Review Article

Evidence-Based Use of Pulsed Electromagnetic Field Therapy in Clinical Plastic Surgery

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Background: The initial development of pulsed electromagnetic field (PEMF) therapy and its evolution over the last century for use in clinical surgery has been slow, primarily because of lack of scientifically-derived, evidence-based knowledge of the mechanism of action.

Objective: Our objective was to review the major scientific breakthroughs and current understanding of the mechanism of action of PEMF therapy, providing clinicians with a sound basis for optimal use.

Methods: A literature review was conducted, including mechanism of action and biologic and clinical studies of PEMF. Using case illustrations, a holistic exposition on the clinical use of PEMF in plastic surgery was performed.

Results: PEMF therapy has been used successfully in the management of postsurgical pain and edema, the treatment of chronic wounds, and in facilitating vasodilatation and angiogenesis. Using scientific support, the authors present the currently accepted mechanism of action of PEMF therapy.

Conclusions: This review shows that plastic surgeons have at hand a powerful tool with no known side effects for the adjunctive, noninvasive, nonpharmacologic management of postoperative pain and edema. Given the recent rapid advances in development of portable and economical PEMF devices, what has been of most significance to the plastic surgeon is the laboratory and clinical confirmation of decreased pain and swelling following injury or surgery. (*Aesthetic Surg J 2009;29:135–143.*)

Pulsed electromagnetic field (PEMF) technologies have shown usefulness as adjunctive therapy for the treatment of both delayed-union fractures[1] and chronic wounds.[2] These relatively simple devices use an external, non-invasive PEMF to generate shorts bursts of electrical current in injured tissue without producing heat or interfering with nerve or muscle function. Recently, increased understanding of the mechanism of action of PEMF therapy has permitted technologic advances yielding economical and disposable PEMF devices. With these devices, PEMF therapy has been broadened to include the treatment of postoperative pain and edema in both outpatient and home settings,[3] offering the physician a more versatile tool for patient management.

The initial development of PEMF technology and its evolution over most of the last century was marred by poor presentation and, in many cases, insufficient knowledge of the scientific basis of action. However, plastic and reconstructive surgeons have been early adopters of the therapy and pioneers, along with their basic science colleagues, in developing what is now a significant and rigorous body of evidence around the mechanism of action. In this review, we describe the history, development, and eventual transformation of a marginal therapy into a technology that, should it fulfill its promise, will become a standard part of surgical care and may lead to other, more significant therapies for a variety of acute and chronic conditions.

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SOFT TISSUE HISTORY

The development of modern PEMF has followed two separate pathways. The first pathway originated in more conventional (and still useful) electromagnetic field technologies broadly known as radio frequency (RF) diathermy.[4] Continuous RF produces heat, the therapeutic component frequently employed in physical therapy. One early user of diathermy suspected that it could produce a nonthermal biologic effect.[5] To test this idea clinically, the RF signal was intermittently pulsed, thereby eliminating heat. Positive outcomes, especially in treating inflammatory conditions, were reported.[5] The first therapeutic RF PEMF device, the Diapulse, was commercialized in 1950[6] and was eventually cleared by the U.S. Food and Drug Administration (FDA) for the postoperative treatment of pain and edema in soft tissue. Clinical devices in use since that time typically have consisted of a large signal generator and a bulky coil applicator positioned over the area of injury that delivers therapy noninvasively, through either dressings or clothing. Early devices were expensive, nonportable, and produced significant electromagnetic interference (EMI); these factors restricted more widespread use in outpatient and home settings.

Diathermy-based RF PEMF has been employed in (1) double-blind clinical studies for chronic wound repair, in which actively treated pressure ulcers closed by 84% versus 40% in sham-treated wounds in one study[7] and 60% versus no closure in the control group in another study[8]; (2) studies showing that a decrease in edema in acute ankle sprains was sevenfold versus the control group[9,10]; (3) studies showing a pain decrease in acute whiplash injuries of 50% and a range of motion increase of 75% in treated versus control patients[11,12]; (4) skin microvascular blood flow studies, in which blood flow was enhanced by about 30% in both healthy[13] and diabetic[14] individuals; and (5) studies in which postmastectomy lymphedema was reduced by 56% and skin blood flow increased fourfold.[15]

ORTHOPEDIC HISTORY

In a parallel but separate evolution, orthopedic surgeons, studying the process by which mechanical signals influence bone growth and repair,[16,17] discovered that everyday mechanical signals (walking, jumping, etc.) produced endogenous electrical currents in bone that could modulate bone cell activity.[18] This naturally led to the use of exogenous current for bone repair. The first animal studies employed low (microampere) level direct currents (DC) delivered via implanted electrodes that resulted in new bone formation around the negative electrode (cathode[19]). The first therapeutic devices were based on these early animal studies and used implanted and semi-invasive electrodes delivering DC to the fracture site.[20,21] These early applications required the cathode to be near the fracture site because bone growth was limited to the area immediately adjacent to the electrode surface, where chemical changes related to electrolysis occur.

There followed the development of inductively coupled, externally applied electromagnetic field modalities to affect bone repair.[22,23] Development of the bone growth stimulator (BGS) signal did not follow from diathermy considerations, but rather from the general electrochemical models developed by one of the authors (AAP).[24] As will be seen, although this approach resulted in an effective BGS signal, that signal was not specifically configured for what is now commonly considered to be the PEMF transduction pathway. Nonetheless, a multitude of studies have shown the BGS signal to have sufficient biologic effect to modulate growth factor release.[25] Therapeutic uses of these technologies in orthopedics have led to clinical applications approved by regulatory bodies worldwide for the adjunctive treatment of recalcitrant fractures and spine fusion.[1,26] Several reports have suggested that the overall success rate of BGS is not significantly different from that of the first bone graft,[1] which is a significant benefit for the patient and the health care system.

BASIC SCIENCE HISTORY

The biophysical mechanism(s) of interaction of PEMF on biologic tissues and the biologic transduction mechanism(s) have been vigorously studied.[27] One of the first models created was a linear physicochemical approach,[22,24,27,28] in which an electrochemical model of the cell membrane was employed to predict a range of PEMF waveform parameters for which bioeffects might be expected. The most generally accepted biophysical transduction step is ion/ligand binding at cell surfaces and junctions that modulate a cascade of biochemical processes, resulting in the observed physiologic effect.[25,29-31] A unifying biophysical mechanism that could explain the vast range of reported results and allow predictions of which PEMF signals and exposures are likely to induce a clinically meaningful physiologic effect has been proposed.[22,28] The general application of this approach led to the BGS signal in use today. However, that signal is often only marginally effective because further dose quantification needed specific knowledge of the ion, the target site, its binding kinetics, and the cascade involved.

Studies emerged suggesting that PEMF could modulate the production of growth factors[32] and began to focus on enzyme systems with well-characterized calcium (Ca^{2+}) dependence. By the mid-1990s, researchers were investigating the effects of electrical[33] and PEMF signaling on intracellular Ca^{2+}, specifically the binding of Ca^{2+} to calmodulin (CaM), using the knowledge that CaM-dependent cascades were involved in tissue repair.[34] One important early study showed that RF PEMF could increase Ca^{2+}, binding kinetics to CaM by measuring the phosphorylation of myosin light chains in an enzyme assay.[35] This and other studies[36,37] clearly showed the dependence of the PEMF effect upon free Ca^{2+} at levels mimicking those found in the living cell. Therefore, PEMF modulates a physiologically relevant cascade involving

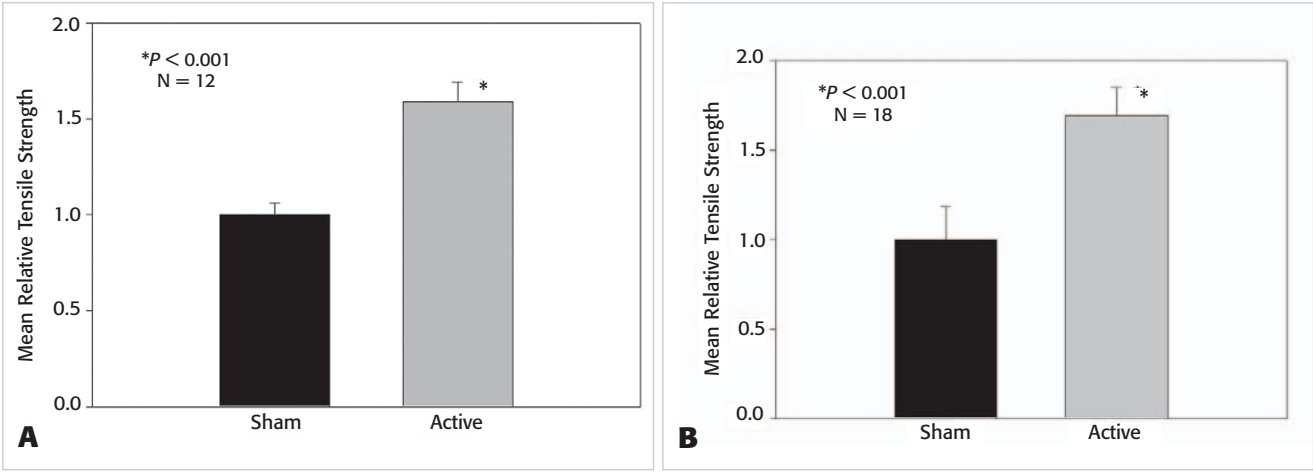

Figure 1. Effect of pulsed electromagnetic field therapy, configured for the calcium/calmodulin pathway, on (**A**) a cutaneous full-thickness wound and (**B**) a transected Achilles' tendon healing in the rat. Pulsed electromagnetic field therapy treatment was administered for 30 minutes twice daily for 21 days. The results showed a 59% increase in the tensile strength of the treated wound and a 69% increase in the tensile strength of the tendon. (Courtesy Strauch et al.[49,50])

Ca^{2+}, binding to CaM. The Ca/CaM complex then binds to and activates myosin light chain kinase (MLCK), which in turn catalyzes myosin phosphorylation.[38]

Once it was established that Ca^{2+} binding to CaM was a potential transduction pathway for PEMFs, the electrochemical model was employed to configure RF signals that would efficiently couple to Ca^{2+}-binding kinetics[28] using rate constants, which are well studied for the Ca/CaM system.[39] This enabled the diathermy-based PEMF signal to be reconfigured so that its frequency spectrum more closely matched the dielectric properties of Ca^{2+}-binding kinetics at CaM. The result is a PEMF device that uses 100 times less peak power to produce a biologically effective signal dose in the body. Initial confirmation of these predictions of the electrochemical model were reported for the MLCK enzyme assay, neurite outgrowth, and bone repair in a rabbit model.[40] All of the limitations of the original diathermy-based devices were therefore addressed, potentially providing the physician with a more versatile and economical tool for postoperative pain and edema management with no known side effects.[3]

The most recent studies of the PEMF transduction pathway have concentrated upon the Ca/CaM-dependent nitric oxide (NO) cascades. It is within this system that the effectiveness of PEMF is now understood to function. However, those linkages were dependent on the discovery that NO is a signaling molecule.[41] NO is synthesized via nitric oxide synthase (NOS), that has several different isoforms.[42] When injury occurs, large amounts of NO are produced by long-lived inducible nitric oxide synthase (iNOS). In this cascade, tissue levels of NO persist and the prolonged presence of this free radical is proinflammatory,[43] which accounts for the leaky blood vessels associated with pain and swelling.[44] In contrast, the endothelial and neuronal nitric oxide synthase isoforms (eNOS and nNOS, respectively) produce NO in short bursts that can immediately relax blood and lymph vessels.[45,46] These short bursts of NO also lead to the production of cyclic guanosine monophosphate, which in turn drives growth factor production.[47] Interestingly, iNOS is not dependent on CaM,[43] while the constitutive or cNOS (eNOS or nNOS) cascade is dependent on the binding of Ca/CaM. Therapies that could accelerate Ca/CaM binding, therefore, should impact all phases of tissue repair, from initial pain and swelling to blood vessel growth, tissue regeneration, and remodeling.[42]

CURRENT STATUS

The basic science work accomplished to date provides strong support for the proposal that modulation of Ca^{2+} binding to CaM, upon a transient increase in intracellular calcium when homeostasis is interrupted,[48] is an important PEMF transduction pathway. It is likely that the disruption of the tightly regulated Ca^{2+} balance in cells is the natural signal to provoke the endogenous tissue repair and regeneration mechanism, hence the apparent simple acceleration of normal healing activity by targeted PEMF signals. Ca/CaM catalyzes eNOS, which allows the PEMF signal to modulate the release of NO from eNOS and potentially affect the entire tissue repair pathway, from pain and edema to angiogenesis, bone and tissue regeneration, and other regenerative actions. PEMF signals configured to target the Ca/CaM pathway have been applied to rat tendon and wound healing.[49,50] In both studies, tendon and wound healing rates were seen to significantly increase by 59% ± 4% (Figure 1, *A*) and 69% ± 5% (Figure 1, *B*) in PEMF-treated animals.

It is interesting to note that one of the authors (BS) showed significant increases in angiogenesis in an arterial loop model in the rat using the early diathermy-based RF device (Figure 2).[51,52] It is also interesting that the use of the BGS signal on human umbilical vein endothelial cells in culture significantly augmented tubule formation[53] via a PEMF effect on the production of fibroblast growth factor 2 (FGF-2). When FGF-2 was inhibited, the PEMF effect disappeared. This study was extended to

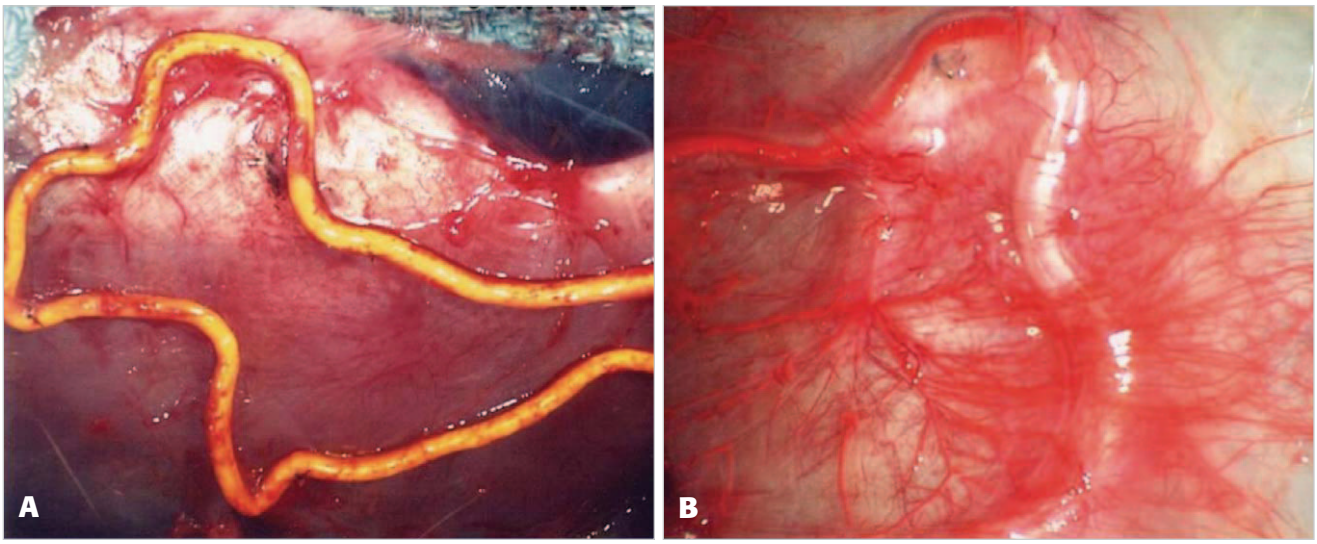

Figure 2. Effect of diathermy-based athermal pulsed electromagnetic field therapy on angiogenesis in a transplanted arterial loop in the rat groin. **A**, Control. **B**, Results after 8 weeks of 30-minute pulsed electromagnetic field therapy, given twice daily. Angiogenesis was reported to be 500% greater in the treated animals. (Courtesy Roland et al.[51])

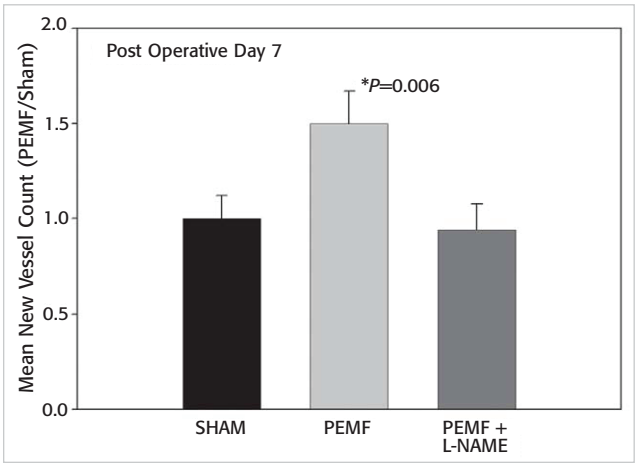

Figure 3. NG-nitro-L-arginine methyl ester, a nitric oxide synthase inhibitor, eliminates the pulsed electromagnetic field effect on angiogenesis in a thermal myocardial necrosis model, suggesting calcium binding to calmodulin in the nitric oxide signaling cascade as the pulsed electromagnetic field transduction mechanism (unpublished results, BS and AAP).

examine the effect of BGS on wound repair in diabetic and normal mice,[54] in which it was also shown that PEMF significantly increased neovascularization, particularly in diabetic mice, via endogenous FGF-2 increase.

Although the aforementioned studies suggest that PEMF effects on the Ca/CaM/NO cascades were responsible for the reported biologic effects, cellular and animal studies in which the use of inhibitors for selected steps in this cascade provide the strongest support. One well-designed study clearly showed DNA synthesis in articular chondrocytes in vitro was increased by PEMF via a NO pathway. This study systematically used CaM, NOS, and cGMP inhibitors that individually eliminated the PEMF effect on DNA synthesis.[55] PEMF effects on osteoblast proliferation and differentiation were shown to be mediated by NO.[56] Direct evidence of the effect of a PEMF signal configured for the Ca/CaM pathway on real-time NO production in a neuronal cell line, which could be eliminated by CaM and NOS inhibitors, has also recently been reported.[57,58] Finally, 2 of the authors (BS and AAP) showed that PEMFs configured for the NO pathway significantly increased angiogenesis in a thermal myocardial injury in the rat.[59,60] This effect was eliminated in rats who were fed NG-nitro-L-arginine methyl ester (L-NAME), a NOS inhibitor (Figure 3).

Considered together, all available evidence provides strong support for Ca/CaM-dependent transient NO production as an important PEMF transduction pathway for tissue repair. One of the authors (AAP) has recently proposed the PEMF mechanism as a working model for PEMF therapeutics (Figure 4).[61] This mechanism suggests that the primary effect of clinically relevant PEMF signals is to increase the rate of Ca^{2+} binding to CaM, which then catalyzes cNOS (eg., eNOS), producing an immediate (within seconds) production of NO, which can orchestrate an antiinflammatory response via increased blood and lymph flow. NO, in turn, regulates cGMP production (within minutes), which cascades to the appropriate growth factor release dependent on the stage of healing (eg., FGF-2 for angiogenesis).

It is important to note that PEMF effects are immediate and are not limited by pharmacokinetics because the induced currents are instantaneously present when the coil applicator is transmitting into the affected area. For example, studies designed to assess PEMF effects on pain and edema in a carrageenan rat hind paw model have reported a 100% inhibition of pain and a 50% reduction of edema in treated animals over a time span of 225 minutes[62] compared with aspirin or nitroaspirin, which only caused about 50% pain inhibition at 200 minutes, using maximum dose in the same model.[63] It is also important to note that resting cells (in homeostasis), in which there is no transient increase in cytosolic free Ca^{2+}, do not appear to respond to PEMF, providing one explanation for the reports of no known side effects from PEMFs since the clearance of BGS devices in 1979.

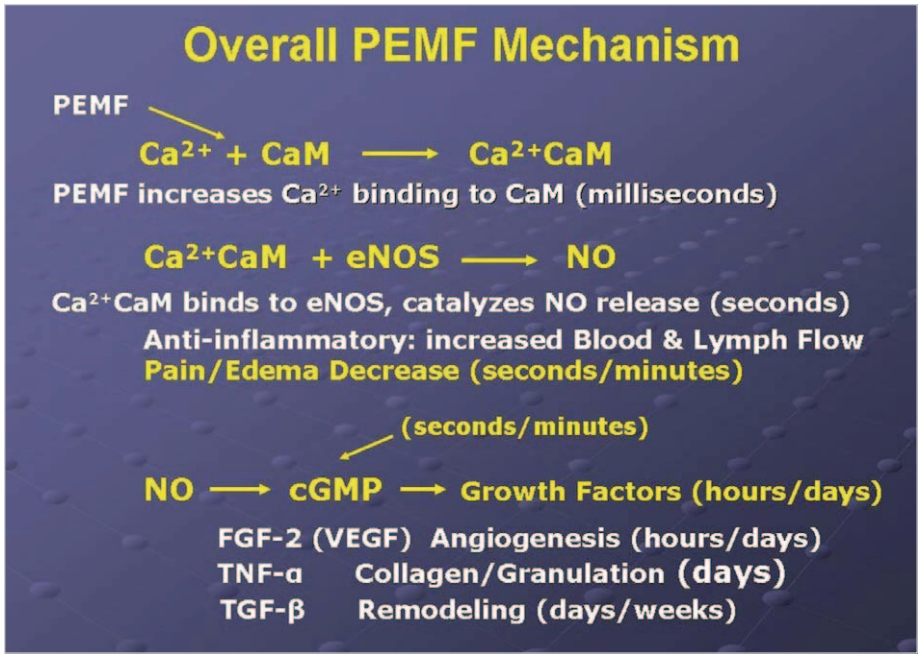

Figure 4. Pulsed electromagnetic field (PEMF) transduction mechanism based on evidence to date that many athermal PEMF effects depend upon nitric oxide cascades. PEMFs can be configured to modulate calcium-binding kinetics to calmodulin. Calcium/calmodulin then activates nitric oxide synthase and the relevant cascade ensues dependent upon stage of tissue repair process. This mechanism has been proposed as a working model for PEMF therapeutics.[61]

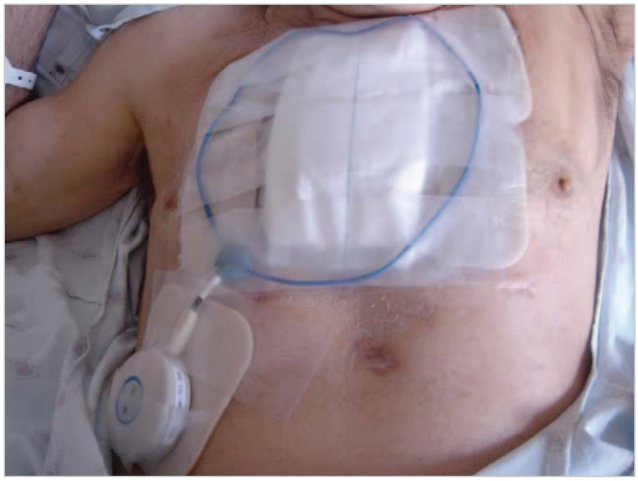

Figure 5. A modern portable, disposable pulsed electromagnetic field device is incorporated into a dressing for the postoperative treatment of an incisional wound.

CLINICAL APPLICATIONS

Given the recent rapid advances in the development of portable and economical PEMF devices, of most significance to the plastic surgeon has been the laboratory and clinical confirmation of decreased pain and swelling following injury or surgery.[3,62] Indeed, PEMF configured for the Ca/CaM pathway has been shown to significantly accelerate postsurgical pain relief with a concomitant reduction in pain medications in a randomized, doubl-blind study in patients who underwent breast augmentation.[3] Because of the unique biologic mechanism of the PEMF effect, this modality can be combined quite effectively with other therapies for additive or supradditive effects to promote pain relief, healing, and recovery. Treatment regimens may be manual or automatic and scheduled as frequently as every hour for particularly acute situations. The device is noninvasive and can be applied over a dressing; it and may even be part of a dressing for postoperative treatment of an incisional wound (Figure 5). Treatment begins in the recovery room and, to treat pain and edema, is generally administered every 4 hours for 30 minutes for 3 days, and then every 8 hours for the next several days until pain and edema are not significant. For the treatment of chronic wounds, the regimen is 30 minutes twice a day until healed.

Figure 6 illustrates typical configurations of the PEMF units used in aesthetic surgery. Figure 6, *A* has a dual coil applicator for breast surgery. Figure 6, *B* demonstrates a single coil that is used for local pain relief following abdominoplasty in which the experience of one of the authors (BS) has shown that postoperative pain and edema is rapidly resolved and patients are ready for discharge on the first postoperative day following abdominoplasty for massive weight loss.

PEMF allows for almost immediate increase in vascular flow, enhancing circulation and reducing edema, such as in the series on a nasal defect demonstrated in Figure 7. Another important use of PEMF configured for the Ca/CaM/NO pathway is in the treatment of chronic nonhealing wounds. The recommended treatment is 30 minutes twice per day until the wound is closed. Closure of chronically open wounds may be seen in 6 to 10 weeks with this treatment (Figures 8 and 9).

PULSED ELECTROMAGNETIC FIELD THERAPY IN PLASTIC SURGERY PRACTICE

The PEMF devices described in this review (Ivivi Technologies, Montvale, NJ) have been cleared by the FDA for the treatment of postoperative pain and edema

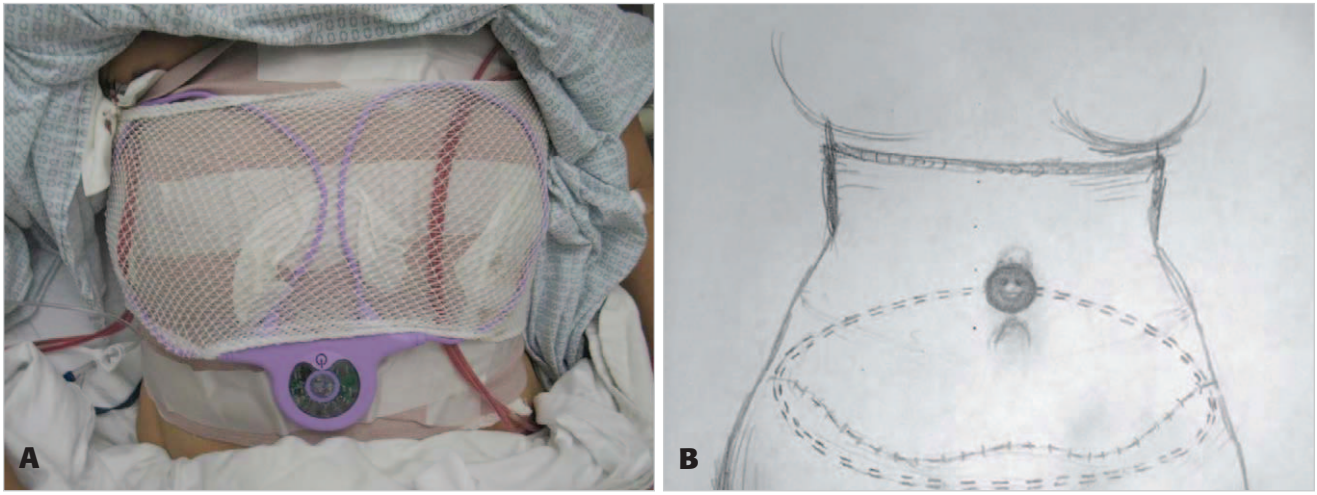

Figure 6. Illustrations of some current postsurgical uses of portable/disposable pulsed electromagnetic field devices with signals configured for the calcium/calmodulin/nitric oxide pathway. **A**, Application to breast augmentation/reduction. The devices are incorporated in dressings/bras and activated immediately after surgery. **B**, Application to abdominoplasty. The device is incorporated into the dressing and activated immediately after surgery. The device is applied over the dressing and autoactivated every 4 hours for 72 hours and then every 8 hours for 72 hours and, finally, twice a day until it is no longer needed.

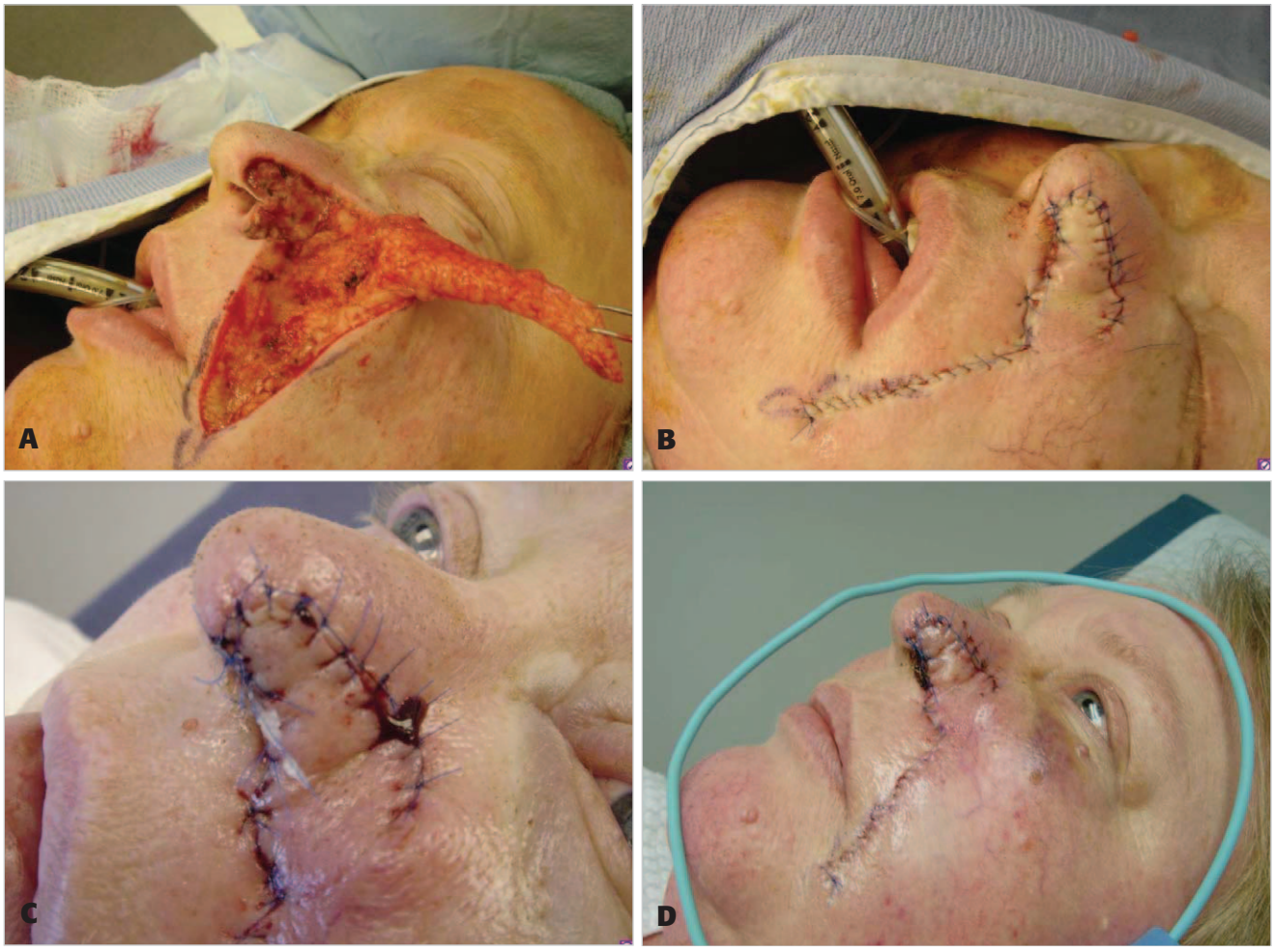

Figure 7. Nasal defect with long nasolabial flap. **A**, Immediate postoperative view with poor circulation in flap. **B**, After 30 minutes of pulsed electromagnetic field therapy (PEMF) in the recovery room, obvious vasodilatation is shown. **C**, Postoperative view after 24 hours and 2 30-minute PEMF treatment sessions showing minimal edema and good vascularization **D**, Patient did not require pain medication and was maintained on 30-minute PEMF treatments twice a day for 1 week.

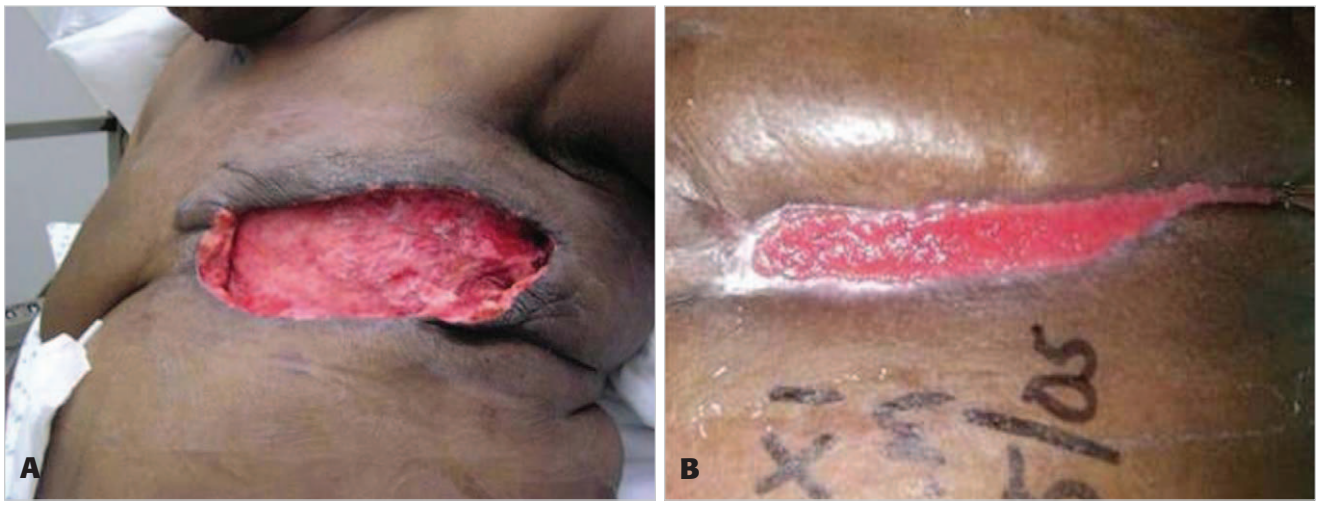

Figure 8. **A**, Poorly vascularized chest wound following 2 excision procedures and 2 courses of radiotherapy. Two attempts at flap closure failed. **B**, Wound is resolved following 9 weeks of pulsed electromagnetic field therapy (PEMF) for 30 minutes twice per day. The wound was treated simultaneously with PEMF and sponge suction for 1 week and then PEMF alone until closure.

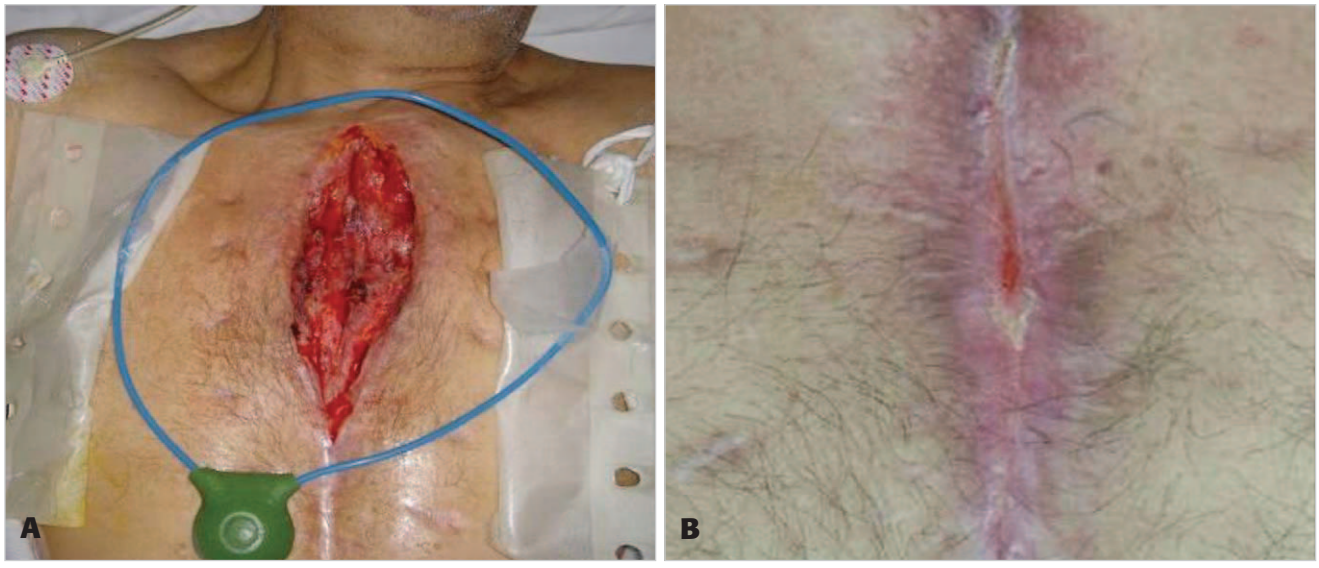

Figure 9. Nonhealing episternal abscess wound in an elderly male following cardiac surgery. **A**, The open cardiac wound is seen following drainage of abscess and start of pulsed electromagnetic field therapy (PEMF). **B**, Wound closure is shown 8 weeks after 30-minute PEMF treatments twice daily. Patient was cared for in a hospital for 1 week and was then transferred to a nursing home with a portable PEMF unit until complete healing occurred.

and are currently available. PEMF therapy is typically used for postoperative pain management with the expectation of a significant reduction in the use of narcotics and/or nonsteroidal antiinflammatory drugs, earlier hospital discharge, and/or an earlier return to function. As indicated in this review, PEMF may also be used in challenging cases such as irradiated tissue or other wounds in poorly vascularized tissue. In practice, PEMF is delivered via a circular coil that is always placed so that the tissue target is encompassed within the coil perimeter. The device can be applied over dressings, braces, or clothing. Treatment regimens may be manual or automatic. For postoperative use, treatment begins in the recovery room and is generally administered every 4 hours for 30 minutes for 3 days, and then every 8 hours for the next several days until pain and edema are not significant. For the treatment of chronic wounds, the regimen is 30 minutes twice a day until healed. PEMF device operation is simple and patients may easily be instructed on its use in both outpatient and home settings.

CONCLUSIONS

PEMFs have been in clinical use for generations. For most of that time, however, PEMFs have been relegated to second or even third tier status, with some ardent supporters, a number of skeptics, and most clinicians and patients simply unaware of their benefits. Without substantive information about a mechanism of action and frequently being the subject of overzealous marketing and inflated claims, PEMF devices lacked credibility. When the knowledge base in basic sciences allowed for

the critical examination of PEMF in the laboratory and provided techniques for both targeting and engineering, the system advanced and the many effects of PEMF signals could be rationalized within at least 1 biologic cascade—one that is dependent on an electrochemical process and can be affected by exogenous signals. It was clear from this work that different PEMF signals and configurations produce widely different results depending on how well targeted those signals are to naturally occurring and biologically salient electrochemical processes. As this body of evidence grows and clinical experience widens, the gaps in the current knowledge (especially concerning optimal treatment regimens for specific conditions) will be filled. At the same time, we anticipate that improved signals and products that are more effective and more ergonomically designed will be developed, and that other electrochemical pathways will be targeted for additional indications. This may finally be the century of electrotherapy. In the meantime, plastic surgeons have at hand a powerful tool for the adjunctive management of postoperative pain and edema and wound repair. PEMF therapy is simple, cost-effective, has no known side effects, and may well play a large role in treatment of otherwise intractable wounds while reducing the cost of health care. ◗

DISCLOSURES

Drs. Strauch and Pilla are paid consultants for, and shareholders, of Ivivi Technologies, Inc. Dr. Ignarro is on the Board of Directors of Ivivi Technologies, Inc. Drs. Dabb and Herman have no financial interest in and have received no compensation from the manufacturers of products mentioned in this article. Ivivi Technologies, Inc. did not in any way contribute to the writing of this article.

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Accepted for publication January 28, 2009.

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1090-820X/$36.00

doi:10.1016/j.asj.2009.02.001