Vacuum-Assisted Closure: Microdeformations of Wounds and Cell Proliferation

Vishal Saxena, S.M., Chao-Wei Hwang, M.D., Ph.D., Sui Huang, M.D., Ph.D.,
Quentin Eichbaum, M.D., Ph.D., M.P.H., Donald Ingber, M.D., Ph.D., and Dennis P. Orgill, M.D., Ph.D.

Cambridge and Boston, Mass.

The mechanism of action of the Vacuum Assisted Closure Therapy (VAC; KCI, San Antonio, Texas), a recent novel innovation in the care of wounds, remains unknown. In vitro studies have revealed that cells allowed to stretch tend to divide and proliferate in the presence of soluble mitogens, whereas retracted cells remain quiescent. The authors hypothesize that application of micromechanical forces to wounds in vivo can promote wound healing through this cell shape-dependent, mechanical control mechanism. The authors created a computer model (finite element) of a wound and simulated VAC application. Finite element modeling is commonly used to engineer complex systems by breaking them down into simple discrete elements. In this model, the authors altered the pressure, pore diameter, and pore volume fraction to study the effects of vacuum-induced material deformations. The authors compared the morphology of deformations of this wound model with histologic sections of wounds treated with the VAC. The finite element model showed that most elements stretched by VAC application experienced deformations of 5 to 20 percent strain, which are similar to in vitro strain levels shown to promote cellular proliferation. Importantly, the deformations predicted by the model also was similar in morphology to the surface undulations observed in histologic cross-sections of wounds. The authors hypothesize that this tissue deformation stimulates individual cells, thereby promoting proliferation in the wound microenvironment. The application of micromechanical forces may be a useful method with which to stimulate wound healing through promotion of cell division, angiogenesis, and local elaboration of growth factors. Finite element modeling of the VAC device is consistent with this mechanism of action. (Plast. Reconstr. Surg. 114: 1086, 2004.)

Wounds are a major public health issue worldwide. In 1995, lower extremity ulcers alone cost the U.S. Medicare system $1.5 billion. 1 Unless wound therapies are substantially improved, the aging population and surge in diabetes prevalence will further escalate treatment costs. One exciting novel therapeutic approach to wounds is the Vacuum Assisted Closure Therapy (VAC) device (KCI, San Antonio, Texas). At our institution, the VAC has become the most common treatment modality for complex wounds. The device consists of a porous open-cell sponge (polyurethane or polyvinyl alcohol) applied to a wound and covered with an occlusive dressing. A tube connecting the sponge to a vacuum pump applies subatmospheric pressure to the sponge (Fig. 1, above, left). In a porcine wound model, the VAC has been shown to increase blood supply and reduce the incidence of infection. 2 The VAC has been proven effective at treating both acute and chronic wounds. 3,4,5

Some have suggested that the major mechanism of action of the VAC device is the reduction of tissue edema through the application of subatmospheric pressure (vacuum). 2,3 Although this may be an important mechanism for a selected subset of wounds, we have observed many VAC-treated wounds in which minimal fluid was extracted; nevertheless, dramatic healing responses were observed.

In addition, many have noticed increased granulation tissue, decreased bacterial levels, and increased cell growth in VAC-treated wounds.
wounds. We have observed similar changes in our own patients but believe that the cause may be secondary to an underlying biologic effect. For this reason, we set out to investigate other possible mechanisms of action.

In previous in vitro work, we have shown that only cells allowed to stretch can divide and proliferate in response to soluble growth factors (Fig. 2), whereas cells that are not stretched and assume a more spherical shape...
are cell-cycle arrested and tend to undergo apoptosis.\textsuperscript{5,7} Directional growth of capillary sprouts is also promoted by tension application in three-dimensional angiogenesis models in vitro.\textsuperscript{8} Moreover, it is known that vascular endothelial cells express a different array of genes depending on whether they were exposed to static, laminar, or turbulent flow.\textsuperscript{9-11} It is apparent that cells are able to sense mechanical forces and respond through the regulation of specific genes and the induction of cellular programs.

The exact mechanisms for these effects are not fully understood but likely are related to conformational changes in the cytoskeleton in response to mechanical forces. We hypothesize that the application of mechanical force to wounds induces tissue deformation at the level of individual cells, leading to cell stretch, thereby providing a powerful mechanism for inducing cell proliferation and angiogenesis and hence promoting wound healing (Fig. 1, above, right).

We present our computer model (finite element) of VAC application to a wound to demonstrate that the predicted microdeformations of the wound bed are comparable to histologic evidence of wound tissue microdeformation in clinical wounds treated with the VAC (Fig. 1, below). As many of the concepts used in this analysis may be unfamiliar to plastic surgeons, we have included a detailed appendix defining these terms.

Finite element analysis is commonly used in engineering to define complex systems such as suspension bridges and high-rise buildings by breaking them down into simple discrete elements. Finite element analysis has found applications in plastic surgery ranging from the analysis of craniofacial stress,\textsuperscript{12} to burn heat-transfer,\textsuperscript{13} to skin deformation.\textsuperscript{14}

We simulated the wound by using mechanical properties from the literature and assumed that these properties were constant in all directions (isotropic). By altering the distance between struts and the thickness of the struts, we changed the physical properties of the sponge referred to as pore diameter and pore volume fraction. We further show how the finite element analysis model can be used to optimize the set of conditions that define the VAC system.

**Materials and Methods**

**Histologic Processing**

Routine biopsy specimens of five clinical wounds treated with the VAC for 4 to 7 days were stored in formalin, embedded in paraffin, sectioned in 5-\textmu m sections perpendicular to the wound surface, and stained with hematoxylin and eosin. Biopsy sections were evaluated for surface undulations and cellular and vascular structures.

**Finite Element Modeling**

ADINA Version 8.0 (Adina R&D, Watertown, Mass.), finite element software, was used to formulate the finite element analysis simulations in this study. The validity of these analyses was checked by the solution of closed form analytic equations. An order of magnitude estimation is included in the Appendix.

**The VAC Computational Model**

The VAC device consists of a highly porous polyurethane sponge with spatial connections between the pores, allowing subatmospheric pressure applied to the sponge to be distributed equally throughout the sponge. The VAC device used today applies a 70- to 150-mmHg vacuum.

The VAC is modeled as a series of pores with the polyurethane sponge in contact with the wound. We assume the pores to be symmetric and that there is no lateral displacement in the center of the pore. Furthermore, where the wound contacts the sponge, we expect no vertical displacement. These boundary conditions and pressure are applied in a two-dimensional finite element model.

The wound is modeled as a linear, homogenous, isotropic, elastic material. Although a nonlinear stress-strain relationship exists for the skin and other connective tissues, the skin shows a fairly linear stress-strain curve in the observed strain ranges.\textsuperscript{15} Furthermore, we varied the compressibility of the material (Poisson's ratio) to study this effect on wounds.

Five parameters were studied: stiffness of the wound (Young's modulus of elasticity); compressibility of the wound (Poisson's ratio); pore diameter of the sponge, defined by the distance between two struts in the model; pore volume fraction of the sponge; and pressure applied to the sponge (or differential thereof). We modeled variation in each of the above parameters (Fig. 3). As each parameter was sequentially varied, all other parameters were assigned "standard" values usually observed in the application of the VAC (Table I).
Fig. 3. Finite element calculations of wound behavior with stiffness, compressibility, pore diameter, pore volume fraction, and applied pressure.

**TABLE 1**

Finite Element Parameters Studied

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<tr>
<th></th>
<th>E (elastic modulus, kPa)</th>
<th>l (pore diameter, mm)</th>
<th>N (Poisson’s ratio)</th>
<th>P (pressure, mmHg)</th>
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* Changes to V use strut sizes of 0.15, 0.3, and 0.5 mm; 0.15 mm is used when strut thickness is not varied.

**Simulation Parameters**

*Constraint boundary conditions.* The system is modeled as a large number of pores with associated struts such that the centerlines underneath the struts impose a symmetric boundary condition. At the centerline underneath each strut, we assume no lateral displacement. Vertical displacement will be slight because of the almost incompressible condition imposed on Poisson’s ratio. This symmetric boundary condition was modeled using half the strut thickness in the analyses.

*Force boundary conditions.* In this static case, no shear stresses are imposed on the wall; therefore, all the forces act perpendicular to the wall. Thus, we impose only a uniform pressure boundary condition in our analysis.

**RESULTS**

**VAC Device Increases the Microscopic Surface Area of the Wound**

Histologic sections of wounds were studied comparing areas treated with a VAC for 4 to 7
Finite element analysis of the wound-VAC system was conducted to directly predict the strain imposed by the VAC sponge on wound tissue. Visible in the finite element analysis is tissue stiffness (characterized by Young’s modulus), tissue compressibility (characterized by Poisson’s ratio), sponge pore diameter, pore volume fraction, and variability of wound tissue strain over a range of imposed pressure (Fig. 3). Higher strains can be induced by increasing pressure, increasing pore diameter, or decreasing strut thickness. Strains are also predicted to be greater when mechanical properties of the wound such as the Young’s modulus or Poisson’s ratio are decreased.

Using physiologic values for tissue, typical sponge pore diameter, and pressures used clinically results in a striking resemblance between the finite element analysis output and the histologic cross-section (Fig. 5). Point-wise strain

Fig. 4. Three-dimensional diagram of the VAC. Contact with the sponge can increase the surface area of the wound (left) by inducing microdeformations of the surface (right) without increasing the overall dimensions of the wound.

Fig. 5. Wound biopsy specimen 7 days after VAC application (left) shows remarkable similarity to deformation predicted by finite element analysis model (right).
along the simulated wound surface was maximal in the regions close to the struts and, consistent with a model of a thin membrane acted on by a uniform pressure, nearly constant across the majority of the wound tissue.

Strain Variability along the Wound Surface

Surface strain varies in a repeating pattern across the wound tissue. Strain is negative (compression) immediately underneath the sponge struts, as they indent the surface of the wound. At an applied pressure of 15 kPa (~110 mmHg) typical of the VAC, the tissue quickly reaches a peak strain of 125 percent immediately adjacent to the struts (0.15 mm), as the forces of strut compression and vacuum suction oppose each other maximally and most directly at the edges of the sponge pores. The bulk of the wound tissue within the sponge pore, however, experiences lower strains (5 to 20 percent), with tissue at the center of the sponge pore experiencing the lowest strains (up to 5 percent) (Fig. 6). These strains are dependent on wound thickness. At a wound thickness of 1 mm, the center strains were 0.67 percent, whereas for the most superficial wounds (0.5 mm), the center strains were 5.1 percent.

Wound Healing Affects Tissue Strain

During wound healing, tissue elasticity and compressibility change, and wound displacements induced by the VAC, even at constant pressures, are likely highly time-dependent. As wounds heal, they tend to become fibrotic with increasing stiffness (Young’s modulus of elasticity), thereby decreasing average wound strain. For example, increasing the stiffness from 50 kPa to 70 kPa would lower the average wound surface strain from 35 percent to 12 percent, with a concomitant decrease in peak strains from 200 percent to 125 percent (Fig. 7, above).

As tissue becomes fibrotic or edematous, the Poisson’s ratio may increase, further decreasing the average and peak surface strains. In the simulation, raising Poisson’s ratio from 0.36 to 0.50 (incompressible tissue) resulted in the decrease of average surface strains from 26 percent to 22 percent (Fig. 7, below). In the ranges studied, surface strains also appear to be far more sensitive to changes in tissue stiffness than tissue compressibility. Our model shows that raising tissue stiffness by 40 percent causes a nearly 66 percent decrease in the surface strain, whereas an equivalent change in compressibility results in only a 15 percent decrease. This suggests that changes in the stiffness of the wound over time may be an important factor to consider when optimizing therapies for healing wounds.

Fig. 6. Strain variability across the wound surface.

Fig. 7. Surface strain as a function of wound properties: (above) Young’s modulus and (below) Poisson’s ratio.

Applied Strains Are Device-Dependent

It has been suggested that cells can be induced to respond to growth factors and proliferate when undergoing an optimal degree of strain. To examine how changes in VAC device properties can be harnessed to produce optimal wound tissue strain, finite element
analysis models of the VAC were constructed with varying pore diameter, strut thicknesses, and imposed pressures.

Strain is very sensitive to changes in pressure. Doubling applied pressure from 10 kPa to 20 kPa also doubles average surface strain (Fig. 8, above), but doubling average pore diameter from 0.8 mm to 1.6 mm results in only a 50 percent increase in surface strain (Fig. 8, center). In addition, decreasing the thickness of the sponge struts causes a decrease in the average surface strain (Fig. 8, below). Considered together, these results suggest an exquisite sensitivity of the imposed strain to VAC device properties and demonstrate a broad dynamic range of achievable strains in the wound tissue achieved by varying device parameters.

**Fig. 8.** Surface strain as a function of device properties: (above) applied pressure, (center) sponge pore diameter, and (below) sponge strut thickness.

### Discussion

**Physiologic Basis of VAC**

Numerous theories have been advanced to explain the physiologic basis for the marked improvement in clinical outcomes achieved by the VAC. One theory proposes that the application of suction evacuates interstitial fluid and cellular debris and reduces local edema, decreasing the likelihood of wound infection. Moreover, the resulting hypobaric pressure and increase in blood flow to the wound bed have been shown to accelerate the formation of granulation tissue. Interestingly, intermittent application of subatmospheric pressure has produced superior results, possibly because of mitigating the cellular desensitization that occurs with exposure to continuous subatmospheric pressure. Although it is likely that each of these factors plays a role in the action of the VAC, we propose that the application of micromechanical forces to the wound site may be the most significant mechanism of action.

Micromechanical forces have long been known to be responsible for the induction of cell proliferation and division. Plastic surgeons use tissue expansion to expand soft-tissue envelopes in reconstructive surgery, and orthopedic surgeons and maxillofacial surgeons use distraction osteogenesis (based on the work of Ilizarov) to lengthen bones. During morphogenesis, site-specific cell proliferation in response to local strain from tissue expansion, as in bud formation of glandular branches or gyri formation in the brain, help to sculpt tissue architecture and organ shape. Ingber et al. have shown that for cells to respond to soluble mitogenic factors and proliferate, they must extend, generating isometric tension either by adherence to a stiff substrate or by external application of mechanical forces. Cells that cannot extend assume a more spherical shape (e.g., by spatial restriction of cell spreading, or by growing on a malleable substrate that cannot resist cell contractility and thus dissipates cell tension) are growth-arrested and tend to undergo apoptosis. Cells are thus observed to recognize mechanical signals and increase their rates of proliferation. This behavior provides a natural mechanism for tissue homeostasis: where tissue mass expands, cells are stretched and thus stimulated to divide.

Our results suggest that the application of the VAC exerts micromechanical forces on in-
individual cells in the wound bed, thus stimulating cell proliferation and accelerating wound healing. Indeed, our finite element analysis model demonstrates that at typical clinical settings, the VAC is able to induce average tissue strains in the range of 5 to 20 percent, depending on the stage of wound healing. These strains are consistent with the range of stretch shown to promote cellular proliferation in vitro.\textsuperscript{7,17}

Soluble growth factors and attachment to extracellular matrix proteins, although essential, are not sufficient to stimulate cell proliferation.\textsuperscript{19} Cell cycle progression also requires the appropriate physical context to respond to these two chemical stimuli. This structural requirement may be absent in wounds, as the normal matrix is degraded or altered such that it fails to form a mechanically continuous structure to provide the scaffold on which cells normally stretch and build up isometric tension. The mechanical strain generated by the VAC in the microscopic tissue domains may, in addition to other benefits of suction, overcome this loss of tissue integrity and substitute for the missing structural basis necessary for cell proliferation.

Enhancing the VAC Device

The finite element analysis results obtained here, particularly with respect to pore diameter and strut thickness, may be helpful in optimizing VAC device design. For instance, if higher strains are desired to facilitate cell proliferation, our data might suggest that both increasing the pore diameter and decreasing the strut thickness will increase overall average wound strains. Unfortunately, the model also implies that the higher average strains thus achieved will inevitably be associated with tremendous spikes in strains and stresses in regions immediately adjacent to the struts, which may cause local damage to the wound. Moreover, larger pore diameters may also simultaneously result in larger areas with locally suboptimal strains. Indeed, our model suggests strains peak immediately adjacent to the strut, become optimal (\textasciitilde10 percent) farther away from the strut, and become suboptimal (\textasciitilde5 percent) with increasing distance. Optimizing sponge pore design thus becomes a delicate balance between minimizing the central suboptimal strain regions and minimizing high local strains caused by increasing the number of struts. Our finite element analysis results imply that some of these issues might be addressed through the use of stress concentration-reducing rounding of struts. A great deal of work in the biomechanics literature correlates changes in elastic modulus and Poisson’s ratio with changes in tissue abnormality and injury, tissue type, and age-related modifications.\textsuperscript{15} By combining these data with the kind of systematic analysis presented in this article, our model could be extended to different tissue types or even to the same tissue as it changes over time.

Limitations of the Model

Although biologic tissue is a nonlinear viscoelastic system,\textsuperscript{15} our model was constructed as a linear elastic system. The linear assumption was deemed reasonable, as the tissue stress-strain relationship remained linear over the relatively small range of strains on most elements. Destruction of tissue architecture was assumed to render the normally anisotropic material properties of healthy tissue close to isotropic in the wounded tissue. Furthermore, the biologic system is dynamic, and local cell growth partially relieves stresses that occur in wounds. These aspects of the wound-healing process were not studied in our model. We assumed the struts in this model to be fixed in space and completely incompressible. However, as the actual struts likely have a degree of compressibility, the model may overestimate the peak strain spikes near the struts of the VAC device.

Dennis P. Orgill, M.D., Ph.D.
Division of Plastic Surgery
Brigham and Women’s Hospital
75 Francis Street
Boston, Mass. 02115
dorgill@partners.org

APPENDIX

Definition of Terms

Boundary condition. Characteristics of the boundary of an element in a finite element analysis model. Like edges of a puzzle, finite element models have fixed or defined boundaries with the outside world. For example, if one end of a strut is fixed in space, this is defined as a boundary condition. Boundary conditions are defined mathematically and are needed to solve integrals and differential equations used in finite element analysis.

Elastic. Describes a reversible displacement of a material as a result of an applied force. For
example, when a small force is involved, a stretched spring will return to its original length on release. Were the force too large for the system, the displacement would be inelastic, and the spring would be permanently deformed.

**Finite element analysis.** A system for defining and calculating the mathematical relationships between the simple components that describe larger, more complex systems. Structural analysis of simple structures requires elementary engineering calculations. However, for more complicated structures, variability in structural elements, forces, materials, and so forth results in a problem that cannot be defined by analytical equations (for the whole system). Finite element analysis uses computers to perform calculations that would otherwise take many hours by hand.

**Isotropic/anisotropic.** Assumes the stiffness of a material is the same along any axis. A biologic example of an isotropic material is fat. In contrast, many biologic materials are anisotropic: they are very strong along one axis and weak perpendicular to that axis. For example, a tendon is very stiff along its longitudinal axis and much less stiff across its transverse axis.

**Linear.** Assumes data can be fit to an equation of a line. For most biologic materials such as skin, the relationship between stress and strain is nonlinear and exponential in nature over large strains. To simplify the model, a linear stress-strain relationship is assumed over small displacements.

**Poisson’s ratio (v).** Index of compressibility of a material (Fig. 9). When most materials are stretched, such as a rubber band, they thin out. This can be described mathematically as a ratio of strain parallel to the axis of stress to the strain perpendicular to the axis of stress.

**Pore volume fraction (Vp).** Proportion of sponge occupied by air; pore diameter divided by the pore diameter plus strut thickness.

**Pressure (P).** Force per unit area. For an ideal gas, pressure is proportional to temperature and inversely proportional to volume. Absolute pressure has the same value in all directions and is always a positive number. The atmosphere at sea level exerts a pressure of 760 mmHg, and the application of a vacuum results in a lower value or subatmospheric pressure. Gauge pressure (measuring pressure differences) compares the pressure of a system with that of a reference (usually atmospheric) and is often reported as a negative value for vacuum systems.

**Strain (ε).** Percent increase or decrease in length when force is applied (Fig. 9). For example, if an applied force stretches 1.0 cm of skin to 1.1 cm, the strain is 10 percent. For structures under compression (e.g., the femur during walking), a negative strain results. Like stress, strain depends on direction as well, as a body may deform more in one direction than in another.

**Stress (σ).** A measure of traction on a body, in units of force per cross-sectional area (Fig. 9). Stress is dependent on direction. For example, a blood vessel wall experiences a different stress in the radial direction (blood pressure) versus the axial direction (shear stress).

**Young’s modulus of elasticity (E).** A quantitative measure of the stiffness of a material, calculated as a ratio of stress to strain (force per unit area, measured in pascals; 1 pascal = 1

![Fig. 9. Engineering concepts that describe forces and displacements in tissues.](image-url)
newton/1 m²) (Fig. 9). For each biologic material, the modulus of elasticity indicates how much change in length is expected given the same applied force. For example, as bone is relatively stiff, it has a far higher modulus of elasticity than muscle or skin.

**Order of Magnitude Approximation**

For the case of wound tissue exposed to vacuum generated by a hemispheric suction device, stress within the tissue is defined by Laplace’s law as follows: (0)

\[
\sigma = \frac{\Delta P r}{2t}
\]

where \( \Delta P \) is the pressure difference created by the suction device, \( r \) is pore diameter, and \( t \) is wound thickness. Given the VAC sponge’s typical pore radii and a wound thickness of \(~1\) mm, the stress generated within the tissue is \( \sigma = 9000 \) Pa. Thus, for a typical tissue modulus of elasticity of \( 50 \) kPa, strain is (0)

\[\varepsilon = \frac{\sigma}{E} \approx 18 \text{ percent},\]

comparable to our measured strains.

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