Continuing their clinical research to determine if HVPC augments ischemic wound healing and increases periwound microcirculation, Goldman et al conducted a prospective, randomized, single-blinded, sham-controlled clinical pilot study on a homogenous subset of patients with infrapopliteal ischemic wounds. For the purpose of their study, they defined ischemia as periwound TCPO₂ less than 20 mm Hg, which they deemed the threshold below which healing is not favorable. Eight patients were enrolled with ischemic wounds at or below the knee, periwound TCPO₂ less than 20 mm Hg, with wounds open for at least 4 weeks before enrollment in the study, and arteriosclerotic disease was confirmed by magnetic resonance angiography, pulse volume recording, or anigamogram. Patients were randomized to have their wounds treated with active or placebo HVPC. Active HVPC or placebo HVPC was applied at home 1 hour per day, 7 days per week, for 14 weeks. Wounds were monitored at regular intervals for wound area, wound appearance, and microcirculation, the latter of which was measured by TCPO₂ and laser Doppler flow. After 4 weeks, wounds treated with placebo HVPC increased in area by 50%, which was expected since ischemic wounds tend to increase in size. During the same period, wounds treated with active HVPC underwent a significant decrease in size (P < 0.05). After week 4, wounds in both groups demonstrated positive healing rates, but the healing rate in the control group continued to lag behind the healing rate of the active HVPC-treated wounds during the remainder of the 14-week period.

Most recently, Burdge et al reported positive limb salvage outcomes following HVPC adjunctive treatment of 40 full-thickness diabetic wounds on the lower extremities of 30 patients. The wounds had a mean age of 25 weeks and a mean surface area of 7.8 cm². Comorbid conditions that contributed to the complexity of these wounds included neuropathy (83.3%), peripheral vascular disease (76.7%), cardiac disease (36.7%), infection (33.3%), osteomyelitis (16.7%), and morbid obesity (10.0%). ES was added to the conservative management of these wounds after they had failed to improve, despite previous interventions that included vascular evaluation, surgical treatment as indicated, aggressive off-loading, infection control, and débridement. The mean number of ES treatments was 22.3. During a mean time of 14.2 weeks, 35 (77.8%) wounds healed, and during a mean follow-up of 39.8 weeks, 31 (68.9%) wounds remained closed. Of the four wounds (8.9%) that recurred, additional ES treatments healed two wounds, one required below knee (BK) amputation, and treatment options were being considered for the fourth wound. Ten (22.2%) wounds failed to heal, resulting in a transmetatarsal amputation for one patient (one wound) and BK amputations for five patients (six wounds).

**High-Voltage, Biphasic Multimodulated Current**

Recently, investigators have reported use of a conductive electrical stimulation device called Aptiva™ Move (Lorenz Neurovasc, Mississauga, Ontario, Canada), which has a biphasic, asymmetrical charge-balanced waveform with an adjustable negative phase amplitude between 0 and 300 V, a variable pulse frequency between 0 and 1 pps, and a pulse duration that varies between 10 and 100 μsec. (Fig. 26.31) During therapy with this device, electrical stimulation is described as sequences of negative phase signals with multiple modulations of pulse amplitude, frequency, and duration. The combination of these modulations is termed Frequency Rhythmic Electrical Modulation System or FREMS™. Although no studies on the effects of FREMS on wound healing were found, two studies describe its effects on painful diabetic neuropathy and on the induced expression of vascular endothelial growth factor (VEGF) in patients with diabetic polyneuropathy. In a study by Bosi et al, 31 patients with painful diabetic neuropathy who had decreased nerve conduction velocity (<40 m/sec) and increased vibration perception threshold (>25 V) were enrolled in a randomized, double-blind, crossover study designed to compare the effects of active and placebo FREMS. Each patient received two series of 10 treatment of either FREMS or placebo in random sequence, with each series lasting no more than 3 weeks. The investigators found that patients treated with active FREMS had a significant decrease in daytime and nighttime VAS pain scores (both P < 0.02). In addition, these patients also demonstrated significant increase in sensory tactile perception as assessed by monofilament, a decrease in foot vibration perception threshold as measured by a bioesthesiometer, and an increase in motor nerve conduction velocity (all P < 0.01). No significant changes were observed in patients who received placebo FREMS. The same measurements taken at 4-month follow-up and compared with baseline measurements showed that a significant carryover benefit had persisted for all measures that had shown improvement at the end of the study. No carryover effect was apparent with the crossover analysis. The authors concluded that FREMS is a safe and effective treatment of diabetic neuropathic pain.

**Figure 26.31** The Aptiva Move HVBPC device used in clinical studies on neuropathic pain and expression of VEGF (Lorenz Neurovasc, Mississauga, Ontario, Canada).
and is able to modify some parameters of peripheral nerve function.

In the second study, Bevilacqua et al assessed the effects of the FREMS signal versus a standard TENS signal on the expression of VEGF in 10 subjects (four males and six females) with type 2 diabetic polyneuropathy and 10 nondiabetic subjects (five males and five females). Subjects received TENS for 10 min followed by 30 min without ES, followed by FREMS for 10 min over the forearm volar surface. Blood samples for VEGF assay were obtained from the contralateral arm every 2 min during TENS/FREMS applications and every 10 min during the 30-min intervals. Laboratory analysis revealed a significant increase in plasma VEGF during FREMS in both nondiabetic and diabetic subjects (maximum response $89.4 \pm 80.3$ pg/mL and $48.5 \pm 18.3$ pg/mL, respectively; $P < 0.01$ versus baseline), with a lower but still significant response in diabetic subjects. No changes in VEGF were observed during TENS stimulation. The authors hypothesized that VEGF expression during FREMS stimulation may help explain the positive effects on nerve conduction velocity in diabetic polyneuropathy, possibly mediated by favorable effects on vasa nervorum microangiopathy. The findings from these two studies may have implications for the treatment of pain associated with diabetic polyneuropathy and for enhancing wound healing, but additional research is needed to support these assumptions.

**Strength of Evidence for Electrical Stimulation as a Wound Healing Intervention**

For the healing of chronic wounds by ES, the strength of evidence based on clinical trials is substantial. In 2000 the Paralyzed Veterans of America provided administrative and financial support to develop and publish a clinical practice pressure ulcer treatment guideline in which ES was assigned a stand-alone recommendation (number 17) based on a strong strength-of-evidence rating from three RCTs. The recommendation reads, "Use electrical stimulation to promote closure of stage III or IV pressure ulcers combined with standard wound care interventions."

**Meta-Analyses of Electrical Stimulation Wound Healing Research Studies**

Perhaps the most compelling evidence of the efficacy of ES for enhancing the rate of wound healing is supported by two meta-analyses. For their meta-analysis, Gardner et al selected 15 ES studies on chronic wound healing that included placebo-controlled, randomized trials ($N = 8$); nonrandomized trials ($N = 5$); a nonrandomized, placebo-controlled trial ($N = 1$); and one study with a descriptive design. Data analyzed from these studies included 24 ES samples (591 wounds) and 15 control samples (212 wounds) and included ulcers caused by pressure, venous and arterial insufficiency, and diabetic neuropathy. They calculated the mean percentage of healing per week for the ES and control samples and found that the percentage of healing per week was 22% for the ES samples versus 9% for control samples. The net effect of ES on chronic wounds was reported to be a mean percentage of healing per week of 13.5%, which represented a 144% increase in healing of ES-treated wounds over control wounds. Based on 95% confidence intervals for ES and control samples, the studies revealed a 90% probability that the net healing effect of ES is 3.7% per week or more, which conservatively represents an increase of 40% or more over the control rate. These findings were similar for both placebo-controlled studies and for all the studies reviewed, including non-placebo-controlled trials.

More recently, Houghton and Woodbury performed a meta-analysis that assessed the effect of ES on promoting chronic wound closure. They searched electronic databases and bibliographies to find articles published before October 2006. To qualify for inclusion in the meta-analysis, studies had to meet inclusion criteria that included (1) controlled clinical trials that had a between-group statistical comparison, (2) a population of adult humans with chronic skin ulcers who had undergone ES treatment using surface electrodes, and (3) wound size that was assessed objectively before and after treatment. In addition, consensus between four independent reviewers was required to reject articles. Of 2265 articles reviewed, 19 studies were selected for the review that involved a total subject number of 888 (ES group = 522; control group = 366). Of the 19 studies selected, 12 had data to support the ES accelerated wound healing whereas seven studies reported no differences between ES and control groups. Data were pooled from five studies that assessed the proportion of completely healed wounds. The overall effect size in favor of ES treatment was 3.93 ($P < 0.0006$). Studies that tended to show better responses to ES were those that used randomization, large sample sizes ($N = 25$), had similar subject characteristics at baseline, pressure ulcers, or used ES parameters, including a monophasic PC, negative or alternating polarity, and a relatively high pulse frequency (64pps). The evidence from this meta-analysis provides strong support that ES can significantly improve the proportion of chronic wounds healed.

Most recently, the European Pressure Ulcer Advisory Panel and the USA National Pressure Ulcer Advisory Panel jointly developed the International Pressure Ulcer Treatment Guide, which states: "Consider the use of direct contact (capacitive) electrical stimulation (ES) in the management of recalcitrant Category/Stage III and IV pressure ulcers to facilitate wound healing. (Strength of Evidence = A, based on data from Sackett Level 1 studies)."

**Considerations for Wound Treatment with Conductive Electrical Stimulation**

The clinical studies cited in the previous sections have confirmed that ES combined with standard wound care accelerates the rate of wound healing faster than standard care alone, despite the fact that clinical researchers in