# Shock Wave Therapy in Wound Healing

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**Background:** Recently, shock wave therapy has been investigated as an adjuvant therapy in the treatment of acute and chronic wounds. There are several devices with focused and unfocused shock waves that have been administered to a heterogenous group of wounds. Encouraging preclinical and clinical studies suggest that shock wave therapy may promote wound healing with little or no adverse events, prompting investigations into the mechanism of action and additional clinical trials.
**Methods:** The peer-reviewed literature within the past 10 years was studied using an evidence-based approach.
**Results:** Preclinical studies demonstrate that shock wave therapy affects cellular function and leads to the expression of several genes and elaboration of growth factors known to promote wound healing. Limited clinical trials are encouraging for the use of shock wave therapy in the treatment of acute and chronic wounds. Serious complications, including wound infections, bleeding, hematomas, seromas, and petechiae, have not been reported in the largest of these studies.
**Conclusions:** Shock wave therapy is an intriguing physical modality that may play an important role as an adjuvant therapy in wound healing. To date, there is no consensus on which wounds are most likely to benefit from shock wave therapy and what the optimal power, degree of focus, and frequency or number of cycles should be. Well-designed preclinical and clinical studies are necessary to better understand shock wave therapy in wound healing. (*Plast. Reconstr. Surg.* 128: 721e, 2011.)

Extracorporal shock wave therapy has revolutionized the treatment of urolithiasis, allowing fragmentation of stones at a distance, avoiding invasive surgery in most cases. Variants of this technology have been used to treat fractures,[1–4] osteonecrosis of the femoral head,[5] plantar fasciitis,[6,7] and critical myocardial and limb ischemia.[8] Most recently, shock wave therapy has been used in the treatment of acute and chronic wounds, burns, and skin flaps.

Shock waves are biphasic high-energy acoustic waves that can be generated by electrohydraulics. A high-voltage spark is discharged under water, causing vaporization and the release of acoustic waves with high peak pressures that rapidly decline over 10 μsec.[9,10] As the shock wave propagates over distance, energy is absorbed by the tissue. The degree of focus can be modulated by parabolic reflectors, resulting in a variable concentration energy at a desired location (Fig. 1). Shock waves are defined by their waveform, the number of impulses, the frequency of impulses, and energy flux density (in millijoules per square millimeter).

The mechanisms of biological changes that result from shock waves are not entirely clear. One hypothesis is that shock waves act as transient micromechanical forces that induce perturbations at the cell structural level, thereby altering biological activity. Mechanotransduction results from geometric changes in the cellular cytoskeleton, which is analogous to design concepts of tensegrity ar-

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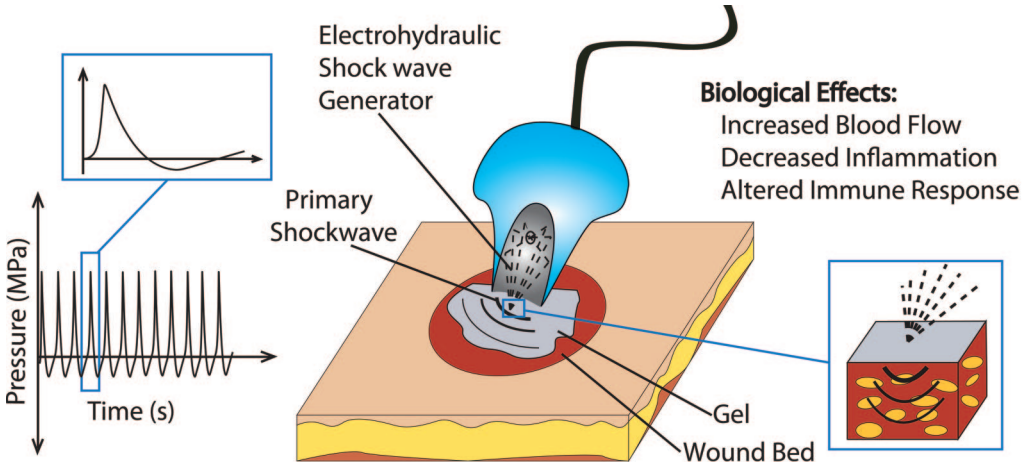


**Fig. 1.** Schematic diagram of shock wave therapy for wounds. A shock wave is produced by a sparkplug in a conductive device and can be focused with a parabolic reflector and conductive gel. The waveform shows peak pressures of 100 MPa after approximately 10 $\mu$sec, followed by a brief period of subatmospheric pressure. The wave is attenuated as it traverses the tissue.

ticulated by the architect Buckminster Fuller and the sculptor Kenneth Snelson[11] and applied to biological systems by Ingber. Briefly, external deformations can be transduced to an already "prestressed" or internally balanced cytoskeleton through tensile linkages or cell surface receptors that would initiate a cascade of intracellular events leading to changes in cell activity.[12] Such an explanation for shock wave therapy would parallel our existing understanding of soft-tissue expanders in reconstructive surgery, distraction osteogenesis and, most recently, wound healing with the vacuum-assisted closure device, in which micromechanical forces promote wound healing through increased cell division, angiogenesis, and release of growth factors in the wound bed.[13]

Preclinical experience using shock wave therapy suggests a potentially important role in promoting healing in diabetic wounds, flap necrosis, and burns. There have been clinical studies with low levels of evidence based on the criteria of the Center for Evidence-Based Medicine.[14] Among these studies, only a few have been prospective, randomized, controlled studies that fail to meet several key Consolidated Standards of Reporting Trials criteria.[15] The limited clinical evidence and lack of rigorous study design have made it difficult for clinicians and regulators to fully support shock wave therapy in wound healing at this time. Several questions, including optimal shock wave therapy parameters, timing of treatments, and types of wounds most suited for shock wave therapy remain unanswered and warrant further clinical studies.

## PATIENTS AND METHODS

### Literature Search

We searched Medline, the Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register. The search strategy we used included the MeSH terms "wounds and injuries/therapy," "wounds and injuries/pathology," "soft tissue injuries/pathology," "soft tissue injuries/therapy," "ultrasonic therapy/methods," and "high-energy shock waves/therapeutic use" along with text words. No other limits were applied to any of the searches. In addition, reference lists of full-text articles obtained through these searches were searched.

### Selection

We included shock wave therapy preclinical studies in animals, in vitro studies, and clinical studies, including prospective and retrospective trials that included wound healing, flap necrosis, and burns. Because of the scarcity of shock wave therapy clinical trials, we did not exclude nonrandomized or poorly controlled trials. Outcomes of interest included improved wound healing, flap necrosis, and reepithelialization of burns.

### Data Abstraction

Review of randomized controlled trials was carried out based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16]

### Data Analysis

The Centre for Evidence-Based Medicine Levels of Evidence[14] were applied to the clinical studies reviewed. In addition, the Consolidated Standards of Reporting Trials checklist of information was applied to those that were randomized controlled studies.[15]

## RESULTS

### Wound Healing

Two preclinical studies have looked at shock wave therapy in diabetic wounds. Kuo et al.[17] administered unfocused shock wave therapy (800 impulses at 0.09 mJ/mm$^2$) to streptozotocin-induced diabetic rats with dorsal skin defects. Shock wave therapy significantly reduced wound size in diabetic rats, with greater reductions seen with more treatment (Table 1).[17–24] There was increased blood perfusion; decreased proinflammatory activity; and increased vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase, and proliferating cell nuclear antigen expression.[17]

A more recent study[18] in db+/db+ mice with full-thickness dorsal skin defects found that unfocused shock wave therapy (200 impulses at 0.1 mJ/mm$^2$) led to a prolonged and elevated expression of gene subsets. Shock wave therapy had no effect on wound closure in diabetic or control mice. Multiple treatments with unfocused shock wave therapy further delayed wound healing after initially increasing the size of the wound.[18]

Schaden et al.[19] found a 75 percent treatment response (as defined by 100 percent wound epithelization) in a level IIb study of 208 patients with heterogeneous wounds treated with débridement and unfocused shock wave therapy (100 to 1000 impulses at 0.1 mJ/mm$^2$) with a mean of three treatments. One-third of wounds were acute and nearly 40 percent of wounds had either partial or complete failure to heal after primary surgical closure, an important confounder unaccounted for in the analysis. Excluding venous stasis and arterial insufficiency ulcers, wound cause did not affect treatment success, but statistical analyses to justify this conclusion were not performed. Analyses based on wound size and duration revealed that small wounds (<10 cm$^2$) of short duration (<1 month old) were most likely to rapidly completely reepithelialize.

Saggini et al.[20] led a level IIIb study with 30 consecutive patients treated with focused shock wave therapy (100 impulses at 0.037 mJ/mm$^2$) every 2 weeks (range, four to 10 sessions) until complete healing was achieved. Unlike others, this study used focused shock wave therapy and a lower energy flux density. A 50 percent complete healing response (parameters not defined) with no adverse events was reported. This conclusion was obtained by grouping a heterogeneous patient population and their individual responses: posttraumatic ulcers (69 percent complete healing), venous ulcers (36 percent complete healing), and diabetic ulcers (25 percent complete healing). No subset analysis based on wound cause was conducted. In the remaining ulcers without complete healing, increased wound bed blood supply was observed (data not provided). A significant decrease in pain based on the pain self-assessment numeric box scale in treated patients was also reported.

Wang et al.[21] found complete healing (parameters not defined) in 31 percent of patients in a level IIb study with 72 patients with chronic diabetic foot ulcers treated with focused shock wave therapy (300 ± 100 impulses/cm$^2$ at 0.11 mJ/cm$^2$) every 2 weeks for 6 weeks. Increased perfusion, cell concentration, and activity were noted. Notably, the control arm received hyperbaric oxygen therapy instead of standard therapy. The wounds studied were relatively large (shock wave therapy, 11.2 ± 20 cm$^2$; hyperbaric oxygen, 10.5 ± 20 cm$^2$). Shock wave therapy was found to be superior to hyperbaric oxygen. The rationale for treatment parameters and details of the clinical assessment are lacking. Because the

**Table 1. Wound Healing**

| Reference | No. of Subjects | Size of Injury | No. of Pulses | Density of Energy (mJ/mm$^2$) | Focused or Unfocused |
|---|---|---|---|---|---|
| Kuo et al., 2009[17] | 30 ESW, 20 control* | 6 × 5 cm | 800 | 0.09 | Unfocused |
| Zins et al., 2010[18] | 15 ESW, 15 control* | Circular 19-mm diameter (280 mm$^2$) | 200 | 0.1 | Unfocused |
| Schaden et al., 2007[19] | 208 | Differing per patient | 100 | 0.1 | Unfocused |
| Saggini et al., 2008[20] | 30 ESW, 10 control | Differing per patient | 100 | 0.037 | Focused |
| Wang et al., 2009[21] | 40 ESW, 42 HBO | 11.2 ± 20 cm$^2$ | 500 | 0.11 | Focused |
| Moretti et al., 2009[22] | 15 ESW, 15 control | 300 ± 130 mm$^2$ | 100 | 0.03 | Unfocused |
| Dumfarth et al., 2008[23] | 50 ESW, 50 control | Differing per patient | 25 | 0.1 | Unfocused |
| Ottomann et al., 2010[24] | 28 | Differing per patient | 100 | 0.1 | Unfocused |

ESW, extracorporal shock wave therapy; HBO, hyperbaric oxygen.
*Preclinical.

study did not have long-term follow-up, the natural history of diabetic ulcers treated with shock wave therapy remains unknown.

Moretti et al.[22] conducted a level IIb study of 30 diabetic patients with neuropathic foot ulcers treated with débridement followed by unfocused shock wave therapy (100 pulses of 0.03 mJ/mm$^2$) for three sessions every 72 hours and wound care. The control arm was treated with débridement, pressure relief, and treatment of infection. The wounds studied were small (shock wave therapy, 300 ± 130 mm$^2$; control, 250 ± 100 mm$^2$, mean size ± SD). Shock wave therapy parameters were based on the authors' clinical experience with shock wave therapy in orthopedics. In 20 weeks, the treatment arm had a healing rate of 53 percent versus 33 percent in the control. Although randomized, the random allocation sequence, its mechanism, and its implementation were not explained. The study excluded chronic diabetic ulcers greater than 5 cm to avoid selection bias.

Dumfarth et al.[23] carried out a level IIb study with 100 patients undergoing vein harvesting for coronary artery bypass graft surgery, half of whom received unfocused shock wave therapy (25 impulses at 0.1 mJ/mm$^2$) at the wound closure site of the vein graft. Treated patients had lower ASEPSIS scores (i.e., serous discharge, erythema, purulent exudates, separation of the deep tissue, isolation of bacteria, and duration of inpatient stay) on postoperative days 3 and 7, with no reported complications from treatment, suggesting better wound healing. Treated patients had a statistically significant lower use of antibiotics for leg wounds. However, the study was not powered for its primary outcome. The long-term effects of shock wave therapy in these surgical wounds were not assessed.

Recently, Ottomann et al.[24] conducted a level Ib study with 28 patients with acute traumatic wounds and burns requiring skin grafting treated with unfocused shock wave therapy (100 impulses at 0.1 mJ/mm$^2$) to the skin graft donor site immediately after skin harvest. A significantly decreased time for reepithelialization of skin graft donor sites in the shock wave therapy arm (13.9 ± 2.0 days) versus the control arm (16.7 ± 2.0 days) was reported. The study was powered to detect a difference in time to epithelialization with adequate randomization and blinding. However, the sample size was too small to study other outcomes, including pain and the cosmesis of donor sites, and did not have long-term follow-up.

### Flap Necrosis

Several preclinical studies examined the role of shock wave therapy in preventing necrosis of skin flaps in animal models, after the orthopedic and trauma literature suggested shock wave therapy could induce neovascularization and increase VEGF expression among other proangiogenic genes[25,26] (Table 2).[27–35] Meirer et al.[27] applied shock wave therapy (2500 impulses at 0.15 mJ/mm$^2$) to the random portion of an epigastric skin flap model immediately after surgery. There was significantly less necrotic surface area in shock wave therapy–treated rats (2.2 ± 1.9 percent) at 1-week follow-up versus control rats (17.4 ± 4.4 percent).[27] In a later study, shock wave therapy was hypothesized to decrease flap necrosis through reciprocal increase in VEGF expression in adjacent skin, but the detected difference in expression failed to reach statistical significance at value of a $p = 0.05$.[28]

The same group compared shock wave therapy to gene therapy with VEGF and found shock wave therapy–treated rats to have significantly smaller necrotic zones of the flap[29] in a study where surgical procedures were performed by three different plastic surgeons and analyses were not blinded. Shock wave therapy was found to be

**Table 2. Flap Necrosis**

| Reference | No. of Subjects | Size of Injury (cm) | No. of Pulses | Density of Energy (mJ/mm$^2$) | Focused or Unfocused |
|---|---|---|---|---|---|
| Meirer et al., 2005[27] | 10 ESW, 10 control | 8 × 8 | 2500 | 0.15 | Focused |
| Meirer et al., 2007[28] | 20 ESW, 20 control | 8 × 8 | 500 | 0.11 | Focused |
| Meirer et al., 2007[29] | 10 ESW, 10 control | 8 × 8 | 500 | 0.11 | Focused |
| Huemer et al., 2005[30] | 10 ESW, 10 control, 10 TGF-$\beta$ | 8 × 8 | 750 | 0.15 | Focused |
| Yan et al., 2008[31] | 42 study, 42 control | 3 × 10 | 750 | 0.09 | Focused |
| Kuo et al., 2007[32] | 36 | 10 × 3 | 500 | 0.15 | Focused |
| Kuo et al., 2009[33] | 36 | 10 × 3 | 500 | 0.15 | Focused |
| Reichenberger et al., 2009[34] | 10 ESW, 10 control | 6 × 10 | 500 | 0.11 | Focused |
| Kamelger et al., 2010[35] | 36 | 8 × 8 | 200, 500, 1500, 2500, 5000, and 0 | 0.11 | Focused |

ESW, extracorporal shock wave therapy; TGF, transforming growth factor.

superior to gene therapy with transforming growth factor-$\beta$ in a study of shock wave therapy (750 impulses at 0.15 mJ/mm$^2$) administered immediately after raising an epigastric skin flap in rats.[30] However, there was no significant difference in flap vascularization assessed by CD31 staining between shock wave therapy– and gene therapy–treated rats. The rationale for shock wave therapy parameters was also lacking.

Yan et al.[31] administered shock wave therapy (750 impulses at 0.09 mJ/mm$^2$) to the mid and distal portions of a cranially based random pattern flap model in rats and found increased blood perfusion and expression of nitric oxide and VEGF. Shock wave therapy parameters were based on pilot studies, although it is unclear whether focused or unfocused shock wave therapy was used. There was increased vasodilation of preexisting vessels in the early postoperative period, with neovascularization apparent on postoperative days 3 and 10.[31] This study suggested that shock wave therapy administered immediately postoperatively starts a series of discrete events that could explain when certain changes in the flap are seen.

Two studies have looked at the immunologic changes induced by focused shock wave therapy in flap necrosis models. Kuo et al.[32] applied focused shock wave therapy (500 impulses at 0.15 mJ/mm$^2$) to five areas of a rat dorsal random flap model. Increased VEGF and proliferating cell nuclear antigen expression, reduced leukocyte infiltration, and decreased TNF-$\alpha$ expression in flap tissue ischemic zones were found, suggesting that shock wave therapy may dampen the inflammatory response in ischemic tissue.[32] Kuo et al.[33] repeated the same experiment and found decreased leukocyte infiltration and tissue apoptosis, increased recruitment of skin fibroblasts, down-regulation of oxygen radical burst, and increased endothelial nitric oxide synthase expression.[33]

One study compared preoperative shock wave therapy to no treatment in an epigastric skin flap model and noted a significant reduction in necrotic flap area.[34] However, a head-to-head comparison of preoperative versus postoperative shock wave therapy to determine optimal timing of shock wave therapy has not been conducted. Kamelger et al.[35] assessed a dose-dependent effect of shock wave therapy in a murine epigastric skin flap model by varying impulses (200, 500, 1500, 2500, 5000, and 0) at 0.11 mJ/mm$^2$. Optimum enhancement of skin flap survival was at 500 impulses, with no significant increase at 1500 and 2500 impulses and increased necrosis observed at 5000 impulses. Changes in expression of growth factors or neovascularization with different impulses were not assessed. No clinical studies of shock wave therapy for the prevention of flap necrosis have been conducted.

### Burns

The application of shock wave therapy was examined in a murine model with full-thickness cutaneous burns[36] (Table 3).[36–38] Gene expression studies showed a greater than fivefold increase in chemokine and proinflammatory cytokine genes 4 hours after burn that were not seen in shock wave therapy–treated wounds. Davis et al.[36] found that administration of unfocused shock wave therapy (200 impulses at 0.1 mJ/mm$^2$) 1 hour after burn led to a significant reduction in neutrophil infiltration at the wound margin and central wound bed at 4 and 24 hours after burn. No significant differences in macroscopic wound closure contraction, degree of subeschar keratinocyte migration, rate of wound reepithelialization, or granulation development were found. The study was neither randomized nor powered for its primary outcomes.

Meirer et al.[37] described a level IV case report of a patient with deep partial-thickness burns of the forearm who refused skin grafting for cosmetic reasons and instead received shock wave therapy (1500 impulses at 0.11 mJ/mm$^2$) on days 3 and 7 after burn. The patient had nearly complete reepithelialization on day 15 and a well-healed wound without scarring at 6-month follow-up. Recently,

**Table 3. Burns**

| Reference | No. of Subjects | Size of Injury | No. of Pulses | Density of Energy (mJ/mm$^2$) | Focused or Unfocused |
|---|---|---|---|---|---|
| Davis et al., 2009[36] | 20 ESW, 20 control* | 15% TBSA (10-wk-old mice) | 200 | 0.1 | Unfocused |
| Meirer et al., 2005[37] | 1 | Unknown, right forearm deep partial-thickness burn | 1500 | 0.11 | Focused |
| Arnó et al., 2010[38] | 15 | <5% TBSA deep partial/full-thickness skin burns | 500 | 0.15 | Unfocused |

ESW, extracorporal shock wave therapy; TBSA, total body surface area.
*Preclinical.

Arnó et al.[38] conducted a level IV case-series study of 15 patients with less than 5 percent total body surface area deep partial/full-thickness skin burns who received unfocused shock wave therapy (500 impulses at mJ/mm$^2$) on days 3 and 5 after burn. Patients underwent débridement and split-thickness skin grafting in the absence of burn reepithelialization 2.5 weeks or more after shock wave therapy. Eighty percent of the patients healed before 3 weeks, 15 percent of patients required surgical débridement and split-thickness skin graft, and 5 percent developed hypertrophic scarring. An increase in perfusion based on laser Doppler imaging was also observed.

## DISCUSSION

The advent of shock wave therapy provides a potential new therapeutic modality for acute and chronic wounds that likely acts through mechanotransduction and immunomodulatory mechanisms. Shock wave therapy promotes expression of macromolecules in wound healing, including VEGF, endothelial nitric oxide synthase, and proliferating cell nuclear antigen. Because of the large experience using this technology to treat urolithiasis and other conditions in humans, it appears to be a safe technology. The clinical efficacy of this technology in specific wound types and the precise mechanisms of action are now beginning to be understood.

Shock wave therapy may be perceived by cell surface receptors through extracellular matrix and fluid effects. Mechanoreceptors, including integrins, ion channels, connexins, and/or the lipid component of the plasma membrane activation, could all possibly be affected by shock wave therapy. Akt-mediated mechanotransduction in fibroblasts has been show to play a role in hypertrophic scar formation in response to mechanical forces, suggesting that Akt and other upstream components such as focal adhesion kinase would be important candidates to study in the future for shock wave therapy.[39] Future studies may further elucidate the mechanotransduction effects of shock wave therapy. Shock waves may also stimulate sensory nerve fibers, including nociceptors that produce the somatic sensation of mechanical force, which may explain why some patients treated with shock wave therapy report decreased pain.

Clinical studies of shock wave therapy in wound healing suggest that wound cause, size, and chronicity may impact response to shock wave therapy. However, the actual administration of shock wave therapy in current clinical studies varies in type (unfocused versus focused), total number of impulses, energy flux density, and frequency. Although the physics of shock wave therapy and preclinical studies suggest that unfocused shock wave therapy is superior for the treatment of superficial soft-tissue defects, there has been no direct comparison of unfocused and focused shock wave therapy in clinical trials to date. Therefore, whether there is a clinically relevant difference in unfocused versus focused shock wave therapy remains unknown. Many authors who studied shock wave therapy in other clinical settings used the same devices in their studies of wound healing. To our knowledge, there have been no preclinical or clinical studies that have published data to suggest that there are experimental limitations that did not permit use of either type of shock wave therapy. Similarly, we do not have a complete understanding of the optimal shock wave therapy settings.

Additional basic science studies along with randomized controlled trials and registry studies powered to detect clinically relevant outcomes will be necessary to increase our understanding of this technology. Specifically, better characterization of the effects of shock wave therapy in homogenous groups of wounds would lead to identification of subsets of patients who are ideal candidates for shock wave therapy. To achieve this, thoughtful investigations to determine the type and specific parameters of shock wave therapy suited for different wounds must be determined first.

Currently, the U.S. Food and Drug Administration has approved devices that administer shock wave therapy for the treatment of plantar fasciitis and lateral epicondylitis but has not approved use of such devices to treat acute and chronic wounds. Shock wave therapy shows promise in improving our ability to enhance wound healing through mechanotransduction or immunomodulatory mechanisms. We look forward to future innovation in this field to understand more fully the mechanisms of action and optimal treatment of specific wound types.

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