Chapter 4

Electrical Stimulation and Wound Healing

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4.1 Theoretic and Scientific Basis

A number of interesting and thought-provoking studies of electrotherapy and tissue repair have been done in recent years. In light of this research, possible mechanisms attributed to electrotherapy and the stimulation of tissue repair are examined here, starting with the theory of skin battery voltage, and healing.

Various living organisms, including humans, have a skin battery potential that is negatively charged on the surface (skin) and positively charged in deeper tissues[126, 127]. Research has demonstrated the presence of an electrical current in the wounds and injuries of human beings and other living organisms. Intact skin has a small negative charge, and wounds are positively charged[128]. The strength of the endogenous wound EFs measured in animals and humans that have been observed to direct cell migration (electrotaxis) after wounding have been quantified between 10 and 100 μA/cm[129]. In summary, there appears to be a relationship between the electrical "current of injury" and the repair, regeneration, and growth of tissue. Electrotherapy may mimic the body's own bioelectrical signal and promote healing in chronic wounds that have an impaired or insufficient "current of injury" [130].

Research findings have provided a basis for the use of electrotherapy to augment the healing process. Many effects of electrotherapy on the healing of wounds have been reported. An extensive review of the electrotherapy and tissue healing literature is not provided here, but a synopsis of pertinent human and animal research on the effects of electrotherapy appears in Table (2). And figure (9)

Table 2. *The general cellular effect of electrical stimulation under cathode and anode.*

Cellular effects	
Epidermal cell migration[132]	
Increased fibroblast proliferation[133]	
Anode	Cathode
Neutrophils attracted[134]	Neutrophils attracted[134]
Macrophages attracted[135]	Fibroblasts attracted[139]
Mast cells (associated with abnormal fibrotic healing) migration inhibited[136]	Epidermal cell migration[140]
Leukocytes attracted[137]	Leukocytes attracted (when infection/inflammation present)[141]
Thrombosis of small vessels[137]	Increased blood flow[141]
Bactericidal[138]	Decreased edema[142]
	Bactericidal[143]

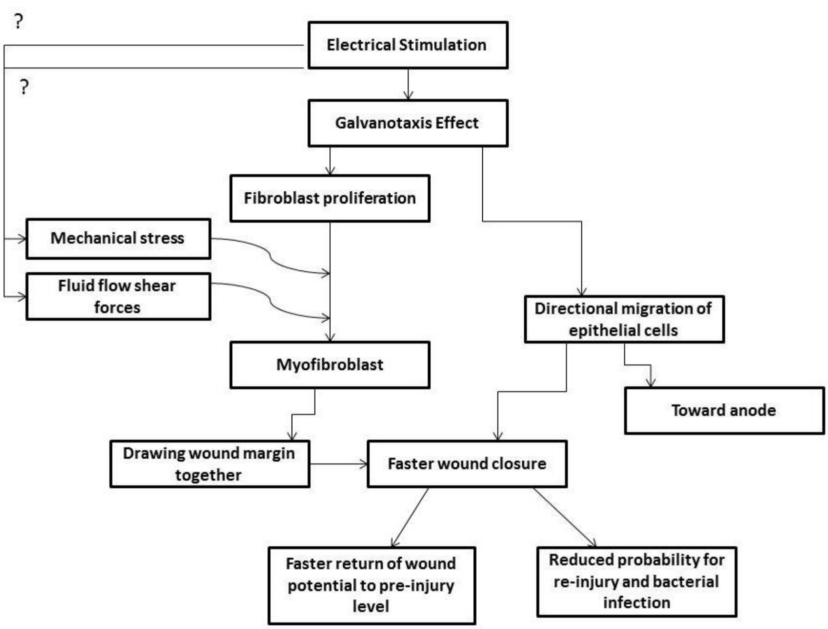


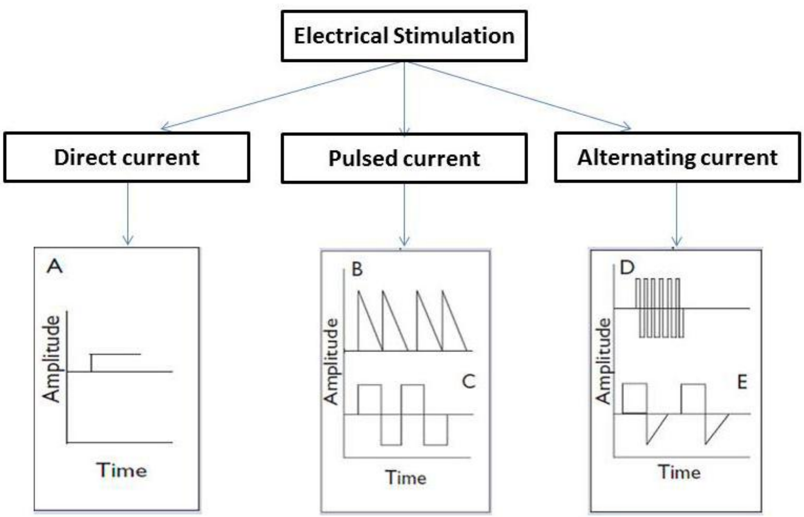
Figure 9. *Schematic illustration showing the effect of ES on wound closure.*

4.2 Types of Electrical Stimulation Current

Three main types of electrical stimulation can be used to induce the above cellular effect

- Direct current
- Pulsed current
- Alternating current

The differences between these currents are illustrated in the following figure (figure 10)[131].



A= Constant direct current, **B**= High voltage pulsed current, or intermittent low intensity direct current , **C**= low voltage pulsed current, **D**= TENS , **E**= balanced symmetrical biphasic current

Figure 10. *The different types of electrical stimulation currents.*

4.2.1 HVPC for Wound Healing

A trial concerning the effects of HVPC was reported by Kloth and Feedar[144]. A group of 16 patients with stage IV decubitus ulcers were recruited for the trial and all had lesions that had been unresponsive to previous treatment. Patients were allocated randomly to a treatment group (n=59) or sham treatment) group (n=57). The ES consisted of monophasic twin-pulse stimulation at 105 pps. delivered at a voltage just below that required to achieve visible muscle contraction (typically 100–175V). These stimulation parameters are reported as being arbitrarily set. ES was given for one 45 minute session a day for 5 days a week. Sham group patients had electrodes placed in the same way, but the machine output was set to zero. Electrode polarity was set initially for the wound electrode to be positive, with the negative electrode placed on the skin surface proximally. If a healing plateau was reached during the trial, the wound electrode was made negative and the treatment continued. If a second plateau was reached, the electrode polarity was reversed daily thereafter. Whichever electrode was placed at the wound site, the relative arrangement was maintained in that the positive electrode was always placed cephalad in relation to the negative electrode. All patients in the treatment group achieved complete healing of their ulcers (on average over 7.3 weeks at a mean healing rate of 44.8% per week). The control group patients did less well with an increase in mean wound size of almost 29% between the first and last treatments. A subgroup of patients who were in the control group went on to complete a course of ES following the main trial; the three patients achieved full healing of their ulcers over 8.3 weeks with an average healing rate of 38% per week.

Griffin et al.[145] assessed the effects of HVPC on pressure ulcer healing in a group of patients with spinal cord injury. Seventeen patients were assigned randomly to either a treatment or a control (sham treatment) group. ES treatments were carried out for 1 hour a day for 20 consecutive days with repeated wound assessments during this period. HVPC was delivered by means of a negative wound electrode with the stimulator delivering 100 pps. at an intensity of 200 volts using similar twin pulses to the previous study. The percentage change (decrease) in ulcer size for the treatment group was significantly greater at days 5, 15 and 20 and the average change for all ulcers in the treatment group was an 80% size reduction compared with a 52% decrease for the control group.

A more recent study by Houghton et al.[146] involved 27 patients with a total of 42 chronic leg ulcers of varying etiology (diabetic, arterial, venous) and employed a placebo controlled RCT design. Following initial assessment, there was a stable (baseline) period during which only 'conventional' therapy was employed, followed by a 4 week treatment phase with the patients divided into treatment or sham groups. The high voltage pulses were delivered at 150V, 100 pps and 100μsec duration, using 45 minute treatment periods, 3 times a week for the 4 weeks. The wound electrode was made negative throughout the treatment period i.e. no polarity reversal. Assessment included a one month follow up period. The treatment group wounds significantly reduced in size (mean 44% of original) compared with the sham group (mean 16%). The significant differences were not maintained at the 1 month follow up assessment, though there was a clear trend seen in the results.

Goldman et al.[147] aimed to evaluate the ability of high voltage pulsed current (HVPC) to increase microcirculation in critically ischemic wounds and, as a result, to improve wound healing. The diabetic patients presented with maleolar ischaemic lesions and serial measures were made of wound parameters, including oxygen tension. The results indicated that the use of electrical stimulation with these patients objectively improved tissue oxygenation and improved the anticipated wound healing profile.

In addition to the wound healing / wound closure studies[148, 149], HVPC has been shown (with other stimulation modalities) to have both a germicidal and antibacterial effect.

Finally the parameters of application of high voltage galvanic stimulation can be summarized in (table 3).

Table 3. *High voltage pulsed galvanic stimulation proposed parameters on the basis of protocols used in studies.*

Inflammation and proliferation phase: • Cathode on wound. • Frequency: 30 pps. • Intensity: 100-150 V. • 60 min once a day 5-7 times/wk.
Epithelialization phase: • 3 days cathode followed by 3 days anode; continue the 3 days alternations. • Frequency: 100-128 pps. • Intensity: 100-150 V. • 60 min once a day 5-7 times/wk.
Remodeling /maturation phase: • Alternate polarity daily. • Frequency: 60-64 pps. • Intensity: 100-150 V. • 60 min once a day 5-7 times/wk.

4.2.2 Micro-current and Wound Healing

Low-intensity electric currents or microcurrents (MCs) are currents of an intensity less than or equal to 1 mA (1000 µA, µA = microampere). The current may be direct or alternating of varying - mainly rectangular - waveforms, frequency, and pulse duration. Low-intensity currents were formerly known as MC electrical neuromuscular stimulators, but were later named microcurrent electrical stimulator (MES) (MC electrical stimulator)[150].

Microcurrents are produced by low-voltage generators or combined electrotherapy units. Such generators or units can produce a range of waveforms, from monophasic to square or rectangular biphasic, with a range of frequencies from 0.3 to 50 Hz. Electrotherapeutic units of low voltage may produce currents of intensities up to a few milliamperes in which case sensory stimulation or muscular stimulation results. Pulse duration may also be modified from 1 to 500 milliseconds at low frequencies or may be preselected when pulsed current is utilized[150].

4.2.3 Low-intensity Direct Current

Low-intensity direct current (LIDC) is the most common type of LIC studied in research. Wolcott et al.[151] studied wound healing resulting from application of LIDC in 83 patients with ischemic wounds. Three sessions per day took place, each lasting 2 hours. Intensity ranged from 200 to 800 μA, the negative electrode was placed on the wound and the positive electrode proximally. After 3 days, polarity was reversed provided that no infection had appeared. In the event of presence of infection, reversal was postponed until infection had subsided and was then delayed for an additional 3 days. Afterward, polarity was reversed each time healing reached a plateau. The rationale of the delay of polarity reversal may be attributed to the study of Rowley et al.[152], where by placing the negative electrode on the wound in similar parameters, the current presented with antimicrobial effects. Forty-five percent of wounds healed completely around a mean of 9.6 weeks, and the rest reached partial healing up to 64.7% over 7.2 weeks. Direct comparison of 2 treatments, standard treatment versus LIC, on the same subjects also took place, a fact that eliminated confounding factors stemming from differences among individuals such as age, sex, general health, and underlying pathology (eg, diabetes). Eight of the patients presented with bilateral wounds. One side was treated with LIDC (n = 8) and the other received standard care (n = 8). Six of 8 LIDC-treated ulcers completely healed, while the rest 2 of 8 healed up to 70%. In the other side, 3 of 8 ulcers did not heal, 3 of 8 healed less than 50%, and 2 out of 8 healed no more than 75%. In another clinical study[153], LIDC stimulation was applied to 6 patients with bilateral ischemic skin ulcers. The parameters of LIDC were same as in the study by Wolcott et al.[151], only polarity was reversed once. One side received standard treatment, whereas the other side ulcer received the same treatment plus LIDC stimulation. The healing rate of the non-LIDC side was 14.7% compared with 30% in the LIDC-treated side. A significant enhancement of healing was observed. A total of 100 patients also received LIDC treatment on ischemic wounds including the six patients previously mentioned. Mean healing rate amounted to 28.4% per week.

The positive effect of LIDC on chronic leg ulcers nonresponsive to other treatment has also been supported in a case study by Assimacopoulos et al.[154], in which, LIDC was applied on 3 patients with venous leg ulcers. Healing occurred in all 3 patients in 6 weeks, by applying a current of 100 μA. No control group was available, and being a case study, the strength of the results is somewhat limited.

Carley and Wainapel[155] applied LIDC (200–800 μA) on 30 patients with ulcers of various pathologies located over the sacrum or the lower limb below the knee. Patients were assigned in an electrical stimulation treatment group (n = 15) or conventional treatment group (n = 15) matched according to age, diagnosis, etiology, and wound size, thus ensuring that confounding factors were controlled to a considerable extent. Both groups received standard conservative treatment. The treatment group received additional electrical stimulation of 200 to 800 μA for 2 hours, twice daily, with an interval of at least 2 to 4 hours, 5 days per week, for 5 weeks. The negative electrode was placed on the wound and the positive electrode proximally. Reversal of polarity took place, as in the study by Wolcott et al.[151], and treatment was continued until full wound healing was reached. Finally the parameters of low intensity direct current used in accelerating wound healing can be summarized in table (4).

Table 4. *Low-intensity direct current proposed parameters on the basis of protocols used in studies.*

Intensity	**200–800 µA (negative electrode on wound)**
Treatment time	2 h
Times/d	2 to 3 sessions with a 2- to 4-h interval
Times/wk	5 d/wk
Duration of treatment	5 to 9 wk

4.2.4 Low-intensity Pulsed Direct Current

Low-intensity current provides minor stimulation to the healing site, being an LIC. One might expect that by using a pulsed form of this current, effectiveness would probably decrease because stimulation might be even less.

In a double-blind study by Wood et al.[156], 74 patients with stages II and III chronic decubitus ulcers in 4 centers, were randomly allocated in a treatment group (n = 43) and a placebo (sham treatment) group (n = 31), which received standard treatment. Treatment composed of electrical stimulation using low-intensity pulsed direct current (LIPDC) of 300 to 600 µA. After 8 weeks of treatment, 58% of ulcers in the treatment group had healed, whereas in the placebo group only 1 healed, and in the rest of the ulcers, ulcer area increased. A statistically significant accelerated rate of healing (P< .0001) was observed.

Reversal of polarity of pulsed direct current during the healing period has been studied. Junger et al.[157] investigated the effect of LIPDC on venous leg ulcers of 15 patients who had not responded to standard compression treatment over 79 months. An intensity of 630 µA was selected initially (frequency: 128 pulses per second; pulse duration: 140 µs) with the cathode placed on the wound for 7 to 14 days. The following 3 to 10 days, the positive electrode was positioned on the wound, and after that specific time frame polarity was reversed again. As soon as significant healing had occurred, intensity was reduced to 315µA (64 pulses per second). Treatment was performed on a daily basis, each session lasting 30 minutes. Mean ulcer area was reduced to 63% ($P< .01$). Furthermore, capillary density was increased to 43.5% ($P< .039$), and improvement of skin perfusion was observed ($PtCo_2$ = 13.5 increased to 24.7 to 40 mm Hg being normal). Finally the parameters of low intensity pulsed direct current used in accelerating wound healing can be summarized in table (5).

Table 5. *Low-intensity pulsed direct current proposed parameters on the basis of protocols used in studies.*

Intensity	300 to 630 µA (negative electrode on wound, stable polarity or reversal of polarity on 3 to 10 days or when on plateau)
Treatment time or times/wk	30 minutes minimum per day
Frequency	130 Hz
Duration of treatment	4 to 8 wk

The evidence available indicates that LIC appear to accelerate wound healing. Regarding the selection of intensity, LIDC (continuous or pulsed) appears to be effective in the range of 200 to 800 µA, and polarity may or may not be reversed. Further research is required to elucidate the effect of LIC on wound healing.

4.2.5 Alternating Current (AC)

AC has been applied to chronic wounds in two types of protocols: symmetric square -wave, most commonly delivered using a portable TENS device, or asymmetric biphasic pulsed wave. As opposed to DC or PC stimulators, AC stimulation is generally delivered by electrodes adjacent to the wound rather than directly overlying it.

(a) TENS

Initial case report[158] and uncontrolled case series[159] is treating patients with TENS applied to nerves in the vicinity of the wounds suggested this approach might be beneficial, The etiologies of the treated ulcers were varied, but included neurotrophic lesions, with the rationale that the neural stimulation provided by TENS would enhance healing. One interesting study by Kaada and Emru[160] used TENS therapy to treat 32 patients with longstanding lower leg ulcers secondary to leprosy. Patients received trains of 5 pulses (25 mA at 100 pps, 0,1 to 0-2 millisecond duration) for 30 minutes sessions, twice daily for 5 to 6 days per week. Twelve weeks post-treatment, 59% of the patients healed completely. All those who completed therapy healed completely with a mean healing time of 5.2 weeks. All the above TENS studies were uncontrolled studies, and all used different treatment regimens, making conclusions difficult to draw. Thus far there has been only one randomized controlled study of the effect of TENS on wound healing. Lundeberg et al. studied 161 the effect of TENS on diabetic patients with stasis ulcers. The patients received either TENS therapy (treatment parameters not given) for 20-minutes, twice daily for 12 weeks or sham treatment. The polarity was changed after each session. All patients received standard wound care, which was a compression dressing. After 12 weeks, 42% of the treated group healed compared to 15% of the control, with statistical significance. This study does support a role of TENS stimulation in the treatment of ulcers in diabetic patients.

(b) Biphasic Pulsed

Asymmetric biphasic pulsed waveforms have been used in some wound healing studies, presumably because the asymmetry of the waveform allows the polarity of one pole to predominate One case series[162] and one non-randomized control trial[163] have suggested that this modality may be useful in enhancing healing in a wide array of chronic ulcers. However, only one randomized controlled trial has evaluated the efficacy of this modality.

Baker et al.[164] evaluated the effects of two stimulation waveforms on healing rates in patients with diabetic ulcers, Patients received stimulation with either an asymmetric biphasic or symmetric biphasic square-wave pulse both at 50 pps, at unreported amplitudes, A third group received a sham ES. All patients in the study received standard wound care. In this study, treatment with asymmetric biphasic ES showed a statistically significant 60% increase in the healing rate, as compared to controls. This study suggests that the asymmetric biphasic wavelength may be more advantageous in ulcers in diabetic patients. The rationale for this is not entirely clear.

It appears that most of the studies on the efficacy of AC stimulation for wound healing evaluated patients with decubitus ulcers, so no inferences may be comfortably extended to other types of non-healing wounds. The double-blind randomized controlled study by Lundeberg et al.[161] is particularly strong, and its results do support a role for AC therapy in decubitus ulcers, Its efficacy in other chronic wounds remains to be evaluated.

Reger et al.[165] reported changes in surface area and volume of induced pressure ulcers after using DC (current amplitude about 0.7 mA and current density of 30–200 lA/cm^2) and alternating current(AC; 300 l s pulse duration, 40 Hz, and current density of 1,189 – 219 lA/cm^2) stimulation. Wound contraction occurred more rapidly in stimulated animals than in the controls. No histological changes were noted between the AC and DC stimulated wounds in the early phase of healing. Tissue perfusion was enhanced more by DC than by AC stimulation. A shorter wound area time constant and a higher rate of wound area reduction were noted after DC compared with AC ES. AC stimulation reduced wound volume more than DC.

4.3 Effect of Electrical Stimulation on Different Types of Wounds

4.3.1 Effect of Electrical Stimulation on Skin Flap Survival

Kjartansson et al.[166] investigated the effect of segmental and extra segmental transcutaneous electrical nerve stimulation (monophasic PC) with a different frequency and amplitude on survival of the dorsal musculocutaneous flap in rat. They raised the flaps (2 cm to 7 cm) from the deep fascia of the muscles and then sutured these back into position. ES was delivered as monophasic PC with a 0.2 ms pulse duration, a frequency of 80 or 2 pps, and an intensity of 20 or 5 mA. In the segmental mode, ES was delivered to the base of the flap; in the extra segmental method, ES was delivered at the base of the animal's tail. Preoperative ES did not increase flap survival area when compared with the untreated control group. The highest flap survival was obtained with repeated segmental ES applied postoperatively with a high intensity. The authors showed that flap survival was not related to the frequency used.

4.3.2 Effect of Electrical Stimulation on Hypertrophic Scar

Reich et al.[167] designed one study to examine the effects of ES on the proliferation of mast cells in acute wounds. They made 80 wounds in 4 pigs (20 wounds in each animal): The wounds of 2 animals were treated using positive monophasic pulsed ES (38 mA, 140mspulse duration, and 128 pps), twice a day, for 1.5 h in each treatment session. The number of mast cells was significantly lower in these ES treated wounds than in the control wounds at days 1, 2, and 3. They speculated that this decrease may be related to a reduction in either proliferation or migration of mast cells. Positive pulsed ES reduces wound vascularity and may be responsible for mast cell reduction[168, 169]. Keloids and hypertrophic scars, in particular, are often associated with increased numbers of mast cells[170]. Surgical flap survival rate is increased in mast cell deficient rats[171], indicating that ES may affect scar formation and should be considered in future animal studies.

4.4 Contraindications and Precautions

Before finishing the review of electrotherapy and its effects on healing, a look at the adverse effects, precautions, and contraindications is needed. Few adverse effects are cited in the literature; except for complaints of tingling or prickly feelings and occasional skin irritation[172]. The possibility that electrotherapy may cause an increase in the pain of patients with peripheral vascular disease. As mentioned earlier, the clinician must ensure that there is no foreign material, medications, heavy metals, or other topical substances in the wound that may hinder the treatment or adversely affect the care of the wound. In light of these possibilities, electrotherapy should be utilized with caution[173]. Contraindications to the use of electrotherapy are listed in Table (6). Before a wound is treated electro therapeutically, the patient should be screened for these conditions.

Table 6. *The precaution and contraindication of electrical stimulation.*

Precaution of electrical stimulation	Contraindication to electrical stimulation
Pregnancy	Unstable cardiac condition
Epilepsy	Implanted pacemaker
Decreased sensation	Acute hemorrhage
No stimulation over carotid sinus	Acute thromboembolism
No stimulation over laryngeal nerve	
Do not stimulate over skin diseases	
Avoid grounding faults	