdeformation in conjunction with the study of the optimal waveform should be very important for the design of new therapies. Understanding the response of cell deformation, cell wall tension, and cell shape, as well as fluid flow past cells may also add new knowledge to the mechanism of action.

Although the VAC device has caused a major shift in wound care practice, the therapy is not beneficial for the treatment of all wounds. In addition, the use of the VAC device is expensive and should not be used in wounds that derive no clinically important benefit. Some patients find the device cumbersome to wear as an outpatient and are happy to switch to a less complex modality. Although most patients have reduced pain using the VAC device,[69] some patients have reported significant pain. Caution should be used with patients that are anticoagulated or with bleeding that has not completely stopped before application. Increased levels of bacteria in certain wounds can cause increased odor or delay healing. A better understanding of the mechanisms of bacterial growth when the device is used and the effect of biofilms would be helpful. The introduction of a silver-impregnated VAC device[61] and VAC devices irrigated with antibiotic solutions[70] may provide more effective methods to treat an increased bacterial load, but there are little published data to support their use.

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Since being introduced just more than 10 years ago, the VAC device has had a major impact on the clinical care of complex wounds throughout the world. Like with any new technology, clinicians are still learning the optimal methods of application. As more is discovered about the mechanism of action, clinicians will learn the most appropriate use of VAC therapy in specific wound types and better devices may be designed in the future for the increasing number of complex wounds seen each year.

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