Mechanotransduction in Wound Healing: From the Cellular and Molecular Level to the Clinic

Siqi Fu, MD, PhD, Attending Physician, Department of Dermatology, The Second Ziangya Hospital, Changsha, Hunan Province, China
Adriana Panayi, MD, Instructor, Harvard Medical School, Boston, Massachusetts
Jincai Fan, MD, PhD, Professor, Plastic Surgery Hospital, Peking Union Medical College, Shijingshan District, Beijing, China
Horacio F. Mayer, MD, Interim Chief, Plastic Surgery Department, Hospital Italiano de Buenos Aires, University of Buenos Aires, School of Medicine and Hospital Italiano de Buenos Aires University Institute, Buenos Aires, Argentina
Mahendra Daya, MD, PhD, Principal Specialist, Department of Plastic and Reconstructive Surgery, Nelson R. Mandela School of Medicine, University of Kwazulu, Natal, South Africa
Roger K. Khouri, MD, Hand and Plastic Reconstruction Surgeon, Miami Breast Center, Key Biscayne, Florida
Geoffrey C. Gurtner, MD, FACS, Johnson and Johnson Distinguished Professor of Surgery, Division of Plastic and Reconstructive Surgery, Department of Surgery, Stanford University School of Medicine, Stanford, California
Rei Ogawa, MD, PhD, Professor and Chief, Department of Plastic, Reconstructive and Aesthetic Surgery, Nippon Medical School Hospital, Tokyo, Japan
Dennis P. Orgill, MD, PhD, Associate Professor of Surgery, Harvard Medical School, Boston, Massachusetts

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GENERAL PURPOSE: To review the various mechanical forces that affect fibroblasts, keratinocytes, endothelial cells, and adipocytes at the cellular and molecular level as well as scar-reducing mechanical devices currently in clinical use.
TARGET AUDIENCE: This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.
LEARNING OBJECTIVES/OUTCOMES: After participating in this educational activity, the participant will:
1. Compare and contrast the responses of various types of cells to mechanical forces.
2. Identify the mechanical devices and techniques that can help restore skin integrity.

ABSTRACT
Skin provides a critical protective barrier for humans that is often lost following burns, trauma, or resection. Traditionally, skin loss is treated with transfer of tissue from other areas of the body such as a skin graft or flap. Mechanical forces can provide powerful alternatives and adjuncts for skin replacement and scar modulation. This article first provides an overview of the various mechanical forces that affect fibroblasts, keratinocytes, endothelial cells, and adipocytes at the cellular and molecular level. This is followed by a review of the mechanical devices currently in clinical use that can substantially augment the restoration of skin integrity and reduce scarring. Methods described include tissue expanders, external volume expansion, negative-pressure wound therapy, and skin taping.
KEYWORDS: adipocytes, fibroblasts, keratinocytes, mechanical forces, mechanotransduction, negative-pressure wound therapy, scar, skin taping, tissue expander, wound healing

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INTRODUCTION

Humans have the remarkable ability to heal most disruptions to their integument. Common skin injuries usually heal with minor interventions. For open wounds, there is a well-orchestrated healing cascade that promotes wound closure through the processes of contraction and scar formation. Interestingly, these processes are seen in mammals, but not in other species such as amphibians that heal through regeneration.[1] The accelerated response of scarring may have evolved to minimize the detrimental effects of wound infections.

The ability of mammals to regenerate is not completely lost; visible scarring is mainly seen when the deep dermis is damaged. Dunkin et al[2] performed an experiment in normal volunteers that showed that when forearm incisions are less than 0.56 mm (approximately one-third of the thickness of the skin), no visible scar occurs. Various superficial skin therapies such as lasering, chemical peels, or cryoablation depend on this because they act on superficial areas of skin and can improve texture without scarring. Further, Tam et al[3] showed that very small, full-thickness columns of skin can be removed without a visible scar. This principle has been applied in fractional laser ablation.

In some cases, humans heal with an excess scar response resulting in what are referred to as hypertrophic scars (HTSs) and keloids. These are more frequently seen in wounds that heal slowly and are more common in patients of African and Asian descent.

Plastic surgeons have developed techniques to close large skin defects. Moderate-sized injuries can be repaired with simple suturing under tension. Larger defects require more invasive surgical procedures such as skin grafts and flaps. Both procedures usually result in scars at the donor sites.

During wound healing, a variety of cells in the skin and subcutaneous layer respond to mechanical stress and adapt to the new environment through shape modification, migration, proliferation, differentiation, and other biologic behaviors. The process through which cells perceive and respond to mechanical forces is called *mechanotransduction*. The mechanisms of mechanotransduction that modulate wound healing and scarring are only just beginning to be understood.

Mechanical forces can be utilized as medical treatment (Huang et al[4] call this *mechanotherapy*) and applied to cells, tissues, or organs. In the following sections, mechanotransduction from the cellular and tissue perspective will be discussed, followed by a description of the current clinical applications of mechanotherapy.

MECHANOTRANSDUCTION PRINCIPLES AND PATHWAYS

The concept of "tension integrity," or *tensegrity*, was first used by Ingber[5] to describe the cell structure as networks under mechanical forces that fulfill behaviors including formation, growth, proliferation, differentiation, migration, and apoptosis. The elements of tensegrity involved in the skin include (macroscopically) the dense fibers in the dermis and the extracellular matrix (ECM) and (microscopically) the cytoskeleton and nuclear skeleton.[5] Similar to architectural structures, skin and its constitutive cells support physiologic balance. When skin is disrupted by trauma or infection, some skin disorders such as fibrogenesis or keratinocyte overproliferation are triggered.

Fibroblasts

Fibroblasts align and elongate according to the direction of mechanical strain. Tension can markedly alter fibroblast expression of matrix remodeling and inflammatory genes.[6] High-tension wounds are more likely to result in severe scar formation, and mechanical forces are concentrated in the margin region of keloids. For example, HTSs can be induced on murine dorsal skin with a biomechanical bidirectional loading device.[7] Tension-stimulated skin fibrogenesis is dependent on three mechanisms: ECM crosslinking and stiffening, mechanotransduction with integrin and focal adhesion kinase (FAK), and integrin-mediated transforming growth factor β (TGF-β) signaling.[8]

The ECM-integrin-cytoskeleton mechanism is the classical pathway of mechanotransduction that regulates fibroblast viability, collagen production, and myofibroblast transformation. Integrins are important mechanical sensors and bidirectional information transducers between cells and the ECM.[9] The ECM in turn influences cell activity, determines cell shape, controls cell differentiation, and is involved in cell migration with the assistance of the cytoskeleton.[10]

Focal adhesion complexes (eg, talin, vinculin, and paxillin) are intracellular binding proteins involved in the cell-ECM interaction that activates FAK.[11] Collectively, ECM transmits the mechanical signals to the cell cytoskeleton through integrin-FAK signaling. In the HTS model, FAK promotes human dermal fibroblast generation of chemokine monocyte chemoattractant protein 1. When FAK is knocked out in a murine model, both inflammatory cell recruitment and fibrosis are reduced.[12]

The stiffness of the ECM can influence mechanical signaling and induce expression of TGF-β1 (an isoform of TGF-β), fibroblast-to-myofibroblast transition, and collagen production. A stiff ECM triggers integrins to activate and release TGF-β1. Activated TGF-β1 binds to TGF-β1R on myofibroblasts, leading to an increase in TGF-β1 and α-smooth muscle actin, which increases stiffness in the ECM creating a positive feedback loop for fibrogenesis. Soft ECM reduces the release of TGF-β1 and binding to its receptor and suppresses expression of TGF-β1 and α smooth muscle actin.[8]

Keratinocytes

Mechanical forces result in the expansion of the skin near the wound base through the stimulation of epidermal cell proliferation and inflammation in the dermis.[13] Cultured human keratinocytes and fibroblasts on a collagen membrane in a tensile device showed asymmetric keratinocyte migration regulated by epidermal growth factors secreted from fibroblasts.[14]

Keratinocyte proliferation under tension occurs via three main mechanisms: matrix-integrin signaling, a mitogen-activated protein kinase-associated pathway, and epithelial-mesenchymal interactions.[15]

Keratinocyte migration and re-epithelialization require integrins and facilitate wound closure.[16] In an experiment by Wong et al,[12] FAK was knocked out in keratinocytes, which had an atrophic effect on the dermis. This emphasizes the complexity of communication between different cell layers in mechanical signaling of multicellular tissues. Under mechanical stimulation, ECM-integrin is involved in the upstream pathway that activates multiple downstream proteins in keratinocytes.

Mitogen-activated protein kinases, which include p38 kinase, play a prominent role in the biologic response to wound tension.[17] Keratinocyte culturing in a mechanical pressure unit showed that mechanical pressure stimulates p38 phosphorylation.[14] Keratinocyte-mesenchymal transition is involved in wound healing, as well as in the pathogenesis of fibrosis. Culturing human keratinocytes under continuous mechanical tension results in increased cell proliferation as well as keratinocyte-mesenchymal transition, a result replicated in vivo in stretched murine skin.[18]

Endothelial Cells

Skin has a complex microvascular anatomy. During skin tissue expansion, vascular endothelial cells, similar to keratinocytes and fibroblasts, are subjected to mechanical forces, including shear stress. Numerous studies have shown that mechanical forces can promote angiogenesis and vessel remodeling. Specifically, use of a rat ear stretch model under continuous or cyclic tension showed that the number of epidermal cells, as well as blood vessel density, increases under mechanical load.[19] Moderate-intensity, intermittent, external volume expansion (EVE) was shown to increase skin vascular density, skin thickness, and subcutaneous soft tissue in a murine model.[20] The increased vessel density comprised the modification of existing vessels, as well as the generation of new vessels.

Prior research has found there are more vessels and vascular dysfunction in HTSs and keloids. Ogawa and Akaishi[21] characterized HTSs and keloid scars as vascular diseases. In addition, electron micrography of keloid tissue shows endothelial cell and lymphocyte infiltration.

Negative-pressure wound therapy (NPWT), a well-known model of mechanotransduction and mechanotherapy, accelerates wound healing through stimulation of angiogenesis via increased expression of vascular endothelial growth factor receptors (VEGFRs). A study exploring temporal expression of VEGFRs in rabbits showed that VEGFRs were abundantly and rapidly expressed in rabbits receiving NPWT compared with the control group.[22]

Adipocytes

The subcutaneous adipose tissue is also under the influence of mechanical forces. Adipose tissue includes various cell types, such as adipose-derived stem cells, preadipocytes, and mature adipocytes. Adipose-derived stem cells can be differentiated into adipocyte lineage cells or vascular endothelial cells under suitable mechanical stimulation.[23] However, mature adipocytes have a different effect on adipogenesis compared with preadipocytes when cultured in the cyclic stretching system: Tension activates a signaling pathway in adipocytes that results in cell hypertrophy,[24] whereas that pathway is decreased in preadipocytes.[25]

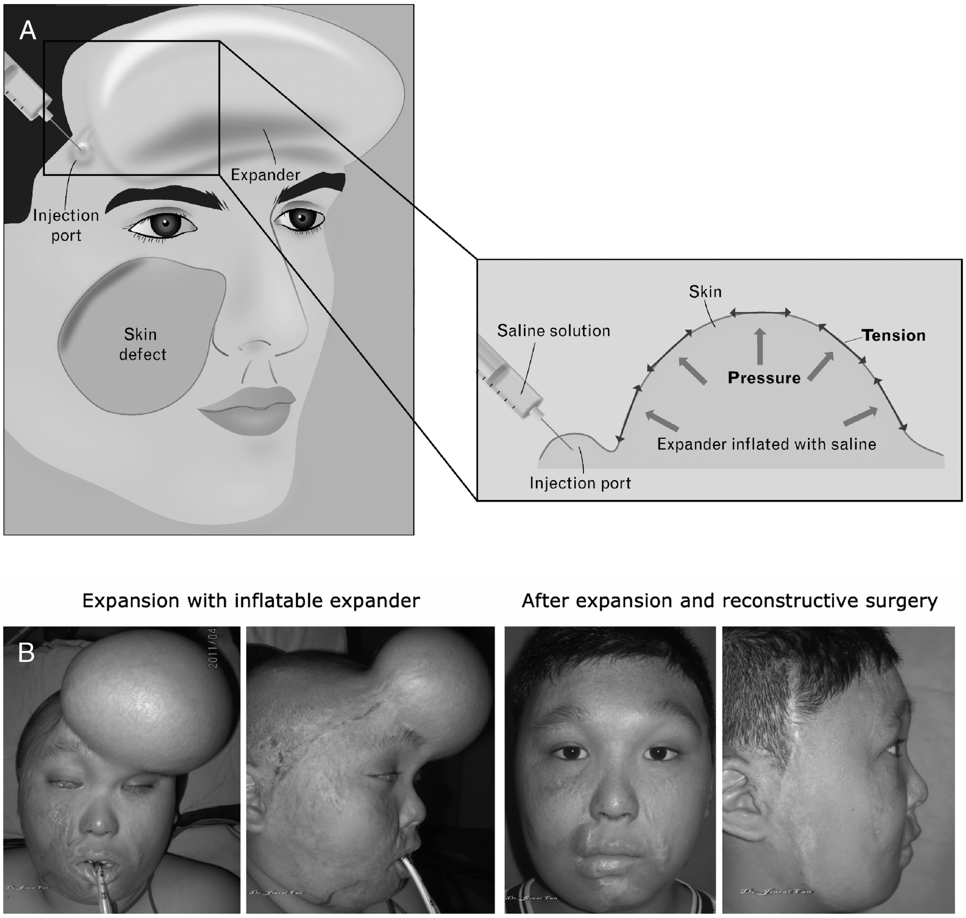
CLINICAL APPLICATIONS

Traditional Tissue Expansion

In 1957, Neumann[26] pioneered a new method for ear reconstruction whereby he created a subcutaneous balloon to allow for skin expansion. A decade later, Gibson and Kenedi[27] described two biomechanical principles of skin under tension: creep and stress relaxation. *Creep* describes the expansion of skin over time under stretching, whereas *stress relaxation* indicates that the force required to maintain the skin at a fixed distance decreases with time. Tissue expansion has now become a common popular technique used to repair skin defects with adjacent normal tissue of similar tone, color, and texture.

Skin can be stretched and expanded when an inflatable expander is inserted under the skin and periodically filled with saline solution or air. The skin formed as a result can then be used to repair an adjacent defect. Tissue expanders have been applied on large scars and benign skin tumor excisions, in ear reconstruction, and in implant-based breast reconstruction. Extreme tissue expansion can provide remarkable areas of coverage in the head and neck. For example, Fan et al[28] applied a bilateral-pedicled expanded forehead flap to full-perioral and cervical scars, as well as combined the single-pedicled expanded forehead flap with microsurgery to resurface large facial scars.[29] This modified technique has also been used to repair major electrical pubic burn scars with the use of expanded free forehead skin flap with hair from the parietal region (Figure 1).[30]

Figure 1. FOREHEAD EXPANSION
A, An inflatable expander is inserted under the skin and expanded by periodically filling with saline (eg, weekly). B, A single-pedicled expanded forehead flap with microsurgery is used to resurface large facial scars.



Photos included with appropriate patient/guardian consent.

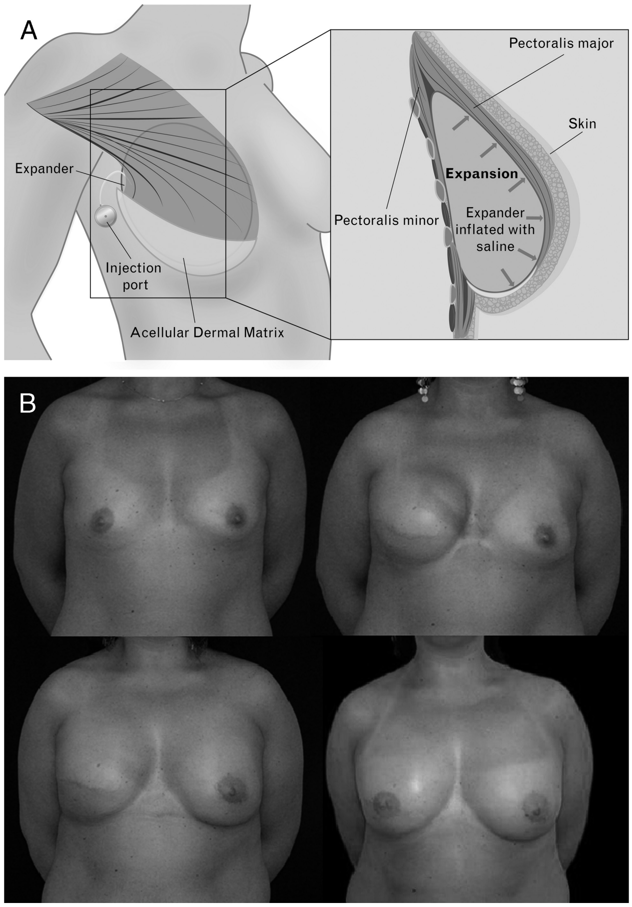
Implant-based breast reconstruction with the use of an initial tissue expander is one of the most common methods of breast reconstruction throughout the world. An expander is applied under the pectoralis major during or after mastectomy. With the injection of saline, both muscle and skin expand to allow for the second stage of surgery, in which the tissue expander is exchanged with a permanent implant. The second surgery stage offers a unique opportunity for pocket work maneuvers to maximize the aesthetic results of these procedures (Figure 2). Mayer and Loustau[31] showed that capsular tissues, which are a result of acute expansion, are highly vascularized and can be used as flaps or grafts at the inframammary fold for immediate implant-based breast reconstruction in patients with prior augmentation.

External Volume Expansion

In EVE, a vacuum-based device is placed over the skin and soft tissues (Figure 3). This device was originally designed for use in cosmetic nonsurgical breast augmentation. The device causes the soft tissues to expand by inducing edema. The mechanical forces applied stimulate the formation of new blood vessels in soft tissues as well as growth of adipose cells. This device has been used to enhance autologous fat grafting after breast cancer surgery.[32] Breast reconstruction historically required the use of a prosthesis or skin and musculocutaneous flaps. Autologous fat grafting in combination with EVE provides a novel method of breast reconstruction with minimal skin incisions, because fat can be harvested through very small skin incisions. In addition, the minimal incisions improve aesthetics and skin sensation and can be substantially less costly than other traditional methods. Currently, patients can wear these bra-like devices for 10 hours a day preoperatively and apply cyclic suction over a 3-week period. After surgery, a more flexible device is used that acts like a splint to retain volume. Fat-graft survival has been reported between 53% and 82%.[33] Complications include skin irritation, edema, bruising, blister formation, and fat necrosis. Vacuum-based EVE devices not only promote

Figure 2. IMPLANT-BASED BREAST RECONSTRUCTION WITH USE OF A TISSUE EXPANDER

A, An expander is placed under the pectoralis major and saline is injected. This allows for both the muscle and skin to expand in preparation for a second stage of surgery, during which the expander is exchanged for a permanent implant. B, A 46-year-old patient underwent skin-sparing mastectomy and immediate two-stage implant-based breast reconstruction. The second surgical stage allowed pocket maneuvers and contralateral breast augmentation for symmetry.



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adipogenesis but stimulate the proliferation and angiogenesis of skin tissue.[34]

Skin Taping and Scar Offloading

Skin taping is a simple method where simple medical skin tape can be applied to expand skin. Paper taping has mainly been used to reduce the tension around a scar and minimize or prevent scaring. This technique has shown demonstrable success in managing abnormal scars.[35] It can also be used for pre-expansion of the skin by the patients at home before surgical excision of a large scar. Daya and Nair[36] described this technique as *traction-assisted dermatogenesis* (Figure 4). The advantages of skin taping include its noninvasive application and ease of application by patients without professional assistance. One randomized, double-blind trial using the taping technique on torso scars after dermatologic surgery showed an overall improvement in scar appearance. When compared with normal dressings, skin taping on torso wounds for 12 weeks resulted in better scar appearance at 6 months.[37]

Other skin closure and tension-relieving devices have been developed for scar modulation. For example, Longaker et al[38] developed an elastomeric device that relieves tension at the site of wound closure and compresses the underlying scar. In a prospective, randomized, multicenter clinical trial, the device was applied to abdominoplasty incisions and showed a significant reduction in scarring. Most standard tapes are less flexible, acting as a static splint compared with the elastomeric device.[38]

Surgical Techniques to Reduce Tension in Scarring

Scars under tension are more prone to scar hypertrophy and keloid formation. Ogawa et al[39] performed a finite element analysis of the mechanical force distribution around keloids. The study showed that both the skin tension on and inflammation within the keloid are particularly high at the leading keloid edges. Surgical tension-reducing techniques such as specialized incisions, for example, small-wave incision design and Z-plasty, silicon sheeting, and subcutaneous suturing, can result in substantial improvement.[39–42] Gurtner et al[43] utilized a mechanomodulating stress-shielding polymer device to treat wounds after abdominal surgery and showed significant improvement in scar appearance, with a decrease in HTS.

Shockwave Therapy

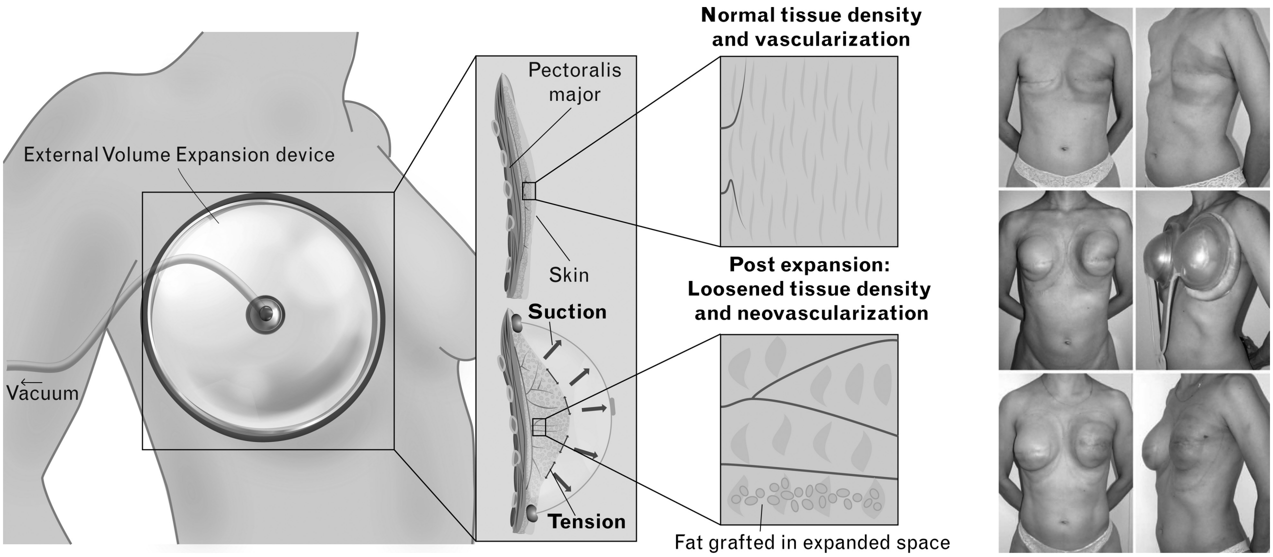
Plastic surgeons have more recently used electromagnetic, electrohydraulic, and piezoelectric technologies that generate high-energy acoustic waves. Specifically, rhinoplasty has traditionally been performed using mechanical instruments such as rasps, saws, and chisels. Piezoelectric instruments now allow nasal bone modification with higher precision and minimal damage to the surrounding soft tissues.[44] In wound healing, extracorporeal shockwave therapy, a lithotripsy technique, has been used to treat diabetic and surgical wounds.[45,46] Improved wound healing is believed to be attributable to mechanotransduction that increases angiogenesis and collagenesis, improves vascularization, and decreases apoptosis.[47–51]

Negative-Pressure Wound Therapy

Negative-pressure wound therapy or vacuum-assisted closure was first introduced in 1997.[52] It involves a porous sponge covered with an occlusive dressing connected to a suction source. These devices have now

Figure 3. EXTERNAL VOLUME EXPANSION

A, An external vacuum-based device is placed over the skin and soft tissues, and the mechanical forces applied stimulate angiogenesis and adipogenesis. B, A patient underwent mastectomy and external volume expansion on both breasts in preparation for autologous fat transfer.



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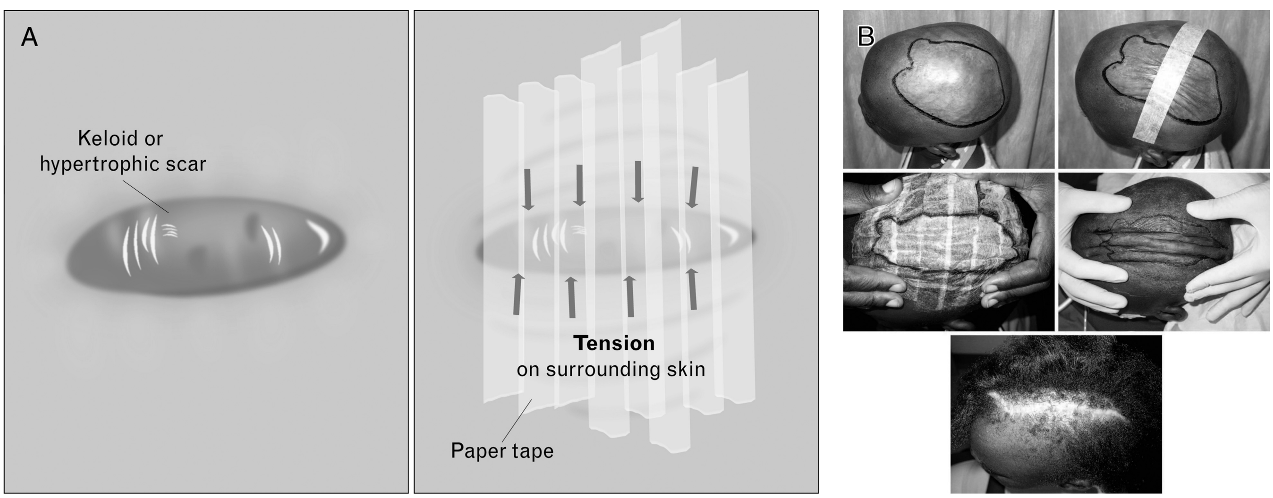
become the most common treatment modality for large complex wounds in many parts of the world.

Despite many studies looking at the mechanism of NPWT, the exact detailed molecular signaling pathway has not been fully elucidated. It has been suggested that under suction, microorganisms and inflammatory and cytotoxic factors are partly removed to promote granulation tissue formation. In addition, tissue edema decreases with interstitial fluid removal. Micromechanical forces promote cell proliferation and differentiation and increase vascular angiogenesis, as well as local collection of growth factors.[53] With continuous or cyclic pressure, blood flow in the wound is increased, and tissue remodeling is stimulated. The porous material and the film keep the periwound environment moist, facilitating healing.[54]

Providers use NPWT in the treatment of both acute and chronic wounds, as well as to improve outcomes in skin graft and flap surgery. It is also a useful option for complicated surgical incision management. For

Figure 4. TRACTION ASSISTED DERMATOGENESIS

A, Simple medical skin tape can be applied to expand the skin and reduce the tension around a scar to minimize scaring. B, Skin tape was used to pre-expand the scalp skin followed by excision for resurfacing an area of burn alopecia in a child.



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example, NPWT has been applied to split-thickness skin grafting instead of traditional bolster dressings.[55] It stabilizes the pressure, promoting re-epithelialization and enhancing revascularization, and even minimizing skin loss when used on special skin graft donor sites.[56] Finally, NPWT may be of benefit in pedicle or free-flap surgery where partial or total flap congestion has occurred.[57]

CONCLUSIONS

Mechanical forces exist throughout the human body, acting at cellular and molecular levels. Skin can grow and regenerate to form new tissue, it can be replaced by scar tissue, and it can also generate HTSs and keloids. These clinical observations are dependent on the basic biology of mechanotransduction and underlie several effective mechanotherapies. Better understanding and strategic application of mechanical forces will provide future therapies that can improve function while minimizing the detrimental effects of scarring.

PRACTICE PEARLS

- Mechanical forces can be used as medical treatment. This is called mechanotherapy.
- Fibroblast, keratinocyte, endothelial cell, and adipocyte processes are affected by mechanical forces.
- Tissue expanders can be used in the reconstruction of skin defects.
- External volume expansion can be used to improve breast augmentation outcomes.
- Providers can use NPWT in the treatment of acute and chronic wounds and to improve outcomes of skin grafts and flaps. ●

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