Electrotherapy Reoxygenates Inframalleolar Ischemic Wounds on Diabetic Patients
A Case Series

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Lower extremity amputation is an expensive complication of diabetes mellitus. Risk factors such as peripheral neuropathy and angiopathy can lead to distal lower extremity ischemic skin lesions and can possibly result in amputation. If feasible, ischemic ulcers are treated by surgical revascularization. A patient is not an operative candidate, however, if he or she has critical occlusive disease but no suitable outflow vessel for the bypass conduit or if the patient has a profound comorbidity that makes anesthesia a high risk. Unfortunately, numerous patients with peripheral vascular disease and diabetes have these impediments to surgery. Too often, the end result is a lower extremity amputation.

High voltage pulsed current (HVPC; also known as electrical stimulation) has been employed by health care practitioners to augment the healing rate of chronic wounds with few adverse events, according to prospective, randomized, blinded clinical trials and a recent meta-analysis. The salutary effect reported for HVPC has been attributed, at least in part, to increased blood flow to wounds. Increased blood flow to tissue from electrotherapy is reported by many clinical and in vitro studies.

Cutaneous microcirculation consists of nutritional capillaries of the papillary dermis and nonnutritional arteriovenous plexuses of the subpapillary dermis and subdermis. Skin blood flow is quantified by laser blood flow, skin temperature, and transcutaneous oxygen (TcPO2). TcPO2 is an absolute measure of oxygen in units of partial pressure in the dermis. In prospective trials, TcPO2 is an independent predictor of future lower extremity amputation. A TcPO2 measurement less than 50 mm Hg carries a 3-fold increased risk for amputation. In addition, TcPO2 predicts the healing success of residuum incisions for amputation at a transtibial level. A below-knee TcPO2 measurement greater than 40 mm Hg carries a good prognosis; a TcPO2 measurement less than 20 has a poor prognosis.

For intact limbs, TcPO2 predicts healing of infrapopliteal wounds in diabetic subjects better than segmental volume plethysmography or toe segment pressure.

ABSTRACT

OBJECTIVE: To retrospectively evaluate the ability of high voltage pulsed current (HVPC) to increase microcirculation in critically ischemic wounds (transcutaneous oxygen [TcPO2] less than 10 mm Hg) and, as a result, to improve wound healing.

DESIGN AND METHODS: Clinical case series with successive adult diabetic subjects (3 men and 3 women) with nonsurgical ischemic malleolar or inframalleolar skin lesions, each subject serving as his or her own control. Wound area and TcPO2 were measured periodically. Presence of distal arteriosclerosis was assessed on 5 patients by 2-dimensional, time-of-flight magnetic resonance angiography. End point was either complete wound closure or leg amputation.

RESULTS: Maximum mean TcPO2 was 2 ± 2 mm Hg at the wound edge before the start of electrotherapy. After electrotherapy began, maximum TcPO2 was 33 ± 18 mm Hg (N=6; P<.05, Wilcoxon signed rank test). After treatment with HVPC, 4 patients’ wounds healed and 2 patients underwent amputation. As expected, healed patients initially deteriorated after the start of treatment, but their wounds began healing when the perilesion TcPO2 measurement exceeded 20 mm Hg. Thereafter, the wounds closed at a predictable rate. Complete closure occurred for patients who had a relatively low atherosclerotic burden.

CONCLUSION: The results of this clinical case series suggest that electrotherapy can improve periwound microcirculation of ischemic inframalleolar skin lesions.

Submitted October 11, 2000; accepted in revised form June 11, 2001.

Acknowledgments

Alan H. Stolpin, MD, PhD; Mark Rosen, MD, PhD; and David A. Roberts, MD, PhD, of the Department of Radiology, University of Pennsylvania, for interpretation of magnetic resonance angiograms. Andrew J. Cucchiara, PhD, of the General Clinical Research Center, University of Pennsylvania, for statistical analysis. Joseph Cavorisi, MD, and Pam Unger, PT, of the Institute for Advanced Wound Healing, St Joseph’s Hospital Medical Center, Reading, PA, for expertise on wound healing and electrotherapy. Funding and equipment for this research was provided by the University of Pennsylvania Research Foundation; University of Pennsylvania Pilot Grant for Patient-Oriented Research; National Heart, Lung, and Blood Institute, Lung and Blood 1R41HL61983-01; Chattanooga Group, Hixson, TN; and Universal Technology Systems, Jacksonville, FL.
sures. In addition, TcPO2 may have sensitivity and specificity approaching 80% in the ability to infer flow of underlying macrovessels of the leg and foot. Normal perilesion TcPO2 measurement is greater than 50 mm Hg; less than 20 mm Hg is ischemic, and less than 10 mm Hg is critically ischemic. Critically ischemic wounds have a guarded prognosis for complete closure. For the present study, critical ischemia was defined as a periwound TcPO2 measurement less than 10 mm Hg.

An increase in tissue microperfusion has been observed in response to a variety of electrotherapy parameters, including less than 500 microseconds (µs) pulse duration, less than 100 pulses per second (pps), 100 ma amplitude, and direct coupling. Direct coupling indicates that current flows through tissue directly between treatment electrode(s) and non-treatment (dispersive) electrode(s) applied directly to the wound and the intact skin of the ipsilateral lower extremity, respectively. Beyond these similarities, signals may be monophasic (eg, positive pulse or zero voltage baseline) or biphasic (eg, positive pulse, followed by negative pulse above and below a zero baseline). Examples of monophasic (HVPC) and biphasic pulsed currents and direct current are illustrated in a standard reference.

The HVPC signal is produced by devices classified by the Food and Drug Administration (FDA) as powered muscle stimulators. The FDA allows manufacturers to claim 6 indications for the use of powered muscle stimulators, one being to improve local blood flow. Although blood flow increase to muscle is implied, a HVPC device may reasonably be used to improve local blood flow to ischemic ulcers in a clinical setting, with the goal being to resolve ischemia. Although this may represent an off-label application, physicians have sanction to use drugs or devices for reasonable off-label applications as part of the practice of medicine. Similarly, physical therapists have used HVPC off-label for decades to promote healing of chronic wounds.

HVPC increases microcirculation to skin by a fast response and a slow response. A fast response is the transient increase in skin perfusion during a single electrotherapy session. Mawson studied transient sacral microcirculation change of spinal cord injured volunteers in response to HVPC. For these subjects, 30 minutes of HVPC applied between T6 and T12 caused a significant, but transient, 35% increase in sacral TcPO2 (from 49 mm Hg ± 21 mm Hg to 66 ± 18 mm Hg; P < .0001). The 6 controls demonstrated no such increase.

In contrast, a slow response is the gradual increase in perfusion or skin oxygenation over multiple treatment sessions. A slow response has been clinically noted by many investigators employing transcutaneous and epidural high voltage electrotherapy. Likar et al applied a biphasic symmetrical signal across wounds and found that dysvascular amputees with previously slow-closing stump wounds responded to electrotherapy with a slow rise in TcPO2 over weeks of a daily electrotherapy program. Using a biphasic pulse, Lundeberg et al directly measured dermal perfusion by laser Doppler flow technology and found convincing evidence of slowly increasing, long-lasting microperfusion of ischemic grafts, associated with increased breast flap rescue rate. Claeyss et al found epidural spinal cord electrical stimulation was associated with reoxygenation of skin around ischemic leg and foot ulcers. During several months of daily spinal electrotherapy, wounds closed and ischemic pain was reduced in cases where resting TcPO2 increased. After electrotherapy ended, TcPO2 was within normal limits at the 1-year follow-up.

Although hypothesis testing must be asserted with caution for a retrospective clinical case series, the intention of the present study was to evaluate whether HVPC increases microcirculation to ischemic wounds over time to a point where the wounds are no longer ischemic. Clinical observation of 6 patients with critical ischemic foot lesions consistently demonstrated that HVPC induced a slow, persistent increase in TcPO2, which may have contributed to complete wound healing in 4 of the cases. This preliminary clinical evidence suggests that HVPC may offer an innovative, noninvasive option to promote healing of ischemic skin lesions and potentially improve the odds of limb salvage.

METHODS

Patient selection

Six successive patients who presented with nonoperative malleolar and inframalleolar ischemic wounds between 1997 and 1999 were included in the study because they were determined to be candidates for HVPC (inclusion and exclusion criteria follows). Patients were drawn from the wound care population of the University of Pennsylvania’s Comprehensive Chronic Wound Clinic, Philadelphia, PA. In addition to adjunctive electrotherapy, all wounds were treated with standard local wound care.

Criteria for treatment with HVPC were established. HVPC was considered for subjects with (1) an inframalleolar skin lesion, including incisions and wounds with a black, yellow, or red base; (2) TcPO2 less than 10 mm Hg at the periwound skin, or at the closest available site; and (3) reasonable motivation to perform this clinical technique at home with or without supervision by a family member or visiting nurse. Electrotherapy was done at home because the wound center did not have staff available for daily outpatient HVPC. In addition, transportation issues precluded frequent
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Exclusion criteria for HVPC were (1) the presence of a pacemaker; (2) the presence of an active or untreated abscess or cellulitis; (3) the presence of necrosis or dry gangrene that was extensive, rapidly extending, or that involved an entire digit; (4) plantar ulcer directly on a weight-bearing bony prominence; (5) a venous ulcer with hyperpigmentation, lipidermosclerosis, edema, and a red base, for which edema may artificially decrease $TcPO_2$; (6) exposed tendon or bone at the base of the wound; (7) candidates for arterial bypass, regardless of whether a previous bypass had been attempted or completed; (8) urgent need for amputation; and (9) extensive, marginally compensated and worsening multisystem disease.

Electrotherapy

The HVPC device used in this study was the PGS 3000 portable stimulator (Universal Technology Systems [UTS], Inc, Jacksonville, FL). This device is a small, handheld unit used in general clinical practice. It has separate controls for amplitude (in volts), pulse duration, AC adapter, on/off switch, and 3 outputs (1 dispersive and 2 active electrodes). For this protocol, the unit supplied HVPC between 80 to 330 volts peak amplitude, up to 100 pps, for treatments of approximately 1 hour per day, 7 days per week. Amplitudes were initially set at 100 volts and then increased until sensory threshold or until the maximum of 330 volts was reached. Initial stimulation parameters were set at negative polarity, 80 to 100 pps. The initial negative polarity was reversed when healing progress stopped, although no plateau was clinically apparent in 4 of 6 subjects and polarity remained negative throughout the study.

The HVPC signal has been visualized with an HP TDS 310 digital oscilloscope. The output of the device from UTS is a twin-peak signal repeating at 100 pps. The first phase of the twin pulse has a duration of 91 µs, immediately followed by a second phase of 179 µs. Each phase rises sharply to a peak voltage (with a rise time of less than 1 µs), then decays to zero voltage exponentially. The time constants of decay of the first and second phases are 25 and 50 µs, respectively.

Coulombs per second have been determined for an HVPC signal amplitude typically employed for reoxygenation of ischemic wounds, utilizing the same electronic test setup employed by Feedar et al. For a HVPC device set to an amplitude of 200 volts and delivering current through a 1 K ohm resistance, charge/second is 1250 microcoulombs. This is 2-fold to 4-fold higher than the range of charges calculated to be effective for healing chronic nonischemic wounds.

An initial educational session was conducted at the clinic prior to treatment, at which time electrode positioning was demonstrated. The 100 cm² dispersive electrode was positioned on the ipsilateral thigh or leg of the treated foot. Active electrodes were placed directly over the wound and delivered electrical current to the tissues through a sterile conductive hydrogel sheet (Vigilon; Bard Medical Division, Covington, GA). If the ischemic lesion was greater than 5 cm², both active electrodes were placed over it to ensure current reached all areas of the lesion. If the lesion was less than 5 cm², 1 treatment electrode was placed over the lesion and the other was placed more proximal, at the ipsilateral fibular head. An exception was made if the ischemic wound was on the medial hallux. In this case, the treatment electrode was placed more distal on the hallux tip so that current could pass (in theory) through the entire digit. Once electrodes were placed, amplitude was set by the physician. Electrotherapy was applied daily at home.
by the patient, caregiver, or visiting nurse following receipt of oral and written instructions on the technique. Compliance with daily electrotherapy treatment was confirmed by patient reports at subsequent visits and as independently reported by a visiting nurse. There were no formal or objective means established to ensure compliance. Once initiated, daily HVPC sessions continued uninterrupted until wound closure or amputation occurred.

**Standard wound care**

In addition to electrotherapy, all subjects received conventional wound care including (1) protection of ischemic skin lesions from mechanical trauma and excessive pressure and shear through the use of padding and protection (eg, non-adherent gauze pads, ABD pads, Kerlex, and DH walker); (2) silver sulfadiazine ointment applied to black or yellow eschar; (3) antibiotic ointment or hydrocolloid applied to granulating wound base to maintain a moist environment;25 (4) application of topical PDGF-BB (becaplermin [Regranex; Ortho-McNeil, Raritan, NJ]) if perilesion TcPO2 was greater than 30 mm Hg;26 (5) periodic sharp debridement of nonischemic wounds;27 and (6) visiting nurse follow-up28 for patient- and caregiver-performed wound care at home.

**Wound measurement**

Wound area was determined during every clinic visit. The time interval between area determinations was 19 ± 9 days (mean ± standard deviation [SD]). Wound areas were measured using digital planimetry, which has excellent reported intrarater and interrater reliability and concurrent validity compared with other objective methods of determining wound area.29 The digital planimetry method employed in this study was almost identical to the method described by Charles.30 For each determination, wound edges were outlined on an acetate sheet. Then, wound edges were traced using a digital artpad (Model ET-0405-L1; Wacom Company, LTD, Taiwan, China) into ImageJ (version 1.09y; National Institutes of Health, Washington, DC), from which areas were calculated. The average of 2 area calculations was taken to be the wound area. Using this method, intrarater reliability and interrater reliability were both 0.99, exceeding published figures for these measures.

**TcPO2 measurement**

Cutaneous microcirculation was quantified by TcPO2, which measures absolute, rather than relative, oxygen partial pressure in the dermis.14,18 The time interval between TcPO2 determinations was 42 ± 26 days (mean ± SD). TcPO2 determinations were triggered by clinical events. At least one TcPO2 was performed before HVPC started. TcPO2 determinations were performed more frequently just after the beginning of treatment and less frequently as wounds responded to treatment.

The TcPO2 monitor used in this study has 3 electrodes (Novametrix 800 system; Novametrix Medical Systems Inc, Wallingford, CT). One electrode was placed on periwound skin or as close as possible to the ischemic area of interest; the second was placed within 10 cm of the wound on nearby skin (ie, on the plantar arch or dorsum of the foot); and the third electrode was placed on a farther removed, well-perfused area (ie, the upper leg). Once recording sites were selected and baseline values established for a subject, sites remained the same during successive TcPO2 measurements. TcPO2 recording sites were carefully selected to avoid areas of edema, bony prominences, or callus. To test repeatability of this technique, 3 TcPO2 electrodes were fitted to the medial leg, foot dorsum, and midfoot plantar on a healthy individual for 2 readings, 2 weeks apart. The upper medial leg reading was 55 and 70 mm Hg; foot dorsum, 48 and 53 mm Hg; and plantar midfoot, 38 and 41 mm Hg. These results suggest good repeatability.

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**Table 2. WOUND CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Patient, Wound Duration Before Electrotherapy</th>
<th>Etiology and Location</th>
<th>Initial Wound Area (cm²)</th>
<th>Initial Appearance</th>
<th>Initial Periwound TcPO2 (mm Hg)</th>
<th>Duration of Electrotherapy (months)</th>
<th>Sensation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1; 6 months</td>
<td>Pressure; lateral malleolus</td>
<td>1.6</td>
<td>Yellow</td>
<td>6</td>
<td>9</td>
<td>S</td>
<td>Healed</td>
</tr>
<tr>
<td>2; 8 months</td>
<td>Pressure; instep</td>
<td>0.2</td>
<td>Yellow</td>
<td>3</td>
<td>6</td>
<td>S</td>
<td>Healed</td>
</tr>
<tr>
<td>3; 3 months</td>
<td>Pressure; medial hallux</td>
<td>6.1</td>
<td>Black</td>
<td>1</td>
<td>5</td>
<td>S</td>
<td>Healed</td>
</tr>
<tr>
<td>4*; 1 month</td>
<td>Surgical; wound at site of digit V amputation</td>
<td>10.2</td>
<td>Yellow</td>
<td>0</td>
<td>9</td>
<td>V</td>
<td>Healed</td>
</tr>
<tr>
<td>5; 1 week</td>
<td>Surgical; TMA</td>
<td>Incision</td>
<td>Livido</td>
<td>1</td>
<td>1</td>
<td>S</td>
<td>Amputation</td>
</tr>
<tr>
<td>6; 3 months</td>
<td>Pressure; medial hallux</td>
<td>2.4</td>
<td>Black</td>
<td>1</td>
<td>1</td>
<td>S</td>
<td>Amputation</td>
</tr>
</tbody>
</table>

*TMA=transmetatarsal amputation.

S=periwound sensation intact to light touch or the 5.07 monofilament; V=periwound sensation absent to the 5.07 monofilament.
bility in performing TcPO$_2$ determinations.

For TcPO$_2$ monitoring, 3 Clark polaro-
graphic electrodes at 44°C were calibrat-
ed to 0 and 157 mm Hg (the partial pres-
sure of molecular oxygen [O$_2$] in air at
sea level). Calibrated electrodes were
coated with contact solution, then affixed
to skin by circular double-stick tape at
the anatomic locations previously
described. Once electrodes were placed,
TcPO$_2$ was followed on a strip chart
recorder on the Novametrix 800 TcPO$_2$
monitor. TcPO$_2$ typically fell exponential-
ly to baseline over 30 to 60 minutes; final
reading was determined after no change
(± 5%) in baseline over 10 minutes or
limit of subject tolerance to maintaining a
supine posture. Serial TcPO$_2$ determi-
nations were separated by a minimum of 1
week and a maximum of 8 weeks to
determine response to treatment.

Initially, after an ischemic periwound
TcPO$_2$ was measured on a subject, an
imaging study was ordered to evaluate
for arterial disease. T ypically, magnetic
resonance angiography (MRA) was
employed.

Magnetic resonance angiography
If possible, distal arteriosclerosis was
described anatominically by MRA, which
has excellent specificity and selectivity for
detection of infrapopliteal patent arterial
segments. When directly compared with
intraoperative angiography, there was a
sensitivity of 87.5% and a specificity of
95%. In addition, MRA may be more
sensitive than conventional contrast
angiography to detect patency of small
distal runoff arteries.32

MRA was performed on 5 of 6 subjects
using standard 1.5 Tesla superconducting
systems with transmit-receive extremity
coils and commercial pulse sequences.
(Typical MRA protocols employ 2-dimen-
sional, time-of-flight techniques with at
least 2 stations from the lower third of
the leg to the toes.) MRA images were
interpreted in an unblinded fashion by a
board-certified radiologist to categorize
arteriosclerosis below the midleg, accord-
ing to the method described by
McDermott. The leg and foot arteries
were divided into 9 segments; anterior
tibial, peroneal, posterior tibial (leg), pos-
terior tibial (foot), medial plantar, lateral
plantar, arterial arch, dorsalis pedis (dis-
tal), and dorsalis pedis (proximal).
Segments were defined as either patent
or occluded. Stenosed arteries were
included in the patent group. Occluded
arteries were evidence of collateralization
and were included in the occluded group.

Other vascular measurement
methods
A widely used noninvasive method to
determine large-artery blood flow in the
lower extremity is segmental volume
plethysmography, known as pulse vol-
ume recordings (PVRs). However, a limi-
tation of PVRs is the inability to compress
the leg artery due to calcification of the
tunicia media, particularly in patients with
diabetes and chronic renal disease.
Patients with these 2 conditions dispropor-
tionately present with ischemic
wounds of the ankle and foot. In fact, all
subjects in this study had diabetes and 2
had a history of chronic renal failure. For
subjects with these conditions, segmental
volume plethysmography may be limited
in its ability to predict healing. For sub-
jects with diabetes and chronic renal dis-
ease in this study, PVRs were not used to
guide treatment. Nevertheless, PVRs
were available as measured by accred-
ited vascular laboratories for 5 of 6 subjects
201 ± 203 days before onset of elec-
trotherapy. Ipsilateral ankle brachial
index (ABI) at the posterior tibial artery
was 1.05 ± 0.50 (mean ± SD) and ABI at
the dorsalis pedis artery was 1.21 ± 0.48.
As expected, ankle brachial indices were

![Figure 1. TcPO$_2$ BEFORE AND AFTER DAILY ELECTROTHERAPY](image-url)

Periwound microcirculation demonstrated marked improvement (as indicated by changes in maximum TcPO$_2$) in all 6 wounds following daily electrotherapy when compared with TcPO$_2$ before daily electrotherapy (left pair of bars; *P < .05; Wilcoxon signed rank test). Four wounds that showed evidence of healing improved (center pair of bars) more than the 2 wounds that resulted in amputation (right pair of bars).
not definitive for subjects with diabetes with or without renal failure.

Nonparametric inferential statistics were used (Wilcoxon signed rank test) for post hoc analysis of maximum TcPO2 difference from baseline. Each subject's maximum TcPO2 pretreatment with HVPC was paired with maximum TcPO2 after start of HVPC.

RESULTS

Three men and 3 women were included in the case series. The mean age of the subjects was 61 ± 10 years (SD). Two subjects had type 1 diabetes and 4 subjects had type 2 diabetes; 3 were insulin dependent and 3 had end-stage renal disease. Two subjects were immunosuppressed, with functioning renal allograft. One subject had insensitivity to 5.07 monofilament and 2 subjects had undergone previous major contralateral leg amputations. Wound healing occurred in 4 subjects; 2 subjects underwent amputation (Table 1).

Before electrotherapy, the maximum mean TcPO2 measurement at a wound edge was 2 ± 2 mm Hg (mean ± SD) (Table 2). Overall TcPO2 increased for all subjects after starting electrotherapy. The maximum mean TcPO2 noted 157 ± 114 days after the start of electrotherapy was 33 ± 18 mm Hg (P < .05, nonparametric Wilcoxon signed rank test; Figure 1). The significant TcPO2 improvement was most pronounced for the 4 subjects whose wounds closed. Complete closure occurred 207 ± 107 days after the start of electrotherapy. For the 4 subjects whose wounds healed, TcPO2 tended to increase from 3 ± 3 mm Hg to nearly normal (40 ± 17 mm Hg; nonsignificant). A more modest trend toward increase was noted for the 2 subjects who ultimately underwent amputation (1 ± 0 mm Hg to 19 ± 5 mm Hg; nonsignificant).

All wounds that healed initially demonstrated a slow, inexorable increase in area, characteristic of many ischemic wounds (Figure 2a). After the healing rate turned positive, wounds generally proceeded to heal with slow but predictable changes in wound area. The reason for this rate reversal was attributed, at least partially, to improved microperfusion, indicated by an increase of TcPO2 measurements. With onset of electrotherapy, there was a marked and persistent increase in TcPO2 that tended to rise according to an exponential function (Figure 2b). As the exponential increase in periwound TcPO2 exceeded 20 mm Hg (about 40 days into the electrotherapy protocol), the healing rate turned positive. Consistent with a positive healing rate, TcPO2 continued to rise asymptotically to a weighted curve fitting in excess of 40 mm Hg, which is below normal but still compatible with healing.

In Figure 2a, wound areas were determined by digital plainimetry. Areas were then divided by a wound-specific maximum area to determine the percentage of maximum. For the 4 wounds, area (as percentage of maximum) was plotted against time (Figure 2b). The changes in area and TcPO2 over time are consistent with increased microcirculation and reoxygenation of the wound edges.
versus time to illustrate a trend. Healing rate, per se, was not calculated, but was rather graphically presented as an aggregate of all normalized wound areas of subjects that healed. The normalization process was performed by calculating the maximum wound area of all wound areas calculated by plainimetry for a given patient. A straightforward normalization was then performed by dividing each wound area by the maximum for that subject in order to allow all wound areas for all subjects to be plotted on the same graph. Because the reliability of absolute wound areas is about 0.99, the reliability of normalized areas was expected to be excellent. A weighted curve fitting algorithm (Statview for Windows, Version 5; SAS Institute, Cary, NC) was used in Figure 2a, and an exponential algorithm was used in Figure 2b to describe a best-fit trend only. Time at zero is defined as the point at which the electrotherapy protocol was initiated.

Whether a slow, steady increase in TcPO2 resulted in healing of ischemic ulcers may be at least partially related to the number of infrapopliteal occluded arteries. The atherosclerotic burden, defined as the number of artery segments occluded below midleg, tended to be higher for the 2 subjects whose outcome was amputation (3 and 6 of 9 segments). Three subjects whose wounds healed had 0, 2, and 4 segments occluded. One subject had no vessels occluded and all vessels open; this subject was an intractable, active smoker.

The duration of electrotherapy was significantly longer for those subjects who healed (180 ± 59 days) compared with those for whom amputation was the end result (32 ± 25 days). Coincidentally, amputation occurred for the same 2 subjects who had preexisting contralateral major amputation. The success of HVPC treatment did not appear to have a relationship to anticoagulation therapy or compression therapy. None of the subjects were on oral anti-coagulants during treatment and no compression garments or dressings were used for any subject until ischemia resolved, which was 2 months after HVPC onset at the earliest. Compression was then used to reduce leg edema in 2 of 6 patients.

Figure 3 shows the case of patient 3, whose ischemic hallux ulcer initially covered with eschar healed 133 days after the start of HVPC.

**DISCUSSION**

Infra-malleolar ischemic wounds are not uncommon in diabetic patients with or without neuropathy and comorbidities, including distal arteriosclerosis, end-stage renal disease, and smoking history. These wounds are caused by innocuous trauma and worsen because of circulatory impairment. Circulatory impairment in this subgroup of diabetic individuals is a complex entity consisting of large-vessel arteriosclerosis and poorly defined small-vessel disease; this often leads to necrosis and gangrene. For at-risk tissue, standard care includes angioplasty or bypass; however, if neither of these invasive methods is indicated, the prognosis for limb salvage is poor. A more favorable prognosis may follow treatment with HVPC, which has shown in this study to putatively enhance microcirculation slowly and persistently during the course of repeated treatments.

This case series verifies the hypothesis that in these subjects, HVPC was associated with an increase in periwound TcPO2 over weeks of treatment to the point where wounds were no longer ischemic. However, the increase in
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TcPO2 that led to wound closure in 4 of 6 cases could just as plausibly be attributed to careful application of conservative wound healing strategies and/or resolution of inflammation. Therefore, it is not possible to generalize the clinical findings of this case series to the total population of ischemic diabetic wounds.

HVPC may be important in reoxygenation of ischemic wounds; however, once periwound TcPO2 approaches normal, it is not clear what additional benefit HVPC may elicit. Because there is little guidance from the literature at this point, HVPC was applied in this study until complete closure or as long as tolerated. It could reasonably be argued that the longer period of time electrotherapy is applied after TcPO2 returns to near normal, the less important it may be when compared with conservative wound care or surgical strategies such as skin grafting. Nevertheless, HVPC may promote wound healing by additional means after TcPO2 normalizes. These means include enhanced fibroblast proliferation, enhanced collagen synthesis, and resolution of edema. These mechanisms are consistent with positive results from clinical trials in which electrotherapy was applied to nonischemic chronic wounds.

Dosimetry of HPVC is only beginning to be understood. Some investigators have proposed that the key input variable should be charge/second because a window of effectiveness of 250 to 600 microcoulombs/second has been reported in several investigations of pulsed current and wound healing. The present study calculated charge/second for reperfusion of ischemic wounds to be about 1250 microcoulombs/second, which is 2-fold to 4-fold higher than what has been reported to be effective for nonischemic wound healing. Although the dose (charge/second) used in this study is higher than used in other published reports, the calculations are based on assumptions that must be carefully considered. For instance, calculation of charge/pulse is based on a 1 K ohm resistance. There is no assurance that the human resistance through a direct-coupled circuit (including electrodes) is actually 1 K ohm. In addition, the assertion that dose is charge/pulse is open to challenge. Other parameters that may best define dose include current density and electric field. Only dose-response testing on animal or in vitro models will ultimately determine which physical parameter best defines dose and what is the physiologic pattern of response to that dose.

A slow, steady increase in TcPO2 resulting in wound healing may be at least partially related to the number of infrapopliteal occluded arteries. Patients with less arteriosclerotic disease in this study tended to recover microcirculation better than those with more arteriosclerosis. If HVPC enhances microcirculation, the mechanism(s) that underlies the effect remain unclear. Recent advances in the understanding of endothelial cell physiology suggest a balance between nitric oxide (NO) and superoxide in microvessels. A relatively high concentration of superoxide occurs during ischemia. In addition, there is an NO deficit within diabetic tissue, which may worsen tissue ischemia caused by minor trauma. NO is released and is associated with a skin perfusion increase during HVPC-like stimulation. NO protects against reperfusion injury and is a vasodilator; liberation of NO may be a mechanism for HVPC-associated microcirculation increase.

For this study, critical ischemia was defined as periwound skin with TcPO2 less than 10. There is ample justification for this definition, based on studies that successfully predict wound healing in patients with end-stage renal disease and diabetes. Diabetes often confounds measurements of ABI due to medial calcinosis. It must be cautioned, however, that TcPO2 readings are low in areas of edema, callous, or infection. Therefore, TcPO2 electrodes were placed to avoid these confounding factors. Wounds above the ankle were excluded from this study, partially because they are frequently associated with edema from venous insufficiency.

An outcomes study is outside the realm of this clinical case series; however, if complete closure of an ischemic wound were to take 24 weeks, the cost would be less than an amputation and subsequent rehabilitation and prostheses, estimated at $100,000. The cost of conservative closure is about $20,000, or one fifth of the amputation cost by informal analysis. This included an estimate of typical Medicare reimbursement costs of dressings and other supplies ($6000), nursing visits ($8000), physician visits ($1200), HVPC durable medical equipment rental ($1200), and diagnostic studies (MRI, MRA, TcPO2, PVR, but not angiography; $2500). This analysis does not factor in the quality of life differences between amputation and limb salvage. Future studies may elucidate the relative cost of conservative closure, including electrotherapy versus amputation.

CONCLUSIONS

HVPC improves microperfusion in the vicinity of inframalleolar ischemic skin lesions and tends to promote healing if microperfusion improves sufficiently to reach near-normal physiologic levels. A controlled clinical trial is needed to confirm these speculative positive clinical findings.

REFERENCES

ELECTROTHERAPY REOXYGENATES INFRAMALLEOLAR ISCHEMIC WOUNDS ON DIABETIC PATIENTS

Diabetes Care 1997;20:405-12.